Amphotericin B: 30 Years of Clinical Experience

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Amphotericin B, the first commercially significant antifungal drug, has been available for more than 30 years. This polyene macrolide antifungal agent continues to play a major role in the treatment of systemic fungal infections, despite the introduction of newer agents such as the azoles. Given the proved efficacy of amphotericin B—and the increasing number of indications for antifungal agents—an extensive review of this drug is warranted. This paper discusses the clinical uses of amphotericin B, including its application in AIDS-related fungal infections, in neutropenic cancer patients who are persistently febrile, and in infections of the central nervous system, lung, peritoneum, genitourinary system, eye, and skin. The paper also reviews the drug's adverse reactions, with a discussion of administration techniques that may reduce these reactions, and its spectrum of activity, pharmacokinetics, and dosage and administration.

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I. Introduction

For 30 years, amphotericin B has played a major role in the management of systemic fungal infections. Despite the introduction and investigation of azoles for the treatment of such infections (recently reviewed by Saag and Dismukes [1]), amphotericin B's widespread use continues to grow in many institutions [2], resulting in an extensive body of data regarding its safety and efficacy. Amphotericin B remains the treatment of choice for many conditions [3–6, 7]. In addition, more recent investigations have examined this drug's safety and effectiveness as local therapy for the treatment of fungal cystitis [8–19], peritonitis [20–23], dermatoses [24, 25], and intraocular infections [26–30], among others. This article reviews the pharmacology, pharmacokinetics, and clinical applications of amphotericin B, with emphasis on the more recent advances that have been made in defining its optimal administration.

II. Chemistry, Mechanism, and Spectrum of Antifungal Activity

Amphotericins A and B are isolated as byproducts resulting from the fermentation process of Streptomyces nodosus, a soil actinomycete. According to historical accounts by Dutcher, they were first isolated at Squibb Laboratories in 1953, with the ini-
tial reports of antifungal activity published in 1956 [31]. The commercially available preparation of amphotericin B for intravenous administration (Fungizone Intravenous) is marketed in 50-mg vials and may contain a small amount (not more than 5%) of amphotericin A and other minor impurities [32, 33]. Amphotericin B is amphoteric, forming soluble salts in both acidic and basic environments. It is not soluble in water and is solubilized by the addition of sodium deoxycholate, which, when combined with amphotericin B, forms a colloidal dispersion [32, 33].

Amphotericin B is a member of the polyene macrolide class of antibiotics. Other drugs in this class are currently available in the United States and include nystatin and natamycin. Natamycin is available only for ophthalmic use. The antifungal activity of amphotericin B may be fungistatic or fungicidal (depending on drug concentration and sensitivity of the organism) [4, 6] and is influenced in vitro by pH, with optimal activity between pH 6.0 and 7.5 [34]. Its mechanism of action is due at least in part to its binding to a sterol (ergosterol) present in the membrane of sensitive fungi [32, 33, 35]. The polyenes alter membrane permeability, causing leakage of cell components, with subsequent cell death. In addition to this antifungal activity, amphotericin B may stimulate cell proliferation and has potent cell-mediated immunostimulant effects in mice [36, 37]. However, activation or depression of lymphocyte and macrophage function may depend on the dose and timing of administration [38]. The clinical significance of such effects is not yet known.

Kucers and Bennett have published an extensive review of the in vitro activity of amphotericin B [4]. In brief, this compound has demonstrated activity against a wide variety of fungal species, including Torulopsis glabrata, Blastomyces dermatitidis, Cocciidoides immitis, Cryptococcus neoformans, Paracoccidioides brasiliensis, Histoplasma capsulatum, and Sporothrix species [4, 33, 34, 39]. While Candida albicans is generally quite sensitive, non-albicans species of Candida may be less susceptible [40]. Variable activity is demonstrated against Aspergillus species and Mucorales, whereas Actinomycetes species and those organisms known to cause chromoblastomycosis are generally considered resistant [4]. Pseudallescheria boydii may often be resistant, and infections due to P. boydii are best treated with alternative antifungal agents [25]. Data are also reviewed by Kucers and Bennett that suggest in vitro activity against Prototheca species, Naegleria, Leishmania, and both chloroquine-sensitive and -resistant Plasmodium falciparum parasites [4]. Amphotericin B has no significant activity against bacteria, rickettsiae, or viruses [4]. All in vitro data must be interpreted with caution, however, due to a lack of standards for measuring fungal susceptibility [41] and a lack of correlations established with clinical outcomes.

Although acquired resistance of C. albicans and C. immitis has been demonstrated in the laboratory [42], it is considered unusual during clinical use [4, 43]. Tolerance was demonstrated by Seidenfeld et al. with Candida parapsilosis [44].

Results of in vitro and animal studies examining the combination of amphotericin B with imidazoles (such as ketoconazole, miconazole, or clotrimazole) are conflicting. Although the combination of amphotericin B and ketoconazole has been reported to be synergistic against most Candida species and C. neoformans [45], other studies suggest that prior exposure of fungal strains (e.g., Candida and Aspergillus species) to imidazoles increases the minimal fungicidal activity of amphotericin B against these strains [46-49]. It has been postulated that imidazoles, by way of their inhibitory effect on ergosterol synthesis, might deprive amphotericin B of its binding site on the fungal cell membrane [50, 51].

Recently, Schaffner and Frick [49] showed that prior exposure of neutropenic mice to ketoconazole abolished the protective effect of subsequent amphotericin B against experimental aspergillosis. In a single case report [52], amphotericin B resistance developed in a strain of Candida guilliermondii during treatment with miconazole. The pathogen thus developed resistance in the absence of exposure to amphotericin B. The potential for interaction in humans and its clinical significance is unknown. Wilson and Peacock [50] have advised caution in the widespread use of imidazoles for fungal disease in immunocompromised patients until further studies have proven that the potential role of imidazoles in the induction of resistance to amphotericin B is not a clinically relevant problem.

Limited studies in animal models and selected in vitro data suggest that both rifampin [53] and tetracycline [54] have demonstrated synergy with amphotericin B against selected organisms. Data also exist that suggest synergistic activity of amphotericin B with flucytosine against Candida species and a proportion of isolates of C. neoformans [55].
Stamm and Dismukes propose that such synergy with rifampin or flucytosine may be useful in resistant cases of aspergillosis [3]. The clinical significance of these findings, however, has yet to be determined. These in vitro results can be conflicting and depend on the design of the test used to measure synergy. With the exception of the trial published by Bennett et al. demonstrating the superiority of combined amphotericin B and flucytosine therapy for cryptococcal meningitis when compared with amphotericin B alone [56], no controlled trials are available to demonstrate the superiority of combination therapy. Medoff and Kobayashi recommend caution when attempting to extrapolate in vitro results to clinical use [57].

### Table 1. Pharmacokinetics of amphotericin B.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Oral</td>
<td>Poor</td>
</tr>
<tr>
<td>Intramuscular</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td></td>
</tr>
<tr>
<td>Initial phase</td>
<td>24-48 h</td>
</tr>
<tr>
<td>Terminal phase</td>
<td>15 d</td>
</tr>
<tr>
<td>Apparent volume of distribution</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
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</tr>
<tr>
<td>Central compartment</td>
<td>0.44 L/kg</td>
</tr>
<tr>
<td>Fast compartment</td>
<td>0.35 L/kg</td>
</tr>
<tr>
<td>Slow compartment</td>
<td>3.20 L/kg</td>
</tr>
<tr>
<td>Urinary recovery at 24 hours</td>
<td>3%</td>
</tr>
<tr>
<td>Binding to β-lipoproteins</td>
<td>91%-95%</td>
</tr>
</tbody>
</table>

### III. Pharmacokinetics

An excellent review of the data on antifungal pharmacokinetics has been prepared by Daneshmend and Warnock [34]. To summarize, amphotericin B is poorly absorbed following oral administration. Louria reported serum levels ranging from 0.04 µg/mL to 0.5 µg/mL following administration of daily doses of 1.6–5 g/d for 2 days to 13 adult patients [58] (table 1). This was consistent with the findings of Hofstra et al., who found that doses of 1.5–2 g/d were required in healthy volunteers to obtain detectable serum levels [59]. However, Ching et al. reported up to 9% of an oral dose absorbed in cancer patients receiving a 10-mg lozenge three to four times per day [60]. Absorption was thought to be due in part to the influence of mucosal irritation. Because of its irritant effect and poor absorption following intramuscular administration, this route of administration is not recommended.

