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REVIEW

Invasive fungal infections in neonates: a review

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Invasive fungal infections remain the leading causes of morbidity and mortality in neonates, especially preterm and very low birth weight infants. Most invasive fungal infections are due to *Candida* or *Aspergillus* species, and other fungi are increasingly reported and described. Appropriate identification and treatment are required to augment activity and reduce the toxicity of antifungal drugs. Successful use of antifungals in the vulnerable neonatal population is important for both prevention and treatment of infection. Strategies for prevention, including prophylactic antifungal therapy as well as reducing exposure to modifiable risk factors, like limiting antibiotic exposure, discontinuation of central catheters, and hand hygiene are key techniques to prevent and decrease rates of invasive fungal infections. In conclusion, this is a review of the most common causes, prevention strategies, prophylaxis, and treatment of invasive fungal infections in neonates.

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INTRODUCTION

Invasive fungal infections (IFI) are a leading cause of morbidity and mortality in neonates, especially preterm and very low birth weight (VLBW, <1500 g birth weight [BW]) infants in the neonatal intensive care unit (NICU).[1] These infants are immunocompromised, exposed to broad-spectrum antibiotics, have immature epithelial barriers, and often undergo invasive procedures, putting them at increased risk for opportunistic fungal infections. The majority of IFI are due to *Candida* species; however, cases due to other fungi are increasingly reported. Having a high index of suspicion is crucial for early diagnosis and treatment. However, morbidity and mortality are high for some IFI, even with appropriate therapy. Strategies for prevention, including prophylactic antifungal therapy as well as reducing exposure to modifiable risk factors, like antibiotic exposure, have decreased rates of some infections. We will review the most common causes of IFI in neonates, treatment, and prophylaxis strategies.

INVASIVE CANDIDIASIS

Epidemiology

Candida species, commensal yeast, and common nosocomial pathogen are the most common fungal infection in neonates. They are colonizers of the skin as well as oral, gastrointestinal (GI), and vaginal mucosal surfaces, and infection occurs when this balance is disrupted. Invasive candidiasis (IC) is the third most common cause of late-onset sepsis in VLBW infants and a significant cause of morbidity and mortality in the NICU.[1,2] The incidence of IC in the NICU range from 0.5 to 20% and vary significantly by center, patient population, and have an inverse correlation with BW, with the highest incidence among ELBW infants (5–20%).[1–7] A recent study suggests that the incidence of IC in the NICU is decreasing, likely secondary to fluconazole prophylaxis, decreased use of broad-spectrum antibiotics, and improved care of central venous catheters.[7,8] *Candida albicans* is the most frequently isolated species, accounting for 60–75% of infections, followed by *C. parapsilosis* (14–30%).[3,9,10] Other species, including *C. tropicalis*, *C. lusitaniae*, *C. glabrata*, and C. *krusei* are a much less common cause of infection. IC is associated with significant morbidity and mortality (~30%), with one study reporting 73% death or neurodevelopmental impairment in ELBW infants with IC.[1,2,11,12]

Risk factors

Risk factors for IC encompass three main domains, (1) immunocompromised host, (2) disruption of epithelial barriers, and (3) level of colonization (Table 1).

Immunocompromised host. Neonates, particularly those that are preterm, have immature innate and adaptive immune systems that predispose them to infection.[13–16] Neutropenia is associated with IC in neonates.[17,18] In addition, several studies have shown an association between IC and lower gestational age (GA) and BW, with younger and smaller infants being at the highest risk.[2,5,6,12,19] Mortality from IC is also inversely proportional to BW.[12] Finally, the use of corticosteroids, an immunosuppressant, has been associated with an increased risk of IC in preterm infants.[12,20,21]

Disruption of epithelial barriers. Preterm infants have thin and incompletely developed epidermal and mucosal layers that allow pathogens to penetrate more easily, increasing the risk for IC.[22,23] In addition, procedures and equipment used in the NICU disrupt epithelial barriers and are associated with IC, including endotracheal tubes and central venous catheters[17,24,25]. Delayed catheter removal (>1 day after antifungal initiation) is also associated with an increased risk of death or neurodevelopmental impairment.[2] Disruption of the GI tract, allowing translocation of *Candida* out of the intestines, is also a frequent source of IC,

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Table 1. Risk factors for common fungal infections in the neonatal intensive care unit.

Infection	Risk factors
Candida spp.	Prematurity, low birth weight, colonization by vertical or horizontal transmission, neutropenia, use of corticosteroids, central catheters, prolonged or broad-spectrum antibiotic use, histamine-2-receptor antagonists, intravenous lipid emulsions, and delayed enteral feeding[6,17,20,31,142,143]
Aspergillus spp.	Prematurity, low birth weight, neutropenia, use of corticosteroids, central catheters, prolonged or broad-spectrum antibiotics, hospital gauze, adhesive tape, bedding, dressings, hospital renovations, and construction[73,79,80,144–146]
Zygomycetes	Prematurity, low birth weight, broad-spectrum antibiotics, use of corticosteroids, central catheters, contaminated wood tongue depressors, adhesives, and linens[86,87,89,90]
Malassezia spp.	Prematurity, central catheters, broad-spectrum antibiotics, intravenous lipid emulsions, and skin emollients[99,100]

including necrotizing enterocolitis (NEC), spontaneous intestinal perforation, GI anomalies, and other abdominal surgeries.[12,17,26–28]

Colonization. Several studies demonstrated a correlation in VLBW infants between IC and *Candida* colonization, with the risk increasing with number and type of site (high risk vs. low risk).[18,29,30] In addition, numerous studies have shown an association between antibiotic use, which decreases commensal bacteria and can increase *Candida* colonization, and IC in VLBW infants, particularly the use of prolonged or broad-spectrum antibiotics (third-generation cephalosporins).[2,4,6,17,19,24,31,32] Other factors that increase the risk of IC through overgrowth or increased colonization of *Candida* include use of postnatal steroids, histamine-2-receptor antagonists, and intravenous lipid emulsions.[6,12,20,21,24]

Clinical presentation

Infants with IC often present with a sepsis-like illness, including lethargy, apnea, respiratory distress, cardiovascular instability, and/or feeding intolerance that is similar to infants with other late-onset infections. Although nonspecific, persistent hyperglycemia and thrombocytopenia are associated with fungal infections and should prompt further evaluation.[24,33–36] Candidemia, especially when present >5 days, can spread to multiple organ systems via hematogenously or via septic emboli leading to fungal masses and inflammation, most commonly in the kidneys (5–30%), heart (5–15%), central nervous system (CNS, 5–64%), eyes (chorioretinitis and endophthalmitis, 3–50%), bones/joints, skin, and lungs.[37–46] *Candida* CNS disease usually presents as meningoencephalitis in the setting of candidemia, but can also present as brain abscesses, ventriculitis and vasculitis, and with a negative blood culture.[2,47]

Congenital cutaneous candidiasis (CCC) is an invasive infection of the dermis and epidermis acquired in utero or at the time of delivery. Infection can occur in term and preterm neonates, but the risk for systemic disease is greatest for extremely low birth weight (ELBW, <1000 g BW) infants. In an 11-year study of over 19,000 NICU admission (two units), Kaufman et al. reported a CCC incidence of 0.1%, with >90% of affected infants <37 weeks GA and the highest incident in ELBW infants (0.6%).[48] Risk factors for CCC include prematurity, vaginal foreign bodies (intrauterine device, cerclage), ruptured membranes, chorioamnionitis, and history of vaginal candidiasis (Table 1).[48–50] CCC typically presents with a rash in the first few days of life (71% on the first day, 0–6 days median)[48]. The rash can consist of one or more of the following: peeling, sloughing, or desquamation (62%); maculopapular rash (48%); pustule/papule (40%); diffuse erythema (33%); yellow plaques or secretions (19%); dry flaking, scaling, or cracking skin (19%).[48] The majority of infants (57%) had two or more of these skin findings and 19% had funisitis. The most commonly involved surfaces include the back, extensor surfaces of extremities, skin folds, and, unlike other common neonatal rashes, the palms and soles.[49] Preterm infants with CCC often present with respiratory distress, elevated white blood cell count, and hyperglycemia.[49] CCC is associated with disseminated infection and high mortality (40% <1000 g, 14% 1000–2500 g, 4% >2500 g)[49]; however, early systemic therapy can significantly reduce morbidity and mortality (95% survival).[48]

