CHAPTER

31 Antibiotic- and Immunosuppression-Related Renal Failure

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AMINOGLYCOSIDE ANTIBIOTICS

Nephrotoxic injury is a common complication of aminoglycoside antibiotic therapy. Studies that have used well-defined measures of nephrotoxicity indicate an incidence rate of 7% to 36%.[1–9] This variability reflects differences with respect to the nephrotoxicity potentials of aminoglycoside antibiotics in clinical use as well as differences among patients receiving these drugs. A survey of clinical studies published between 1975 and 1982 revealed that the average incidence of nephrotoxicity caused by specific aminoglycoside antibiotics was gentamicin, 14%; tobramycin, 12.9%; amikacin, 9.4%; and netilmicin, 8.9%.[10] In critically ill patients, the incidence of aminoglycoside nephrotoxicity may rise twofold.[11]

Clinical Aspects

The clinical expression of aminoglycoside nephrotoxicity has been well described.[12–16] Lopez-Novoa and colleagues wrote a comprehensive review on the mechanisms of aminoglycoside nephrotoxicity.[17] The earliest and most common expression of aminoglycoside renal tubular cell alterations is increased urinary excretion of low molecular weight proteins[18,19] and of lysosomal and brush-border membrane enzymes.[18–21] These changes may be detected within 24 hours of initiating drug therapy, and the frequency and magnitude of these changes increase as a function of dose and duration of therapy. Unfortunately, these changes do not predict which patients will progress to acute renal failure (ARF). This probably reflects the fact that several mechanisms underlie the expression of the enzymuria and proteinuria.[13] With repeated dosing, the amount of enzymes and low molecular weight proteins excreted in the urine may increase quite sharply, which may signify the onset of proximal tubular cell necrosis.[13]

Nonoliguric renal failure is a common expression of aminoglycoside nephrotoxicity[22] and may reflect a direct inhibitory effect on solute transport along the thick ascending limb of Henle's loop[23] or possibly tubulointerstitial cell injury,[24] which results in impaired ability to maintain a hypertonic medullary interstitium. Inhibition of adenylate cyclase may also contribute to the polyuria.[25] Neither mechanism, however, adequately explains the maintenance of normal to high urine output, even in the face of severe depression of whole kidney glomerular filtration rate (GFR). The slow evolution of ARF, which has been attributed to a variable susceptibility of renal proximal tubular cells to aminoglycoside toxicity,[12,26] may allow for the development of maximal compensatory adaptation by residual intact nephrons. In addition, micropuncture experiments[27] implicate a marked depression of solute and water transport along the proximal tubule such that the large increase in the fraction of filtrate escaping reabsorption along the proximal tubule may overwhelm the reabsorptive capacity of the distal nephron and contribute to the pattern of nonoliguric renal failure. When oliguria occurs, it usually signifies the influence of one or more complicating factors (e.g., ischemia or another nephrotoxin), especially if the oliguria appears early in the course of aminoglycoside administration. Studies in animals have shown that aminoglycoside therapy sensitizes the kidney to a subsequent ischemic or nephrotoxic insult,[28–37] such that the severity of the ARF is substantially greater than that predicted by the sum of the individual insults. Deterioration of other proximal tubular transport processes may occur during aminoglycoside toxicity and, in rare cases, may mimic a Fanconi-like syndrome.[38] Hypokalemia and hypomagnesemia secondary to renal potassium and magnesium wasting may also appear.[39,40]

Depression of GFR is a relatively late manifestation of aminoglycoside nephrotoxicity. In humans, depression of GFR typically does not occur before 5 to 7 days of therapy have been completed[15] unless there has been a major complicating factor such as renal ischemia. Studies in animal models of aminoglycoside nephrotoxicity have implicated activation of the renin–angiotensin system,[41] reduction in the size and density of glomerular endothelial fenestrae,[42–44] tubular obstruction,[45] tubular back leak,[27] and release of platelet activating factor from mesangial cells[46] as pathogenic factors causing depression of GFR.

The majority of patients with aminoglycoside nephrotoxicity recover renal function clinically, although in some cases the time to recovery may be prolonged.[16] Chronic renal failure is a distinctly uncommon complication of pure aminoglycoside

nephrotoxicity in humans, so that when it occurs, it usually signifies the contribution of some additional factor. Animal studies indicate, however, that incomplete regeneration with interstitial fibrosis does occur,[47] and the same may be true for humans.[48]

Morphologic Alterations

Aminoglycosides cause tubular cell necrosis that in animal models is largely confined to the proximal convoluted tubule and pars recta.[49–51] In humans, the renal tubular site of injury is less well established,[24,52] due in part to the fact that little human biopsy material has been available for study. Moreover, in human subjects, the development of ARF in conjunction with aminoglycoside administration typically occurs in association with other insults such as sepsis and renal ischemia,[24,53,54] and each of these insults has been shown to interact synergistically with aminoglycoside antibiotics to magnify the severity and sites of tubular cell injury.[31–37]

The earliest lesion seen by electron microscopy is an increase in the number and size of secondary lysosomes, also called cytosegrosomes or phagosomes.[49–51] Examples of this

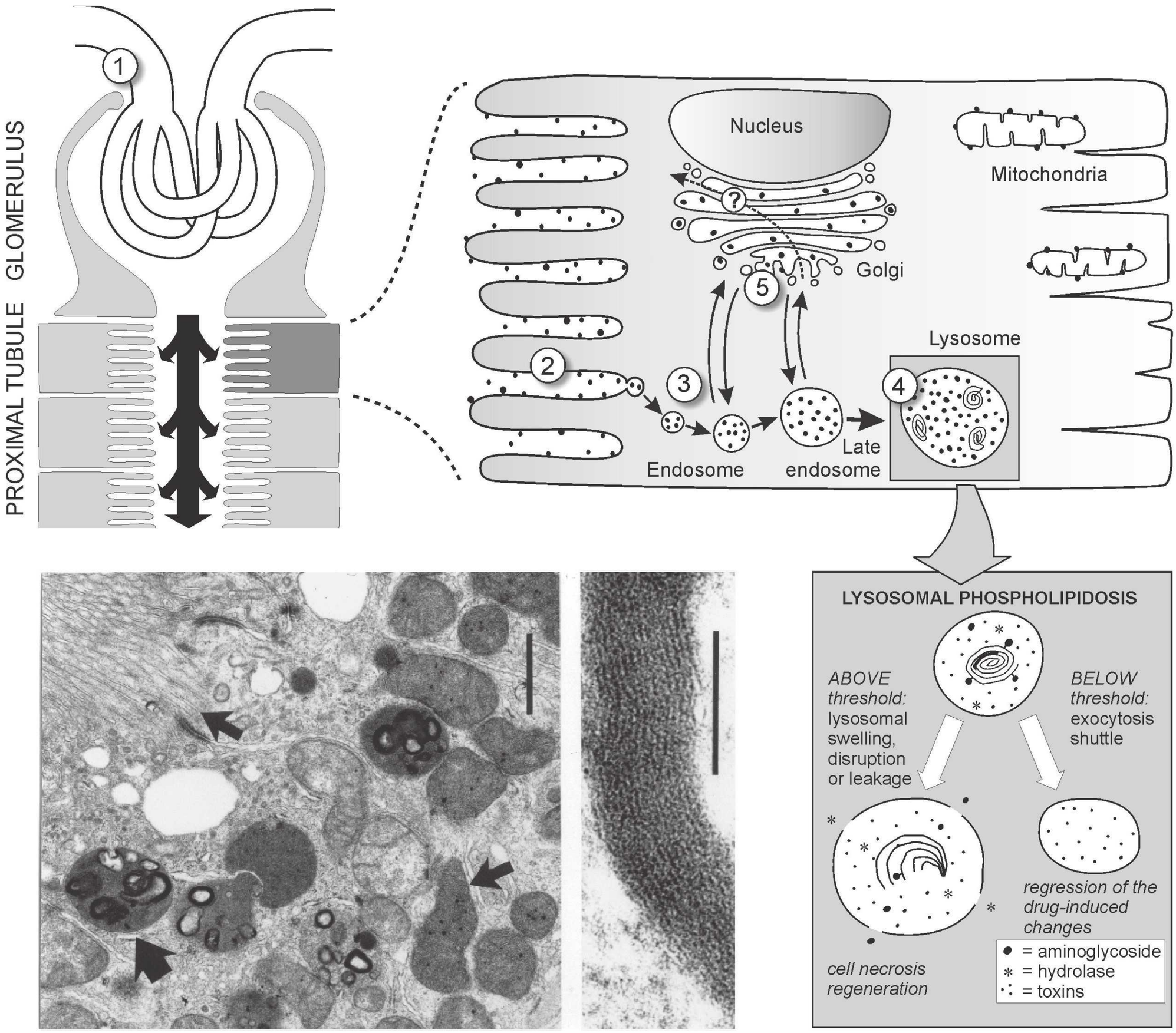

FIGURE 31.1 **Above**: Binding uptake and intracellular trafficking of gentamicin in renal proximal tubular cells. **A:** After glomerular filtration (*1*), gentamicin (•) is shown binding to the surface membrane (*2*) and being internalized by a receptor (megalin) mediated endocytic process (*3*). Gentamicin also enters the cell through fluid phase endocytosis. It moves through the endocytic system into late endosomes and from there into lysosomal structures (*4*). A small but quantifiable fraction (5%–10%) of gentamicin directly traffics from the surface membrane into the trans-Golgi network (*5*) and from there throughout the Golgi Apparatus. **Below left**: Ultrastructural appearance of proximal tubular cells after 4 days of gentamicin treatment, showing lysosomes containing dense lamellar and concentric structures (*large arrow*), while brush-border, mitochondria (*small arrow*), and peroxisomes are unaltered. Upon higher magnification the structures in lysosomes show a periodic pattern. Bar left = 1 μm, middle = 0.1 μm. **Below right**: Internalization and lysosomal sequestration of gentamicin. (Adapted from Verpooten GA, Tulkens PM, Molitoris BA. Aminoglycosides and vancomycin. In: De Broe ME, Porter GA, Bennett VM, Verpooten GA, eds. *Clinical Nephrotoxins – Renal Injury from Drugs and Chemicals,* 2nd ed. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2003:151–170.)

lesion are shown in Figure 31.1. Secondary lysosomes are primary lysosomes that have coalesced with endocytic or autophagic vacuoles. Many of these lysosomes contain myeloid bodies, electron-dense lamellar structures of concentrically arranged and densely packed membranes. These lysosomal alterations probably represent autophagic vacuoles arising from sequestration of fragments of membranes and organelles damaged in the early phase of toxicity and are undergoing lysosomal processing. In experimental animals receiving single parenteral drug doses or continuous drug infusion, these changes have been observed as early as 6 to 12 hours posttreatment.[56] Both the number and size of lysosomal myeloid bodies increase as a function of dose and duration of drug therapy and are accompanied by progressive expansion of the volume of the cell occupied by engorged lysosomes.[50,56,57] These morphologic alterations also have been convincingly demonstrated in human kidney material.[58,59] Studies in experimental animals and in cultured cells have demonstrated that the myeloid bodies are composed of membranes rich in phospholipids[60,61] and form as a consequence of the lysosomal accumulation in high concentration of aminoglycosides. This lysosomal accumulation of aminoglycosides inhibits lysosomal phospholipases[62,63] and possibly other lysosomal enzymes and impairs the degradation of cell membrane.[61,64] Similar alterations have been induced by a variety of compounds that accumulate within the lysosomal compartment and interfere with the activity of lysosomal enzymes.[65–67]

Following lysosomal alterations, the following occurs: a decrease in the density and height of brush-border microvilli, dilation of the cisternae of rough endoplasmic reticulum, and the appearance of cytoplasmic vacuolization in tubular epithelial cells.[51,56] As injury progresses, brush-border membrane fragments and extruded myeloid bodies, membrane vesicles, and cytoplasmic debris begin to be seen within tubular lumina.[51,68] Later in the course of nephrotoxicity, mitochondrial swelling becomes evident, and patchy but extensive tubular epithelial cell necrosis and desquamation occur. Many tubules, both proximal and distal, are filled with eosinophilic, granular material that, by electron microscopy, is composed of cytoplasmic debris, membrane fragments, and myeloid bodies. Transmission electron microscopy of the urine reveals the presence of myeloid bodies and fragments of brush-border membranes.[68–70]

Proximal tubular cells manifest an apparent variable susceptibility to aminoglycoside toxicity evident by the appearance of cell regeneration simultaneously with ongoing cell necrosis.[26,47,50,57,71] In several animal studies virtually complete recovery of renal structure and function has been observed during continued aminoglycoside administration.[72,73] One explanation for these observations is that the renal tubular epithelium had acquired resistance to the nephrotoxic effects of the aminoglycoside antibiotic. Sundin and colleagues[74] report that the "acquired resistance" reflects selective inhibition of aminoglycoside uptake by renal proximal tubular cells, the mechanism of which does not involve a reduction in the membrane content of phosphatidylinositol or megalin. In animal models, cell regeneration can be detected by [^{3}H]thymidine incorporation into DNA after only 4 days of low-dose aminoglycoside administration and before cell necrosis is evident by light microscopy.[57,74] The magnitude of DNA labeling correlates with the dose and duration of drug administration.[75] Of particular interest is the observation that quantitatively similar labeling is observed in renal cortical interstitial cells as in tubular epithelial cells.[57,75,76] This finding raises the question of the role of these interstitial cells in the pathogenesis of aminoglycoside toxicity. Eventually most areas of the affected kidney regain normal architecture and function, but residual scarring containing collections of collapsed, atrophic tubules may occur focally in the cortex.[47,48,51] In animal models of aminoglycoside nephrotoxicity, the degree of tubular cell necrosis correlates reasonably well with the decline in renal excretory function. A similar correlation is lacking in human material.[24,52,58]

Pathogenesis

The pathogenesis of aminoglycoside nephrotoxicity is intimately linked to the renal pharmacology of these drugs.[77–80] Aminoglycoside antibiotics are organic polycations with a net cationic charge that, at pH 7.4, ranges from +4.47 in the case of neomycin to +2.39 for amikacin. Because these compounds are highly hydrophilic, they are poorly absorbed across the intestinal tract and therefore must be given parenterally. They are distributed in a volume slightly greater than extracellular volume and are eliminated from the body without metabolic transformation. The route of elimination is almost exclusively by the kidneys, and the principal mechanism of excretion is glomerular filtration. Of toxicologic significance is the fact that small amounts of aminoglycoside antibiotics are selectively transported into proximal tubular cells by adsorptive endocytosis,[81–83] which has been shown to occur across the basolateral as well as the apical membrane.[83] Several lines of evidence have implicated anionic phosphatidylinositol as a membrane binding site for aminoglycosides.[84,85] More recent studies also suggest a role for megalin, an endocytic receptor for cationic ligands, in the uptake of aminoglycoside antibiotics across the brush-border membrane of renal proximal tubular cells.[86] Indeed, by using the specific antagonist receptor-associated protein, blocking the activity of megalin in perfused rat proximal tubules, a reduction of 20% in gentamicin clearance ensued. Nagai demonstrated similar results in rats treated with maleate, impairing the receptor-mediated uptake of megalin ligands.[87] Megalin knockout mice are protected against aminoglycoside nephrotoxicity.[88]

Following endocytosis, the aminoglycosides are translocated into the lysosomal compartment, where they accumulate in millimolar concentrations and reside with a half-life measured in days.[78] As noted, the lysosomal compartment is the site of myeloid body formation consequent to aminoglycoside-induced inhibition of lysosomal enzymes such as phospholipase, sphyngomyelase, etc. When the concentration of drug and/or the amount of lysosomal phospholipid reaches a critical threshold, an injury cascade is triggered that eventuates in irreversible cell injury with

progression to necrosis.[56] However, neither the sequence nor the specific mechanisms involved in the progression to cell death have been clearly established. Sandoval and colleagues report that within 15 minutes of endocytosis gentamicin traffics to the Golgi complex as well as to the lysosomal compartment of LLC-PK1 cells[89,90] and rat renal proximal tubular cells.[91] These observations raise the possibility that the Golgi complex may provide a pathway for the redistribution of aminoglycoside antibiotics to other intracellular compartments and thereby broaden the potential for these drugs to disrupt a variety of organellar functions. For example, the depression of protein synthesis observed early in the course of gentamicin administration may signify retrograde transport of gentamicin to the endoplasmic reticulum.[91] The reason gentamicin and presumably other aminoglycoside antibiotics are transported from the endosomal compartment to the Golgi complex is not known; but, it may reflect an effect of these agents to perturb endosomal fusion[92] possibly as a consequence of binding to megalin[92] or to membrane-acidic phospholipids.[93,94]

A growing body of evidence supports the view that the pathogenesis of aminoglycoside toxicity is causally related to the capacity of these cationic drugs to bind to and perturb the function and structure of biologic membranes. Aminoglycosides have been shown to bind to anionic[62,84,95–102] but not to neutral phospholipids.[62,84,96,98] Among the anionic phospholipids, aminoglycosides bind most avidly to phosphatidylinositol 4,5-bisphosphate (PIP_2).[84,97,103–105] Several approaches have been used to gain insight into the molecular interaction between aminoglycosides and anionic phospholipids.[84,95,98,101,102,106–108] All models indicate an electrostatic interaction between a protonated amino group and the anionic phosphate group. Ramsammy and Kaloyanides[107] propose a model that, in addition to an electrostatic interaction between a protonated amino group and the phosphate group, also involves formation of hydrogen bonds between an amino group of gentamicin and the carbonyl groups of glycerol. This model explains aminoglycoside-induced changes in the biophysical properties of artificial membranes (i.e., an increase in the transition temperature and a decrease in glycerol permeability of phosphatidylinositol [PI]-containing liposomes).[100] Both changes signify that gentamicin induces a decrease in membrane fluidity, and this finding has been confirmed in brush-border membranes as assessed by changes in the fluorescence polarization of membrane probes[96] and by electron spin resonance spectroscopy.[109] Aminoglycosides also have been shown to promote membrane aggregation,[106,110] a process that requires neutralization of surface charge. In a comparative study of aminoglycoside-induced aggregation of PI-containing liposomes,[106] it was observed that the rank order with respect to efficacy in neutralizing membrane surface charge was neomycin > gentamicin = tobramycin = netilmicin = spermine. The rank order for inducing aggregation of liposomes was neomycin > gentamicin > tobramycin > netilmicin = spermine and was identical to the rank order of these agents with respect to depressing glycerol permeability.[106] This rank order also coincides precisely with the established clinical nephrotoxicity potentials of these drugs. Because depression of glycerol permeability was shown to be dependent on hydrogen bonding between one or more amino groups of the drug and carbonyl groups of the glycerol backbone,[107] these data suggest that the membrane toxicity of aminoglycosides is closely linked to their potentials to engage in hydrogen bonding. Importantly, the rank order in terms of nephrotoxicity potentials does not coincide with the net cationic charge of these agents.[106] This observation emphasizes that spatial orientation of charge rather than net charge is a critical determinant of toxicity.

