Published in final edited form as:
Semin Perinatol. 2012 December ; 36(6): 416–423. doi:10.1053/j.semperi.2012.06.003.

Treatment and Prophylaxis of Invasive Candidiasis

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Abstract

Invasive candidiasis (IC) is a leading cause of morbidity and mortality in preterm infants. Even if successfully treated, IC can cause significant neurodevelopmental impairment. Preterm infants are at increased risk for hematogenous Candida meningoencephalitis owing to increased permeability of the blood–brain barrier, so antifungal treatment should have adequate central nervous system penetration. Amphotericin B deoxycholate, lipid preparations of amphotericin B, fluconazole, and micafungin are first-line treatments of IC. Fluconazole prophylaxis reduces the incidence of IC in extremely premature infants, but its safety has not been established for this indication, and as yet, the product has not been shown to reduce mortality in neonates. Targeted prophylaxis may have a role in reducing the burden of disease in this vulnerable population.

Keywords

invasive candidiasis; preterm infants; antifungals

Invasive candidiasis (IC) is a leading cause of death in preterm infants, and survivors often suffer from multiple morbidities.[1] In a prospective study of 6 neonatal intensive care unit patients, IC (*Candida* infections of the blood and other sterile body fluids) was found in only 0.26% of infants weighing ≥2500 g, but the incidence increased to 3.1% in very-low-birth-weight (VLBW) infants weighing ≤1500 g and 5.5% in extremely-low-birth-weight (ELBW) infants weighing ≤1000 g.[2] A more recent National Institute of Child Health and Human Development Neonatal Network prospective study found similar incidence of 7% in ELBW infants, with center-specific incidence ranging from 2%–28%.[3] Of the ELBW infants with neonatal candidiasis, 73% suffered death or neurodevelopmental impairment.[3] Other adverse outcomes associated with IC include chronic lung disease, advanced retinopathy of prematurity, and periventricular leukomalacia.[4–6]

Innate characteristics of preterm infants make them particularly vulnerable to IC. Preterm infants are relatively immunodeficient owing to decreased T-cell count, decreased neutrophil number and function, immature skin, and disruption of cutaneous barriers.[7,8] Other risk factors include decreasing gestational age and birth weight, broad-spectrum antibiotic use (third-generation cephalosporins, carbapenems, and β-lactam/β-lactamase products), histamine-2 blocker use, presence of a central venous catheter or endotracheal tube, and abdominal surgery.[2,9] Colonization with *Candida* was thought to be a risk factor based on several single-center studies and secondary analyses of randomized trials,[10–12] but a large,

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prospective, multicenter study[2] found that colonization with *Candida* species was not an independent risk factor for IC. However, subsequent single-center studies suggested that colonization of multiple sites is an independent risk factor.[13,14]

The presentation of an infant with IC is subtle and nonspecific and may include apnea, increased respiratory support, hypotonia or lethargy, abdominal distention, feeding intolerance, or guaiac-positive stools.[15] A prospective observational study in the National Institute of Child Health and Human Development Neonatal Network demonstrated that a predictive model based on risk factors was more accurate than clinical judgment in predicting IC.[9] The standard for diagnosis of IC is blood culture, but in adults, the sensitivity of blood cultures is as low as 50%.[16] Cultures in neonates are performed with small volumes of blood (0.5–1 mL), and consequently, the sensitivity may be even lower. Given the significant morbidity and mortality associated with IC, effective and prompt treatment is critical. Morbidity and mortality in preterm infants are significant even with antifungal treatment, and treatment failure increases with decreasing gestational age.[1,3,4,17] Prophylaxis in high-risk infants may reduce the incidence of IC and its associated complications.

Persistent candidemia (*Candida* infection of the blood) despite antifungal treatment increases the likelihood of end-organ damage, although end-organ damage can still occur in the setting of 1 positive culture.[18,19] A meta-analysis of 21 studies of neonatal candidemia found significant heterogeneity in the reported prevalence of end-organ damage, such as endophthalmitis, meningitis, brain abscess or ventriculitis, endocarditis, renal invasion, or positive urine culture in neonates with candidemia. [20] However, the prevalence of end-organ involvement was high enough that all infants with candidemia should have additional evaluation, including urine and cerebrospinal fluid (CSF) cultures and imaging of the heart.[20]