Candida are also a common cause of urinary tract infections (UTIs) in the NICU.[51,52] Symptoms are nonspecific and include apnea, bradycardia, and, if obstruction is present, decreased urine output. Infection can range from cystitis, especially in those with indwelling catheters, to renal parenchymal disease with mycetoma formation.[53,54] Up to 30% of infants with candidemia have renal involvement, and a candidal UTI can progress to disseminated disease.[40,51] Isolated IC of other organ systems (cardiac, CNS, ophthalmologic, musculoskeletal) can also occur, especially in the presence of indwelling devices.

Finally, IC can lead to peritonitis with spontaneous intestinal perforation or NEC-like presentation. It is unclear in these cases whether *Candida* causes the mucosal damage and/or perforation or if it invades after a primary insult.[26,27,55]

Diagnosis

Candidemia. Blood culture is the gold standard for diagnosis of IC. *Candida* can be detected the typical blood culture media used for bacteria. Historically, while the specificity was high (100%), sensitivity was low.[56,57] However, newer blood culture techniques are available that are more accurate.[58] For infants not on antifungal therapy, the median time to positivity was 36 h, with 97% of blood cultures positive by 72 h. This increased to a median of 42 h and 91% positive by 72 h for infants on antifungal therapy.[59] In addition, the majority of infants with Candidemia have more than one positive culture (median 3–5 days).[2,40]

Infants with a high clinical suspicion for IFI should be started on empiric antifungal therapy until IC is ruled out and a positive culture for *Candida* should never be considered a contaminant.

Beta-D-glucan (BDG) is a cell wall component found in many fungi and may aide in the in diagnosis of IFI. BDG is frequently used to aide in the diagnosis of IC in adults, with sensitivity of up to 97% and specificity up to 93%.[60] A study of 61 neonates in the NICU found that BDG levels were significantly higher in infants with IC, but a higher cutoff level of ≥125 pg/mL was needed (compared to >80 pg/mL recommended by the assay kit).[61] Another study reported similar findings in neonates with invasive yeast infections, with a cutoff of 105 pg/mL, and a higher sensitivity/specificity if only looking at IC. For both studies, the change in BDG levels were useful for monitoring treatment efficacy over time. The authors hypothesized that the higher baseline BDG levels could be due to higher rates of *Candida* colonization or a false positive. BDG is not specific to *Candida* and previous studies have reported false positives secondary to antibiotic exposure, some bacterial infections, albumin, and transfusion of blood products.[62–68] Currently, BDG is most useful in neonates for to aide in the decision to start empiric antifungal therapy and to monitor response to therapy.

Polymerase chain reaction (PCR)-based assays that detect the ribosomal subunit of fungi are being developed, but are not as sensitive (77–95%) or specific (70–95%) as culture.[57] In addition, these assays cannot provide sensitivity data and there is concern

Table 2. Most commonly used systemic antifungals and their recommended indications.

Drug class	Drug name	Common indication(s)	Comments	Monitoring
I. Polyenes	Amphotericin B deoxycholate	Invasive *Candida* infections (including diffuse mucocutaneous infections), primary cutaneous or invasive *Aspergillus* infection, primary cutaneous or gastrointestinal zygomycosis, invasive *Malassezia*[134,147–150]	Nephrotoxicity Increased liver enzymes Anemia/thrombocytopenia[151]	Adequate sodium- and potassium-containing intravenous fluids Complete metabolic panel (including renal and hepatic function) Complete blood count with differential until values normalize Frequency: twice weekly to once a week
	Lipid-based amphotericin B preparations	Infants with infusion-related reactions during amphotericin B administration or those with renal dysfunction[70]	Poor penetration of renal tubules, and should not be used for renal candidiasis[152]	
II. Azoles	Fluconazole	Alternative to amphotericin B deoxycholate for susceptible *Candida* isolates.[134] First choice for prophylaxis in high-risk infants[134]		
	Itraconazole			Peak and trough drug plasma levels[153]
	Voriconazole	Second- or third-line in resistant invasive aspergillosis infections[154]	Highly effective against *Aspergillus* spp. High CNS penetration[155,156]	Peak and trough drug plasma levels[157]
	Posaconazole			Peak and trough drug plasma levels[158]
	Isavuconazole			
III. Echinocandins	Caspofungin	Infections secondary to *Candida* spp. resistant to amphotericin B and fluconazole	Well tolerated in neonates (transient anemia/thrombocytopenia)	Complete blood count Liver function tests during the first week of treatment[159]
	Micafungin			
	Anidulafungin			
IV. Nucleoside analogs	Flucytosine	Occasional use in infants with disseminated candidiasis with central nervous and urinary tract involvement[153]	Extensive penetration into tissues and fluids Bone marrow toxicity	Peak and trough plasma levels[160]

about contamination and detecting colonization rather than infection.

Congenital cutaneous candidiasis. Diagnosis is made by identification of budding yeast and pseudohyphae on a Gram stain or potassium hydroxide (KOH) preparation of skin scrapings, vesicular contents, or skin biopsy. Evaluation for systemic infection should be done with cultures of blood, urine and cerebrospinal fluid, and can aid in the diagnosis.

Urinary tract infection. A diagnosis of candidal UTI is made based on a positive urine culture (>1000 colony-forming units per mL (CFU/mL) from suprapubic aspiration or >10,000 CFU/mL from catheterized specimen).[69,70] Urine culture is a poor predictor of renal involvement and should not be used to rule out renal involvement.[57]

CNS infection. As with blood, diagnosis of *Candida* CNS disease is made by isolating the fungi from cerebrospinal fluid (CSF) culture. CSF of infants with *Candida* meningitis can have normal gram stain, cell count, and chemistries because of a low or delayed inflammatory response or localized CNS infection (abscess) and negative blood cultures.[43,47] In a study of 20 infants with culture-positive *Candida* meningitis, 43% (3/7) had normal CSF parameters and 63% (11/19) had a negative blood culture.[47]

Multisystem or disseminated disease. As mentioned previously, IC is frequently a multisystem disease. *Candida* detected in one system should prompt evaluation of other systems for involvement, including blood culture, urine culture, lumbar puncture, echocardiogram, dilated eye exam, head ultrasound, and ultrasound of the liver, spleen, and kidneys to determine guide antifungal therapy and duration (Table 2).[71]

ASPERGILLOSIS

Epidemiology

Aspergillus species are ubiquitous molds found throughout the environment, including in air, soil, plants, and food. *Aspergillus* is a leading cause of IFI in immunocompromised adults and children, but is uncommon in neonates.[1,72] There are over 200 known species, with at least 20 known to cause human disease. *Aspergillis fumigatus* is the most commonly isolated species, followed by *Aspergillus flavus* and *A. niger*.[72–75] *Aspergillus* is associated with high morbidity and mortality and there are an increasing number of case reports in neonates.[5,72,73]

Risk factors

As with IC, risk factors for aspergillosis in neonates include factors that increase host susceptibility, disrupt epithelial barriers, and disrupt the normal flora, including prematurity, VLBW, exposure to broad-spectrum antibiotics, central venous catheters, and corticosteroids.[72,73] However, there are also environmental factors that can increase the risk of *Aspergillus* infection in an at-risk host, including hospital construction or renovations, contaminated gauze, bedding, tape, and other dressings (Table 1).[73,76,77]

