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Review

Treatment of fungal infections: an update

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Abstract

Fungal infections represent a serious problem in neonatal intensive care units (NICUs) worldwide. Preterm infants are a vulnerable population for major events and adverse sequelae from fungal sepsis. The primary fungus of concern in neonates is *C. albicans*, whose colonization is associated with devastating complication and high rate of mortality. Among the risk factors responsible for development of invasive fungal infections, previous mucosal and skin colonization are of primary importance. Fungal colonization in neonates may be secondary to either maternal transmission or nosocomial acquisition in the nursery.

Antifungal prophylaxis is currently applied in different NICUs and in various patients groups with successful results. Prophylactic drugs can include oral nystatin and oral or intravenous fluconazole. To date, antifungal prophylaxis with fluconazole is the recommended approach for neonates lower than 1,000 g and/or 27 weeks' gestation or less, manly in NICUs with relatively high frequency of invasive candidiasis.

First-line treatment of invasive fungal infections includes amphotericin B deoxycholate, lipid preparations of amphotericin B, fluconazole, or micafungin. However, data on pharmacokinetic, schedule treatment and appropriate dosage of antifungal agents in neonates, mainly in premature, are still limited.

Future strategies to reduce neonatal morbidity and mortality derived from invasive fungal infections include new echinocandins not yet approved

for neonatal use (caspofungin or anidulafungin) and other adjuvant treatments as intravenous immunoglobulin, lactoferrin or probiotics. Since current therapies for systemic fungal diseases are not universally successful and morbidity remains high, future efforts will be also focused on better prevention of fungal diseases and understanding of appropriate dosing schedule of the available antifungal agents.

Keywords

Invasive fungal infection, candidiasis, neonates, preterm infants, prophylaxis, treatment.

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Fungal infections in neonates

Neonates are predisposed to infections during the perinatal period due to multiple exposures and a relatively compromised immune system [1]. Worldwide, it is estimated that more than 1.4 million neonatal deaths annually are the consequence of invasive infections [1]. Invasive fungal infections (IFIs) represent an increasing cause of severe morbidity and mortality in most neonatal intensive care units (NICUs), especially among infants who receive broad spectrum antimicrobial agents, in very preterm (< 32 weeks) and very low birth weight (VLBW, < 1,500 g) infants [2-4]. The highest incidence of IFIs in VLBW infants is recorded between the second and sixth weeks after birth [5]. Most IFIs are the consequence of *Candida spp.* colonization, spreading and disseminating from peripheral entry site, while other fungi (e.g. *Aspergillus spp.*) are very uncommon [6]. However, although less prevalent, fungi other than *Candida spp.* should be considered when signs and symptoms of sepsis arise in neonates, also because response to antifungal treatment is limited in this population, leading to death for disseminated fungal infection in most of affected neonates. Colonization with *Candida spp.* in neonates may be secondary to either maternal vertical transmission or horizontal (nosocomial acquisition) in the nursery or NICUs [5].

In VLBW infants, candidemia is associated with a mortality rate of 21-32% in multicenter studies. Less than 26 weeks' gestation and a birth weight of less than 1,000 g correlate with increased mortality rates (40-50%) [7]. IFIs are associated with poor early and late outcomes (neurological impairment, chronic lung disease, retinopathy of prematurity) and severe neurodevelopmental impairment at 18 months of age affects up to 57% of survivors [2].

There is a huge variability of reported incidence rates of IFIs from NICU to NICU, with a range of 2-25% [8]. An incidence of invasive candidiasis (IC) of 7-8% has been reported in extremely low birth weight (ELBW) infants. Lower incidence has been reported in a 14-year study period (from 1997 to 2010) [9]. This wide reported difference in incidence rates may depend on a number of variables as the diagnostic criteria of IFIs, the use of fluconazole prophylaxis and empirical antifungal therapy, and a decreased use of broad-spectrum antibiotics.

Many conditions, treatments, and procedures in the NICUs place neonates at an increased risk for fungemia. Some risk factors are included in the standard risks that pertain to adult patients, such as central venous catheter or antibacterial agents' use [10]. However, in the neonates, both incidence and outcomes are also linked to other risk factors as the gestational age and the birth weight of the baby. In a multicenter, retrospective, cohort study of NICUs patients (n = 6,172), newborns born at a gestational age between 25 and 27 weeks (odds ratio [OR]: 2.02; 95% confidence interval [CI]: 1.52-3.05) and less than 25 weeks (OR: 4.15; 95% CI: 3.12-6.29) were at higher risk of developing candidemia than were children who were born at more of 28 weeks [11]. Furthermore, in the same study, thrombocytopenia and cephalosporin or carbapenem use in the 7 days before obtaining the blood culture were risk factors for subsequent candidemia [11].

