Research and Reports in Neonatology

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REVIEW

Updated Perspectives on the Diagnosis and Management of Neonatal Invasive Candidiasis

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Abstract: Invasive candidiasis can cause severe illness in immunocompromised hosts, such as premature infants. Clinical presentation in neonates is variable and often characterized by non-specific signs with potential to involve several organ systems. Awareness of risk factors for *Candida* infections in the neonatal intensive care unit (NICU) can aid in screening infants with signs and symptoms of generalized illness. Cultures of blood, urine, and cerebrospinal fluid are the main diagnostic tools available in this population of infants, but several biomarkers and alternate identification methodologies such as 1,3-β-D-glucan, serum mannan or anti-mannan, and T2 magnetic resonance testing are being studied in the neonatal population. Prompt diagnosis of *Candida* infection, in conjunction with a comprehensive assessment of disease progression and organ involvement, is critical for optimizing treatment and patient outcomes. Supportive care and systemic antifungal medications remain the mainstay of treatment, and the efficacy and safety of newer therapeutic agents continue to be evaluated in neonates. Disease prevention strategies must be thoughtfully implemented and customized to each individual NICU based on local incidence of *Candida* infection, practice patterns, and risk factors, and may include prophylactic antifungal therapy. This review summarizes the evidence for current approaches to diagnosis and management of neonatal invasive candidiasis and provides an overview of the newer diagnostic tools and therapeutic agents on the horizon.

Keywords: *Candida*, infant, biomarkers, amphotericin B, fluconazole, prophylaxis

Introduction

Invasive candidiasis is an important contributor to neonatal morbidity and mortality. Although this fungal organism colonizes human skin and mucosa and may cause only limited mucocutaneous disease in immunocompetent hosts,[1,2] immunocompromised hosts, such as premature infants, with invasive candidiasis can suffer from severe and life-threatening illness.

The incidence of invasive candidiasis in extremely low birth weight infants is approximately 9%, although this incidence varies by neonatal intensive care unit (NICU) from 2% to 28%.[3] *Candida* can spread to premature infants via vertical and horizontal transmission.[4] Vertical transmission to newborns can occur from the maternal genitourinary tract during labor.[5] A significantly higher incidence of colonization is seen after vaginal delivery compared to infants delivered via caesarean section.[6] Alternatively, horizontal transmission may occur from exposures within the NICU environment.[5] Once acquired, *Candida* invasion can lead to severe disease in nearly any organ system of an infant, including the eyes, brain, heart, liver, spleen, genitourinary system, bones, and joints.[7,8]

Most cases of neonatal invasive candidiasis are caused by *Candida albicans* and *Candida parapsilosis*.[7] *Candida glabrata, Candida tropicalis*, and *Candida krusei* are also pathogens in infants,[9] and *Candida auris* has recently emerged as a significant threat to neonates as it can cause severe systemic disease and is resistant to many first-line antifungal agents.[10] In low- and middle-income countries, a higher proportion of infections are caused by non-*albicans Candida* species as compared to high-income countries.[11] Species identification is an important step in diagnosis of invasive candidiasis as it can predict mortality risk and guide treatment decisions.[12]

Received: 14 August 2023
Accepted: 25 October 2023
Published: 9 November 2023

Table 1 Risk Factors for Neonatal Invasive Candidiasis

	Non-Modifiable	Potentially Modifiable
Prenatal	Prematurity Low birth weight Vaginal delivery	
Postnatal	Skin or GI colonization at delivery Low Apgar scores Hospitalization >7 days GI or mucosal compromise Sepsis or shock Disseminated intravascular coagulation Thrombocytopenia	Central venous catheters Groin catheters Mechanical ventilation Broad-spectrum antibiotics H2 blockers Systemic steroids Parenteral nutrition Intravenous lipid emulsion use

Abbreviations: GI, gastrointestinal; H2, histamine-2.

Risk factors for invasive candidiasis are commonly present in the NICU patient population (Table 1). While prematurity and extremely low birth weight are commonly cited predisposing factors, other important considerations include delayed enteral feeding; use of broad-spectrum antibiotics, H2 blockers, or systemic steroids; *Candida* colonization of skin or gastrointestinal (GI) mucosa; invasive instrumentation via central venous catheters (CVC), urinary catheters, or mechanical ventilation; hospitalization longer than 7 days; presence of sepsis or shock; and coagulation derangements such as disseminated intravascular coagulation or thrombocytopenia.[3,4,7,13] Factors such as translocation across the GI tract after colonization are major sources of invasive infection but not easily modifiable.[14] Use of central lines, on the other hand, is a potentially modifiable risk factor and a potential source of intervention to mitigate the risk of invasive infection.[8] Of note, these risk factors are most predictive of invasive candidiasis infections for neonates in high-income countries; invasive candidiasis infections occur more frequently in neonates born at later gestational ages and higher birth weights in low- and middle-income countries.[15]

Although the incidence of invasive neonatal candidiasis has decreased over the past few decades, it continues to be a significant source of neonatal morbidity and can cause life-threatening illness.[16] The Centers for Disease Control and Prevention's population-based surveillance demonstrates that rates of invasive candidiasis in infants from the United States have dropped dramatically from 2009 to 2012. Since then, rates continue to slowly decline, with an estimated incidence of 9.6% in 2019 for children less than 1 year old.[17] Incidence is lower in other high-income countries, such as Italy, the United Kingdom, Canada, and Australia.[18–21] Incidence of invasive candidiasis in pediatric intensive care units is significantly higher in low- and middle-income countries when compared to high-income countries; however, the incidence in the neonatal population has not been well characterized.[11,15]

Over 20% of infants with invasive candidiasis die in spite of systemic antifungal treatment, and those who survive are at high risk for neurodevelopmental impairment.[12,22,23] Other long-term consequences of this illness include risk of moderate or severe cerebral palsy, blindness, deafness, and increased healthcare costs.[7,12] Early identification and prompt initiation of appropriate treatment can optimize both short-term and long-term outcomes for premature infants receiving care in the NICU.[24] This review summarizes the evidence for current approaches to diagnosis and management of neonatal invasive candidiasis and provides an overview of the newer diagnostic tools and therapeutic agents on the horizon.