Clinical presentation

Aspergillosis typically begins as a pulmonary infection, but in neonates, other sites of entry include invasive catheters, the GI system, sites of skin breakdown from medical equipment (tape, arm boards), and wounds.[78]

Primary cutaneous aspergillosis (PCA). PCA occurs most commonly in hospitalized, preterm infants.[73] Lesions vary, but usually start as an erythematous patch or plaque that changes to a pustule, and then ulcerates to form a necrotic eschar.[79] The mean age of appearance is 10 days (3–33 days range) and the lesions are usually found on the back or sites of trauma.[72,73,80] If treatment is not started early, PCA can progress to a system infection.[77,80]

Invasive aspergillosis. Invasive aspergillosis most commonly presents as pulmonary or disseminated disease in neonates, but can also present in the CNS and GI tract.[73,81,82] Like with PCA, localized invasive *Aspergillus* often progresses to disseminated disease, especially if treatment is not started early.[83] *Aspergillus* can invade blood vessels, leading to thrombus formation or hemorrhage, or other tissues, including pulmonary, cardiac, muscles, and bone.[82,83]

Diagnosis

In adults and pediatric patients, imaging studies, particularly of the chest, are a mainstay of diagnosis. However, neonates do not usually present with these classic findings.[72] Diagnosis of *Aspergillus* infection in neonates typically relies on culture or histopathological examination of body fluid or tissue sample. PCR assays for *Aspergillus* have been developed and may aide in the diagnosis, especially of CSF, but have low sensitivity and specificity (80% for both) and are not available at all centers.[83] Galactomannan antigen testing is useful for diagnosis of *Aspergillus* in adults, but are not recommended for neonates because of the risk of false positives.[72,84]

ZYGOMYCOSIS

Epidemiology

Zygomycetes are ubiquitous fungi found in soil and vegetation and encompass the orders Entomophthorales and Mucorales (*Rhizopus*, *Rhizomucor, Mucor*, *Absidia*).[85] Zygomycosis is rare in neonates, but associated with high mortality and reported cases neonates as increased significantly since 1990.[86] *Rhizopus* (44–72%) and *Mucor* (4–15%) are the most commonly isolated species in neonates.[86,87]

Risk factors

As with other invasive fungal infections, the greatest risk factor for zygomycosis is prematurity.[86,87] Broad-spectrum antibiotics, corticosteroid therapy, invasive catheters, acidosis and hyperglycemia are also associated with zygomycosis in neonates.[86–88] Finally, outbreaks of zygomycosis have been associated with contamination of wooden tongue depressor, adhesives and hospital linens (Table 1).[89–91]

Clinical presentation

Zygomycetes are invasive fungi and often lead to tissue necrosis, thrombosis, and disseminated disease.[92] In neonates, zygomycosis typically presents as a cutaneous disease (36%) or GI disease (51%), and both often lead to disseminated disease (56%).[87]

Primary cutaneous disease. Cutaneous lesions can remain localized or extend to invasive or systemic diseases.[86] Lesions often begin as erythema and induration, particularly around sites of trauma and skin breakdown, and then progress to deep necrotic eschars that can extend through multiple layers of skin.[93,94]

GI disease. The clinical presentation of GI disease is very similar to NEC, except that there is no pneumatosis intestinalis or other hallmark radiologic findings and, while NEC is generally limited to the small bowel, zygomycosis can extend from the esophagus to the large intestines.[87,88,95] Skin lesions may or may not be present with GI disease and it is associated with a very high mortality (78%).[87]

Neonates treated with a combination of surgery/surgical debridement and antifungal therapy have the highest reported rates of survival (30% mortality), although studies are small (Table 2). Cutaneous disease also has a higher survival compared

to GI disease—77% cutaneous vs. 39% GI survival for infants who had surgery and antifungal therapy (Table 2), likely due at least impart to delayed diagnosis.[86] Interestingly, surgery did not seem to increase survival in GI zygomycosis. Early diagnosis and initiation of antifungal therapy is crucial to survival.

Diagnosis

Zygomycosis is difficult to diagnose in neonates. Diagnosis relies on histopathologic examination of a tissue sample with culture confirmation, if available. However, Zygomycetes are very difficult to grow in culture and many cases have been diagnosed on autopsy.[86] PCR and other molecular assays are being developed, but are not readily available in most locations and have not been tested in neonates.[96] Zygomycetes do not have the cell wall components detected by BDG and galactomannan assays.

MALASSEZIA

Epidemiology

Malassezia are lipophilic yeasts and a part of the normal human skin flora.[97] Infection in neonates is uncommon. The most commonly isolated species from neonatal infections are *Malassezia furfur*, *M. pachydermatis*, *M. globus*, and *M. sympodialis*.[98] *Malassezia* cannot synthesize medium- and long-chain fatty acids and require an exogenous supply for growth.

Risk factors

Risk factors associated with *Malassezia* in neonates include prematurity, intralipid emulsions, invasive catheters, skin emollients, prolonged NICU stay, and broad-spectrum antibiotics (Table 1).[99–101]

Clinical presentation

In healthy children and adults, *Malessezia* generally cause superficial skin infections like pityriasis versicolor, seborrheic dermatitis, and folliculitis. Neonates, especially preterm infants in the NICU, can present with systemic disease. Symptoms are nonspecific and similar to other etiologies of late-onset sepsis, including apnea, bradycardia, respiratory distress, and thrombocytopenia.[102,103] Skin findings are uncommon with systemic disease. Like other fungi, *Malassezia* are also associated with thrombus formation.[103,104]

Diagnosis

As with other fungal pathogens, diagnosis of *Malessezia* in neonates is difficult and clinicians must have a high index of suspicion. Diagnosis is made by histologic identification or positive culture from a normally sterile tissue or body fluid. *Malassezia* do not grow in typical culture media because they require fatty acids for growth and can take up to 2 weeks to grow. Histopathologic identification can be confirmed with culture using specialized media. The BDG assay does not detect *Malassezia*.[105] Newer molecular methods of diagnosis (PCR, mass spectrometry) are becoming more common, but have not been widely tested in neonates.[101,106,107]

UNCOMMON FUNGAL PATHOGENS

Blastomycosis

Blastomyces are dimorphic fungi found in soil and near water, particularly along St. Lawrence and Mississippi rivers in North America. Blastomycosis, most commonly caused by *Blastomyces dermatitidis*, occurs in both immunocompetent and immunocompromised hosts, usually from inhalation of spores. A handful of cases have been reported in neonates and were thought to be secondary to in utero or perinatal transmission.[108,109] Reported neonatal cases presented as invasive pulmonary and disseminated diseases and were universally fatal. Diagnosis of *blastomyces* is typically by histopathologic examination or culture of infected respiratory secretions and/or tissue.

Coccidiodomycosis

Coccidioides immitis is a dimorphic fungi endemic in the Southwestern United States and is the causative agent of coccidiodomycosis. Infection occurs in immunocompetent and immunocompromised hosts, usually via inhalation of athroconidia. As with blastomycosis, a handful of cases have been reported in neonates, the majority of which were thought to occur secondary to maternal transmission; however, environmental acquisition has been reported.[110–113] Coccidiodomycosis in infants often presents as disseminated and fatal disease. Serologic testing is frequently used for diagnosis in adults and children. However, for early and severe disease, as in neonates, diagnosis via histopathologic examination or culture of infected secretions or tissue is required because there has not been enough time for sufficient antibody production.

