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Review
Challenging issues in neonatal candidiasis

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Abstract

In an era of quality improvement and 'getting to zero (infections and/or related mortality),' neonatal candidiasis is ripe for evidence-based initiatives. Knowledge of each institution's invasive *Candida* infection (ICI) incidence and infection-related mortality is critical to evaluate disease burden and effective interventions. Evidenced-based interventions include: antifungal prophylaxis, starting with appropriate dosing, and prompt removal of central venous catheters (CVC). There is A-I evidence supporting antifungal prophylaxis with fluconazole, and it should be considered in every neonatal intensive care unit (NICU). The literature supports targeting infants <1000 g and/or ≥27 weeks, because this group has high infection-related mortality and neurodevelopmental impairment in 57% of survivors. Antifungal prophylaxis has been shown to nearly eliminate infection-related mortality. Interventions start with prenatal initiatives, with women being treated for vaginal candidiasis, especially with preterm labor or complications. Targeting modifiable risk factors, including restriction policies for use of third- and fourth-generation cephalosporins, carbapenems, H2-antagonists, proton pump inhibitors, and postnatal steroids; guidelines for CVC care and removal; and feeding practices, with promotion of early feedings and breast milk, may also reduce risk. A few studies have emerged on empiric antifungal therapy with sepsis evaluations for preterm infants <1500 g and other high-risk patients that have shown favorable effects of eliminating mortality, but these have not been compared to appropriate antifungal therapy and central line removal. Further study of empiric therapy, prospective treatment studies with higher targeted dosing of amphotericin B preparations, fluconazole, and new antifungals with prompt CVC removal may contribute to a 100% survival rate for those infants >1000 g and ≥28 weeks not receiving antifungal prophylaxis. Evaluation of ICI incidence and mortality by gestational age and birth week should be followed in each NICU, to evaluate infection control and prevention.

Introduction

A comprehensive review of invasive *Candida* infections (ICI) and published in the neonatal intensive care unit (NICU) has been previously presented and published[1]. This follow-up review focuses on future challenges that remain in eliminating these infections and their associated mortality and neurodevelopmental impairment in the NICU.

Case 1

An intubated 24-week gestation infant at day of life 23 develops new-onset thrombocytopenia and hypotension. Cultures are obtained and nafcillin and gentamicin started. He was on a slow-feeding advance with breast milk, and was made NPO (nothing by mouth) due to an ileus with this sepsis evaluation. After 2 days of antibiotics, there is no growth from his cultures. Platelet count has decreased from 155,000 to 65,000/mL.

For almost every sepsis evaluation, empiric therapy is initiated for the most common and likely organisms. In the NICU, this varies depending on the timing of infection. For early-onset infections, the most common organisms have been group B streptococcus and *Escherichia coli*; therefore, ampicillin or penicillin and

an aminoglycoside are most commonly administered pending culture results. For late-onset infections in very-low birth weight (VLBW, <1500 g) infants, gram-positive organisms occur in 70% of infections, with coagulase-negative staphylococcus (CoNS) species occurring 50% of the time, followed by gram-negative infections (20%) and fungal infections (10%)[2]. Nafcillin or oxacillin with an aminoglycoside are most often initiated pending culture results. Despite CoNS being the most common organism, most centers do not start with vancomycin due to concern for resistance. It is also juxtaposed with the fact that only one in four sepsis evaluations actually yield an organism[2]. Therefore, although CoNS is responsible for 50% of the infections, with each work up, only 12.5% of the time is it due to CoNS. Translating this into fungal infections, 2.5% (one in 40) of sepsis evaluations would be due to a fungal bloodstream infection (BSI) in VLBW infants.