Diagnosis

Manifestation of Disease

Neonates with invasive candidiasis often present with nonspecific signs similar to that of sepsis, including lethargy, apnea, feeding difficulties, and hemodynamic instability.[7,8,25] However, nearly every organ system can be affected. Neurologic invasion is more commonly characterized by meningoencephalitis, which may present as seizures or

intraventricular hemorrhage,[7,26] and less commonly by obstructive hydrocephalus with ventriculitis or cerebral abscesses.[27] The most common ophthalmologic manifestation is endophthalmitis, an infection of the internal ocular spaces that occurs through hematogenous spread[28,29] and is characterized by chorioretinitis and/or vitreal lesions.[26] The cardiovascular system is rarely involved, presenting as endocarditis or pericarditis.[7,10] Hepatosplenic abscesses and hepatosplenic candidiasis should be considered when there is disseminated candidiasis, persistent fever, and abdominal symptoms.[26,27] Intestinal perforation has also been associated with candidemia.[30] Genitourinary system involvement takes many forms, including fungal bezoars leading to obstructive nephropathy and renal parenchymal abnormalities.[26,31] Bones and joints can be involved through osteoarticular lesions.[26] Skin involvement is a hallmark of congenitally acquired disease and consists of a widespread, erythematous, vesiculopapular rash that can progress to severe illness.[25]

Testing and Imaging Considerations

The diagnostic approach to invasive candidiasis in neonates should be comprehensive, including physical examination, laboratory testing, and evaluation for multiorgan involvement (Table 2). The most common sites of infection are blood, urine, and cerebrospinal fluid (CSF);[1] therefore, cultures of these sites are recommended as an initial step in diagnosis. It is important to note that routine blood cultures are sufficient for recovering all varieties of *Candida* species, and the use of fungal blood cultures, intended to recover intracellular or more fastidious fungi, does not improve recovery rates.[32–35] Other sites that raise suspicion for infection, such as peritoneal fluid and tracheal aspirate, can also be collected and cultured to evaluate for *Candida* infection.[36] The major advantage of microbiologic diagnosis via cultures is species identification and susceptibility testing, especially in the setting of drug-resistant strains of *C. glabrata, C. parapsilosis*, and *C. auris*.[37] Newer microbiologic methods for rapid identification of species such as the multiplex polymerase chain reaction (PCR) FilmArray blood culture identification panel (bioMéieux, Inc.) may facilitate more prompt initiation of optimal antifungal therapy.[38]

Table 2 Tools for Diagnosis of Neonatal Invasive Candidiasis: Strengths and Limitations

Test	Benefits	Limitations
Microbiologic culture	Species identification Antibiotic susceptibility testing	Long mean time to positivity (36–42 hours)[39] Low sensitivity (~50%)[40] High rate of intermittently or falsely negative cultures (21%)[12] Requires a relatively large volume blood sample
Hyperglycemia, thrombocytopenia, leukocytosis	Rapid results	Conflicting data on significance
1,3-β-D-glucan	Sensitive (89%)[31] Can be used to monitor response to treatment	Not specific (60%)[31]
Serum mannan/anti-mannan	Rapid results Sensitive (94.4%)[41] Specific (94.2%)[41] High negative predictive value (98%)[41]	Minimal sensitivity for *C. parapsilosis* and *C. krusei* infection
Blood T2Candida	Rapid results Sensitive (100%)[42] Specific (94.1%)[42]	Only identifies 5 species – *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei* High percentage (~10%) of invalid results[43] Limited availability
Panfungal PCR	Available 2.2 days before culture on average Sensitive (87.5%)[44] Specific (81.6%)[44] High NPV in low prevalence settings (99%)[37]	Lack of standardization Limited studies in neonates Low PPV in low-prevalence cohort (16.7%)[44]

Abbreviations: PCR, polymerase chain reaction; NPV, negative predictive value; PPV, positive predictive value.

While cultures remain the gold standard for diagnosis, they have important limitations (Table 2). A study of 74 infants with invasive candidiasis calculated a median of 36 hours between blood culture draw and *Candida* detection for infants not on antifungal therapy and 42 hours for infants on empiric antifungal therapy.[39] Additionally, the sensitivity of routine blood cultures incubated on conventional automated blood culture systems in diagnosing any form of invasive candidiasis in any age group is approximately 50% with an average detection time ranging from 14 to 38 hours.[40,45] A study of 150 NICUs demonstrated that of 19 infants with culture-positive *Candida* meningoencephalitis, only 37% had positive blood cultures.[46] The sensitivity of blood cultures to detect *Candida* may be related to total disease burden. In one small study of autopsies on infants with invasive candidiasis, blood cultures were positive in 28% of patients with one infected organ, whereas blood cultures were positive in 78% of patients with greater than 3 infected organs.[47] Furthermore, cultures can be persistently positive despite systemic antifungal treatment, as demonstrated by a prospective study in 2006 where 10% of neonates had candidemia for greater than or equal to 14 days after starting therapy.[12] Negative cultures do not preclude a diagnosis of invasive candidiasis; neonates can have invasive candidiasis in the absence of proven candidemia and therefore are at risk for mortality and lasting neurodevelopmental delay if infection is not identified promptly.[37,48]

A barrier to optimizing the yield of blood cultures in premature infants is the blood volume required for detection.[37] One must balance obtaining adequate volume for diagnosis while not exceeding the threshold that results in hemodynamic and cardiorespiratory instability.[49,50] In adults, a blood culture volume of approximately 10 mL is standard;[51] in infants, recommendations vary. Existing pediatric guidelines recommend volume limits between 1% and 5% of total blood volume over 1 day and up to 10% of total blood volume over 8 weeks.[52] The 2018 update by the Infectious Diseases Society of America (IDSA) and American Society for Microbiology recommends collecting 4% of total blood volume in a single aerobic blood culture in patients weighing less than 2 kg and 3% in patients weighing 2.1–12.7 kg.[51] A 2015 in vitro study on banked adult whole blood demonstrated that at low concentrations (1–10 CFU/mL), *Candida albicans* and *Candida parapsilosis* were detected in volumes as low as 0.5 mL.[53] At very low concentrations (<1 CFU/mL), a volume of 3 mL was required for detection of *Candida albicans* and *Candida parapsilosis*.[53] However, obtaining these volumes is not always feasible. A study of pediatric blood cultures at Royal Children's Hospital Melbourne determined that 39% of blood samples drawn in infants younger than 1 month of age had negligible volume for culture.[54]

In the setting of positive blood or urine cultures, the 2016 IDSA clinical practice guidelines for the management of candidiasis recommend a lumbar puncture and dilated retinal examination to assess for meningoencephalitis and endophthalmitis, respectively.[7] The IDSA strongly recommends a computerized tomography scan or ultrasound of the genitourinary tract, liver, and spleen when blood cultures are persistently positive to identify other potential sites of infection.[7] Tissue biopsy can also be performed to detect invasive candidiasis via microscopy and histologic examination, especially in cases of suspected hepatosplenic candidiasis; however, the rates of detection are low at approximately 50%.[55]