Schacht and colleagues[97,99,104,111] utilize a variety of methods to assess aminoglycoside-induced perturbations of PIP_2-containing membranes as a measure of the ototoxicity potentials of these antibiotics. Increased fluorescence of 1-anilino-8-naphthalenesulfonate,[99] increased permeability to carboxy fluorescein,[104] and increased surface tension of monomolecular film of phosphatidylcholine (PC)/PIP_2[111] were shown to correlate precisely with the ototoxicity potentials of aminoglycoside antibiotics. These studies have led to the hypothesis that the ototoxicity of aminoglycosides is causally related to their binding to PIP_2 and disruption of this signaling mechanism.[112]

The studies cited here provide the foundation for the hypothesis that the toxicity of aminoglycoside antibiotics is causally related to their capacity to interact electrostatically and by hydrogen bonding to membrane anionic phospholipids and, thereby, to perturb the biophysical properties and function of cell membranes. It is well established that these drugs interact with and perturb the function of plasma membranes,[13,113–116] lysosomes,[13,56,57–64,117–122] mitochondria,[51,123–126] and microsomes.[127–129] It remains unclear, however, whether toxicity results from disruption of a single critical membrane function or multiple membrane functions. It is possible that the injury cascade is triggered by the rupture of lysosomes engorged with aminoglycoside antibiotic and with myeloid bodies. The resultant release of potent acid hydrolases and high concentrations of drug into the cytoplasm might cause disruption of a number of critical intracellular processes including mitochondrial respiration,[51,123–126] microsomal protein synthesis,[127–129] intracellular signaling via the PI cascade[130–133] as well as generation of hydroxyl radicals[134–136]—all of which have been observed in experimental models of aminoglycoside toxicity. However, the observation that gentamicin is transported to the Golgi complex shortly after endocytic uptake[89,90] provides an alternate mechanism by which these drugs gain access to other organelles. Recently, proteomic analysis following gentamicin administration indicates energy production impairment and a mitochondrial dysfunction occurring in parallel to the onset of nephrotoxicity.[137]

Further insight into the pathogenesis of aminoglycoside nephrotoxicity has been gleaned from studies of interventions that modify the severity of this disorder in

experimental animals. Williams and colleagues[138–140] first reported that polyasparagine and polyaspartic acid (PAA) inhibited binding of gentamicin to rat renal brush-border membrane in vitro and when injected in vivo conferred protection against the development of aminoglycoside nephrotoxicity without inhibiting the renal cortical accumulation of drug. These findings have been confirmed and extended by three groups of investigators.[141–149] The mechanism by which PAA protects against aminoglycoside nephrotoxicity was shown to be related to the ability of PAA, a polyanion, to form electrostatic complexes with the polycationic aminoglycoside antibiotics[146,150,151] presumably within the endocytic compartment,[148] thereby preventing aminoglycosides from binding to anionic phospholipids, from inhibiting lysosomal phospholipase degradation of phospholipid, from forming lysosomal myeloid bodies, and from disrupting the PI cascade.[150] Additional support for this theory is provided by the observation that PAA prevented gentamicin from depressing glycerol permeability or aggregating PI-containing liposomes,[150] effects previously shown to be dependent on gentamicin binding electrostatically and by hydrogen bonding to PI.[100,107] Subsequently, other compounds capable of forming electrostatic complexes with aminoglycosides have been reported to protect against nephrotoxicity.[152–155]

An analog of pentoxifylline, HWA-448, was shown to protect against gentamicin toxicity in a cell culture model.[156] Similar to PAA, HWA-448 did not depress the membrane binding or cellular uptake of gentamicin. It remains unknown whether HWA-448 forms a complex with gentamicin within the endosomal compartment.

Recently, it was demonstrated that glibenclamide (a sulfonylurea) has protective effects against gentamicin-induced nephrotoxicity in rats.[157] Morales et al. suggest that the pleiotropic effects of metformin can decrease gentamicin nephrotoxicity by improving mitochondrial homeostasis.[158]

31.1 Risk Factors for Aminoglycoside Nephrotoxicity

Patient factors
- Older patients[a]
- Preexisting renal disease
- Magnesium potassium, calcium deficiency[a]
- Intravascular volume depletion,[a] hypotension[a]
- Hepatic syndrome
- Sepsis syndrome[a]
Aminoglycoside factors
- Recent aminoglycoside therapy
- Larger doses[a]
- Treatment of three or more days[a]
- Drug choice: gentamicin,[a] amikacin[a]
- Frequent dosing interval[a]
Concomitant drugs
- Amphotericin B
- Cephalosporines
- Cisplatin
- Clindamycin
- Cyclosporine
- Foscarnet
- Furosemide
- Intravenous radiocontrast agents
- Piperacillin
- Vancomycin

[a]Concurrent with experimental nephrotoxicity data.
Adapted from Verpooten GA, Tulkens PM, Molitoris BA. Aminoglycosides and vancomycin. In: De Broe ME, Porter GA, Bennett VM, Verpooten GA, eds. Clinical Nephrotoxins – Renal Injury from Drugs and Chemicals, 2nd ed. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2003:151–170.

Treatment and Prevention of Aminoglycoside Nephrotoxicity

The efficacy of PAA and other anionic compounds in preventing nephrotoxicity in humans has yet to be established. Therefore, the primary focus of treatment is prevention, and this can be accomplished by understanding and modifying, when possible, the risk factors (Table 31.1) for this complication.[159–161] Risk factors may be categorized into those that are determined by the individual patient and not easily influenced, if at all, and those that are determined by the clinician and potentially controllable (Table 31.1).

Prominent among the risk factors peculiar to the patient and not modifiable is advanced age.[159] The mechanism is probably multifactorial and includes age-related decline of renal function that, if not appreciated and corrected for, results in excessive dosing.[162] Animal studies suggest that aging is associated with altered renal pharmacokinetics accompanied by increased renal cortical accumulation of drug.[163] Increased susceptibility of the aging kidney to aminoglycoside toxicity has also been suggested,[164] possibly on the basis of an age-related impaired capacity for cellular repair and regeneration. Male gender has been shown to carry increased risk for aminoglycoside nephrotoxicity in the rat,[165] whereas female gender has been identified as a risk factor in humans.[159] The reason for this difference has not been established.

Obesity carries increased risk for aminoglycoside nephrotoxicity that is unexplained by differences in the volume of distribution or renal clearance of drug.[166] The increased risk associated with chronic liver disease[159] may be related to the alterations in extracellular volume, hemodynamics, and electrolyte balance commonly observed in this disorder, all of which are known to promote renal cortical accumulation of drug.[78] Preexisting chronic renal insufficiency is associated with increased risk primarily due to failure to adjust appropriately the dose of aminoglycoside for the level of impaired kidney function.[167] Renal hypoperfusion from any

cause carries an increased risk of aminoglycoside nephrotoxicity whether the renal ischemic insult occurs before,[85] during,[34] or after drug administration.[32] The latter observation is particularly worthy of note because it implies that the increased risk of nephrotoxicity persists even after the drug has been discontinued. The prolonged half-life of aminoglycosides in renal cortex[78] may contribute to this risk. Three components of the septic state—renal hypoperfusion, endotoxemia, and hyperthermia—have been identified as factors contributing to the heightened risk of nephrotoxicity during aminoglycoside therapy.[35–37] Renal hypoperfusion[35,85] and endotoxemia[33,168] are associated with increased accumulation of drug in renal cortex; however, this factor alone does not explain the increased risk.

Of those risk factors that are potentially modifiable by the clinician, the most important are daily drug dose, interval of dosing, and the duration of therapy. A direct relationship between total dose (daily dose plus duration of therapy) and nephrotoxicity has been consistently found in experimental animals[26,47,51,56,71] and in humans.[9,15,159,160,167] Animal studies have shown that the same dose of a drug administered in two or three divided doses leads to greater renal accumulation of the drug and greater nephrotoxicity than if it was given as a single dose.[169,170] Two trials in humans found that the dosage schedule had a critical effect on the renal uptake of gentamicin, netilmicin,[171] amikacin, and tobramycin.[172] The study was carried out in patients with normal renal function (serum creatinine between 0.9 and 1.2 mg per dL, proteinuria lower than 300 mg per day) who had renal cancer and submitted to nephrectomy. Before surgery patients received gentamicin (4.5 mg/kg/day), netilmicin (5 mg/kg/day), amikacin (15 mg/kg/day), or tobramycin (4.5 mg/kg/day), as a single injection or as a continuous intravenous infusion over 24 hours. The single-injection schedule resulted in a 30% to 50% lower cortical drug concentration of netilmicin, gentamicin, and amikacin compared with administration by continuous infusion (Figs. 31.2 and 31.3). For tobramycin, in humans as well as in rats, no difference in renal accumulation could be found, indicating the linear cortical uptake of this particular aminoglycoside. Administration of drug by continuous intravenous (IV) infusion carries the highest risk of nephrotoxicity with respect to gentamicin, tobramycin, and netilmicin but not amikacin.[80,170,173] These observations have stimulated studies in humans to assess the antimicrobial efficacy of once per day dosing with an aminoglycoside administered alone or in combination with a β-lactam antibiotic.[174–177]

Several meta-analyses pooled the data of individual randomized controlled trials (RCTs) (Table 31.2),[178–187] including a meta-analysis specifically of the studies in immunocompromised patients.[187] It is apparent that only the meta-analyses that combine the results of the individual RCT by means of a fixed-effects model yielded significant results in favor of less nephrotoxicity in the single daily dose regimens. However, given the inhomogeneity of the study designs and the different aminoglycoside used, it seems

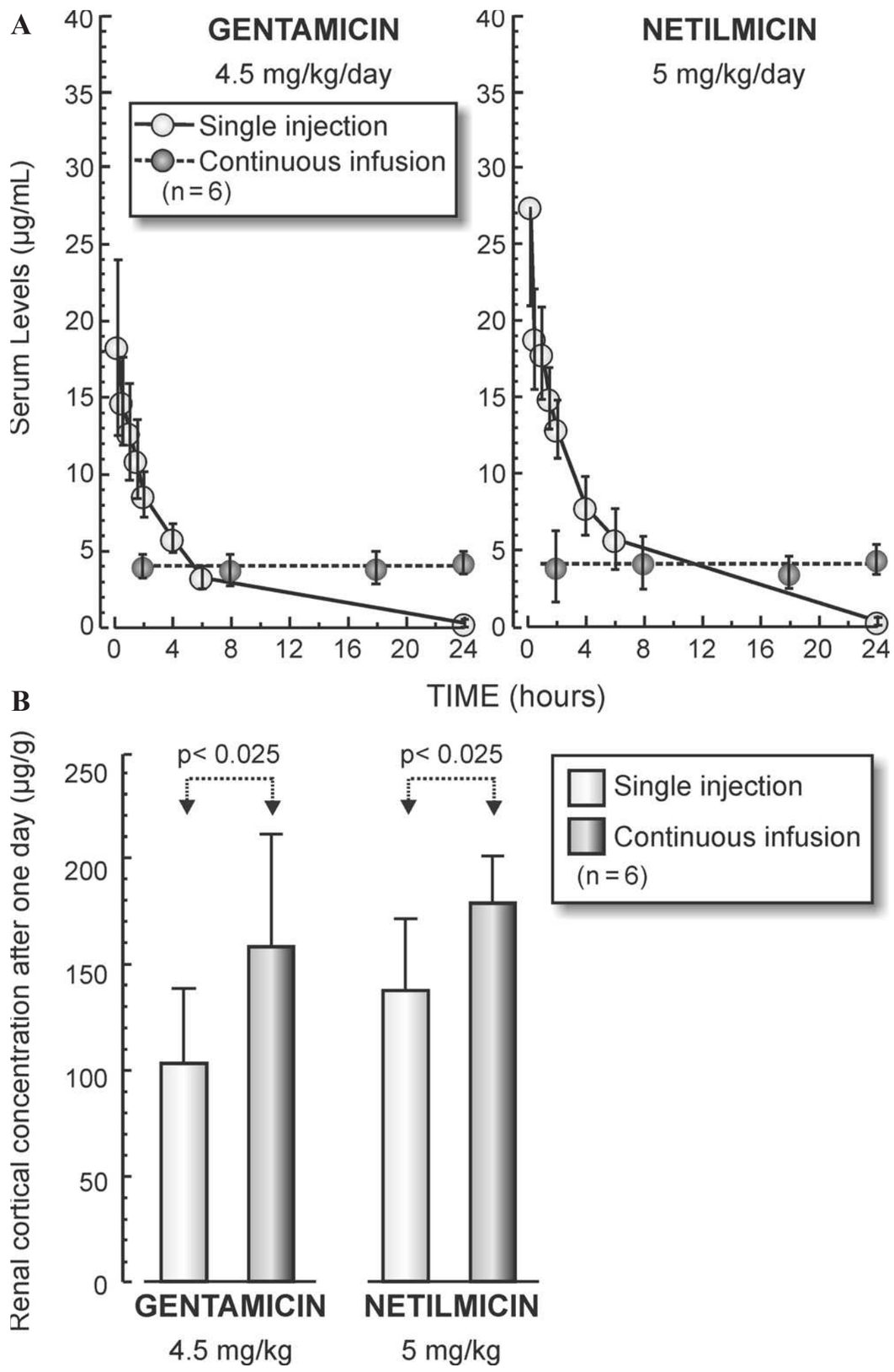

FIGURE 31.2 **A:** Course of serum concentrations of gentamicin and netilmicin after administration of the dose by a 30-minute intravenous injection or by continuous infusion of 24 hours. **B:** Cortical concentration of gentamicin and netilmicin after administration by the previously mentioned administration schedules. (From Verpooten GA, et al. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. *Clin Pharmacol Ther.* 1989;45:22, with permission.)

prudent to use the random effects model to combine the individual studies. The meta-analyses that used this technique did not show a significant difference in the two dosing regimens. Nevertheless, in all analyses the single daily dose regimen was associated with a decrease in nephrotoxicity. Even the most recent prospective study[188] evaluating the efficacy and nephrotoxicity of once daily administration of gentamicin versus multiple daily administration in 52 children could not show a difference in incidence of nephrotoxicity in both groups. Although a decrease in nephrotoxicity rates in once daily dose regimens has not been established, extended interval dosing strategies have never been associated with an increased risk of nephrotoxicity. The main reason why the majority of acute care hospitals[189] have adopted this strategy

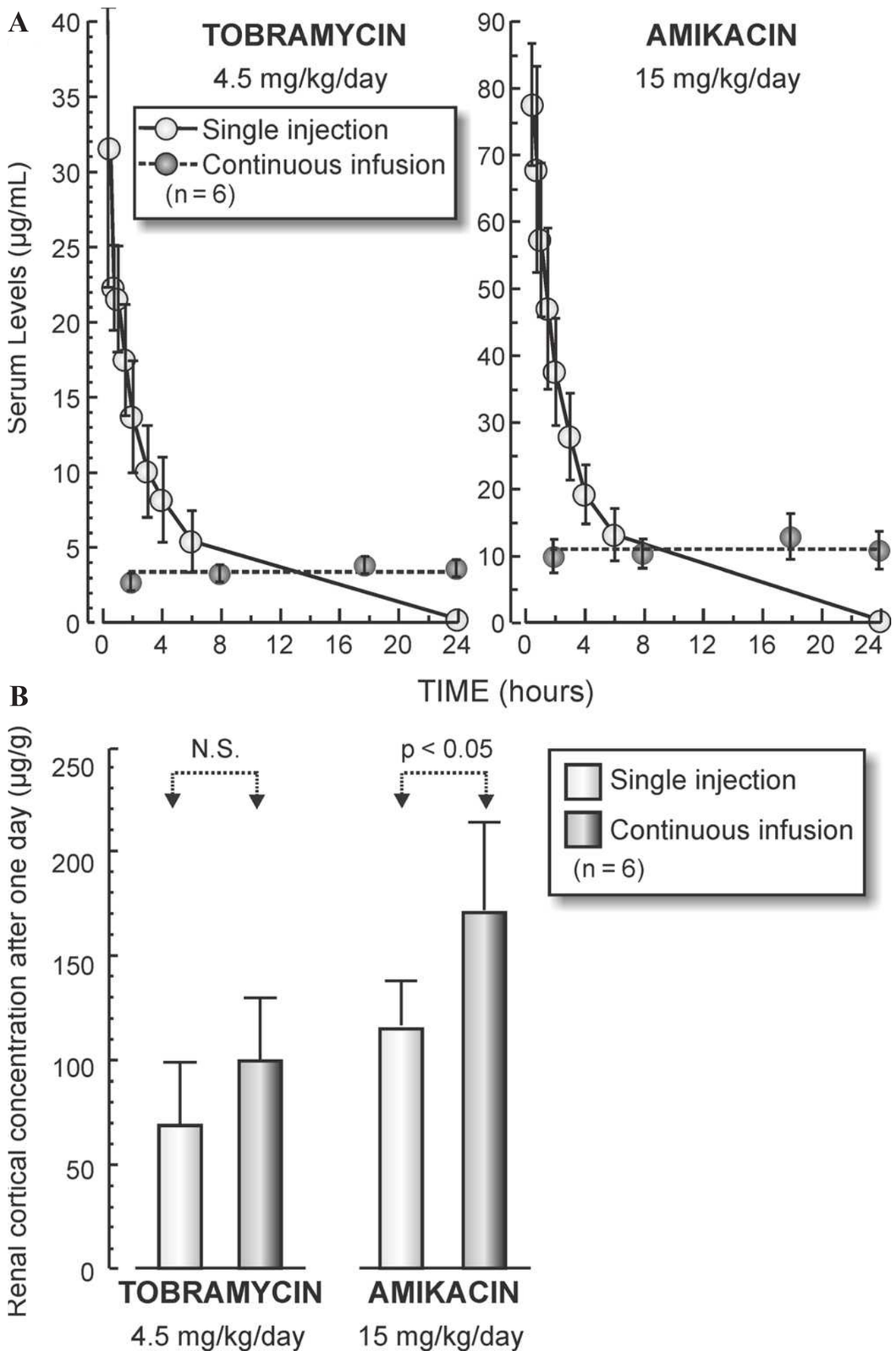

FIGURE 31.3 **A:** Course of serum concentrations of tobramycin and amikacin after administration of the dose by a 30-minute intravenous injection or by continuous infusion of 24 hours. **B:** Cortical concentration of tobramycin and amikacin after administration by the previously mentioned administration schedules. (From De Broe ME, Giuliano RA, Verpooten GA. Influence of dosage schedule on renal cortical accumulation of amikacin and tobramycin in man. *J Antimicrob Chemother.* 1991;27[Suppl C]:41, with permission.)

is that once daily dosing provides a cost-effective method for administration of aminoglycosides by reducing work load among service personnel and by reducing or even eliminating the need for therapeutic drug monitoring.[190–192]

Volume depletion,[193] hypokalemia,[194] hypomagnesemia,[195] and metabolic acidosis[196] all carry increased risk for nephrotoxicity. In the case of volume depletion and hypokalemia, the increased risk appears to be related to increased accumulation of drug in renal cortex.[78] The mechanism underlying the increased risk associated with hypomagnesemia has not been definitely established but may relate to the competition between divalent cations and the cationic aminoglycoside antibiotics for critical membrane binding sites.[197] In the case of metabolic acidosis, the reduced pH promotes increased protonation of aminoglycoside antibiotics and augments the reactivity of these organic polycations with membrane anionic phospholipids.[64,101,119]

In rats it was shown that uric acid worsens gentamicin-induced nephrotoxicity. The mechanism is likely to implicate downregulation of MMP9.[198]

Finally, the risk of nephrotoxicity has been shown to be augmented when aminoglycoside antibiotics are administered in conjunction with certain drugs and pharmaceutical agents, some of which have intrinsic nephrotoxicity potential. These include amphotericin B,[177] cephalothin but not third generation cephalosporins,[199] vancomycin,[200,201] cisplatin,[202] furosemide,[203] calcium channel blockers,[204] radiocontrast agents,[205] and nonsteroidal anti-inflammatory drugs.[206] Many of these synergistic interactions have been identified in animal studies so that the relevance of these observations to humans remains to be established. Nevertheless, prudence dictates that potentially nephrotoxic drugs should be avoided if possible in patients who are receiving or have recently completed therapy with aminoglycoside antibiotics.