Serum levels following intravenous administration of amphotericin B may be related to dose, frequency, and rate of infusion. Fields and colleagues reported mean serum concentrations of 1.2, 0.62, and 0.32 µg/mL at 1, 18, and 42 hours after the intravenous administration of a 50-mg dose to 20 subjects [61]. Peak levels were noted during the first hour after a 4- to 6-hour infusion; these levels persisted for 6–8 hours. Bindschadler and Bennett reported serum levels of 0.14–2.39 µg/mL 4 hours after administration of 5–70 mg, but alternate-day doses of 25–105 mg resulted in serum concentrations of 1.0–2.4 µg/mL [62]. Minimum serum concentrations were not influenced by administration of twice the daily dose on alternate days [62]. A dose proportionality was demonstrated between daily administration of 5–50 mg, but doses exceeding 50 mg exhibited a plateau effect in serum concentrations. Powderly et al. confirmed a relationship of the dose to serum level [63]. These investigators reported peak (1 hour after infusion) levels of $1.2 \pm 0.33 \mu g/mL$ and $2.4 \pm 0.97 \mu g/mL$ and trough (23 hours after infusion) levels of $0.5 \pm 0.27 \mu g/mL$ and $1.1 \pm 0.54 \mu g/mL$ after more than 3 days of 0.5 mg/kg and 1.0 mg/kg, respectively. Rapid (45-minute) infusion times may increase the mean serum concentration 1 hour after completion of the infusion, but concentrations did not differ at 18 and 42 hours postinfusion [64].

Distribution of amphotericin B is thought to follow a three-compartment model [65], with an apparent volume of distribution of 4 L/kg. On the basis of data from animal models, distribution into tissues includes liver, spleen, lungs, kidney, muscle, skin, and adrenal glands [66–68]. Christiansen et al. reported data obtained at autopsy from eight patients receiving doses ranging from 101 to 2,688 mg [59], and Collette and colleagues obtained postmortem samples from 13 patients receiving total doses of 75–1,110 mg [70]. Concentrations were highest in lung and spleen, with high concentrations also detected in kidney and lung tissues. The high degree of protein binding (91%–95%) [71, 72], primarily to lipoproteins, erythrocytes, and cholesterol, may account for the low concentrations found in these body tissues and fluids. Furthermore, the limited tissue penetration may account for the fact that fungicidal titers of amphotericin B were rarely observed in tissues of patients [70]. Uremic patients, however, may have a higher percentage of unbound drug (4.15%...
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Polack [73] concluded, on the basis of animal and human data, that the peritoneal, pleural, and synovial fluids usually contain less than half of the simultaneous serum concentration. Penetration into bronchial secretions is also poor [74]. Poor peritoneal penetration after intravenous administration was confirmed by Kerr et al. [23]. CSF concentrations are thought to be approximately 2%-4% of simultaneous serum concentrations after intravenous administration to adult patients [75] but were undetectable in some studies [62, 76, 77]. Animal model data, however, suggest that meningeal levels may be higher than CSF levels [78]. Biliary concentrations may be high [34]. Amphotericin B is thought to cross the placental barrier, with cord blood and amniotic fluid levels reported by Ismail and Lerner on the basis of one case [79] to be less than that of maternal blood levels.

The metabolism of amphotericin B is poorly understood because no metabolites have been identified [34, 69]. Only a small amount (3%) is generally detected in the urine after 24 hours [65], with less than half of the dose accounted for by biliary and renal clearance [68]. Sixteen to sixty percent of the total dose has been recovered at autopsy [69].

A biphasic elimination from serum was reported by Atkinson and Bennett, with a comparatively rapid initial serum half-life of 24-48 hours, followed by a terminal half-life of up to 15 days [65]. The total body clearance reported by Atkinson and Bennett averaged 30 mL/min. Detectable levels have been reported in bile for up to 12 days and in urine for 27-35 days after administration [67]. Collette et al. believed that biliary elimination may account for 0.8%-14% of the excretion of the daily dose administered as the deoxycholate salt [70].

No accumulation of amphotericin B was demonstrated in six patients receiving repeated daily administrations over 1-3 weeks [63]. Bindschadler and Bennett also failed to demonstrate accumulation despite therapy of up to 3 months [62]. However, repeated administration is thought to increase the half-life in the CSF [80].

Blood levels are not influenced by hepatic or renal failure [34, 65]. Morgan et al. reported on seven patients with creatinine clearances ranging from zero to normal [72]. The total clearance ranged from 16.7 mL/min to 39.9 mL/min, correlating with plasma creatinine and inversely with clearance. However, steady-state plasma clearance of unbound drug was not altered by renal impairment. Powderly et al. reported similar levels in five patients with serum creatinine values >1.5 mg/100 mL when compared with patients with normal renal function [63]. Bindschadler and Bennett, however, noted a positive correlation of serum peak levels of amphotericin B to serum creatinine [62]. Biliary obstruction resulted in increases of mean serum amphotericin B concentrations of approximately 20% in dogs [81]. However, no differences in serum levels were reported in four patients with serum bilirubin values >3.5 mg/100 mL [63]. Hemodialysis does not generally reduce blood levels [71]. Block et al. studied four patients requiring hemodialysis while receiving amphotericin B and reported amphotericin B clearance of 3%-5% of the simultaneous creatinine clearance [71].

The pharmacokinetic profile of amphotericin B in children is poorly defined. Starke et al. have recently reported data for five children less than 3 months of age who were receiving doses of 1 mg/kg [82]. Mean peak (30-45 minutes after infusion) and trough levels were 0.96 µg/mL (range, 0.31-2.08 µg/mL) and 0.28 µg/mL (range, 0.47-0.66 µg/mL), respectively, after administration of 0.25 to 1.0 mg/kg. In the same report, five children 7.5 months to 15 years of age received a dose of 0.75 mg/kg. Mean peak (30-45 minutes after infusion) and trough levels were 0.52 µg/mL (range, 0.47-0.66 µg/mL) and 0.09 µg/mL (range, 0.03-0.11 µg/mL), respectively. No differences in serum levels were noted by Ward et al. in one premature infant [83]. Baley et al. reported data on 13 neonates (mean birthweight, 1.1 ± 0.8 kg, gestational age 27 ± 5 weeks) [84]. Ten infants were given increasing doses of 0.1-0.5 mg/[kg·d], whereas three were given 0.8-1 mg/[kg·d]. Four of 13 showed drug accumulation at steady state. The serum half-life was 25.5 ± 25.5 hours; volume of distribution, 4.7 ± 6.1 L/kg; plasma clearance, 26.3 ± 20 mL/min; and peak serum concentration of 0.5-4 µg/mL. They concluded that initial doses should be at least 0.5 mg/[kg·d], with an interval of at least 24 hours, obtaining serum levels that avoid accumulation.

IV. Clinical Uses

Extensive reviews of the clinical uses of amphotericin B have recently been published [3, 4, 6, 85].
A. CNS Infections

Salaki et al. have recently published a review of fungal and yeast infections of the CNS [86]. The authors state that "amphotericin B is still the most effective antifungal agent available in the treatment of CNS fungal and yeast infections." It is not known at this time whether azole agents with penetration into the CNS (such as fluconazole) may offer an alternative therapy for acute CNS fungal infections.

Cryptococcal meningitis is the most common form of fungal meningitis in the United States and is a significant cause of morbidity and mortality among immunocompromised patients [86, 87]. The treatment of cryptococcal CNS infections generally consists of the administration of amphotericin B with or without flucytosine [86, 87]. Surgical intervention may also be required to drain abscesses.

