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Special Article

Recommendations for the management of candidemia in neonates in Latin America

María E. Santolaya[a,m,*], Tito Alvarado Matute[b,m], Flavio de Queiroz Telles[c,m], Arnaldo Lopes Colombo[d,m], Jeannete Zurita[e,m], Iris Nora Tiraboschi[f,m], Jorge Alberto Cortes[g,m], Luis Thompson-Moya[h,m], Manuel Guzman-Blanco[i,m], Jose Sifuentes[j,m], Juan Echevarría[k,m], Marcio Nucci[l,m]

[a] *Hospital Luis Calvo Mackenna, Universidad de Chile, Santiago, Chile*
[b] *Hospital Escuela, Tegucigalpa, Honduras*
[c] *Hospital de Clínicas Universidade Federal do Paraná, Paraná, Brazil*
[d] *Federal University of São Paulo, São Paulo, Brazil*
[e] *Hospital Vozandes Facultad de Medicina, Pontificia Universidad Católica del Ecuador, Quito, Ecuador*
[f] *Hospital de Clínicas José de San Martín, University of Buenos Aires, Buenos Aires, Argentina*
[g] *Universidad Nacional de Colombia, Bogotá, Colombia*
[h] *Clínica Alemana, Universidad del Desarrollo, Santiago, Chile*
[i] *Hospital Privado Centro Médico de Caracas, Caracas, Venezuela*
[j] *National Institute of Medical Sciences and Nutrition, Tlalpan, Mexico*
[k] *Universidad Peruana Cayetano Heredia, Lima, Perú*
[l] *Federal University of Rio de Janeiro, Rio de Janeiro, Brazil*
[m] *Latin America Invasive Mycosis Network*

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ABSTRACT

Candidemia is one of the most frequent opportunistic mycoses worldwide. Limited epidemiological studies in Latin America indicate that incidence rates are higher in this region than in the Northern Hemisphere. Diagnosis is often made late in the infection, affecting the initiation of antifungal therapy. A more scientific approach, based on specific parameters, for diagnosis and management of candidemia in Latin America is warranted.

'Recommendations for the diagnosis and management of candidemia' are a series of manuscripts that have been developed by members of the Latin America Invasive Mycosis Network. They aim to provide a set of best-evidence recommendations for the diagnosis and management of candidemia.

This publication, 'Recommendations for the management of candidemia in neonates in Latin America', was written to provide guidance to healthcare professionals on the management of neonates who have, or who are at risk of, candidemia.

Computerized searches of existing literature were performed by PubMed. The data were extensively reviewed and analyzed by members of the group. The group also met on two occasions to pose questions, discuss conflicting views, and deliberate on a series of management recommendations.

'Recommendations for the management of candidemia in neonates in Latin America' includes prophylaxis, empirical therapy, therapy for proven candidemia, patient work-up following diagnosis of candidemia, central venous catheter management, and management of complications.

This manuscript is the fourth of this series that deals with diagnosis and treatment of invasive candidiasis. Other publications in this series include: 'Recommendations for the diagnosis of candidemia in Latin America', 'Recommendations for the management of candidemia in adults in Latin America', and 'Recommendations for the management of candidemia in children in Latin America'.

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* Corresponding author.
E-mail address: msantola@med.uchile.cl (M.E. Santolaya).

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Recomendaciones para el manejo de la candidemia en neonatos en América Latina

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R E S U M E N

La candidemia es una de las micosis oportunistas más frecuentes en todo el mundo. El escaso número de estudios epidemiológicos llevados a cabo en América Latina indica que las tasas de incidencia en esta región son mayores que las descritas en el hemisferio norte. A menudo el diagnóstico de la infección se establece tardíamente, lo que afecta el inicio del tratamiento antimicótico. Por esta razón, para el diagnóstico y el manejo de la candidemia está justificada una estrategia más científica, basada en parámetros específicos.

Recomendaciones para el diagnóstico y manejo de la candidemia constituye una serie de artículos preparados por miembros del grupo Latin America Invasive Mycosis Network. Su objetivo es proporcionar las mejores evidencias disponibles para el diagnóstico y el manejo de la candidemia.

El presente artículo, *Recomendaciones para el manejo de la candidemia en neonatos en América Latina*, ha sido redactado con el objetivo de orientar a los profesionales de la salud en el manejo de los neonatos que padecen, o pueden padecer, candidemia.

Mediante la base de datos PubMed se emprendió una búsqueda informatizada de los estudios publicados. Los miembros del grupo revisaron y analizaron exhaustivamente los datos. El grupo también se reunió en dos ocasiones para proponer preguntas, abordar los puntos de vista conflictivos y deliberar sobre las recomendaciones terapéuticas.

Recomendaciones para el manejo de la candidemia en neonatos en América Latina incluye aspectos sobre profilaxis, terapia empírica, tratamiento de la candidemia demostrada, evaluación y seguimiento del paciente después del diagnóstico de candidemia, manejo de los recién nacidos con infección por *Candida* del catéter venoso central y manejo de otras complicaciones.

Este manuscrito es el cuarto de los artículos de esta serie dedicada al diagnóstico y tratamiento de las candidiasis invasoras. Otras publicaciones de esta serie son *Recomendaciones para el diagnóstico de la candidemia en América Latina, Recomendaciones para el manejo de la candidemia en adultos en América Latina, y Recomendaciones para el manejo de la candidemia en niños en América Latina.*

Este artículo está publicado en español en este mismo número. Puede encontrarlo en http://dx.doi.org/10.1016/j.riam.2013.06.002

Epidemiologic features of candidemia in pediatrics

There is limited information on the epidemiology of candidemia in pediatric populations. One retrospective study of the incidence of candidemia in the USA in 2000 reported 43 pediatric cases (<18 years of age) per 100,000 hospital admissions.[103] Candidemia-associated mortality in pediatric patients is generally lower than in adults, ranging from 13% to 23% in children and 43% to 54% in infants.[31,102,103]

Candida is the third most common cause of late-onset sepsis in preterm neonates.[57,91] Results from a worldwide survey (1997–2000) on *Candida* isolates, which included hospitals from the USA, Canada, Latin America, and Europe, demonstrated that *Candida albicans* was the most common cause of infection with among all age groups investigated (≤1, 2–15, 16–64, and ≥65 years), with uniform rates of infection observed across the ages.[73] Among infant and pediatric patients (children ≤1 year and 2–15 years of age), the dominant causes of infections were *C. albicans* and *Candida parapsilosis*; very few infections were due to *Candida krusei* and *Candida glabrata* (3%). In neonates, higher mortality has been reported with infections due to *C. albicans* compared with those due to other *Candida* species[16,27,91]: 43% in *C. albicans*, compared with 20% *C. parapsilosis*, and 0% *Candida tropicalis* candidemia[16]; 24% in *C. albicans*, compared with 0% in *C. parapsilosis* invasive candidiasis[27]; 44% in *C. albicans*, compared with 16% in *C. parapsilosis* sepsis.[91]

Latin American data

Epidemiologic information on pediatric candidemia in Latin America is limited.[70,76,79] In a prospective surveillance study in children and adults from 23 hospitals throughout eight Latin American countries (Argentina, Brazil, Chile, Colombia, Ecuador, Honduras, Mexico and Venezuela) between November 2008 and October 2010, 302 of the 752 clinical isolates (40%) were from patients <18 years of age, with a mean incidence of 0.98/1000 admissions. Of these 302 episodes of candidemia, 89 (29%) occurred in neonates (≤28 days), with a median age at candidemia presentation of 16 days (range 1–28 days). Among the 213 children, median age was 2 years (range 0.2–18 years). The main species isolated in neonates and children were *C. albicans* (44% and 36%, respectively), *C. parapsilosis* (27% and 26%), *C. tropicalis* (15% and 15%), and *Candida guilliermondii* (5% and 13%) (Table 1).[85] Overall mortality was 31% in the pediatric population: 41% in neonates, 26% in children from 1 month to 1 year, 24% in children from 1 to 12 years, and 35% in patients between 13 and 18 years of age ($p = 0.049$ comparing neonates with non-neonates).[85]

Additional data are needed to better characterize candidemia in neonates and children. Such data include: demographics, clinical presentation, risk factors, treatment, outcome and mortality,

Table 1
Species distribution in 302 episodes of candidemia in children in 23 hospitals from eight countries in Latin America.

Species	Neonates $n = 89$ (%)	Non-neonates $n = 213$ (%)
Candida albicans	39 (43.8)	76 (35.7)
Candida parapsilosis	24 (27)	56 (26.3)
Candida tropicalis	13 (14.6)	31 (14.6)
Candida guilliermondii	4 (4.5)	27 (12.7)
Candida krusei	4 (4.5)	5 (2.3)
Candida glabrata	3 (3.4)	7 (3.3)
Other*	2 (2.2)	11(5.1)

Source: Santolaya et al.[85]

*Other: neonates: *Candida lusitaniae* (1), *Candida intermedia* (1); non-neonates: *Candida haemulonii* (3) *Candida pelliculosa* (3), *Candida intermedia* (2), *Candida norvegensis* (1), *Candida lusitaniae* (1), *Candida albicans* + *Candida glabrata* (1).

Table 2
Incidence of candidemia in neonates by gestational age and weight at birth.