Cryptococcus

Cryptococci are encapsulated fungi found in soil throughout the world, particularly in areas contaminated by pigeon feces. Cryptococcal infection most commonly occurs in immunocompromised hosts, particularly those with AIDS, and *Cryptococcus neoformans* is the most commonly isolated species. Infection in the neonate is rare, but when it occurs, it results in multisystem dissemination, including to the brain, meninges, liver, spleen, and eyes.[114,115] Most reported infants survive with appropriate therapy. There is little data, but risk factors for neonatal cryptococcus are thought to be similar to those for other invasive fungal infections.[114] Transplacental transmission has been reported in the setting of maternal human immunodeficiency virus.[116,117] Diagnosis is made by India ink staining or cryptococcal antigen testing of infected fluids. Culture can be used to confirm the diagnosis.

Trichosporon

Trichosporon are ubiquitous fungi commonly found in soil that can colonize human skin, respiratory, and GI tracts. They generally cause superficial infection of hair shafts (white piedra), but rarely can cause invasive disease in susceptible hosts. A handful of cases in the NICU have been reported.[118] Risk factors for neonatal infection include prematurity, VLBW, and broad-spectrum antibiotics.[118] Cutaneous infections generally present as 0.5 mm painless white nodules along the hair shaft. Reported systemic disease in infants includes UTI, catheter-associated infection, and disseminated disease (pulmonary, GI, renal).[118] *Trichosporon* can also cause invasive skin lesions with central necrosis and ulceration.[119,120] Diagnosis is made by KOH preparation of affected hair shaft, or culture and/or histopathology of blood or affected tissue.

Pichia

Pichia are ubiquitous yeast and opportunistic pathogens found in the environment (soil, water, plants, fruits, insects) and may be contaminants in foods and drinks—some species are used in cheese and wine making. Isolated neonatal infections, as well as outbreaks in NICUs, have been reported. *Pichia anomala* is the most commonly isolated species, followed by *P. fabianii*, *P. ohmeri*, and *P. kudriavzevii*.[121–125] Identified risk factors include prematurity, VLBW, invasive catheters, previous antibiotic use, total parenteral nutrition with lipid emulsion, and invasive procedures.[121,122,126] Some outbreaks were linked to carriage by healthcare providers.[122,126] *Pichia* can lead to fungemia and ventriculitis and symptoms are similar to other late-onset illnesses, including respiratory failure, apnea, and bradycardia.[121] As with other opportunistic fungi, colonization can occur without infection. Diagnosis is by a culture of infected bodily fluid. However,

Table 3. Recommendations for the length of treatment[134,137].

Name	Dose	Indication	Duration of therapy
Amphotericin B deoxycholate	1 mg/kg IV daily	Uncomplicated candidemia, catheter-associated candidemia (with the removal of the central catheter), urinary tract infection	14 days from first negative culture
		Central nervous system infection	>3 weeks
		Complicated candidemia associated with focal infection (endocarditis, renal)	4–6 weeks
Fluconazole[a]	12 mg/kg/day IV or enterally	Uncomplicated candidemia/catheter-associated candidemia (with the removal of the central catheter)	14 days from first negative culture
		Urinary tract infection	10–14 days
		Complicated candidemia associated with focal infection (endocarditis, renal)	4–6 weeks
Liposomal formulation of amphotericin B[b]	3–5 mg/kg IV daily	Similar to amphotericin B (not superior and more expensive)	
Micafungin[c]	4–10 mg/kg/day	Resistant infections	Based on indication

[a]The European Society for Clinical Microbiology and Infectious Diseases recommends a loading dose of 25 mg/kg, followed by 12 mg/kg in neonates who have not received fluconazole.
[b]This should be used with caution in the presence of urinary tract involvement and concern for renal fungal abscess.
[c]Echinocandins should be reserved for salvage therapy in the setting of toxicity from or resistance to other agents.

PCR or other molecular assays may be needed for appropriate identification.[122,126,127]

ANTIFUNGAL PROPHYLAXIS FOR PREVENTION OF INVASIVE INFECTIONS

As discussed above, extremely premature infants are at high risk for developing IFI, which are associated with significant mortality, devastating morbidities, and long-term neurodevelopmental impairment in survivors. For this reason, fluconazole prophylaxis should be considered in high-risk infants, and especially those admitted to NICUs with high rates of IC.

Multiple trials have demonstrated the dosing, safety, and efficacy of using fluconazole prophylaxis against IC.[128–132] In a patient-level data meta-analysis of four randomized, placebo-controlled trials including preterm infants from the United States, fluconazole prophylaxis decreased the odds of IC [odds ratio (OR) 0.20, 95% confidence interval (CI) 0.08–0.51], as well as the composite outcome of death or IC (OR 0.48, 95% CI 0.30–0.78).[133] In addition, fluconazole prophylaxis reduced the odds of *Candida* spp. colonization (OR 0.28, 95% CI 0.18–0.41).[133]

The Infectious Diseases Society of America (IDSA) currently recommends the use of intravenous or oral fluconazole prophylaxis at a dose of 3–6 mg/kg twice weekly for 6 weeks in infants with birthweights <1000 g who are admitted to NICUs with high rates (>10%) of IC.[134] However, even in centers with low rates of IC, fluconazole prophylaxis should be considered in high-risk ELBW infants, particularly those with central line catheters, and those receiving broad-spectrum antibiotics.[135]

TREATMENT OF SYSTEMIC INFECTIONS

Appropriate use of antifungals in the neonatal population is important for both prevention and treatment of infection with IFI. Empiric antifungal therapy is often instituted in infants given the poor performance of laboratory assays, the long turnaround time for culture results, and inaccuracy in clinician diagnosis.[24,56] Empiric antifungal therapy in infants with birthweight <1000 g has been shown to increase survival without neurodevelopmental impairment.[136] In order to maximize the activity of antifungals and minimize toxicity in this vulnerable population, isolation, and identification of a specific fungus should then guide further treatment (Table 2).

There are currently four main classes of antifungals that are used in infants, including polyenes, pyrimidine analogs, azoles, and echinocandins (Table 2).[137] The most commonly used antifungals in the NICU are fluconazole and amphotericin B deoxycholate.[138] Tables 2 and 3 below list recommendations for treatment of IFIs along with monitoring parameters. In addition to pharmacologic treatment, consideration should be given to the removal of indwelling catheters, due to biofilm formation, surgical debridement (*Zygomycetes* spp.), and cessation of intralipid emulsions as able (*Malassezia* spp.).[86,139,140] Because of the limited data, variation in choosing a first-line agent in the NICU still exists, and future pharmacokinetic studies will inform neonatal practice better.[141]

CONCLUSION

In summary, in this era of improved survival of extremely premature ELBW infants, the risk of IFIs is extremely high. These infants have immature skin integrity, and coupled with their innate immunosuppression and other life-supporting therapies, they are at high risk of lethal IFIs. While *Candida* spp. are the most common causative organisms, others have been reported in the literature. Attempting to modify risk factors through care bundles, antibiotic stewardship programs, discontinuation of central catheters, and hand hygiene are key techniques to prevent IFIs. Maintaining a high index of suspicion for fungal infections to appropriately identify and promptly treat is critical. Consideration to fluconazole prophylaxis in high-risk infants should be given to reduce infection rates of IFIs. Further studies evaluating the safety, efficacy, and drug pharmacokinetics will allow targeted therapies in this vulnerable population.

REFERENCES

1. Stoll, B. J. et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* **110**, 285–291 (2002).
2. Benjamin, D. K. et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* **117**, 84–92 (2006).
3. Fridkin, S. K., Kaufman, D., Edwards, J. R., Shetty, S. & Horan, T. Changing incidence of *Candida* bloodstream infections among NICU patients in the United States: 1995-2004. *Pediatrics* **117**, 1680–1687 (2006).

