

Evolving Invasive Neonatal Systemic Candidiasis, a Review

Abstract

Preterm and low birth weight (LBW) infants are vulnerable to invasive candidiasis, usually caused by *Candida albicans* and *Candida parapsilosis*. Neonatal candidiasis, acquired after 6 days of life, is the most common form of invasive candidiasis in neonates. Once the *Candida* species penetrate any organ system, it can lead to complications such as meningitis, endocarditis, pyelonephritis, septic arthritis and pneumonia. In recent years, the incidence of invasive candidiasis has decreased in neonatal intensive care units (NICU) due to improvements in neonatal care; however, in the affected neonates, mortality remains a major concern. This is primarily attributable to the limitations of currently used diagnostic tests and delay in treatment. In addition, there is a lack of data on pharmacokinetics and pharmacodynamics of various anti-fungal therapeutic regimens in neonates. This review provides an overview of invasive candidiasis in neonates, including modes of transmission, its risk factors, and management, with special focus on the recent updates in diagnosis and treatment.

Keywords: Anti-fungal; Invasive candidiasis; Neonatal candidiasis; Neonates, Systemic candidiasis; Management

Introduction

Preterm and low birth weight (LBW) infants are commonly susceptible to invasive candidiasis, usually caused by *Candida albicans* and *Candida parapsilosis* [1-5]. Other non-albicans *Candida* species found to be associated with invasive candidiasis include: *C. glabrata*, *C. tropicalis*, *C. lusitanae*, *C. guilliermondii*, *C. pelliculosa*, *C. zeylanoides* and *C. krusei* [1-4].

Invasive candidiasis can be either acquired in-utero (within 6 days of life) or post-partum (after 6 days of life). If acquired in-utero, it is referred to as congenital candidiasis (CC). CC is usually cutaneous initially and becomes systemic later, known as congenital systemic candidiasis. It is a rare form of invasive candidiasis with very few cases (around 100) reported in medical literature [6,7]. The other type of infection is acquired after 6 days of life and is referred to as neonatal candidiasis. It is the common form of invasive candidiasis in neonates [6].

Once the *Candida* species enter blood stream, it is likely to penetrate into various body organs including central nervous system (CNS), heart, kidneys, liver, spleen and eyes. This can lead to complications such as meningitis, endocarditis, candida pyelonephritis, renal papillary necrosis, multiple parenchymal abscesses, endophthalmitis, septic arthritis and osteomyelitis, peritonitis, and pneumonia [8-10].

With advances in neonatal management, incidence of invasive candidiasis has decreased in neonatal intensive care units (NICUs) over the years. A study by Aliaga et al. (2014) reported a decrease in the annual incidence of invasive candidiasis from 3.6 episodes per 1000 patients to 1.4 episodes per 1000 patients among all infants from 1997 to 2010. On the basis of birth weight, the incidence decreased from 24.2 to 11.6 episodes per 1000 patients

among infants with a birth weight of 750-999 g, and from 82.7 to 23.8 episodes per 1000 patients among infants with a birth weight <750 g [11]. Another study by Chitnis et al. (2010) assessed the incidence of *Candida* species central line-associated bloodstream infections (CLABSIs) in US NICUs from 1999 to 2009. The study results showed a significant decrease in the incidence of CLABSIs due to *Candida* species (pooled mean rate of *Candida* spp. CLABSIs per 1000 central line-days reduced from 0.9 in 1999 to 0.2 in 2009; $p < 0.001$) [12]. However, the mortality rate associated with invasive candidiasis is reported to range from 19.6% to 63% and remains a major concern [1,4,13].

Despite the decrease in incidence of invasive candidiasis in neonates, the associated mortality rate is high in preterm and very LBW infants. High mortality can be attributed to the limitations of routinely used diagnostic tests (such as longer duration and insufficient amount of sample for testing) and delay in treatment (due to longer time taken for confirmation of diagnosis and lack of sufficient data on adequate dosing of antifungal therapy in neonates) [8,10,14]. Although, various antifungals have been developed for treatment of invasive candidiasis, there is scarcity of data on their pharmacodynamics and pharmacokinetics in neonates and children [15]. All these factors highlight the need for appropriate diagnosis and management of neonatal candidiasis.