	Incidence of candidemia (%)
Gestational age (weeks)	
<25	>20
25 to <26	10–20
26–27	5–10
≥28	<5
Weight at birth (g)	
<750	>10
750–999	5–10
1000–1500	<5

Adapted from Kaufman.[43]

microbiology issues, antifungal susceptibility, the affected population (neutropenic vs. non-neutropenic children, intensive care unit [ICU] vs. non-ICU patients), species distribution, epidemiology of resistant isolates, the effects of prophylaxis on resistance,[6] mortality and long-term outcomes (particularly neurodevelopmental consequences),[22] timing of infection, and characteristics of late-onset vs. early-onset infection.[6] Large, randomized controlled trials are also needed to evaluate the efficacy of different treatments.[6]

A better understanding of candidemia in neonates and children will help to define the best practices for management. Currently, there are no separate treatment guidelines for children and neonates with candidemia, and no consensus treatment guidelines exist in Latin America exclusively for candidemia. The following guidelines provide recommendations for the treatment of candidemia in neonates in Latin America and are based on current clinical evidence, the regional situation regarding candidemia in pediatric patients, and the expert opinions of the authors.

Unique clinical features that affect management of candidemia in neonates

Risk factors for Candida infection

The clinical features of neonates born prematurely and with low birth weights (particularly those with extremely low birth weight [ELBW], weighing less than 1000 g and born before 28 weeks gestation) increase their susceptibility to *Candida* infections[7] and are important considerations in the management of infections (Table 2). Premature newborns are born without fully competent immune systems; thus, they may lack basic immunologic functions, such as chemotaxis, cytokine production, antibody production, and phagocytosis.[61] Premature newborns are often in need of aggressive supportive care and medical interventions and, as a result, may have many risk factors for candidemia, including total parenteral nutrition (TPN), central venous catheters (CVCs), mechanical ventilation, broad-spectrum antibiotics, H_2 blockers, steroids, prolonged neonatal intensive care unit (NICU) stays, and abdominal or thoracic surgery.[16,24,72,84]

Persistent candidemia and neurodevelopmental impairment

Neonates frequently have persistent candidemia; that is, positive blood cultures (BCs) for more than 72 h in a patient receiving effective therapy. Neonates with candidemia may develop serious complications resulting from spread of infection to the central nervous system (CNS), heart, eyes, kidneys, spleen, and liver. Those with CNS complications may experience neurodevelopmental impairment, which may continue following resolution of the *Candida* infection. In one study, 73% of ELBW neonates with candidemia had died or showed signs of neurodevelopmental impairment by 18–22 months follow-up.[16] Compared with neonates not infected with *Candida*, those with *Candida* infections were more likely to have moderate or severe cerebral palsy, and to be blind or deaf.[16]

Summary of unique clinical features of neonates

Risk factors for infection with Candida *spp.*

1. Gestational age of <28 weeks.
2. Weigh at birth <1000 g.
3. TPN.
4. CVC.
5. Mechanical ventilation.
6. Broad-spectrum antibiotics.
7. H_2 blockers.
8. Steroids.
9. Prolonged neonatal intensive care unit stays.
10. Abdominal or thoracic surgery.

In neonates with invasive candidiasis:

1. Persistent candidemia can be common.
2. There is the possibility of false-negative BCs.
3. Infection may spread to the CNS, heart, eyes, kidneys, spleen, and liver, resulting in serious complications.

Candida prophylaxis in neonates

Support for prophylaxis in neonates

The high risk of candidemia in neonates provides a strong rationale for prophylaxis. Candidemia is highly prevalent in ICU-admitted ELBW neonates and very low birth weight (VLBW) neonates (weighing less than 1500 g).[44,50] Up to 60% of VLBW neonates may become colonized with *Candida* in their first month in the NICU, and up to 20% of these infants may develop an invasive fungal infection.[44] Invasive candidiasis can be difficult to diagnose in neonates and may be advanced by the time of diagnosis, owing to the non-specific clinical features of the disease and the poor sensitivity of diagnostic tests leading to late recognition of infection.[60]

The high incidence of complications associated with *Candida* infection in neonates, including neurodevelopmental impairment, to which neonates are already prone, further supports the use of prophylaxis. In addition, ophthalmologic, cardiac, and visceral involvement, are also associated with *Candida* infections in neonates.[53,68] At the time of hospital discharge, *Candida*-infected ELBW neonates, compared with non-infected ELBW neonates, were associated with higher rates of chronic lung disease, periventricular leukomalacia, and severe retinopathy.[33]

The risk–benefit ratio of prophylaxis in neonates

The potential benefits of *Candida* prophylaxis must be weighed against the risks by considering the efficacy of prophylaxis, incidence of candidiasis, associated mortality, short- and long-term safety, potential for the development of resistant pathogens, and possible alternatives (Table 3).

Prophylaxis in neonates has a favorable risk–benefit ratio when considering the high mortality associated with *Candida* infection in this population. However, mortality data are limited, as multicenter studies often report only all-cause mortality associated with fungal infections, rather than mortality specifically and directly related to candidemia. Among VLBW neonates with fungal sepsis, death rates from multicenter studies were 28% (odds ratio, fungi vs. other organisms, 1.67; $p < 0.05$) compared with 7% among VLBW neonates without an infection.[90] All-cause mortality is higher among ELBW

Table 3
Efficacy of *Candida* prophylaxis in neonates.

Trial	Methods	Intervention	Results	Conclusion
Kaufman et al.[44]	Prospective, double-blind, single-site RCT 100 ELBW neonates. Wkly surveillance cultures	IV FLU vs. PBO, 3 mg/kg/day for 6 wks Wks 1-2: every third day. Wks 3-4: every other day. Wks 5-6: daily	Lower rates of documented fungal colonization with FLU 60% of PBO vs. 22% of FLU (RD: 0.38; 95% CI: 0.18, 0.56; $p = 0.002$). Lower rates of IFI in FLU group 20% of PBO vs. 0% of FLU (RD: 0.20; 95% CI: 0.04, 0.36; $p = 0.008$)	Prophylactic FLU is effective in preventing fungal colonization and IFI in ELBW infants
Manzoni et al.[60]	Prospective, double-blind, multicenter RCT VLBW neonates. Wkly surveillance cultures and susceptibility testing	IV FLU vs. PBO from birth to day 30 of life (day 45 for ELBW neonates). Dosing: 6 mg/kg or 3 mg/kg vs. PBO (1:1:1 randomization)	Fungal colonization 9.8% in FLU 6 mg group, 7.7% in FLU 3-mg group, 29.2% in PBO group, $p < 0.001$. IFI 2.7% in FLU 6-mg group, 3.8% in FLU 3-mg group, 13.2% in PBO group ($p = 0.005$). FLU use did not modify the relationship between colonization and development of IFI	FLU reduces the incidence of colonization and IFI in VLBW neonates. Unclear benefit of *Candida* colonization
Kicklighter et al.[50]	Prospective, ITT RCT VLBW neonates. Rectal cultures at days 0, 7, 14, and 28. FLU toxicity by AST and ALT levels. Susceptibility testing	IV or oral FLU vs. PBO. Dosing: 6 mg/kg from birth to day 28 of life. Every 72 h until day 7. Every 24 h until day 28	Rectal colonization 15% FLU group, 46% PBO group ($p = 0.0005$). No difference in risk factors known to increase candidal septicemia in VLBW infants. ALT levels: FLU 18.1 IU/l vs. PBO 15 IU/l ($p = 0.008$). *C. albicans* most common species isolated. No difference in FLU MIC for all *C. albicans* isolates in either group	FLU decreases colonization. No effect in candidal septicemia. Larger studies are required to ascertain effect of resistance
Kaufman et al.[45]	Prospective, double-blind, RCT ELBW infants with CVC and/or endotracheal tube. Wkly surveillance cultures	Compare two dosing schedules of FLU 3 mg/kg/day over 6 wks. Schedule A: every 72–48 and 24 h. Schedule B: twice a wk	*Candida* colonization detected in 12% Group A and 10% Group B ($p = NS$). *Candida* sepsis developed in 5% Group A and 3% in Group B RD: −0.02 (95% CI: −0.14, 0.10; $p = 0.68$). All fungal isolates remained sensitive to fluconazole. No AEs reported	Twice-wkly prophylactic similar to other dosing schedules. Less frequent dosing may delay/prevent antifungal resistance
Arrieta et al.[5]	Prospective, open-label, RCT, VLBW neonates. Wkly surveillance cultures. Renal and hepatic tests) and mortality	Once-wkly L-AmB 5 mg/kg vs. PBO from first wk of life, for 6 wks, or until discontinuation of high-risk treatments and invasive devices	Higher colonization in L-AmB group before study drug administration 20% L-AmB vs. 5% PBO (reduced colonization in L-AmB group during study period: 5% L-AmB and 15% PBO subjects). Candidiasis: no L-AmB subjects and 1 PBO subject. No clinical differences between groups for safety and mortality	Once-wkly L-AmB was well tolerated in VLBW infants. Efficacy was not evaluated (data did not permit)
Aydemir et al.[8]	Prospective, RCT 278 VLBW neonates. Wkly surveillance cultures and systemic fungal susceptibility testing	Nystatin (1 ml, 100,000 U/ml/8 h) or FLU (3 mg/kg every third day) or PBO, from birth to day 30 (VLBW) or day 45 (ELBW)	Lower rates of fungal colonization with nystatin and FLU; 11.7% nystatin, 10.8% FLU, and 42.9% control ($p < 0.001$). Lower incidence of IFI with nystatin and FLU: 4.3% nystatin, 3.2% FLU, and 16.5% control ($p < 0.001$)	Nystatin and FLU reduce colonization and IFI in VLBW neonates. Nystatin is a well-tolerated and effective alternative
Romeo et al.[82]	Prospective study in 249 pre-term newborns. Probiotics in GI colonization and late-onset sepsis by *Candida* spp., neurological assessment at 1 year	Three groups: *Lactobacillus reuteri* (5 drops/day = 1×10^8 CFUs), *Lactobacillus rhamnosus* (1 capsule/day = 6×10^9 CFUs), no intervention (randomization: 1:1:1)	Significantly higher *Candida* stool colonization in control group vs. probiotic groups ($p < 0.01$). No statistical significance was observed for *Candida* spp. infections in the control group vs. probiotic groups ($p = NS$). Statistically significant lower incidence of abnormal neurological outcome in the probiotic groups vs. control group ($p < 0.05$)	Use of probiotics is effective in the prevention of *Candida* GI colonization and late-onset sepsis and reduces abnormal neurological outcomes
Manzoni et al.[59]	Secondary analysis of data from a multicenter RCT. Prophylactic oral bLF in 472 VLBW neonates	Group A1: 100 mg/day bLF Group A2: bLF + *L. rhamnosus* GG (10^6 CFUs per day). Group B: PBO for 6 wks	Similar incidence of fungal colonization between groups A1 17.6%, A2 16.6%, B 18.5% ($p = 0.89$). IFIs decreased in groups A1 and A2 (0.7–2.0%) compared with B (7.7%; $p = 0.002$). No IFI-attributable deaths in A1 and A2 groups, vs. 2 in the PBO group	bLF reduces the incidence of IFI in preterm VLBW neonates