The prior colonization by the same fungus is the condition most frequently associated with IFIs. In a prospective study including 593 neonates during 12 months, fungal colonization was detected in 12% of neonates, being *C. albicans* the most common colonizing pathogen (42% of colonized neonates) [12]. The Authors found a rate of 1% of

IFIs. However, these episodes occurred in 6.9% of colonized neonates, and in only 0.76% of non-colonized infants (p = 0.002), suggesting that monitoring for colonization in the highest-risk infants may be beneficial [12]. In a large Italian study, colonization occurred in 32.1% of VLBW neonates, and IFIs occurred in 8.1% of them [13]. At univariate analysis, 10 factors (low birth weight, low gestational age, use of third-generation cephalosporins, endotracheal intubation, duration of stay in the NICU, bacterial sepsis, colonization of central venous catheter, of endotracheal tube, of gastric aspirate, or in multiple sites) were associated with an increased risk to develop IFIs. However, following logistic regression, only colonization of central venous catheters and colonization at other sites remained significant for IFIs [13].

Prophylaxis of fungal infections

Diagnosis of IFIs 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 effort directed toward prevention, and antifungal prophylaxis has been investigated as a potential preventive measure.

Fluconazole is an azole with a long half-life, very good cerebrospinal penetration, low protein binding and good tissue, body fluids and mucocutaneous areas levels (higher than plasma ones). These characteristics allow an excellent tissue penetration and easy elimination of this drug. At present time, antifungal prophylaxis with fluconazole is routinely used in about 40% of European NICUs and there is a trend towards an increasing use of this practice [14]. The studies of fluconazole prophylaxis have both significantly reduced fungal infections, as well as nearly eliminated *Candida*-related mortality [15]. Since eliminating *Candida*-related adverse events is critical in preterm infants, prophylaxis appears to be the best approach in infants lower than 1,000 g. In other groups of neonates, the correct management is still controversial because of lacking of randomized controlled trials (RCTs). Waiting for positive cultures, or using empiric antifungal therapy with all sepsis evaluations in infants of less than 1,500 g or using a risk-based approach in this groups are still debated [15].

Nystatin was the first antifungal studied in preterm infants. However, nystatin prophylaxis has been investigated in only one RCT and few retrospective or epidemiologic studies [16-18]. In a recent systematic review of nine RCTs including 2,029 infants, both fluconazole and oral nystatin were demonstrated highly effective in preventing IFIs in VLBW infants [19]. Both agents were safe without significant toxicities [19]. On the other hand, in another trial in ELBW infants, Violaris et al. found no significant difference in IC in fluconazole-treated infants (5.3%) compared with nystatin-treated group (14.3%), but all-cause mortality was zero in the fluconazole-treated group compared to 7.5% in the nystatin-treated one (p = 0.03) [20]. These data raised the question of whether nystatin is safe to give enterally to extremely preterm infants. To date, safety data on nystatin are lacking.

In a review meta-analysis including seven trials (n = 880 infants) on systemic antifungalprophylaxis versus placebo or no drug, a statistically significant reduction in the incidence of IFIs in VLBW infants who received systemic antifungal prophylaxis was found [21]. However, the Authors concluded that this finding should be interpreted cautiously since the incidence of IFIs was very high (16%) in the control groups of most of the included trials. A meta-analysis does not demonstrate a statistically significant effect on mortality [21]. Furthermore, limited data on the long-term neurodevelopmental outcome in infants exposed to fluconazole prophylaxis are available.

In a very recent randomized, blinded, placebo-controlled trial of fluconazole (6 mg/kg of body weight) in 361 premature infants weighing less than 750 g at birth, 42 days of fluconazole prophylaxis compared with placebo did not result in a lower incidence of death or IC [22].

Furthermore, concerns regarding resistance of fungal strains should be considered when a prophylactic treatment is started. However, the available studies have shown no fluconazole-resistant strains of *Candida spp.* or an increased likelyhood of invasive infections with resistant strains [23].