The present review discusses the overview of invasive candidiasis in neonates, modes of transmission, its risk factors, and neurodevelopmental outcomes. Further, the review explains

Review Article

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the diagnosis and treatment of invasive candidiasis in neonates, with special focus on the recent updates in its management.

Modes of Transmission

Candidal infections can be transmitted in neonates *via* two modes:

i. Vertical transmission: It occurs due to maternal vaginal infection. *C. albicans* is responsible for 90% of the vaginal fungal colonization during pregnancy. Increased adherence of *Candida* to intermediate layers in the vaginal tract increases the risk of exposure of infants delivered vaginally to candidal infections [10]. CC occurs *via* vertical transmission and reported to occur rarely in medical literature [6].

ii. Horizontal transmission: It occurs nosocomially *i.e.*

acquired in hospitals, and is transmitted *via* contaminated medical devices, hands of healthcare workers, catheters, *etc.* *C. parapsilosis* is found to be the most common *Candida* species present on the hands of healthcare workers [16].

Risk Factors

Multiple risk factors in neonates contribute to invasive candidiasis. LBW (<2500 g) and earlier gestational age (29–32 weeks) are found to be commonly associated with invasive candidiasis in neonates. Other risk factors identified in clinical studies to be associated with invasive candidiasis are vaginal birth, central catheters, day of life (>7), use of broad-spectrum antibiotics in neonates, antenatal steroids, premature rupture of membranes, mechanical ventilation, necrotizing enterocolitis and parenteral nutrition (Table 1) [1,14,13,17].

Table 1 : Studies Assessing Risk Factors for Invasive Candidiasis in Neonates.

	Patient Population	Risk Factors
Barton et al. [13]	N (cases) = 49	<ul style="list-style-type: none"> · NEC (OR: 4.81 [95% CI: 1.14-20.41]; $p = 0.03$)
	N (control) = 90	
Lee et al. [51]	N = 330 (> 1500 g)	<ul style="list-style-type: none"> · Day of life >7 (OR 25.2; 95% CI 14.6–43.3)
		<ul style="list-style-type: none"> · Vaginal birth (OR 1.6 [1.2–2.3])
		<ul style="list-style-type: none"> · Central venous line (OR 1.8 [1.3–2.6])
		<ul style="list-style-type: none"> · Exposure to broad-spectrum antibiotics (OR 1.6 [1.1–2.4])
Oeser et al. [52]	N = 98	<ul style="list-style-type: none"> · Platelet count <50,000/mm³ (OR 3.7 [2.1–6.7])
		<ul style="list-style-type: none"> · NEC: 24 (30%)
		<ul style="list-style-type: none"> · Respiratory support: 73 (92%)
		<ul style="list-style-type: none"> · CVC: 51 (61%)
		<ul style="list-style-type: none"> · PN within 48 h: 77 (94%)
		<ul style="list-style-type: none"> · Trophic feeds within 48 h: 52 (63%)
		<ul style="list-style-type: none"> · Receipt of systemic corticosteroids: 8 (10%)
Wadile et al. [53]	N = 108	<ul style="list-style-type: none"> · H₂ receptor antagonists: 10 (12%)
		<ul style="list-style-type: none"> · Insulin 16 (20%)
		<ul style="list-style-type: none"> · Previous abdominal surgery: 11 (13%)
		<ul style="list-style-type: none"> · Intrapartum use of broad-spectrum antibiotics: 59 (95.16%)
		<ul style="list-style-type: none"> · Prematurity: 38 (61.29%)
		<ul style="list-style-type: none"> · LBW: 47 (79.03%)
Khan et al. [17]	N = 560 (36%) had positive cultures. <i>Candida</i> was isolated in 49 (8.8%) neonates with positive cultures.	<ul style="list-style-type: none"> · Indwelling catheters: 5 (8.06%)
		<ul style="list-style-type: none"> · Artificial ventilation: 26 (41.94%)
		<ul style="list-style-type: none"> · Male sex: 37 (59.67%)
		<ul style="list-style-type: none"> · Vaginal delivery: 53 (85.48%)
		<ul style="list-style-type: none"> · Mechanical ventilation: 41 (83.7%)
		<ul style="list-style-type: none"> · Prior antibiotic therapy: 45 (92%)
		<ul style="list-style-type: none"> · Partial PN 15 (30%)

*NEC: Necrotizing enterocolitis; PN: Parenteral nutrition

Neurodevelopment Outcomes in Neonates with Invasive Candidiasis

Invasive candidiasis in neonatal survivors is found to be associated with adverse neurodevelopmental outcomes. A study by Benjamin et al. (2006) reported neurodevelopmental impairment (NDI) or mortality in 73% of infants with invasive candidiasis. Moreover, infants who had delayed removal or replacement of central catheters (>1 day after initiation of antifungal therapy) were at increased risk of NDI [18].