In addition to the dilated retinal examination recommended by the IDSA, new imaging technologies to diagnose *Candida* endophthalmitis are in development. The currently recommended evaluation tool, a dilated fundoscopic exam, may show retinal lesions, which would correspond to hyperfluorescent lesions with ill-defined margins and irregular edges on fluorescein angiography.[56] However, B-scan ultrasound and handheld spectral-domain optical coherence technology (HH-SD OCT) may identify pathology beyond retinal lesions. B-scan ultrasound has been used in neonates and can show infiltrates in the vitreous cavity, subretinal fluid, and/or retinal detachment.[29] HH-SD OCT, the newest of these technologies, has been used in neonates for retinopathy of prematurity evaluations but can also demonstrate vitreal lesions in addition to retinal lesions.[56]

Serum Biomarkers

Because of the aforementioned limitations of diagnosing candidiasis with blood cultures, other surrogate markers of invasive fungal infection in blood and serum can be employed to make a more timely diagnosis, leading to faster initiation of treatment (Table 2). Laboratory derangements frequently associated with invasive candidiasis include thrombocytopenia, hyperglycemia, and leukocytosis. Neonates with sepsis from *Candida* are more likely to have thrombocytopenia and hyperglycemia than infants with bacterial sepsis.[3,57] However, there is conflicting evidence on

the significance of thrombocytopenia as a marker for fungal sepsis.[8,58–60] Leukocytosis is not a reliable marker as up to 40% of infants with fungal sepsis have a normal white blood cell count.[61]

Three additional markers targeting specific *Candida* fungal components are 1,3-β-D-glucan, serum mannan or anti-mannan, and T2 magnetic resonance testing (T2Candida). 1,3-β-D-glucan is a constituent of the cell wall of many fungi and can be detected in the serum during invasive fungal infection. Its concentration is significantly higher in infants with invasive candidiasis as compared to those without disease.[8,31] This molecule can be detected via a variety of widely available assays, including the Fungitell Assay (Associates of Cape Cod, Inc., Massachusetts, USA) and the Wako β-Glucan test (Fujifilm Wako Pure Chemical Corp, Tokyo, Japan). A 2013 meta-analysis of neonatal studies demonstrated that the serum tests to detect this polysaccharide have a sensitivity of 89% and specificity of 60% in diagnosis of neonatal candidiasis, although there was considerable variability between studies.[62] The average baseline 1,3-β-D-glucan level in healthy children and infants is higher than in adults, which should be considered when interpreting these test results;[63] when using a higher positivity threshold, sensitivity and specificity were 81% and 80%, respectively.[62] 1,3-β-D-glucan levels may also be used to monitor response to treatment, as they decrease over the course of appropriate antifungal therapy.[31] A major limitation of 1,3-β-D-glucan testing is the high false-positive rate.[64,65] False positives can occur with the use of various beta-lactam antibiotics, the administration of blood products (such as albumin or intravenous immune globulin), bacterial infections, the use of surgical gauze and other related materials, the use of leukocyte-removing filters or extracorporeal membrane treatments, and sample collection from contaminated central venous catheters – many factors frequently seen in hospitalized neonates.[66–68] Further investigation is still needed to better understand this marker's ability to accurately identify disease and monitor progression.

Mannan is an abundant constituent of the *Candida* cell wall. Therefore, detection of mannan antigen and serum anti-mannan antibodies in the serum or plasma represent potential targets for the diagnosis of invasive candidiasis. The best performance using this combined mannan/anti-mannan antibody testing approach has been observed with the commercial PLATELIA™ *Candida* Ag Plus system (Bio-Rad Laboratories, Marnes-la-Coquette, France), which has been studied predominantly in immunosuppressed hosts with neutropenia and/or impairment in cell-mediated immunity. While evaluation of the performing characteristics of this test in neonates is very limited, a preliminary study of 70 neonates reported a sensitivity of 94.4% and specificity of 94.2% with a positive predictive value of 85% and negative predictive value of 98% based on a prevalence of 6.5%.[41] However, similar investigation in adults demonstrated high specificity but low sensitivity, particularly for *C. parapsilosis* and *C. krusei* infection, thought to be due to differences in mannose epitopes across species.[8,41] Ultimately, utilizing this test in combination with blood cultures may improve the diagnosis of early invasive candidiasis.[41] This testing is more commonly used in European centers and rarely employed for diagnosis in North America.[40]

T2Candida (T2 Biosystems, Inc., Wilmington, MA, USA) is an FDA-approved test that combines amplification steps and magnetic resonance imaging to rapidly identify the 5 most common *Candida* species in blood samples in an average of 4.4 hours.[43] In a 2022 retrospective single-center study of 106 pediatric patients, including neonates, the T2Candida assay was 100% sensitive, 94.1% specific, and provided definitive organism identification in 3.7 hours on average; however, only 4 patients with positive blood cultures for *Candida* were included in the study.[42] In another small pediatric study, blood T2Candida correctly identified more candidemia diagnoses than blood cultures.[69] Like 1,3-β-D-glucan testing, T2Candida outperformed blood cultures for monitoring candidemia and therefore could be useful for following treatment response.[70] While multicenter studies have demonstrated high sensitivity and specificity for targeted *Candida* species, the sensitivity in clinical practice is low, ranging from 33% to 45% for deep-seated candidiasis and 65–83% for candidemia.[43,71] Limitations of this test include the need for implementation in high pre-test probability settings, such as critical care settings with risk factors for invasive candidiasis, and the need for onsite testing to yield short turnaround times. However, evaluations indicate that its use is cost effective, including in resource-limited settings.[72,73]

Identification Methods

Matrix-assisted laser deposition/ionization time-of-flight (MALDI-TOF) is a common method used to identify organisms, including a variety of *Candida* species, isolated from positive microbiological cultures. Traditionally, clinical microbiological identification often required growth from subcultures, which may take 24 to 72 hours; however, more recent

studies have demonstrated that direct identification can be done from positive blood culture specimens, decreasing time to diagnosis.[74–76] This test can identify over 200 species of bacteria and yeasts with just 1 minute of hands-on time and 5 minutes of turn-around time.[48] In a pre-post quasi-experimental study of adults with bacterial and fungal bloodstream infections, including *Candida*, use of MALDI-TOF in conjunction with antibiotic stewardship decreased time to organism identification and time to antifungal therapy, which was associated with a decrease in mortality and ICU length of stay.[77]

Fluorescent in-situ hybridization (FISH), a technique that uses fluorescent microscopy to identify hybridization of probes to organism-specific rRNA, has also been studied to rapidly identify *Candida* species from positive blood cultures.[78] Like MALDI-TOF, this test is fast, requiring only 5 minutes of hands-on time and 90 minutes of turn-around time after culture growth and positivity.[48] Another unique aspect of FISH testing is its ability to detect *Candida* in peritoneal fluid in addition to blood.[78] A 2018 analysis of the Peptide Nucleic Acid FISH Yeast Traffic Light System (AdvanDx, Woburn, MA) demonstrated that this test could quickly and accurately diagnose candidemia, as it identified *Candida* in 96.4% of patients not yet on antifungal therapy.[79] However, drawbacks of this test include false positive and negative results related to polymicrobial infections and that few clinical laboratories currently employ this technique.

