

funding, expert testimony, and membership on company advisory committees. Decisions were made on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts of interests are listed in the Acknowledgments section.

Consensus Development Based on Evidence

The panel obtained feedback from 3 external peer reviewers. The guidelines were reviewed and endorsed by the MSG, the American Academy of Pediatrics (AAP) and the Pediatric Infectious Diseases Society (PIDS). The guideline was reviewed and approved by the IDSA SPGC and the IDSA Board of Directors prior to dissemination.

Revision Dates

At annual intervals, the panel chairs will be asked for their input on the need to update the guideline based on an examination of the current literature. The IDSA SPGC will consider this input and determine the necessity and timing of an update. If warranted, the entire panel or a subset thereof will be convened to discuss potential changes.

BACKGROUND

Antifungal Agents

Pharmacologic Considerations for Therapy for Candidiasis

Systemic antifungal agents shown to be effective for the treatment of invasive candidiasis comprise 4 major categories: the polyenes (amphotericin B [AmB] deoxycholate, liposomal AmB, AmB lipid complex [ABLC], and amphotericin B colloidal dispersion [ABCD, not available in the United States]), the triazoles (fluconazole, itraconazole, voriconazole, and posaconazole), the echinocandins (caspofungin, anidulafungin, and micafungin), and flucytosine. Data from a recently completed clinical trial comparing isavuconazole to an echinocandin for treatment of invasive candidiasis are unavailable at this time. Clinicians should become familiar with strategies to optimize efficacy through an understanding of relevant pharmacokinetic properties.

Amphotericin B

Most experience with AmB is with the deoxycholate preparation. Three lipid formulations of AmB have been developed and approved for use in humans: ABLC, ABCD, and liposomal AmB. These agents possess the same spectrum of activity as AmB deoxycholate, but daily dosing regimens and toxicity profiles differ for each agent. The 3 lipid formulation AmB agents have different pharmacological properties and rates of treatment-related adverse events and should not be interchanged without careful consideration. In this document, a reference to AmB, without a specific dose or other discussion of form, should be taken to be a reference to the general use of any of the AmB preparations. For most forms of invasive candidiasis, the typical intravenous dosage for AmB deoxycholate is 0.5–0.7 mg/kg daily, but dosages as high as 1 mg/kg daily should be

considered for invasive *Candida* infections caused by less susceptible species, such as *C. glabrata* and *C. krusei*. The typical dosage for lipid formulation AmB is 3–5 mg/kg daily when used for invasive candidiasis. Nephrotoxicity is the most common serious adverse effect associated with AmB deoxycholate therapy, resulting in acute kidney injury in up to 50% of recipients and an electrolyte-wasting tubular acidosis in a majority of patients [40, 41]. Lipid formulations of AmB are more expensive than AmB deoxycholate, but all have considerably less nephrotoxicity [42, 43]. Most observers agree that lipid formulations, with the exception of ABCD, have fewer infusion-related reactions than AmB deoxycholate. The impact of the pharmacokinetics and differences in toxicity of lipid formulations of AmB have not been formally examined in clinical trials. We are not aware of any forms of candidiasis for which lipid formulations of AmB are superior to AmB deoxycholate in terms of clinical efficacy. In addition, we are not aware of any situation in which lipid formulations should not be used, with the exception of urinary tract infections, because of reduced renal excretion of these formulations. Animal model studies suggest a pharmacokinetic and therapeutic advantage for liposomal AmB in the CNS [44]. Data demonstrating that AmB deoxycholate-induced nephrotoxicity is associated with a 6.6-fold increase in mortality have led many clinicians to use lipid formulations of AmB in proven or suspected candidiasis, especially among patients in a high-risk environment, such as an ICU [45].

Triazoles

Fluconazole, itraconazole, voriconazole, posaconazole, and a new expanded-spectrum triazole, isavuconazole, demonstrate similar activity against most *Candida* species [46–51]. Each of the azoles has less activity against *C. glabrata* and *C. krusei* than against other *Candida* species. All of the azole antifungals inhibit cytochrome P450 enzymes to some degree [52]. Thus, clinicians must carefully consider the influence on a patient's drug regimen when adding or removing an azole. In large clinical trials, fluconazole demonstrated efficacy comparable to that of AmB deoxycholate for the treatment of candidemia [21, 22] and is also considered to be standard therapy for oropharyngeal, esophageal, and vaginal candidiasis, as well as urinary tract infections [53, 54]. Fluconazole is readily absorbed, with oral bioavailability resulting in concentrations equal to approximately 90% of those achieved by intravenous administration [55]. Absorption is not affected by food consumption, gastric pH, or disease state. Among the triazoles, fluconazole has the greatest penetration into the cerebrospinal fluid (CSF) and vitreous, achieving concentrations of >70% of those in serum [56–59]. For this reason, it is often used in the treatment of CNS and intraocular *Candida* infections. Fluconazole achieves urine concentrations that are 10–20 times the concentrations in serum and, thus, is the preferred treatment option for symptomatic cystitis [59]. For patients with invasive candidiasis, fluconazole