Treatment

Antifungal treatment of IC in neonates is not well defined owing to a lack of well-powered randomized controlled clinical trials. Infectious Disease Society of America guidelines recommend initial therapy with amphotericin B deoxycholate (1 mg/kg/d), fluconazole (12 mg/kg/d), and, when there is a negative urine culture, amphotericin lipid complex formulations (5 mg/kg/d; Table 1).[21] Based on several recent trials in neonates[22–24] and animal bridging studies,[25] micafungin (10 mg/kg/d) is also considered a first-line agent. Increased permeability of the blood– brain barrier in neonates means that all dosing should cover presumed hematogenous *Candida* meningoencephalitis (HCME), a characteristic that distinguishes neonatal candidemia from that affecting other patient populations.

Candida species are prone to forming biofilms on implanted devices, such as indwelling catheters or prosthetic heart valves. These biofilms are often resistant to common antifungal agents.[26] As such, treatment of IC involves not only antifungal agents but also the removal or replacement of indwelling catheters.

Amphotericin B Deoxycholate and Lipid Preparations of Amphotericin B

Amphotericin B deoxycholate binds to sterols in the cell membranes of fungal cells, thereby impairing membrane integrity and causing cell death. It is one of the first-line therapies for invasive fungal infections because most clinically relevant *Candida* species are susceptible to it, with the exception of *Candida lusitaniea* and occasionally *Candida glabrata* and *Candida krusei*.[27] However, safety and efficacy data in neonates are limited. Electrolyte abnormalities, such as hypokalemia, are not uncommon.[28] Because immediate hypersensitivity reactions are rare in neonates, test doses are not necessary.[29] Nephrotoxicity is the most concerning side effect in adults but is less common in neonates.[28,29]

Furthermore, *Candida* species can invade nephrons and cause an increase in creatinine. In the context of treatment with amphotericin B deoxycholate, the increased creatinine may be misinterpreted as nephrotoxicity secondary to treatment and may lead providers to reduce the dose of amphotericin B deoxycholate. This can lead to a spiral of worsening infection, increasing creatinine, and further dose reduction. Greater pharmacokinetic (PK) variability and longer half-life have been reported in neonates compared with adults.[30] CSF penetration is also better in neonates compared with adults, an important consideration because all antifungal therapy in neonates must cover presumed HCME. The recommended dose is 1 mg/kg given intravenously every 24 hours.[30]

Lipid preparations of amphotericin B are generally given in the setting of renal failure or intolerance to or failure of standard preparations.[28] These formulations of amphotericin are thought to have decreased renal toxicity, even with relatively higher doses of the parent drug.[29] The decreased nephrotoxicity is due, in part, to lesser renal tissue penetration, which concomitantly makes liposomal preparations of amphotericin B poor candidates for the treatment of neonatal candiduria.[31] A controlled trial compared the effectiveness and tolerability of 3 antifungal preparations in 56 infants (including 36ELBWinfants): amphotericin B deoxycholate (n = 36), liposomal amphotericin B (n = 6), and amphotericin B colloidal dispersion (n = 16).[28] Overall mortality rate in the study population was 14.8%, and there were no significant differences in mortality between groups (amphotericin B deoxycholate, 14.7%; liposomal amphotericin B, 16.7%; amphotericin B colloidal dispersion, 14.2%).[28] Sterilization rates with monotherapy, duration of fungemia, and duration of hospitalization were also not significantly different between the groups. No renal toxicity or hepatotoxicity was observed in any of the groups.[28] Current dosing recommendations for lipid preparations in infants are 5 mg/kg/d.[21,28,32–34]

Azoles

Fluconazole is a first-generation triazole that inhibits ergosterol synthesis and thus alters fungal cell membranes. It is fungistatic; penetrates the kidneys, CSF, and liver; and is available in both oral and intravenous forms. The most common side effects in children are gastrointestinal irritation and mild elevation of liver enzymes.[35] Fluconazole is excreted unchanged in the urine and not extensively metabolized by the liver. However, rare cases of idiosyncratic liver failure possibly related to fluconazole have been reported in adults.[36–38] Dose-dependent hepatotoxicity has also been reported in 2 adults with renal insufficiency.[39,40] Dose adjustment is recommended in the context of decreased renal function. [40,41]

