RISK FACTORS FOR AMINOGLYCOSIDE NEPHROTOXICITY

Patient-Related Factors	Aminoglycoside-Related Factors	Other Drugs
Older age*	Recent aminoglycoside therapy	Amphotericin B
Preexisting renal disease		Cephalosporins
Female gender	Larger doses*	Cisplatin
Magnesium, potassium, or calcium deficiency*	Treatment for 3 days or more*	Clindamycin
Intravascular volume depletion*		Cyclosporine
Hypotension*	Dose regimen*	Foscarnet
Hepatorenal syndrome		Furosemide
Sepsis syndrome		Piperacillin
		Radiocontrast agents
		Thyroid hormone

* Similar to experimental data.

FIGURE 11-8

Risk factors for aminoglycoside nephrotoxicity. Several risk factors have been identified and classified as patient related, aminoglycoside related, or related to concurrent administration of certain drugs.

The usual recommended aminoglycoside dose may be excessive for older patients because of decreased renal function and decreased regenerative capacity of a damaged kidney. Preexisting renal disease clearly can expose patients to inadvertent overdosing if careful dose adjustment is not performed. Hypomagnesemia, hypokalemia, and calcium deficiency may be predisposing risk factors for consequences of aminoglycoside-induced damage [13]. Liver disease is an important clinical risk factor for aminoglycoside nephrotoxicity, particularly in patients with cholestasis [13]. Acute or chronic endotoxemia amplifies the nephrotoxic potential of the aminoglycosides [14].

PREVENTION OF AMINOGLYCOSIDE NEPHROTOXICITY

- Identify risk factor
  - Patient related
  - Drug related
  - Other drugs
- Give single daily dose of gentamicin, netilmicin, or amikacin
- Reduce the treatment course as much as possible
- Avoid giving nephrotoxic drugs concurrently
- Make interval between aminoglycoside courses as long as possible
- Calculate glomerular filtration rate out of serum creatinine concentration

FIGURE 11-9

Prevention of aminoglycoside nephrotoxicity. Coadministration of other potentially nephrotoxic drugs enhances or accelerates the nephrotoxicity of aminoglycosides. Comprehension of the pharmacokinetics and renal cell biologic effects of aminoglycosides, allows identification of aminoglycoside-related nephrotoxicity risk factors and makes possible secondary prevention of this important clinical nephrotoxicity.

Amphotericin B

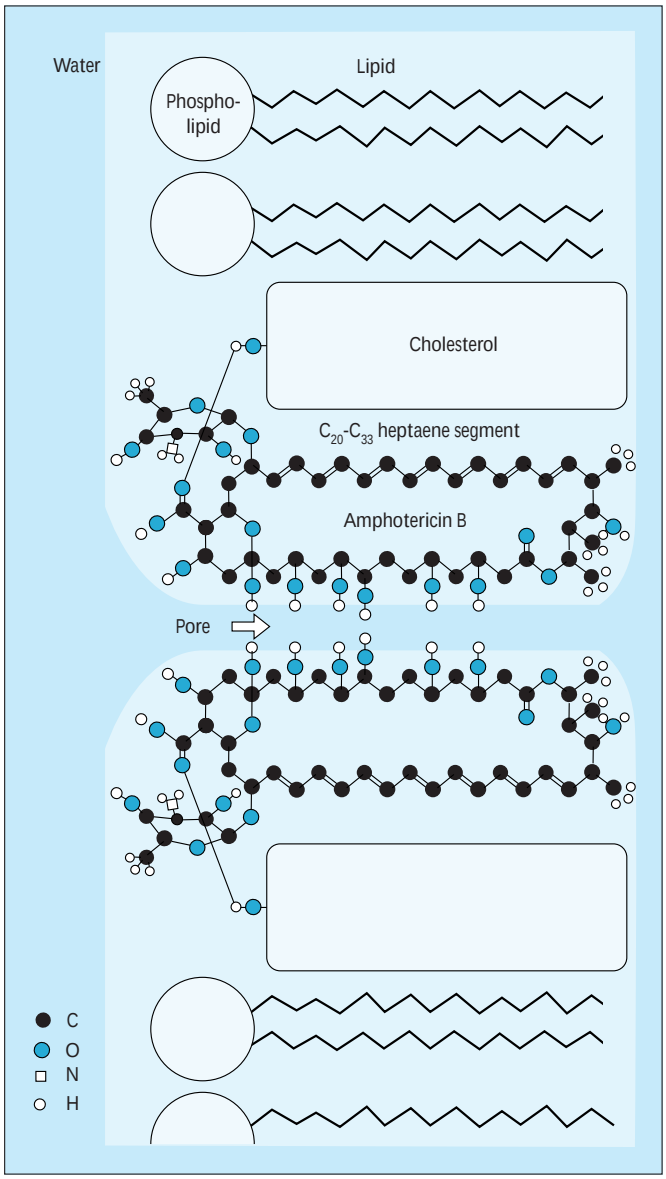

FIGURE 11-10

Proposed partial model for the amphotericin B (AmB)–induced pore in the cell membrane. AmB is an amphipathic molecule: its structure enhances the drug's binding to sterols in the cell membranes and induces formation of aqueous pores that result in weakening of barrier function and loss of protons and cations from the cell. The drug acts as a counterfeit phospholipid, with the C_{15} hydroxyl, C_{16} carboxyl, and C_{19} mycosamine groups situated at the membrane-water interface, and the C_1 to C_{14} and C_{20} to C_{33} chains aligned in parallel within the membrane. The heptaene chain seeks a hydrophobic environment, and the hydroxyl groups seek a hydrophilic environment. Thus, a cylindrical pore is formed, the inner wall of which consists of the hydroxyl-substituted carbon chains of the AmB molecules and the outer wall of which is formed by the heptaene chains of the molecules and by sterol nuclei [15].