According to these findings, the Scientific Societies are currently supporting the use of fluconazole prophylaxis at a dosage of 3-6 mg/kg twice weekly (intravenous or orally) for all neonates < 1,000 g or ≤ 27 weeks gestational age admitted in NICUs with relatively high frequency (5-10%) of IFIs (AI level of evidence) [24, 25]. For NICUs with a lower incidence of IFIs (< 2%) and in other neonates-related conditions (e.g. birth weight of 1,000-1,500 g), the decision to use fluconazole prophylaxis regimen should be made on a case by case basis, and a risk stratification strategy (e.g. presence of central venous catheters or ongoing

antibiotic therapy) should be applied (BII level of evidence) [25].

Treatment of fungal infections

A number of variables need to be carefully evaluated when instituting antifungal treatment in neonates. Considering that *C. albicans* is the predominant isolate in many neonatal fungal bloodstream infections, fluconazole is commonly used as empiric antifungal therapy in NICUs. However, efficacy data on antifungals, dosing regimens and duration of treatment of IFIs are scant, mainly in preterm infants.

A major point is the proper assessment of the causative fungal pathogens involved. *C. albicans* ranks first (58% of cases) and *C. parapsilosis* second (34%); however, other *Candida spp.* may be involved, that are inherently resistant (partially or totally) to fluconazole [26].

Because cultures from deep sites are frequently negative in neonates, a definitive diagnosis of IFIs in this population may be problematic. Furthermore, although blood cultures are the gold standard for detecting candidemia, they have low sensitivity for IC [27]. In presence of a blood culture positive for *Candida spp.*, cultures from other sites as urine and/or cerebrospinal fluid (CSF) should be obtained [27]. A positive urine culture in a premature infant, obtained by either sterile urethral catheterization or suprapubic aspiration, should be viewed as equivalent to positive blood cultures and it warrants a prompt antifungal treatment [27, 28]. In a recent analysis including 1,515 infants, no difference in death or neurodevelopmental impairment was found between infants with candiduria and those with candidemia, providing evidence that also ELBW infants with candiduria are at substantial risk of death or neurological sequelae [28].

Before choosing an antifungal as empirical or treatment therapy for *Candida spp.* infections, clinicians should also know whether their center routinely uses fluconazole as prophylaxis.

In spite of the need for aggressive treatment, few antifungal drugs are available and their use is characterized by a large inter-NICU variability in dose and scheme. Amphotericin compounds and fluconazole provide coverage for the most common neonatal *Candida spp.* and, consequently, they represent the best choices pending species identification [29].

Amphotericin B deoxycholate is a polyene with a very broad spectrum, including most species of *Candida* [27]. It is the mainstay in the treatment of IFIs in newborns. Typical dosing of 1 mg/kg daily is recommended [24]. Nephrotoxicity is an important side effect observed with use of amphotericin B deoxycholate[30]. Other amphotericin B lipid products (liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion) are widely used in NICUs [31]. These formulations seem to have no significant renal or hepatic toxicities [30]. However, because renal penetration is limited with lipid formulations, negative urine cultures should be documented in infants for whom these preparations are used as monotherapy.

Fluconazole is well tolerated and it is effective against most *Candida spp.*, with the exception of *C. glabrata* and *C. krusei* [27]. Due to its long half-life, a therapeutic serum concentration may not be achieved until several days into therapy. Recently, it has been reported that an effective dosing strategy to reach therapeutic serum concentrations quickly is to start with a loading dose of 25 mg/kg followed by 12 mg/kg/day [32]. This schedule was safe with no adverse events, although it was tested in a small cohort of young infants. Fluconazole has excellent penetration into the central nervous system, achieving CSF concentrations similar to serum levels [31, 33]. Furthermore, fluconazole should be considered as a first-line therapy in infants with candiduria because it is primarily excreted unchanged in the urine, while amphotericin lipid products do not penetrate well into the kidney [27]. Although it is an "old" antifungal drug, a recent multicenter study has shown that fluconazole treatment for neonatal sepsis is scantly used in Italian NICUs (45% of cases) [34]. Major concerns are related to its efficacy in the treatment of IFIs [34]. There are no data available in neonates on second-generation triazoles as voriconazole, posaconazole and ravuconazole.