Fluconazole is currently the main alternative to amphotericin B deoxycholate in neonatal candidiasis. One small randomized trial described the successful use of fluconazole as a single agent for neonatal *Candida* infections.[42] Twenty-three infants were randomized to either intravenous fluconazole or amphotericin B deoxycholate. There was no statistically significant difference in survival (67% vs 55%), but infants receiving fluconazole experienced less hepatotoxicity and required fewer days of intravenous therapy.[42]

A population PK study derived from 357 fluconazole plasma concentrations from 55 infants established 12 mg/kg/d as the appropriate dose to treat IC in preterm infants.[43] However, this dosing regimen requires several days to reach therapeutic serum concentrations.[43,44] A follow-up study established that a loading dose of 25 mg/kg on day 1 followed by 12 mg/kg/d achieves therapeutic concentrations within 24 hours of the loading dose.[45] The higher dosing was safe in the small cohort of infants and children who received the product, and the loading dose achieved exposures comparable with an 800-mg load followed by 400 mg/d in adults.

Candida albicans and *Candida parapsilosis* are almost always susceptible to fluconazole in neonates; however, *C glabrata* and *C krusei* are usually resistant.[46,47] Voriconazole is a second-generation triazole that is effective against *Candida* species, including *C glabrata* and *C krusei*.[48] It is associated with elevated transaminases, visual disturbances, and photosensitivity in children aged 9 months to 15 years.[49] Studies in neonates are limited to case reports and case series.[49–56] Because of these potential toxicities, voriconazole is considered a second-line agent after fluconazole, amphotericin B, or micafungin. Additionally, the central nervous system (CNS) penetration of voriconazole in neonates is unknown. The limited PK data available suggest that voriconazole dosing does not correlate with serum drug concentrations.[56] If voriconazole therapy is absolutely necessary, we recommend a starting dose of 7 mg/kg intravenously every 12 hours combined with therapeutic drug monitoring. The target range of serum concentration is 1–5 μg/mL.[50,57–60]

Flucytosine (5-Fluorocytosine, 5-FC)

Flucytosine is a pyrimidine analog that disrupts RNA synthesis and eventually protein synthesis and inhibits fungal DNA synthesis. Resistance develops rapidly for this molecule when it is used as monotherapy, there is no intravenous formulation. Flucytosine has limited and contradictory benefits,[3,61] shows variability in gastrointestinal absorption, and exhibits dose-dependent bone marrow suppression that results in agranulocytosis and aplastic anemia, with serum concentrations > 100 μg/mL.[62] It should be rarely used in neonates, and if given, serum concentrations should be followed in neonates, with a recommended trough of 20-40 μg/mL and peak of 50-80 μg/mL.[63]

Echinocandins

The echinocandins (micafungin, caspofungin, and anidulafungin) inhibit (1,3)-β-D-glucan synthase enzyme. This leads to cell wall incompetence and eventual cell lysis. Echinocandins are thought to be active against all *Candida* species[64]; however, a potential mechanism of resistance has been identified, and a small number of case reports have documented failure of caspofungin therapy.[65]

Micafungin has been well studied in neonates. It is a first-line agent for candidiasis along with fluconazole and amphotericin B. The initial trial examined doses of 0.75, 1.5, and 3 mg/kg and noted a faster clearance and lower exposure in neonates compared with children and adults.[66]

A dose of 5–7 mg/kg was deemed necessary to reach serum concentrations equivalent to standard adult dosing; however, it was unclear whether there was adequate CNS penetration. Because of the danger of HCME in neonates, Hope et al[25] evaluated the PKs and pharmacodynamics of micafungin in a rabbit model of HCME. The authors translated their findings to humans through a bridging study that demonstrated that a dose of 9–15 mg/kg should induce near-maximal effect in a majority of neonates with HCME.[25] To verify these observations, this study was followed by a clinical trial in neonates with suspected IC and a population PK study in neonates that showed doses of 10 mg/kg achieved concentrations necessary to treat CNS infection.[23] Side effects of micafungin include elevated alanine/aspartate aminotransferases, hypokalemia, hyperbilirubinemia, and hypertension; however, these events are rare even at doses up to 15 mg/kg.[22–24,66]