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bLF, bovine lactoferrin; CFUs, colony-forming units; CI, confidence interval; CVC, central venous catheter; ELBW, extremely low birth weight (<1000 g); FLU, fluconazole; GI, gastrointestinal; IU/l, international units/litre; IFI, invasive fungal infection; ITT, intent to treat; IV, intravenous; L-AmB, liposomal amphotericin B; MIC, minimum inhibitory concentration; NS, not significant; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; VLBW, very low birth weight (<1500 g); Wk, week; Wkly, weekly.

neonates, ranging from 37% to 40%.[33,44,46] The number of deaths directly attributable to fungal infections is most likely smaller than the all-cause mortality reported in many studies. Single-center studies with smaller samples of patients have found lower mortality when reporting mortality directly attributable to fungal sepsis.[46]

The benefits of prophylaxis must also be balanced against the risk of selecting for resistant organisms. Based on studies of neutropenic and HIV-infected adults, the use of antifungal agents is associated with the development of fluconazole resistance in previously susceptible species, as well as with the emergence of intrinsically resistant species.[1,41,51,67] A systematic review of randomized clinical trials found that fluconazole prophylaxis

increased the risk of colonization but did not significantly affect the risk of invasive infections, with fluconazole-susceptible dose-dependent or resistant *Candida* species; however, the overall sample size was limited and data came from neonatal, pediatric, and adult patients. The authors noted that breakthrough infection remains a concern.[19] By contrast, multiple randomized controlled trials (Table 3) and observational studies in neonates have noted no increase in resistant species; however, these studies may not have been adequately powered to detect such differences.[8,34,44,58,60,62,95]

Long-term outcomes of *Candida* prophylaxis have not been studied in a large, multicenter, randomized controlled trial (Table 3).[6,22,28] Because neonates are at increased risk of cholestasis, administration of a potentially hepatotoxic drug is of particular concern.[2] One retrospective, non-randomized study with historical controls found an increase in conjugated hyperbilirubinemia in ELBW neonates who received fluconazole prophylaxis compared with neonates who did not receive prophylaxis.[2] In a similar study, there was an increase in cholestasis in neonates who received fluconazole prophylaxis. However, two-thirds of patients had other predisposing conditions for cholestasis, mainly the duration of TPN.[34]

Although some studies have reported no significant incidence of fluconazole-related toxicity,[8,9,44,95] one study found a temporary elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in fluconazole-treated neonates, which returned to normal levels within 2 weeks (Table 3).[60] A follow-up study of survivors aged 8–10 years old found that fluconazole prophylaxis for the prevention of invasive *Candida* infections in ELBW neonates did not appear to be associated with any long-term adverse effects.[48]

While trials generally show efficacy of prophylaxis with fluconazole, the actual rates of candidiasis and efficacy vary by country and NICU.[49] Therefore, an accurate assessment of the risks and benefits of prophylaxis depends on local or at least country-specific information. There are few alternatives to prophylaxis with antifungal agents for the prevention of *Candida* infections in neonates. One alternative in VLBW neonates was recently reported: prophylactic bovine lactoferrin reduced the incidence of invasive fungal infection in preterm VLBW neonates (Table 3).[59] Prevention is otherwise limited to monitoring high-risk patients and using infection control measures to prevent the spread of identified cases; however, data on these methods are limited. Accurate and early diagnosis of invasive *Candida* disease in neonates remains a challenge, as BCs – the 'gold standard' for diagnosis – have low sensitivity.[25]

Identifying neonates for prophylaxis

Not all neonates need prophylaxis for invasive candidiasis. Multiple studies have identified risk factors associated with invasive candidiasis, and these characteristics can be used to identify neonates at high risk of infection as candidates for prophylaxis. As previously mentioned, birth weight, prematurity, intubation, length of hospital or NICU stay, presence of CVCs, and use of broad-spectrum antibiotics (e.g. third-generation cephalosporins), H_2 blockers, and TPN are associated with invasive candidiasis.[29,57,84] Some studies also report associations with gastrointestinal pathology[29] and bacterial sepsis.[57]

Multiple studies have investigated the use of prophylaxis in select groups of neonates, including VLBW infants,[50,56] ELBW neonates (Table 3),[2,44,45] VLBW neonates with central vascular access,[17] and VLBW neonates with one additional risk factor (treatment with a third-generation cephalosporin, treatment for >10 consecutive days with systemic broad-spectrum antibiotics, or fungal colonization from surface sites and a CVC *in situ*).[62] The Infectious Diseases Society of America (IDSA) recommends prophylaxis for ELBW neonates in nurseries with high rates of invasive candidiasis; but the IDSA also notes that antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed.[71]

Prophylaxis with fluconazole

Despite potential concerns regarding cost,[63,66] antifungal prophylaxis with fluconazole has been found to be inexpensive and cost-effective.[49] A comparison of costs before and after initiation of fluconazole prophylaxis in neonates at high risk for invasive fungal infections in a single-institution observational trial found that fluconazole prophylaxis was cost-effective.[95] Compared with lower and less frequent dosing, twice-weekly dosing of prophylactic fluconazole can decrease cost and patient exposure to the drug in high-risk, preterm ELBW neonates while also decreasing *Candida* colonization and invasive infection.[45]

Prophylaxis recommendation

Based on these considerations, the Working Group recommends fluconazole prophylaxis (3 mg/kg twice weekly for 6 weeks) in ELBW neonates[44,60] who are in NICUs that have a high incidence of invasive candidiasis defined as ≥5%. If the incidence is not known, fluconazole prophylaxis could be considered (Fig. 1). A summary of efficacy data for *Candida* prophylaxis in neonates that has been reported in systematic reviews and meta-analyses is presented in Table 4.

Recommendations summary for *Candida* prophylaxis in neonates:

Risk factors to identify neonates as candidates for prophylaxis are mainly:

1. Low birth weight (<1000 g) and extreme prematurity (<28 weeks).
2. Fluconazole prophylaxis (3 mg/kg twice weekly for 6 weeks) is recommended in ELBW neonates who are in NICUs that have a high incidence of invasive candidiasis (≥5%).
3. If the incidence is not known or is <5%, fluconazole prophylaxis could be considered according to risk factors.

Empiric treatment for invasive candidiasis in neonates

The Working Group cannot provide a recommendation for the empiric treatment of invasive candidiasis, as there are no validated tools to identify candidates, and only a few studies (none of which were prospective trials) have investigated strategies for empiric treatment. In a retrospective study of neonates at the Hospital de Clínicas de Porto Alegre, Brazil, *Candida*-related mortality occurred in 11/18 historic control patients compared with 0/6 patients who received empirical treatment for invasive candidiasis.[74] In this study, empiric therapy was given to VLBW or very ill neonates who had clinical signs of infection and/or neutropenia and who had been treated with antibiotics (vancomycin or third-generation cephalosporins) for 7 or more days, in association with TPN, mechanical ventilation, postnatal corticosteroids, H_2 blockers or mucocutaneous candidiasis. Based on a database of 6172 neonates born at <1250 g and with a BC after the third day of life, a predictive multivariate model demonstrated that thrombocytopenia and cephalosporin or carbapenem use in the 7 days prior to BC were risk factors for subsequent invasive candidiasis.[13] In addition, neonates who were 25–27 weeks estimated gestational age or born before 25 weeks were also at increased risk.