4. Cotten, C. M. et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics* **118**, 717–722 (2006).
5. Clerihew, L., Lamagni, T. L., Brocklehurst, P. & McGuire, W. Invasive fungal infection in very low birthweight infants: National Prospective Surveillance Study. *Arch. Dis. Child. Fetal Neonatal Ed.* **91**, https://doi.org/10.1136/adc.2005.082024 (2006).
6. Saiman, L. et al. Risk factors for candidemia in neonatal intensive care unit patients. *Pediatr. Infect. Dis. J.* **19**, 319–324 (2000).
7. Aliaga, S. et al. Changes in the incidence of candidiasis in neonatal intensive care units. *Pediatrics* **133**, 236–242 (2014).
8. Chitnis A. S. et al. Trends in Candida central line-associated bloodstream infections among NICUs, 1999-2009. *Pediatrics* **130**, https://doi.org/10.1542/peds.2011-3620 (2012).
9. Benedict, K. et al. Neonatal and pediatric candidemia: results from population-based active laboratory surveillance in four US locations, 2009-2015. *J. Pediatr. Infect. Dis. Soc.* **7**, E78–E85 (2018).
10. Lausch, K. R. et al. Pediatric Candidemia epidemiology and morbidities: a nationwide cohort. *Pediatr. Infect. Dis. J.* **38**, 464–469 (2019).
11. Makhoul, I. R., Sujov, P., Smolkin, T., Lusky, A. & Reichman, B. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. *Pediatrics* **109**, 34–39 (2002).
12. Adams-Chapman, I. et al. Neurodevelopmental outcome of extremely low birth weight infants with Candida infection. *J. Pediatr.* **163**, https://doi.org/10.1016/j.jpeds.2013.04.034 (2013).
13. Correa-Rocha, R. et al. Preterm neonates show marked leukopenia and lymphopenia that are associated with increased regulatory T-cell values and diminished IL-7. *Pediatr. Res.* **71**, 590–597 (2012).
14. Carr, R. Neutrophil production and function in newborn infants. *Br. J. Haematol.* **110**, 18–28 (2000).
15. Arsenault, A. B. & Bliss, J. M. Neonatal candidiasis: new insights into an old problem at a unique host-pathogen interface. *Curr. Fungal Infect. Rep.* **9**, 246–252 (2015).
16. Levy, O. Innate immunity of the newborn: basic mechanisms and clinical correlates. *Nat. Rev. Immunol.* **7**, 379–390 (2007).
17. Yu, Y. et al. Risk factors and clinical analysis for invasive fungal infection in neonatal intensive care unit patients. *Am. J. Perinatol.* **30**, 589–594 (2013).
18. Mahieu, L. M., Van Gasse, N., Wildemeersch, D., Jansens, H. & Ieven, M. Number of sites of perinatal *Candida* colonization and neutropenia are associated with nosocomial candidemia in the neonatal intensive care unit patient. *Pediatr. Crit. Care Med.* **11**, 240–245 (2010).
19. Saiman, L. et al. Risk factors for *Candida* species colonization of neonatal intensive care unit patients. *Pediatr. Infect. Dis. J.* **20**, 1119–1124 (2001).
20. Botas, C. M., Kurlat, I., Young, S. M. & Sola, A. Disseminated Candidal infections and intravenous hydrocortisone in preterm infants. *Pediatrics* **95**, 883–887 (1995).
21. Stoll, B. J. et al. Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics* **104**, e63–e63 (1999).
22. Neu, J. Gastrointestinal development and meeting the nutritional needs of premature infants. *Am. J. Clin. Nutr.* **85**, 629S–634S (2007).
23. Evans, N. J. & Rutter, N. Development of the epidermis in the newborn. *Biol. Neonate* **49**, 74–80 (1986).
24. Benjamin, D. K. et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics* **126**, https://doi.org/10.1542/peds.2009-3412 (2010).
25. Faix, R. G., Kovarik, S. M., Shaw, T. R. & Johnson, R V. Mucocutaneous and invasive candidiasis among very low birth weight (<1,500 grams) infants in intensive care nurseries: a prospective study. *Pediatrics* **83**, 101–107 (1989).
26. Adderson, E. E., Pappin, A. & Pavia, A. T. Spontaneous intestinal perforation in premature infants: a distinct clinical entity associated with systemic candidiasis. *J. Pediatr. Surg.* **33**, 1463–1467 (1998).
27. Coates, E. W., Karlowicz, M. G., Croitoru, D. P. & Buescher, E. S. Distinctive distribution of pathogens associated with peritonitis in neonates with focal intestinal perforation compared with necrotizing enterocolitis. *Pediatrics* **116**, e241–e246 (2005).
28. Shetty, S. S. et al. Determining risk factors for candidemia among newborn infants from population-based surveillance: Baltimore, Maryland, 1998-2000. *Pediatr. Infect. Dis. J.* **24**, 601–604 (2005).
29. Manzoni, P. et al. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. *Pediatrics* **118**, 2359–2364 (2006).
30. Manzoni, P. et al. Type and number of sites colonized by fungi and risk of progression to invasive fungal infection in preterm neonates in neonatal intensive care unit. *J. Perinat. Med.* **35**, 220–226 (2007).
31. Bendel, C. M. Colonization and epithelial adhesion in the pathogenesis of neonatal candidiasis. *Semin. Perinatol.* **27**, 357–364 (2003).
32. Lee, J. H. et al. Risk factors for invasive candidiasis in infants >1500g birth weight. *Pediatr. Infect. Dis. J.* **32**, 222–226 (2013).
33. Manzoni, P. et al. Hyperglycaemia as a possible marker of invasive fungal infection in preterm neonates. *Acta Paediatr.* **95**, 486–493 (2006).
34. Guida, J. D., Kunig, A. M., Leef, K. H., McKenzie, S. E. & Paul, D. A. Platelet count and sepsis in very low birth weight neonates: Is there an organism-specific response. *Pediatrics* **111**, 1411–1415 (2003).
35. Benjamin, D. K. et al. When to suspect fungal infection in neonates: a clinical comparison of *Candida albicans* and *Candida parapsilosis* fungemia with coagulase-negative staphylococcal bacteremia. *Pediatrics* **106**, 712–718 (2000).
36. Manzoni, P. et al. Is thrombocytopenia suggestive of organism-specific response in neonatal sepsis? *Pediatr. Int.* **51**, 206–210 (2009).
37. Kassner, E. G. et al. Pulmonary candidiasis in infants: clinical, radiologic, and pathologic features. *Am. J. Roentgenol.* **137**, 4 (1981).
38. Bodey, G. P. & Luna, M. Skin lesions associated with disseminated candidiasis. *JAMA* **229**, 1466–1468 (1974).
39. CHEN, J. -Y. Neonatal candidiasis associated with meningitis and endophthalmitis. *Pediatr. Int.* **36**, 261–265 (1994).
40. Noyola, D. E., Fernandez, M., Moylett, E. H. & Baker, C. J. Ophthalmologic, visceral, and cardiac involvement in neonates with candidemia. *Clin. Infect. Dis.* **32**, 1018–1023 (2001).
41. Benjamin, D. K., Poole, C., Steinbach, W. J., Rowen, J. L. & Walsh, T. J. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. *Pediatrics* **112**, 634–640 (2003).
42. Fernandez, M., Moylett, E. H., Noyola, D. E. & Baker, C. J. Candida meningitis in neonates: a 10-year review. *Clin. Infect. Dis.* **31**, 458–463 (2000).
43. Faix, R. G. Systemic *Candida* infections in infants in intensive care nurseries: high incidence of central nervous system involvement. *J. Pediatr.* **105**, 616–622 (1984).
44. Oleinik, E. M., Della-Latta, P., Rinaldi, M. G. & Saiman, L. Candida lusitaniae osteomyelitis in a premature infant. *Am. J. Perinatol.* **10**, 313–315 (1993).
45. Evdoridou, J., Roilides, E., Bibashi, E. & Kremenopoulos, G. Multifocal osteoarthritis due to *Candida albicans* in a neonate: serum level monitoring of liposomal amphotericin B and literature review. *Infection* **25**, 112–116 (1997).
46. Harris, M. C. et al. Candidal arthritis in infants previously treated for systemic candidiasis during the newborn period: report of three cases. *Pediatr. Emerg. Care* **16**, 249–251 (2000).
47. Cohen-Wolkowiez, M. et al. Neonatal Candida meningitis: significance of cerebrospinal fluid parameters and blood cultures. *J. Perinatol.* **27**, 97–100 (2007).
48. Kaufman, D. A., Coggins, S. A., Zanelli, S. A. & Weitkamp, J.-H. Congenital cutaneous candidiasis: prompt systemic treatment is associated with improved outcomes in neonates. *Clin. Infect. Dis.* **64**, 1387–1395 (2017).
49. Darmstadt, G. L., Dinulos, J. G. & Miller, Z. Congenital cutaneous candidiasis: clinical presentation, pathogenesis, and management guidelines. *Pediatrics* **105**, 438–444 (2000).
50. Roqué, H., Abdelhak, Y. & Young, B. K. Intra amniotic candidiasis. Case report and meta-analysis of 54 cases. *J. Perinatal Med.* **27**, 253–262 (1999).
51. Robinson, J. L. et al. 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.* **9**, 183 (2009).
52. Phillips, J. R. & Karlowicz, M. G. Prevalence of *Candida* species in hospital-acquired urinary tract infections in a neonatal intensive care unit. *Pediatr. Infect. Dis. J.* **16**, 190–194 (1997).
53. Benjamin, D. K., Fisher, R. G., McKinney, R. E. & Benjamin, D. K. Candidal mycetoma in the neonatal kidney. *Pediatrics* **104**, 1126–1129 (1999).
54. Bryant, K., Maxfield, C. & Rabalais, G. Renal candidiasis in neonates with candiduria. *Pediatr. Infect. Dis. J.* **18**, 959–963 (1999).
55. Kaplan, M., Eidelman, A. I., Dollberg, L. & Abu-Dalu, K. Necrotizing bowel disease with *Candida peritonitis* following severe neonatal hypothermia. *Acta Paediatr. Scand.* **79**, 876–879 (1990).
56. Berenguer, J. et al. Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis disseminated versus single-organ infection. *Diagn. Microbiol. Infect. Dis.* **17**, 103–109 (1993).
57. Baley, J. E., Kliegman, R. M. & Fanaroff, A. A. Disseminated fungal infections in very low-birth-weight infants: clinical manifestations and epidemiology. *Pediatrics* **73**, 144–152 (1984).
58. Methee Chayakulkeeree, P. P. Recent progress in the diagnosis of pathogenic *Candida* species in blood culture. *Mycopathologia* **181**, 363–369 (2016).
59. Schelonka, R. L. & Moser, S. A. Time to positive culture results in neonatal *Candida septicemia*. *J. Pediatr.* **142**, 564–565 (2003).
60. Karageorgopoulos, D et al. EV-CI, 2011 undefined. β-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. *Clin. Infect. Dis.* **52**, 750–770 (2011).
61. Goudjil, S. et al. (1–3)-β-D-glucan levels in candidiasis infections in the critically ill neonate. *J. Matern. Fetal Neonatal Med.* **26**, 44–48 (2012).

