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An outbreak of *Candida parapsilosis* fungemia among preterm infants

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ABSTRACT. In this article, we describe the first outbreak of *Candida parapsilosis* fungemia in our hospital. We examined a cluster of four nosocomial cases of *C. parapsilosis* fungemia that occurred in the neonatal intensive care unit (NICU) of the Affiliated Xingtai People's Hospital of Hebei Medical University over a two-week period. We ascertained patient parameters including clinical characteristics, blood and sputum cultures, and drug sensitivity test results. Cultures from eight blood samples obtained from the four infected preterm infants showed identical characteristics and were identified as *C. parapsilosis*. In order to determine the infection-related factors and to control the spread of the infection among the population, we immediately initiated the emergency plan. All four of the preterm infants recovered from the infection; there

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were no deaths. Outbreaks of *C. parapsilosis*, mostly involving preterm infants of very low birth weight or extremely low birth weight, can and do occur in NICUs. Cultures prepared using multiple samples taken from different patients contribute to a more definitive diagnosis. Established measures that control and prevent the infection, as well as effective and comprehensive treatments, can lead to a favorable outcome. That is to say, improving both disinfection and isolation, as well as interrupting the pathway of transmission, is the key to controlling the spread of infection.

Key words: Preterm infants; Sepsis; *Candida parapsilosis*; Outbreak

INTRODUCTION

A large number of very low birth weight (VLBW) and extremely low birth weight (ELBW) infants now survive in neonatal intensive care units (NICUs) because of the introduction of new medical therapies, such as antenatal steroid administration, postnatal surfactant replacement, the use of intravenous fat emulsions, and improved technological interventional techniques. Unfortunately, the increased survival rate of these high-risk infants has led to a concomitant rise in the incidence of *Candida* infections; over the past decade, the incidence of *Candida parapsilosis* has dramatically increased. In fact, reports indicate that *C. parapsilosis* is often the second most common *Candida* species isolated from blood cultures (Kuzucu et al., 2008; Hinrichsen et al., 2008; Pfaller et al., 2010; Aydin et al., 2011).

In this article, we describe the first outbreak of *C. parapsilosis* fungemia in our hospital. We examined a cluster of four nosocomial cases of *C. parapsilosis* fungemia that occurred in the NICU of the Affiliated Xingtai People's Hospital of Hebei Medical University over a two-week period - from the March 15th, 2014 to March 31st, 2014. In all four cases, *C. parapsilosis* infection was confirmed by blood culture; nonetheless, we investigated several patient parameters including clinical characteristics, blood and sputum cultures, and drug sensitivity test results in order to ascertain the infectious agent involved. In order to determine the infection-related factors and to control the spread of the infection among the population, we immediately initiated the emergency plan. All four of the preterm infants recovered from the infection; there were no deaths.

MATERIAL AND METHODS

Patients

A total of 102 preterm infants were admitted to the NICU of Xingtai People's Hospital (60 beds) from March 15th, 2014 to March 31st, 2014. Four of these (3.92%) had fungal sepsis. The mean gestational age of the infected infants was 31.25 weeks (range: 29-32 weeks), and the median birth weight was 1112.50 g (range: 880-1280 g). Furthermore, the median postnatal age at onset of infection was 21.75 days (range: 14-28 days). All preterm infants had been treated using more than two of the following antibiotics prior to contracting the infection: mezlocillin, piperacillin, tazobactam, ceftazidime, sulbactam/cefoperazone, tienam, meropenem, vancomycin, teicoplanin, and metronidazole. Invasive treatments were also used, namely, endotracheal

intubation, mechanical ventilation, thoracic closed drainage, and peripherally inserted central catheter (PICC). All preterm infants received parenteral nutrition. Further palliative treatment was provided as necessary on the basis of symptoms. The clinical characteristics of the four patients are summarized in Table 1.

Table 1. Clinical characteristics of the patients.