Should an antifungal be used and, if so, which one should be used as empiric therapy with sepsis evaluations is an issue in neonatology, with few studies centered on this topic. Nearly all the studies have focused on the VLBW infant population. It has been proposed to use risk factors to determine how and when empiric antifungal therapy should be considered. New-onset thrombocytopenia (<100,000/mL) in VLBW infants occurs in 85% of fungemia cases and persists for a mean of >2 days[3]. Comparatively, 75% of gram-negative and 45% of gram-positive infections are accompanied by thrombocytopenia <100,000/mL. The fall in platelet count is 50% in fungemia cases, nearly 40% in gram-negative, and 25% in gram-positive bacteremia cases. Other studies concur that it may not be organism specific although it is common with ICI[4,5]. The same authors have proposed using the following risk factors alone or in combination to determine therapy: gestational age, exposure to third-generation cephalosporins in the previous 7 days, and thrombocytopenia[6]. These have not been prospectively studied to date.

A few small, single-center studies where empiric antifungal therapy was used showed that *Candida*-related mortality was eliminated. Makhoul *et al.* administered empiric antifungal therapy to all VLBW infants when undergoing evaluation for late-onset sepsis[7]. All 35 infants who developed fungal sepsis received empiric antifungal therapy and survived. In one retrospective study, empiric antifungal therapy was used in neonates who were <1500 g or considered 'very sick' in the NICU[8]. Empiric antifungal therapy was started in those high-risk patients if they had (a) received vancomycin plus a third-generation cephalosporin for 7 days, and (b) had one or more of the following infection risk factors: total parenteral nutrition, mechanical ventilation, steroids, H2 blocker use, or signs of a *Candida* rash or thrush. *Candida*-related mortality occurred in 11 of 18 historic control patients who did not receive empiric therapy compared with none of six of those receiving empiric therapy.

Many factors differ among NICUs, and mortality rates also may differ among them depending on: their infected patients (how many are extremely low birth weight or have necrotizing enterocolitis [NEC]); the starting dose of antifungal therapy; immediate central line removal with treatment of proven fungal BSIs; and how aggressive the intensive care is within the unit. This last factor is hard to quantify.

The goal of empiric therapy is to attack the infection when it is believed that the number of organisms infecting a host would be lower, at around presentation compared with 24 to 48 hours later when the cultures most commonly become positive[9]. Empiric antifungal therapy may also work via intermittently decreasing the fungal burden in select patients. For example in VLBWs, it would be used for approximately 40 sepsis evaluations to every one culture-proven fungal infection. Its use may also decrease the fungal burden in the NICU in general and prevent possible horizontal transmission. Another issue with empiric antifungal therapy is that it is only part of the treatment for fungal BSIs, with delayed line removal contributing to mortality as well.

Finally, empiric therapy cannot be discussed alone without consideration of whether prophylaxis would be more beneficial for a patient group. The studies of fluconazole prophylaxis have both significantly reduced fungal infections, as well as nearly eliminated *Candida*-related mortality. At one center, *Candida*-related mortality was eliminated not only in the patients who received fluconazole prophylaxis, but also in the entire NICU, including those patients >1000 g who did not receive prophylaxis[10]. The NICU used appropriate antifungal dosing of amphotericin B (AmB) and had prompt catheter removal. These investigations highlight what is lacking in studies to date: standardized treatment in terms of antifungal used, dose administered and prompt catheter removal.

What is the best evidence-based approach: waiting for positive cultures, or using empiric antifungal therapy with all sepsis evaluations in infants <1500 g, or a risk-based approach in those infants <1500 g? (Table 1). There are no randomized controlled trials (RCTs) in this area to control for the many variables affecting survival and compare prompt treatment with appropriate dosing and line removal to empiric therapy. Eliminating *Candida*-related mortality is critical, and since prophylaxis has proven to prevent infection and eliminate mortality and is the best approach in infants <1000 g, study of empiric therapy should be focused on those patients >1000 g, and considered in all patients who are not responding to empiric antibacterials after 48 hours and where thrombocytopenia persists and new cultures are drawn. More prospective studies are needed.

Table 1. Should empiric antifungal therapy be administered with sepsis evaluations?