The prevention of aminoglycoside nephrotoxicity requires that these drugs be used only for well-defined indications and that they be prescribed in the appropriate dose and for the appropriate duration to achieve the therapeutic goal. Optimization of therapy for aminoglycosides requires understanding the relationship between exposure and response as well as that between exposure and toxicity. Furthermore, daily administration is much preferred, and stopping therapy as quickly as possible (a week or less may be optimal) will contribute to the ability to optimize therapy.[207] Dosing based on individualized drug pharmacokinetics derived from measurements of serum drug concentration would appear to be a rational approach. Unfortunately, prospective studies have failed to demonstrate that dosing based on drug pharmacokinetics reduces the incidence of nephrotoxicity.[208] Indeed, eight prospective, RCTs specifically designed to investigate the effect of pharmacokinetic dosing[209] on aminoglycoside expression of nephrotoxicity could be identified from the literature.[210–217] These individual studies have been unable to detect any change in the incidence of this adverse event. Nevertheless, close monitoring of serum drug concentration is still warranted, especially in high risk patients to ensure that therapeutic concentrations are achieved. Even when those factors known to influence risk are absent or have been minimized or eliminated, aminoglycoside nephrotoxicity will still occur in a certain percentage of appropriately dosed patients. These patients exhibit excessive renal accumulation of drug or increased sensitivity to a given level of drug accumulation.[218] The clinician must be constantly alert to the possibility of aminoglycoside nephrotoxicity and monitor all patients on aminoglycoside therapy for this potential complication. The intensity of monitoring is dictated in part by the relative risk factors present. At a minimum, frequent measurements of serum creatinine concentration,

31.2 Meta-analysis of the Incidence of Nephrotoxicity in Single Daily Dosing versus Multiple Dosing of Aminoglycosides

Author	No. of RCT	Method	Results (95% CI)
Blaser and König, 1995[172]	24	Summation	RR 0.82
Galloe et al., 1995[173]	16	Not given	RR 1.00 (0.98–1.02)
Barza et al. 1996[174]	21	Random effects model	RR 0.78 (0.57–1.07)
Munckhof et al., 1996[175]	15	Random effects model	RD −1.3% (−5%–3.1%)
Ferriols-Lisart and Alos-Aliminanan, 1996[176]	18	Fixed effects model	OR 0.60 (0.40–0.86)
Freeman and Strayer, 1996[177]	15	Fixed effects Peto	OR 0.70 (0.51–0.94)
Hatala et al., 1996[178]	13	Random effects model	RR 0.87 (0.60–1.26)
Ali and Goetz, 1997[179]	26	Random effects model	RD −0.18% (−0.99%–3.75%)
Bailey et al., 1997[180]	22	Random effects model	RD −0.6% (−2.4%–1.1%)
Hatala et al., 1997[181]	4	Random effects model	RR 0.78 (0.31–1.94)

CI, confidence interval; OR, odds ratio; RR, risk ratio; RD, risk difference; RCT, randomized controlled trials.
Adapted from Verpooten GA, Tulkens PM, Molitoris BA. Aminoglycosides and vancomycin. In: De Broe ME, Porter GA, Bennett VM, Verpooten GA, eds. Clinical Nephrotoxins – Renal Injury from Drugs and Chemicals, 2nd ed. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2003:151–170.

generally every 2 to 3 days, should be performed. In high risk patients, daily creatinine clearances and urinalysis may be required to detect early signs of toxicity before a rise in serum creatinine concentration or serum trough level of drug becomes evident. Hoffmann et al. showed in rats that a number of recently developed urinary markers (among them Kim-1) had an increased sensitivity of aminoglycoside nephrotoxicity in rats.[219,220] How far this can be extrapolated to the human situation has not been studied thouroughly. If renal injury occurs, then the drug should be stopped if possible or the dosage should be reduced to prevent the accumulation of drug in serum and further toxic injury related thereto. Careful attention must be paid to maintaining fluid and electrolyte balance and avoiding potential insults to the kidney related to renal hypoperfusion or exposure to other potential nephrotoxins. Even when nephrotoxicity is recognized early and the drug is discontinued, renal failure may progress over the next 5 to 10 days, with the serum creatinine and blood urea nitrogen (BUN) rising to disturbingly high levels, where they may remain for a number of days before renal function slowly begins to improve. No specific therapy for hastening recovery has been identified to be effective in humans. In an animal model, epidermal growth factor was shown to accelerate recovery.[221] The prognosis for recovery of renal function is generally good except in those cases where the underlying disease exposes the kidney to persisting or recurrent insults related to sepsis, hypotension, and hypoperfusion.

Nagai and Takano reviewed the possibility of coadministration of agents which may inhibit the binding of nephrotoxicity drugs (particularly aminoglyclosides) to receptor(s) responsible for the endocytic processes in renal proximal tubular cells which might reduce the incidence of nephrotoxicity.[222]

Trimetazidine is an anti-ischemic metabolic agent improving cardiac glucose utilization through inhibition of fatty acid. Gentamicin nephrotoxicity is attenuated by the cytoprotective effect of trimetazidine. It may be inferred that trimetazidine inhibits also the reabsorption and consequently the accumulation of gentamicin in the proximal tubular cell.[223]

β-LACTAM ANTIBIOTICS

The β-lactam antibiotics comprise the penicillins, cephalosporins, and carbapenems. ARF has been observed with this class of antibiotics as a result of acute proximal tubular cell necrosis or allergic interstitial nephritis. Studies in animals have established the relative nephrotoxicity potentials of β-lactam antibiotics as cephaloglycin > cephaloridine >> cefaclor > cefazolin > cephalothin >>> cephalexin, ceftazidime, and penicillins, which do not exhibit clinical

nephrotoxicity.[224] The selective toxic potential of β-lactam antibiotics toward renal proximal tubular cells appears to be causally linked to their concentrative uptake by the organic anion transport system and their intrinsic reactivity toward sensitive intracellular target proteins.[224,225] The importance of the organic anion transport system to the nephrotoxic potential of these agents is supported by the observations that (1) toxicity is restricted to β-lactams that are secreted by this transport system, (2) toxicity can be prevented by inhibition of organic anion transport, and (3) maneuvers that increase the intracellular uptake of drug augment toxicity.[224,225] The product of intracellular drug concentration and time, defined as the area under the curve (AUC), is an important determinant of toxicity. Among the cephalosporins, the greatest AUC is observed with cephaloridine.[224,225] This agent is readily transported into proximal tubular cells across the basolateral membrane; however, its egress across the apical membrane is retarded due to the fact that cephaloridine is a zwitterion and the cationic moiety impedes its permeation across the luminal membrane.[226] Therefore, at equivalent doses, the AUC for cephaloridine is significantly higher than that of other cephalosporins. Cephaloglycin, the most nephrotoxic of the cephalosporins released for clinical use, has a renal cortical AUC only one fifth that of cephaloridine.[227] The greater nephrotoxicity of cephaloglycin reflects the fact that it is far more reactive than cephaloridine toward sensitive intracellular target proteins.[224,228] Three molecular mechanisms have been implicated in the pathogenesis of cephaloridine nephrotoxicity: (1) lipid peroxidation,[229] (2) competitive inhibition of mitochondrial carnitine transport and fatty acid oxidation,[230,231] and (3) inhibition of mitochondrial respiration consequent to inactivation by acylation of mitochondrial anionic substrate transporters.[232,233]

In the case of the other nephrotoxic β-lactam antibiotics, the pathogenesis of toxicity appears to be linked primarily to depression of mitochondrial respiration. This conclusion is supported by the following observations from in vivo animal studies.[224,225,227,232,233]

1. The nephrotoxic potential of β-lactams correlates with the magnitude of inhibition of mitochondrial respiration.
2. Irreversible inhibition of mitochondrial respiration occurs within 1 hour after administration of a nephrotoxic dose.
3. Inhibition of respiration precedes the appearance of ultrastructural mitochondrial damage that resembles ischemic and cyanide injury.

Although only a limited number of β-lactam antibiotics cause toxic injury after in vivo exposure, many of these agents exhibit the capacity to inhibit in vitro mitochondrial respiration, especially that component supported by succinate.[234] Inhibition of mitochondrial respiration is observed within 5 minutes of in vitro drug exposure. Increasing the concentration of succinate reverses the inhibition, presumably as a consequence of competitive displacement of drug from the mitochondrial membrane anionic carrier. However, as the exposure of mitochondria to drug is augmented by raising the product of drug concentration and time, inhibition of mitochondrial respiration becomes progressively irreversible, which has been attributed to drug-induced acylation and inactivation of the transporter.[224,225] The rank order of cephalosporins with respect to their potential to acylate target proteins in vitro is ceftazidime > cefaclor > cephaloglycin > cephalothin > cephaloridine > cefazolin >> cephalexin, and several penicillins.[224,225] This order is at variance with their in vivo nephrotoxicity potential, which is cephaloglycin > cephaloridine >> cefaclor > cefazolin > cephalothin >>> cephalexin, ceftazidime, and the penicillins. The explanation for the differences between the in vitro and in vivo toxicity potentials of these drugs resides in the important role of concentrative uptake of these drugs into intact proximal tubular cells by the organic anion transport system. Although ceftazidime and cefaclor exhibit high acylation activity in vitro, the AUC of these agents is low (only 7% that of cephaloridine and only 37% that of cephaloglycin), and this severely restricts their interaction with the mitochondrial anion transporter.[224,225] Mitochondrial injury also has been implicated as the major mechanism of nephrotoxicity caused by imipenem.[235,236] This drug is marketed in combination with cilastin, which inhibits the enzymatic breakdown of imipenem by cytoplasmic and brush-border dihydropeptidase and also inhibits its nephrotoxicity.

The therapeutic–nephrotoxic ratio of these agents is much more favorable than that of aminoglycoside antibiotics. The incidence of serum creatinine elevations is difficult to say with certainty, but severe nephrotoxic ARF is uncommon.[237,238] Similar to other antibiotics, high doses and prolonged therapy elevate the risk of nephrotoxicity. In animal studies, the incidence and severity of toxicity associated with β-lactam antibiotics were augmented by combined therapy with aminoglycoside antibiotics,[239] by renal ischemia,[240] and by endotoxemia.[241] In three prospective studies in human subjects, the combination of an aminoglycoside antibiotic with cephalothin was associated with a significantly higher incidence of nephrotoxicity.[242–244] Early reports suggested a possible interaction between several second generation cephalosporins and aminoglycoside antibiotics.[245] In contrast, a recent prospective study provides no evidence that combination therapy with third generation cephalosporins and an aminoglycoside antibiotic potentiates the risk of nephrotoxicity.[177]

The diagnosis of nephrotoxic ARF secondary to β-lactam antibiotics is suggested by the appropriate clinical setting in combination with a urine sediment and urinary indices typical of acute tubular cell necrosis. Establishing the precise diagnosis may be difficult in the presence of septicemia, hypotension, or other nephrotoxic drugs. It should be kept in mind that β-lactam antibiotics also cause ARF secondary to allergic interstitial nephritis.[246] The pattern of the rise in the BUN and serum creatinine may be indistinguishable from that seen with acute tubular cell necrosis.

The presence of large numbers of red and white blood cells in the urinary sediment, especially if associated with eosinophiluria and systemic signs of hypersensitivity (rash, fever, and eosinophilia), strongly suggests the diagnosis of allergic interstitial nephritis. However, in many patients, these clues are equivocal so that it may be necessary to perform a kidney biopsy to establish the correct diagnosis.

VANCOMYCIN

Vancomycin use in clinical medicine has increased significantly in recent years as a consequence of the rise in the incidence of methicillin-resistant staphylococcal infections. Because this antibiotic is poorly absorbed from the gastrointestinal tract, it is usually administered intravenously for the treatment of systemic infections. Vancomycin is not appreciably metabolized, and it is excreted essentially (80%–90%) entirely by the kidneys, primarily by glomerular filtration, as there is no evidence that the drug undergoes tubular absorption or secretion.[247] Therefore, drug dosing must be modified in subjects with renal failure.[248] Animal studies demonstrated that vancomycin had nephrotoxic and ototoxic potential.[249] The present data[250] suggest that oxidative stress and oxidative phosphorylation play an important role in vancomycin-induced nephrotoxicity. Erythropoietin seems to act as an antioxidant, diminishing the toxic oxidative effects of vancomycin on renal tissue. Early clinical experience in human subjects revealed a significant incidence of nephrotoxicity, which in retrospect may have been due to impurities generated during the initial manufacturing process.[251] More recent reports indicate that the incidence of nephrotoxicity associated with vancomycin ranges between 0% and 7% when given as sole therapy.[252] Animal studies initially suggested that vancomycin and aminoglycoside antibiotics interacted synergistically to cause ARF.[253] Recent reports indicate that a similar interaction occurs in humans.[201,202] Indeed, in a meta-analysis the incidence of nephrotoxicity associated with combination therapy was 13.3% greater than therapy with vancomycin alone. In a prospective study, comparing continuous versus intermittent infusion of vancomycin in severely ill patients, Wysocki et al.[254] found a significant rise in serum creatinine during treatment only in those patients who received vancomycin with other antibiotics including aminoglycosides. Monitoring vancomycin serum concentrations is not cost-effective in preventing vancomycin-induced nephrotoxicity in patients with normal renal function because the correlation between serum levels and antibacterial efficacy or toxicity remains controversial.[255] It should be noted that vancomycin has been reported to cause allergic interstitial nephritis[256]; however, this appears to be an uncommon complication. Teicoplanin, a glycopeptide antibiotic similar to vancomycin, is devoid of nephrotoxicity.

Recent data suggest higher rates of nephrotoxicity with recently recommended doses aiming to achieve the currently recommended trough level of 15 to 20 μg per mL.[257–260] These studies show an incremental risk of nephrotoxicity associated with higher vancomycin doses, ranging from 12% to 42.7% of patients. The risk increases with higher vancomycin maximum trough levels, longer duration of vancomycin use, concomitant use of other nephrotoxic agents, and in paitents who are crtically ill or have a previously compromised renal function.

Vancomycin has been a cornerstone antibiotic for the treatment of severe gram-positive infections in dialysis patients for decades. Whereas subtherapeutic vancomycin levels convey a risk of treatment failure and the further emergence of resistance in staphylococci, supratherapeutic vancomycin levels are associated with a dose-related incremental risk for nephrotoxicity and ototoxicity. Consequently, a narrow therapeutic range with a trough-level target between 15 and 20 μg per mL is recommended. Vancomycin dosing in hemodialysis patients is mainly influenced by the timing of administration (during or after dialysis), the type of filter used, and the duration of dialysis. Actual body weight, the interdialytic interval, and residual renal function are also considerations. As in patients with normal kidney function, a weight-based loading dose of 20 to 25 mg per kg should be used in dialysis patients. Although most fixed-dose maintenance regimens fail to reach target levels in the majority of hemodialysis patients, straightforward evidence on optimal maintenance dosing is lacking.[261]

Studies on the optimal dosing strategy for vancomycin in chronic kidney disease (CKD) patients and those on dialysis are needed.

SULFONAMIDE ANTIBIOTICS

The sulfonamide antibiotics and their metabolites are excreted primarily by the kidneys by a process involving glomerular filtration, tubular absorption, and tubular secretion.[262] The high incidence of nephrotoxic ARF observed with the first generation sulfonamides was due to their low solubility and the resultant precipitation of drug in the form of crystals that caused intratubular obstruction.[263] Sulfadiazine, a poorly soluble sulfonamide, continues to be used today in combination with pyrimethamine for the treatment of Toxoplasma encephalitis; nephrotoxicity manifested as hematuria, crystalluria, renal colic, and ARF may complicate therapy in 5% of cases.[264,265] These abnormalities usually subside with hydration and alkalinization of the urine.

Trimethoprim-sulfamethoxazole is administered intravenously in high concentration as therapy for Pneumocystis jiroveci pneumonia. Although the solubility of sulfamethoxazole is high, ARF secondary to crystal deposition of the parent drug or a metabolite has been reported.[266,267] More commonly, the elevation of serum creatinine observed in patients treated with this combination drug reflects inhibition of tubular secretion of creatinine by trimethoprim.[268,269] This effect is more pronounced in subjects with baseline elevation

of the serum creatinine secondary to underlying chronic renal insufficiency. Failure of the BUN to rise in proportion to the rise in serum creatinine should call attention to the correct diagnosis.

Sulfonamides including sulfamethoxazole also have been implicated in causing acute hypersensitivity reactions and ARF secondary to allergic interstitial nephritis.[246]

ANTIFUNGAL AGENTS

Amphotericin B is widely used as the drug of choice for the therapy of systemic fungal infections, especially in immunocompromised patients.[270,271] Unfortunately, the clinical application of this drug is accompanied by a number of dose-dependent toxic side effects, the most serious of which is ARF.[272,273] Amphotericin B is a polyene that consists of a large lactone ring with seven conjugated double bonds, seven hydroxyl groups, and a sugar moiety. It exhibits the propensity to bind to membrane sterols and form membrane pores, which in mammalian cells are estimated to be composed of eight molecules of cholesterol alternating with eight molecules of drug.[274] The resultant increase in membrane permeability to small electrolytes is thought to be a dominant factor in the toxicity of the drug. Amphotericin B binds preferentially to ergosterol, the major sterol of fungi, and this presumably explains the selective toxicity of this and similar drugs for fungi.[275]

The reason amphotericin B causes nephrotoxicity in humans and experimental animals is not apparent from its pharmacokinetics.[276,277] Because amphotericin B is poorly transported across the gastrointestinal tract, it must be administered intravenously. Its volume of distribution is about 4 L per kg. Up to 95% of drug in serum is bound, primarily to β-lipoproteins. The major depot site for amphotericin B is the liver, where up to 41% of administered drug can be recovered compared to 6% in the lung and 2% in the kidney. The elimination of amphotericin B from serum can be described by a triexponential curve, the half-lives of which are 24 hours, 48 hours, and 15 days, respectively. Less than 10% of administered drug is recovered in the urine, and there are no known metabolites.

Although the kidney is not a major route of amphotericin B elimination, it is the major site of toxicity, the incidence of which is influenced by daily drug dose, duration of therapy, and the presence of potentiating factors.[278,279] The clinical expression of amphotericin B nephrotoxicity is dominated by the appearance of azotemia and creatininemia, which may occur early in the course of drug therapy[279–281] and reflects depression of renal blood flow and GFR secondary initially to a reversible rise in renal vascular resistance. With prolonged therapy, depression of renal function may persist as a consequence of injury to tubular epithelium[282] and possibly the renal vasculature.[283] A variety of abnormalities of tubular function may be seen as well. These include incomplete distal renal tubular acidosis,[284] hypokalemia and hypomagnesemia secondary to renal tubular wasting of these cations,[285,286] and loss of urine concentrating capacity.[287] The urinary sediment frequently contains evidence of microscopic hematuria, pyuria, and cylinduria. Although most of these abnormalities are reversible after the drug is discontinued, full recovery may be delayed for a number of months. Chronic renal insufficiency may occur with prolonged or multiple courses of therapy.

Insight into the pathogenesis of amphotericin B nephrotoxicity has been gleaned from studies in experimental animals.[288] It has been shown that intravenous administration of amphotericin B elicits an acute depression of renal blood flow and GFR in association with an increase in renal vascular resistance that is not mediated by the renal nerves, by angiotensin II, by endothelium-dependent factors, or by tubular glomerular feedback.[289–292] These hemodynamic alterations have been shown to be modifiable by a variety of interventions including administration of calcium channel blockers,[293] a selective dopamine-1 receptor agonist,[294] saline loading,[295,296] atrial natriuretic peptide,[292,297] and theophylline suggesting its direct vasoconstrictive effect.[292] Depolarization of vascular smooth muscle consequent to the formation of membrane pores was postulated as the basic mechanism by which amphotericin B augmented renal vascular resistance.[288,292] Amphotericin B also induces tubular dysfunction in the rat that mimics alterations observed in humans.[297] The dominant site of tubular injury in the rat is the inner stripe of the outer medulla,[298] a zone that functions on the verge of hypoxia even under physiologic conditions. Investigators have postulated that hypoxic injury to this zone results from the demand for increased oxygen to support increased sodium transport stimulated by the heightened influx of sodium across the apical membrane made permeable by amphotericin B at a time when the supply of oxygen is reduced as a consequence of amphotericin B-induced reduction in renal blood flow.[298,299]

A contributory factor to the toxicity of amphotericin B is deoxycholate, the vehicle in which the drug is suspended. Deoxycholate was shown to be cytotoxic to renal tubular cells in vitro.[300] Various alternate vehicles and formulations for suspending amphotericin have been investigated in an attempt to reduce toxicity. Administration of amphotericin B in liposomes[276,301] or with other lipid preparations[302] has been reported to reduce the nephrotoxicity of this agent without compromising its therapeutic efficacy.