62. Goudjil, S. et al. Blood product transfusions are associated with an increase in serum (1-3)-beta-d-glucan in infants during the initial hospitalization in neonatal intensive care unit (NICU). *J. Matern. Fetal Neonatal Med.* **30**, 933–937 (2017).
63. Usami, M. et al. Positive (1->3)-beta-D-glucan in blood components and release of (1->3)-beta-D-glucan from depth-type membrane filters for blood processing. *Transfusion* **42**, 1189–1195 (2002).
64. Smith, P. B. et al. Quantification of 1,3-β-D-glucan levels in children: preliminary data for diagnostic use of the β-glucan assay in a pediatric setting. *Clin. Vaccin. Immunol.* **14**, 924–925 (2007).
65. Mennink-Kersten, M. A., Warris, A. & Verweij, P. E. 1,3-β-D-Glucan in patients receiving intravenous amoxicillin–clavulanic acid. *N. Engl. J. Med.* **354**, 2834–2835 (2006).
66. Marty, F. M. et al. Reactivity of (1→3)-β-D-glucan assay with commonly used intravenous antimicrobials. *Antimicrob. Agents Chemother.* **50**, 3450–3453 (2006).
67. Mennink-Kersten, M. A., Ruegebrink, D. & Verweij, P. E. *Pseudomonas aeruginosa* as a cause of 1,3-beta-D-glucan assay reactivity. *Clin. Infect. Dis.* **46**, 1930–1931 (2008).
68. Mennink-Kersten, M. A. & Verweij, P. E. Non-culture-based diagnostics for opportunistic fungi. *Infect. Dis. Clin. N. Am.* **20**, 711–727 (2006).
69. Hellerstein, S. Urinary tract infections: old and new concepts. *Pediatr. Clin. N. Am.* **42**, 1433–1457 (1995).
70. Karlowicz, M. G. Candidal renal and urinary tract infection in neonates. *Semin. Perinatol.* **27**, 393–400 (2003).
71. Wynn, J. L. et al. Outcomes following candiduria in extremely low birth weight infants. *Clin. Infect. Dis.* **54**, 331–339 (2012).
72. Steinbach, W. J. Pediatric aspergillosis: disease and treatment differences in children. *Pediatr. Infect. Dis. J.* **24**, 358–364 (2005).
73. Groll, A. H. et al. Invasive pulmonary aspergillosis in a critically ill neonate: case report and review of invasive aspergillosis during the first 3 months of life. *Clin. Infect. Dis.* **27**, 437–452 (1998).
74. Kimura, H., Mitsuto, I., Taguchi, R., Anzawa, K. & Mochizuki, T. Primary cutaneous aspergillosis caused by *Aspergillus tamarii* in a premature infant with extremely low birthweight: a case report with short review. *J. Dermatol.* **45**, 622–625 (2018).
75. Burgos, A. et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. *Pediatrics* **121**, e1286–e1294 (2008).
76. Singer, S. et al. Outbreak of systemic aspergillosis in a neonatal intensive care unit. *Mycoses* **41**, 223–227 (1998).
77. McCarty, J. M., Flam, M. S., Pullen, G., Jones, R. & Kassel, S. H. Outbreak of primary cutaneous aspergillosis related to intravenous arm boards. *J. Pediatr.* **108**, 721–724 (1986).
78. Rowen, J., Correa, A., Sokol, D., Hawkins, H., Levy, M. & Edwards, M. Invasive aspergillosis in neonates. The Pediatr Infect Dis J. **11**, 576–582 (1992).
79. Woodruff, C. A. & Hebert, A. A. Neonatal primary cutaneous aspergillosis: case report and review of the literature. *Pediatr. Dermatol.* **19**, 439–444 (2002).
80. Gallais, F. et al. Simultaneous primary invasive cutaneous aspergillosis in two preterm twins: case report and review of the literature. *BMC Infect. Dis.* **17**, https://doi.org/10.1186/s12879-017-2646-8 (2017).
81. Phute, S. U. & Bhakre, J. B. *Aspergillus fumigatus* meningitis in a preterm. https://pubmed.ncbi.nlm.nih.gov/21149907/ (2010).
82. Roncati, L., Barbolini, G., Fano, R. A. & Rivasi, F. Fatal *Aspergillus flavus* infection in a neonate. *Fetal Pediatr. Pathol.* **29**, 239–244 (2010).
83. Herron, M. D., Vanderhooft, S. L., Byington, C. & King, J. D. Aspergillosis in a 24-week newborn: a case report. *J. Perinatol.* **23**, 256–259 (2003).
84. Warris, A. et al. ESCMID-ECMM guideline: diagnosis and management of invasive aspergillosis in neonates and children. *Clin. Microbiol. Infect.* **25**, 1096–1113 (2019).
85. Voigt, K. & Kirk, P. M. in *Encyclopedia of Food Microbiology* 2nd edn, 54–67 (Elsevier, 2014).
86. Roilides, E., Zaoutis, T. E., Katragkou, A., Benjamin, D. K. & Walsh, T. J. Zygomycosis in neonates: an uncommon but life-threatening infection. *Am. J. Perinatol.* **26**, 565–573 (2009).
87. Roilides, E., Zaoutis, T. E. & Walsh, T. J. Invasive zygomycosis in neonates and children. *Clin. Microbiol. Infect.* **15**, 50–54 (2009).
88. Agarwal, K., Sharma, M., Singh, S. & Jain, M. Antemortem diagnosis of gastrointestinal mucormycosis in neonates: report of two cases and review of literature. *Indian J. Pathol. Microbiol.* **49**, 430–432 (2006).
89. Mitchell, S., Gray, J., Morgan, M. & Lancet, M. H.-T. *Nosocomial Infection with Rhizopus Microsporus in Preterm Infants: Association with Wooden Tongue Depressors* (Elsevier, 1996).
90. Duffy, J. et al. Mucormycosis outbreak associated with hospital linens. *Pediatr. Infect. Dis. J.* **33**, 472–476 (2014).
91. Centers for Disease *Control* and Prevention. Nosocomial outbreak of Rhizopus infections associated with Elastoplast wound dressings-Minnesota. *Morbid. Mortal. Wkly Rep.* **27**, 33–34 (1978).