Empiric Antifungal Therapy Approaches	Comments
Not needed	• Treat infections promptly when positive growth from cultures and remove CVC with bloodstream infections (Pickering, 2009)[12] • No randomized controlled studies comparing prompt treatment, including CVC removal to empiric therapy • Antifungal prophylaxis use nearly eliminates infection-related mortality (Kaufman, 2008; Healy, 2008)[10,39] • Fungal cultures have positive growth by 48 hours (Schlenoka, 2003)[9]
All infants <1500 g <1500 g (or >1500 g and critically ill) + risk factors	• One epidemiologic study suggesting this approach (Makhoul, 2001)[7] • Small prospective study with historic controls showing benefit in mortality (Procianoy, 2006)[8] • *Candida*-related mortality rates in other studies range from 0% to 66%
After 48 hours of empiric antibacterials, with continued signs and symptoms of sepsis and new cultures resent	• Needs further study (Schelonka, 2003)[9]
New-onset thrombocytopenia	• Needs further study (Benjamin, 2003)[6] • Many organisms are associated with thrombocytopenia (Guida, 2003; Manzoni, 2009; Bhat, 2009)[3–5] • Fungal infections are associated with the greatest decrease (50%) in platelet counts, similar to gram-negative infections (Guida, 2003)[3]

CVC = central venous catheter.
Empiric therapy: starting antifungal therapy when cultures performed with signs and symptoms of sepsis.

Case 2

An intubated 36-week gestation infant with gastroschisis has been NPO, had a silo in place for 14 days, and had been receiving antibiotics for 21 days when at day of life 23 develops new-onset thrombocytopenia and hypotension. Blood culture grows Candida parapsilosis. Amphotericin B deoxycholate is started at 1 mg/kg per day, a peripheral intravenous (IV) line is placed, and the central venous catheter (CVC) is removed.

Treatment of invasive fungal infections

Treatment studies have not uniformly defined exact dosing combined with prompt CVC removal (for BSI). AmB deoxycholate (1 mg/kg) and lipid preparations (5 mg/kg) provide coverage for the most common neonatal *Candida* species[11–13]. They are the best choices pending species identification. Most species have favorable susceptibility to AmB, and 95% to 97% of neonatal isolates are susceptible to fluconazole. Additionally, if fluconazole is being used for prophylaxis, a different antifungal should be used for treatment in that NICU.

Pharmacokinetic data have recently been published for fluconazole, micafungin, and caspofungin[14–23]. With studies examining pharmacokinetic data targeting comparable levels in adults, neonatal data are needed regarding safety. As new dosing information has emerged, there are also case reports of possible adverse effects of these medications. Conversely, new studies have added safety data for AmB deoxycholate and have demonstrated a lack of significant nephrotoxicity; they reiterate the need for careful monitoring and adjustment of intake of sodium and potassium and monitoring renal function[24–26]. Studies of liposomal AmB products indicate that 5 mg/kg should be the starting dose and administered over 2 hours[27,28]. Recent publications of fluconazole demonstrate that a dose of 12 mg/kg is comparable to adult dosing; however, the safety of this dosing has not yet been studied in neonates[19,20]. The echinocandins may have effects that are unknown; monitoring of liver function tests, electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, and magnesium should be done daily for several days initially and then periodically if normal throughout treatment. Regarding caspofungin dosing, neonatal clinical studies had used 1 to 2 mg/kg, but pharmacokinetic data indicate that 2.5 mg/kg should be used. For micafungin dosing, pharmacokinetic data suggest a dose of 10 mg/kg[21–23,29,30]. A micafungin RCT is currently suspended for further pharmacodynamic studies (www.Clinicaltrials.gov Identifier: NCT00815516). Echinocandins may have higher minimum inhibitory concentrations (MICs) with C *parapsilosis*; speciation and susceptibility testing should be performed with their use in neonates[31]. The severity of ICI with its high mortality and morbidity in many cases has lead to the need to better study the current antifungals, new dosing information, and new antifungals for neonates. As mentioned in other sections, the need to standardize central line removal with candidemia in studies of antifungals for treatment is critical to interpret outcomes.