Lipid preparations of amphotericin B, commonly used to treat fungal infections, have been demonstrated to have reduced nephrotoxicity compared to conventional amphotericin B. However, a comprehensive comparison of nephrotoxicity induced by different lipid preparations of amphotericin B has not been performed. A meta-analysis was conducted to evaluate nephrotoxicity associated with amphotericin B lipid complex (ABLC) and liposomal amphotericin B (L-AmB).[303] Eleven studies reported between 1995 and 2008 were identified comparing nephrotoxicity resulting from the use of these agents. Eight of the 11 studies

were included in the meta-analysis. The Cochran-Mantel-Haenszel test was used to determine odds ratio (OR) and relative risk (RR), and the Breslow-Day test was used to analyze homogeneity of ORs across different studies. Analysis of all 8 studies (n = 1160) included in the meta-analysis showed an increased probability of nephrotoxicity in patients treated with ABLC versus L-AmB (OR, 1.75; RR, 1.55), but there was a significant lack of homogeneity across these studies ($P < 0.001$). After excluding the study by Wingard et al.,[304] the probability of experiencing nephrotoxicity was more similar between the two AmB lipid preparations (OR, 1.31; RR, 1.24; n = 916), particularly when the analysis included only the salvage patient population reported by Hachem et al.[305] (OR, 1.12; RR, 1.09; n = 839); the seven remaining studies were more homogeneous by Breslow-Day test ($P = 0.054$). Their results suggest that nephrotoxicity is generally similar for ABLC and L-AmB in patients receiving antifungal therapy and prophylaxis.

In a recent retrospective study conducted in 100 consecutive patients receiving L-AmB atdoses of 1, 3, and 5 mg per kg, hepatotoxicity was defined as an increase of bilirubin greater than 1.5 mg per dL or AST and ALT greater than three times the normal range. Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg per dL or an increase of 50% from baseline. Overall nephrotoxicity with L-AmB was common and often multifactorial. Lipid amphotericin B products are associated with lower rates of nephrotoxicity than conventional amphotericin; however, in this analysis, L-AmB was associated with a high incidence of nephrotoxicity.[306]

A recent study aimed at comparing the available evidence on the efficacy and safety of deoxycholate and lipid amphotericin B formulations (AMBF) in the treatment of invasive fungal disease in neonates.[307] The reviewed reports show that both amphotericin B deoxycholate (DAMB) and lipid formulations appear to have equal efficacy in treating invasive fungal disease (IFD) in neonates. The adverse effects of DAMB in neonates are considerably less than those in older children and adults. There is a trend of more nephrotoxicity reported with DAMB than with lipid formulations; however, the range reported is very wide (0%–70%). Neonates with normal baseline renal function appeared to tolerate DAMB relatively well. DAMB is inexpensive and effective in treating neonatal IFD. It appears to be safe for use as first-line therapy if the underlying risk for nephrotoxicity is low. Renal function and potassium have to be monitored closely. A sodium intake of 4 mEq/kg/day may significantly reduce DAMB nephrotoxicity.

A number of factors have been identified as potentiating the risk of amphotericin B nephrotoxicity (Table 31.3), and the physician should strive to eliminate or minimize these risk factors whenever possible. Fisher and coworkers[278] observed a 1.8-fold increase in risk of nephrotoxicity for each 0.1 mg per kg increment in the daily dose of amphotericin B. The risk of nephrotoxicity was increased 15.4-fold in patients who had an elevated serum creatinine prior to the start of amphotericin B therapy and 12.5-fold in patients who received diuretics during the course of amphotericin B therapy. The latter observation may reflect the powerful influence of sodium depletion on this complication. Sodium loading has been shown to minimize amphotericin B nephrotoxicity[279] so that special attention should be paid to ensure that the patient is optimally volume-repleted prior to the initiation of therapy with this agent (Fig. 31.4).

31.3 Risk Factors for Amphotericin B Nephrotoxicity

Daily drug dose
Duration of therapy
Chronic renal insufficiency
Sodium depletion
Renal hypoperfusion
Concomitant drug therapy/exposure
Diuretics
Aminoglycosides
Cisplatin
Radiocontrast agents
Cyclosporine

ANTIVIRAL AGENTS

Acyclovir is a potent antiviral agent effective in the treatment of infections caused by herpes simplex viruses.[309] Its major route of excretion is the kidney, which accounts for approximately 80% of total body clearance.[310] Given the fact that the renal clearance of acyclovir exceeds the creatinine clearance by severalfold, it follows that a substantial fraction of drug must be eliminated by tubular secretion, which promotes the attainment of tubular fluid concentrations in excess of the drug's estimated solubility of 1.3 mg per L.[310] The objective of the study by Gunness P et al.[311] was to determine whether acyclovir is a substrate for human BCRP. Transfected human embryonic kidney (HEK293) cells (containing the wild-type ABCG2 gene) were exposed to [8-(14) C]acyclovir (1 μmol per L) in the presence or absence of the BCRP inhibitor fumitremorgin C (FTC). Intracellular acyclovir accumulation was assessed using a liquid scintillation counter. Coexposure to FTC resulted in a significant (five-fold) increase in the intracellular accumulation of acyclovir.

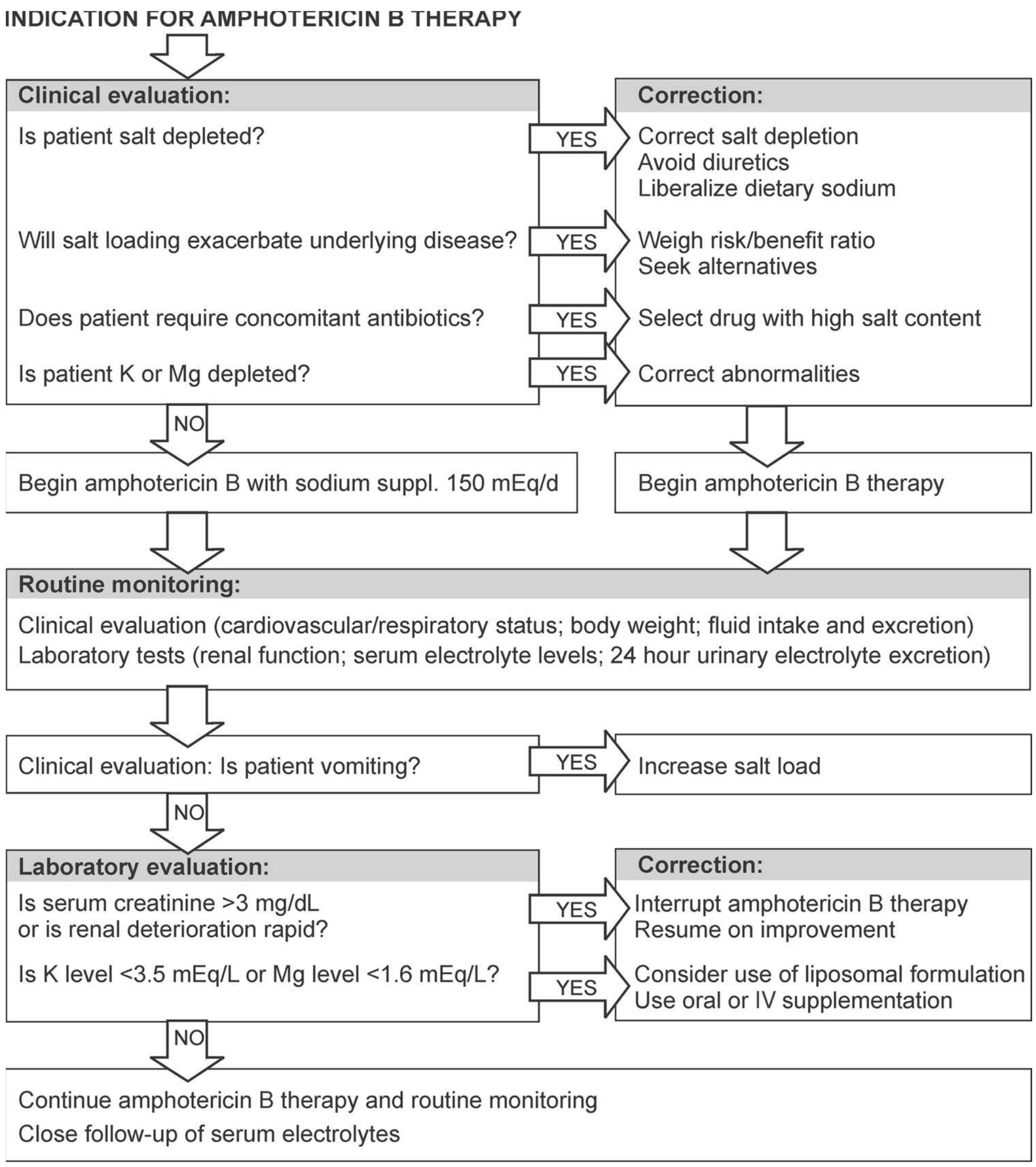

FIGURE 31.4 Proposed approach for management of amphotericin B therapy. (From Bernardo JF, Sabra R, Vyas SJ, Branch RA. Amphotericin B. In: De Broe ME, Porter GA, Bennett VM, Verpooten GA, eds. *Clinical Nephrotoxins – Renal Injury from Drugs and Chemicals,* 2nd ed. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2003:199–222.)

They found that acyclovir is a substrate for human BCRP/ABCG2. The study provides direct evidence for the role of human BCRP in acyclovir transport and its potential significance with respect to renal tubular transport of acyclovir and the direct renal tubular insult (nephrotoxicity) induced by the drug. Approximately 85% of the drug recovered in the urine is unchanged; the remainder is recovered as the principal metabolite, 9-carboxymethoxymethylguanine.[310] In several large series, acyclovir has been reported to cause elevation of the BUN and serum creatinine in 10% to 15% of cases.[312,313] In one series of 23 patients, an incidence of acute renal insufficiency of 48% was reported.[314] The clinical expression of nephrotoxicity may range from asymptomatic azotemia to renal colic with nausea and vomiting. Examination of the urinary sediment may reveal microscopic hematuria, pyuria, and birefringent crystals. The pathogenesis of acyclovir-induced ARF has been attributed to intratubular obstruction caused by precipitation of drug[313] as well as direct tubular cell toxicity.[315,316] High drug dose, rapid drug infusion, and low urine volume predispose to the development of ARF. In about half the cases, the onset of azotemia occurs during the first few days of therapy; it is usually transient and frequently resolves in response to increased fluid intake even when drug therapy is continued. Severe renal failure has been reported, however, even in patients who were prehydrated.[317] Fortunately, even in these cases, renal function usually recovers. In the rat infusion of acyclovir caused a decrease in whole kidney and single nephron GFR and renal plasma flow in association with an increase in renal vascular resistance.[318]

A retrospective review was conducted by Schreiber et al.[319] on all children (mean age 81 months; n = 126 [74 boys])

who were treated with aciclovir in a tertiary center between July 2005 and January 2006 and who met our inclusion criteria. GFR was calculated on the first day of treatment and at the peak measured creatinine level while on therapy, using Schwartz's method. Aciclovir therapy was associated with a significant increase in serum creatinine levels and a parallel decrease in GFR (n = 93; both P ≤.0001). Children with immunosuppression who received a variety of other nephrotoxic drugs exhibited more severe nephrotoxicity than those not receiving nephrotoxic drugs. In multiple regression analysis, the use of nephrotoxic drugs (P = .02) and impaired GFR at baseline (P = .04) were predictive for nephrotoxicity. Within the recommended age-dependent dosage schedule of aciclovir there was no effect of dose per kilogram, age, or sex on nephrotoxicity. The predictors of aciclovir nephrotoxicity were the concomitant use of nephrotoxic drugs and impaired GFR at baseline.

Foscarnet is an antiviral agent that is being used with increasing frequency for the treatment of cytomegalovirus infections and acyclovir-resistant herpes virus infections, particularly in immunocompromised individuals.[320,321] This agent is excreted unchanged in the urine by glomerular filtration and tubular secretion.[322] Major complications of therapy include ARF, often severe and of uncertain pathogenesis,[323,324] and electrolyte abnormalities that include hypercalcemia, hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia.[265,325] ARF secondary to crystal deposition has been described as well.[326] Volume expansion by infusing saline has been reported to greatly reduce the incidence and severity of ARF.[324,327]

Cidofovir is an antiviral nucleotide analog indicated for the treatment of cytomegalovirus retinitis in patients with AIDS.[328] The drug is eliminated primarily by the kidneys by glomerular filtration and tubular secretion via the organic acid transport system.[329] The major complication of therapy with this agent is nephrotoxic injury to proximal tubular cells but this complication can be significantly reduced by the coadministration of probenecid which presumably blocks the renal tubular uptake of cidofovir and decreases the renal elimination of the agent.[330]

Atazanavir belongs to the protease inhibitor class and is used in combination with other antiretroviral drugs. Recently stone formation and less common crystal nephropathy was decribed with this drug.[331,332] Atazanavir is metabolized in the liver and only 6% is excreted unchanged by the kidneys and insoluble at acid pH. Consequently risk factors to develop renal complications are volume depletion, alkaline urine, and liver dysfunction resulting in a decrease of metabolism of the drug.[333]

Tenofovir, another antiretroviral drug, has gained widespread use on the basis of its efficacy, tolerability, and patient-friendly dosing schedule.[334] Herlitz and colleagues[335] demonstrated that tenofovir is a proximal tubular mitochondrial toxin in humans. Renal histology in 10 HIV patients with tenofovir associated clinical nephrotoxicity demonstrated that proximal tubular injury with tenofovir was associated with nephrotoxicity and varying degrees of chronic tubulointerstitial scarring. Prominent eosinophilic inclusions within proximal tubular cell cytoplasm, which represented giant, abnormal mitochondria, were noted on light microscopy. These inclusions are easily identifiable, as they stain brightly with hemaotxylin and eosin stain or fuchsinophilic with trichrome stain. On electron microscopy, mitochondria varied widely in shape and size; some were small and rounded, whereas others were swollen with irregular contours. Loss and disorientation of cristae were observed in enlarged mitochondria, whereas the overall number of mitochondria was significantly decreased in some tubular cells.

These drugs act primarily by decreasing mitochondrial DNA (mtDNA) replication by inhibiting mitochondrial DNA polymerase-γ, which is the only enzme capable of replicating mtDNA. As a result, mtDNA and a number of the mtDNA-encoded enzymes involved in electron transport chain function and oxidative phosphrylation are depleted resulting in disturbed mitochondrial function. This ultimately causes, among other effects, a deficit in adenosine triphosphate production, impaired cell function, and cell injury and/or death.[336,337]

Renal handling of tenofovir consists in a combination of glomerular filtration and proximal tubular secretion, which in part explains the proximal tubular toxicity of tenofovir.[338] Tenofovir is transported via organic anion transporter-1 (OAT-1) from the basolateral into proximal tubular cells, where it is translocated into the urine through apical efflux transporters such as multidrug resistance protein-2 (MRP-2) and MRP-4. Using kidney tissue from OAT-1, MRP-4 knockout mice and wild type mice, Kohler et al. demonstrated that both OAT1 and MRP4 have a direct role in transport and efflux of tenofovir, regulating levels of tenofovir in proximal tubules. Disruption of OAT1 activity prevents tenofovir toxicity but loss of MRP4 can lead to increased renal proximal tubular toxicity. These data help to explain mechanisms of human TDF renal toxicity.[339] Impaired MRP-driven efflux activity can reduce tenofovir secretion and increase intracellular concedntrations. A single-nucleotide polymorphism in the MRP-2 efflux transporter gene (ABCC2) has been documented in HIV-positive patients who developed tenofovir-induced nephrotoxicity, supporting this hypothesis.[340] Endogenous anions and other drugs may compete with tenofovir for these efflux transport pathways. The excretory pathway defects can lead to increased tenofovir trafficking through and/or increased concentrations within proximal tubular cells, enhancing risk for mtDNA depletion and mitochondrial dysfunction. Genetic factor testing (for the single-nucleotide polymorphism in ABCC2) to identify high-risk patients and targeted interventions reduces OAT-1 transport of tenofovir into tubular cells and may allow HIV-positive patients to be protected from nephrotoxicity of the drug. Out of these series of observations, one may conclude that tenofovir may cause toxic tubular damage (mitochondrial toxin) in exposed HIV patients. The clinical expression

of this form of nephrotoxicity can develop at any time point during treatment with this drug. Patients may not recover from the injury and develop CKD. The renal handling of tenofovir can explain the small subset of HIV patients developing this form of nephrotoxicity.

PENTAMIDINE

Pentamidine has been used for the treatment of P. jiroveci pneumonia since the 1950s. In the pre-AIDS era, pentamidine therapy was complicated by ARF in about 25% of cases.[341] The incidence of ARF in patients with AIDS treated with pentamidine appears to be substantially higher than this figure, and it is unexplained by greater drug dose, longer duration of therapy, or concomitant therapy with other potentially nephrotoxic agents.[342] The mechanism of pentamidine-induced ARF has not been established. Although pentamidine is concentrated in the kidney,[343–345] pharmacokinetic studies utilizing a high-performance liquid chromatography assay indicate that <5% of the drug is excreted in the urine each day.[344,346] The mechanism of renal elimination is not known.

Pentamidine nephrotoxicity presents as nonoliguric ARF beginning 7 to 10 days after the start of therapy. Urinalysis reveals mild proteinuria, microscopic hematuria, pyuria, and cylinduria. Most patients experience mild to moderate ARF, but occasionally severe renal failure necessitating dialysis therapy occurs. In one series, azotemia was accompanied by hyperkalemia in association with a picture of hyperchloremic metabolic acidosis.[342] Renal magnesium wasting has been observed in several cases.[347] Recovery of renal function usually begins within a week after stopping drug therapy and in most cases returns to baseline within several weeks.

Chronic renal insufficiency, volume depletion, cumulative dose, and concurrent use of other nephrotoxic drugs heighten the risk of pentamidine nephrotoxicity in humans.[269,348] In the rat, pentamidine nephrotoxicity was potentiated by amphotericin B, tobramycin, and cyclosporine, whereas it was ameliorated by fosfomycin, D-glucaro-1,5-lactam, verapamil, and enalapril.[349]

NEPHROTOXICITY OF CYCLOSPORINE

Since its clinical use as an immunosuppressant drug in the early 1980s, cyclosporin A (CsA) has tremendously improved the outcome of solid organ (kidney, heart, liver, lung, and pancreas) and bone marrow transplants.[350,351] In more recent years, the immunosuppressive properties of CsA have also been used in the treatment of autoimmune diseases (psoriasis, uveitis, and severe rheumatoid arthritis) as well as steroid-resistant nephrotic syndrome.

The major side effect of CsA is its renal toxicity. Although, in preclinical animal studies, renal side effects were not observed,[352–354] early reports from clinical practice revealed the nephrotoxicity of CsA.[355–357] Since that time, numerous observations have added to the overwhelming evidence of three different forms of cyclosporine nephrotoxicity.[358–366] This toxicity is not restricted to only the field of kidney transplantation but has also unequivocally been documented in heart,[367,368] bone marrow,[368] liver,[369,370] and pancreas transplantation,[371] as well as in a variety of autoimmune diseases,[372–375] in which a priori rejection of the kidney graft is absent.