Clinical characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Gestational age	29 weeks	32 weeks	32 weeks	32 weeks
Birth weight	1190 g	880 g	1280 g	1100 g
Age of onset	28 days	23 days	22 days	14 days
Underlying diseases	RDS, prematurity, VLBL intrauterine infection, pneumonia	RDS, prematurity, ELBW, intrauterine infection pneumonia	Prematurity, PDA, apnea, VLBW	Neonatal asphyxia, eonatal pneumonia, VBLW
PICC	Yes	Yes	Yes	Yes
Mechanical ventilation	Yes	Yes	Yes	Yes
Bladder catheter	Yes	No	No	No
Parenteral nutrition	Yes	Yes	Yes	Yes
No. of blood cultures (culture site)	2 peripheral veins	2 peripheral veins	2 peripheral veins	2 peripheral veins
Catheter removal	Yes	Yes	Yes	Yes
Catheter-related candidemia	Yes	Yes	Yes	Yes
Antifungal therapy	Fluconazole	Fluconazole	Fluconazole	Fluconazole
Course of antifungal therapy (days)	19	17	20	21
Candidemia	Cleared	Cleared	Cleared	Cleared
Outcome	Recovery	Recovery	Recovery	Recovery

A blood sample was immediately taken using the central venous catheter when patients began to show three of these four symptoms simultaneously: 1) intolerance to feeding, 2) apnea, 3) hyperthermia, or 4) dyspnea. This sample was used to measure routine blood parameters, as well as to prepare a blood culture. In addition, antifungal therapy was begun (fluconazole: 6 $mg \cdot kg^{-1} \cdot day^{-1}$) on the basis of the original symptoms, before the blood culture results were known. The NICU was insulated and ventilated, and disinfected every day. What is more, samples were taken and cultures prepared from a broad variety of potential fomites and other possible sources of infection within the environment of the ward, namely, floors, disinfectant solutions, multi-dose vials, infusion pumps, commercially prepared parenteral nutrition bags, the inner wall of the infant incubator, other medical equipment, and the hands of healthcare workers. Finally, compliance with standard infection control measures, including rigorous hand-washing, was emphasized.

Strains

All of the *C. parapsilosis* strains were isolated from the blood cultures of the four infected preterm infants. In all cases, two consistently positive blood culture results were obtained using blood samples collected at the same time from two different parts of the body.

Fungal culture and antifungal susceptibility testing

Fungal cultures were prepared using Sabouraud culture medium and CHROMagar™ chromogenic culture medium (Guangzhou Detgerm Microbiology Technology Co., Ltd., China). API20CAUX yeast identification strips and ATBFUNGUS3 antifungal drug susceptibility tests were obtained from bioMérieux Ltd., France.

RESULTS

Etiology training results

Cultures prepared from eight blood samples obtained from the four infected preterm infants all showed identical phenotypic characteristics and were identified as *C. parapsilosis*. The quality of *C. parapsilosis* identification, performed using the ID 32C, was acceptable in all strains. Yeasts were identified morphologically as *C. parapsilosis* on corn meal agar plates. All isolates were susceptible to amphotericin B (MIC, 0.125 µg/mL), fluconazole (MIC, 0.125 µg/mL), voriconazole (MIC, 0.250 µg/mL), and caspofungin (MIC, 0.062 µg/mL).

Microorganism culture results of samples taken from the NICU environment

Gram-positive cocci were found in disinfectant solutions, multi-dose vials, and commercially prepared parenteral nutrition bags, as well as on floors, infusion pumps and other medical equipment, and the hands of healthcare workers. All microorganisms identified using these cultures were conditional pathogenic bacteria; no definitive source of the fungal strains could be found.

General condition of the four infected preterm infants

All the infants had concomitant diseases, such as neonatal respiratory distress syndrome (RDS), neonatal pneumonia, and patent ductus arteriosus (PDA). Feeding intolerance, apnea, hyperthermia, dyspnea, and low responsiveness were the common clinical signs. Laboratory blood examinations revealed two cases in which both platelet (PLT) and white blood cell (WBC) count were markedly lower than the expected value. Moreover, immature to total neutrophil (I/T) ratio was extremely high in four cases; while in three cases, C-reactive protein (CRP) level was high. The results of these laboratory blood examinations are summarized in Table 2.

Table 2. Laboratory blood examinations of all patients.

Laboratory examination	Patient 1	Patient 2	Patient 3	Patient 4
WBC ($x10^9$/L)	5.03	1.0	2.86	37.86
RBC ($x10^{12}$/L)	4.53	3.05	3.64	3.89
HB (g/L)	145	104	114	148
Coenocytes (%)	62	29	33.9	65.3
PLT ($x10^9$/L)	9	44	112	188
I/T (ratio)	4.4	1.2	1.8	3.8
CRP (mg/L)	13.57	0.61	40.29	12.04

Outcome

All the four preterm infants were isolated and received antifungal treatment; specifically, fluconazole was administered for 17-21 days as required. Supportive treatment, such as intravenous immunoglobulin and plasma, was also provided. Blood culture became negative after 7-14 days of antifungal treatment. All four preterm infants recovered from the infection; there were no deaths.