A recent and successful approach to the treatment of cryptococcal meningitis is the combined use of amphotericin B in reduced dosage (0.3 mg/[kg·d]) with flucytosine (150 mg/[kg·d]), administered in divided doses every 6 hours. In a collaborative, multicenter study of 50 patients with cryptococcal meningitis, Bennett et al. [56] compared the intravenous administration of amphotericin B alone (0.4 mg/[kg·d] increased to 0.8 mg/[kg·d]) for 8 weeks vs. amphotericin B (0.3 mg/[kg·d]) combined with oral flucytosine (150 mg/[kg·d]) for 6 weeks. The authors concluded that the combination therapy was the regimen of choice. Although given for a shorter period, the combination cured or improved more patients (16 of 24 vs. 11 of 27) and produced fewer failures or relapses, more rapid sterilization of the CSF, and a reduced frequency of nephrotoxicity. The difference in efficacy rates, however, was not statistically significant. Mortality rates for the two treatments were similar.

More recently, Dismukes et al. [87] compared 4 and 6 weeks' therapy with the combined regimen in 194 patients with cryptococcal meningitis. Multifactorial analysis of pretreatment factors suggested that the 4-week regimen should be reserved for patients who have meningitis without neurologic complications, underlying disease, or immunosuppressive therapy; a pretreatment CSF leukocyte count >20/mm³; a serum cryptococcal antigen titer <1:32; and at 4 weeks of therapy, a negative CSF India ink preparation and serum and CSF cryptococcal antigen titers <1:8. Other patients not meeting these criteria should receive at least 6 weeks of therapy. Patients with cryptococcal meningitis whose infection is severe or unresponsive to treatment, even with high-dose intravenous amphotericin B, usually require additional treatment with intrathecal or intraventricular amphotericin B.

Several investigators have had good results treating patients who were severely ill with cryptococcal meningitis with intraventricular amphotericin B delivered via a subcutaneous reservoir [88, 89]. Polsky et al. recently reported retrospective data in non-AIDS patients receiving intravenous amphotericin B with (n = 6) or without (n = 7) intraventricular administration [88]. One death was reported with combination therapy as compared with six deaths in those treated with intravenous therapy alone. This method of administration, however, is generally reserved for severely ill patients. In addition to initial therapy, prophylactic administration of low doses of amphotericin B (i.e., 100 mg weekly) may be required to prevent relapse in patients with AIDS [90].

Intravenous amphotericin B, in combination with intrathecal administration, may be required for severe, life-threatening coccidoidal CNS infections [3]. The total duration of therapy depends on such factors as a decrease in CSF white blood cell count, protein level, and complement-fixing antibody titer; an increase in CSF glucose concentration; and CSF culture negativity. The drug may need to be given for several years before the possibility of a cure can be considered [91]. Labadie and Hamilton [92] found that treatment with high intrathecal doses of amphotericin B (up to 1.5 mg/dose), in combination with intrathecal hydrocortisone, resulted in a 91% survival rate during a 75-month follow-up of all patients.

Although experience with candidal meningitis is limited, intravenous amphotericin B, alone or in combination with oral flucytosine, is currently the treatment of choice. Again, intrathecal administration of amphotericin B may be necessary in severe cases [93].

Intravenous amphotericin B is the only drug shown to be probably beneficial in treating the rare cases of CNS infections caused by B. dermatitidis, Sporothrix schenckii, and Aspergillus species [86]. Histoplasma meningitis has been treated successfully with intravenous amphotericin B, and most investigators think that intrathecal therapy is not usually needed [86]. Intravenous amphotericin B is the only potentially effective treatment for cerebral zygomycosis [94].

In summary, for fungal CNS infections, intrave-
nous amphotericin B at usual doses with or without intrathecal administration appears to be the drug therapy of choice [86]. A low-dose regimen combined with oral flucytosine is specifically recommended for cryptococcal infections in non-AIDS patients [87]. Intrathecal administration of amphotericin B (up to 0.5 mg dissolved in CSF and injected one to three times weekly into lumbar, cisternal, or ventricular CSF) is necessary for patients with coccidioidal infection or recalcitrant cryptococcal infection [86]. Intrathecal doses as high as 1.5 mg may be necessary [86].

B. Peritonitis

Amphotericin B has become the drug therapy of choice for the treatment of fungal peritonitis. Such use, however, has been based largely on clinical experience rather than on controlled studies. Numerous case reports have appeared in the literature, and two recent reviews by Eisenberg et al. [20] and Hartman [21] summarize these reports.

Hartman classified fungal peritonitis into two principal types: dialysis-related and non-dialysis-related (usually resulting from visceral perforation) [21]. Most cases of fungal peritonitis are caused by *C. albicans* and, less commonly, by other *Candida* species as well as by *Aspergillus* and other rare fungi and yeasts.

Hartman evaluated retrospectively a total of 56 long-term dialysis patients with fungal peritonitis. The catheter was removed or retained in 39 and 17 patients, respectively, and the corresponding cure rates were 92% and 65%. About 60% of the patients received some form of antifungal therapy, and the majority of these received intravenous or intraperitoneal amphotericin B. For optimal treatment of fungal peritonitis, early removal of the catheter is suggested, together with low-dose amphotericin B (a total dose of 2–10 mg/kg given over 7–14 days) [20–23]. If required, interim hemodialysis can substitute for peritoneal dialysis. Alternatively, if hemodialysis is contraindicated, the peritoneal catheter can be changed and a cure attempted with intraperitoneal amphotericin B (1–2 mg/L of peritoneal dialysis fluid up to a total dose of 1,500 mg) either with or without low-dose intravenous amphotericin B (a total dose of 2–10 mg/kg given over 7–14 days) [20, 21]. If the patient is not severely ill, the same procedure can be adopted without removing or changing the peritoneal catheter, although the catheter should be removed if the peritoneal dialysate remains cloudy or the patient worsens over 5–7 days. Hartman states, “Currently, amphotericin B should be the drug of choice until additional studies show that other agents are equally effective” [21].

Hartman also reviewed the results of 67 non-dialysis patients with fungal peritonitis; 17 received systemic antifungal therapy (intravenous amphotericin B in all but one patient), and 50 received no therapy [21]. Death rates were 59% and 64%, respectively. However, the groups may not have been directly comparable, and it appeared that intravenous amphotericin B was particularly beneficial if the patient had not yet developed fungemia or renal failure (survival rates were 83% and 58%, respectively, in these subgroups). Thus, in peritonitis associated with visceral perforation, the recommended therapy is surgical correction, peritoneal lavage, and broad-spectrum antibacterial therapy. If gram stain or culture demonstrates fungi and the patient is not doing as well as expected, early low-dose intravenous amphotericin B should be instituted, particularly if the patient has not yet developed fungemia or renal failure. Higher dosages of amphotericin B should be started immediately if the infection persists or disseminates. Of note is the general finding that intraperitoneal or low-dose intravenous amphotericin B is not associated with significant systemic toxicity [21].

Eisenberg et al. retrospectively evaluated just under 100 patients with peritoneal dialysis-related fungal peritonitis [20]. Their conclusions were far less definitive than those of Hartman, but they do state, “The most commonly made serious error in caring for these patients is the failure to institute appropriate therapy quickly enough on the basis of these diagnostic parameters.” The parameters include hospitalization, recent prior episodes of peritonitis, antibacterial therapy, and differentiation from bacterial peritonitis by gram stain and culture of dialysate. However, the investigators do state that the choice of antifungal therapy, route of administration, and duration of treatment are controversial. While amphotericin B has been a standard therapy for deep-seated mycoses in a variety of clinical settings, results in fungal peritonitis have been less clear. Intravenous therapy alone without catheter removal, however, is likely to have a high failure rate [20]. Eisenberg et al. also concluded that intraperitoneal administration was associated with a higher likelihood of peritoneal fibrosis and pain than other interventions. Reported experience with other antifun-
al agents, such as flucytosine and the imidazoles, is too limited to be analyzed rigorously.