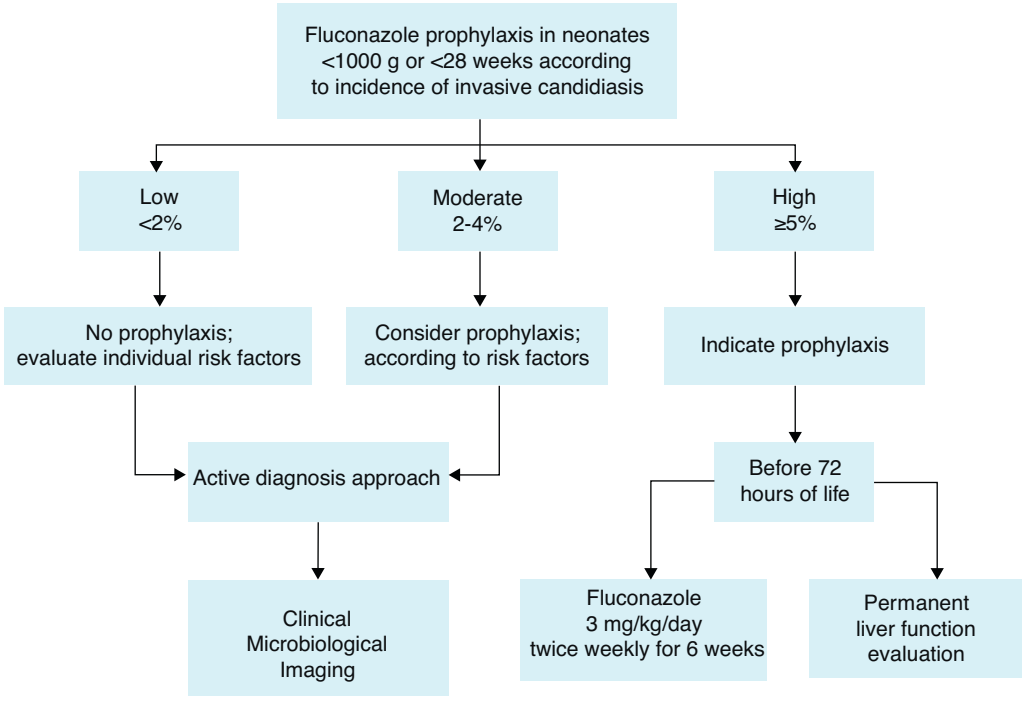


Fig. 1. Fluconazole prophylaxis in neonates according to gestational age and weight of birth.

Recommendations summary for empiric treatment in neonates:

Based on the lack of validated tools to identify candidates for empirical treatment of invasive candidiasis and the paucity of studies investigating strategies for empirical treatment, no recommendations can be made.

Treatment of invasive candidiasis in neonates

Based on available data and clinical experience, amphotericin B (AmB), either AmB deoxycholate (AmB-d) or liposomal-AmB (L-AmB) or an echinocandin (micafungin or caspofungin) are the first options recommended for the treatment of neonatal candidiasis (Table 5).

Amphotericin B deoxycholate or liposomal amphotericin B

Data on the treatment of neonatal candidiasis are very limited, and only one trial provides comparative data.[75] This multinational, double-blind, randomized controlled trial studied first-line treatment of invasive candidiasis with micafungin (2 mg/kg) compared with L-AmB (3 mg/kg). There was a sub-study of 106 pediatric patients (ITT population), 19 were premature at birth. Of the 106 pediatric patients, 98 had a confirmed diagnosis of candida at baseline (MITT) and were included in the efficacy analysis. In the MITT population treatment was successful in 35/48 (72.9%) patients who received micafungin and 38/50 (76.0%) patients who received L-AmB. Efficacy was consistent regardless of patient age. Both treatments were well tolerated, but the incidence of adverse events leading to discontinuation was lower in the micafungin group (2/52, 3.8%) compared with the L-AmB group (9/54, 16.7%; $p = 0.05$). Within the subgroup of neonatal patients (0 days to <4 weeks old) only, 4/7 (57.1%) who received L-AmB experienced treatment success.

Despite the efficacy of L-AmB, this therapy is not available in the majority of hospitals in Latin America; however, AmB-d is more freely available, has been widely used in neonates, and is better tolerated in this population than in adults.[94] It also appears to be at least as efficacious as L-AmB in the treatment of invasive candidiasis in neonates and infants.[94] However, L-AmB has a better safety profile than AmB-d,[52] and the long-term consequences of AmB-d treatment in this patient population are not known.

Echinocandins

Micafungin and caspofungin are also recommended for the treatment of neonatal candidiasis. CNS involvement should be ruled out prior to their use owing to unknown efficacy in treating CNS infection (see the management of complications section below). Small trials have shown efficacy of micafungin[75] and caspofungin[69] in the treatment of neonates with invasive candidiasis. Although data are limited, preliminary investigations have demonstrated that micafungin is well tolerated in neonates.[4,35,75,89] Single doses of micafungin (0.75–3.0 mg/kg) were well tolerated in premature infants weighing more than 1000 g; however, increased clearance of the drug resulted in low plasma concentrations.[35] Subsequent investigation demonstrated that repeat 15 mg/kg doses were also well tolerated in neonates and resulted in plasma levels equivalent to a dosage of 5 mg/kg in adults.[89] Data on the use of caspofungin in neonates are also limited; preliminary investigations showed that once-daily caspofungin (25 mg/m^2) was well tolerated in neonates and infants (<3 months), and that this dose provided similar plasma exposure to that obtained in adults receiving 50 mg/day.[83]

Fluconazole

Fluconazole is efficacious and well tolerated in neonates. However, because this treatment is primary fungistatic rather than fungicidal, it is not considered a first-line option for neonatal invasive candidiasis, except for the case of urinary-tract candidiasis. Additionally, neonates may have already received fluconazole

Table 4
Efficacy of *Candida* prophylaxis in neonates (systematic reviews and meta-analyses).

Trial	Assessment	Methods	Results	Conclusion
Clerihew et al.[22]	Effect of prophylactic systemic antifungal therapy vs. PBO, no drug, another antifungal agent or dose regimen on mortality and morbidity in VLBW infants	Standard Cochrane Neonatal Review Group search strategy for RCTs. Seven eligible trials, 638 infants. Meta-analysis of data from four trials compared prophylactic FLU vs. PBO	Reduction in IFI in infants with prophylaxis. RR: 0.23 (95% CI: 0.11, 0.46); RD: -0.11 (95% CI: -0.16, -0.06); NNT: 9 (95% CI: 6, 17) No difference in death. RR: 0.61 (95% CI: 0.37, 1.03), RD: -0.05 (95% CI: -0.11, -0.00). No differences in neurological impairment	Prophylactic systemic antifungal therapy reduces the incidence of IFI in VLBW infants. Interpret results with caution. No effect in mortality
Austin et al.[6]	Effect of prophylactic oral/topical non-absorbed antifungal therapy (nystatin or miconazole) on the incidence of IFI, mortality and morbidity in VLBW infants	Standard Cochrane Neonatal Review Group search strategy for RCTs. Effect of prophylactic oral/topical non-absorbed antifungal therapy vs. PBO, no drug, another antifungal agent or dose regimen. Three eligible trials, 1625 infants	Significantly reduction in incidence of IFI: RR: 0.19 (95% CI: 0.14, 0.27), RD: -0.19 (95% CI: -0.22, -0.16). Substantial statistical heterogeneity. No effect in mortality: RR: 0.88 (95% CI: 0.72, 1.06), RD: -0.02 (95% CI: -0.06, 0.01). Long-term outcomes not assessed	Methodological weaknesses, results should be interpreted with caution. Further RCTs are required and should include an assessment of neurodevelopmental outcomes
McGuire et al.[63]	Effect of prophylactic IV antifungal on mortality and adverse neurodevelopmental outcomes in VLBW infants	Standard Cochrane Neonatal Review Group search strategy for RCTs. Effect of prophylactic IV antifungal therapy vs. PBO, no drug, or another antifungal agent in VLBW infants. Three eligible trials 214 infants	Significantly reduced risk of death prior to hospital discharge for infants receiving FLU: RR: 0.44 (95% CI: 0.21, 0.91), RD: -0.11 (95% CI: -0.21, -0.02), NNT: 9 (95% CI: 5, 50). No long-term outcome data available	One fewer death in every nine infants treated with FLU; with wide 95% CI. Neurodevelopment consequences have yet to be determined. Need to identify subgroups of VLBW infants who benefit from this intervention
Mohan et al.[64]	Effect of patient-isolation measures for infants with *Candida* colonization or infection on the transmission of *Candida* to other infants in the neonatal units	Types of interventions: A policy of patient-isolation measures (single-room isolation or cohorting of infants with *Candida* colonization or infection) compared with routine isolation measures	No eligible trials identified	No evidence found to either support or refute patient-isolation measures in neonates with *Candida* colonization or infection
Zhang et al.[104]	Effect of FLU in prophylaxis of fungal infection in VLBW infants	Several databases searched from Jan 1994 to Jan 2009 for case control studies on the effect of FLU in prophylaxis of fungal infection in VLBW infants. Five eligible RCTs included	FLU reduces fungal colonization, RR: 0.32 (95% CI: 0.23, 0.44, $p < 0.00001$). FLU reduces fungal infections, RR: 0.44 (95% CI: 0.29, 0.65, $p < 0.0001$). No effect in mortality RR: 0.68 (95% CI: 0.43, 1.07, $p = 0.09$)	Prophylactic FLU reduces the incidence of fungal colonization and IFI in VLBW infants. Further trials needed to provide an assessment on mortality, neurodevelopment and the emergence of resistance
Clerihew et al.[23]	Incidence of fungal colonization and invasive infection, mortality prior to hospital discharge, neurodevelopmental outcomes and changes in patterns of FLU resistance and neurodevelopmental outcomes	Meta-analysis. Heterogeneity NNT (VLBW and ELBW). Four good methodological quality trials comparing FLU vs. PBO. 536 participants	FLU reduces incidence of IFI. RR: 0.23 (95% CI: 0.11, 0.46), RD: -0.11 (95% CI: -0.16, -0.06). NNT to prevent one IFI case in VLBW infant is 130 (95% CI: 112, 185) and in ELBW infants is 62 (95% CI: 54, 88). No difference in all-cause mortality: RR: 0.61 (95% CI: 0.37, 1.03), RD: -0.05 (95% CI: -0.11, 0.00). No difference in developmental outcome. No difference in FLU MIC during study period	Prophylactic FLU reduces incidence of IFI in VLBW infants. Further trials needed to provide more precise estimates of effect size and to assess impact on mortality, neurodevelopment and the emergence of antifungal resistance

CI, confidence interval; ELBW, extremely low birth weight (<1000 g); FLU, fluconazole; IFI, invasive fungal infection; IV, intravenous; MIC, minimum inhibitory concentration; NNT, number needed to treat; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; RR, relative risk; VLBW, very low birth weight (<1500 g).

treatment as prophylaxis. De-escalation to fluconazole treatment may be possible when the patient is stable and susceptibility information is known.