In a study by De Hann et al. (2013), 29 neonates who survived *Candida* sepsis were followed up at 24 months to assess the neurological outcomes. Of the 29 neonates, 17 appeared for follow-up, and neurological examination showed mild and severe abnormality in 9 (53%) and 1 (6%) infants, respectively. The median value of Bayley Psychomotor Development Index (PDI) and Bayley Mental Development Index (MDI) were 76 (59-100) and 92 (78-108), respectively. Hearing disabilities and visual impairment occurred in 4 (24%) and 3 (18%) infants, respectively [19]. Another study by Adams-Chapman et al. (2013) assessed the neurodevelopmental outcomes of extremely LBW infants who survived following sepsis with *Candida* infection or non-*Candida* sepsis at 18 months of age. The study reported that 31% of infants in each group (with *Candida* sepsis and non-*Candida* sepsis) had NDI at 18 months. However, infants with *Candida* sepsis (OR: 1.83; 95% CI: =1.83 [1.01-3.33], $p = 0.047$) were reported to be at increased risk of NDI as compared to uninfected infants [20].

Another study assessed the neurodevelopmental outcomes in infants (≤ 1000 g) with invasive candidiasis who were receiving empirical antifungal therapy. The study reported that incidence of death or NDI was less in infants who received empirical antifungal therapy (19/38, 50%) compared with those who had not (55/86, 64%; OR = 0.27 [95% CI 0.08-0.86]). It was suggested that empirical antifungal prophylaxis should be initiated in LBW infants with risk of fungal infections to improve neurodevelopmental outcomes [2].

Management of Invasive Candidiasis

Diagnosis

Rapid diagnosis is the best possible way to successfully manage the preterm or full-term neonate with invasive candidiasis.

Body fluids culture: Blood culture is the most common diagnostic procedure used for detection of candidiasis [14]. Other commonly used methods include culture/microscopic examination of urine, cerebrospinal fluid, peritoneal fluid and other sterile body fluids [10].

However, blood culture to confirm diagnosis of invasive candidiasis in neonates has several limitations. Firstly, the availability of less amount of blood (0.5 to 1 mL) for culturing makes it difficult to isolate *Candida* in neonates. Secondly, the median time taken by blood culture to detect *Candida* species in infants is 36 hrs and might reach 42 hrs, if the infant is receiving antifungal therapy prior to blood culturing [14]. Further, speciation and susceptibility testing following isolation from blood culture adds on more days for diagnosis [21].

Also, the negative cerebrospinal fluid (CSF) culture in infants does not exclude the presence of candida meningitis. A study

reported presence of normal CSF parameters in almost half of the study patients with *Candida* meningitis [22]. Thus, new diagnostic methods are being investigated to overcome the limitations associated with the culturing method.

Rapid diagnostic methods

Peptide Nucleic Acid Fluorescence In Situ Hybridization (PNA FISH): Once the blood culture turns out to be positive, technique like PNA FISH can be used to shorten the time required for speciation.[21] A recent study compared the compatibility of the peptide nucleic acid fluorescent in situ hybridization Yeast Traffic Light (PNA FISH® YTL) with VITEK 2 System in early identification of *Candida* spp. directly from positive blood cultures (n = 15) and other clinically significant specimens (n = 10). The study reported assay identification compatibility of PNA FISH® YTL with VITEK 2 System in 21/25 (84%) specimens tested, and suggested that this assay can be used to identify *Candida* from blood cultures, urine cultures, peritoneal fluid cultures and catheter tip cultures.[23] Although this test appears to be clinically beneficial, its use is limited due to several factors such as lack of specificity, requirement of a positive blood culture, and inability to distinguish between all clinically relevant *Candida* species.[21]

Polymerase Chain Reaction (PCR): Is being studied to identify *Candida* infection in neonates more rapidly and with higher sensitivity. PCR also makes it feasible to use small amount of blood to detect *Candida* infection [10,24,25]. Table 2 presents studies evaluating the use of PCR in neonates with invasive candidiasis.