There have been encouraging recent reports on the intraperitoneal treatment of candidal peritonitis in patients with indwelling peritoneal catheters for use in chronic ambulatory peritoneal dialysis. Struijk et al. [22] found that intraperitoneal amphotericin B (1.5–2 mg/L of peritoneal dialysis fluid) plus flucytosine (50–100 mg/L of peritoneal dialysis fluid) for 16–28 days was effective in six of nine episodes of candidal peritonitis without removal of the catheter. Despite descriptions of addition of amphotericin B to peritoneal fluid, there are currently no published reports regarding the stability of this mixture. Analysis of data obtained from a study by these authors and others at Duke University Medical Center reveals acceptable stability (<10% decline in initial amphotericin B concentrations) 4 hours after addition to buffered and nonbuffered commercially available peritoneal fluids.

In summary, early institution of antifungal treatment appears to be necessary in patients with fungal peritonitis. The absence of any prospective, controlled experience with amphotericin B alone or in combination with other antifungal agents suggests that intraperitoneal amphotericin B with or without intravenous therapy as an alternative to 5-flucytosine administration represents a therapeutic alternative in the management of these patients.

C. Genitourinary Infections

Current reviews on the treatment of candidal cystitis often recommend amphotericin B continuous bladder irrigation as initial therapy if clinical evidence of systemic candidiasis is lacking and if radiographs reveal no evidence of pyelonephritis, papillary necrosis, or ureteral obstruction [8–10].

The first effective technique used to treat candidal cystitis was intermittent amphotericin B bladder instillation [11]. Subsequent reports have confirmed the effectiveness of this technique [12, 13] and, although no comparison has been made with continuous irrigation, both techniques appear to have similar effectiveness [10]. Additionally, while continuous irrigation solutions of amphotericin B, 50–75 mg/L in 5% dextrose, have effectively treated candidal cystitis [14, 15], the use of this diluent should be discouraged since 5% dextrose may promote fungal and bacterial growth [16]. We therefore recommend that sterile water for irrigation be used as the vehicle.

Several studies have provided detailed results on amphotericin B continuous bladder irrigation in hospitalized patients with indwelling urethral catheters and persistent candiduria. In two studies, amphotericin B, 50 mg in 1,000 mL of sterile water, was instilled over 24 hours via a three-way catheter. In the first study [17], 10 patients were treated continuously for 5 days; eradication was achieved in seven of these patients (70%). In a second study [18], 40 patients were treated continuously for 5–10 days, and eradication was achieved in 37 patients (92.5%). In five of the six cases of treatment failure, there was evidence of disseminated infection that required systemic therapy. It is unclear whether the higher response rate in the second study resulted from the longer treatment duration. There were no adverse effects or any evidence of significant systemic absorption of amphotericin B from the bladder. A placebo control group was not included [18], because a higher mortality rate has been noted in patients with candiduria who were not given antifungal treatment [19]. Consideration should also be given to relapse rates, since Wise et al. reported that approximately 40% of patients having fungal cultures after amphotericin B bladder irrigation were recolonized [18].

Thus, in patients with persistent candiduria, continuous irrigation via a three-way catheter with amphotericin B, 50 mg in 1,000 mL of sterile water/d for 5–10 days, is recommended in those patients who are either at risk of dissemination or for whom the catheter cannot be removed. Irrigation is recommended over intermittent instillation because of the solution’s increased contact time with the bladder and also because there exists more extensive documentation of efficacy [18]. Irrigation should be continued until urine cultures are negative. Low-dose amphotericin B (i.e., 0.3 mg/kg) given intravenously over 4 hours as a single dose was reported in four patients by Fisher et al. for fungal infections caused by Candida species [95]. Three patients responded, with follow-up ranging from 10 days to 11 months. Amphotericin B was detected in the urine for up to 5 days in three patients.

Continuous irrigation with amphotericin B is preferred to oral flucytosine monotherapy because of flucytosine’s potential for toxicity and for development of resistance. Reports of flucytosine monotherapy have generally been limited to treating lower urinary tract candidal infections and to combination therapy with amphotericin B [6]. No comparison of eradication rates has been made between these
In the past 5 years, both well-controlled prospective clinical trials and uncontrolled, retrospective studies have examined the value of empiric intravenous amphotericin B therapy in cancer patients with fever and granulocytopenia. As the term suggests, therapy with amphotericin B is begun without confirmation (e.g., positive fungal culture) of an active fungal infection. Stein and colleagues [98] argued that the empiric use of amphotericin B should be evaluated on the basis of the following observations: (1) prolonged neutropenia and broad-spectrum antibiotics predispose leukemic patients to fungal infections; (2) delayed institution of amphotericin B therapy is associated with an increased frequency of fatal outcome in patients with fungal pneumonia; (3) fungal infections, in particular aspergillus pneumonia, are becoming more frequent in patients with acute myelogenous leukemia; and (4) no reliable tests are available to identify febrile leukemic patients not responding to antibiotics from whom amphotericin B can safely be withheld [40].

A number of investigators [99-103] have concluded that empiric therapy with amphotericin B is of significant benefit in managing patients with acute myelogenous leukemia. In general, intravenous amphotericin B was added to the antimicrobial regimen 5-7 days after combination antibiotic therapy had failed to improve fever and granulocytopenia. Empiric antifungal therapy is sometimes continued in these patients until recovery of granulocytes occurs, often in the face of negative fungal cultures. retrospective, uncontrolled data also suggest that continued antibiotic therapy reduces bacterial infections and that empiric antifungal therapy is necessary to prevent fungal superinfections and to control clinically undetected fungal invasion [101]. Therefore, amphotericin B therapy may be an important aspect in the treatment of unexplained fever unresponsive to antibacterial agents [98-103].

Most recently, intravenous amphotericin B, 0.6-1 mg/kg daily, and oral ketoconazole, 200 mg every 6 hours, were compared in treatment of fungal infections (usually fungemia, pneumonia, and esophagitis) in 172 neutropenic cancer patients [104]. The investigators were unable to find statistically significant differences in efficacy with the two drugs, except that amphotericin B was found to be more effective than ketoconazole in the treatment of infections caused by Aspergillus species and Candida tropicalis, and it was possibly more effective in treatment of pneumonia. The overall response rate with amphotericin B was 66%; with ketoconazole, 57%. Note that in this study, the investigators followed the evolving practice of starting antifungal therapy sooner—within 3-4 days after failure of antibacterial therapy, compared with 7 days in earlier studies [104].

Meunier reviewed data from studies in which various doses of amphotericin B were administered orally (200-1,500 mg/d) for prophylaxis of fungal infections in the immunocompromised patient [105]. These data suggested an overall reduction in gastrointestinal fungal colonization, but they are unclear as to the decrease in clinical infections because of lack of control groups [105]. Other reports of amphotericin B, 10 mg (in lozenge form) four times daily with 2 g orally (as a suspension) [106], and combination
therapy with amphotericin B-containing oral gels [107, 108] have also been reported. Prophylactic administration of amphotericin B (10 mg/d) via nasal sprays has been reported in preliminary trials and was promising in reducing colonization and the rate of aspergillus infections when used in combination with environmental measures [109].

Despite these findings, prophylactic use of amphotericin B or other antifungal agents in all granulocytopenic cancer patients is not universally employed at all institutions because of the toxicity of these agents, the lack of placebo-controlled trials, fear of resistance, and cost. Environmental measures may help to decrease the frequency of fungal infections in this patient population [105].

F. Amphotericin B Therapy in Patients with AIDS

Patients with AIDS are characterized by a suppressed cell-mediated immune system with subsequent risk of opportunistic infection. Superficial and invasive infections caused by fungal organisms are among the many infectious processes observed in these patients and are the subject of several recently published reviews [110-117]. In fact, esophagitis caused by Candida; pneumonia, meningitis, and encephalitis caused by Cryptococcus; and candidiasis, aspergillosis, and zygomycosis were among the original Centers for Disease Control surveillance criteria for the diagnosis of AIDS [110].

Oral candidiasis occurs frequently in patients infected with the human immunodeficiency virus (HIV) [110, 111]. More extensive involvement (e.g., esophagitis) has been reported in up to one-third of patients with AIDS [112, 118]. Other forms of disseminated candidiasis (such as involvement of the larynx, trachea, bronchi, and lungs) can occur, especially in pediatric patients with AIDS [111]. However, according to a review by Macher et al., life-threatening infection due to widespread visceral dissemination of candidiasis is infrequent [111]. Superficial fungal infections are also common in AIDS patients, but they can often be ignored if involvement is limited and occurring concurrently with more fulminant opportunistic infections [111]. Disseminated sporotrichosis [113, 114], aspergillosis and invasive aspergillosis, and zygomycotic infections can also be observed in AIDS patients [111].