The increase in neonatal fungal sepsis and resistant organisms has highlighted the need to review use of routine empiric fluconazole, to implement preventive measures, and to develop new antifungal drugs. In recent years, the development of new agents has significantly improved therapeutic outcomes in neonates with IFIs. Echinocandins are effective against all species of *Candida* [27]. They are non-competitive inhibitors of 1,3-β-D-glucan synthase, enzyme necessary for the synthesis of 1,3-β-D-glucan which preserve the integrity of fungal wall cell [30]. The echinocandins are increasingly used for

treatment of IC in the NICUs, although higher doses seem to be required in neonates than in older children and adults [29]. These drugs are effective against *C. albicans* isolates with high minimum inhibitory concentrations compared to fluconazole, as well as often-resistant *C. glabrata* and *C. kruseii* [29]. Monitoring of liver function tests, electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, and magnesium should be done daily for several days initially and then periodically if normal throughout treatment with these drugs [15]. There are currently three echinocandins (caspofungin, micafungin, and anidulafungin) available and marketed for adult use in the United States (**Tab. 1**). Micafungin is the only echinocandin, to date, authorized for neonatal use in Europe. The recommendation for micafungin 4-10 mg/kg/day (BII level of evidence) is based on pharmacokinetic studies [25]. A micafungin dosing of 10 mg/kg/day also appears to be safe for use in term and preterm infants for management of IC [35]. Regarding caspofungin dosing, neonatal clinical studies had used 1 to 2 mg/kg, but pharmacokinetic data indicate that 2.5 mg/kg should be used [15]. Anidulafungin is currently not approved for use in children. A better understanding of proper dosing and safety of these new antifungal agents in neonates is needed. Observational and pharmacokinetic studies are emerging, but to date there are no RCT comparing these to other antifungals as fluconazole.

In conclusion, in a neonate with proven or suspected IFI, an appropriate dose of fluconazole, amphotericin product, or micafungin should be given. If the patient is receiving fluconazole prophylaxis or if *C. glabrata* (which is often resistant to fluconazole) is isolated, an amphotericin product or micafungin should be used [27]. In all cases, the total course of therapy should be 21 days after microbiologic clearance is documented, and neurodevelopmental follow-up of survivors is recommended [27].

Table 1. Indication of echinocandins use in neonates.

	Studies in neonates	Neonatal indications	Recommended dosing
Micafungin	Yes	Yes in Europe	4-10 mg/kg/day
Caspofungin	Few	No[a]	2.5 mg/kg/day or 25 mg/m^2/day[b]
Anidulafungin	Scarce	No	1.5 mg/kg/day

[a]Approved for infants > 12 months; [b]the use of body surface area as a metric of size may be inaccurate in neonates.

Future strategies

Administration of intravenous immunoglobulin (IVIG) has been recently hypothesized as a possible strategy to prevent and treat infectious morbidity and mortality [36, 37]. IVIG may be an appealing strategy to fight sepsis mainly in preterm infants because they have less endogenous immunoglobulins (IgG) whose transplacental transfer mainly occurs after 32 weeks of gestation.

Results of a recent trial, which enrolled 3,493 neonates receiving antibiotics for suspected or proven serious infection and randomly assigned them to receive 2 infusions of either polyvalent IgG (500 mg per kilogram of body weight) or placebo, showed no significant differences in the rates of death, major or non major disabilities at 2 years of age [38]. Following this trial, in a Cochrane review on the use of IVIG in neonates with sepsis, the Authors concluded that, on the bases of the available studies, routine administration of IVIG to prevent mortality in infants with suspected or proven neonatal infection is not recommended [36]. In another Cochrane review, the same Authors reported that in preterm and/or low birth weight infants, IVIG administration resulted in a 3% reduction in sepsis and a 4% reduction in one or more episodes of any serious infection, but it was not associated with reductions in other clinically important outcomes, including mortality [37]. Furthermore, prophylactic use of IVIG was not associated with any short-term serious side effects.

In a pilot retrospective study, IgM enriched immunoglobulins (IgM-eIVIG) have been demonstrated effective as adjuvant therapy in reducing short-term mortality in VLBW infants with proven sepsis [39]. When compared with IVIG, IgM-eIVIG show more efficient complement activation, better opsonisation, greater neutralization of the streptococcal superantigen SpeA and better binding both to bacterial antigens and toxins all possibly due to their pentameric structure [40]. This biological background together with some positive effects of this therapeutic strategy obtained in other settings may increase the interest towards IgM-eIVIG use in VLBW infants with sepsis.