The PKs of caspofungin was described in a trial of infants <3 months of age, including 13 premature neonates, and showed that linear weight-based extrapolation from adult data resulted in subtherapeutic serum concentrations.[67] However, a dose of 25 mg/m^2/d achieved similar exposure to adults and older infants and children.[67] Of note, there was a considerable amount of variability in peak and trough concentrations among the infants.[67] Only 1 CSF

sample was available in this study, so it was not possible to evaluate whether this dosage was sufficient for CNS penetration.[67] No bridging studies have been completed to guide dosing in neonates.[67] Thus, CNS penetration information is incomplete, and this product should be considered second line among the echinocandins in neonates. Side effects of caspofungin include hypokalemia, elevated transaminases, and anemia, but these were rare in a small cohort of neonates, in children, and in adolescents, and did not require discontinuation of caspofungin therapy.[67–69]

Anidulafungin has a favorable safety profile in adults,[70] lacks hepatic metabolism, and is not renally cleared.[71] Rather, it undergoes chemical degradation in the blood, limiting its interaction with other drugs and making dose adjustment unnecessary in patients with hepatic or renal insufficiency.[70–72] A small single-site study of neonates (2–30 days) and infants (>30 days to <2 years) suggested that a loading dose of 3 mg/kg followed by 1.5 mg/kg/d produces similar drug exposures as in older children with the same weight-based dosing regimen and adults receiving a dose of 100 mg/d.[73] There were no adverse events attributable to anidulafungin in the neonatal cohort. Further study is needed in a larger multicenter cohort that incorporates informative dosing based on a bridging study.

New Antifungal Agents

Posaconazole is a second-generation triazole that inhibits ergosterol synthesis and causes cell lysis. It has a wide spectrum of action, including activity against *Candida*, *Aspergillus*, *Fusarium*, and *Zygomycetes*. Posaconazole PKs have been evaluated in adults for both therapy and prophylaxis.[74,75] An open-label study and a retrospective survey of posaconazole use, including 27 children aged 3–17 years suggested that it was safe and well tolerated in these patients.[76,77] To our knowledge, there are no data on the PKs, safety, or efficacy of posaconazole in neonates.

Ravuconazole is a second-generation triazole that is currently in clinical trials in adults. Ravuconazole is often fungicidal, [78,79] has 47%–74% bioavailability, with near linear PKs, and a half-life of about 100 hours.[80] The concentration of ravuconazole was 2–6 times higher in healthy rat tissue than the corresponding blood concentration.[81] It was well tolerated in healthy human subjects in single[80] and multiple doses.[82] This drug is not Food and Drug Administration approved. To our knowledge, there are no reports of ravuconazole use in young infants. Other new antifungals that are currently in development are the triazoles isavuconazole and albaconazole; an echinocandin aminocandin; and MK-3118, an inhibitor of β-(1,3)-D-glucan synthesis.

Extracorporeal Membrane Oxygenation and Antifungals

IC is a leading cause of infection-related death in children supported by extracorporeal membrane oxygenation (ECMO). It is particularly problematic because removal of the large catheters that connect the infant to the ECMO machine is not possible. ECMO is thought to alter drug PKs secondary to a larger volume of distribution with the addition of priming fluid and potential sequestration of drug in the circuit itself. Ex vivo studies as well as case reports in adults have suggested that ECMO alters the PKs of voriconazole and caspofungin in adults.[83–85] Fluconazole has been studied in children on ECMO. Investigators reported that children on ECMO had higher volume of distribution but similar clearance of fluconazole as compared with critically ill children not on ECMO. A dose of 25 mg/kg once weekly of fluconazole provided similar exposure as that of 6 mg/kg every 72 hours, and should be adequate for prophylaxis against *Candida* infections. However, a dose of 25 mg/kg would not achieve the treatment target, and doses of 30–50 mg/kg are likely needed within the first 24 hours of therapy.[86] The proper dose and frequency for treatment are still under investigation.

Nonpharmacologic Treatment

Although initiation of proper antifungal therapy is important for successful treatment of IC, it is not sufficient. Prompt removal or replacement of central venous catheters is critical because delays in removal are associated with increased mortality and poor neurodevelopmental outcomes.[87,88] In a cohort study of 4579 ELBW infants, 320 developed candidiasis, and delayed removal of central catheters was associated with worse short- and long-term outcomes.[3] The mortality rate with delayed removal or replacement was significantly higher compared with prompt removal/replacement (37% vs 21%, $P < 0.024$). Furthermore, there was increased neurodevelopmental impairment at 18–22 months (delayed: 63% vs prompt: 45%, $P = 0.08$). The association between death/neurodevelopmental impairment and delayed removal remained strong in a multivariate logistic regression adjusting for gestational age, gender, and center (odds ratio = 2.96, 95% confidence interval = 1.25–5.79).[3]