Histoplasmosis and coccidioidomycosis are reported with increasing frequency in patients with AIDS, according to a review by Minamoto and Armstrong [115]. Such cases are no longer restricted to endemic areas, since most histoplasmosis is assumed to be reactivation of latent infection [115]. Fungal infection resulting from C. neoformans was reported by Grant and Armstrong [117] to be the fourth most common opportunistic pathogen affecting patients with AIDS, and it can be observed in 6%-13% of such patients [119].

In general, amphotericin B treatment of noninvasive fungal infections (most commonly involving candidal infections of the oropharynx or esophagus) may be initiated when the infection is no longer controlled by simpler measures (such as topical antifungals, oral rinses, or oral azole therapy).

Disseminated forms of histoplasmosis in patients with AIDS are often less responsive to amphotericin B therapy than in other immunocompromised patients [115]. Initial therapy with amphotericin B in total doses of 2-2.5 g is recommended over therapy with ketoconazole, since the latter therapy has been associated with frequent treatment failures [115]. This treatment, however, is rarely considered curative in the patient with AIDS, and chronic suppressive therapy with either amphotericin B or ketoconazole may be required [115]. McKinsey and colleagues recently reported data on the efficacy of amphotericin B maintenance therapy for preventing disseminated histoplasmosis relapse in 14 patients with AIDS receiving weekly infusions of 50-100 mg after initial therapy with 1-2 g [120]. During a median follow-up period of 9.5 months (range, 2.5-16 months), only one patient relapsed, after a brief course of corticosteroids and interrupted amphotericin B maintenance therapy. Renal tubular acidosis, however, was reported in eight of 14 patients.

Like treatment for disseminated histoplasmosis, amphotericin B therapy for AIDS patients with disseminated coccidioidomycosis is not generally considered to be curative [115, 116]. Initial therapy often requires amphotericin B therapy in cumulative doses of 2-2.5 g [115]. Although symptoms may improve or resolve, relapses can occur [116]. Therefore, chronic suppressive therapy, as for histoplasmosis, may require indefinite therapy with either ketoconazole or amphotericin B.

Amphotericin B (0.5-1 mg/[kg·d]), alone or in combination with fluconazole, may be successful in the acute management of cryptococcal infections in this patient population [117]. Such success may be independent of the ability to detect measurable levels of amphotericin B in CSF [77]. Therapy is con-
continued until indicated by patient response, cultures, and antigen titers. Chronic suppressive therapy is necessary because of high relapse rates following initial successful therapy [117, 121, 122].

Recently, Zuger et al. reported data on 13 patients receiving maintenance therapy with amphotericin B, 0.7–1.5 mg/(kg·w), after successful initial therapy with amphotericin B, 1,600–2,760 mg total dose [121]. The length of maintenance therapy ranged from 6 to 77 weeks, with varying degrees of patient compliance. Two patients had relapses of their disease within 6 and 13 weeks. None of the remaining patients had relapsed at the time of the report, but several had discontinued therapy for various reasons. The authors concluded that maintenance therapy with amphotericin B does not ensure protection against relapse of cryptococcosis in patients with AIDS. In addition, continued, long-term maintenance therapy with amphotericin B may be undesirable to many patients and physicians. Ongoing trials are being conducted by the AIDS Cooperative Treatment Group and the National Institutes of Allergy and Infectious Diseases (NIAID) Mycosis Study Group to compare the efficacy of fluconazole therapy with amphotericin B for chronic maintenance and acute treatment of cryptococcal meningitis.

G. Dermatologic Uses

In the United States, amphotericin B is available in a 3% lotion, cream, and ointment and is approved by the U.S. Food and Drug Administration for the treatment of cutaneous and mucocutaneous mycotic infections caused by *Candida* species [33]. These may include perleche, intertriginous candidiasis, and paronychia. Topical imidazole creams are alternative treatment. Amphotericin B is not active against dermatophytes.

H. Pulmonary Infections

Extensive reviews have been published by Stamm and Dismukes [3] and Sarosi [123] regarding the use of amphotericin B in a variety of fungal infections involving the lungs. Amphotericin B alone (for blastomycosis, sporotrichosis, zygomycosis, or coccidioidomycosis), with or without the addition of 5-flucytosine (for invasive pulmonary or extrapulmonary aspergillosis, candidiasis, or cryptococcosis), or with rifampin (for aspergillosis) is identified as primary or alternative treatment for these infections.

The use of flucytosine- or rifampin-containing regimens remains controversial for treating pulmonary aspergillosis, since no controlled trials are available to demonstrate an increasing efficacy of combination therapy when compared with amphotericin B alone [123]. In addition, the routine use of amphotericin B has been questioned for aspergillosis lung infections in patients without bronchial invasion, given the relative resistance of this infection to amphotericin B administration [123]. However, with the exception of itraconazole, the oral imidazoles generally lack activity in vitro against *Aspergillus*.

Flucytosine therapy with or without amphotericin B or ketoconazole is recommended as the treatment of choice for patients with chromomycoses, since failure rates with the use of amphotericin B are high. The potential role of oral imidazole therapy in these conditions (either as primary therapy or for continuation of long-term therapy after initial treatment with amphotericin B) was also reviewed by Saag and Dismukes [1]. In general, pulmonary infections such as blastomycosis, coccidioidomycosis, and histoplasmosis in immunocompetent patients may be considered for oral imidazole therapy [1, 3, 123]. However, most investigators recognize the limited utility of the oral agents in the acutely ill patient because of the slow onset of activity.

I. Candidemia

*Candida* species, most commonly *C. albicans*, constitute the most common etiology for serious fungal infections in the United States today [124–126]. Systemic infections caused by *Candida* species are routinely treated with amphotericin B. Currently, however, there are no controlled studies to establish the optimal dose and duration of amphotericin B treatment of candidemia or other forms of systemic candidiasis [127]. Anecdotal reports by Carruthers [128] and Medoff et al. [129] suggest that disseminated candidiasis may be successfully treated with doses of 15–30 mg/d for 1 week [128]. Successes have been reported with total doses as small as 80–355 mg [129]. Medoff [130], however, advises caution in extrapolating this experience to other patients and recommends 5–20 mg/kg total over 3–6 weeks. An ongoing trial has been initiated by members of the NIAID Mycoses Study Group to address the question of optimal dose and length of therapy.
A summary of the clinical uses of amphotericin B appears in table 2.

V. Adverse Drug Reactions

Published reports of toxicity have permitted a clear understanding of the types of associated toxicities as well as possible strategies to prevent and manage undesirable events. A comprehensive review of these toxicities was published by Maddux and Barriere [131]. Despite the differences in affinity of amphotericin B for ergosterol and cholesterol, nonselective disruption of mammalian cells is postulated as the etiology of many of the toxicities of this compound [4, 131-133]. Some authors think that amphotericin B is generally better tolerated in pediatric patients when given in similar doses based on body weight [82].

A. Renal Toxicity

Renal damage is the most significant potential toxic effect of amphotericin B administration. Although the exact mechanism(s) is not defined, the drug causes declines in glomerular filtration rate and renal blood flow [4, 134, 135] as well as impaired proximal and distal tubular reabsorption of electrolytes [134-138]. Clinical and laboratory manifestations of amphotericin B nephrotoxicity, therefore, may include evidence of renal tubular acidosis, casts in the urine, azotemia, oliguria, and magnesium and potassium wasting [131, 134, 136-138]. The main mechanism may involve effects on membrane permeability [134, 136-138]. Pathologic changes of tubular lesions associated with calcium deposition and cortical ischemia were observed in 24 of 26 patients in one study [137]. Other proposed mechanisms include amphotericin B-induced activation of an intrarenal mechanism known as tubuloglomerular feedback regulating proximal and distal tubule delivery of ions [135].