Fluconazole (12 mg/kg) is recommended for the treatment of urinary tract candidiasis in neonates.[97] It is highly water-soluble, primarily excreted in urine in its active form, and easily achieves urine levels exceeding the minimum inhibitory concentration for most *Candida* strains.[18] Small studies have described successful fluconazole treatment of infants and newborns with a *C. albicans* urinary-tract infection.[36,93]

Infection control

Studies have found evidence for transmission of *Candida* through direct and indirect contact and cross-infection by health-care workers; however, in neonates with *Candida* colonization or infection, there is no evidence to support or refute the use of patient-isolation measures (single-room isolation or cohorting) beyond routine infection control measures (e.g. hand washing) that exist in the neonatal units (Table 4).[64,80,92] Infection control measures to prevent invasive candidiasis might

Table 5
Pharmacological treatment of neonatal candidiasis.

Drug	Dose	Efficacy/pharmacokinetics	Safety
AmB-d	0.35–0.5 mg/kg/day once daily over 2–4 h	In a study that compared AmB-d, AmB colloidal dispersion, and L-AmB for treatment in neonates with candidemia there was no difference in time to clear infection observed.[55] Pharmacokinetic data in neonates are derived from small studies and exhibit considerable variability.[3,32] CSF penetration, which is only 5-10% of serum levels in adults, may reach 40% of serum levels in preterm neonates[12]	Side effects observed in VLBW neonates include electrolyte abnormalities and nephrotoxicity.[11] There is a trend of more nephrotoxicity with AmB-d than with lipid formulations, with a wide range reported (0–70%).[94] Neonates with normal baseline renal function appeared to tolerate AmB-d well; a sodium intake of 4 mg/kg/day may significantly reduce AmB-d nephrotoxicity[94]
L-AmB	3–5 mg/kg/day, once daily	Similar efficacy to AmB-d. In the treatment of systemic candidiasis in VLBW infants, the fungal eradication rate and the time to eradication were 84% and 9 ± 8 days, respectively, in the L-AmB group, and 89% and 10 ± 9 days in the AmB group ($p = 0.680$ and $p = 0.712$)[40]	Well tolerated.[40,101] Major adverse effects were lower in the L-AmB-treated than in the AmB-treated VLBW infants (renal toxicity, 21% vs. 55%, $p = 0.029$; hepatotoxicity, 25% vs. 65%, $p = 0.014$)[40]
Micafungin	15 mg/kg/day once daily	Similar efficacy to L-AmB. Successful treatment of neonates with invasive candidiasis in 7/7 infants who received micafungin and 4/7 (57.1%) infants who received L-AmB.[75] Shorter half-life (8 h) with more rapid clearance rate (approximately 39 ml/h) in premature infants compared with older children and adults.[35] Doses up to 15 mg/kg/day corresponded to an exposure of 5 mg/kg in adults[89]	Well tolerated.[15,35,89] Among pediatric patients (neonate to 16 yrs), those treated with micafungin had a lower incidence of adverse events that led to discontinuation (2/52, 3.8%) compared with those treated with L-AmB (9/54, 16.7%) ($p = 0.05$, Fisher exact test)[75]
Caspofungin	25 mg/m^2 once daily	Superior efficacy to AmB[99] and AmB-d.[69] In neonates with invasive candidiasis, caspofungin was superior, with a favorable response in 86.7% of patients compared with 41.7% of those who received AmB ($p = 0.04$).[99] 25 mg/m^2 once daily was well tolerated in neonates/infants of <3 months of age and provided relatively similar plasma exposure to that obtained in adults receiving 50 mg/day[83]	Well tolerated.[69,99] Among term and preterm neonates with invasive candidiasis, there were no clinical or laboratory adverse events related to caspofungin administration.[69] In a study that compared caspofungin with AmB in neonates, there were significantly fewer adverse events in the caspofungin group than in the AmB group[99]
Fluconazole	12 mg/kg/day, once daily	Fluconazole compared favorably with AmB-d.[26] Long half-life that decreases with increasing postnatal age.[86] A population pharmacokinetic study in 55 neonates and young infants suggests that maintenance fluconazole doses of 12 mg/kg/day are necessary to achieve exposures similar to older children and adults[98]	Well tolerated.[39,87] Among newborns and infants (median birth weight of 1120 g and born within gestational weeks 23–38), no serious side effects were observed[87]

AmB, amphotericin B; AmB-d, amphotericin B deoxycholate; CSF, cerebrospinal fluid; L-AmB, liposomal amphotericin B; VLBW, very low birth weight (<1500 g).

include prenatal detection and eradication of maternal vaginal candidiasis, and stewardship programs to limit the use of broad-spectrum antibiotics (specifically third generation cephalosporins and carbapenems), H_2 blockers, and postnatal dexamethasone, particularly during high-risk periods for infection (e.g. when neonates require CVCs, TPN, or endotracheal tubes).[47] In addition, having feeding protocols and encouraging breastfeeding may help prevent necrotizing enterocolitis, which has been associated with invasive candidiasis. Having standardized protocols for the insertion and management of CVCs may also be an effective infection control measure.[49]

Recommendations summary for the treatment of invasive candidiasis in neonates:

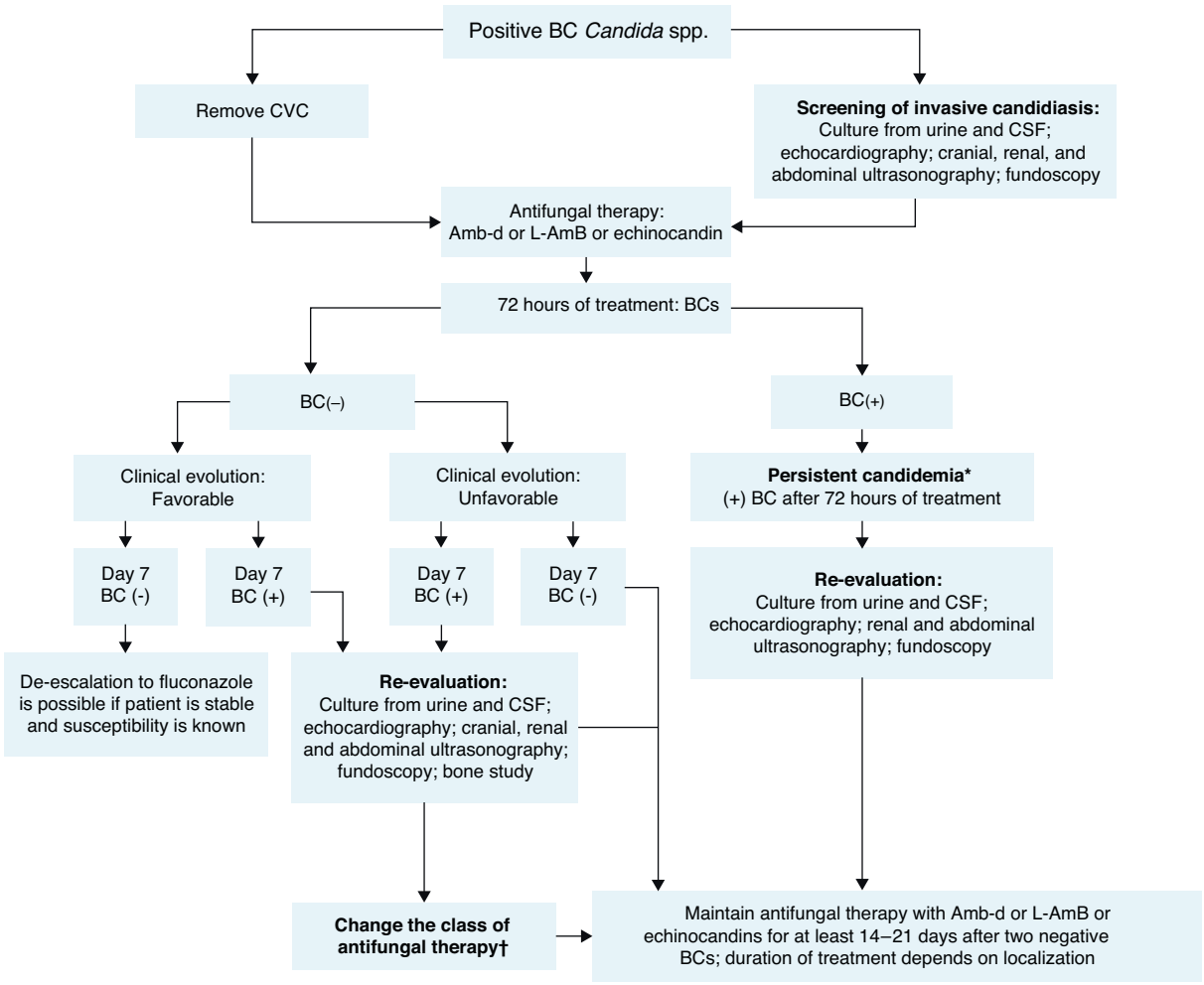
1. AmB (either AmB-d or L-AmB) or an echinocandin (micafungin or caspofungin) are the first options recommended for the treatment of neonatal invasive candidiasis.
2. CNS involvement should be ruled out prior to echinocandin use.
3. De-escalation to fluconazole treatment may be possible when the patient is stable and susceptibility information is known.
4. Fluconazole is recommended for the treatment of urinary-tract candidiasis in neonates.