Based on experimental data and clinical experience, this chapter intends to summarize the present knowledge about the three different forms of cyclosporine nephrotoxicity: ARF (with sometimes protracted course evolving to chronicity); the hemolytic–uremic-like syndrome; and chronic irreversible nephrotoxicity.

Clinical Pharmacology of Cyclosporin A

The selective immunosuppressive effects of CsA were described for the first time in 1976.[376] CsA is a lipophilic fungal peptide with a molecular weight of 1.203 daltons, consisting of 11 amino acids (Fig. 31.5). As a consequence of its high hydrophobicity, CsA interacts easily with phospholipid bilayer membranes, whereas some CsA amino acids form a hydrophilic active immunosuppressive site.[377]

CsA is available for clinical use in three formulations: one stabilized in castor oil (Cremophor) for IV injection, the second as a microemulsion formulation (Neoral), and a third formulation as soft gelatin capsules. The pharmacokinetic profile of the conventional CsA formulation (Sandimmune) exhibits a high degree of interpatient and intrapatient variability.[378–380] Pharmacokinetic studies in healthy subjects and renal transplant recipients have shown that the more recent microemulsion formulation of CsA possesses superior pharmacokinetic characteristics, with more complete and predictable absorption of the drug from the gastrointestinal tract, resulting in less pharmacokinetic variability.[381,382] In clinical trials, the microemulsion formulation of CsA increased drug exposure and reduced the incidence of acute rejections, without incremental toxicity.[383–385]

In the circulation, CsA is mainly bound to high, low, or very low density lipoproteins and to chylomicrons.[386] Only a small fraction of CsA circulates unbound. The volume of distribution ranges from 4 to 8 L per kg of body weight.[387] Due to its hydrophobicity, CsA dissolves extensively in cell membranes and tissue lipids.[388] CsA accumulates in lymphocytes, liver, kidney, heart, lung, and neural and muscle cells.[389]

CsA has a median half-life of 6.4 to 8.7 hours and is predominantly eliminated by hepatic metabolism through specific isoenzymes of the cytochrome P-450 superfamily.[390] More than 90% of the parent compound and the metabolites are excreted in the bile, whereas only 6% is eliminated by the kidneys.[388] Significant individual differences in CsA clearance rates,[390,391] with a median value of 12 mL/min/kg, can be explained by wide genetic differences among individuals in the content of cytochrome P-450 isoenzymes, as well as a variety of other factors such as patient age,[392] the functional status of the liver,[393] and interactions with other

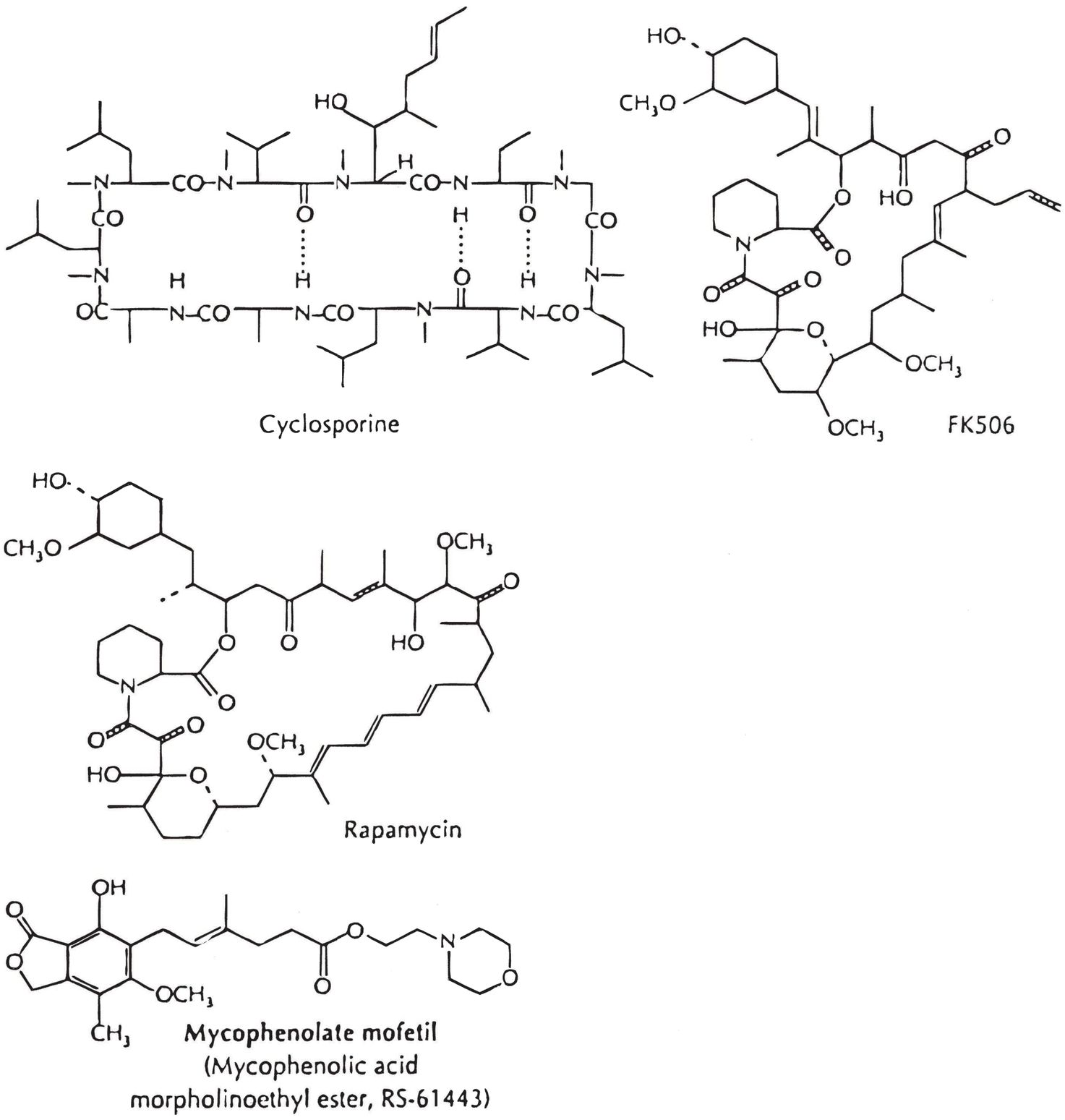

FIGURE 31.5 Structure of new immunosuppressive drugs.

drugs.[394] Independent of the intrinsic nephrotoxicity of CsA, its complex clinical pharmacokinetic profile entails the potential hazard of incorrect dosing, ultimately resulting in irreversible renal damage or acute rejection of the graft.

To optimize CsA therapy, monitoring of CsA trough levels in serum, plasma, or whole blood by means of radioimmunoassays or high-performance liquid chromatography is common clinical practice.[395] Monitoring CsA trough levels has limited value, however, for the assessment of adequate immunosuppression or predicting protection from nephrotoxicity.[396,397] The AUC is more informative and a better indicator of drug exposure[398] but is expensive and time consuming. Large-scale clinical trials using Neoral C_2 monitoring in renal and liver transplant recipients have demonstrated low acute rejection rates and good tolerability with a low adverse event profile to at least one year posttransplant.[399–403] Neoral C_2 monitoring provided a more accurate assessment of delayed and/or low absorbers of CsA in these studies. Neoral C_2 monitoring in maintenance renal transplant recipients showed that 26% to 49% of the patients, managed by monitoring of cyclosporine trough levels, were treated with excessive doses of CsA, adversely affecting graft function.[404–406] Dose reduction to optimal C_2 levels, between 600 and 800 ng per mL, in these patients, resulted in improvement of graft function, without increased risk for rejection.[404] These data provide evidence that monitoring of C_2 levels may result in more adequate dosing of cyclosporine.

Immunosuppressive Mechanism of Cyclosporin A

CsA blocks the activation of T cells, mainly through inhibition of transcription of lymphokines, most notably interleukin-2 (IL-2), the main growth factor for T cells.[407] By inhibiting IL-2 expression in T cells, CsA prevents helper T cells from orchestrating a response to foreign antigens.

The immunosuppressive effect of FK506 (tacrolimus) is similar to that of CsA,[408] as a logical consequence of a similar molecular mechanism of action of both drugs (Fig. 31.6).[409] CsA and FK506 bind with high affinity to intracellular target proteins, called immunophilins, which possess cis–trans isomerase activity. These immunophilins have been identified respectively as cyclophilins in the case of CsA[410] and FK-binding proteins in the case of FK506 and rapamycin.[411] The binding of CsA or FK506 is a prerequisite of their immunosuppressive potential because it has been demonstrated that the CsA- or FK506-immunophilin complex competitively binds directly to the serine–threonine phosphatase

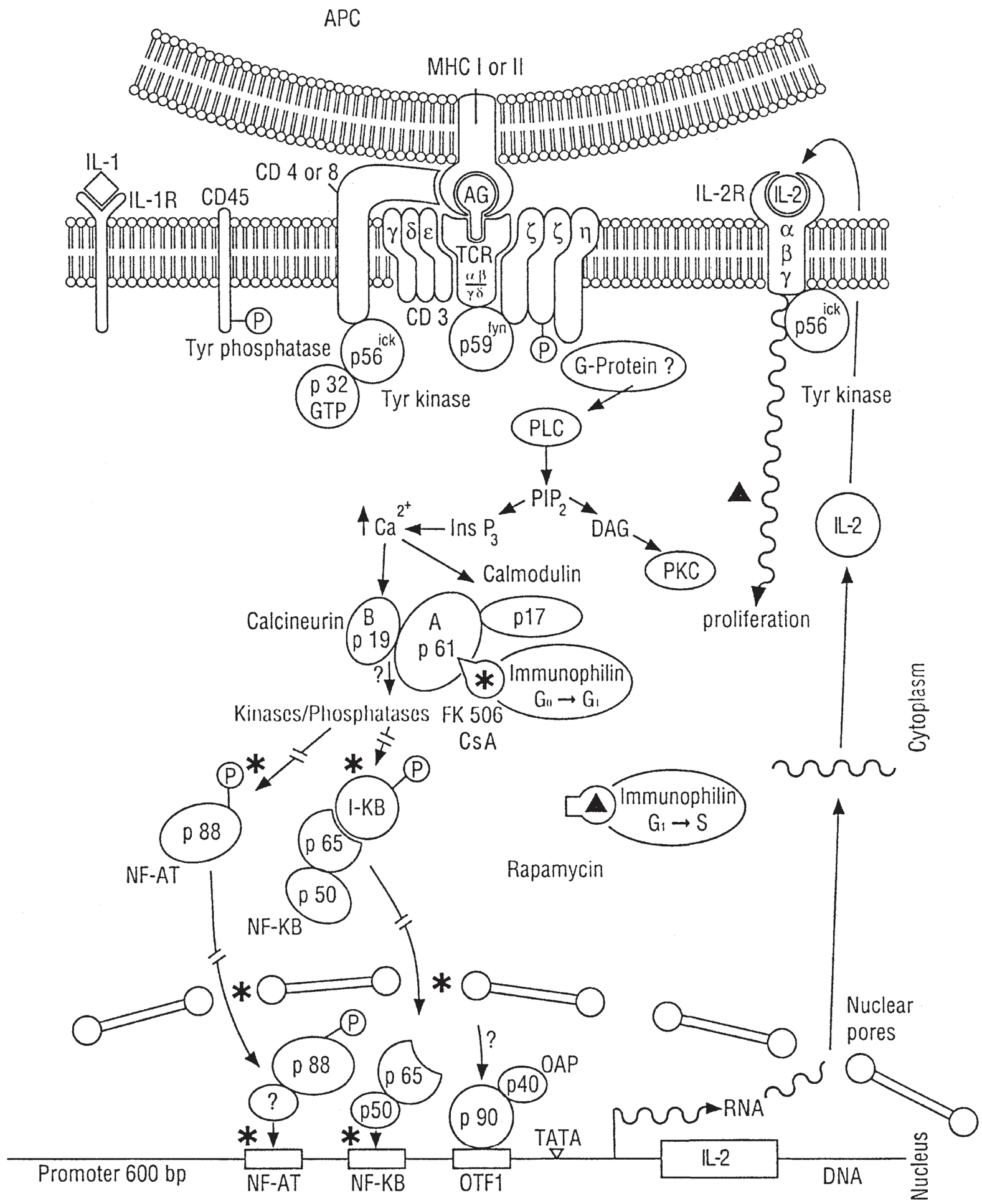

FIGURE 31.6 Cyclosporine (CsA) and FK506 both interfere, by binding to their respective immunophilins, with the function of intracellular molecules that transmit calcium-associated signals between the cell receptor (TCR) and the activation of lymphokine genes (interleukin-2) in the nucleus. Transcriptional regulation of interleukin-2 (IL-2) gene expression is modulated by the combination of transcription factors (e.g., NF-AT, NF-κ B, OTF-1) interacting with their corresponding recognition sites at the IL-2 promoter. These DNA/protein complexes, together with RNA polymerase II (RNA pol II), result in the antigen-inducible transcription of IL-2. Potential intervention sites for the pentameric complex (Calcineurin A [p61], B [p19], calmodulin [p17], immunophilin, drug), involving (e.g., modification and translocation) antigen-inducible transcription factors (NF-AT [p88], NF-κ B [p50, p65]), are indicated by *asterisks*. CyA and FK506 interfere with the G_0 to G_1 transition of the cell cycle, whereas rapamycin interferes with the G_1 to S transition (indicated by a *triangle*). *AG,* antigen; *APC,* antigen presenting cell; *DAG,* diacylglycerol; *Ins P_3,* inositoltriphosphate; *MHC,* major histocompatibility class; *PiP_2,* phosphatidylinositolbiphosphate; *PKC,* protein kinase C; *PLC,* phospholipase C. (From Baumann G. Molecular mechanism of immunosuppressive agents. *Transplant Proc.* 1992;24[Suppl 2]:4, with permission.)

calcineurin[412,413] in the presence of Ca^{2+}. The inhibition of calcineurin by the drug–immunophilin complex results in an altered modification pattern of the cytoplasmic components of transcription factors, thereby disturbing their nuclear translocation.[409]

Potential substrates for calcineurin are the nuclear factor of activated T cells (NF-AT) and the nuclear factor of immunoglobulin (light chain in B cells) (NF-κB), which were both reported as being affected in their IL-2 promoter binding activity by CsA and FK506, but not by rapamycin. This could explain the similarity of the immunosuppressive effect of CsA and FK506, in contrast to rapamycin, although rapamycin shares the same affinity as FK506 for the FK-binding protein.[414,415]

Experimental Nephrotoxicity of Cyclosporin A

Much of our knowledge of cyclosporine nephrotoxicity derives from experimental studies in animal models. The understanding of the pathogenesis of chronic cyclosporine nephrotoxicity has long been hampered, however, by the lack of an experimental model until a number of investigators developed a suitable animal model of chronic cyclosporine nephrotoxicity.[416–420]

Functional Alterations Induced by Cyclosporin A

It has been unequivocally established that CsA profoundly alters renal and glomerular hemodynamics. Acute and/or chronic CsA administration induces a decline in GFR, with a concomitant reduction in renal blood flow and an increase in renal vascular resistance as a consequence of vasoconstriction,[421–424] preferentially at the level of afferent arterioles.[425] These hemodynamic effects are mainly responsible for the acute cyclosporine nephrotoxicity and probably contribute also to the pathogenesis of chronic nephrotoxicity by inducing chronic renal ischemia. The possible underlying mechanisms of this vasoconstrictor effect of CsA are discussed in "Pathophysiologic Studies of Cyclosporine Nephrotoxicity."

Although early pathologic studies suggested that CsA is a primary tubular toxin,[425] the results of clearance experiments conflict with that premise.[426] CsA reduces the end proximal tubular flow rate[427] and increases proximal fractional reabsorption.[428] The latter is due to an inadequate adaptive reduction in the absolute rate of proximal reabsorption.[429] CsA causes a resetting of the tubuloglomerular feedback with onset at lower tubular flow rates and greater maximum response.[430]

CsA-treated rats show a reduction of sodium chloride reabsorption in the distal nephron, including Henle's loop,[427,428] most likely as a secondary response to the decreased proximal tubular fluid delivery. This reduced sodium delivery to and reabsorption from the distal nephron results in reduced distal acidification and potassium secretory capacity through a decreased generation of a negative transmembrane potential. This explains the observed hyperkalemic metabolic acidosis in CsA-treated rats[431] as well as in CsA-treated kidney transplant recipients.[432]

In summary, CsA reduces renal blood flow and GFR predominantly through vasoconstriction of the afferent arterioles. Effects of CsA on tubular function consist of increased proximal tubular reabsorption and decreased distal sodium delivery, which induce hyperkalemic metabolic acidosis.

Morphologic Alterations Induced by Cyclosporin A

The renal pathology induced by CsA is largely dose-related and time-related. For clarity, we focus on two distinct pathologic patterns: the acute (potentially reversible) toxic injury and the chronic (essentially irreversible) nephrotoxicity induced by CsA.

At supratherapeutic levels (100 mg/kg/day by mouth [PO]), CsA induces mainly tubular pathology consisting of isometric vacuolization of tubular cells, accumulation of eosinophilic bodies often representing giant mitochondria, and microcalcifications in proximal tubules by 21 days.[425,433–435] The effects on the proximal tubule tend to be most prominent in the S3 segment[436] and become more widespread at very high doses. These pathologic alterations are reversible after dose reduction or withdrawal of CsA. In contrast to the acute toxic injury, chronic administration of CsA (12.5 mg/kg/day) for 3 to 10 weeks induces striking morphologic alterations in the medullary rays of the cortex of the rat.[416] These changes progress in time and result in areas of focal or striped interstitial fibrosis with foci of atrophic proximal tubules, which are most prominent in the subcapsular cortex.[437,438] The severity of the lesion progresses with treatment and is exacerbated by salt depletion.[420] Withdrawal of CsA does not reverse the observed structural changes.[437]

Besides the striped interstitial fibrosis, mild glomerular endothelial damage, glomerular hypercellularity, and mesangial matrix expansion[417] are observed after long-term CsA administration. Morphometric analysis with three-dimensional reconstruction of individual glomeruli[439] shows subsets of glomeruli with small volume with significant reduction in GFR,[440] alternating with hypertrophic glomeruli.

At the vascular level, scanning electron microscopy shows focal narrowing of the afferent arteriolar diameter that progresses with time of CsA treatment and parallels the decrease in inulin clearance.[362] CsA nephropathy is associated with degenerative hyaline changes in the walls of afferent arteriolar-sized blood vessels,[441] which can disappear after discontinuation of CsA.[442,443]

Pathophysiologic Studies of Cyclosporine Nephrotoxicity

Numerous studies have focused on different pathophysiologic mechanisms of cyclosporine nephrotoxicity. We sequentially discuss mechanisms of renal vasoconstriction, cellular and molecular mechanisms, mechanisms of matrix protein accumulation, and studies on lipid peroxidation.

Mechanisms of Cyclosporin A-Mediated Renal Vasoconstriction. As mentioned previously, administration of CsA induces a marked afferent arteriolar vasoconstriction resulting in decreased renal blood flow and GFR. The renal sympathetic nervous system has been implicated in the renal functional effects of CsA because the α-adrenergic antagonists phenoxybenzamine[421] and prazosin[444] prevent a CsA-induced fall in renal blood flow and GFR. Moreover, a significant increase in renal afferent and efferent nerve activity has been demonstrated in CsA-treated rats.[445] The relevance of the activated sympathetic nervous system to the pathophysiology of cyclosporine nephrotoxicity in kidney transplantation is questionable, however, because the renal allograft is denervated. Nevertheless, increased sensitivity of the denervated organ to circulating catecholamines[445] or significant reinnervation of renal allograft after transplantation[446] is a possible explanation.