Prophylaxis

Diagnosis of IC is challenging, and even infants who are successfully treated are at increased risk of adverse long-term outcomes. As a result, there has been significant research effort directed toward prevention. Wide center variation in the incidence of IC suggests that differences in practice may affect infection rates.[9] Standard precautions include hand-washing, prompt removal of unnecessary catheters, and prudent use of broad-spectrum antibiotics in the absence of a proven bacterial infection.[3,9,89] Antifungal chemoprophylaxis has also been investigated as potential preventative measure.

Prophylaxis with fluconazole has been shown to reduce fungal colonization and infection in adults and children undergoing bone marrow and solid-organ transplant, patients with hematologic malignancies, high-risk surgical patients, neutropenic cancer patients, and patients with human immunodeficiency virus infection.[90–99] Fluconazole is an attractive agent for chemoprophylaxis owing to its long half-life, good enteral absorption, and excellent CSF penetration.[100] It is metabolized by the kidney and is excreted 80% unchanged in the urine.[100] Furthermore, if resistance develops, amphotericin B and micafungin are appropriate alternatives and should still cover the infecting species.[43,44,101]

There is evidence to suggest that fluconazole prophylaxis is safe and efficacious in preventing IC and colonization in premature infants. A total of 645 ELBW and VLBW infants have been enrolled in 4 randomized controlled trials (Table 2).[12,102–104] Fluconazole dosing of 3–6 mg/kg daily to twice weekly depending on postnatal age decreased the incidence of colonization and IC compared with placebo. However, there was no difference in mortality between groups. No clinically significant adverse effect was noted, and none of the infants was withdrawn from their study owing to changes in liver function tests.[12,102,103] The minimum inhibitory concentration of fluconazole did not change in isolated species over the study periods (ranging from 8 weeks to 30 months),[12,102,103,105] and there was no increased isolation of *Candida* species natively resistant to fluconazole.[102,103]

Manzoni et al[106] examined the incidence rates of colonization and infection with the natively fluconazole-resistant candidal strains *C glabrata* and *C krusei* over a 4-year preprophylaxis period and a 6-year prophylaxis period. Colonization and invasive infection by resistant species were similar in the preprophylaxis versus prophylaxis periods (colonization: 3.7% vs 4.1%, $P = 0.84$; invasive infection: 1.4% vs 1.1%, $P = 0.76$), respectively. A number of retrospective studies with historical control groups also did not note an increase in fluconazole resistance in colonizing or infecting *Candida* species.[107–116] Data from an in vivo murine model suggest that maintenance of serum concentrations at a

level more than the minimum inhibitory concentration of resistant strains of *Candida* for >50% of the dosing interval prevents the development of fluconazole resistance.[117]

Although these randomized controlled trials suggest that fluconazole prophylaxis shows promise in reducing the burden of IC in ELBW and VLBW infants, they must be interpreted with caution. The trials were performed at centers where the incidence of IC was 3- to 10-fold higher than the median incidence in the United States, and 10- to 20-fold higher than the incidence in most Canadian and many European centers.[3,89,118] Thus, although prophylaxis may curb IC in these high-incidence centers, the benefit in medium-to-low incidence centers is unclear. Secondly, although randomized controlled trials have demonstrated reduced incidence of IC or colonization, none has studied the composite outcome of infection or death. The randomized controlled trials described earlier in the text have suggested that fluconazole prophylaxis does not reduce mortality,[12,102] and a meta-analysis of randomized controlled trials comparing the efficacy of fluconazole prophylaxis versus placebo found no difference in risk of death before discharge (typical risk difference: −0.04, 95% confidence interval: −0.14 to −0.03).[118] Before instituting widespread prophylaxis, it should be shown that prophylaxis improves outcomes.