Patient work-up after candidemia diagnosis

The management of neonates following a diagnosis of candidemia is shown in Fig. 2.

The baseline patient work-up in neonatal invasive candidiasis includes urine culture; lumbar puncture and cerebrospinal fluid (CSF) evaluation (to include culture of CSF, as cultures may be positive despite normal cell counts)[14,71]; cranial ultrasound; abdominal and renal ultrasound to look for abscesses in the kidney, spleen, and liver (to be carried out in all neonates with candidemia); an echocardiogram[14] (recommended in neonates with candidemia to look for endocarditis); and dilated fundoscopic evaluation (ophthalmoscopy – recommended for all neonates with candidemia to rule out retinitis or endophthalmitis).[14,71]

BC should be done after 72 h of treatment and then every 48 h until sterilization of the blood is achieved (two consecutive negative BCs). In infants, the volume of blood collected for culture is based on age and body weight, with a blood-to-broth ratio of 1:5 or 1:10, according to technique recommendations.[77] If cultures remain positive despite appropriate treatment (≥72 h after initiation of antifungal therapy), secondary work-up to evaluate possible focal sites of infection is recommended (similar to baseline work-up). If BC remains positive at day 7 of therapy, an echocardiogram should be performed to rule out endocarditis and imaging of the bones and brain (ideally with magnetic resonance imaging or X-ray computed tomography) to evaluate further spread of the infection.



Amb-d=amphotericin B deoxycholate; BC=blood culture; CSF=cerebrospinal fluid; CVC=central venous catheter; L-AmB=liposomal amphotericin B.
*Persistent candidemia: positive blood culture after 72 hours of treatment.

†To change the class of antifungal therapy: if patient is using AmB-d or L-AmB change to echinocandin; if patient is using an echinocandin, change to Amb-d or L-AmB.

Fig. 2. Management of invasive candidiasis in neonates.

Recommendations summary for patient work-up after candidemia diagnosis in neonates

1. Baseline patient work-up:
   a. Urine culture.
   b. Lumbar puncture and CSF evaluation.
   c. Cranial ultrasound.
   d. Abdominal ultrasound.
   e. Echocardiogram.
   f. Fundoscopy.
2. BC should be done after 72 h of treatment and then every 48 h until sterilization (two consecutive negative BCs)
3. Secondary patient work-up (if cultures remain positive at 72 h of treatment):
   a. The same as baseline work-up.
4. Secondary patient work-up (if BCs remain positive at day 7 of treatment):
   a. The same as baseline work-up plus imaging of the bones and brain.

Duration of candidemia treatment in neonates

Neonates with candidemia without septic complications should be treated until at least 2 weeks after two negative BC are obtained (Fig. 2).[43] Treatment should be extended in neonates with persistent candidemia or candidemia with septic complications, as discussed below. In these situations, the duration of treatment should be determined using a case-by-case approach based on clinical features and patient characteristics.

Catheter management in neonates

Epidemiologic data related to catheter management and outcomes associated with catheter removal are limited and are not available for the Latin American region. In a study of ELBW neonates with candidemia, the rates of death and neurodevelopment impairment were greater for infants with delayed removal or replacement of catheters (>1 day after initiation of antifungal treatment) compared with infants in whom catheters were removed or replaced promptly.[16] Another study found that in neonates with early catheter removal (≤3 days after first *Candida*-positive BC), candidemia resolved more quickly and the case fatality rate was

Recommendations summary for catheter management in neonates:

1. Remove catheters in neonates with candidemia.
2. Vascular access removal should be weighed against the need for intravenous access.

lower compared with neonates with delayed catheter removal (>3 days).[42] The Working Group recommends that catheters should be removed from neonates with candidemia. The decision to remove a catheter from a neonate with candidemia should be carefully considered and weighed against the need for intravenous access, given the potential challenge of finding a new catheter site in these patients.

Management of complications in neonates

Persistent candidemia

In addition to being linked with high mortality, candidemia is associated with considerable morbidity.[14] End-organ damage may involve the CNS, eyes, heart, bones, kidneys, spleen, and liver. Persistent positive cultures are associated with focal complications (ophthalmologic, renal, and cardiac) and/or death. Therefore, serial cultures of the infected site (or sites) should be obtained to predict the need for aggressive surveillance and intervention for focal complications (Fig. 2).[21,68] No differences in baseline characteristics were found in two studies comparing neonates with and without persistent candidemia.[21,54] In one of these studies, persistent infection was defined as positive repeat BC obtained ≥24 h after attaining target dose of antifungal therapy.[21] In the other, candidemia was considered persistent when it ranged in duration from 7 to 22 days.[54] A duration of >1 day between the time of BC and the initial dose of systemic antifungal treatment places neonates at increased risk of developing persistent candidemia.[78] In one prospective, single-institution, cohort study of VLBW neonates diagnosed with candidiasis, 10% had persistent candidemia, defined as positive culture for ≥2 weeks despite antifungal therapy.[16] In the same study of 307 neonates with candidemia, up to 21% of infants had intermittent false-negative BCs while receiving antifungal therapy.[16] This demonstrates that subsequent cultures in a neonate previously diagnosed with candidemia could yield false-negative results. In this context, one negative BC is not enough to indicate absence of infection in these patients, and at least two negative BCs are required to confirm absence of infection.[43]

Treating complications

Treatment of the complications resulting from the spread of *Candida* infection is not well defined by clinical trials; however, the tissue penetration of potential therapies is an important consideration. Fluconazole has excellent tissue penetration and approximately 70% of it is excreted unchanged in the urine; therefore, fluconazole is the best choice for isolated renal infections due to *Candida*.[18,88,100] An alternative to fluconazole is AmB-d. L-AmB is not indicated in renal infection by *Candida*, owing to limited tissue penetration.[71] Endocarditis is most often associated with prolonged candidemia;[53,54,81] however, fungal endocarditis has also been observed in a patient with only a single positive BC.[14,68] The treatment approach for neonates with endocarditis due to *Candida* includes treatment with echinocandins (micafungin or caspofungin) or L-AmB (as these therapies can penetrate biofilms), extended duration of treatment, prompt removal of CVCs, and probably surgery. Owing to the high mortality risk, it is difficult to decide whether to perform surgery in neonates and, usually, surgeons prefer that patients could be treated for 2–3 weeks prior to considering surgery.

Treatment of osteomyelitis due to *Candida* requires surgery and prolonged duration of therapy for at least 4–6 weeks. Treatment options include 2–4 weeks of lipid formulation AmB (3–5 mg/kg/day), AmB-d (0.5–1 mg/kg/day), or an echinocandin (micafungin or caspofungin), followed by fluconazole (12 mg/kg/day).[96]

Infants with candidemia lasting ≥5 days may be more likely to develop ophthalmologic abnormalities. Endophthalmitis may occur as early as the first day of infection; however, it becomes a more probable complication with prolonged candidemia. Systemic antifungal therapy is usually adequate to successfully treat this complication.[10] There is a widely reported range of ocular involvement in infants with invasive candidiasis (0–44%). In one retrospective study, retinal abnormalities were observed in 6% (4/67) of infants when indirect ophthalmoscopy examination was performed. In cases of ocular involvement in infants with invasive candidiasis, prolonged treatment with AmB-d or L-AmB is recommended.[20] The possible benefits of echinocandin use might be limited, owing to their undetectable vitreous concentrations.[96]

Central nervous system infection

CNS infection is a relatively frequent complication of candidemia; however, CSF culture findings are varied, and normal CSF may not exclude CNS infection.[30] In neonates, concentrations of AmB-d in the CSF may reach 40–90% of serum values (i.e. it penetrates reasonably well).[12] For CNS infection, treatment with AmB-d should be considered, as the efficacy of this therapy has been demonstrated in the treatment of *Candida* meningitis in neonates.[30] Lipid formulations of AmB can be administered at higher doses owing to their decreased renal toxicity, and they may have better CNS penetration compared with AmB-d.[100] In a multicenter observational study, clearance from CSF was longer among neonates who received AmB-d and flucytosine, compared with those who received only AmB.[16]

Data to guide the use of other treatments for *Candida* meningitis are lacking. Preclinical data suggest that micafungin penetrates most sub-compartments of the CNS; however, clinical investigations are needed to establish the efficacy in treatment of neonatal CNS infection. Higher doses of micafungin may be needed to achieve adequate concentrations within the CNS.[37] In a study of the safety and pharmacokinetics of micafungin in infants, a dosage of 10 mg/kg/day resulted in 82.6% of patients having a maximal decline in fungal burden within the CNS.[38] Two studies of the treatment of candidemia with caspofungin demonstrated efficacy of caspofungin in a few neonates with *Candida* meningitis.[65,69] Although further investigation is needed, echinocandins are not indicated to treat CNS complications.

Recommendations summary for management of complications in neonates:

Renal infection:

1. Fluconazole, 12 mg/kg/day

Endocarditis:

1. Prolonged treatment with L-AmB or echinocandins
2. Prompt removal of CVCs
3. Surgery (after antifungal treatment)

Osteomyelitis:

1. Surgery
2. Prolonged treatment with AmB-d, L-AmB or echinocandins, followed by fluconazole

Ocular involvement:

1. Prolonged treatment with AmB-d or L-AmB

CNS infection:

1. Prolonged treatment with AmB-d or L-AmB

Conflict of interests

A.L. Colombo has received research grants from Pfizer, MSD, United Medical and Luminex, medical education grants from Pfizer, MSD, United Medical and Astellas. Moreover, he has also been a consultant for MSD, Pfizer and Gilead. *J.A. Cortes* has received research grants and support to attend educational meetings from Pfizer and MSD. *M. Nucci* has received research grants from Pfizer and MSD, and has acted as a consultant and speaker for Pfizer, MSD, Astellas and Gilead. *F de Queiroz-Telles* has participated in Continuing Education activities in laboratories for Astellas, MSD, Pfizer and United Medical, and in research activities in laboratories for Astellas, MSD and Pfizer. *I. N. Tiraboschi* has been a speaker for Pfizer and Gilead. *J. Zurita* has been advisory board member and consultant for Pfizer, and has received research grants from Wyeth and MSD for participating in the SMART study.