A meta-analysis of 23 studies evaluating efficacy of PCR and other hybridization methods in diagnosis of neonatal sepsis concluded that molecular techniques cannot replace culture methods presently due to insufficient sensitivity, although they can be used as an add-on to culture methods [26]. A review by Paolucci et al. highlighted that lack of sensitivity could be attributed to varied amount of blood collected in different studies (200 μ L to 2 mL) [27]. Moreover, there is lack of studies on standardization and validation of PCR in neonates [28]. PCR use is further limited due to likelihood for sample contamination (leading to false-positive results), lack of probes with capability to detect multiple *Candida* species, and difficulty in sample preparation [21]. Thus, more studies need to be conducted to assess the validity and reliability of PCR and other molecular techniques in neonates.

Biomarkers: Researchers are also investigating the use of biomarkers of fungal disease in diagnosis such as (1, 3)- β -D-Glucan (present in fungal cell wall), D-arabinitol, anti-*Candida* antibodies, Mannan antigen, and fungal chitin synthase.[10, 29] Very few studies have been conducted in neonates on usability of these biomarkers in diagnosis of invasive candidiasis (Table 2). Although these tests show encouraging results, cost and lack of substantial data in neonates prevent their use in standard practice presently.

Other diagnostic tests: Neonates with persistent candidemia are likely to have end-organ dissemination (EOD). Thus, it is suggested to screen for EOD using renal and cranial ultrasound/ magnetic resonance imaging (MRI), echocardiogram and ophthalmologic examination, either prior to initiation of the therapy or after 5-7 days of the initiation of the treatment. Abdominal ultrasound is suggested to assess for peritoneal, splenic or liver involvement[10].

Table 2: Studies Assessing the Use of Molecular Diagnostic Tests in Neonatal Candidiasis.

Studies	Type of Study	Patient Population	Diagnostic Technique Assessed	Outcomes
Zhao et al. [29]	Case control study	63 preterm infants with IFD, 160 preterm infants without sepsis (preterm control), and 41 preterm infants with bacterial sepsis	BG and platelet parameters (PC, PCT, PDW and MPV)	Sensitivity and specificity of BG: 68.3% and 75.6%; PC: 78% and 95%, and PCT: 83% and 85%, respectively
Taira et al. [25]	Prospective study	54 pediatric patients (24 neonates)	BC and PCR	BC and multiplex nested PCR were positive in 14.8% vs 24.0% of patients, respectively.
Goudjil et al. [54]	Retrospective study	Infected (n = 18) or non-infected (n = 43) neonates	BG I	BG level was significantly higher in the infected group (364 pg/mL [131–976]) as compared to non-infected group (89 pg/mL [30–127]; $p < 0.001$).
Oliveri et al. [55]	Observational study	N= 70 pre-term infants	Mannan antigen test	Overall sensitivity and specificity of the assay was 94.4% and 94.2%, respectively and culture-proven sensitivity and specificity was 92% and 84%, respectively
Mularoni et al. [56]	Case series	N = 4 (2 low-birth-weight neonates and 2 stem cell transplant recipients)	BG test	Plasmatic levels of BG were >523 pg/mL. BG test might be used to identify IFD in pediatrics

*IFD: Invasive fungal disease; BG: (1, 3)- β -D-Glucan; PC: Platelet count, PCT: plateletcrit; PDW: platelet distribution width; MPV: Mean platelet volume; BC: Blood culture

Treatment

There is lack of data on efficacy and safety of antifungals in neonates. The studies conducted until date have only focused on pharmacokinetics and pharmacodynamics evaluations of the antifungal agents. However, the recent updated guidelines from the Infectious Diseases Society of America (IDSA) (2016) presented recommendations for management of invasive candidiasis in neonates based on the available clinical data. The European Society of Clinical Microbiology and Infectious Disease (ESCMID) also released guidelines on the diagnosis and management of invasive candidiasis in neonates [30].

