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The Use of Antifungal Therapy in Neonatal Intensive Care

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Invasive candidiasis in extremely premature infants is the second most common cause of infectious disease-related death.[1] Birth weight is strongly related to the incidence of invasive candidiasis (1% of infants born weighing 1000–1500 g versus up to 12% of infants born weighing 401–750 g).[2] The morbidity and mortality of premature infants with invasive candidiasis are high.[3,4] In a cohort of 320 extremely-low-birth-weight (ELBW, <1000 g birth weight) infants with invasive candidiasis, 73% died or were neurodevelopmentally impaired at 18–22 months corrected age.[3]

A unique characteristic of invasive candidiasis in infants is the frequent involvement of the central nervous system (CNS). The incidence of *Candida* meningitis among candidemic infants varies from 5–25%.[3,5,6] Meningitis is not the only manifestation of CNS disease; parenchymal abscesses and vasculitis are also frequent in infants with invasive candidiasis.[7] Therefore, CNS involvement in invasive candidiasis among infants can best be termed meningo-encephalitis. In meningo-encephalitis due to *Candida*, cerebrospinal fluid (CSF) cultures are often negative, CSF parameters (e.g., white blood cell count) are often normal,[5] and imaging is unreliable.

Given the high incidence of meningo-encephalitis in the setting of candidemia and the lack of reliability of testing, the presence of meningo-encephalitis should be assumed in the candidemic neonate. This assumption influences length of therapy, dosing, and other key components of antifungal drug development and selection.

Although antifungals have long been used in infants, their efficacy in this population is based on extrapolation from trials performed in adults.[8] Randomized trials to evaluate prophylactic systemic antifungal agents in very-low-birth-weight (VLBW, <1500 g birth weight) and ELBW infants exist, but no well-powered trials exist to guide treatment for

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invasive fungal infection in preterm infants.[9–13] However, a number of pharmacokinetic (PK) antifungal studies have been completed (Table 1). In this article, we summarize those findings.

POLYENES

Amphotericin B deoxycholate

Amphotericin B deoxycholate was approved for use in adults in 1958 and is now approved for use in children and adults. It acts by binding to a cytoplasmic membrane ergosterol of the fungus, thereby creating pores in cell membranes.[26] Amphotericin B deoxycholate is poorly absorbed after oral administration and is highly protein-bound (95%).[27] It is widely distributed in the body and can be detected in the liver, spleen, and kidneys.[27]

Amphotericin B deoxycholate has a longer half-life in infants (15 hours) than in adults and greater potential for drug accumulation.[14] The half-life, volume of distribution, and clearance are highly variable in infants.[14] CSF penetration in infants is higher than in adults, with concentrations 40–90% of the serum concentrations[14]; importantly, the amphotericin products tend to have substantial brain tissue penetration.

Nephrotoxicity is an important side effect observed with use of amphotericin B deoxycholate.[14,28,29] In a retrospective study evaluating 92 infants with a median gestational age of 26 (range 23–41) weeks, 16% experienced nephrotoxicity and 17% had hypokalemia.[30] However, in another study designed to compare the effectiveness and tolerability of 3 antifungal preparations—amphotericin B deoxycholate, liposomal amphotericin B (L-amB), and amphotericin B colloidal dispersion (ABCD)—no infant (n=56) experienced renal function deterioration during treatment.[15]

Amphotericin lipid formulations

Three lipid formulations of amphotericin are available: L-amB (or AmBisome), amphotericin B lipid complex (ABLC or Abelcet), and ABCD (or Amphotec). The Food and Drug Administration (FDA) has approved L-amB for use in children ≥1 month of age, ABLC for children ≥16 months of age, and ABCD for children and adults.