Reversible impairment of renal function occurs early during treatment (within 2 weeks) and may occur in more than 80% of patients receiving therapy [137]. Renal function may return to pretreatment levels in some patients after a brief cessation of therapy and (rarely) even with continued use [135]. However, returns to pretreatment values may take several months in some patients [137]. Irreversible renal dysfunction has been reported [139, 140], but it is generally considered rare and it is not known whether this is related to total dose or individual susceptibility to toxicity.

Renal tubular acidosis can occur in patients receiving total doses of 0.5–1 g or more, and it is generally reversible if therapy is discontinued [134, 138, 141]. The associated hypokalemia may be observed within the first 2 weeks of therapy [131]. Unless the total dose of amphotericin B exceeds 4–5 g [137], the re-

<table>
<thead>
<tr>
<th>Disease</th>
<th>General adult dosage guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Cryptococcal 1 mg/[kg·d] maximum iv; 0.3 mg/[kg·d] amphotericin B with 150 mg/[kg·d] flucytosine for 4–6 w</td>
</tr>
<tr>
<td>Coccidioidal</td>
<td>Amphotericin B, up to 1.5 mg/dose, with hydrocortisone intrathecally; may be supplemented by iv administration in selected patients with refractory disease</td>
</tr>
<tr>
<td>Candidal</td>
<td>0.5–1 mg/[kg·d] iv alone or with flucytosine</td>
</tr>
<tr>
<td>Fungal peritonitis</td>
<td>Total dose of 2–10 mg/kg × 7–14 days iv Amphotericin B, 1.5–2 mg/L, in peritoneal dialysis fluid, up to a total dose of 1,500 mg alone or with flucytosine</td>
</tr>
<tr>
<td>Genitourinary infections</td>
<td>50 mg/L in sterile water, instilled by catheter</td>
</tr>
<tr>
<td>Ophthalmic mycoses</td>
<td>7.5 mg total subconjunctival dose; concomitant systemic therapy usually indicated</td>
</tr>
<tr>
<td>Empiric therapy</td>
<td>Neutropenic cancer patients 0.5 mg/[kg·d] AIDS patients 0.5 mg/[kg·d] AML* patients 0.5 mg/[kg·d]</td>
</tr>
<tr>
<td>Pulmonary infections</td>
<td>Aspergillosis, disseminated 0.5–1 mg/[kg·d] iv, total 2–4 g (up to 6–8 g in resistant forms) Blastomycosis 0.5–1 mg/[kg·d] iv, total 1.5–2 g Coccidioidomycosis 1–1.5 mg/[kg·d] iv, total 1.5–2 g Histoplasmosis 0.6 mg/[kg·d] iv, total 2–2.5 g Other Candidiasis, invasive, life-threatening 0.5–1 mg/[kg·d] iv, total dose 2–4 g Candidiasis, non-life-threatening Amphotericin B, 0.5–1 mg/[kg·d] iv × 7–14 d plus flucytosine, 150 mg/[kg·d] Histoplasmosis, disseminated 0.6 mg/[kg·d] iv, total 2 g Mucormycosis 1 mg/[kg·d] iv × 2–3 mo</td>
</tr>
</tbody>
</table>

* Acute myelogenous leukemia.
nal toxicity is generally reversible. Miller and Bates [142] and Branch [135] failed to show an association with either total dose [142] or length of therapy [135]. Discrepancies between reports regarding the relationship of renal dysfunction and the total dose may be due in part to differing lengths of follow-up, variations in toxicity determinations, and failures to account for the underlying disease of the population studied.

1. Reversing sodium depletion. Conflicting data evaluate the effectiveness of administration of mannitol to prevent amphotericin B–induced nephrotoxicity [143]. However, recent case reports, retrospective studies, and prospective observational studies suggest that sodium loading may minimize this complication [135]. Heidemann et al. [144] described a group of five patients in whom amphotericin B-induced renal impairment. These patients had evidence of sodium depletion caused by low sodium intake, diuretic administration, and vomiting. Dietary sodium loading was associated with improved renal function, and it permitted reintroduction of amphotericin B in four patients and continuation in the fifth without evidence of residual renal impairment.

More recently, Branch et al. [145] described further observations suggesting that routine sodium supplements limit the nephrotoxic potential of amphotericin B. Retrospectively, 21 patients who received amphotericin B (25 mg/d for 1 month) without sodium supplements were compared with 17 patients who received amphotericin B combined with ticarcillin and its obligatory parenteral sodium load of 100–150 mEq per day with usual dosages. Impaired renal function (defined as either an increase in serum creatinine of ~2 mg/dL with normal baseline renal function or a 100% increase with impaired baseline renal function) developed in fewer patients receiving parenteral sodium loading (11% vs. 67%, \(P < .01\)). These authors further described 20 patients who received 24 courses of amphotericin B therapy (40 mg/d for 1 month) with 1 L of iv 0.9% NaCl daily. Two patients (10%) developed nephrotoxicity, but no dosage adjustment was required.

The observations, despite the lack of prospective, controlled, randomized studies, suggest that sodium supplementation may minimize the nephrotoxic potential of amphotericin B. Branch has published a nomogram outlining steps to reduce the risk of amphotericin B nephrotoxicity [135]. Following assessment of the sodium status of the patient (and correction of sodium depletion), determination of the risk-benefit ratio of sodium supplementation is initiated. Otherwise healthy subjects may tolerate supplements of 150 mEq/d over normal sodium intake without difficulty. Patients with underlying conditions such as congestive heart failure, cirrhosis with ascites, or renal failure are unlikely to tolerate such supplements. Routine clinical and laboratory monitoring are undertaken to monitor fluid and sodium status, with sodium supplements increased in patients with prolonged or severe vomiting. Interruption of amphotericin B therapy may be needed if significant or rapid declines in renal function are observed, with resumption of therapy upon improvement.

2. Monitoring for hypomagnesemia and increased serum creatinine. Magnesium wasting as a consequence of amphotericin B administration has also been evaluated, but results are conflicting. Barton et al. [146] examined 10 patients aged 30–68 years receiving amphotericin B for systemic fungal infections. These investigators reported mild to moderate hypomagnesemia after 2 weeks of therapy (total dose, 208 ± 40 mg) and suggested a plateau effect of such a toxicity. They proposed a tubular defect in magnesium resorption as the etiology. Hypokalemia is common in almost all patients receiving therapy, and it may be either a consequence of enhanced excretion, resulting from infusion-related hyperkalemia (in patients with normal renal function), or a direct result of distal tubule damage [147].

Daily monitoring of serum creatinine during the acute stages of therapy has been recommended by Maddux and Barriere [131]. Most clinicians experienced in amphotericin B administration recommend slow daily titrations to the target dose unless the patient is seriously ill and needs immediate institution of a maximal dose. With rises in serum creatinine >3 mg/100 dL, the dosage should be reduced or therapy with the drug interrupted for 24–48 hours to prevent uremia [148] and allow stabilization of renal function. Some clinicians advocate the use of alternate-day administration to reduce renal toxicity, but there is little evidence to justify this approach. Levels of electrolytes such as potassium and levels of magnesium should also be monitored closely.

B. Fever and Chills

Shaking chills and fever are experienced by more than half of the patients receiving this drug. Some patients tolerate these effects well, but others, such as elderly or critically ill patients, may find them par-
ticularly uncomfortable. While the mechanism of these reactions is unknown, they may be mediated by prostaglandins. Amphotericin B is a potent inducer of prostaglandin E₂ synthesis in vitro [149]. In a double-blind, placebo-controlled trial, administration of oral ibuprofen (10 mg/kg) 30 minutes before amphotericin B administration significantly \((P < 0.01)\) reduced the rate of occurrence of chills from 87% to 49% [149]. The rate of 87%, however, is generally considered higher than that reported in other evaluations.

The efficacy of intravenous administration of meperidine to terminate fever and chills has been examined. In a randomized, double-blind study, a mean dose of 45 mg of meperidine (range, 25–60 mg) stopped all reactions (nine of nine) within 30 minutes (mean time to cessation, 10.8 minutes) [150]. This compared favorably with placebo, which stopped three of 10 reactions (mean time to cessation, 37.4 minutes). Gross et al. reported data on three patients with severe amphotericin B–induced rigors refractory to management with meperidine that improved or disappeared with the intravenous administration of dantrolene [151]. However, these authors cautioned that routine use of this agent could not be recommended at this time.