Panfungal PCR tests can identify several common *Candida* species that cause bloodstream infections in NICU patients.[44] The main advantages of PCR tests are their speed and sensitivity; positive PCR results are available on average 2.2 days before positive blood culture results.[80,81] PCR has also demonstrated greater sensitivity than blood cultures for detecting neonatal invasive candidiasis in very low birth weight infants, for whom obtaining adequate volume for blood culture is especially difficult. A 2017 multicenter, observational case–control study in very low birth weight infants reported panfugal PCR testing sensitivity of 87.5% and specificity of 81.6%; PCR targets were identified in 17.4% of septic patients with negative blood cultures.[44] In low prevalence settings, panfungal PCR has a high negative predictive value, which can be useful when deciding to start and/or stop antifungal therapy, thereby limiting potential drug toxicity.[37] This test has several disadvantages, including its lack of standardization and approval for use in the United States, limited study in neonates, and low positive predictive value in low prevalence cohorts.[37,44,82] One subtype of PCR-based testing is cationic conjugated polymer fluorescence resonance energy transfer. This system, composed of a cationic conjugated polymer fluorescent probe and pathogen-specific DNA labeled with fluorescent dyes, was developed to diagnose neonatal invasive fungal infection quickly and accurately with a detection limit that is one-tenth that of real-time PCR testing.[83,84] The system's major disadvantage is the need for optimization and judicious primer selection.[83]

Metagenomic next-generation sequencing is a newer testing methodology that simultaneously sequences billions of nucleic acid fragments in parallel, allowing for the rapid identification of bacteria, viruses, and fungi.[85] This method has been used in pediatric populations in the evaluation of sepsis, meningitis, and encephalitis and shown promise in positively impacting clinical care.[86,87] A 2023 systematic review on next-generation sequencing determined that this technology improves etiologic identification of neonatal and pediatric fungal sepsis, but neonatal data is limited and requires further characterization.[87] The major advantage of this technology is its unbiased approach to identifying all potential pathogens within the same test without the use of specific primers or probes.[85] Disadvantages of this method include its inability to distinguish organisms that are pathogenic versus those which are colonizers, its high cost, and long turnaround time. Only one commercially available laboratory can perform this testing at this time (Karius, Redwood City).[85] While next-generation sequencing has been applied to the diagnosis of invasive mold infections in immunocompromised hosts, there is a paucity of evidence in invasive *Candida* infections, particularly in the neonatal population.[88,89]

Management

Once invasive candidiasis has been diagnosed, expedient and effective management is critical to minimize risk of long-term morbidity. A combination of supportive care and antifungal therapeutics is often employed. Supportive care mostly centers on device management; indwelling materials are potential reservoirs for continued infection despite treatment with systemic antifungal therapy. Infection risk increases with duration of CVC use, as indwelling catheters provide a means for *Candida* to enter the bloodstream and create a surface for biofilm formation.[8] The most recent IDSA guidelines strongly recommend removal of CVCs and central nervous system (CNS) devices in the setting of invasive

candidiasis.[7] Prompt removal of CVCs in infants with invasive candidiasis is critical; it is associated with better immediate and long-term outcomes as well as lower rates of neurodevelopmental impairment.[12]

Therapeutics

The mainstay of treatment for neonatal invasive candidiasis is systemic antifungal therapy (Table 3). Prompt administration of antifungal therapeutics is essential; neonatal mortality increases as the duration between onset of symptoms and initiation of antifungal therapy increases.[24] Extrapolation of adult data regarding therapy selection and dosing warrants caution due to important differences in immune response, disease pathology, and drug metabolism in neonates.[90] However, neonatal treatment guidelines are mostly based on small, single-center studies and a limited number of multicenter cohort studies.[7]

Amphotericin B is a first-line therapy for the treatment of invasive candidiasis of neonates, as recommended by the IDSA,[7] European Society for Clinical Microbiology and Infectious Diseases (ESCMID),[91] and the joint German Speaking Mycological Society (DMYG) and Paul Ehrlich Society for Chemotherapy (PEG) guidelines (Table 4).[9,55] It is most commonly administered in the amphotericin B deoxycholate form in neonates; the lipid formulations are rarely

Table 3 Overview of Antifungal Therapy Used in the Treatment of Neonatal Invasive Candidiasis

Drug Class	Mechanism of Action	Drug	Important Properties	Notable Side Effects
Polyene	Interacts with ergosterol, leading to formation of pores in cell membrane	Amphotericin B deoxycholate	Highly protein-bound Excreted in urine and feces Variable volume of distribution and clearance in neonates Good CSF penetration	Infusion-related reactions Hypokalemia Questionable renal toxicity
Triazoles	Inhibit CYP450 enzyme that synthesizes ergosterol	Fluconazole	1st generation triazole Concentration-dependent activity Fungistatic activity Low protein binding High tissue, urine, and CSF penetration Renal elimination Requires dose adjustment based on gestational and postnatal age Strong CYP2C9 and CYP3A4 inhibitor	Gastrointestinal symptoms Rash Hepatotoxicity QT prolongation
		Itraconazole	1st generation triazole Concentration-dependent activity Fungistatic activity Variable, dose-dependent oral bioavailability Highly protein bound Extensive hepatic metabolism Excreted by liver and kidneys CYP3A4 inhibitor	Gastrointestinal symptoms
		Voriconazole	2nd generation triazole Concentration-dependent fungistatic activity Moderate protein binding Good tissue, CSF penetration Extensive CYP2C19 metabolism FDA approved for ages 2 and older Need for drug monitoring	Elevated transaminases Skin photosensitization

(*Continued*)

Table 3 (Continued).