L-amB at a dose 1 mg/kg daily demonstrated cumulative dose effect, and the peak plasma concentrations were higher in adults compared with children and infants.[31] Accumulation of amphotericin B in rabbits' kidneys following 5 mg/kg/day of L-amB was only 0.87 μg/g compared with 12.7 μg/g following 1 mg/kg/day of amphotericin B deoxycholate.[32] The clearance of ABLC in infants was similar to that observed in older patients.[33] The recommended dose for ABLC is 2.5–5 mg/kg/day.[33]

Infants in a prospective single-center study were given 1 mg/kg/day of amphotericin B deoxycholate (n=34) if their serum creatinine was <1.2; otherwise, they were given either 5 mg/kg/day of L-amB (n=6) or 3 mg/kg/day of ABCD (n=16). No statistical difference in mortality was noted among the 3 groups.[15] In a study of 46 VLBW infants who received L-amB at a dose of 1–3 mg/kg/day (26 infants) or amphotericin B deoxycholate at a dose of 0.5–1 mg/kg/day (20 infants), the fungal eradication rate was similar between groups: 84% of the L-amB group and 89% of the amphotericin B deoxycholate group.[26] Effectiveness of L-amB was 73% (n=44) in a prospective cohort of infants with invasive candidiasis and 63% (n=21) among VLBW infants.[34] L-amB was effective in 95% of infants (n=41) with invasive candidiasis (28 were ELBW) treated with a high dose (5–7 mg/kg/day). The infection cleared faster if the target dose was reached earlier.[16]

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In a prospective cohort of 21 VLBW infants receiving L-amB, hypokalemia was the only side effect observed and was supplementation responsive.[34] The number of studies of ABLC and ABCD in pediatric populations is small, but both agents were well-tolerated.[33,35,36] In a prospective study comparing the 3 formulations, no significant renal or hepatic toxicities were noted with any of the preparations.[15] Because renal penetration is limited with lipid formulations, the clinician should document negative urine cultures in infants for whom these preparations are used as monotherapy.[32]

NUCLEOSIDE ANALOGS

Flucytosine

Flucytosine (5-FC), through its antimetabolite 5-fluoracil, alters RNA and DNA synthesis of the mycotic cell. 5-FC is converted to 5-fluoracil by cytosine deaminase, a fungi enzyme absent from human cells.[37] Flucytosine is active against *Candida sp*., *Aspergillus sp*., and *Cryptococcus sp*.[37] The occurrence of resistance with the use of 5-FC as monotherapy precludes its use as a single agent.[38] 5-FC is highly bioavailable and has excellent penetration of body fluids, with CSF concentrations at 74% of plasma levels.[37] 5-FC is FDA-approved only for use in adults.[39] The recommended dose is 25–100 mg/kg/day.[14] In 13 infants (24–40 weeks' gestational age), the median half-life was twice that of adults, with considerable inter-individual variability.[14] 5-FC can be toxic and can result in hepatic injury, bone marrow suppression, and gastrointestinal intolerance.[40] The risk for developing toxic events increases when 5-FC levels exceed 100 mg/L; therefore, therapeutic drug monitoring is necessary.[40,41]

The PK data in infants are limited, and there has been no clinical trial to evaluate 5-FC efficacy in this population. A cohort study of 27 ELBW infants with meningo-encephalitis showed that time to clear infection was longer in infants given combination flucytosine and amphotericin B deoxycholate than in those treated with amphotericin B deoxycholate alone.[3] 5-FC use is limited by its toxicities and the need for oral dosing, and we typically discourage its use except in rare circumstances.

TRIAZOLES

Fluconazole

Fluconazole is a water-soluble triazole whose mode of action is inhibition of the demethylase enzyme that is involved in the synthesis of ergosterol.[42] Fluconazole is available in both oral and intravenous formulations, with oral bioavailability greater than 90%. Fluconazole is labeled by the FDA for use in children ≥6 months of age. The volume of distribution in adults is 0.7 L/kg with a low plasma protein-binding (12%). Plasma half-life is ~30 hours in adults.[43]

The PK properties of fluconazole are well-described in children. The volume of distribution varies with age; it is greatest during the neonatal period and decreases by young adulthood. In children, fluconazole clearance is more rapid than in adults, with a mean half-life of 20 hours. Fluconazole is eliminated renally; therefore, dosing adjustments are necessary in patients with substantial renal impairment.[44,45] In the premature infant, we typically reserve dose adjustment for the infant with substantially impaired urine output and elevated creatinine.[17]

Fluconazole is commonly used to treat candidiasis in infants and is active against the most frequently isolated species of *Candida*.[46] Infants with invasive candidiasis should receive 12 mg/kg/day of fluconazole to achieve an area under the curve of >400 mg*h/L.[47] A loading dose of 25 mg/kg on the first day is likely to provide optimal exposure; otherwise, infants

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may not reach target exposures for several days.[18] Fluconazole is also well-absorbed in infants[48] and is found in the CSF at 80% of the levels observed in plasma.[49]