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References

1. Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis. 1997;24:1122–8.
2. Aghai ZH, Mudduluru M, Nakhla TA, Amendolia B, Longo D, Kemble N, et al. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. J Perinatol. 2006;26:550–5.
3. Almirante B, Rodriguez D. Antifungal agents in neonates: issues and recommendations. Paediatr Drugs. 2007;9:311–21.
4. Arrieta AC, Maddison P, Groll AH. Safety of micafungin in pediatric clinical trials. Pediatr Infect Dis J. 2011;30:e97–102.
5. Arrieta AC, Shea K, Dhar V, Cleary JP, Kukreja S, Morris M, et al. Once-weekly liposomal amphotericin B as *Candida* prophylaxis in very low birth weight premature infants: a prospective, randomized, open-label, placebo-controlled pilot study. Clin Ther. 2010;32:265–71.
6. Austin N, Darlow BA, McGuire W. Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. Cochrane Database Syst Rev. 2009;4:CD003478.
7. Avila-Aguero ML, Canas-Coto A, Ulloa-Gutierrez R, Caro MA, Alfaro B, Paris MM. Risk factors for *Candida* infections in a neonatal intensive care unit in Costa Rica. Int J Infect Dis. 2005;9:90–5.
8. Aydemir C, Oguz SS, Dizdar EA, Akar M, Sarikabadayi YU, Saygan S, et al. Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. Arch Dis Child Fetal Neonatal Ed. 2011;96:F164–8.
9. Aziz M, Patel AL, Losavio J, Iyengar A, Berven M, Schloemer N, et al. Efficacy of fluconazole prophylaxis for prevention of invasive fungal infection in extremely low birth weight infants. Pediatr Infect Dis J. 2010;29:352–6.
10. Baley JE, Ellis FJ. Neonatal candidiasis: ophthalmologic infection. Semin Perinatol. 2003;27:401–5.
11. Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low-birth-weight infants: therapeutic toxicity. Pediatrics. 1984;73:153–7.
12. Baley JE, Meyers C, Kliegman RM, Jacobs MR, Blumer JL. Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. J Pediatr. 1990;116:791–7.
13. Benjamin Jr DK, DeLong ER, Steinbach WJ, Cotton CM, Walsh TJ, Clark RH. Empirical therapy for neonatal candidemia in very low birth weight infants. Pediatrics. 2003;112:543–7.
14. Benjamin Jr DK, Poole C, Steinbach WJ, Rowen JL, Walsh TJ. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. Pediatrics. 2003;112 3 Pt 1:634–40.
15. Benjamin Jr DK, Smith PB, Arrieta A, Castro L, Sanchez PJ, Kaufman D, et al. Safety and pharmacokinetics of repeat-dose micafungin in young infants. Clin Pharmacol Ther. 2010;87:93–9.
16. Benjamin Jr DK, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117:84–92.
17. Bertini G, Perugi S, Dani C, Filippi L, Pratesi S, Rubaltelli FF. Fluconazole prophylaxis prevents invasive fungal infection in high-risk, very low birth weight infants. J Pediatr. 2005;147:162–5.
18. Brammer KW, Farrow PR, Faulkner JK. Pharmacokinetics and tissue penetration of fluconazole in humans. Rev Infect Dis. 1990;12 Suppl. 3:S318–26.
19. Brion LP, Uko SE, Goldman DL. Risk of resistance associated with fluconazole prophylaxis: systematic review. J Infect. 2007;54:521–9.
20. Butler KM, Rench MA, Baker CJ. Amphotericin B as a single agent in the treatment of systemic candidiasis in neonates. Pediatr Infect Dis J. 1990;9:51–6.
21. Chapman RL, Faix RG. Persistently positive cultures and outcome in invasive neonatal candidiasis. Pediatr Infect Dis J. 2000;19:822–7.
22. Clerihew L, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2007;4:CD003850.
23. Clerihew L, Austin N, McGuire W. Systemic antifungal prophylaxis for very low birthweight infants: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2008;93:F198–200.
24. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin Jr DK. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006;118:717–22.
25. Downey LC, Smith PB, Benjamin Jr DK, Cohen-Wolkowiez M. Recent advances in the detection of neonatal candidiasis. Curr Fungal Infect Rep. 2010;4:17–22.
26. Driessen M, Ellis JB, Cooper PA, Wainer S, Muwazi F, Hahn D, et al. Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial. Pediatr Infect Dis J. 1996;15:1107–12.
27. Faix RG. Invasive neonatal candidiasis: comparison of *albicans* and *parapsilosis* infection. Pediatr Infect Dis J. 1992;11:88–93.
28. Fanaroff AA. Fluconazole for the prevention of fungal infections: get ready, get set, caution. Pediatrics. 2006;117:214–5.
29. Feja KN, Wu F, Roberts K, Loughrey M, Nesin M, Larson E, et al. Risk factors for candidemia in critically ill infants: a matched case–control study. J Pediatr. 2005;147:156–61.
30. Fernandez M, Moylett EH, Noyola DE, Baker CJ. Candidal meningitis in neonates: a 10-year review. Clin Infect Dis. 2000;31:458–63.
31. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis. 1992;15:414–21.
32. Frattarelli DA, Reed MD, Giacoia GP, Aranda JV. Antifungals in systemic neonatal candidiasis. Drugs. 2004;64:949–68.
33. Friedman S, Richardson SE, Jacobs SE, O'Brien K. Systemic *Candida* infection in extremely low birth weight infants: short term morbidity and long term neurodevelopmental outcome. Pediatr Infect Dis J. 2000;19:499–504.
34. Healy CM, Campbell JR, Zaccaria E, Baker CJ. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant *Candida* species. Pediatrics. 2008;121:703–10.
35. Heresi GP, Gerstmann DR, Reed MD, van den Anker JN, Blumer JL, Kovanda L, et al. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. Pediatr Infect Dis J. 2006;25:1110–5.
36. Hitchcock RJ, Pallett A, Hall MA, Malone PS. Urinary tract candidiasis in neonates and infants. Br J Urol. 1995;76:252–6.
37. Hope WW, Mickiene D, Petraitis V, Petraitiene R, Kelaher AM, Hughes JE, et al. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous *Candida* meningoencephalitis: implications for echinocandin therapy in neonates. J Infect Dis. 2008;197:163–71.
38. Hope WW, Smith PB, Arrieta A, Buell DN, Roy M, Kaibara A, et al. Population pharmacokinetics of micafungin in neonates and young infants. Antimicrob Agents Chemother. 2010;54:2633–7.
39. Huang YC, Lin TY, Lien RI, Chou YH, Kuo CY, Yang PH, et al. Fluconazole therapy in neonatal candidemia. Am J Perinatol. 2000;17:411–5.
40. Jeon GW, Koo SH, Lee JH, Hwang JH, Kim SS, Lee EK, et al. A comparison of AmBisome to amphotericin B for treatment of systemic candidiasis in very low birth weight infants. Yonsei Med J. 2007;48:619–26.
41. Johnson EM, Warnock DW, Luker J, Porter SR, Scully C. Emergence of azole drug resistance in *Candida* species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidosis. J Antimicrob Chemother. 1995;35:103–14.