RISK FACTORS IN THE DEVELOPMENT OF AMPHOTERICIN NEPHROTOXICITY

Age
Concurrent use of diuretics
Abnormal baseline renal function
Larger daily doses
Hypokalemia
Hypomagnesemia
Other nephrotoxic drugs (aminoglycosides, cyclosporine)

FIGURE 11-11

Risk factors for development of amphotericin B (AmB) nephrotoxicity. Nephrotoxicity of AmB is a major problem associated with clinical use of this important drug. Disturbances in both glomerular and tubule function are well described. The nephrotoxic effect of AmB is initially a distal tubule phenomenon, characterized by a loss of urine concentration, distal renal tubule acidosis, and wasting of potassium and magnesium, but it also causes renal vasoconstriction leading to renal ischemia. Initially, the drug binds to membrane sterols in the renal vasculature and epithelial cells, altering its membrane permeability. AmB-induced vasoconstriction and ischemia to very vulnerable sections of the nephron, such as medullary thick ascending limb, enhance the cell death produced by direct toxic action of AmB on those cells. This explains the salutary effect on AmB nephrotoxicity of salt loading, furosemide, theophylline, or calcium channel blockers, all of which improve renal blood flow or inhibit transport in the medullary thick ascending limb.

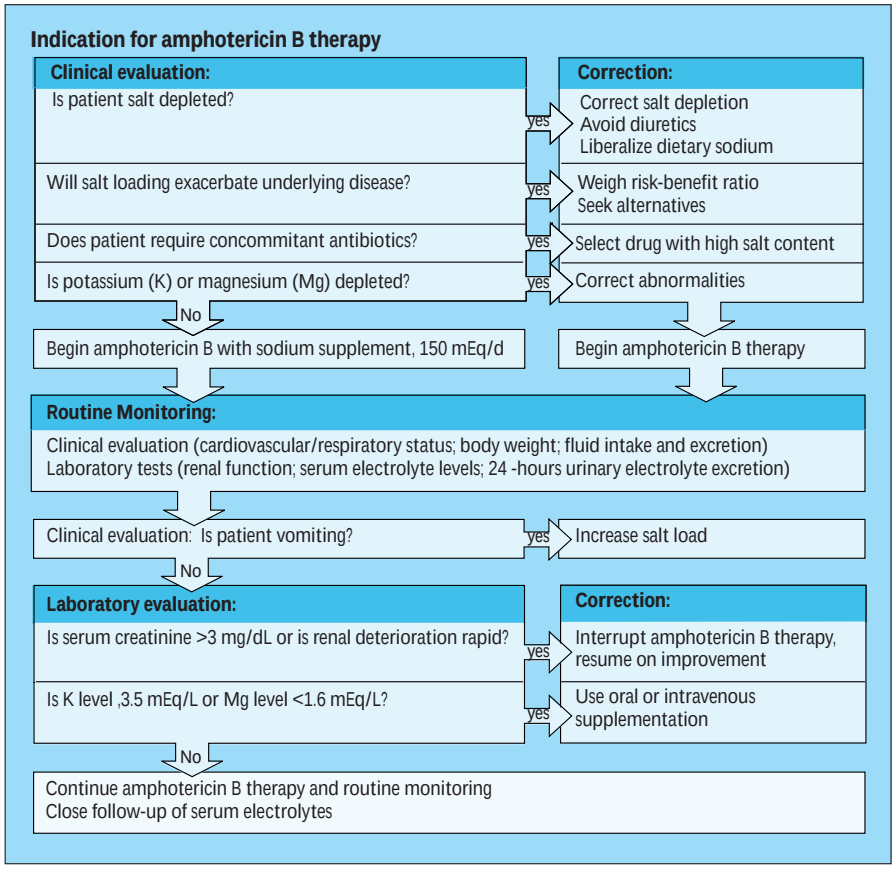

FIGURE 11-12

Proposed approach for management of amphotericin B (AmB) therapy. Several new formulations of amphotericin have been developed either by incorporating amphotericin into liposomes or by forming complexes to phospholipid. In early studies, nephrotoxicity was reduced, allowing an increase of the cumulative dose. Few studies have established a therapeutic index between antifungal and nephrotoxic effects of amphotericin. To date, the only clinically proven intervention that reduces the incidence and severity of nephrotoxicity is salt supplementation, which should probably be given prophylactically to all patients who can tolerate it. (*From* Bernardo JF, *et al.* [16]; with permission.)