Fluconazole appears to be safe in infants. Laboratory abnormalities in patients receiving fluconazole are uncommon; a transient increase in liver enzymes was seen in <5% of children (n=564; from premature neonatal age to 17 years of age).[50] Fluconazole was given to 493 infants in clinical trials to evaluate fluconazole prophylaxis, and no serious adverse events were found.[9–13,51] One trial showed differences in liver enzyme levels for fluconazole patients compared with controls (alanine transaminase 18 IU/ml and 15 IU/ml for treated vs. controls, respectively), but levels returned to baseline levels after the end of therapy.[11]

Several randomized trials and a number of prospective cohort studies found that antifungal prophylaxis with fluconazole decreased the incidence of invasive candidiasis (Table 2).[9–13,52–58] Although fluconazole prophylaxis decreases invasive candidiasis in high-risk populations, it is unknown if prophylaxis decreases overall mortality, decreases candidiasis in low-incidence settings, or what the effects of prophylaxis may be on long-term neurodevelopment. There are also concerns that antifungal prophylaxis may increase the incidence of fluconazole-resistant *Candida*.[61]

Voriconazole

Voriconazole, a second-generation triazole, exhibits broad-spectrum antifungal activity against fungal pathogens such as *Candida spp*., *Aspergillus spp*., and *Cryptococcus neoformans*, and less common mold pathogens including several species of *Fusarium* and *Penicillium marneffei*.[62] Voriconazole has high oral bioavailability (90%) and a mean half-life of 6 hours.[62] It is FDA-approved for children ≥12 years of age. CSF penetration is high, and the drug is metabolized by the liver cytochrome P4502C19; genetic polymorphisms of this enzyme play a role in its PK.[62,63]

Walsh et al. demonstrated a non-linear elimination for the dose range of 4 mg/kg every 12 hours and 8 mg/kg every 12 hours.[64] The clearance in children is higher than in adults, and the bioavailability is lower (65%); a dose of 7 mg/kg may provide plasma concentrations comparable to exposures in adults given 4 mg/kg.[64,65] Plasma levels of voriconazole in children are highly variable; this is especially true in young infants. Plasma levels should therefore be monitored in a neonate who receives this product.[66–68] In a study of 10 children with a median age 17 months (range 2 weeks–35 months), voriconazole trough concentrations were highly variable and did not correlate with the dose administered.[69]

Voriconazole is safe in adults. Children and adults experience the same adverse effects: transient visual disturbances and photosensitivity.[64,67,70–72] Mild transient elevation of hepatic enzyme levels has also been observed.[64,67] Voriconazole clinical trials have not been performed in infants.[73] This product should be reserved as a second- (or third-) line agent, primarily in the context of resistance or in the rare case of invasive aspergillosis in the nursery.

Posaconazole

Posaconazole is available in an oral formulation and has extended activity against *Candida spp*., *Aspergillus spp*., *C. neoformans*, and zygomycetes.[74,75] Posaconazole is approved for prophylaxis of invasive *Aspergillus* and *Candida* infections and for treatment of oropharyngeal candidiasis in patients ≥13 years of age.

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Posaconazole has a half-life of 25 hours[76] and is excreted unchanged in the feces; renal elimination is minor, and the drug is not a substrate for the cytochrome P-450 enzymatic system.[77]

Experience with posaconazole in children is limited. In a retrospective study including 15 patients aged 3–17 years, posaconazole was used as salvage therapy for invasive fungal infections in immuno-compromised children and adolescents.[78] In a PK study that included 12 patients <18 years of age, posaconazole concentrations in plasma were similar for juvenile and adult patients, following a dose of 400 mg/kg twice daily.[79] There are no published studies in infants, but higher doses are likely needed for younger patients.