Finally, there are limited data on potential long-term effects of fluconazole prophylaxis on preterm infants. Kaufman et al[12] performed a follow-up study examining neurodevelopmental outcomes and quality of life of 38 of the original 100 participants in a previous randomized controlled trial of fluconazole prophylaxis at 8–10 years of age.[119] The primary outcomes were neurodevelopmental status and quality of life. Vineland Adaptive Behavior Scales—II Domain scores were similar for communication (94.6 vs 92.6, $P = 0.65$), daily living skills (87.9 vs 87.4, $P = -0.89$), socialization (97.2 vs 94.4, $P = 0.31$), and motor skills (92.1 vs 95.1, $P = 0.57$). Child Health Questionnaire—Parent-Completed Form 28 scores demonstrated no difference in satisfaction with school, friendships, and life, or with self-esteem, emotional difficulties, or behavioral problems.[119] Although this small study suggests fluconazole prophylaxis may not adversely affect long-term neurodevelopmental outcomes, we must approach prophylaxis with caution until more is known.

Trials are ongoing to assess the effects of fluconazole prophylaxis on neurodevelopmental outcome.[120] Prophylaxis is reasonable in high-incidence centers, but should not be routinely implemented in all neonatal intensive care units until more is known about its potential neurodevelopmental effects. Doses of 3–6 mg/kg twice weekly have been shown to be effective in preventing IC in randomized controlled trials.[12,43,102,104,105]

Summary

IC is a common and devastating complication in preterm infants. First-line treatment includes the antifungal agents amphotericin B deoxycholate, lipid preparations of amphotericin B (provided the urine culture is negative), fluconazole, or micafungin, and prompt removal of indwelling catheters. Targeted fluconazole prophylaxis may play a role in preventing IC. Although there are a number of therapeutic options for the treatment of IC in preterm infants, PK data in neonates are still limited. Linear weight-based extrapolation from adult data is inadequate and too often results in drug under- or overexposure. This places children at risk for unacceptable therapeutic failure or toxicity. By combining animal studies with bridging and PK studies in neonates (eg, micafungin), antifungal PKs, safety, and efficacy can be accurately described in this vulnerable population.

Acknowledgments

N.T. was supported in part by Duke University's CTSA grant TL1RR024126 from NCRR/NIH. K.W. receives support from the United States Government (5T32HD043029-09) and the Thrasher Research Fund for his work in pediatric research. D.K.B. receives support from the United States Government for his work in pediatric and neonatal clinical pharmacology (1R01HD057956-02, 1R01FD003519-01, 1U10-HD45962-06, 1K24HD058735-01, and is the Principal Investigator of the Pediatric Trials Network, Government Contract HHSN275201000002I); from the nonprofit organization Thrasher Research Foundation for his work in neonatal candidiasis (http://www.thrasherresearch.org); and from industry for neonatal and pediatric drug development (http://www.dcri.duke.edu/research/coi.jsp).

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Table 1

Dosing Recommendations for Antifungal Treatment in Neonates

Agent	Treatment Dosing
Amphotericin B deoxycholate	1 mg/kg/d
Amphotericin B lipid preparations	5 mg/kg/d
Fluconazole	25 mg/kg loading dose, then 12 mg/kg/d
Voriconazole	Therapeutic drug monitoring; target 1–5 μg/mL
Micafungin	10 mg/kg/d
Caspofungin	Unknown
Anidulafungin	Unknown

Table 2

Randomized Controlled Trials of Fluconazole Prophylaxis

Study	N	Study Population Weight	Trial Design	Primary End Point	IC and Mortality: Fluconazole Group	IC and Mortality: Placebo Group	Comments
Kaufman et al[12]	100	<1000 g	Single-center RCT	IC Mortality	0/50 4/50 (8.0%)	10/50 (20.0%) 10/50 (20.0%)	Reduced IC but not mortality
Kicklighter et al[104]	103	<1500 g	Single-center RCT	Colonization Mortality	8/53 (15.1%) 5/53 (9.4%)	23/50 (46.0%) 10/50 (20%)	Did not reduce invasive candidiasis or mortality
Manzoni et al[102]	322	<1500 g	Multicenter, 3 arm RCT	IC Mortality	7/216 (3.2%) 18/216 (8.3%) Post hoc 3 + 6 mg composite	14/106(13.2%) 10/106(9.4%)	Reduced IC but not mortality
Parikh et al[104]	120	<1500 g	Single-center RCT	IC Mortality	16/60 (26.7%) 17/60 (28.3%)	15/60 (25.0%) 17/60 (28.3%)	No difference in IC or mortality

IC, invasive candidiasis; RCT, randomized controlled trial; PNA, postnatal age; DOL, day of life.