Guideline Recommendations and Optimal Management

- 1. Pharmacological Management:** Figure 1 presents an overview of recommendations by IDSA on antifungal therapy in neonates with special recommendations for neonates with CNS involvement and those in ICU [31].
 - i. Amphotericin:** IDSA guidelines recommends Amp B deoxycholate (D-Amp B) as the first treatment option for neonates with disseminated candidiasis (category A-II) [31]. ESCMID guidelines also recommend the use of D-Amp B in neonates with invasive candidiasis, but the recommendation is supported by limited clinical data as well as pharmacokinetic data (category B-II) [30]. D-Amp B is reported to be associated with nephrotoxicity. Holler et al. conducted a study to assess the effects of fluid and electrolyte management on reducing the Amp B-induced

nephrotoxicity among 753 extremely LBW infants with systemic fungal sepsis. The study showed that Amp B when given with adequate hydration and increased sodium intake (>4 mEq/kg/day) may help in reducing the associated nephrotoxicity [32].

The lipid-based formulations *i.e.* Amphotericin B Liposomal Complex (ABLC) used to treat invasive candidiasis in neonates. ABLC has received a grading of B-III and B-II in ISDA and ESCMID guidelines, respectively, for use in neonates with invasive candidiasis [30,31]. Although the safety of liposomal formulations of Amp B has only been assessed in some observational uncontrolled studies, results have been favorable [33,34]. However, there is lack of recent data evaluating the safety of ABLC in neonates. Moreover, there are only few studies comparing ABLC with other therapies including Amp B. A recent study compared the use of ABLC with conventional Amp B in infants (≤ 120 days of age) who had confirmed diagnosis of invasive candidiasis. The study reported increased mortality rate and treatment failure for neonates receiving lipid formulations compared with Amp B (OR: 1.96 [95% CI: 1.16, 3.33]; $p = 0.01$) [35]. Further well-designed studies (randomized) need to be conducted to assess the efficacy and safety of ABLC in neonates.

- ii. Fluconazole:** Is recommended as an alternative treatment option for neonates with candidemia and invasive candidiasis and as the first treatment option for neonates in intensive care units.^[31] However, results of the recent study by Benjamin et al. (2014) showed that fluconazole prophylaxis (for 42 days) in

infants with a birth weight < 750 g did not show reduction in the incidence of composite of death or invasive candidiasis [36]. Another recent study by Lee et al. (2016) also assessed efficacy and safety of fluconazole prophylaxis in comparison to non-prophylaxis in infants with extremely LBW in NICU. The study reported that fungal colonization rate reduced significantly with fluconazole prophylaxis (59.1 % vs. 33.9 %, $p < 0.001$). However, fluconazole prophylaxis resulted in increased incidence of invasive infections involving fluconazole-resistant *C. parapsilosis* (0% vs. 41.7%, $p = 0.11$), although it was

statistically insignificant. This study also supports the findings that fluconazole is not efficacious in infants with extremely LBW in reducing invasive fungal infections [37]. Also, there is a need for clinical studies to be conducted to assess the long-term effect of fluconazole therapy on development of antifungal resistance. ESCMID guidelines recommend that the decision to use fluconazole prophylaxis in NICUs with lower incidence of invasive candidiasis (< 2%) should be made on case-by-case basis [30].