ECHINOCANDINS

Echinocandins are non-competitive inhibitors of 1,3-β-D-glucan synthase, an enzyme that is necessary for the synthesis of 1,3-β-D glucan. Without this component, the fungal wall cell is compromised.[80] The echinocandins have a large molecular weight and poor penetration into the CSF[81]; however, micafungin and anidulafungin can be given in dosages in which the products successfully achieve maximum killing concentrations inside the CNS. These studies have been conducted in a series of animal model experiments followed by neonatal PK trials.[82,83]

Micafungin

Micafungin exhibits broad-spectrum activity against clinically important pathogens including azole-resistant *Candida albicans*.[84] It is fungicidal against *Candida spp*. and fungistatic in vitro against *Aspergillus spp*.[84,85] Micafungin is an intravenous antifungal approved in the United States for adult patients and has been approved for use in children (including infants) in Europe for treatment of invasive candidiasis.[86] Trials in patients >16 years of age (and 1 including children from 0 week to 16 years of age) found that micafungin has the same efficacy against invasive candidiasis as amphotericin B,[87–89] fluconazole,[90] or caspofungin[91] with fewer adverse events than amphotericin B deoxycholate.[87,88]

Micafungin has a half-life of approximately 12 hours in adults; the highest drug concentrations are detected in the lungs, liver, spleen, and kidneys.[92,93] Micafungin is highly plasma protein-bound. Metabolism occurs mainly in the liver but, because the echinocandins are poor substrates for the cytochrome P450 enzymes, few drug interactions are described. Fecal excretion is the major route of elimination.[81]

Of the echinocandins, the PK of micafungin is the best described across all pediatric age groups. In children with fever and neutropenia, micafungin (0.5–4 mg/kg/day) demonstrated linear PK, and clearance was inversely related to age.[94] To achieve micafungin exposures equivalent to adults, children require dosages >3 mg/kg.[19] However, the clearance of micafungin in premature infants is faster than in older children and adults; age-dependent serum protein-binding of micafungin might be responsible for its higher clearance.[95]

Elevated dosing in the premature infant is thought to be critical for getting micafungin into the central nervous system.[82] After administration of >2 mg/kg of micafungin to rabbits, micafungin was detected in most brain compartments (meninges, spinal cord, choroid, cerebrum, cerebellum, and aqueous humor).[82] For lower doses (0.5–1.0 mg/kg), micafungin was not detected.[82] PK data obtained in 12 premature infants (mean gestational age of 27 weeks) suggest that a micafungin dose of 15 mg/kg/day achieves similar exposures to those observed in adults receiving 5 mg/kg/day.[96] A dose of 10 mg/kg/day provided target

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systemic exposure corresponding to levels adequate to provide CNS penetration and is thought to be the optimal dose for premature and term infants.[20,97]

The most common adverse events related to micafungin include: gastrointestinal tract manifestations (nausea, diarrhea), hypersensitivity reactions, elevation of liver enzymes, and hypokalemia.[89,94] King et al. presented a case of hepatitis related to micafungin in a 44–day-old infant.[98] Micafungin doses from 0.75–15 mg/kg/day have been studied in children.[21,96,99]

Anidulafungin

Anidulafungin has activity against *Candida* and *Aspergillus sp*. in adults. It has been used in the treatment of esophageal and systemic candidiasis[100–102] and is FDA-approved for use in adults. Anidulafungin demonstrates linear PK with a long half-life: approximately 26 hours for adults and 20 hours for children. [22,103] Clearance of anidulafungin appears to be primarily due to slow chemical degradation, and it is eliminated in the feces predominantly as a degradation product. Fecal elimination likely occurs via biliary excretion. Once it is degraded in the blood, it does not require dosage adjustment in subjects with hepatic or renal impairment.[104] The tissue concentrations after multiple dosing are highest in the lungs, liver, spleen, and kidneys, with measurable concentrations in the brain tissue.[105]

Children ages 2–17 years with neutropenia were given anidulafungin (1.5–3 mg/kg loading dose, 0.75–1.5 mg/kg/day maintenance dose) and had exposures similar to adult patients receiving the same weight-adjusted dose; they achieved steady-state plasma concentrations after administration of a loading dose.[22] Anidulafungin was administered to 15 patients <18 months of age intravenously as a loading dose of 3 mg/kg on day 1, with daily maintenance dosages of 1.5 mg/kg. Among the patients, there were 8 newborns with a median gestational age of 27 weeks (range 26–39), median birth weight of 1120 g (770–3730), and median postnatal age of 28 days (range 2–451).[23] Infants receiving 1.5 mg/kg/day had similar anidulafungin exposures compared with children receiving similar weight-based dosing and adult patients receiving 100 mg/day. [22,23,100] Two patients supported by extracorporeal membrane oxygenation had lower drug exposure.[23,106] High-dose anidulafungin (10 mg/kg/day) reduced fungal load in murine brains, but a lower dose (5 mg/kg/day) in the same animal model was not effective.[83] The adequate dose for infants to achieve CNS penetration with anidulafungin is unknown.