Rodent models of cyclosporine nephrotoxicity consistently show activation of the renin–angiotensin–aldosterone axis, in contrast to results in humans. Besides increased plasma renin activity in CsA-treated rats,[434,447] hyperplasia of the juxtaglomerular apparatus,[419,448,449] as well as elevated renin synthesis and release in juxtaglomerular cells,[450,451] has been documented in experimental animals during CsA therapy. However, angiotensin-converting enzyme (ACE) inhibitors show conflicting effects on renal blood flow in CsA-treated rodents, with improvement in some studies[421,452] but not in others.[422,453] More recent experimental studies suggest that CsA-related chronic interstitial injury is mediated by angiotensin II, because renin–angiotensin blockade prevents CsA-induced tubulointerstitial fibrosis.[454,455] However, in human cardiac and renal allograft recipients treated with CsA, plasma renin is suppressed,[367,456] suggesting that the renin–angiotensin system is not of primary importance in human cyclosporine nephrotoxicity.

Hypovolemia could contribute to renal vasoconstriction with CsA therapy because CsA-treated rats have reduced plasma volume and saline expansion reverses the deficits in renal blood flow and GFR.[457] Studies with furosemide,[458] mannitol,[459] and chronic sodium depletion[416] have demonstrated that hypovolemia potentiates cyclosporine nephrotoxicity. Sodium depletion enhanced fibrosis and the expression of TGF-β1 and matrix proteins in experimental CsA nephropathy.[460] However, there is evidence implicating hypovolemia and sodium-depletion as an exacerbating rather than as a causative factor of human cyclosporine nephrotoxicity.

Much attention has been paid to the potential role of an altered eicosanoid metabolism in cyclosporine nephrotoxicity. In animal models, CsA consistently increases the generation of thromboxane A_2 (TxA_2), a potent renal vasoconstrictor,[461–463] whereas its effects on vasodilatory prostaglandins are controversial.[457,464,465] Pharmacologic manipulation of thromboxane metabolism with a specific TxA_2 receptor antagonist[466,467] or a TxA_2 synthase inhibitor[468] partially prevented the CsA-induced acute decline in GFR and renal blood flow in normal rats. The TxA_2 receptor antagonist also attenuated chronic cyclosporine nephrotoxicity in rats with renal isograft.[469] The relevance of these data to human cyclosporine nephrotoxicity, however, is controversial.[470,471]

Another potential mediator of CsA-induced vasoconstriction is the platelet activating factor (PAF) because it has been demonstrated that rat mesangial cells release increased quantities of PAF when incubated with CsA, and CsA-stimulated cell contraction is abolished by the PAF antagonists BN52021 and alprazolam.[472] Chronic cyclosporine nephrotoxicity is also attenuated in rats treated with the PAF antagonist BN52063.[473]

More recently, the role of endothelin, the most potent vasoconstrictor yet identified, has been advocated in CsA-induced vasoconstriction. CsA treatment has been shown to stimulate endothelin production[474,475] and promote glomerular endothelin binding in vivo.[476] Endothelin appears to mediate CsA-induced renal vasoconstriction in the rat.[477] The resulting reduced single-nephron GFR and glomerular plasma flow rate, as well as the decreased glomerular capillary pressure, were attenuated by an antiendothelin antibody.[478] Similarly, the endothelin receptor antagonist BQ123 has the potential to prevent hypoperfusion and hypofiltration induced by CsA.[479] Recent work additionally demonstrated that CsA selectively modulates renal mRNA expression for endothelin peptide and one of its receptor subtypes in a site-specific way.[478] In humans, the endothelin receptor antagonist bosentan markedly blunted the renal hypoperfusion effect of CsA.[480]

Experimental data indicate that an enhanced 5-HT2 (serotonin)-mediated vasoconstriction plays an important role in the suppression of renal blood flow (RBF) autoregulation induced by CsA, because the administration of ritanserin, a pure 5-HT2 antagonist, restored the RBF autoregulation.[481] In vivo studies in humans demonstrated reduced basal and stimulated NO production from the endothelium of forearm resistance vessels in cyclosporine-treated renal transplant recipients.[482] This suggests endothelial dysfunction and may provide a potential mechanism to explain cyclosporine-induced hypertension.

Elevated cytosolic calcium is yet another attractive candidate to explain the CsA-induced vasoconstriction. This has been demonstrated in cultured rat mesangial cells[483] as well as in vascular smooth muscle cells.[484] The augmented transmembrane Ca^{2+} influx and intracellular Ca^{2+} mobilization could account for the protective effects of calcium channel antagonists in acute[485–487] as well as chronic[488,489] cyclosporine nephrotoxicity.

In summary, the acute or subacute effects of CsA on renal hemodynamics are likely mediated by a number of vasoactive substances such as endothelin, serotonin, impaired NO production, TxA_2, and PAF. At the cellular level, CsA induces increased intracellular Ca^{2+}, resulting in contraction of vascular smooth muscle cells as well as mesangial cells. Calcium channel blockers are able to protect against these effects.

Cellular and Molecular Mechanisms of Cyclosporine Nephrotoxicity. CsA modulates mitochondrial calcium fluxes, resulting in reduced mitochondrial swelling, respiration, and calcium discharge.[490,491] Additionally, CsA modulates cytosolic calcium regulation in mesangial cells.[483,492]

In T lymphocytes, CsA only affects calcium-dependent pathways on T-lymphocyte activation. As stated previously in "Immunosuppressive Mechanism of Cyclosporin A," the immunophilin-ligand complex inhibits the Ca^{2+}-dependent phosphatase calcineurin, which is an important step in signal transmission pathways. The analogy of immunosuppressive effect of FK506, as well as its nephrotoxicity, has led to an attractive hypothesis stating that cyclosporine nephrotoxicity could be inherent to its immunosuppressive effect[493]; a similar hypothesis was formulated with regard to FK506.[494]

The mechanisms underlying the linkage of nephrotoxic effects to immunosuppressive effects of CsA or FK506 are still unknown. However, the blocking of T cell activation by CsA or FK506 is an attractive explanation because it has been shown that a mononuclear cell infiltrate is part of cyclosporine nephrotoxicity.[495] Alteration of the repair function of these cells could therefore be a possible mechanism inducing interstitial fibrosis.

Administration of CsA in vivo to rats causes a marked impairment of microsomal protein synthesis.[496] Additional studies have shown a dose-dependent and time-dependent translational alteration of intracellular protein synthesis produced by cyclosporine.[497]

The role of this decreased renal microsomal protein synthesis induced by CsA is speculative but could, if persistent with long-term cyclosporine treatment, alter renal cell matrix and interstitial cell interactions favoring fibrosis.[497]

Recent in vitro studies showed that CsA induces apoptosis in tubular epithelial cells in a dose-dependent and time-dependent manner.[498–501] This effect was mediated by the induction of iNOS,[498] caspases,[499] or Fas.[500]

Mechanisms of Matrix Protein Accumulation. Interstitial fibrosis, the end point of chronic cyclosporine nephrotoxicity, results from an excessive extracellular matrix accumulation, which represents an imbalance between rates of extracellular matrix production and degradation. Cyclosporine has been shown to enhance the production of specific extracellular matrix components in mouse and rat kidney,[502,503] as well as in renal cells in culture.[504] In the presence of CsA, angiotensin II is known to induce interstitial collagen formation.[505] Blockade of the renin–angiotensin system with angiotensin II receptor antagonists or ACE inhibitors markedly abrogated the tubulointerstitial fibrosis without improving renal hemodynamics.[454,455,506] The location of the angiotensin receptor type 1 mRNA in the outer medulla and medullary rays might explain the peculiar striped pattern of fibrosis noted in an experimental model of chronic cyclosporine nephrotoxicity.[507] All together, these data strongly suggest that CsA-induced interstitial fibrosis could be mediated by angiotensin II, independent of its hemodynamic effects.

Several recent studies also implicated transforming growth factor-β1, a potent immunosuppressive and fibrogenic cytokine, as a potential mediator of CsA-induced interstitial fibrosis.[508–514] Enhanced intragraft expression of TGF-β was associated with interstitial fibrosis in patients treated with CsA.[508] In animals, CsA induced an increased expression of TGF-β1, both at the mRNA and the protein level, again associated with tubulointerstitial fibrosis.[509–511,514] Similarly, CsA stimulated expression of TGF-β1 in renal cells.[512,513] The fibrogenic effects, induced by CsA, were abrogated by a neutralizing anti-TGF-β1 antibody.[513,514]

In contrast to the already mentioned enhanced collagen formation induced by CsA, recent work demonstrates an increased expression at both the transcriptional (mRNA) level and protein level of tissue inhibitor of metalloproteinases (TIMP-1) in a rat model of chronic cyclosporine nephrotoxicity.[515,516] Moreover, Duymelinck and associates show that cholesterol feeding accentuates the cyclosporine-induced elevation of renal plasminogen activator inhibitor type 1 (PAI-1).[517] This increased expression and production of TIMP-1 and PAI-1, induced by CsA, could result in a decreased degradation of extracellular matrix, which would in turn lead to progressive extracellular matrix accumulation and interstitial fibrosis.

In summary, CsA-induced interstitial fibrosis results from a combination of increased synthesis of matrix components, as well as decreased degradation of extracellular matrix. Angiotensin II and transforming growth factor-β1 may play a role in the process of increased collagen formation induced by CsA, whereas the TIMP-1 and the PAI-1 likely mediate the decreased degradation of extracellular matrix induced by CsA.

Studies on Lipid Peroxidation. It has been shown that in vitro incubation of rat renal microsomes or human liver microsomes with CsA induces dose-related lipid peroxidation.[518,519] Lipid peroxidation seems to be the main mechanism of free-radical toxicity.[520–522] Reactive oxygen species through a peroxidative process may increase the availability of arachidonate metabolites and enhance prostanoid production.[523–525] Recent in vivo studies in the rat indicated that cyclosporine nephrotoxicity is accompanied by dose-related systemic and renal lipid peroxidation,[526] preceding the fall in GFR.[527] Concurrent treatment with antioxidants (i.e., vitamin E,[526] melatonin,[528] or N-acetylcysteine[529]), suppressed CsA-induced lipid peroxidation and reduced functional and structural damage. The mechanism by which CsA-induced lipid peroxidation could contribute to cyclosporine nephrotoxicity is putative, including direct cellular toxicity,[530] thromboxane-mediated ischemia,[531] or peroxidation-linked excess extracellular matrix production.[532] Several reports suggest that calcineurin inhibitors, CsA and tacrolimus, have pro-oxidant activity and they increase the susceptibility of low density lipoprotein to oxidation in humans.[533–535]

Clinical Nephrotoxicity of Cyclosporin A

CsA can cause a wide spectrum of renal functional and morphologic impairments, including a marked and rapidly reversible decrease in GFR and renal plasma flow[359] and a chronic form of renal damage in patients treated for more than 6 months with a potential evolution to end-stage renal disease.[364,367] Thrombotic microangiopathy is another relatively uncommon but serious adverse effect of cyclosporine.[362,536]

Acute Renal Failure Induced by Cyclosporin A

Acute cyclosporine renal dysfunction is not infrequent in clinical practice and occurs not only in patients with kidney transplantation[355] but also in heart,[537] liver,[358] and bone marrow[356] transplant recipients. This acute form of nephrotoxicity may occur within weeks following initiation of CsA therapy and can also be observed after years of drug therapy.[538] The incidence of this acute renal injury can be enhanced by extended graft preservation,[361] preexistent renal histologic lesions,[539] donor hypotension, and perioperative complications.[540]

Acute cyclosporine nephrotoxicity has clinical features similar to those of acute renal allograft rejection, including an abrupt fall in GFR, impaired urinary concentrating capacity, and sodium retention.[541] Hypertension is observed in up to 50% of patients, whereas metabolic acidosis, hyperkalemia, and hyperuricemia are less frequent.[542] Characteristic of this syndrome of acute reversible renal dysfunction induced by CsA is the rapid recovery of renal function on reduction of the CsA dose.[359,543]

Delayed kidney graft function is a less frequent severe form of protracted ARF with oliguria induced by CsA.[541] Its incidence varies largely between centers,[544,545] presumably reflecting different strategies of immunosuppressive treatment or variations in time of ischemia of the kidney before transplantation.[546,547]

Although nephrotoxicity due to cyclosporine alone is rarely observed with CsA trough blood levels below 200 ng per mL,[380,548] blood level monitoring has proved unreliable in the differential diagnosis between acute cyclosporine nephrotoxicity and acute rejection of kidney allografts.[380]

The difficulty in differentiating acute rejection from cyclosporine nephrotoxicity in the setting of kidney transplantation often compels performance of a kidney biopsy.[549,550] On a histologic basis, cyclosporine nephrotoxicity is often a diagnosis of exclusion with the absence of definite signs of acute rejection, such as intimal arteritis[551,552] or intratubular lymphocytes.[553] Histologic features of cyclosporine nephrotoxicity are nonspecific and include arteriolar hyalinosis,[554,555] as well as isometric vacuolization of proximal tubular cells.[556]

Analogous to experimental data obtained in animal models, CsA causes a dose-related and time-related fall in GFR and renal plasma flow in humans induced by renal vasoconstriction.[557,558] In two studies, the intrarenal blood flow was significantly reduced after oral cyclosporine intake, but hypoperfusion could not be elicited by tacrolimus.[559,560] The beneficial effects of different calcium channel blockers on this CsA-induced renal hypoperfusion[561–566] suggest this vasoconstriction is mainly affected at the afferent arteriolar level because it has been demonstrated that calcium antagonists preferentially reduce glomerular afferent arteriolar tone.[567]

In contrast, coadministration of indomethacin unmasks CsA-induced renal vasoconstriction and potentiates cyclosporine nephrotoxicity by reducing the intrarenal prostaglandins.[568] This suggests a role for the eicosanoids in the CsA-induced vasoconstriction. Further arguments in favor of this possibility are the partial beneficial effects observed with a specific TxA_2 synthase inhibitor[471] and with dietary regimens with omega-3 polyunsaturated fatty acids.[569]

Although a role for increased vascular renin activity in cyclosporine-induced renal and peripheral vasoconstriction has been suggested,[570,571] investigators have never detected any significant preventive effect of ACE inhibition on the decline in renal blood flow and the increase in renal vascular resistance induced by CsA.

Unlike in animal models, prazosin did not significantly affect GFR, renal plasma flow, or renal vascular resistance in patients who had undergone transplant and were treated with CsA,[572] thus questioning the role of the sympathetic nervous system in cyclosporine nephrotoxicity.

Endothelin has been implicated as a causative agent in CsA-induced vasoconstriction (see "Experimental Nephrotoxicity of Cyclosporin A"). Although intrarenal injections of antiendothelin antibodies protected against the effects of cyclosporine,[474] administration of specific endothelin receptor antagonists has shown conflicting results.[479,573]

Chronic Cyclosporine Nephrotoxicity

The main clinical issue associated with CsA treatment is, however, the chronic nephrotoxicity[367] that is clinically defined by progressive renal dysfunction with hypertension. Histologic lesions can already appear after 6 months of CsA therapy,[364,574] with progression over time, even after CsA dose reduction.[371] As mentioned previously, chronic cyclosporine nephrotoxicity has been documented in other clinical settings besides kidney transplantation.[367–375] Chronic cyclosporine nephrotoxicity is related to the cumulative CsA dose[371,575] and may be irreversible even after CsA discontinuation.[576]

The clinical features of chronic cyclosporine nephrotoxicity are nonspecific, including a slowly progressive decline of renal function over months or years, severe arterial hypertension, mild proteinuria, and tubular dysfunction.[541] In renal allografts, differential diagnosis with chronic rejection is often impossible on clinical grounds alone, thus necessitating the performance of a kidney biopsy.[577]

The histopathologic lesions of chronic cyclosporine nephrotoxicity have been extensively studied and are now well known.[365,366,578,579] Histopathologic findings in 2-year protocol biopsies from a randomized study showed

comparable lesions in renal allografts under cyclosporine and tacrolimus treatment.[580] They include renal arteriolar damage (the so-called CsA-associated arteriolopathy), tubular atrophy, and (striped) interstitial fibrosis, as well as glomerular sclerosis. These lesions are nonspecific, however, except for the CsA-associated arteriolopathy.

The vascular lesions are located almost exclusively in the arterioles and arteries, with up to two layers of smooth muscle cells, and usually consist of circular nodular protein deposits or mucoid thickening of the intima, which contributes to narrowing or occlusion of the lumen.[365] CsA-associated arteriolopathy affects a limited number of arterioles in a dose-related manner.[579]

Tubulointerstitial changes may be nearly diffuse, but usually there are narrow stripes of atrophy and fibrosis, apparently corresponding to areas of cortex with afferent arteriolar lesions.[365] This interstitial fibrosis progresses over time.[371] Tubular atrophy is nearly always found in areas with interstitial fibrosis[581] and likewise progresses with time.[371] CsA-induced glomerulopathy consists of global or focal and segmental sclerosis.[366,582] Again, the number of affected glomeruli increase with time.[371]

Although the histologic features of chronic cyclosporine nephrotoxicity have been well characterized, the differential diagnosis with chronic rejection of the renal allograft in kidney transplantation still often remains difficult.[583]

A great matter of debate is whether prolonged therapy with CsA can result in progressive, irreversible renal damage, ultimately leading to end-stage renal disease. This was advocated by some authors[584,585] but denied by others.[572,586] Multicenter studies in renal transplant patients showed reduced but stable renal function after up to 3 to 5 years of CsA treatment.[587,588] Conversion from CsA to azathioprine in kidney transplant recipients after 3 months significantly improved the creatinine clearance at 5 years' posttransplantation.[589] In patients who have undergone pancreas transplant, a sequential functional and morphologic study has unequivocally shown the progressive character of the histologic lesions due to cyclosporine nephrotoxicity.[371] This was strongly correlated with CsA blood levels, CsA dose, and magnitude of the decline in creatinine clearance during the first posttransplant year.[371] Analysis of sequential protocol biopsies of renal allografts over a period of 10 years, in a prospective study of 120 kidney-pancreas transplant recipients, confirmed this progressive character of renal histologic lesions, induced by calcineurin inhibitors.[590] In this study, severe histologic damage was present in 58.4% of the renal allografts by 10 years.

Altogether, these data point out that chronic cyclosporine nephrotoxicity has a progressive and irreversible character once the histologic lesions have arisen. Assessment of the renal function, be it by means of serum creatinine or creatinine clearance, underestimates the magnitude of the problem due to the relatively low sensitivity of those methods and to the slow progression of the renal damage induced by cyclosporine.

The pathophysiology of chronic cyclosporine nephrotoxicity in humans is a matter of extensive investigation, mainly through experimental models (see "Pathophysiologic Studies of Cyclosporine Nephrotoxicity").

Hemolytic–Uremic-like Syndrome Induced by Cyclosporin A

Thrombotic microangiopathy is a relatively uncommon but serious adverse effect of cyclosporine in renal[362] and nonrenal[536] transplant recipients, with an overall 43% graft survival rate.[591,592] The most striking morphologic changes are an extensive thrombotic process in the renal microcirculation, with several glomerular capillaries occluded by thrombi extending from the afferent arterioles and containing platelet aggregates.[365] Laboratory anomalies include thrombocytopenia, hemolytic anemia, and deterioration of the renal function.[362] In the setting of kidney transplantation, the differential diagnosis of hemolytic–uremic syndrome and vascular rejection is not obvious.[591] According to a retrospective study of 29 patients with calcineurin-inhibitor induced thrombotic microangiopathy, repeated plasma-exchange induced a recovery of the renal allograft function in 80% of the patients.[593]

This hemolytic–uremic-like syndrome induced by CsA reinforces the concept that the vascular endothelium is the main target in this form of CsA toxicity. That CsA can damage vascular endothelium is confirmed by the high plasma concentration of factor VIII-related antigen, found in recipients of renal allograft given CsA and having clinical signs of nephrotoxicity.[594] Recent work shows significantly higher plasminogen-activator inhibitor levels in patients treated with CsA who underwent renal transplant, compared to patients who were not treated with CsA, suggesting a decreased fibrinolytic activity in the former patients.[595] This could account for the increased risk of hemolytic–uremic syndrome induced by CsA.