Other possible strategies for prevention and treatment of sepsis in neonates include the use of

molecules that target inflammation, as lactoferrin, or modulate intestinal microbioma [41-43].

Oral lactoferrin prophylaxis (100 mg/day) seems to reduce the incidence of late-onset sepsis in infants weighing less than 1,500 g and most effective in infants weighing less than 1,000 g [44]. Studies evaluating the effects of lactoferrin in the prevention of neonatal sepsis are currently in progress, with promising results. However, more data are mandatory to verify the safety and efficacy of lactoferrin as an immunoprophylactic agent and/or therapeutic adjuvant in vulnerable preterm neonates.

In newborns, interactions between the host and the microbiome operate synergistically, modulating host immune function and shaping the microbiome. It is hypothesized that probiotics act to down-regulate pathogenic organisms and protect against intestinal inflammation. Dysbiosis seems to be involved in infection-related disease states, including neonatal late-onset sepsis [42]. Studies of oral probiotic (*Lactobacillus casei subsp. rhamnosus* 10^6 colony-forming units per day) administered from the third day of life until either the end of the sixth week of life or until discharge from the NICU suggest that this approach prevents enteric colonization by *Candida spp.*, but has no impact on the overall incidence of IC [45]. More data on the probiotic species to be used, the optimal dose, dosing strategy and duration of treatment are needed.

Finally, antibodies or their engineered derivatives directed against cell-wall polysaccharides and glycopeptides, and some protein epitopes of *C. albicans* appear to be a promising novel approach for prophylaxis against *Candida spp.* infection and deserve further investigations [46].

Conclusions

Neonatal IFIs are associated with significant morbidity and mortality. The incidence of fungal infection, however, varies greatly by center. Blood culture, although not a sensitive test, remains the only reliable method for diagnosis of invasive *Candida spp.* infection.

Fluconazole prophylaxis has been shown, in several carefully performed, randomized, placebo-controlled studies, to reduce *Candida spp.* colonization and IFIs rates without emergence of drug resistance and without adverse effects during extended periods of time. However, future studies will have to provide additional information on some unsolved issues like the effect of fluconazole on overall mortality, efficacy of prophylaxis for shorter periods of time, interaction with other drugs and identification of subpopulations with the most beneficial outcome. As well, a carefully monitoring of the possible development of fluconazole resistance is needed.

Amphotericin B deoxycholate, fluconazole, or micafungin represent the treatment of choice in infants with IFIs. However, optimal dosage and duration of antifungal agents have not been fully tested in neonates, mainly in preterm infants, and their use still represent a challenge for neonatologists.

Because current therapies for systemic fungal diseases are not universally successful and morbidity remains high, research should be focused on preventing invasive disease by interrupting the process of colonization and preventing the development of serious fungal infections. It is desirable that most of the clinical and laboratory investigative efforts, already performed in adults to enhance the understanding of the epidemiology and treatment of IFIs, should be also incorporated in neonatal care.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Shane AL, Stoll BJ. Neonatal sepsis: progress towards improved outcomes. J Infect. 2014;68(Suppl 1):S24-32.
2. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, Duara S, Poole K, Laptook A, Goldberg R. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117(1):84-92.
3. Robinson JL, Davies HD, Barton M, O'Brien K, Simpson K, Asztalos E, Synnes A, Rubin E, Le Saux N, Hui C, Langley JM, Sauve R, de Repentigny L, Kovacs L, Tan B, Richardson SE. Characteristics and outcome of infants with candiduria in neonatal intensive care – a Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study. BMC Infect Dis. 2009;9:183.
4. Wynn JL, Tan S, Gantz MG, Das A, Goldberg RN, Adams-Chapman I, Stoll BJ, Shankaran S, Walsh MC, Auten KJ, Miller NA, Sánchez PJ, Higgins RD, Cotten CM, Smith PB, Benjamin DK Jr. Outcomes following candiduria in extremely low birth weight infants. Clin Infect Dis. 2012;54(3):331-9.
5. Leibovitz E. Strategies for the prevention of neonatal candidiasis. Pediatr Neonatol. 2012;53(2):83-9.
6. Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. Am J Perinatol. 2013;30(2):131-41.

7. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, Higgins RD. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19):2357-65.
8. Burwell LA, Kaufman D, Blakely J, Stoll BJ, Fridkin SK. Antifungal prophylaxis to prevent neonatal candidiasis: a survey of perinatal physician practices. Pediatrics. 2006;118(4):e1019-26.
9. Aliaga S, Clark RH, Laughon M, Walsh TJ, Hope WW, Benjamin DK, Kaufman D, Arrieta A, Benjamin DK Jr, Smith PB. Changes in the incidence of candidiasis in neonatal intensive care units. Pediatrics. 2014;133(2):236-42.
10. Steinbach WJ. Epidemiology of invasive fungal infections in neonates and children. Clin Microbiol Infect. 2010;16(9): 1321-7.
11. Benjamin DK Jr, DeLong ER, Steinbach WJ, Cotton CM, Walsh TJ, Clark RH. Empirical therapy for neonatal candidemia in very low birth weight infants. Pediatrics. 2003;112(3 Pt 1):543-7.
12. Farmaki E, Evdoridou J, Pouliou T, Bibashi E, Panagopoulou P, Filioti J, Benos A, Sofianou D, Kremenopoulos G, Roilides E. Fungal colonization in the neonatal intensive care unit: risk factors, drug susceptibility, and association with invasive fungal infections. Am J Perinatol. 2007;24(2):127-35.
13. Manzoni P, Farina D, Leonessa M, d'Oulx EA, Galletto P, Mostert M, Miniero R, Gomirato G. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. Pediatrics. 2006;118(6):2359-64.
14. Kaguelidou F, Pandolfini C, Manzoni P, Choonara I, Bonati M, Jacqz-Aigrain E. European survey on the use of prophylactic fluconazole in neonatal intensive care units. Eur J Pediatr. 2012;171(3):439-45.
15. Kaufman DA. Challenging issues in neonatal candidiasis. Curr Med Res Opin. 2010;26(7):1769-78.
16. Sims ME, Yoo Y, You H, Salminen C, Walther FJ. Prophylactic oral nystatin and fungal infections in very-low-birthweight infants. Am J Perinatol. 1988;5(1):33-6.
17. Ozturk MA, Gunes T, Koklu E, Cetin N, Koc N. Oral nystatin prophylaxis to prevent invasive candidiasis in Neonatal Intensive Care Unit. Mycoses. 2006;49(6):484-92.
18. Ganesan K, Harigopal S, Neal T, Yoxall CW. Prophylactic oral nystatin for preterm babies under 33 weeks' gestation decreases fungal colonisation and invasive fungaemia. Arch Dis Child Fetal Neonatal Ed. 2009;94(4):F275-8.
19. Blyth CC, Barzi F, Hale K, Isaacs D. Chemoprophylaxis of neonatal fungal infections in very low birthweight infants: efficacy and safety of fluconazole and nystatin. J Paediatr Child Health. 2012;48(9):846-51.
20. Violaris K, Carbone T, Bateman D, Olawepo O, Doraiswamy B, LaCorte M. Comparison of fluconazole and nystatin oral suspensions for prophylaxis of systemic fungal infection in very low birthweight infants. Am J Perinatol. 2010;27(1):73-8.
21. Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2013;4:CD003850.
22. Benjamin DK Jr, Hudak ML, Duara S, Randolph DA, Bidegain M, Mundakel GT, Natarajan G, Burchfield DJ, White RD, Shattuck KE, Neu N, Bendel CM, Kim MR, Finer NN, Stewart DL, Arrieta AC, Wade KC, Kaufman DA, Manzoni P, Prather KO, Testoni D, Berezny KY, Smith PB. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. JAMA. 2014;311(17):1742-9.
23. Lollis TR, Bradshaw WT. Fungal prophylaxis in neonates: a review article. Adv Neonatal Care. 2014;14(1):17-23.
24. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(5):503-35.
25. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC, Arikan-Akdagli S, Bassetti M, Bille J, Cornely OA, Cuenca-Estrella M, Donnelly JP, Garbino J, Herbrecht R, Jensen HE, Kullberg BJ, Lass-Flörl C, Lortholary O, Meersseman W, Petrikkos G, Richardson MD, Verweij PE, Viscoli C, Ullmann AJ. ESCMID guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clin Microbiol Infect. 2012;18(Suppl 7):38-52.
26. Manzoni P, Stronati M, Jacqz-Aigrain E, Maragliano R, Ruffinazzi G, Rizzollo S, Castagnola E, Farina D. Correct choices for correct treatments: key issues in the management of Candida infections in preterm neonates. Early Hum Dev. 2012;88(Suppl 2):S98-100.
27. Hsieh E, Smith PB, Jacqz-Aigrain E, Kaguelidou F, Cohen-Wolkowiez M, Manzoni P, Benjamin DK Jr. Neonatal fungal infections: when to treat? Early Hum Dev. 2012;88(Suppl 2):S6-10.
28. Wynn JL, Tan S, Gantz MG, Das A, Goldberg RN, Adams-Chapman I, Stoll BJ, Shankaran S, Walsh MC, Auten KJ, Miller NA, Sánchez PJ, Higgins RD, Cotten CM, Smith PB, Benjamin DK Jr. Outcomes following candiduria in extremely low birth weight infants. Clin Infect Dis. 2012;54(3):331-9.
29. Ericson J, Benjamin DK Jr. Old and new: Appropriate dosing for neonatal antifungal drugs in the nursery. Early Hum Dev. 2013;89:S25-7.
30. Testoni D, Smith PB, Benjamin DK Jr. The use of antifungal therapy in neonatal intensive care. Clin Perinatol. 2012;39(1): 83-98.
31. Ascher SB, Smith PB, Watt K, Benjamin DK, Cohen-Wolkowiez M, Clark RH, Benjamin DK Jr, Moran C. Antifungal therapy and outcomes in infants with invasive Candida infections. Pediatr Infect Dis J. 2012;31(5):439-43.
32. Piper L, Smith PB, Hornik CP, Cheifetz IM, Barrett JS, Moorthy G, Hope WW, Wade KC, Cohen-Wolkowiez M, Benjamin DK Jr. Fluconazole loading dose pharmacokinetics and safety in infants. Pediatr Infect Dis J. 2011;30(5):375-8.
33. Brammer KW, Farrow PR, Faulkner JK. Pharmacokinetics and tissue penetration of fluconazole in humans. Rev Infect Dis. 1990;12(Suppl 3):S318-26.