42. Karlowicz MG, Hashimoto LN, Kelly Jr RE, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? Pediatrics. 2000;106:E63.
43. Kaufman D. Neonatal candidiasis: clinical manifestations, management and prevention strategies. J Pediatr. 2010;156 4 Suppl. 2:S53–67.
44. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med. 2001;345:1660–6.
45. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Grossman LB. Twice weekly fluconazole prophylaxis for prevention of invasive *Candida* infection in high-risk infants of <1000 grams birth weight. J Pediatr. 2005;147:172–9.
46. Kaufman D, Fairchild KD. Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. Clin Microbiol Rev. 2004;17:638–80.
47. Kaufman DA. Challenging issues in neonatal candidiasis. Curr Med Res Opin. 2010;26:1769–78.
48. Kaufman DA, Cuff AL, Wamstad JB, Boyle R, Gurka MJ, Grossman LB, et al. Fluconazole prophylaxis in extremely low birth weight infants and neurodevelopmental outcomes and quality of life at 8 to 10 years of age. J Pediatr. 2011;158:759–65.e1.
49. Kaufman DA, Manzoni P. Strategies to prevent invasive candidal infection in extremely preterm infants. Clin Perinatol. 2010;37:611–28.
50. Kicklighter SD, Springer SC, Cox T, Hulsey TC, Turner RB. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. Pediatrics. 2001;107:293–8.
51. Law D, Moore CB, Wardle HM, Ganguli LA, Keaney MG, Denning DW. High prevalence of antifungal resistance in *Candida* spp. from patients with AIDS. J Antimicrob Chemother. 1994;34:659–68.
52. Leenders AC, Daenen S, Jansen RL, Hop WC, Lowenberg B, Wijermans PW, et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. Br J Haematol. 1998;103:205–12.
53. Levy I, Shalit I, Askenazi S, Klinger G, Sirota L, Linder N. Duration and outcome of persistent candidaemia in newborn infants. Mycoses. 2006;49:197–201.
54. Levy I, Shalit I, Birk E, Sirota L, Ashkenazi S, German B, et al. *Candida* endocarditis in neonates: report of five cases and review of the literature. Mycoses. 2006;49:43–8.
55. Linder N, Klinger G, Shalit I, Levy I, Ashkenazi S, Haski G, et al. Treatment of candidaemia in premature infants: comparison of three amphotericin B preparations. J Antimicrob Chemother. 2003;52:663–7.
56. Manzoni P, Arisio R, Mostert M, Leonessa M, Farina D, Latino MA, et al. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. Pediatrics. 2006;117:e22–32.
57. Manzoni P, Farina D, Leonessa M, d'Oulx EA, Galletto P, Mostert M, et al. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. Pediatrics. 2006;118:2359–64.
58. Manzoni P, Leonessa M, Galletto P, Latino MA, Arisio R, Maule M, et al. Routine use of fluconazole prophylaxis in a neonatal intensive care unit does not select natively fluconazole-resistant *Candida* subspecies. Pediatr Infect Dis J. 2008;27:731–7.
59. Manzoni P, Stolfi I, Messner H, Cattani S, Laforgia N, Romeo MG, et al. Bovine lactoferrin prevents invasive fungal infections in very low birth weight infants: a randomized controlled trial. Pediatrics. 2012;129:116–23.
60. Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Vetrano G, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. N Engl J Med. 2007;356:2483–95.
61. Marodi L. Neonatal innate immunity to infectious agents. Infect Immun. 2006;74:1999–2006.
62. McCrossan BA, McHenry E, O'Neill F, Ong G, Sweet DG. Selective fluconazole prophylaxis in high-risk babies to reduce invasive fungal infection. Arch Dis Child Fetal Neonatal Ed. 2007;92:F454–8.
63. McGuire W, Clerihew L, Austin N. Prophylactic intravenous antifungal agents to prevent mortality and morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2004;1:CD003850.
64. Mohan P, Eddama O, Weisman LE. Patient isolation measures for infants with *Candida* colonization or infection for preventing or reducing transmission of *Candida* in neonatal units. Cochrane Database Syst Rev. 2007;3:CD006068.
65. Natarajan G, Lulic-Botica M, Rongkavilit C, Pappas A, Bedard M. Experience with caspofungin in the treatment of persistent fungemia in neonates. J Perinatol. 2005;25:770–7.
66. Neely MN, Schreiber JR. Fluconazole prophylaxis in the very low birth weight infant: not ready for prime time. Pediatrics. 2001;107:404–5.
67. Nguyen MH, Peacock Jr JE, Morris AJ, Tanner DC, Nguyen ML, Snydman DR, et al. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am J Med. 1996;100:617–23.
68. Noyola DE, Fernandez M, Moylett EH, Baker CJ. Ophthalmologic, visceral, and cardiac involvement in neonates with candidemia. Clin Infect Dis. 2001;32:1018–23.
69. Odio CM, Araya R, Pinto LE, Castro CE, Vasquez S, Alfaro B, et al. Caspofungin therapy of neonates with invasive candidiasis. Pediatr Infect Dis J. 2004;23:1093–7.
70. Paganini H, Rodriguez Brieshcke T, Santos P, Seu S, Rosanova MT. Risk factors for nosocomial candidaemia: a case–control study in children. J Hosp Infect. 2002;50:304–8.
71. Pappas PG, Kauffman CA, Andes D, Benjamin Jr DK, Calandra TF, Edwards Jr JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503–35.
72. Pera A, Byun A, Gribar S, Schwartz R, Kumar D, Parimi P. Dexamethasone therapy and *Candida* sepsis in neonates less than 1250 grams. J Perinatol. 2002;22:204–8.
73. Pfaller MA, Diekema DJ. Role of sentinel surveillance of candidemia: trends in species distribution and antifungal susceptibility. J Clin Microbiol. 2002;40:3551–7.
74. Procianoy RS, Eneas MV, Silveira RC. Empiric guidelines for treatment of *Candida* infection in high-risk neonates. Eur J Pediatr. 2006;165:422–3.
75. Queiroz-Telles F, Berezin E, Leverger G, Freire A, van der Vyver A, Chotpitayasunondh T, et al. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. Pediatr Infect Dis J. 2008;27:820–6.
76. Ramirez Aguilar ML, Perez Miravete A, Santos Preciado JI. Biological features and experimental pathogenicity of *Candida* strains isolated by hemoculture at the Hospital Infantil de Mexico "Federico Gomez". Rev Latinoam Microbiol. 1992;34:259–65.
77. Richardson M, Warnock DW. Laboratory diagnosis of fungal infection. Fungal Infection: Diagnosis and Management. Chichester, West Sussex, UK: John Wiley & Sons; 2012. p. 12–30.
78. Robinson JA, Pham HD, Bloom BT, Wittler RR. Risk factors for persistent candidemia infection in a neonatal intensive care unit and its effect on mortality and length of hospitalization. J Perinatol. 2012;32:621–5.
79. Rodero L, Boutureira M, Demkura H, Burkett A, Fernandez C, Losso M, et al. Yeast infections: causative agents and their antifungal resistance in hospitalized pediatric patients and HIV-positive adults. Rev Argent Microbiol. 1997;29:7–15.
80. Rodero L, Hochenfellner F, Demkura H, Pereda R, Cordoba S, Canteros C, et al. Nosocomial transmission of *Candida albicans* in newborn infants. Rev Argent Microbiol. 2000;32:179–84.
81. Rodriguez D, Almirante B, Park BJ, Cuenca-Estrella M, Planes AM, Sanchez F, et al. Candidemia in neonatal intensive care units: Barcelona, Spain. Pediatr Infect Dis J. 2006;25:224–9.
82. Romeo MG, Romeo DM, Trovato L, Oliveri S, Palermo F, Cota F, et al. Role of probiotics in the prevention of the enteric colonization by *Candida* in preterm newborns: incidence of late-onset sepsis and neurological outcome. J Perinatol. 2011;31:63–9.
83. Saez-Llorens X, Macias M, Maiya P, Pineros J, Jafri HS, Chatterjee A, et al. Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. Antimicrob Agents Chemother. 2009;53:869–75.
84. Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J, et al. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey Study Group. Pediatr Infect Dis J. 2000;19:319–24.
85. Santolaya ME, Queiroz-Tellez F, Nucci M. Epidemiology of candidemia in children from Latin America: a key step required to improve disease outcome. In: Libro de resúmenes XXIX Congreso Chileno de Infectología; 2012.
86. Saxen H, Hoppu K, Pohjavuori M. Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. Clin Pharmacol Ther. 1993;54:269–77.
87. Schwarze R, Penk A, Pittrow L. Treatment of candidal infections with fluconazole in neonates and infants. Eur J Med Res. 2000;5:203–8.
88. Shiba K, Saito A, Miyahara T. Safety and pharmacokinetics of single oral and intravenous doses of fluconazole in healthy subjects. Clin Ther. 1990;12:206–15.
89. Smith PB, Walsh TJ, Hope W, Arrieta A, Takada A, Kovanda LL, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. Pediatr Infect Dis J. 2009;28:412–5.
90. Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, Bauer CR, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr. 1996;129:63–71.
91. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110:285–91.
92. Tiraboschi IN, Carnovale S, Benetucci A, Fernandez N, Kurlat I, Foccoli M, et al. *Candida albicans* outbreak in a neonatal intensive care unit. Rev Iberoam Micol. 2007;24:263–7.
93. Triolo V, Gari-Toussaint M, Casagrande F, Garraffo R, Dageville C, Boutte P, et al. Fluconazole therapy for *Candida albicans* urinary tract infections in infants. Pediatr Nephrol. 2002;17:550–3.
94. Turkova A, Roilides E, Sharland M. Amphotericin B in neonates: deoxycholate or lipid formulation as first-line therapy—is there a 'right' choice? Curr Opin Infect Dis. 2011;24:163–71.
95. Uko S, Soghier LM, Vega M, Marsh J, Reinersman GT, Herring L, et al. Targeted short-term fluconazole prophylaxis among very low birth weight and extremely low birth weight infants. Pediatrics. 2006;117:1243–52.
96. Venditti M. Clinical aspects of invasive candidiasis: endocarditis and other localized infections. Drugs. 2009;69 Suppl. 1:39–43.
97. Wade KC, Benjamin Jr DK, Kaufman DA, Ward RM, Smith PB, Jayaraman B, et al. Fluconazole dosing for the prevention or treatment of invasive candidiasis in young infants. Pediatr Infect Dis J. 2009;28:717–23.

98. Wade KC, Wu D, Kaufman DA, Ward RM, Benjamin Jr DK, Sullivan JE, et al. Population pharmacokinetics of fluconazole in young infants. Antimicrob Agents Chemother. 2008;52:4043–9.
99. Wahab Mohamed WA, Ismail M. A randomized, double-blind, prospective study of caspofungin vs. amphotericin B for the treatment of invasive candidiasis in newborn infants. J Trop Pediatr. 2012;58:25–30.
100. Wazir S, Kumar P. Systemic fungal infections in neonates: current issues. J Neonatol. 2005;20.
101. Weitkamp JH, Poets CF, Sievers R, Musswessels E, Groneck P, Thomas P, et al. *Candida* infection in very low birth-weight infants: outcome and nephrotoxicity of treatment with liposomal amphotericin B (AmBisome). Infection. 1998;26:11–5.
102. Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis. 1995;20:1531–4.
103. Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis. 2005;41:1232–9.
104. Zhang JP, Chen C. Meta-analysis of the efficacy and safety of fluconazole in prophylaxis of fungal infection in very low birth weight infants. Zhonghua Er Ke Za Zhi. 2009;47:891–7.