Drug Class	Mechanism of Action	Drug	Important Properties	Notable Side Effects
		Posaconazole	2nd generation triazole Concentration-dependent activity Fungistatic activity Highly protein bound Eliminated mostly in feces but also by kidneys Not FDA approved for infants Need for drug monitoring	Gastrointestinal symptoms
Echinocandins	Inhibit 1,3-β-D-glucan synthase	Micafungin	Concentration-dependent fungicidal activity Highly protein bound Inverse relationship between weight and clearance Dose-dependent CNS penetration Elimination via biliary system	Transaminitis Hypokalemia
		Caspofungin	Concentration-dependent activity Hepatic metabolism Dosing based on body surface area FDA approved for ages 3 months and older	Fever Rash Transaminitis Hypokalemia

Abbreviations: CSF, cerebrospinal fluid; CYP, cytochrome P; FDA, US Food and Drug Administration; CNS, central nervous system.

Table 4 Guidelines for the Treatment of Invasive Candidiasis in Neonates by Infectious Disease Society

IDSA		ESCMID		DMYG/PEG	
Medication	**Dosage**	**Medication**	**Dosage**	**Medication**	**Dosage**
Amphotericin B deoxycholate	1 mg/kg daily	Amphotericin B deoxycholate	1 mg/kg daily		
Fluconazole	12 mg/kg daily	Fluconazole	25 mg/kg loading dose followed by 12 mg/kg daily	Fluconazole	12 mg/kg daily divided over 4 doses
Amphotericin B lipid formulation	3–5 mg/kg daily	Liposomal amphotericin B	2.5–7 mg/kg daily	Liposomal amphotericin B	5 mg/kg daily divided over 4 doses
		Micafungin	4–10 mg/kg daily	Micafungin	2 mg/kg daily divided over 4 doses
				Caspofungin	25 mg/m^2 daily

Abbreviations: IDSA, Infectious Diseases Society of America; ESCMID, European Society for Clinical Microbiology and Infectious Diseases; DMYG, German Speaking Mycological Society (DMYG); PEG, Paul Ehrlich Society for Chemotherapy.

used in infants due to poor urinary tract penetration.[7,90] Alternatively, fluconazole is another first-line therapy supported by the IDSA, ESCMID, and DMYG-PEG.[7,55,91] When treating with fluconazole, the ESCMID recommends a loading dose. Because of its prolonged half-life and large volume of distribution in neonates, a loading dose of fluconazole may be required to quickly achieve adequate antifungal activity in neonates.[92–94] Alternative agents, including micafungin and caspofungin, have poor penetration in the urinary tract and CSF.[12,55,91] Additionally, in the setting of neuroinvasive

disease, 5-flucytosine can be added to the treatment regimen of an infant who does not respond to amphotericin B alone, and fluconazole is recommended as step-down rather than first-line therapy by the IDSA.[7]

Recommended treatment duration depends on extent of disease spread. In candidemia, treatment should be continued for 2 weeks after clearance of blood cultures and until resolution of signs and symptoms of invasive candidiasis.[7] For CNS infection, treatment should be continued for at least 3 weeks and until all signs, symptoms, CSF abnormalities, and imaging abnormalities have resolved.[7,95] For urinary tract infection, therapy for 10 to 14 days is recommended.[95] For invasive candidiasis associated with focal infections, such as endocarditis or renal fungal masses, prolonged therapy for several weeks is needed, in addition to surgical removal of focal infection, until all clinical signs, blood culture, and imaging findings have normalized.[95]

Amphotericin B

Amphotericin B is recommended by all three societies that have published recent guidelines on the treatment of neonatal invasive candidiasis. This compound in the polyene drug class interacts with ergosterol, the main sterol in the cell membrane and cell walls of many fungi, including *Candida*.[36] Interaction with ergosterol leads to the formation of pores in the cell membrane through which electrolytes and proteins can move freely, ultimately leading to cell death.[36] Advantages of this fungicidal drug include its broad spectrum of activity and good tissue penetration, including into the CNS.[7,96] Additionally, this drug is well tolerated in infants and has little risk of nephrotoxicity as compared to adults and older children.[7] However, it lacks adequate oral absorption and has high rates of *Candida auris* resistance (up to 30–40%).[97,98]

There are many formulations of amphotericin B, including amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD). Amphotericin B deoxycholate is the most recommended formulation, administered at a dose of 1 mg/kg/day in neonates.[7,90] It circulates in plasma highly bound to protein, is taken up by reticulo-endothelial organs, and is eventually excreted in urine and feces.[99] The pharmacokinetics of amphotericin B in children are characterized by a lower volume of distribution and faster clearance than adults, but neonate-specific activity is highly variable.[100–105] This formulation also penetrates the CSF well in neonates; amphotericin B CSF concentrations reach 40–90% of simultaneous serum concentrations.[100] Documented side effects include infusion-related reactions, hypokalemia, hepatotoxicity, and renal toxicity; however, in general, neonates tolerate this drug very well.[9,106] The incidence of renal toxicity attributable to amphotericin B deoxycholate, especially in infants, is questionable, as studies yield contradictory conclusions.[90] For instance, a 1990 study of 36 infants determined that 54% of patients who received a total of more than 5 mg/kg had laboratory abnormalities consistent with renal dysfunction.[107] In contrast, a 2003 study of 56 infants demonstrated that no infants on any formulation of amphotericin B had a deterioration in renal function.[108] On the other hand, a 2009 study of 92 infants on amphotericin B concluded that 16% experienced nephrotoxicity, defined as a serum creatinine rise of at least 0.4 mg/dl at any time during antifungal therapy, and this abnormality resolved in all but 1 infant by the end of therapy.[109] One retrospective study of 25 extremely low birth weight infants with fungal sepsis suggested that at least 4 mEq/kg/day sodium intake and adequate hydration while on amphotericin B deoxycholate therapy may adequately reduce the risk of renal injury.[110] Concern for nephrotoxicity should not prevent administration of amphotericin B deoxycholate in neonates.

Although amphotericin B deoxycholate is the most appropriate formulation choice for neonates, lipid formulations of amphotericin B also exist. Drugs within this class include liposomal amphotericin B, ABLC, and ABCD. These larger molecule formulations are attractive due to their side effect profile but cost more than amphotericin B deoxycholate and may be less effective in treating urinary tract disease due to reduced renal excretion.[7,82,90] Additionally, CSF penetration is not well characterized. As CSF and urine are common sites of neonatal invasive candidiasis, these drugs should be used with caution.