34. Pandolfini C, Marco S, Paolo M, Maurizio B. The use of ciprofloxacin and fluconazole in Italian neonatal intensive care units: a nationwide survey. BMC Pediatr. 2013;13:5.
35. Ascher S, Smith PB, Benjamin DK Jr. Safety of micafungin in infants: insights into optimal dosing. Expert Opin Drug Saf. 2011;10(2):281-6.
36. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database Syst Rev. 2013;7:CD001239.
37. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2013;7:CD000361.
38. INIS Collaborative Group, Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, Haque K, Salt A, Stenson B, Tarnow-Mordi W. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med. 2011;365(13):1201-11.
39. Capasso L, Borrelli AC, Parrella C, Lama S, Ferrara T, Coppola C, Catania MR, Iula VD, Raimondi F. Are IgM-enriched immunoglobulins an effective adjuvant in septic VLBW infants? Ital J Pediatr. 2013;39:63.
40. Stehr SN, Knels L, Weissflog C, Schober J, Haufe D, Lupp A, Koch T, Heller AR. Effects of IGM-enriched solution on polymorphonuclear neutrophil function, bacterial clearance, and lung histology in endotoxemia. Shock. 2008;29(2):167-72.
41. Lingappan K, Arunachalam A, Pammi M. Lactoferrin and the newborn: current perspectives. Expert Rev Anti Infect Ther. 2013;11(7):695-707.
42. Berrington JE, Stewart CJ, Cummings SP, Embleton ND. The neonatal bowel microbiome in health and infection. Curr Opin Infect Dis. 2014;27(3):236-43.
43. Indrio F, Neu J. The intestinal microbiome of infants and the use of probiotics. Curr Opin Pediatr. 2011;23(2):145-50.
44. Pammi M, Abrams SA. Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2011;(10):CD007137.
45. Manzoni P, Mostert M, Leonessa ML, Priolo C, Farina D, Monetti C, Latino MA, Gomirato G. Oral supplementation with Lactobacillus casei subspecies rhamnosus prevents enteric colonization by Candida species in preterm neonates: a randomized study. Clin Infect Dis. 2006;42(12):1735-42.
46. Ng TB, Cheung RC, Ye Xj, Fang EF, Chan YS, Pan WL, Dan XL, Yin CM, Lam SK, Lin P, Ngai PH, Xia LX, Liu F, Ye XY, Wang HX, Wong JH. Pharmacotherapy approaches to antifungal prophylaxis. Expert Opin Pharmacother. 2012;13(12):1695-705.