What is the best antifungal for treatment? AmB deoxycholate, AmB lipid preparations, and fluconazole are the most commonly used antifungals in neonates, but head-to-head data have not demonstrated a definitive superior agent. Data are limited in standard dosing, starting with

the highest safe dose on day 1 of treatment, and use with prompt CVC removal with fungemia. A-II evidence supports AmB deoxycholate starting at 1 mg/kg per day, with a recent study demonstrating safety when increasing up to 1.5 mg/kg if needed[32]. Lipid preparations need a similar approach, starting at 5 mg/kg so underdosing does not affect efficacy, and one study has examined increasing to 7 mg/kg[33,34]. Fluconazole dosing of 6 mg/kg has been studied for efficacy and safety; use of higher dosing should be studied for its safety and effect on resistance patterns. The major concern would be the effect of higher dosing on liver function. The dosing of 6 mg/kg achieves blood levels higher than the average area under the curve (AUC)/MICs of most *Candida* species affecting neonates.

The newer echinocandins are still undergoing extensive study on dosing and safety. Observational studies and pharmacokinetic studies are emerging, but to date there are no RCTs comparing these to other antifungals. There are data with caspofungin in neonates using 1 mg/kg and 2 mg/kg, but new data support higher dosing of 2.5 mg/kg[14,15,23]. Micafungin has been studied at doses up to 15 mg/kg, but only in a few patients and with limited safety data. There are limited data to guide dosing of anidulafungin. Neonatal data are needed for all the echinocandins in four major areas: optimal dose, resistance patterns with regards to C *parapsilosis*, safety, and central nervous system penetration[31,35,36]. Their role in treatment or prophylaxis will depend on these findings and the general principle to use one agent for prophylaxis and a different agent for treatment. Their use currently should be in consultation with pediatric infectious disease specialists or as part of research studies.

Central venous catheter removal with fungemia

Multiple studies have consistently demonstrated improved outcomes with prompt CVC removal (A-II evidence)[12,13,37,38]. Removal and use of peripheral IV access until there is documented clearance from the blood with three or more negative blood cultures is supported in the literature[38]. In cases where maintaining central venous access is critical to life-saving measures, removal and replacement at a different site should be done promptly as a second option[38].

Case 2: continued

Blood cultures remain positive for 5 consecutive days. Consultation occurs with pediatric infectious diseases on whether increasing AmB deoxycholate to 1.5 mg/kg, changing to one of the lipid amphotericin preparations, adding fluconazole, or adding one of the new echinocandins would help clear the candidemia, or if there might be a fungal abscess that was undetected in the initial screening for end-organ dissemination.

Screening and re-screening for end-organ dissemination

Most studies report an average time to clearance of 3 to 5 days. Re-screening for end-organ dissemination if cultures are still positive after 5 days of antifungal therapy is recommended. While adding a second antifungal agent could be considered, no prospective study has examined this approach to determine if clearance occurs earlier[9,37,38].

Combination therapy

There are limited data in neonates examining combination therapy. Linder *et al.* reported the use of a second antifungal agent if one of the following was present: (1) fungal sepsis with any abscess; (2) positive urine culture; and/or (3) 10 days of persistently positive cultures[34]. Patients were treated for 14 days or more after negative culture until radiographic resolution of abscess, if present. Overall mortality was 15%. Fungal clearance occurred in 36 (67%) with monotherapy and 52 (96%) with polytherapy. Amphotericin (deoxycholate or a lipid preparation) was used as primary treatment, with fluconazole added as the second agent in most cases[34]. Similar to treatment data, combination therapy studies need to include data on prompt central line removal. There is a paucity of neonatal data in this area in general, with none of it controlling for a second agent, dosing, or prompt CVC removal.

Case 3

A 25-week infant is born via spontaneous vaginal delivery after premature rupture of membranes 7 days prior to delivery, followed by preterm labor not stopped by tocolytics. Infant is intubated in the delivery room and umbilical catheters placed in the NICU. Fluconazole prophylaxis is started on day of life 1. On day of life 4, a peripherally inserted central catheter (PICC) is placed and umbilical lines removed. Full enteral feeds are reached on day 24; PICC is removed and fluconazole prophylaxis is discontinued.