92. Dennis, J. E., Rhodes, K. H., Cooney, D. R. & Roberts, G. D. Nosocomial Rhizopus infection (zygomycosis) in children. *J. Pediatr.* **96**, 824–828 (1980).
93. Mantadakis, E. & Samonis, G. Clinical presentation of zygomycosis. *Clin. Microbiol. Infect.* **15**, 15–20 (2009).
94. Roden, M. M. et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin. Infect. Dis.* **41**, 634–653 (2005).
95. Veleminsky, M. S., Noll, P., Hanzl, M. & Veleminsky, M. J. Necrotizing enterocolitis in children with low birth-weight induced with mucormycose strains. *Neuro Endocrinol. Lett.* **29**, 1021–1025 (2008).
96. Hammond, S. P. et al. Molecular methods to improve diagnosis and identification of mucormycosis. *J. Clin. Microbiol.* **49**, 2151–2153 (2011).
97. Ashbee, H. R., Leck, A. K., Puntis, J. W. L., Parsons, W. J. & Evans, E. G. V. Skin colonization by *Malassezia* in neonates and infants. *Infect. Control Hosp. Epidemiol.* **23**, 212–216 (2002).
98. Zomorodain, K. et al. Molecular analysis of *Malassezia* species isolated from hospitalized neonates. *Pediatr. Dermatol.* **25**, 312–316 (2008).
99. Richet, H. M., McNeil, M. M., Edwards, M. C. & Jarvis, W. R. Cluster of *Malassezia* furfur pulmonary infections in infants in a neonatal intensive-care unit. *J. Clin. Microbiol.* **27**, 1197–1200 (1989).
100. Aschner, J. L., Punsalang, A. J., Maniscalco, W. M. & Menegus, M. A. Percutaneous central venous catheter colonization with *Malassezia furfur*: incidence and clinical significance. *Pediatrics* **80**, 535–539 (1987).
101. Ilahi, A. et al. Molecular epidemiology of a *Malassezia pachydermatis* neonatal unit outbreak. *Med. Mycol.* **56**, 69–77 (2018).
102. Huang, C. Y. et al. Systemic infection caused by *Malassezia pachydermatis* in infants: case series and review of the literature. *Pediatr. Infect. Dis. J.* **39**, 444–448 (2020).
103. Marcon, M. J. & Powell, D. A. Epidemiology, diagnosis, and management of *Malassezia furfur* systemic infection. *Diagn. Microbiol. Infect. Dis.* **7**, 161–175 (1987).
104. Kessler, A. T., Kourtis, A. P. & Simon, N. Peripheral thromboembolism associated with *Malassezia furfur* sepsis. *Pediatr. Infect. Dis. J.* **21**, 356–357 (2002).
105. Cornu, M. et al. Evaluation of the (1,3)-ß-D-glucan assay for the diagnosis of neonatal invasive yeast infections. *Med. Mycol.* **56**, 78–87 (2018).
106. Vuran, E., Karaarslan, A., Karasartova, D., Turegun, B. & Sahin, F. Identification of *Malassezia* species from Pityriasis versicolor lesions with a new multiplex PCR method. *Mycopathologia* **177**, 41–49 (2014).
107. Honnavar, P. et al. Identification of *Malassezia* species by MALDI-TOF MS after expansion of database. *Diagn. Microbiol. Infect. Dis.* **92**, 118–123 (2018).
108. MAXSON, S., MILLER, S. F. & TRYKA, A. F. S. G. Perinatal blastomycosis. *Pediatr. Infect. Dis. J.* **11**, 760–763 (1992).
109. Watts, E. A., Gard, P. D. & Tuthill, S. W. First reported case of intrauterine transmission of blastomycosis. *Pediatr. Infect. Dis. J.* **2**, 308–310 (1983).
110. Linsangan, L. C. & Ross, L. A. *Coccidioides immitis* infection of the neonate: two routes of infection. *Pediatr. Infect. Dis. J.* **18**, 171–173 (1999).
111. Hyatt, H. W. Coccidioidomycosis in a 3-week-old infant. *Am. J. Dis. Child.* **105**, 93–98 (1963).
112. Christian, J. R., Sarre, S. G., Peers, J. H., Salazar, E. & Rosario, J. Pulmonary coccidioidomycosis in a twenty-one-day-old infant: report of a case and review of the literature. *AMA J. Dis. Child.* **92**, 66–74 (1956).
113. Shafai, T. Neonatal coccidioidomycosis in premature twins. *Am. J. Dis. Child.* **132**, 634 (1978).
114. Cheng, M. F., Chiou, C. C., Liu, Y. C., Wang, H. Z. & Hsieh, K. S. *Cryptococcus laurentii* fungemia in a premature neonate. *J. Clin. Microbiol.* **39**, 1608–1611 (2001).
115. Nakwan, N., Ngerncham, S., Srisuparp, P., Lapphra, K. & Chokephaibulkit, K. *Cryptococcus neoformans* septicemia in an immunocompetent neonate: first case report in Thailand. *Southeast Asian J. Trop. Med. Public Health* **39**, 697–700 (2008).
116. Patel, M., Beckerman, K. P., Reznik, S., Madan, R. P. & Goldman, D. L. Transplacental transmission of *Cryptococcus neoformans* to an HIV-exposed premature neonate. *J. Perinatol.* **32**, 235–237 (2012).
117. O'Reilly, D. A. A rare case of neonatal cryptococcal meningitis in an HIV-unexposed 2-day-old infant: the youngest to date? *Paediatr. Int. Child Health* **36**, 154–156 (2016).
118. Salazar, G. E. & Campbell, J. R. Trichosporonosis, an unusual fungal infection in neonates. *Pediatr. Infect. Dis. J.* **21**, 161–165 (2002).
119. Rowen, J. L., Atkins, J. T., Levy, M. L., Baer, S. C. & Baker, C. J. Invasive fungal dermatitis in the < or = 1000-gram neonate. *Pediatrics* **95**, 682–687 (1995).
120. Fisher, D. J. et al. Neonatal *Trichosporon beigelii* infection: report of a cluster of cases in a neonatal intensive care unit. *Pediatr. Infect. Dis. J.* **12**, 149–155 (1993).