Anidulafungin is well-tolerated in the pediatric population.[22,23] Adverse events occurred in few patients; the most commonly reported adverse event was transient liver function test elevations, and 2 infants showed worsening of baseline bilirubin levels.[22,23]

Caspofungin

Caspofungin has activity against both *Candida sp*. and *Aspergillus sp*.[107] Caspofungin is FDA-approved for adults and children >3 months of age. The typical adult dose is 50 mg daily after a 70 mg loading dose.[108,109] The metabolism of caspofungin is hepatic, and its half-life is 9–10 hours.[110] Patients with renal insufficiency do not need dose adjustments[111]; however, decrease of daily dosage is necessary in patients with hepatic insufficiency.[112]

The PK of caspofungin was first evaluated in children in a study of 39 patients aged 2–17 years (29 patients <1 years of age); a dose of 50 mg/m^2/day provided similar exposures to an adult dose of 50 mg/kg.[24] Caspofungin clearance is increased in children, as demonstrated by lower exposures and shorter half-life (8 hours) compared with adults.[24] At the same time, the maximum concentration is higher after a loading dose.[25] In children, the main use of caspofungin has been in refractory cases of invasive candidiasis as a salvage or combination

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therapy.[113,114] Most recently, some studies have made use of the medication as the primary treatment for invasive candidiasis[115] or for empiric antifungal therapy.[116]

In infants and toddlers with fever and neutropenia, caspofungin 50 mg/m^2/day produced similar steady-state exposures as those observed in older children with the same dose.[117] A dose of 25 mg/m^2/day in 18 infants <3 months of age resulted in peak concentrations lower than those in older children given 50 mg/m^2/day and similar concentrations to those seen in adults administered 50 mg/day.[25]

The efficacy of caspofungin against CNS candidiasis has not yet been demonstrated.

The most common adverse events are fever, headache, and rash. Increase of hepatic transaminases and hypokalemia was found in few patients.[24,116] In a cohort of 18 infants (gestational age 24–41 weeks), 94% of the patients presented 1 or more clinical adverse events; none were considered to be related to caspofungin.[25] In a retrospective study with infants (≤3 months of age), caspofungin was not associated with any serious adverse events.[118]

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Summary

Invasive fungal infections remain a significant cause of infection-related mortality and morbidity in preterm infants. CNS involvement is the hallmark of neonatal candidiasis, differentiating the disease's impact on young infants as compared with all other patient populations. As such, CNS involvement substantially influences candidiasis treatment in infants. Over the past decade, the number of antifungal agents in development has grown exponentially, but most are not labeled for use in newborns. More clinical trials and PK studies are required for the new antifungals to be used in infants.

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Synopsis

Invasive fungal infections remain a significant cause of infection-related mortality and morbidity in preterm infants. Central nervous system involvement is the hallmark of neonatal candidiasis, differentiating the disease's impact on young infants from that among all other patient populations. Over the past decade, the number of antifungal agents in development has grown, but most are not labeled for use in newborns. We summarize the findings of a number of antifungal studies that have been completed to date emphasizing those including infant populations. We conclude that more studies are required for antifungals to be used safely and effectively in infants.

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Table 1

Pediatric Antifungal Dosing[14–25]

Drug	Formulation	Infants (31 days–2 years)	Neonates (0–30 days)	FDA label
Polyenes				
Amphotericin B deoxycholate	IV	1 mg/kg/day	1 mg/kg/day	children and adults
ABLC	IV	unknown	unknown	>16 months
ABCD	IV	unknown	unknown	children and adults
L-Amphotericin B	IV	5 mg/kg/day	5 mg/kg/day	≥1 month
Nucleoside analogs				
5-Flucytosine	PO	50–150 mg/kg/day q 6 hr	50–150 mg/kg/day q 6 hr	adults
Triazoles				
Fluconazole	IV, PO	12 mg/kg/day (25 mg/kg/loading dose)	12 mg/kg/day (25 mg/kg load)	≥6 months
Voriconazole	IV, PO	unknown	unknown	≥12 years
Posaconazole	PO	unknown	unknown	≥13 years
Echinocandins				
Caspofungin	IV	50 mg/m^2/day	25 mg/m^2/day	>3 months
Micafungin	IV	10 mg/kg/day	10 mg/kg/day	adults
Anidulafungin	IV	1.5 mg/kg/day (3 mg/kg/loading dose)	1.5 mg/kg/day (3 mg/kg/load)	adults