Prevention

With single and multicenter studies, meta-analyses, and Cochrane review, and the American Academy of Pediatrics (AAP) and the Infectious Diseases Society of America (IDSA) recommendation that there is A-I evidence supporting the use of fluconazole prophylaxis, every NICU should examine its high-risk population and institute prevention measures in an effort to 'get to zero' – 'zero' infections and 'zero' mortality[12,13,39]. Incorporating known risk factors into an infection control medication stewardship, early feeding, CVC bundles, and antifungal

prophylaxis in infants <1000 g can nearly eliminate invasive fungal infections and achieve zero fungal-related mortality.

Preventative strategies can be divided into these main areas: prenatal detection and eradication of maternal vaginal infections, medication, feeding and CVC stewardship in the NICU, and antifungal prophylaxis.

Prenatal detection and eradication of maternal vaginal candidiasis

While most prenatal screening is for viral and bacterial infections, pregnancies complicated by preterm labor or possible delivery should consider screening and treatment of maternal vaginal candidiasis[40,41]. This can be a simple approach to eradication of a pathogen that commonly colonizes preterm infants and in one third of cases leads to invasive infections[42].

Neonatal medication and feeding stewardship

Three medication practices have been associated with an increased risk of ICI: use of broad-spectrum antibiotics (third- or fourth-generation cephalosporins, carbapenems), acid inhibitors (H2 blockers, proton pump inhibitors), and postnatal steroids[38,43–46]. Use of these medications during the high-risk period of infection for preterm infants when they have central venous lines, are not on full enteral feedings, and/or are intubated should be restricted to documented gram-negative infections, gastritis (limit to 3 days), and severe lung disease, respectively. Each NICU establishing guidelines with respect to medication stewardship will lead to the improved compliance. Initial antibiotic steps include using an aminoglycoside instead of a cephalosporin for empiric coverage during sepsis evaluations, and use with documented gram-negative infections, meningitis or resistant infections. Regarding postnatal steroids, dexamethasone has been associated with ICI, while hydrocortisone prophylaxis in one multicenter RCT did not increase ICI but that high-risk group of intubated infants <1000 g had a rate of fungal BSI of 10%[46,47].

Having feeding protocols and promoting breast milk feedings may aid in the prevention of NEC, which is associated with a high rate of fungal infections of 16.5%[37,48]. Early feedings started in the first 3 days of life if possible in hemodynamically stable infants is associated with lower rates of fungal infections in infants <1000 g[38,45]. Early feeding may or may not be feasible in all patients, but in those who are stable, feeding, preferentially with breast milk, will help establish a more favorable and diverse microbiome, thereby helping to prevent fungal proliferation and dissemination.

While these risk factors are associated with increased rates of infection, they have not been definitely proven or subjected to prospective study or RCTs in neonates. Prospective studies of the effect of risk factor reduction on infection would be beneficial.

Central venous catheter management ('bundles')

Currently the placement and management of CVCs, with attention to team work, sterile practices, and hub and dressing care, have become a focus of many collaboratives (such as the New York State California Perinatal Quality Care Collaborative http://www.cpqcc.org/quality_improvement/qi_toolkits/hospital_acquired_infection_prevention_rev_march_2008) and for many NICUs, with the emergence of evidence-based data beginning to appear in the literature[49–53]. There are many differences between these bundles, for example, the use or not of chlorhexidine and the use of disks and their safety in preterm infants and other neonates[54–57]. Publication of the results of these and different central line bundles is critical to our understanding of how to prevent central line-associated bloodstream infection (CLABSI). It is also critical for these studies and the quality care collaborative to report their infection rates and effect on specific infections (CoNS, gram-positive, gram-negative, and *Candida* BSIs). The study by Aly *et al*. demonstrates significant reduction in all CLABSIs and elimination of *Candida* infections[49]. Most importantly, their central line bundle includes antifungal prophylaxis in addition to placement and maintenance interventions. Other studies have lacked the necessary breakdown by type of infections.