121. Murphy, N. et al. Infection and colonisation of neonates by *Hansenula anomala*. *Lancet* **327**, 291–293 (1986).
122. Aragão, P. A. et al. Pichia anomala outbreak in a nursery: exogenous source? *Pediatr. Infect. Dis. J.* **20**, 843–848 (2001).
123. Nagarathnamma, T. et al. Outbreak of *Pichia kudriavzevii* fungaemia in a neonatal intensive care unit. *J. Med. Microbiol.* **66**, 1759–1764 (2017).
124. Taj-Aldeen, S. J., Doiphode, S. H. & Han, X. Y. *Kodamaea* (*Pichia*) *ohmeri* fungaemia in a premature neonate. *J. Med. Microbiol.* **55**, 237–239 (2006).
125. Grenouillet, F. et al. *Pichia fabianii* fungemia in a neonate. *Pediatr. Infect. Dis. J.* **29**, 191 (2010).
126. Chakrabarti, A. et al. Outbreak of *Pichia anomala* infection in the pediatric service of a tertiary-care center in northern India. *J. Clin. Microbiol.* **39**, 1702–1706 (2001).
127. Bhally, H. S. et al. Infection in a neonate caused by *Pichia fabianii*: importance of molecular identification. *Med. Mycol.* **44**, 185–187 (2006).
128. Kicklighter, S. D., Springer, S. C., Cox, T., Hulsey, T. C. & Turner, R. B. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. *Pediatrics* **107**, 293–298 (2001).
129. Manzoni, P. et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N. Engl. J. Med.* **356**, 2483–2495 (2007).
130. Leonart, L. P. et al. Fluconazole doses used for prophylaxis of invasive fungal infection in neonatal intensive care units: a network meta-analysis. *J. Pediatr.* **185**, 129–135.e6 (2017).
131. Benjamin, D. K. et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. *JAMA* **311**, 1742–1749 (2014).
132. Kaufman, D. et al. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N. Engl. J. Med.* **345**, 1660–1666 (2001).
133. Ericson, J. E. et al. Fluconazole prophylaxis for the prevention of candidiasis in premature infants: a meta-analysis using patient-level data. *Clin. Infect. Dis.* **63**, 604 (2016).
134. Pappas, P. G. et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* **62**, e1–e50 (2016).
135. CD, H., DS, B., NM, G., MP, C. & B, J. Review of fluconazole treatment and prophylaxis for invasive candidiasis in neonates. *J. Pediatr. Pharmacol. Ther.* **26**, 115–122 (2021).
136. Greenberg, R. G. et al. Empiric antifungal therapy and outcomes in extremely low birth weight infants with invasive candidiasis. *J. Pediatr.* **161**, https://doi.org/10.1016/J.JPEDS.2012.01.053 (2012).
137. Puia-Dumitrescu, M. & Smith, P. B. Antifungal drugs in newborns and children. *Pediatr. Clin. N. Am.* **64**, 1389–1402 (2017).
138. Hsieh, E. M. et al. Medication use in the neonatal intensive care unit. *Am. J. Perinatol.* **31**, 811–821 (2014).
139. Morrison, V. & Weisdorf, D. The spectrum of *Malassezia* infections in the bone marrow transplant population. *Bone Marrow Transplant.* **26**, 645–648 (2000).
140. Hawser, S. P. & Douglas, L. J. Resistance of *Candida albicans* biofilms to antifungal agents in vitro. *Antimicrob. Agents Chemother.* **39**, 2128–2131 (1995).
141. Ferreras-Antolín, L., Sharland, M. & Warris, A. Management of invasive fungal disease in neonates and children. *Pediatr. Infect. Dis. J.* **38**, https://doi.org/10.1097/INF.0000000000002317 (2019).
142. Kaufman, D. Strategies for prevention of neonatal invasive candidiasis. *Semin. Perinatol.* **27**, 414–424 (2003).
143. Benjamin, D. K. et al. Empirical therapy for neonatal candidemia in very low birth weight infants. *Pediatrics* **112**, 543–547 (2003).
144. Roth, J. G., Troy, J. L. & Esterly, N. B. Multiple cutaneous ulcers in a premature neonate. *Pediatr. Dermatol.* **8**, 253–255 (1991).
145. Amod, F. C., Coovadia, Y. M., Pillay, T. & Ducasse, G. Primary cutaneous aspergillosis in ventilated neonates. *Pediatr. Infect. Dis. J.* **19**, 482–483 (2000).
146. Rowen, J. L., Correa, A. G., Sokol, D. M., Hawkins, H. K. & Levy, M. L. E. M. Invasive aspergillosis in neonates: report of five cases and literature review. *Pediatr. Infect. Dis. J.* **11**, 576–582 (1992).
147. Starke, J. R., Mason, E. O., Kramer, W. G. & Kaplan, S. L. Pharmacokinetics of amphotericin B in infants and children. *J. Infect. Dis.* **155**, 766–774 (1987).
148. Pammi, M. Unusual fungal infections in the neonate. https://www.uptodate.com/contents/unusual-fungal-infections-in-the-neonate#H12 (2021).
149. Spelman, D. M. C. Invasive *Malassezia* infections. https://www.uptodate.com/contents/invasive-malassezia-infections?topicRef=4988&source=see_link#H8 (2021).
150. American Academy of Pediatrics. In: Kimberlin, D. W., Brady, M. T., Jackson, M. A., Long, S. S. editors. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018.
151. Koren, G. et al. Pharmacokinetics and adverse effects of amphotericin B in infants and children. *J. Pediatr.* **113**, 559–563 (1988).
152. Wong-Beringer, A., Jacobs, R. A. & Guglielmo, B. J. Lipid formulations of amphotericin B: clinical efficacy and toxicities. *Clin. Infect. Dis.* **27**, 603–618 (1998).
153. Lestner, J. M., Smith, P. B., Cohen-Wolkowiez, M., Benjamin, D. K. Jr & Hope, W. W. Antifungal agents and therapy for infants and children with invasive fungal infections: a pharmacological perspective. *Br. J. Clin. Pharmacol.* **75**, 1381–1395 (2013).
154. Testoni, D., Smith, P. B. & Benjamin, D. K. Jr. The use of antifungal therapy in neonatal intensive care. *Clin. Perinatol.* **39**, 83 (2012).
155. Walsh, T. J. et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob. Agents Chemother.* **48**, 2166–2172 (2004).
156. Denning, D. W. & Hope, W. W. Therapy for fungal diseases: opportunities and priorities. *Trends Microbiol.* **18**, 195–204 (2010).
157. Neely, M., Rushing, T., Kovacs, A., Jelliffe, R. & Hoffman, J. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin. Infect. Dis.* **50**, 27–36 (2010).
158. Howard, S. J., Felton, T. W., Gomez-Lopez, A. & Hope, W. W. Posaconazole: the case for therapeutic drug monitoring. *Ther. Drug Monit.* **34**, 72–76 (2012).
159. Cinzia, A. et al. High-dose Micafungin in neonates and young infants with invasive candidiasis: results of a phase 2 study. *Antimicrob. Agents Chemother.* **65**, https://doi.org/10.1128/AAC.02494-20 (2021).
160. Soltani, M. et al. Evidence of excessive concentrations of 5-flucytosine in children aged below 12 years: a 12-year review of serum concentrations from a UK clinical assay reference laboratory. *Int. J. Antimicrob. Agents* **28**, 574–577 (2006).

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KEDW, SA and MPD participated in conception and design of the work. KEDW and SA drafted the article. PBS provided critical revision of the article. All authors approved final version for publication.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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