Hydrocortisone has often been added to amphotericin B therapy to reduce febrile reactions. It is usually added to the infusion, although administration before infusion may be more effective. The usual doses of hydrocortisone recommended or used have been 25–100 mg [5, 6, 32, 33, 101, 131]. Tynes et al. demonstrated a statistically significant difference of hydrocortisone, 25 mg, given intravenously at the beginning of the infusion when compared with aspirin and diphenhydramine as premedicants in reducing the frequency of fever, chills, and vomiting [152]. No increase in benefit was demonstrated with a 50-mg dose of hydrocortisone given in a similar manner.

The use of hydrocortisone to reduce adverse effects during intrathecal administration also has been documented [16, 17]. Sugar [153] recommended hydrocortisone, 15–25 mg, and Labadie and Hamilton [92] used 20–50 mg. However, Tynes et al. noted a great deal of interpatient variability in response to this intervention [152]. In addition, administration of corticosteroids and corticotropin (ACTH) can lead to water retention and electrolyte imbalance, including the potentiation of amphotericin B–induced hypokalemia. Therefore, if used, the dosage of corticosteroid should be kept to a minimum. Adequate monitoring of fluid and electrolyte balance should also be instituted.

C. Hematologic Effects

Most patients receiving amphotericin B infusions experience an 18%–35% decrease in hemoglobin concentration [131, 142, 154, 155]. However, such a reaction may not occur until 10 weeks after treatment begins. The anemia is characterized as normocytic and normochromic. It is most likely either related to the direct inhibition of erythrocyte and erythropoietin production [156] or is secondary to its renal toxicity [34]. Data are lacking to demonstrate a dose-related phenomenon. Hematocrit generally returns to normal within several months of discontinuing therapy.

Leukopenia is rarely associated with amphotericin B administration [131]. However, in vitro and animal models suggest that amphotericin B may suppress human lymphocyte function [157], increase the number of antibody-producing cells, and enhance cell-mediated immunity and the phagocytic activity of macrophages [4]. Thrombocytopenia has also been rarely reported [158, 159].

D. Thrombophlebitis

Thrombophlebitis is commonly reported in patients receiving amphotericin B. Proposed etiologies for this problem include the need for prolonged and repeated venipunctures for drug administration and drug coagulation due to an acidic pH of the reconstituted preparation in 5% dextrose solution [131]. Recommendations made to minimize this reaction include infusion of the drug into large distal hand veins, avoidance of the infiltration of the solution into perivascular tissues, use of in-line filters, alternation of infusion sites, use of central venous access, avoidance of amphotericin B concentrations exceeding 0.1 mg/mL, and avoidance of infusion times of less than 4 hours [131]. Although there are no controlled data to support its use, heparin, 500–1,000 units/L, may be added to the solution to minimize the severity of the reaction.

E. Miscellaneous Reactions

Nausea, vomiting, anorexia, headache, myalgias, and arthralgias have all been reported during the initiation of amphotericin B therapy [131]. Acute allergy
Clinical Review of Amphotericin B

reactions including bronchospasm, dyspnea, and tachypnea have been reported, and they may occur more frequently in patients with a history of asthma or chronic obstructive pulmonary disease [160]. Although abnormalities in liver function tests have been reported in patients receiving amphotericin B, the causality of the drug to the abnormalities is questionable [161]. Intrathecal administration has been linked to reactions such as headache, delirium, vomiting, injection site pain, paresthesias, arachnoiditis, radiculopathy, myelopathy, vision impairment, nerve palsies, and meningitis (chemical and bacterial) [3, 86, 131, 154].

VI. Drug Interactions

Patients who receive amphotericin B are generally quite ill and most likely are receiving multiple-drug therapy for concurrent illnesses. Therefore, these patients may be at risk for drug interactions. A number of interactions have been identified.

Amphotericin B may increase the renal toxicity of cyclosporine [162] and aminoglycosides [5]. Antineoplastic agents, such as cisplatin and the nitrogen mustard compounds, may enhance the renal toxicity of amphotericin B, and these agents should be administered concomitantly only with great caution [5]. Amphotericin B-induced hypokalemia may enhance the pharmacologic activity of nondepolarizing skeletal muscle relaxants (e.g., tubocurarine) and digitalis glycosides [34].

Wright et al. postulated an interaction between amphotericin B and leukocyte transfusions [163]. These authors observed a 10-fold risk of acute pulmonary reactions (acute dyspnea, hypoxemia, and radiographic evidence of pulmonary infiltrates) in patients receiving these agents concomitantly when compared with a population receiving leukocyte transfusions alone. Other investigators have disputed the causality of amphotericin B to such reactions on the basis of retrospective clinical investigations and prospective animal studies [3, 164]. However, slow administration of amphotericin B and avoidance of concomitant leukocyte transfusions have been proposed to minimize the potential interaction [163].

Although the additive toxicities of amphotericin B and flucytosine used as combination therapy have been recognized, the potential for enhanced therapeutic efficacy and reduced length of amphotericin B administration is likely to take priority in the treatment of conditions such as cryptococcal meningitis [87]. Either enhanced cellular penetration of the flucytosine or accumulation resulting from amphotericin B–induced renal dysfunction may be responsible for this interaction [165]. Therefore, the dosage of flucytosine should be monitored carefully and decreased if excessive peak serum levels are demonstrated.

VII. Dosage and Administration

A. Recommendations

Recommendations for dosage and duration of amphotericin B therapy are complex and generally are based on clinical experience with the drug as well as on the patient's specific condition. However, certain guidelines have been formulated (table 3).

Amphotericin B is usually administered by slow intravenous infusion over 2–6 hours. The recommended concentration for the infusion is 0.1 mg/mL. Dosage must be adjusted to the specific requirements of each patient because tolerance to amphotericin B varies. A small test dose (1 mg dissolved in 25–50 mL of 5% dextrose) may be infused over 20–30 minutes. If this dose is tolerated, therapy can be in-

Table 3. General guidelines for administration of amphotericin B.

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td>Administer a test dose of 1 mg (either by mixing in 25–50 mL dextrose 5% in water or a 1-mg aliquot of the initial daily dose), infused over 20–30 min.</td>
</tr>
<tr>
<td>If the patient has a reaction to the test dose or develops cardiopulmonary impairment, cautiously try a second test dose of 50–100 μg.</td>
</tr>
<tr>
<td>If tolerated, prepare the drug in a concentration of 0.1 mg/mL of 5% dextrose with phosphate buffers. Do not use 0.9% NaCl solution, which will cause the drug to precipitate.</td>
</tr>
<tr>
<td>Institute therapy with 0.25 mg/kg administered over 2–6 hours.</td>
</tr>
<tr>
<td>Adjust the dosage to the patient's tolerance.</td>
</tr>
<tr>
<td>Increase the daily dose gradually on subsequent days to a maximum of 0.5–0.6 mg/kg in most cases.</td>
</tr>
<tr>
<td>Administer by slow iv infusion (over 4–6 hours).</td>
</tr>
<tr>
<td>Duration of treatment for most deep-seated mycoses is usually 6–12 weeks. In severe or recalcitrant infections, the daily dose may range up to 1 mg/kg for many months.</td>
</tr>
<tr>
<td>If the patient is critically ill or immunocompromised, the first dose of 0.25 mg/kg can be given 2–4 hours after the test dose. The next two or three doses can be given at 8-hour intervals, not exceeding a total of 0.6 mg/kg over 24 hours.</td>
</tr>
<tr>
<td>Amphotericin B can be given on alternate days by doubling the daily dose up to a maximum of 1.5 mg/kg.</td>
</tr>
<tr>
<td>The total daily dose should never exceed 1.5 mg/kg.</td>
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</tbody>
</table>
stituted with 0.25 mg/kg administered over 2-6 hours. If the patient has a severe reaction to the test dose or develops cardiopulmonary impairment, a second test dose of 50-100 μg is recommended. Although the need for this test dose has been questioned by some because of the rare occurrence of hypersensitivity reactions, it does not usually delay therapy to a significant degree.