While the contribution of CLABSI prevention bundles hopefully will contribute to reducing fungal CLABSIs, it is critical to understand that not all *Candida* infections are catheter related; the majority disseminate from other sites, such as the respiratory and gastrointestinal tract, the urinary tract, and the skin (Table 2).

Antifungal prophylaxis

In this area, there is A-I evidence from single and multicenter RCTs of fluconazole prophylaxis demonstrating efficacy without adverse effects or the development of significant antifungal resistance[10,58–69]. Its strongest effect is when it is targeted to high-risk patients <1000 g and begun in the first 2 days of life[39]. Dosing of 3 mg/kg twice-a-week until IV (central or peripheral) access is no longer needed should be used based on its efficacy, safety, and resistance data. This targeted group of preterm infants <1000 g has the greatest number of risk factors, highest *Candida*-related mortality, and 57% neurodevelopmental impairment in survivors[38,70,71]. Both the AAP and the IDSA have statements supporting its use in preterm infants <1000 g[12,13].

Currently there are 14 studies of fluconazole prophylaxis in over 3100 patients consistently demonstrating efficacy and safety, with an overall reduction in ICI by >80% and near elimination of *Candida*-related mortality[10,58–69]. Subanalysis demonstrates that there is also significant

Table 2. Site of action of antifungal prevention strategies.

	Fluconazole (IV)	Fluconazole (PO)	Nystatin	Central Venous Catheter 'Bundles'
Skin	√	√		
Respiratory Tract	√	√		
Gastrointestinal Tract	√	√	√	
Central Venous Catheter	√			√

Table 3. Comparison of antifungal prophylaxis agents.

	Fluconazole	Nystatin
Effect on Colonization	Decreases CVC, skin, gastrointestinal and respiratory colonization	Only decreases gastrointestinal colonization
Route of Administration	Given IV, so can be given in infants not receiving enteral feeds, and those with NEC, FBP, ileus or GI disease	Given enterally Cannot be given if NEC, FBP, GI disease or ileus
Level of Evidence	Multiple RCTs with significant efficacy even in the most extremely preterm infants (A-I) Efficacy and safety data in over 3100 infants in 14 studies	Only one RCT with no effect on BSIs, only significant decrease in UTIs in <1250 g intubated infants Retrospective and epidemiologic data from three other studies (B-II)
Efficacy	~90% decrease in ELBWs	Retrospective studies with ~55% decrease in ELBWs
Extreme Preterm Infants Data	Efficacy ↓95% in <750 g ↓88% in <27 weeks ↓85% in <1000 g	Few infants <750 g or <25 wks Retrospective studies lack data on safety and susceptibility patterns
Combined Outcome (ICI and/or Mortality)	10% (FP) vs. 25% (placebo) patients from RCTs	N/A
Effect on Mortality	*Candida*-related mortality decreased by 96%	N/A
Osmolarity	300 mOsm/L	3002 mOsm/L
Resistance	No *Candida albicans* resistance Rare non-*albicans* resistance	No data. Not examined critically
Dosing Frequency	Twice-a-week dosing	Dosing 3–4 times per day
Cost	Costs less 4-wk prophylaxis: $144	Costs more 4-wk prophylaxis: $314
Cost Benefit	Reduced healthcare cost of ICI by >$500,000 over 18 months	–

BSIs = bloodstream infections; CVC = central venous catheter; ELBW = extremely low birth weight (<1000 g); FBP = focal bowel perforation; FP = fluconazole prophylaxis; GI = gastrointestinal tract; ICI = invasive *Candida* infections (blood, urine, cerebrospinal fluid, or peritonitis); IV = intravenous; N/A = not available from published data; NEC = necrotizing enterocolitis; RCT = randomized controlled trial; UTIs = urinary tract infections.

efficacy in the smallest infants (both when <750 g and <1000 g are examined) and youngest infants (<27 weeks) of approximately 90%[39] (Table 3). Safety and resistance have been studied as well, and detailed in recent reviews[1,39]. No significant adverse effects have been documented, and no significant emergence of resistance due to prophylaxis has been noted, both short term for individual patients or long term for NICUs[10,39,41,58–69,72].