DISCUSSION

Neonatal invasive candidiasis is associated with significant morbidity and mortality. The prevalence of *C. parapsilosis* fungemia has increased over the years, and now, in some areas, it is the second most common species found in candidemia patients (Clark et al., 2004). The reasons for the rising incidence of *C. parapsilosis* candidemia are not completely known. Numerous outbreaks of systemic candidiasis in hospitalized patients have been reported (Zaoutis et al., 2005; Barberino et al., 2006). *Candida* spp were found to be responsible for outbreaks associated with parenteral nutrition, invasive devices, and intraoperative contamination. Additionally, the fungus is known to cause cross-infection via the hands of hospital personnel, or extrinsic contamination of parenteral nutrition solutions that occurs during preparation or administration (Bakir et al., 2006; Falagas et al., 2006; Warren et al., 2006). *C. parapsilosis* is increasingly being recognized as an important cause of invasive candidiasis in hospital patients, and in some centers, the species has overtaken *C. albicans* as the leading pathogen in invasive disease (Trofa et al., 2008; van Asbeck et al., 2009).

C. parapsilosis is not an obligate human pathogen, having been isolated from non-human sources such as domestic animals and insects, as well as from soil and marine environments. *C. parapsilosis* is also a normal human commensal; indeed, it is one of the fungi most frequently isolated from the subungual space of human hands. Furthermore, its transient colonization of the human integument is the basis of much debate as to whether *C. parapsilosis* is a pathogen at all in certain infections, as opposed to simply a “bystander” - an organism present, but uninvolved in the disease state.

C. parapsilosis in particular has been noted to colonize neonates later than *C. albicans* by several weeks (Parm et al., 2011); this is consistent with observations that *C. parapsilosis* is a rare cause of neonatal early-onset sepsis. Moreover, in an American study involving 82 premature infants, four aged between 1 and 2 weeks were found to have *C. parapsilosis* colonies *in their stool* cultures. All four of these went on to develop *C. parapsilosis* candidemia (el-Mohandes et al., 1994). A study in India showed similar trends, adding the observation that central venous catheters were a risk factor for colonization. In the same study, *C. tropicalis* was the most common organism in blood cultures (Singhi et al., 2008). In our study, the median postnatal age at onset of infection was 21.75 days (range: 14-28 days); moreover, two cases were successfully treated using antibiotics within one week.

Virulence factors associated with *C. parapsilosis* include its ability to adhere to a wide array of biological and prosthetic surfaces, to form biofilms on implanted medical devices, to secrete hydrolytic enzymes capable of causing significant tissue damage, and to proliferate rapidly in high concentrations of glucose. Colonization of the skin or gastrointestinal tract is a frequent first step in the pathogenesis of invasive candidal disease. Moreover, most experimental studies have indicated that the adherence of *C. parapsilosis* to acrylic surfaces is greater than that of *C. Albicans* (Ergon and Yucesoy, 2005). Nevertheless, repeated observations have shown that *C. parapsilosis* candidemia can occur in the absence of prior detectable colonization and/or symptomatic infection in other body sites of the same infant. In such cases, transmission usually occurs horizontally via contamination of exogenous articles such as medical facilities or liquids, the hands of health care personnel, prosthetic devices, or catheters (Trofa et al., 2008). The general view, based on observation, is that *C. parapsilosis* outbreaks in NICUs are mainly caused by the deliberate disruption of the skin for administration of invasive therapies, or by the use of monitoring equipment (Lupetti et al., 2002).

In *C. parapsilosis*, two lipase genes, *CpLIP1* and *CpLIP2*, have been identified, although only CpLIP2 codes for an active protein (Neugnot et al., 2002; Brunel et al., 2004). On a related note, lipase inhibitors significantly reduce tissue damage during *C. parapsilosis* infection of reconstituted human tissues (Gácser et al., 2007b). In previous study, the biofilm formation was inhibited with

lipase-negative of *C. parapsilosis* by using lipase inhibitors and their growth was significantly reduced in lipid-rich media. The lipase-negative *C. parapsilosis* were more efficiently ingested and killed by macrophage-like cells, while less virulent in infections models that involve inoculation of reconstituted human oral epithelium or a murine intraperitoneal challenge (Gácser et al., 2007a). Interestingly, *C. parapsilosis* infections frequently occur in patients, often LBW neonates, receiving lipid-rich total parenteral nutrition.

Further reasons VLBW infants are at risk of invasive infection are their immature protective layer of skin, their need for invasive medical devices, and defects in their cellular and humoral responses (Kaufman and Fairchild, 2004).