IV: intravenous; PO: oral

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Table 2

Fluconazole Prophylaxis Studies

Author/Year	Study Design	Population	N	Drug Regimen	Outcomes
Aydemir[9] 2010	RCT	VLBW	93 FP 94 NP 91 Placebo	fluconazole: 3 mg/kg q 3 days nystatin: 1 ml every 8 hours	IC rate 3% FP, 4% NP vs. 17% placebo (p<0.001) Similar mortality: 9% FP, 9% NP, 12% placebo
Rueda[57] 2010	retrospective cohort	<1250 g	252 FP 272 Control	3 mg/kg every q 48 hours	IC rate decreased 8% control – 1% FP (p=0.007) IC-related mortality decreased 6% to 1% (p=0.003)
Aziz[52] 2010	retrospective cohort	ELBW	163 FP 99 Control	3 mg/kg q 48–72 hours	IC rate decreased 7% control – 2% FP (p=0.045)
Weitkamp[58] 2008	retrospective cohort	<750 g	42 FP 44 Control	3 mg/kg twice weekly	IC rate decreased 20% control – 0% FP (p=0.004) Similar mortality: 20% control, 26% FP
Healy[54] 2008	retrospective cohort	ELBW	362 FP 206 Control	3 mg/kg q 24–72 hours	IC rate decreased 7% control – 2% FP (p=0.003) IC-related mortality 2% control, 0% FP (p=0.1)
Parikh[13] 2007	RCT	VLBW	60 FP 60 Placebo	3 mg/kg q 24–72 hours	IC rate 25% placebo – 26% FP (p=0.835) Same mortality: 28% in both groups
Manzoni[12] 2007	RCT	VLBW	112 HD 104 LD 106 Placebo	6 mg/kg (HD) or 3 mg/kg (LD) q 48–72 hours	IC rate decreased 13% (placebo) – 3% HD (p=0.05) and 13.2% (placebo) – 3.8% LD (p=0.002) Similar mortality: 8% HD, 10% LD, and 9% placebo
McCrossan[56] 2007	retrospective cohort	VLBW	31 FP 33 Control	6 mg/kg q 24–72 hours	IC rate decreased 6% control – 0% FP (p=0.03) IC-related mortality: 12% control, 0% FP (p=0.11)
Manzoni[55] 2006	retrospective cohort	VLBW	225 FP 240 Control	6 mg/kg q 48–72 hours	IC rate decreased 17% control – 5% FP (p<0.0001) Similar mortality: 11% control, 11% FP
Kaufman[59] 2005	RCT	ELBW	41 FP previous 40 FP twice/week	3 mg/kg twice weekly or q 24–72 hours	IC rate 5% previous – 3% twice a week (p=0.68) Similar mortality: 13% control, 8% FP (p=8.1%)
Bertini[53] 2005	retrospective cohort	VLBW	136 FP 119 Control	6 mg/kg q 24–72 hours	IC rate decreased from 8% control – 0% FP (p=0.003)
Healy[60] 2005	retrospective cohort	ELBW	240 FP 206 Control	3 mg/kg q 24–72 hours	IC rate decreased 7% control – 2% FP (p=0.01)

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Author/Year	Study Design	Population	N	Drug Regimen	Outcomes
					IC-related mortality: 12% control, 0% FP (p=0.4)
Kicklighter[11] 2001	RCT	VLBW	53 FP 50 Placebo	6 mg/kg q 24–72 hours	Fungal colonization decreased 46% placebo – 15% FP (p=0.0005) IC rate or mortality not related
Kaufman[10] 2001	RCT	ELBW	50 FP 50 Placebo	3 mg/kg q 24–72 hours	IC rate decreased 20% placebo – 0% FP (p=0.008) Similar mortality: 20% placebo, 8% FP (p=0.22)

FP: fluconazole prophylaxis group; NP: nystatin prophylaxis group; IC: invasive candidiasis; HD: high-dosage group; LD: low-dosage group; RCT: randomized controlled trial.