Pharmacogenetics of Calcineurin Inhibitors

With nephrotoxicity continuing to be a major factor in late kidney damage, it is important to understand better the mechanisms of drug-induced nephrotoxicity to develop therapeutic strategies and identify early biomarkers.[596] However, from a clinical point of view, none of these biologic pathways identified in experimental studies brought a clinical benefit for the patients, either in terms of early markers or in terms of therapeutic alternatives, including endothelin inhibitors or angiotensin receptor blockers.

Variability in calcineurin inhibitor (CNI) intestinal absorption and metabolism is attributed, at least in part, to the variability in expression and function of CYP3A enzymes (mainly 3A4 and 3A5) and the ATP dependent multidrug efflux transmembrane transporter P-glycoprotein (Pgp), a product of ABCB1 gene (previously MDR-1).

Pgp, a product of ABCB1 gene (previously MDR1), is a membrane protein that functions as an ATP-dependent

exporter of intracellular xenobiotics. In the kidney, Pgp is constitutively expressed on the brush border of proximal tubular cells and on the distal tubule. It has been suggested that Pgp is instrumental in CsA nephrotoxicity.[597] CsA is a substrate of Pgp, and variations in expression and/or function of Pgp could lead to accumulation of CsA, along with other cytotoxic agents, within the tubular cell.[598]

Already in 1998, Napoli et al. demonstrated a pharmacokinetic interaction between sirolimus CsA increasing the concentration of both immunosuppressive drugs in the renal tissue.[599] In clinical studies, it was noticed that sirolimus had no nephrotoxic effect; however, when used in combination with CsA, the nephrotoxic effect of CsA was potentiated.[600]

Anglicheau et al.[601] studied in vitro the role of P-glycoprotein (Pgp) in CsA cytotoxicity and the CsA-sirolimus interaction. Cyclosporine and sirolimus are Pgp substrates. The authors hypothesized that the Pgp activity level may affect cyclosporine cytotoxicity by interfering with the ability of Pgp to remove cyclosporine from within tubular cells, and that an interaction between cyclosporine and sirolimus on Pgp function may explain the enhancement of cyclosporine nephrotoxicity by sirolimus. Cyclosporine cytotoxicity was evaluated in primary cultures of normal human renal epithelial cells (HRECs) by cell viability and cytotoxicity assays. Verapamil, quinine, PSC833, and PGP-4008 were used as Pgp inhibitors. Rhodamine-123 (R-123), a fluorescent substrate of Pgp, was used to assess Pgp-mediated transport. Cyclosporine exerted a concentration-dependent cytotoxic effect on HRECs that was significantly increased by inhibition of Pgp activity. Sirolimus exerted an inhibitory effect on R-123 efflux in HRECs and increased cellular cyclosporine concentrations in a dose-dependent manner. These data demonstrate that Pgp plays a critical role in protecting renal epithelial cells from cyclosporine toxicity. The inhibitory effect of sirolimus on Pgp-mediated efflux and the cellular concentration of cyclosporine could explain the exacerbation of cyclosporine nephrotoxicity observed clinically.

Transcriptomic analyses of in vitro models of CNI nephrotoxicity have been used to identify two new molecular mechanisms that may play a role in early CNI-induced nephrotoxicity: EMT and endoplasmic reticulum (ER) stress. In vitro evidence that CsA induces EMT in proximal tubular epithelial cells has been provided. Potential mediators and downstream effectors of CsA-induced changes were identified by large-scale expression analysis using Affymetrix microarrays. PKC-β has been identified as a potentially important mediator, which may be responsible for CsA-induced TGF-β1 upregulation. In addition, the E2A transcription factors E12/E47 may play a key role in the altered expression profile of CsA-treated cells and, thus, cell phenotype.[602] These in vitro findings regarding EMT have been translated in vivo. De novo vimentin expression has been used as a marker of tubular mesenchymal transition in rats treated with CsA. Whereas tubular vimentin, a nonspecific marker of regeneration, is virtually absent from vehicle-treated rat kidneys, de novo expression is markedly increased in CsA-treated rat kidneys, together with a CsA-induced increase in collagen 3 and fibronectin mRNA expression, suggesting that CsA induces tubular expression of mesenchymal markers in vivo.[603] Whether CsA EMT is important to the increasingly recognized role of EMT in renal fibrosis needs further investigation using more specific tools indicating EMT.

Endoplasmic reticulum stress results from the accumulation of misfolded proteins within the ER. The relevance of the induction of ER stress by CsA was boosted by the finding that CsA exposure in vivo results in the upregulation of the ER stress marker BiP mRNA in renal allograft biopsies. In a rat model of CsA nephrotoxicity, Han et al. reported that a short-term treatment of CsA for 7 days activated the unfolded protein response, exemplified by the induction of BiP, and a proapoptotic response characterized by the upregulation of capsase 12 and CHOP.[604]

Recent progress in molecular biology and functional genetics like transcriptomics and whole genome studies will lead to the discovery of genes associated with kidney injury and the characterization of stress response pathways.

Summary

CsA is a potent immunosuppressive drug with nephrotoxic side effects. Independent of the intrinsic nephrotoxic properties of CsA, its complex clinical pharmacokinetic profile could cause incorrect dosing, ultimately resulting in irreversible renal damage.

The clinical nephrotoxicity of CsA consists of three entities with different expressions of renal damage induced by CsA (i.e., ARF, hemolytic–uremic-like syndrome, and chronic cyclosporine nephrotoxicity). The ARF is essentially reversible and mainly hemodynamically mediated through afferent arteriolar vasoconstriction. Dosage reduction of CsA reverses the nephrotoxic effects. The hemolytic–uremic-like syndrome consists of an extensive thrombotic process at the level of the glomerular capillaries, causing loss of kidney function in more than half of the cases. Chronic cyclosporine nephrotoxicity is an irreversible renal damage characterized by a specific arteriolopathy and striped interstitial fibrosis, resulting in slow progressive decline of renal function.

TACROLIMUS (FK506)

Tacrolimus (FK506) is a fungal product, a new macrolide immunosuppressant agent, which has shown important potential in transplantation and in the treatment of autoimmune diseases.[605–607] Although it is many times more potent than cyclosporine, allowing the use of lower doses, both drugs have similar nephrotoxic properties.[608,609]

Molecular Action

Cyclosporine and FK506 have dissimilar chemical structures (Fig. 31.5)—nevertheless, both agents bind to a similar class of ubiquitous intracellular receptors: immunophilins,

molecules that are cis–trans prolyl isomerases. These intracellular binding proteins are well conserved through evolution and change the confirmation of cyclosporine and FK506. The cytosolic receptor for FK506 (FKBP) has been well characterized.[610] This drug-immunophilin complex must bind to calcineurin, a calcium-dependent protein phosphatase, to allow the immunosuppressant actions of the drugs in lymphocytes (Fig. 31.6).[611,612] Similar calcineurin-mediated dephosphorylation of cyclosporine and FK506 may lead to inhibition of signal transduction in other cell types and organs, which mediates both the desirable immunosuppressant effects and the possibly toxic effects.

Cyclosporine and FK506 are powerful immunosuppressive drugs that inhibit the calcium–calmodulin-dependent phosphatase calcineurin in T cells, thereby preventing the activation of T cell-specific transcription factors such as NF-AT involved in lymphokine gene expression (Fig. 31.6). Although this may, at least in part, explain the mechanism of cyclosporine and FK506 immunosuppression, additional mechanisms have to be invoked to explain the pharmacologic properties and toxic effect of these drugs such as nephrotoxicity and neurotoxicity. Schwaninger and coworkers[613] studied the effect of cyclosporine and FK506 on calcineurin phosphatase activity and gene transcription mediated by the cyclic adenosine monophosphate-responsive element (CRE), a binding site of the ubiquitous transcription factor CREB. An imported gene was placed under the transcriptional control of the CRE of the rat glucagon gene and transiently transfected into the glucagon expressing cell line αTC2. Cyclosporine and FK506 inhibited depolarization-induced gene transcription in a concentration-dependent manner. Both cyclosporine and FK506 inhibited calcineurin phosphatase activity at the drug concentrations that inhibited gene transcription. The FK506 analog rapamycin had no effect on calcineurin activity and gene transcription, but excess concentrations of rapamycin prevented the effect of FK506 on both calcineurin activity and gene transcription. These results further support the notion that the interaction of drug-immunophilin complexes with calcineurin may be the molecular basis of cyclosporine- and FK506-induced inhibition of CREB/CRE-mediated gene transcription. The ability to interfere with CREB/CRE-mediated gene transcription represents a new mechanism of cyclosporine and FK506 action that may underlie pharmacologic effects and toxic manifestations of these potent immunosuppressive drugs.[613]

A recent report demonstrated that in vivo FK506 treatment eliminated antigen-stimulated T cells through DNA fragmentation (apoptosis), representing one of the mechanisms of immunologic tolerance.[614]

Experimental Studies

Cell Culture

McCauley and colleagues[615] demonstrated a cyclosporine- and FK506-mediated, dose-dependent inhibition of renal cell proliferation using LLC-PK1 cells (an established cell line derived from the pig proximal tubule) in culture. Although FK506 inhibited renal cell proliferation to a greater degree than cyclosporine at the same concentration, when clinically relevant concentrations were compared, FK506 was significantly less inhibitory than cyclosporine. Moutabarrik and associates[616] observed similar effects in the same cell line but could not make a clear distinction between the FK506 and the cyclosporine effects on release of 3H thymidine from prelabeled cells, N-acetyl-β-D-glucosaminidase release, and cell detachment. Ultrastructural changes such as vacuolization, swelling, and mitochondrial enlargement and inhibition of the growth of the cultured tubular cells were also observed at high concentrations of FK506 and cyclosporine. Low concentrations of FK506 and cyclosporine were not cytotoxic and induced only a minimal inhibitory effect on the growth of tubular cells in vitro. Cyclosporine and FK506 also induced a time-dependent stimulation of the secretion of endothelin by cultured tubular cells. The concentration of cyclosporine that induced these effects was 10 to 100 times higher than that required for FK506. The concentrations of FK506 and cyclosporine inducing endothelin secretion were not cytolytic for tubular cells in vitro. Yatscoff and coworkers[617] compare the effect of rapamycin and FK506 on the release of prostacyclin and endothelin in vitro using cultured rabbit mesangial and endothelial cells. The effects of both rapamycin and FK506 on the basal or stimulated release of prostacyclin or endothelin from mesangial cells and endothelial cells are similar with the following exceptions: Rapamycin results in a significant increase in the release of prostacyclin, whereas FK506 results in a significant decrease in the release of prostacyclin from the endothelial cells. Benigni and colleagues[618] review the vascular effects of FK506 as compared to cyclosporine in endothelial cell culture and intact organ. FK506, unlike cyclosporine, is without significant effect on thromboxane B_2, 6-ketoprostaglandin $F_1\alpha$, or endothelin release in bovine aortic endothelial cells grown in culture and does not alter the renal vascular resistance in vivo. These findings suggest that FK506 causes much less pronounced endothelial cell injury, at least in vitro.

Atcherson and Trifillis[619] examine in vitro cytotoxicity of FK506 on normal human proximal tubule cells. They find that FK506 is reversibly and mildly toxic to monolayers of human renal proximal tubule cells.

Edkins and associates[620] compare the effect of FK506 (2.5 mg per kg for 7 days) and cyclosporine (50 mg/kg/day) on renal and hepatic brain and cochlear-reduced glutathione content. Both cyclosporine and FK506 increase glutathione levels in kidney to approximately equivalent levels after 5 days of treatment. Only FK506 increases glutathione levels in liver, and neither drug changes levels in other tissues.

Shah and coworkers[621] show that FK506 exhibits a broad, powerful inhibitory effect on human hepatic microsomal cytochrome P-450-dependent drug metabolism. However, the full potential for drug interactions can only be determined by investigating its effects on other P-450 families using both in vivo and in vitro studies. On the other

hand, Yoshimura and coworkers[622] recently report that, in rats, both FK506 and rapamycin are without significant effects in contrast to cyclosporine on renal microsomal P-450- dependent drug metabolism.

Yoshimura and coworkers[623] review the effect of FK506 and rapamycin on renal P-450 systems in rat models. They find that although cyclosporine has a strong effect on renal P-450 systems and induces such a system in kidney cortex (microsomal P-450), FK506 and rapamycin have no substantial effect on the induction of renal P-450.

The role of intracellular calcium in the pathogenesis of cyclosporine nephrotoxicity has received great attention[624,625] and has resulted in therapeutic implications to prevent nephrotoxic effects of the drug. The effect of cyclosporine and FK506 on microsomes and mitochondria of rabbit renal cortex tissue has been studied by Prasad and associates.[626] Both drugs decrease calcium uptake and A23187-induced calcium release from microsomes and mitochondria in a dose-dependent manner (0.5 to 10.0 μg per mL). The effect of FK506 is significantly less at equivalent concentrations, and microsomal calcium-stimulated ATPase is not changed by either drug.

The potential role of the FK506 binding protein (FKBP12) in cellular calcium homeostasis has been suggested. Indeed, Jayaraman and colleagues[627] find that a 12-kd protein tightly bound to the calcium release channel in skeletal muscles of rabbit is FKBP12. Obviously, if this observation can be confirmed in vascular smooth muscle, it may explain the mechanism of FK506-induced vasoconstriction in renal vasculature. This process also is probably calcineurin-drug complex mediated. A further role of calcineurin in α-adrenergic stimulation of Na^+-K^+-ATPase activity in renal tubular cells is illustrated by Aperia and coworkers.[628] They demonstrate that FK506 inhibited Na^+-K^+-ATPase activity induced by oxymetazoline, an α-adrenergic agonist. This study may suggest a role for FK506-mediated renal nerve changes in sodium and potassium homeostasis. In this context, Palevsky and colleagues[629] report a resistance to the effect of aldosterone on renal cells in cultures exposed to FK506.

Animal Studies

Animal studies have shown both acute and chronic nephrotoxicity produced by FK506.[630] Somewhat different than cyclosporine, FK506 produces toxicity at blood levels that are clinically relevant; however, the doses necessary to achieve these blood levels on a weight basis are at least 10-fold larger than those used clinically. This contrasts with cyclosporine, with which acute and chronic nephrotoxicity can be produced with doses on a weight basis that are very close to those clinically used, particularly in the salt-depleted rat model; however, the blood levels achieved with these doses are at least three to four times those achieved clinically.[631]

Preclinical animal studies gave few hints of nephrotoxicity.[632] However, a troubling series of side effects soon appeared including vasculitis, myocardial necrosis, and severe weight loss. Fortunately, most of these side effects turned out to be species-specific. Nephrotoxicity of FK506 became apparent from the initial series of rescue patients treated with the drug.[633]

Several studies have documented reduction in effective renal plasma flow and GFR in animal models. Ueda and colleagues[634] have measured renal cortical blood flow, using a hydrogen ion clearance method, serum creatinine, and juxtaglomerular cell cross-sectional area in mice treated with FK506, 3 mg/kg/day given subcutaneously as compared with saline-treated control animals. Cortical blood flow is significantly reduced in FK506-treated animals as compared with control animals, as is juxtaglomerular cell area. Kumano and coworkers[635] also note a reduction in GFR and effective renal plasma flow using inulin and p-aminohippuric acid in a heminephrectomized rat model in response to an acute infusion of FK506 and after 21 days of treatment. Proximal tubular vacuolization typical of cyclosporine nephrotoxicity is noted, and diltiazem improves both the functional and morphologic changes caused by FK506. Lieberman and associates[613] note a significant volume reduction in both cyclosporine-treated and FK506-treated glomeruli that are inhibited by verapamil. Mitamura and colleagues[637] review the FK506-induced nephrotoxicity in spontaneous hypertensive rats. These results indicate that the acute nephrotoxicity of FK506 is derived from impaired glomerular function associated with renal arteriolar constriction brought about by the drug. All of these renal disorders induced by FK506 recover completely or partially when the drug is withdrawn for 2 or 4 weeks. Thus, the acute nephrotoxicity of FK506 in spontaneous hypertensive rats is reversible.

Ryffel and colleagues[638] explore the nephrotoxicity of immunosuppressants in rats. Specifically, they compare the nephrotoxic effects of FK506 and rapamycin with that of cyclosporine in male Wistar rats. FK506 causes proximal tubular epithelial changes consisting of atrophy, vacuolization, inclusion bodies, microcalcification, and focal mononuclear interstitial infiltrate as described for cyclosporine. The most striking alteration is hypertrophy of the juxtaglomerular apparatus. The percentage of renin-containing juxtaglomerular apparatus and the extent of renin immunoreactivity along afferent vessels are significantly increased in FK506-treated and CsA-treated rats. By contrast, no renal morphologic lesions are found in rapamycin-treated animals. Renal cortical extracts contain abundant cyclophilin and FK506-binding protein, the main intracytoplasmic receptors for cyclosporine and FK506, respectively. The authors hypothesize that both the immunosuppressive and toxic effects of FK506 and cyclosporine, but not of rapamycin, are mediated through an immunophilin–drug–calcineurin complex. The renal substrate of calcineurin, which mediates renal vasoconstriction, is yet to be identified.

Andoh and associates[639] also compare the acute rapamycin nephrotoxicity with cyclosporine and tacrolimus. They find that cyclosporine and FK506 strikingly decrease

urinary excretion of nitric oxide, renal blood flow, and GFR, whereas rapamycin does not. In contrast, all three of these drugs cause significant hypomagnesemia associated with inappropriately high fractional excretion of magnesium, suggesting renal magnesium wasting. In addition, with all three drugs there are lesions in the rat kidneys consisting of tubular collapse, vacuolization, and nephrocalcinosis. These researchers show that only the calcineurin inhibitors produce glomerular dysfunction in an acute experimental model of nephrotoxicity.

Of interest is the experiment of Hara and colleagues[640] that shows that FK506 is effective in the prevention of the development of rapid glomerular injury in rats with accelerated nephrotoxic serum glomerulonephritis.

Abnormalities in mineral metabolism are common complications of organ transplantation. The role of immunosuppressive agents in alteration of mineral metabolism is not clear. An animal study was conducted to investigate the effects of cyclosporine A (CsA), tacrolimus, and sirolimus on renal calcium, magnesium, and vitamin D metabolism.[641] CsA and tacrolimus induced a two- to threefold and 1.6- to 1.8-fold increase in urinary calcium and magnesium excretion, respectively, whereas rapamycin had no effects on calcium, but doubled the urinary magnesium excretion. CsA and tacrolimus, but not rapamycin, elevated serum 1,25(OH)(2) vitamin D without affecting the parathyroid hormone level. CsA and tacrolimus reduced mRNA abundance in TRPV5 (CsA: 64 ± 3% of control; tacrolimus: 50 ± 3%) calbindin-D28k (CsA: 62 ± 4%; tacrolimus: 43 ± 3%), and vitamin D receptor (CsA: 52 ± 3%; tacrolimus: 58 ± 2%, all $P < .05$). Rapamycin did not affect gene expression in any of studied proteins. The immunofluorescence staining study demonstrated a 50% reduction of TRPV5 and calbindin-D28k by CsA and tacrolimus. The suppression of VDR by calcineurin inhibitors is probably the underlying mechanism of renal calcium wasting. In spite of an increased 1,25(OH)(2) vitamin D level, the kidney is not able to reserve calcium, suggesting a role of vitamin D resistance that may be related to bone loss.