An oral formulation of amphotericin B, encochleated amphotericin B, is currently under investigation. Unlike the other forms of amphotericin B, this drug's composition evades degradation by the GI tract, allowing for oral administration with reduced toxicity.[100] It has demonstrated comparable activity to amphotericin B deoxycholate in vitro and in mouse models, and Phase 1 and 2 trials are ongoing.[111]

Triazoles

Triazoles inhibit the cytochrome P (CYP) 450 enzyme that synthesizes ergosterol.[36,90] First-generation triazoles include fluconazole and itraconazole, and second-generation triazoles include voriconazole and posaconazole. Newer triazoles include isavuconazole and opelconazole, and oteseconazole is a tetrazole currently under investigation. Common pharmacokinetic and pharmacodynamic characteristics of all triazoles include their time-dependent, rather than concentration-dependent, fungistatic activity; their interactions with CYP 450 enzymes; and their relatively safe side effect profiles.

Fluconazole 12 mg/kg/day is the triazole most often recommended for neonatal invasive candidiasis treatment.[7,55,91] Pharmacokinetic and pharmacodynamic characteristics of note include low protein binding, leading to high penetration in tissues, urine and CSF; renal elimination; and higher median 24 hour area under the curve in infants born at less than 30 weeks' gestation compared to infants born at greater than 30 weeks' gestation, necessitating dose adjustment based on gestational and postnatal age.[90,112] A unique feature of fluconazole treatment is the use of a 25 mg/kg loading dose.[91] A prospective, single-center, open-label pharmacokinetics and safety trial in 10 infants <60 days old demonstrated that a 25 mg/kg fluconazole loading dose was effective and well tolerated with few adverse events, with all infants reaching 24-hour trough concentrations of >8 μg/mL following the loading dose and the majority of infants reaching the therapeutic target area under the curve.[94] Benefits of this drug include its efficacy, activity against the most common *Candida* strains,[112] availability in IV and oral formulations, high bioavailability, and tolerability.[90] Of note, strains of *C. glabrata* and *C. krusei* have demonstrated resistance to fluconazole.[90] There are disadvantages to fluconazole use. Fluconazole is a strong CYP2C9 and CYP3A4 inhibitor, which raises concern for potential drug–drug interactions.[90] It requires dose adjustment for renal insufficiency, but specific dose adjustments for renal function in neonates have not been well studied.[112] Side effects are minimal and most commonly include gastrointestinal symptoms or rash but rarely include hepatotoxicity and QT interval prolongation.[90,96] Ultimately, while fluconazole has demonstrated activity against *Candida*, it is generally recommended as first-line therapy only in cases of uncomplicated disease without prior triazole exposure. In the setting of invasive candidiasis, fluconazole is more frequently used as a step-down therapy.[7,55,91]

Itraconazole, another first-generation triazole with fungistatic activity against yeast-like fungi and molds, is well tolerated and available in an oral formulation.[90] Limited safety and efficacy data are available for itraconazole use in infancy. A review of 32 studies in neonates and infants concluded that a dose of 10 mg/kg daily was effective and safe for systemic fungal infections.[113] Specifically, one double-blinded randomized control trial of 43 pediatric patients, including infants, demonstrated that 10 mg/kg/day itraconazole cleared candidemia at a similar rate as fluconazole with very few adverse effects.[114] Like fluconazole, itraconazole exhibits CYP3A4 inhibition, and GI symptoms are the most common side effect.[90] Unlike fluconazole, itraconazole is highly protein bound and undergoes extensive hepatic metabolism before excretion by the liver and kidneys.[90] It additionally exhibits variable, dose-dependent oral bioavailability, which makes predicting its efficacy more difficult.[90] Its oral bioavailability is also determined by stomach pH and gastric retention time; for optimal absorption, the drug should be administered on an empty stomach, which is difficult to accomplish in the neonatal population due to their feeding schedules.[115]

Voriconazole has moderate protein binding, resulting in good penetration into tissues and CSF and extensive metabolism by CYP2C19, but interpatient bioavailability is highly variable.[90,116] Voriconazole is also more potent than other azoles, especially in infections caused by *C. glabrata* and *C. krusei*,[9] and has demonstrated activity against the highly resistant *C. auris*.[10] Voriconazole has been studied in neonates and infants, and children younger than 3 years old require higher daily doses as compared to older children, with dosing recommendations ranging from 2 mg/kg twice daily to 6 mg/kg three times daily.[117–120] Intra-vitreal voriconazole has been used for neonatal *Candida* endophthalmitis with gradual improvement in imaging findings over several weeks.[121] Unlike fluconazole, voriconazole has activity against *Aspergillus* species.[96] However, there is minimal excretion of the active drug into the urine, preventing effective treatment of urinary tract infection.[116] This drug is available in both IV and oral formulations, but the IV formulation should be used with caution in the setting of renal insufficiency.[122] Potential side effects include elevated transaminases, skin photosensitization, and abnormal vision.[90,116] Ultimately, voriconazole is approved by the US Food and Drug Administration (FDA) for children aged 2 years or older.

Like voriconazole, posaconazole is an expanded-spectrum triazole with activity against some first-generation triazole-resistant *Candida* species.[90] This drug is available in IV and oral formulations, but the IV formulation is more commonly used in pediatrics because the highly bioavailable oral formulation is packaged in tablet form. In the body, posaconazole circulates highly bound to protein before being eliminated mainly in the feces but also by the kidneys.[90] The most commonly noted side effect is GI upset.[90] Posaconazole is most notably used in adults as antifungal prophylaxis;[123] there are limited data on the neonatal use of posaconazole, and the drug is not currently FDA approved for use in infants. Drug monitoring is critical if using voriconazole or posaconazole in children and neonates due to the drugs' variable bioavailability and potential for toxicity.[116,124]

Recently developed triazoles include isavuconazole and opelconazole; a tetrazole, oteseconazole, is also under investigation. All three drugs have demonstrated fungicidal activity against *Candida* species, including fluconazole-resistant strains.[90,125] Opelconazole is uniquely available in an inhaled formulation, allowing administration directly to the lungs.[126] Initial studies of isavuconazole and oteseconazole in adults demonstrate that they are well tolerated, with common side effects of headaches, rhinitis, and GI symptoms.[90,126] Isavuconazole was approved by the FDA in 2015 for the treatment of invasive aspergillosis and invasive mucormycosis in the form of isavuconazonium sulfate, and oteseconazole has been approved to reduce the incidence of vulvovaginal candidiasis in adults. Further studies in neonates are still needed.

