

46. An alternative regimen is liposomal AmB, 5 mg/kg daily (*strong recommendation; low-quality evidence*).
47. The addition of flucytosine, 25 mg/kg 4 times daily, may be considered as salvage therapy in patients who have not had a clinical response to initial AmB therapy, but adverse effects are frequent (*weak recommendation; low-quality evidence*).
48. For step-down treatment after the patient has responded to initial treatment, fluconazole, 12 mg/kg daily, is recommended for isolates that are susceptible to fluconazole (*strong recommendation; low-quality evidence*).
49. Therapy should continue until all signs, symptoms, and CSF and radiological abnormalities, if present, have resolved (*strong recommendation; low-quality evidence*).
50. Infected CNS devices, including ventriculostomy drains and shunts, should be removed if at all possible (*strong recommendation; low-quality evidence*).

Evidence Summary

There are limited data to guide therapy for CNS *Candida* infections in the neonate. All AmB preparations, including the lipid formulations, penetrate the CNS and have fungicidal activity in the CNS [44]. AmB deoxycholate and liposomal AmB were found to have greater antifungal efficacy when studied in a rabbit model of *Candida* meningoenkephalitis compared with the other formulations [44]. The clinician must weigh the benefits and drawbacks of using liposomal AmB with its good CSF penetration but poor urine levels vs using AmB deoxycholate with less good CSF levels but better urine levels.

The benefit of adding flucytosine for neonates with CNS candidiasis is uncertain. In the largest prospective study evaluating treatment outcomes of CNS candidiasis in neonates, the median time to clear CSF was longer for those who received flucytosine plus AmB deoxycholate (17.5 days; 6 infants), compared with those who received only AmB deoxycholate (6 days; 18 infants) [279]. In addition, flucytosine is poorly tolerated, and gastrointestinal side effects may hinder oral feeding in neonates. In general, flucytosine is used only in neonates who have not responded to AmB alone.

Data supporting the use of echinocandins in neonates are emerging; however, several key issues require further clarification. The optimal dose of echinocandins in neonates remains uncertain [109, 284, 293–297]. Furthermore, there are concerns regarding the penetration of echinocandins into the CSF. Echinocandins appear to penetrate brain tissue, but not the CSF, and achieve concentrations in brain shown to be effective in animal models when dosages higher than those recommended for humans have been used [298, 299]. Limited clinical data suggest that the echinocandins may be effective for the treatment of CNS infections in neonates, but are not adequate to recommend their use at this time [293].

What Are the Recommendations for Prophylaxis in the Neonatal Intensive Care Unit Setting?

Recommendations

51. In nurseries with high rates (>10%) of invasive candidiasis, intravenous or oral fluconazole prophylaxis, 3–6 mg/kg twice weekly for 6 weeks, in neonates with birth weights <1000 g is recommended (*strong recommendation; high-quality evidence*).
52. Oral nystatin, 100 000 units 3 times daily for 6 weeks, is an alternative to fluconazole in neonates with birth weights <1500 g in situations in which availability or resistance preclude the use of fluconazole (*weak recommendation; moderate-quality evidence*).
53. Oral bovine lactoferrin (100 mg/day) may be effective in neonates <1500 g but is not currently available in US hospitals (*weak recommendation; moderate-quality evidence*).

Evidence Summary

Numerous studies examining fluconazole prophylaxis for the prevention of invasive candidiasis in neonates have consistently demonstrated efficacy and possibly reduced mortality [300–310]. Fluconazole, 3 mg/kg or 6 mg/kg twice weekly, significantly reduced rates of invasive candidiasis in premature neonates weighing <1000 g in nurseries with a very high incidence of *Candida* infections [300, 302]. A 2007 Cochrane review of clinical trials of fluconazole prophylaxis demonstrated efficacy, with a typical relative risk of 0.23 and number needed to treat of 9. The number needed to treat varied substantially depending on the incidence of invasive candidiasis in a particular ICU. The majority of studies have demonstrated the safety of fluconazole prophylaxis and lack of emergence of resistance.

Enteral or orally administered nystatin has been shown to be effective in reducing invasive candidiasis in preterm infants [303, 311–313]. In one study, nystatin prophylaxis was also associated with a reduction in all-cause mortality [313]. However, there remains a paucity of data on nystatin prophylaxis in infants <750 grams (the group at highest risk), and nystatin may not always be able to be administered when there is an ileus, gastrointestinal disease, feeding intolerance, or hemodynamic instability. These clinical situations are very common in low-gestational-age premature infants and limit the broad applicability of nystatin prophylaxis as a preventive strategy.

Lactoferrin is a mammalian milk glycoprotein involved in innate immunity. In a randomized trial of bovine lactoferrin in infants <1500 g, the incidence of late-onset sepsis was significantly lower in the lactoferrin group than in the placebo group [314]. A secondary analysis of the clinical trial showed that lactoferrin also reduced the incidence of invasive fungal infections compared with placebo [314]. Further confirmation of the efficacy and safety of oral bovine lactoferrin for the prevention of invasive candidiasis is needed, especially in infants <750 g, because there were only a few neonates in this category in this trial.