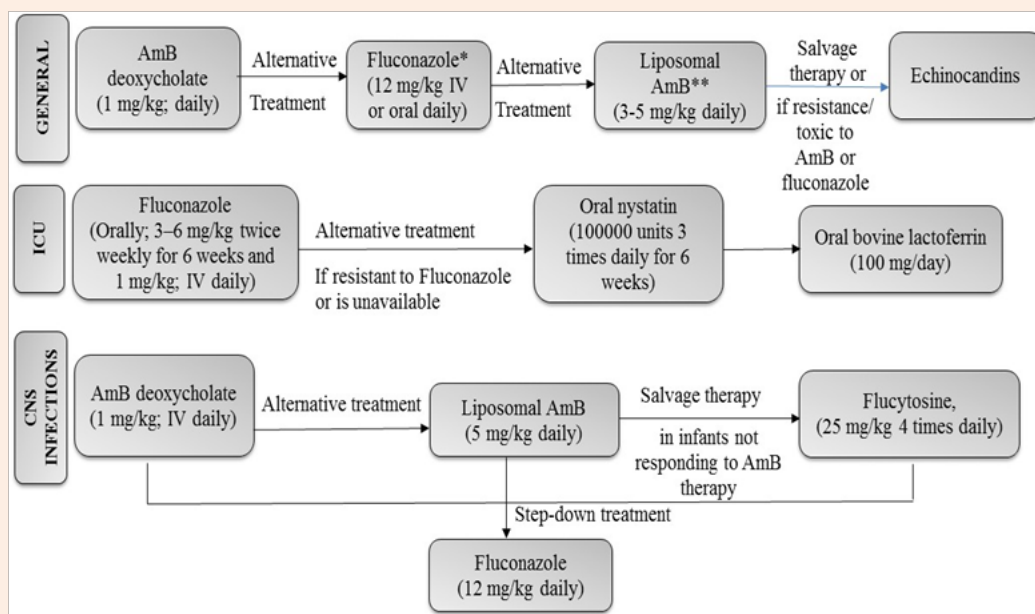


Figure 1: Summary of Recommendations on Management of Invasive Candidiasis in Neonates as per IDSA Guidelines [50].

IV: Intravenous, CSF: Cerebrospinal fluid; CNS: Central nervous system; ICU: Intensive care unit, Amp B: Amphotericin B

*In patients who have not been on fluconazole prophylaxis

**To be used cautiously, particularly in the presence of urinary tract involvement.

iii. Micafungin: Echinocandin, is also considered to be a first line-agent based on clinical data in neonates [38]. A study by Arrieta et al. reported that micafungin is safe in children of all ages. This study included a total of 296 patients (6.5 ± 5.1 years), of which 66 were <1 year of age and 38 were premature (received ≥ 1 dose of micafungin) [39]. Another study by Benjamin et al. also showed similar results supporting safety of micafungin in young infants [40]. However, ESCMID guidelines state that 'black box' warning has been issued by the European Medical Agency (EMA) indicating the use of micafungin only if other agents are not appropriate. EMA has issued this warning due to an increased incidence of hepatic tumors in pre-clinical studies with the use of micafungin for longer durations.[30] A recent systematic review of 9 clinical trials assessing the safety and efficacy of micafungin in premature and non-premature infants with invasive candidiasis showed the drug is well tolerated, but was discontinued due to treatment-related adverse events (TEAEs) in some patients. A total of 2 (4%) premature and 7 (12%) non-premature patients ($p = 0.17$) discontinued the treatment following TEAEs [41].

iv. Caspofungin: Echinocandin, was compared to AmpB in

neonates with invasive candidiasis to assess its efficacy and safety. Thirty-two (32) neonates with invasive candidiasis were randomized to receive either caspofungin ($n = 15$) or AmpB ($n = 17$). Caspofungin showed efficacy in 86.7% of patients as compared with 41.7% of those who received AmpB ($p = 0.04$). Adverse events were significantly lower in the Caspofungin group than in the AmpB group [42]. Jeon et al. (2014) also reported the efficacy and safety of Caspofungin (2 mg/kg/day) in treating premature infants ($n = 7$; gestational age: $23+1-24+6$ weeks, and birth weight: 530-825 g) with persistent candidemia. Caspofungin successfully treated persistent candidemia in all the infants and no adverse effects were reported. None of the infants was found to have recurrent candidemia after discontinuing caspofungin.[43] Although various studies have shown caspofungin to be safe and effective in invasive candidiasis in neonates, the population size in these studies was small. More studies with large population size needs to be conducted. Presently, a grading of C-II is given for caspofungin in ESCMID guidelines [30].

v. Combination therapy: There is a lack of substantial data on the use of combination therapy in neonates with invasive

candidiasis. Conflicting results have been obtained in different studies. A recent case report by Al-Sweih et al. (2015) reported successful treatment of persistent candidemia in a preterm neonate caused by *Candida fermentati* with combination therapy of AmpB and caspofungin (for 30 days). No adverse effects were reported to occur in the patient [44]. Another study reported the use of liposomal AmpB and Voriconazole in 6 infants with very LBW. These newborns were initially treated with AmpB (either conventional or liposomal) and Fluconazole. However, 10 infants developed *Candida* sepsis and candidemia persisted in 6 infants despite receiving these antifungals for 3-21 days. Later, Voriconazole was added as a combination therapy to AmpB which resulted in *Candida* clearance in 3-7 days. Thus, the study results showed that Voriconazole can be used in combination with Amp B for treatment of fungal sepsis in neonates who still have persistent candidemia despite conventional antifungal management [45].