Echinocandins

Echinocandins are an option for salvage therapy of invasive candidiasis in the setting of resistance to or toxicity from other first-line agents.[112] They block cell wall synthesis by inhibiting 1,3-β-D-glucan synthase.[36] This drug class has several advantageous features. Echinocandins have activity against many triazole-resistant species, including certain strains of *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis, C. krusei*, and *C. auris*.[90,127] They are fungicidal against *Candida* and fungistatic against *Aspergillus* species.[96] They are well tolerated with minimal side effects or drug interactions due to their fungus-specific mechanism of action. However, they have relatively poor penetration in the CSF and urine, necessitating high drug concentrations for therapeutic effect.[12] Additional limitations include poor oral availability, requiring IV administration, and elevated minimal inhibitory concentrations against *C. parapsilosis*.[90,128]

Micafungin is the most studied echinocandin in neonates. Important pharmacokinetic and pharmacodynamic characteristics include concentration-dependent fungicidal activity, high protein binding, elimination via the biliary system, and weight-dependent clearance.[90] Micafungin exhibits dose-dependent penetration of the CNS; higher doses should be used for suspected or proven CNS involvement.[7] Additionally, higher doses are required to achieve adequate micafungin exposure as body weight decreases;[129] therefore, young infants with very high clearance require high micafungin doses of 9–15 mg/kg/day to achieve a similar mean area under the curve compared to an adult dose of 150 mg or a pediatric dose of 2 mg/kg/day.[55,90,91,130] Micafungin has demonstrated efficacy against invasive candidiasis in the limited neonatal data that exists and is licensed by regulatory agencies, but knowledge gaps on its use in neonates remain. A Phase 3, randomized, double-blind, multicenter, parallel-group, noninferiority trial performed on infants with invasive candidiasis between 2 and 120 days old showed fungal-free survival in 60% of infants treated with micafungin versus 70% of infants treated with amphotericin B deoxycholate; however, the study ended early due to low recruitment.[131] Another sub-study of a randomized double-blind trial comparing micafungin and liposomal amphotericin B in premature infants and children found that micafungin was similarly effective and better tolerated than liposomal amphotericin B.[132] Micafungin is a relatively safe drug; its most common side effects include transient transaminitis and hypokalemia.[133] Further studies are needed to fully characterize this drug's activity and safety in neonates.

Other echinocandins of note include caspofungin, anidulafungin, and rezafungin. Important features of caspofungin include its concentration-dependent fungicidal activity, hepatic metabolism, and dosing based on body surface area rather than weight with a recommended dose of 25 mg/m^2/day.[7,55,90,134] This medication is generally well tolerated with notable side effects of fever, rash, hypokalemia, and elevated transaminases.[90] However, caspofungin is not FDA approved for neonates younger than 3 months of age. Important features of anidulafungin include its concentration-dependent fungicidal activity, near complete protein binding, and unique metabolism, characterized by slow, non-enzymatic degradation to inactive metabolites.[90] A 2011 pharmacokinetic study of 15 infants and neonates administered 1.5 mg/

kg/day IV anidulafungin found similar exposure levels in neonates as compared to children receiving similar weight-based dosing and adults receiving 100 mg/day; no serious adverse effects were reported.[135] A 2020 study of 19 patients between 1 month and 2 years of age receiving anidulafungin for 5–35 days found a 68.8% global response success rate to therapy.[136] Despite its tolerability with no reported serious adverse effects, there are few trials studying the efficacy of anidulafungin in neonates, and it is FDA approved for infants with candidemia starting at 1-month old.[90] A unique feature of rezafungin is its exceptionally long half-life, which allows for once-weekly dosing.[137] A 2023 multicenter phase 3 clinical trial in adults with candidemia or invasive candidiasis demonstrated that the 30-day all-cause mortality of patients treated with rezafungin was non-inferior to caspofungin.[138] Rezafungin has been approved by the FDA for the treatment of invasive candidiasis in adults with limited or no alternative treatment options, but more studies in neonates are still needed.[139]

5-Flucytosine

5-Flucytosine 25 mg/kg four times daily is an alternative fungistatic agent recommended by the IDSA for CNS invasive candidiasis that does not respond to amphotericin B.[7,96] This antimetabolite drug causes RNA miscoding, which interferes with DNA synthesis.[90] Important pharmacokinetic and pharmacodynamic properties include excellent oral bioavailability, very little protein binding, and high tissue penetration, including in the eye and CNS.[37] This drug is cleared by the kidneys and therefore requires renal adjustment, especially in premature infants, who can quickly accumulate high plasma concentrations as a result of low weight and renal immaturity.[37] Advantages of 5-flucytosine include broad antifungal activity against *Candida* species, with the exception of *C. krusei*,[37] and its aforementioned high eye and CNS penetration. In addition to required renal adjustment, a disadvantage of 5-flucytosine is its high rate of resistance if used alone; therefore, 5-flucytosine should be used in combination with other agents.[37] Another disadvantage is the drug's availability only in an oral formulation. Common side effects include gastrointestinal symptoms, although bone marrow suppression and hepatotoxicity have been noted in adults taking high doses of 5-flucytosine.[140]

Prevention

The most effective method for reducing the morbidity and mortality of invasive candidiasis in neonates is prevention of infection. The main prevention strategies include mitigation of well-known risk factors and thoughtful use of prophylactic antifungal regimens.

Mitigating Risk Factors

Risk factors for neonatal invasive candidiasis infections include prematurity, low birth weight, vaginal birth, skin or GI colonization at delivery, low Apgar scores, hospitalization longer than 7 days, compromise of GI mucosal integrity, presence of sepsis or shock, disseminated intravascular coagulation, and thrombocytopenia (Table 1).[1,4] While many of these are not easily modifiable, factors such as central line placement and utilization, use of groin catheters, mechanical ventilation, broad-spectrum antibiotics, H2 receptor blockers, systemic steroids, parenteral nutrition, and IV lipid emulsion are possible modifiable targets.[1,4]

Antibiotic stewardship is a particularly important intervention to consider. Broad spectrum antibiotic therapy kills the commensal bacteria that combat *Candida* proliferation.[8] An analysis of extremely low birth weight infants demonstrated a nearly 2-fold increased risk of invasive candidiasis when exposed to cephalosporins,[12] and carbapenems may also be associated with increased risk of invasive candidiasis in very low birth weight infants.[60] Judicious use of broad-spectrum antibiotics in neonates is a critical intervention to preclude the selection for *Candida* overgrowth and predisposition to infection that precedes invasive candidiasis.