Clinical Studies

Since the initial reports on the use of tacrolimus in clinical transplantation by Starzl and Shapiro,[642,643] numerous large scale trials compared the efficacy and safety of tacrolimus and cyclosporine mainly in liver[644,645] and kidney[646–648] transplantation. According to five out of six of these large trials, renal function and the incidence of renal impairment were comparable in both treatment arms at 1 year posttransplantation. Similar results were reported in a long-term comparison of nephrotoxicity between tacrolimus and cyclosporine in pediatric heart transplant recipients.[649] In contrast, Ashan and coworkers reported a significantly better renal allograft function at 2 and 3 years under tacrolimus compared to cyclosporine, both in combination with steroids and mycophenolate mofetil.[648,650] However, graft survival at 2 and 3 years was comparable in both groups. In an intention-to-treat analysis, graft survival at 5 years was comparable between patients, initially randomized to tacrolimus or cyclosporine in the large U.S. multicenter trial.[646,651]

In a recent study, once daily administration of tacrolimus may be a good option, considering its nephrotoxic effects for kidney transplant patients. Indeed, the trough levels of tacrolimus showed a slight significant reduction after the conversion from the twice daily to the once daily extended release tacrolimus formulations. Serum creatinine and glomerular filtration rate showed a significant improvement without an association with the tacrolimus trough levels.[652]

Ekberg et al.[653] asked the question if in view of the most common immunosuppressive treatment in de novo renal transplantation being a triple regimen that includes tacrolimus, mycophenolate mofetil (MMF), and corticosteroids, and that may also include antibody induction. Whether nephrotoxicity is an issue with tacrolimus at the currently used dosages remains an open question. Data from three large, randomized, de novo renal transplantation studies (Symphony, Fixed Dose Concentration Controlled [FDCC], and OptiCept) that used variations of the triple regimen with respect to tacrolimus target levels, MMF dosing, and antibody induction were pooled. The analysis population consisted of 998 patients. On average, tacrolimus levels were in a range considered low (mean ± standard deviation 7.2 ± 2.54 ng per mL), and MMF dose was 1.5 ± 0.61 g per day. Lower tacrolimus levels and higher MMF doses were associated with significantly better renal function. There were other variables associated with renal function, most notably acute rejection, donor age, and delayed graft function. Subanalyses in each of the three studies gave a consistent picture. There was no overt difference in the effect sizes when patients with stage II (estimated glomerular filtration rate 60–89 mL per min) or stage III (30–59 mL per min) chronic kidney disease were assessed separately. Tacrolimus seems to have a moderate but consistent nephrotoxic effect even in modern efficient immunosuppressive regimens where it is used at lower doses than in previous years.

In all these large trials, the incidence of acute rejection was significantly lower in the tacrolimus treated patients, compared to the cyclosporine-treated patients. Similarly there was a different profile of adverse effects with higher incidence of posttransplant diabetes mellitus and neurotoxicity under tacrolimus, compared to a higher incidence of hypertension, hyperlipidemia, hirsutism, and gum hyperplasia in cyclosporine treated patients.

According to three studies, the intrarenal hemodynamics are less affected by tacrolimus compared to cyclosporine, with better preservation of the renal plasma flow.[559,560,654]

The histopathologic changes, induced by tacrolimus, in the (transplanted) kidney are entirely comparable to those induced by cyclosporine (i.e., arteriolar hyalinosis and striped interstitial fibrosis).[580,655–658] The intrarenal expression of TGF-β, collagen, fibronectin, MMP-2, TIMP-1, and osteopontin was assessed by RT-PCR, and proved to be similar in kidneys treated with either tacrolimus or cyclosporine.[659]

A recent study in children with liver transplantation investigated the influence of genetic polymorphisms in ABCBA on the incidence of nephrotoxicity and tacrolimus dosage requirements in pediatric patients following liver transplantation.[660] Haplotype analysis showed a significant association between T-T-T haplotypes and an increased incidence of nephrotoxicity at 6 months posttransplantation (haplotype-frequency = 52.9% in nephrotoxic patients vs. 29.4% in controls; P = .029). Furthermore, G2677→T and C3435→T polymorphisms and T-T-T haplotypes were significantly correlated with higher tacrolimus dose-adjusted predose concentrations at various time points examined long after drug initiation. The findings suggest that ABCB1 polymorphisms in the native intestine significantly influence tacrolimus dosage requirement in the stable phase after transplantation. In addition, ABCB1 polymorphisms in pediatric liver transplant recipients may predispose them to nephrotoxicity over the first year posttransplantation. Genotyping future transplant recipients for ABCB1 polymorphisms (G2677→T and C3535→T), therefore, could have the potential to individualize better tacrolimus immunosuppressive therapy and enhance drug safety.

In conclusion, the nephrotoxicity of tacrolimus is functionally and morphologically comparable to the nephrotoxicity of cyclosporine as well in recipients of a renal allograft, as in recipients of a solid nonrenal organ. However, there is evidence that tacrolimus is a more powerful immunosuppressive agent, with a different toxicity profile.

CNI nephrotoxicity was recognized in Cambridge in the late 1970s. The vasoconstrictor impact of CsA, and to a lesser extent tacrolimus, in both acute and chronic settings, results from a decrease in vasodilators and increase in vasconconstrictors whereas direct tubular toxicity results from blockade of mitochondrial permeability transition pores and inhibition of prolyl isomerase. It is thus apparent that we must revisit the data and again question the basis for chronic CNI nephrotoxicity in current clinical practice. This contribution to the debate will focus on the evidence that CNIs are nephrotoxic and that their impact needs to be limited if we are to improve long-term outcomes after transplantation, leaving others to promote the contrary perspective and perhaps also to reflect on the largely unproven impact of the steroid avoidance and other minimization strategies so prevalent today.[661]

MYCOPHENOLATE MOFETIL

MMF, the morpholinoethyl ester of mycophenolic acid (Fig. 31.5), has been developed as an immunosuppressant for prevention of rejection in renal transplantation. In vivo, MMF is deesterified to mycophenolic acid (the active immunosuppressive component), which is a potent and specific inhibitor of the synthesis of guanosine nucleotides and thus a selective suppressor of proliferation of both T and B lymphocytes. MMF, given alone or with corticosteroids or cyclosporine, lowers the frequency of acute rejection after allogeneic organ transplantation in animals.[662,663]

The immunosuppression of MMF appears to be additive with that of cyclosporine and tacrolimus, and MMF does not promote nephrotoxicity.[664] Initial studies indicated that MMF, in combination with cyclosporine and steroids, reduces the incidence of acute rejection in renal transplantation.[665–667]

The Mycophenolate Steroids Sparing (MYSS) study found that in renal transplant recipients who were on immunosuppressive therapy with the cyclosporine microemulsion Neoral, MMF was not better than azathioprine in preventing acute rejection at 21 months after transplantation and was 15 times more expensive. The MYSS Follow-up Study, an extension of MYSS, was aimed at comparing long-term outcome of 248 MYSS patients according to their original randomization to MMF (1 g twice daily) or azathioprine (75 to 100 mg per d). In kidney transplantation, the long-term risk/benefit profile of MMF and azathioprine therapy in combination with cyclosporine Neoral is similar. In view of the cost, standard immunosuppression regimens for kidney transplantation should perhaps include azathioprine rather than MMF.[668]

In the meantime, MMF has been used under several clinical conditions. In cardiac, liver, lung, and pancreas transplantation the use of MMF in association with reduced doses of cyclosporine has resulted in improved renal function and maintained immunosuppression.[669–672] In renal transplantation, Halloran and others[673] summarize the three multicenter trials that confirm, at 1-year posttransplant, MMF is effective in preventing acute renal allograft rejection.[665–667] Two studies address patients with chronic kidney graft dysfunction in whom MMF is introduced and cyclosporine exposure reduced.[674,675] The rationale is that the increased immunosuppressive potency of MMF would allow for a safe reduction of CsA doses. The conclusion from these two studies is that cyclosporine dose reduction in patients on MMF results in an improved graft function with no increased risk of rejection. It must be noted, however, that follow-up was short—less than 1 year—in both studies. In addition, whether MMF does better than azathioprine (AZA) in this setting remains an open question. Indeed, a similar improvement of chronic graft dysfunction is reported when AZA is introduced and cyclosporine doses reduced.[676]

Is there a role for MMF in the attempt to withdraw calcineurin inhibtors in patients with stable renal transplantation? Several randomized,[677–679] as well as nonrandomized,[690] clinical trials in renal transplantation examined the efficacy and safety of calcineurin inhibitors in patients with stable graft function under triple immunosuppressive regimen, consisting of prednisolone, cyclosporine or tacrolimus, and MMF. All these studies reported a significant improvement of the graft function, as well as lower blood pressure, and an improved lipid profile after CNI withdrawal. In contrast, the incidence of acute rejection was higher in the CNI withdrawal group, without any impact on graft survival. Therefore, these studies provide evidence that CNI withdrawal is achievable in renal transplant recipients with stable graft function. CNI withdrawal appears to improve graft function,

hypertension, and hyperlipidemia. However, caution should be paid to the increased incidence of acute rejection after CNI withdrawal, and the short term of follow-up, reported in these studies (6 to 32 months).Whether CNI withdrawal will result in improved graft survival is not yet known.

Because MMF has multiple immunosuppressive and anti-inflammatory modes of actions—including the inhibition of humoral and cellular immunity, antimutagenesis, reduction of mononuclear cell infiltration, and inhibition of vascular smooth muscle and mesangial cell proliferation—it is not surprising that the drug is now used in autoimmune-mediated renal disease.[681] Briggs and colleagues[682,683] report their limited experience in eight patients with different types of nephrotic-type glomerulonephritis and unsatisfactory response to steroids and cyclosporine. Controlled prospective studies are under way to clarify the potential advantages of MMF compared with other immunosuppressive agents in these disease entities.

In conclusion, MMF is a potent, nonnephrotoxic immunosuppressive drug, which significantly reduced the incidence of acute rejection under tripple immunosuppressive regimens with prednisolone and cyclosporine or tacrolimus. In addition, MMF appears to allow dose reduction or even withdrawal of CNI in renal transplant recipients with stable graft function, thereby avoiding the long-term nephrotoxicity, induced by calcineurin inhibtors. Because immunosuppressant-induced nephrotoxicity has been associated with significant financial costs, cyclosporine-sparing and FK506-sparing regimens should result in substantial savings in health care costs (Fig. 31.5).[684] It is important to emphasize here that there are no long-term data for these experimental regimens, but they offer a new direction if these short-term results are confirmed over a more sufficient period of time.

RAPAMYCIN

Rapamycin (sirolimus/SRL) is a macrocyclic fermentation product of Streptomyces hygroscopicus, and was first isolated in 1975.[685] SRL has a similar molecular structure to FK506 and also binds to FKBP12.[686] However, the SRL-FKBP12 complex does not affect the calcineurin phosphatase, but instead binds to a protein, called the mammalian target of rapamycin (mTOR).[687] This binding of the SRL-FKBP12 complex to mTOR inhibits both DNA and protein synthesis, resulting in arrest of the cell cycle in late G1, as it progresses to the S phase.[688]

SRL blocks T-cell proliferation, induced by cytokines, alloantigens, and mitogens in a dose-dependent manner.[689] In addition, SRL acts on B-cells, causing an inhibition of antigen and cytokine driven B-cell proliferation.[690] In vitro studies have demonstrated the synergistic immunosuppressive interaction of CsA and SRL,[691] in contrast to the combination of FK506 and SRL, which produced an antagonistic effect at low doses.[692] Animal studies have confirmed the immunosuppressive potential of SRL,[693] as well as its synergistic interaction with CsA.[694] In contrast to the in vitro studies, FK506 interacted synergistically with SRL in animal studies.[695]

Treatment with CsA or FK alone significantly decreased KLOTHO expression and increased urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) excretion compared with vehicle treatment but sirolimus treatment did not. Treatment SRL+CsA or SRL+FK further decreased KLOTHO expression and increased urinary 8-OHdG excretion compared with treatment of CsA or FK alone. There was a strong correlation between KLOTHO expression and urinary 8-OHdG excretion ($r = -0.893$; $P < .001$). Treatment of CsA or FK alone increased renal ectopic calcification and serum intact parathyroid hormone level and decreased renal FGF23 expression compared with VH treatment ($P < .05$) but SRL treatment did not. Treatment with SRL+CNI aggravated these parameters compared with CNI alone. Sirolimus accelerates the calcineurin inhibitor-induced oxidative process by down-regulating the renal antioxidant KLOTHO expression in the kidney.[696]

Clinical Efficacy of Sirolimus in Renal Transplantation

Based on the results from several multicenter, prospective, randomized trials—including studies based in the United States, globally, a combined European-United States, and two in Europe—SRL was approved in 1999 by the U.S. Food and Drug Administration (FDA) for the prevention of acute rejection in renal transplant recipients. SRL was used in combination with CsA and prednisolone in these studies, and reduced the incidence of acute rejection at 1 year to 10%.[697]

Three prospective, randomized trials in renal transplant recipients compared CsA to SRL in combination with prednisolone and azathioprine or mycophenolate mofetil.[698–700] All these trials showed a comparable incidence of acute rejection in both treatment arms and, more importantly, a superior graft function at 1 year in the SRL-treated patients. In one study, graft function remained significantly better at 3 years in the SRL-treated patients.[701] In addition, the incidence of normal histology in protocol biopsies at 2 years was significantly higher in SRL-treated patients, compared to CsA-treated patients (66.6% vs. 20.8%).[701] These results from three trials provide evidence that avoidance of the long-term nephrotoxicity, induced by calcineurin inhibitors, is achievable in renal transplant recipients.

Several randomized trials in renal transplantation investigated the feasibility and the outcome of early calcineurin inhibitor withdrawal, in triple regimens with SRL and prednisolone.[702–705] Overall, patient and graft survival, as well as the incidence of acute rejection at 1 year, were comparable in both treatment arms (CsA+SRL+ P vs. SRL+P). In contrast, graft function was superior, and the incidence of hypertension was reduced in the patients weaned from CsA. Similarly, the incidence of chronic allograft nephropathy was significantly lower in protocol biopsies at 1 year from patients on SRL+P alone.[705] Again, these data provide strong

evidence that early witdrawal of calcineurin-inhibitors can safely be achieved in renal transplant recipients under SRL, and may avoid long-term nephrotoxicity.

In a recent study of Heilman and colleagues, it was concluded that conversion from tacrolimus-MMF to sirolimus-MMF at 1 month posttransplant in kidney recipients on rapid steroid withdrawal is poorly tolerated and does not improve GFR at 1 year.[706]

The use of SRL in organ transplantation is still a matter of debate as demonstrated by recent pro and contra back-to-back publications.[707] Sirolimus therapy is burdened by a concerning safety profile including high risk of delayed graft function and onset of proteinuria. In addition, several other side effects such as dyslipidemia, diabetes, myelosuppression, delayed wound-healing, infertility, ovarian cysts, and mouth ulcers further limit its use.[708]

A feature of increasing importance is that the mTOR pathway is central for vital aspects of tumor development, including angiogenesis and cell growth; rapamycin, therefore, has anticancer activities, which may prove critical in the fight against high cancer rates in transplant recipients.[707]

Large trials showed that SRL therapy is associated with an increased risk of acute rejections and worse graft function as compared with cyclosporine or tacrolimus.[709] Boosting memory T-cell response by mTOR inhibitor therapy might help induce long-lasting protective immune memory against bacterial or viral pathogens strong enough to prevent their replication,[710] especially in transplant recipients and other immunosuppressed patients with autoimmune disorders. Conversion to mTOR inhibitors may represent a valuable option in those cases with persistent infection resistant to antiviral therapy.[711,712]

A recent intriguing observation[713] adds to the interest of this molecule. Inoki et al. have shown that activity of mTOR complex 1 (mTORC1), a kinase that senses nutrient availability, was enhanced in the podocytes of diabetic animals. Further, podocyte-specific mTORC1 activation induced by ablation of an upstream negative regulator (PcKOTsc1) recapitulated many DN features, including podocyte loss, glomerular basement membrane thickening, mesangial expansion, and proteinuria in nondiabetic young and adult mice. Abnormal mTORC1 activation caused mislocalization of slit diaphragm proteins and induced an epithelial-mesenchymal transition-like phenotypic switch with enhanced ER stress in podocytes. Conversely, reduction of ER stress with a chemical chaperone significantly protected against both the podocyte phenotypic switch and podocyte loss in PcKOTsc1 mice. Finally, genetic reduction of podocyte-specific mTORC1 in diabetic animals suppressed the development of DN. These results indicate that mTORC1 activation in podocytes is a critical event in inducing DN and suggest that reduction of podocyte mTORC1 activity is a potential therapeutic strategy to prevent DN.

One may suggest that no renal transplant patient should receive de novo SRL therapy and that the use of SRL should be restricted to very selected patients, such as those with posttransplant malignancies or, probably, treatment-resistant viral infection. In such patients, the risk/benefit profile of SRL therapy should be carefully considered on a case-by-case basis. On the other hand, in subjects with stable kidney function and no evidence of treatment-related side effects, there is no reason to stop mTOR inhibitor therapy.

Nephrotoxicity of Sirolimus

Studies in pigs and rats have shown that sirolimus has no deleterious effects on GFR or renal blood flow, and caused minimal morphologic signs of toxicity.[714,715] Sirolimus reduced medullary concentrating ability and increased tubular enzymuria in rat kidneys, suggesting that mild tubular injury may occur.[716] In a salt-depleted rat model of CsA toxicity, the combination of CsA with SRL produced a functional and morphologic deterioration.[717]

In clinical studies in renal transplant recipients, sirolimus proved to be an effective immunosuppressive drug, devoid of intrinsic nephrotoxicity (see "Clinical Efficacy of Sirolimus in Renal Transplantation"). However, sirolimus may prolong delayed graft function in renal transplant recipients.[718] In addition, thrombotic microangiopathy has been described under the combination of sirolimus and tacrolimus, after intestinal transplantation.[719] Of concern are the reports on de novo proteinuria, occurring after conversion from a calcineurin inhibitor to sirolimus in renal transplant recipients.[720] Although the exact mechanism for the development of this proteinuria is currently putative, the increased intraglomerular pressure, resulting from the withdrawal of the intrarenal vasoconstriction, induced by CNIs, could be one reasonable explanation.

Recent evidence of a high incidence of proteinuria among de novo sirolimus-based regimens has been reported among renal transplant patients at short-term follow-up. Proteinuria has become a recognized, serious event (5 years incidence of 29%–38%) of primarily sirolimus-treated renal transplants patients, which is most probably of glomerular origin. It has been shown that proteinuria exerts a bad prognostic effect on graft function and subsequent graft survival at 5-year follow-up.[721]

The mechanisms underlying the development of proteinuria in renal transplant recipients converted from calcineurin inhibitors to sirolimus are still unknown. The data suggest that sirolimus-induced proteinuria in humans may be a dose-dependent effect of the drug on key podocyte structures.[722]

In a recent single center experience[723] and confirmed by many other observations, mTORi sirolimus and everolimus associated–pneumonitis is not a rare disease. Pneumonitis is not apparently dependent on the drug dose or the blood levels. Discontinuation of mTORi seems to be the safest treatment option to avoid pulmonary fibrosis or a fatal outcome.

New-onset diabetes after transplantation (NODAT) is a multifactorial, complex metabolic disorder associated with impaired long-term graft function, reduced recipient survival, and increased risks of cardiovascular disease and

infectious complications. Neither calcineurin inhibitor nor SRL or steroids seems to be innocent of contributing to it. Immunosuppressants account for 74% of the occurrence of NODAT. Among modifiable risk factors, obesity is independent and significant, with great prevalence in the population. In additional to lifestyle modifications, the role of bariatric surgery (BS) either before or after transplantation is highlighted herein as a strategy to reduce disease in the view of the results among overweight, nontransplanted patients.[724] Because of the strong association between high glucose values in the early posttransplant period and the development of NODAT, the condition must be recognized early after (or even before) transplantation by intensive screening. Patients at risk for NODAT must modify appropriate risk factors and particularly undergo pretransplant planning and/or posttransplant adjustment individualizing immunosuppressive therapy to mitigate the risk of this serious complication.

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