Another area of interest has been the source of *Candida* spp colonization. The reason for this is the importance of ascertaining the source in cases of invasive infection. On this note, multiple studies have demonstrated horizontal transmission from environmental sources in outbreak settings, with hands of healthcare workers commonly being implicated (van Asbeck et al., 2007; Hernández-Castro R et al., 2010). *C. parapsilosis* is increasingly responsible for hospital outbreaks, and the hands of healthcare workers can be the predominant environmental source, as they have been documented as being a reservoir of *Candida* spp. For this reason, exogenous infection or cross-infection of patients as a result of contact with hospital personnel may be common (Huang et al., 1998; Bonassoli et al., 2005). Additionally, total parenteral nutrition solutions may also promote *C. parapsilosis* adhesion and growth. For instance, biofilm-forming potential was recently cited as a reason that patients with *C. parapsilosis*-infected catheters should have the device removed (Barchiesi et al., 2004). We performed extensive sampling from potential fomites and other possible sources of infection within the ward; namely floors, disinfectant solutions, multi-dose vials, infusion pumps, commercially prepared parenteral nutrition bags, the inner wall of infant incubators and other medical equipment, and the hands of healthcare workers. No definitive source of the fungal strains could be found.

A French study suggested that delaying total enteral nutrition is associated with *C. parapsilosis* colonization. Other suspected risk factors, including number of central venous catheters and the duration of their use, as well as the treatment periods of both antibiotics and mechanical ventilation, were not significantly associated with invasive infection in the same study. Although admittedly, these results may have been influenced by the relatively low number of patients (Gagneur et al., 2001).

Risk factors for candidemia were already identified including vascular catheterization (97%), prior antibiotic therapy (91%), parenteral nutrition (54%), prior surgery (46%), prior immunosuppressive therapy (38%), malignancy (27%), transplant receipt (16%), neutropenia (12%), and prior colonization (11%; Almirante et al., 2006). Of the four infected premature infants we investigated, all had been treated with more than two of the following antibiotics prior to contracting the infection: mezlocillin, piperacillin, tazobactam, ceftazidime, sulbactam-cefoperazone, tienam, meropenem, vancomycin, teicoplanin, and metronidazole. Furthermore, invasive methods that had been used to treat the patients comprised endotracheal intubation, mechanical ventilation, thoracic closed drainage, and PICC; all of them had also received parenteral nutrition. It follows that appropriately limited use of antibiotics, reducing invasive techniques, ensuring aseptic principles such as strict hand hygiene, and moving to enteral feeding earlier to reduce the duration of parenteral nutrition are effective measures that reduce the fungal infection.

It was at times difficult to define *C. parapsilosis* infections according to their clinical manifestations, because the infants often had overlapping respiratory, intracranial, gastrointestinal, and infectious illnesses. All four of the infected premature infants, for example, had concomitant

diseases such as neonatal RDS, neonatal pneumonia, and PDA. Feeding intolerance, apnea, hyperthermia, dyspnea, and low responsiveness were common clinical signs. What is more, laboratory blood examinations revealed two cases in which both platelet (PLT) and white blood cell (WBC) count were markedly lower than the expected value. Moreover, the I/T ratio was extremely high in four cases. Newman et al. (2014) found that routinely calculating the I/T may improve predictions of early-onset sepsis.

Despite the availability of antifungal agents, the mortality rate attributable to neonatal candidemia ranges from 10 to 25% (Benjamin et al., 2006; Pappas et al., 2009). In addition, neonates with candidemia have prolonged hospital stays and increased associated costs. For example, Saiman et al. (2000) found that preterm infants with NICU stayed at hospital for seven days or more, whose might suffer from fungemia sepsis, but there was no statistically significant difference between those stayed for 7 days and more than 21 days. However, there is currently no consensus as to how diseases involving invasive *C. parapsilosis* should be treated, although the therapeutic approach typically includes the extraction of any removable foreign bodies and the administration of a systemic antifungal. Historically, amphotericin B has been the most frequently used antifungal. One disadvantage of such treatment is that the drug does have its associated complications - particularly nephrotoxicity - sometimes necessitating a reduction in dosage (Walsh, 2002) or termination of therapy (Moudgal et al., 2005). Fluconazole is the most frequently administered alternative to amphotericin B, and it holds several potential therapeutic advantages over the latter. For example, fluconazole has an excellent safety profile and is effective at treating >90% of *Candida* isolates that have caused invasive candidiasis in premature infants (Kaufman, 2004). A study involving 384 infants found targeted short-course fluconazole prophylaxis for VLBW and ELBW neonates to be both efficacious and cost-effective (Uko et al., 2006). Piper et al. (2011) subsequently found that a loading dose of fluconazole (25 mg/kg) was safe in this small cohort of young infants, and that it achieved the therapeutic target more rapidly than traditional dosing. In three of our four cases, when the preterm infants presented clinical signs of infection, we administered fluconazole immediately (6 $mg \cdot kg^{-1} \cdot day^{-1}$), and increased the dosage to 12 $mg \cdot kg^{-1} \cdot day^{-1}$ after *C. parapsilosis* was identified using blood culture.