On the other hand, a study by Ascher et al. reported the use of D-Amp B, Fluconazole, Amp B lipid products, or combination therapy in 730 infants. Multivariable regression showed no difference in the duration of candidiasis for infants treated with D-Amp B, Amp B lipid products, Fluconazole, or combination therapy ($p = 0.47$). There was no significant difference in therapy failure rates for Fluconazole and combination therapy compared with D-Amp B [35]. No recommendation has been made in guidelines on the use of combination therapy in neonates [31].

Other antifungals: Use of some other antifungals including Itraconazole, Voriconazole and anidulafungin have been assessed in very few studies in neonates, mainly limited to case reports. Thus, their use is not recommended in clinical practice [46]. Several new antifungals such as Posaconazole, Ravuconazole, 5-Flucytosine, Isavuconazole and Posaconazole have also not been studied in neonates so far [38,46].

Probiotics: Several studies are being conducted to assess the use of probiotics in treatment of late onset sepsis (LOS) in neonates. A recent meta-analysis by Rao et al. systematically reviewed 37 randomized clinical trials comparing probiotics with placebo and control in preterm infants with LOS. Probiotics significantly decreased the risk of LOS (675/4852 [13.9%] vs 744/4564 [16.3%]; relative risk [RR]: 0.86; 95% CI: 0.78-0.94; $p = 0.0007$).^[47] A meta-analysis by Zhang et al. (2016) also reported significant reduction in fungal sepsis (RR 0.57, 95% CI: 0.41-0.78) with enteral probiotic supplementation in preterm neonates with LOS.^[48] Although several studies have shown that probiotics play an important role in preventing *Candida* colonization in neonates with invasive candidiasis (IC), more multicenter clinical trials are needed to evaluate efficacy, safety, dosage, duration and strains (type and single or combination of different strains) of probiotics in prevention of *Candida* colonization and invasive candidiasis [49]. Lactoferrin alone or in combination with *Lactobacillus* is suggested to be equally useful by the ESCMID guidelines [30]. However, no recommendation on their use is given in the recent updated guidelines by ISDA.

An expert opinion states that researchers need to conduct studies assessing the efficacy and safety of antifungals in neonatal

population because data from adult trials cannot be implied to neonates with invasive candidiasis due to differences in pathophysiology of the disease in neonates and adults [46].

2. Non-Pharmacologic Management: The guidelines from IDSA strongly recommend the removal of central venous catheter (CVC) in neonates as a part of non-pharmacologic management of invasive candidiasis [31]. In a study by Benjamin et al. (2006), delayed catheter removal was significantly associated with higher mortality rate (37% vs. 21%; $p < 0.024$) in extremely LBW infants with invasive candidiasis [18]. In neonatal candidiasis with CNS involvement, it is strongly recommended by IDSA to remove all CNS devices (including ventriculostomy drains and shunts), if possible [31].

Conclusion

Neonates with LBW (<2500 g) and early gestational age (29-32 weeks) are at increased risk of developing invasive candidiasis. Other risk factors include vaginal birth, central catheters, day of life (>7), use of broad spectrum antibiotics, antenatal steroids, premature rupture of membranes, mechanical ventilation, necrotizing enterocolitis and parenteral nutrition. High mortality rate associated with invasive candidiasis in neonates necessitates the need to fill the gaps in its diagnosis and treatment. Also, adverse neurodevelopmental outcomes have been reported in neonates with invasive candidiasis. Use of empiric anti-fungal therapy is suggested to help in improving neurodevelopmental outcomes in neonates with invasive candidiasis. Culturing of blood and other body fluids is the conventional method used for diagnosis of invasive candidiasis. However, it leads to delay in diagnosis due to time-consuming procedure. Other molecular techniques including PCR and biomarkers are being investigated for rapid diagnosis; however, no recommendations have been made in international guideline in this regard. In addition there is lack of substantial data on efficacy and safety of antifungals in infants with invasive candidiasis. Accordingly recommendations have been made in guidelines based on the available data. The guidelines have strongly recommended the use of D-Amp B and Fluconazole in neonatal candidiasis. Other therapies including liposomal formulations of Amp B, oral Nystatin, Echinocandins, Flucytosine, and Lactoferrin are suggested as alternatives. In future, there is a need to conduct more studies in large population size and assess the long-term outcomes following antifungal prophylaxis in neonatal invasive candidiasis.

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