Nystatin prophylaxis has been studied in one RCT and three retrospective or epidemiologic studies. Nystatin was the first antifungal studied in preterm infants. Sims *et al.* examined its use in an RCT of 67 intubated infants <1250 g, and found a decrease in BSI and urinary tract infections[73]. Ozturk *et al.* in a quasi-randomized prospective study demonstrated that antifungal prophylaxis was significantly more effective in decreasing fungal BSI when started in the first 48 hours after birth (by 90% to 3.6%) compared with screening for colonization and targeting that subgroup (by 62% to 14%)[74]. In a retrospective study of infants <1500 g ($n = 1055$) in the United Kingdom, nystatin prophylaxis was associated with a 54% decrease in fungal BSI (5.5% to 2.5%, $p < 0.0001$)[75]. Nystatin prophylaxis was not given to infants with peritonitis or NEC. In an epidemiologic study (1993–2006; Australia and New Zealand), oral nystatin prophylaxis decreased BSI or meningitis by 56% in <1500 g infants (1.23% to 0.54%, $p < 0.0001$) and 54% in <1000 g infants (2.67% to 1.23%, $p < 0.0001$)[76].

Many comparisons between fluconazole and nystatin prophylaxis remain unanswered (Table 3). One recent RCT compared oral fluconazole to nystatin prophylaxis started in the first 7 days in infants <1500 g until they reached full enteral feedings[69]. Both were given orally. ICI occurred in two of 38 (5.3%) fluconazole-treated infants compared with 6 of 42 (14.3%) nystatin-treated infants. All-cause mortality was zero in the fluconazole-

Table 4. Preventative strategies and levels of evidence.

Preventative Strategies in the NICU	Guideline	Level of Evidence
Antifungal Prophylaxis	Fluconazole prophylaxis in infants <1000 g while intravenous access (central or peripheral)	A-I
Antifungal Prophylaxis	Nystatin prophylaxis in infants <1500 g	B-II
Antibiotic Stewardship	Restrict third- and fourth-generation cephalosporins and carbapenems to treatment of proven gram-negative infections	B-II
Medication Stewardship	1. Postnatal steroids restriction for severe BPD 2. H2 blockers and proton pump inhibitors for infants with proven gastritis, and use for 3 days or until symptoms resolve	B-II

NICU = neonatal intensive care unit; BPD = bronchopulmonary dysplasia.

treated group compared with six of 42 (7.5%) in the nystatin-treated group ($p = 0.03$). Of the six deaths, three were due to NEC, one was due to focal bowel perforation, and two were sepsis-related (including one *Candida*-related death), and raised the question of whether nystatin is safe to give enterally to extremely preterm infants when they are advancing on feeds. These safety data are lacking among most of the nystatin epidemiologic data, and need to be included. Bloody stool has been reported as an adverse gastrointestinal reaction to nystatin. The oral suspension of nystatin contains a high concentration of sucrose (50% by weight) and a very high osmolality of 1893 mOsm/kg and osmolarity of 3002 mOsm/L[77,78]. Comparatively, oral fluconazole has an osmolarity of 300 mOsm/L. In the neonatal literature, there are several reports of the association of hyperosmolar oral medications and NEC[77,79]. The authors noted that the amounts of nystatin given to the infants were small, and the high concentration of sucrose might have altered the intestinal flora or facilitated bacterial invasion.