The daily dose can be increased gradually on subsequent days, generally to a maximum of 0.5-0.6 mg/kg. Drutz et al. proposed a target peak serum concentration of at least twice that necessary for inhibition of the organism [76]. This was identified in their study as 1.56 μg/mL.

Although a sensitive and specific high-pressure liquid chromatography assay has been described in the literature [166], routine determination of amphotericin B serum levels is not available in most institutions and is probably not warranted in most situations. The exception to this may be the pediatric patient for whom drug accumulation may be demonstrated with repeated administration [84]. If the patient is critically ill, the first dose of 0.25 mg/kg can be given 2-4 hours after the test dose, and the next two or three doses can be given at 8-hour intervals, not exceeding a total of 0.6 mg/kg over a 24-hour period. Medoff and Kobayashi recommend following 0.25 mg/kg with a daily dose of 0.5 mg/kg in these patients to obtain rapid therapeutic serum concentrations [57]. It is not yet known if rapid titrations to full-dose therapy predispose the patient to more adverse effects or toxicities. Atkinson and Bennett recommend 0.3 mg/kg daily for two doses, then increased as tolerated to 0.5 to 0.6 mg/[kg·d] [65]. The drug can be administered on alternate days by doubling the recommended daily dose up to a maximum of 1.5 mg/kg [4, 6, 62, 89, 139]. Under no circumstances should a total daily dose of 1.5 mg/kg be exceeded [33].

The duration of treatment for most deep-seated mycoses is usually 6-12 weeks [3, 5, 6, 57]. However, in cases of severe infections, those caused by less-susceptible pathogens (such as Aspergillus and Coccidioides), those in which infection sites may be poorly penetrated by amphotericin B, or those in which patients are immunocompromised, the daily dose may range up to 1 mg/kg (up to a total of 2-4 g in adult patients), administered for many months.

It has been suggested by Fields et al. and Cleary et al. that less toxicity (e.g., fever, chills) and higher serum levels may occur with infusions given over 45 minutes compared with those lasting 2 hours [64, 167]. Although patients may develop tolerance to these adverse effects more quickly when given the slower infusions, administration of the drug over 45 minutes is safe and may simplify ongoing therapy, particularly in the outpatient setting. These and other authors caution that the intracellular potassium release caused by the membrane-permeabilizing effects of high amphotericin B concentrations may result in complications of hyperkalemia. This may be particularly significant in patients with underlying renal impairment and the resulting inability to renally excrete the increased extracellular potassium. Therefore, dialysis-dependent patients should probably receive amphotericin B therapy during dialysis. Infusion rates of 4-6 hours should be used in all patients with renal dysfunction, regardless of their dialysis status.

B. Other Considerations for Administration

Intravenous solutions prepared in 5% dextrose did not lose potency when exposed to fluorescent light at room temperature for 24 hours [168]. However, their choice of diluent is important. Solutions for intravenous infusion or irrigation should not be prepared in 0.9% NaCl solution or reconstituted with diluents other than sterile water for injection (without bacteriostatic agents), because precipitation of the drug will occur [33]. Phosphate buffering can be added if the pH of the resultant solution is <4.2 [33]. Neither filtration of correctly prepared solutions through a 1-μm membrane filter [169] nor buffering of the solution to pH 6.5 [168] will alter the activity of amphotericin B solution. However, routine use of in-line filters should be avoided, since pore sizes smaller than 1 μ may inhibit passage of the colloidal solution [32, 33]. Adequate monitoring of the infusion flow rate requires an infusion pump.

As previously reviewed, intraventricular and intrathecal amphotericin B administration has been described for treatment of CNS infections caused by Coccidioides and some resistant cases of cryptococcal meningitis [89, 170-173]. Intrathecal administration was performed by instillation of the drug into the lumbar theca or cisterna magna in concentrations of 250 μg/mL at an initial dose of 0.25-0.5 mg diluted with 10-20 mL of CSF. Doses were then increased to the level of toleration, usually 0.5-1 mg given two to four times per week [4]. Alazraki et al. [171] recommended dilution with dext-
trose 10% in water and use of the Trendelenberg position, but this procedure is not widely accepted by other authors [4]. Intraventricular administration via a subcutaneous Ommaya reservoir has also been reported, but such a procedure is not without the complications previously discussed.

Nebulization has also been used in nondisseminated pulmonary fungal infections [174], and intraarticular administration has been used to treat candidal arthritis [175], although controlled and comparative data are lacking regarding the safety and efficacy of these uses when compared with alternative interventions. Intralional (for chromoblastosis), intrapleural (for pleural effusions caused by Histoplasma), and intrabronchial (for pulmonary aspergillus infections) have also been described for cases of severe or unresponsive infections [32].

VIII. Amphotericin Methyl Esters and Liposomal Amphotericin B

Chemical modifications of amphotericin B by esterification have produced the methyl ester form of amphotericin B, which has greater water solubility. Although initial laboratory experiments suggested reduced toxicity and higher serum levels in animal models, the clinical testing of the salts of this compound were halted because of reports of potential neurotoxicity (leukoencephalopathy manifested as progressive neurologic dysfunction with white matter degeneration) [176-178]. Kucers and Bennett reviewed the data and suggest a slight reduction of activity of this compound when compared with that of amphotericin B against pathogenic fungi [4]. Other esterified forms of amphotericin B (such as the N-d-ornithyl methyl ester derivative) are undergoing investigation [179].

Data regarding a lipid-encapsulating form of amphotericin B suggest that this form may be effective and perhaps less toxic for treating experimental and human fungal infections [180-185]. However, optimal preparation of liposome delivery remains to be determined. Furthermore, the sterol composition of these preparations has been the subject of recent research [180, 186-189].

According to a discussion by Patterson and colleagues, cholesterol and ergosterol-containing liposomes formulated in multilamellar vesicles (MLV) and small unilamellar vesicles (SUV) have been compared to pure phospholipid liposome formulations, with varying (and often conflicting) results regarding toxicity and fungicidal activity [180]. In one such study, Szoka et al. reported that no alterations had occurred in the fungicidal activity against C. tropicalis and Saccharomyces cerevisiae in the murine model of candidiasis with use of sterol-containing SUV when compared with pure phospholipid liposomes [186]. However, a significant reduction in toxicity (cytotoxicity decreased three- to 90-fold, and LD50, two- to eight-fold) was thought caused by a reduction in the rate of transfer to a sensitive cellular target. This decrease in toxicity was also observed by other investigators using small liposomes containing sterols [189].

Patterson et al. compared a micellar preparation of cholesterol sulfate complexed with amphotericin B against amphotericin B-deoxycholate in an immunosuppressed rabbit model of invasive aspergillosis [180]. It was concluded in this study that equivalent doses of amphotericin/cholesterol-sulfate complexes were less effective than the deoxycholate salt in eradicating infection, but a fourfold decrease in acute lethality was thought to improve the therapeutic index of amphotericin B. Reductions in both efficacy and toxicity, however, may be explained in part by pharmacokinetic studies of amphotericin B lipid complex demonstrating reductions in the area under the time-serum concentration time curve (AUC) when compared with the commercially available preparation (Fungizone, E. R. Squibb and Sons) [190].

Initial clinical experience with 12 patients having either aspergillosis or candidiasis, in whom amphotericin B treatment had failed, showed clinical cures in three patients and partial responses in five patients who received the pure phospholipid MLV preparation [185]. However, preparations of liposomal amphotericin B have not been standardized, nor has a stable commercially available form been produced to date. Therefore, although preliminary results are promising, further investigations are needed to evaluate the safety and efficacy of liposomal formulations of amphotericin B.

IX. Summary

Amphotericin B retains its role as the mainstay of therapy for serious or disseminated fungal infections caused by a variety of pathogens. However, despite 30 years of clinical use, there is a significant lack of data to determine optimal dose, duration of therapy, and administration techniques, as well as the pharmacokinetic profile in various patient popula-
tions. The lack of data identifying the standard of therapy is likely to compound the confusion as to the role of oral imidazoles in the treatment of such infections.

X. References

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