Prophylaxis

Antifungal prophylaxis for high-risk neonates may prevent invasive candidiasis infection (Table 5). The 2016 IDSA guidelines recommend prophylaxis for neonates weighing less than 1 kg at birth in nurseries with high rates of invasive candidiasis, defined as greater than 10%.[7] The first-line regimen is IV or oral fluconazole 3–6 mg/kg twice weekly for six weeks.[7] If an alternative agent is necessary, the IDSA recommends oral nystatin 100,000 units three times daily for six weeks or oral bovine lactoferrin 100 mg daily.[7] The ESMID strongly recommends IV or oral fluconazole 3–6 mg/kg

Table 5 Prevention of Invasive Candidiasis in Neonates as Recommended by the IDSA and ESCMID

Medication	Dosage
Fluconazole	3–6 mg/kg twice weekly
Nystatin	100,000 units three times daily for six weeks
Oral bovine lactoferrin	100 mg daily

Abbreviations: IDSA, Infectious Diseases Society of America; ESCMID, European Society for Clinical Microbiology and Infectious Diseases.

twice weekly for all neonates weighing less than 1 kg in NICUs with high frequency of *Candida* infections; moderately recommends the use of oral nystatin 100,000 units three times daily to decrease the *Candida* burden in the gastrointestinal tract; and suggests bovine lactoferrin 100 mg/day alone or in combination with a lactobacillus probiotic for neonates weighing less than 1.5 kg.[9,91] The ESCMID also recommends against the use of miconazole gel due to concerns that it may increase fluconazole resistance.[9] Although not recommended by either organization, others advise the use of micafungin for antifungal prophylaxis in high-risk neonates when *Candida auris* colonization is suspected or NICU incidence is high.[30]

Fluconazole is the drug most recommended for prophylaxis against invasive candidiasis in neonates. There is data to support fluconazole prophylaxis in extremely low birth weight infants; a 2021 meta-analysis and systemic review indicated a significant decrease in invasive candidiasis mortality in extremely low birth weight infants on fluconazole prophylaxis compared to those not on prophylaxis.[141] A 2014 randomized, blinded, placebo-controlled trial of 361 infants from 32 different NICUs demonstrated a significantly lower incidence of invasive candidiasis in infants receiving 42 days of fluconazole prophylaxis compared to those receiving a placebo; however, there was not a significant difference in the composite primary end point of death or invasive candidiasis.[142] Other studies showed no difference in incidence of invasive fungal infections[143] or mortality in extremely low birth weight infants.[142] Fluconazole prophylaxis may not be particularly effective given the rise of triazole-resistant species; as epidemiology changes, attention will need to be paid to the rates of resistance, and consideration of alternative agents for prophylaxis may be necessary. Additionally, fluconazole prophylaxis has been associated with an increased minimal inhibitory concentration for *Candida* isolates that colonize infants who receive prophylaxis, potentially necessitating higher treatment doses and therefore increasing risk of drug toxicity.[144]

Nystatin is also recommended in invasive candidiasis prophylaxis guidelines and has been studied in neonates for decades.[145] This medication's oral formulation is not systemically absorbed; instead, it works against fungi in the GI tract, which is a major source of *Candida* colonization.[146] Oral nystatin is also less expensive than the IV formulation and is non-inferior for neonatal antifungal prophylaxis.[147] One prospective, open-labelled, randomized controlled trial in an Indonesian NICU demonstrated significantly lower incidence of fungal colonization, but not overall survival, in neonates who received oral nystatin prophylaxis as compared to those who did not.[146] The side effects and safety profile of nystatin have not been well studied in infants, and there are no blinded randomized control trials showing its benefit.

Another compound mentioned in prophylaxis guidelines is lactoferrin, a mammalian milk glycoprotein involved in innate immune host defenses.[148] This compound appears to be safe and well tolerated, but there is mixed data on its efficacy. Although some studies have determined that bovine lactoferrin, with or without a lactobacillus probiotic, reduces the incidence of sepsis in very low birth weight infants,[148] other studies, including a large, double-blind placebo trial, did not demonstrate beneficial impact on incidence of late-onset sepsis or necrotizing enterocolitis.[149]

Probiotics are considered to minimize risk of necrotizing enterocolitis in neonates, but their role in fungal infections is not well characterized. Infants in the NICU are at risk for microbiome alterations through factors such as delivery via cesarean section, antimicrobial treatment, delayed enteral feeding, and prolonged hospitalizations.[150] There are mixed data on the efficacy of probiotics in the prevention of neonatal sepsis. A 2022 randomized intervention trial in extremely preterm infants determined that daily administration of a probiotic mixture accelerated the maturation of the neonatal microbiome, significantly decreased inflammatory cytokine stool burden, and resulted in a significant decrease in the

relative abundance of *Candida* species.[151] A 2014 Cochrane review of over 5000 preterm infants given enteral probiotic supplementation determined that probiotics did not change incidence of nosocomial sepsis, while a 2017 systemic review found that the use of probiotics was beneficial for the prevention of late-onset sepsis in preterm infants.[152,153] In 2021, the American Academy of Pediatrics stated that the routine use of probiotics in preterm infants was not recommended due to the lack of FDA regulated products, contradictory safety and efficacy data, and potential for harm in this vulnerable population.[154] In September 2023, the FDA cautioned that microorganisms contained in probiotics have been implicated as causes of serious neonatal bacterial and fungal infection, especially in preterm and low birthweight infants.[155–158] These recent changes may influence the clinical use of probiotics in the neonatal population in general.

Conclusion

Invasive candidiasis in neonates leads to substantial short- and long-term morbidity and mortality and poses a significant threat to both short- and long-term outcomes. Although infants with invasive candidiasis often present with non-specific symptoms, awareness of risk factors and utilization of high-yield diagnostic methodologies can identify affected neonates in a timely manner. Understanding the extent of disease involvement and prompt treatment with supportive measures as well as targeted systemic antifungal therapy can optimize short-term and long-term outcomes of affected infants. Prevention strategies, including risk factor mitigation and antifungal prophylaxis, should be considered both at an individual and unit level to reduce the incidence of invasive candidiasis and its effects on preterm infants, who are among the most vulnerable populations at risk for *Candida* infections.

Acknowledgments

We would like to thank Carson Stahlsmith, PharmD, BCPPS (Department of Pharmacy, Duke University Hospital, Durham, North Carolina, USA) for reviewing the manuscript for accuracy of information in the therapeutics section, editing, revising, and correcting errors. We would like to thank Jordan Mah, MD (Department of Medicine, Division of Infectious Diseases, Durham, North Carolina, USA) for reviewing the laboratory testing section of the manuscript, editing, revising, and verifying information.

Disclosure

RGG has received support from industry for research services from Provepharm Inc and Tellus Therapeutics, outside the submitted work. AB reports training grants from Eunice Kennedy Shriver National Institute of Child Health and Human Development (1T32HD094671) and research support from Thrasher Research Foundation, outside the submitted work. The authors report no other conflicts of interest in this work.

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