In all other fluconazole prophylaxis studies, fluconazole was given IV in the first weeks, and in a few studies transitioned to enteral administration when patients were on full enteral feeds without a CVC to finish up 4 or 6 weeks of prophylaxis. Fluconazole is 90% absorbed compared with nystatin, which is nonabsorbable. Because fungal infections can colonize and disseminate from multiple sites, including the skin, gastrointestinal tract, respiratory tract, and/or IV lines (central or peripheral), enteral fluconazole would not cover central line colonization and dissemination and would only achieve 90% of IV levels. This may explain the higher rate of ICI with enteral fluconazole in this study compared with the IV fluconazole prophylaxis studies.

The widespread institution and use of antifungal prophylaxis in high-risk preterm infants needs to be instituted due to the vulnerability of this population. The AAP and IDSA are helping to move this forward, targeting antifungal prophylaxis in high-risk preterm infants <1000 g. The prevention of group B *streptococcus* infections met similar debates over variability of rates in different countries and NICUs, number needed to treat, effect on mortality, and long-term neurodevelopmental outcomes. In extremely preterm (<28 weeks gestation) and extremely low birth weight infants, multiple hurdles exist for survival without neurodevelopmental impairment, which include not only invasive fungal infections, but intraventricular hemorrhage, periventricular leukomalacia, bacterial infections, NEC, focal bowel perforation, bronchopulmonary dysplasia, patent ductus arteriosus, and parental education level. To significantly improve our outcomes for this vulnerable population, multiple interventions are needed as a 'bundle' to increase survival without disability and antifungal prophylaxis is a vital part of this. In preventing ICI, for which there is A-I evidence for fluconazole prophylaxis, ICI can be eliminated as a cause of mortality or neurodevelopmental impairment for our patients born today. Delaying prevention adds risk to these preterm infants of developing an ICI, dying, or surviving with disability in the face of A-I evidence. It is important for NICUs and infection control and prevention societies or groups to examine the magnitude of its effect on NICUs regionally and nationally. For the United States, there are nearly 30,000 preterm infants born each year <1000 g or ≤27 weeks (National Vital Statistics, Centers for Disease Control and Prevention, 2007) which translates into antifungal prophylaxis preventing 2000 to 3000 ICI, 200 to 300 *Candida*-related deaths, and 400 to 500 survivors with neurodevelopmental impairment each year.

Each year we wait denies this A-I level of evidence from benefiting our patients. All agree that there is significant efficacy in preventing ICI with the use of antifungal prophylaxis; some of the debate focuses on whether fluconazole or nystatin would be better[39,80,81]. The data overwhelmingly point to fluconazole for prophylaxis (Table 4). To have the greatest effect and target the highest risk period, antifungal prophylaxis should be started in the first 2 days of life and continue until IV access (central or peripheral) is no longer needed. Future research may test the hypothesis of whether the combination of IV fluconazole with enteral nystatin can get us to zero infections.

Table 5. Top 10 ways to 'get to zero' invasive *Candida* infections and infection-related mortality.

1. Antifungal prophylaxis (for infants <1000 g and/or ≤27 weeks)
2. Treat proven infections with appropriate antifungal dosing
3. Promptly remove central venous catheters with candidemia
4. Decrease broad-spectrum antibiotic use
5. Decrease H2 blocker and proton pump inhibitor use
6. Decrease postnatal steroid use
7. Feed early with breast milk
8. Use central venous catheter 'bundles'
9. Consider fungal infection when performing sepsis evaluations
10. Perform speciation and susceptibility testing on all clinical fungal infections

Conclusions

Treatment and prevention can help get us close to zero ICI and zero *Candida*-related mortality (Table 5). Further studies need to address treatment of infection in conjunction with central line removal, optimal dosing of older (AmB preparations, fluconazole) and new antifungals (echinocandins), empiric therapy, and the effect of central line bundles on all ICI. We need to move forward now, as the benefit of prophylaxis outweighs the risks, and a significant number of infants each year continue to develop ICI, suffer neurodevelopmental impairment, or die when we have A-I evidence for antifungal prophylaxis. Evaluation of these strategies should continue to be assessed by individual, larger group, and national NICU epidemiologic data.

Transparency

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