Outbreaks of *C. parapsilosis*, mostly involving preterm infants of very low birth weight (VBLW) or extremely low birth weight (ELBW), can and do occur in NICUs. Cultures prepared using multiple samples taken from different patients contribute to a more definitive diagnosis. Established measures that control and prevent the infection, as well as effective and comprehensive treatments, can lead to a favorable outcome. That is to say, improving both disinfection and isolation, as well as interrupting the pathway of transmission, is the key to controlling the spread of infection.

Conflicts of interest

The authors declare no conflict of interest

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REFERENCES

Almirante B, Rodríguez D, Cuenca-Estrella M, Almela M, et al. (2006). Epidemiology, risk factors, and prognosis of *Candida parapsilosis* bloodstream infections: case-control population-based surveillance study of patients in Barcelona, Spain, from 2002 to 2003. *J. Clin. Microbiol*. 44: 1681-1685.

Aydin F, Bayramoglu G, Guler NC, Kaklikkaya N, et al. (2011). Bloodstream yeast infections in a university hospital in Northeast Turkey: a 4-year survey. *Med. Mycol.* 49: 316-319.

Bakir M, Cerikcioglu N, Barton R and Yagci A (2006). Epidemiology of candidemia in a Turkish tertiary care hospital. *APMIS* 111: 601-610.

Barberino MG, Silva N, Rebouças C, Barreiro K, et al. (2006). Evaluation of blood stream infections by Candida in three tertiary hospitals in Salvador, Brazil: a case-control study. *Brazil. J. Infect. Dis.* 10: 36-40.

Barchiesi F, Caggiano G, Falconi Di Francesco L, et al. (2004). Outbreak of fungemia due to *Candida parapsilosis* in a pediatric oncology unit. *Diagn. Microbiol. Infect. Dis.* 49: 269-271.

Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, et al. (2006). Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* 117: 84-92.

Bonassoli LA, Bertoli M and Svidzinski TIE (2005). High frequency of *Candida parapsilosis* on the hands of healthy hosts. *J. Hosp. Infect.* 59: 159-162.

Brunel L, Neugnot V, Landucci H, Boze G, et al. (2004). High-level expression of *Candida parapsilosis* lipase/acyltransferase in Pichia pastoris. *J. Biotechnol.* 111: 41-50.

Clark TA, Slavinski SA, Morgan J, Loft T, et al. (2004). Epidemiologic and molecular characterization of an outbreak of *Candida parapsilosis* bloodstream infections in a community hospital. *J. Clin. Microbiol.* 42: 4468-4472.

El-Mohandes AE, Johnson-Robbins L, Keiser JF, Simmens SJ, et al. (1994). Incidence of *Candida parapsilosis* colonization in an intensive care nursery population and its association with invasive fungal disease. *Pediatr. Infect. Dis. J.* 13: 520-524.

Ergon MC and Yucesoy M (2005). Molecular epidemiology of *Candida* species isolated from urine at an intensive care unit. *Mycoses* 48: 126-131.

Falagas ME, Apostolou KE and Pappas VD (2006). Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. *Eur J. Clin. Microbiol. Infect. Dis.* 25: 419-425.

Gácser A, Schäfer W, Nosanchuk JS, Salomon S, et al. (2007a). Virulence of *Candida parapsilosis, Candida orthopsilosis*, and *Candida metapsilosis* in reconstituted human tissue models. *Fungal. Genet. Biol.* 44: 1336-1341.

Gácser A, Trofa D, Schäfer W and Nosanchuk JD (2007b). Targeted gene deletion in *Candida parapsilosis* demonstrates the role of secreted lipase in virulence. *J. Clin. Investig.* 117: 3049-3058.

Gagneur A, Sizun J, Vernotte E, de Parscau L, et al. (2001). Low rate of *Candida parapsilosis*-related colonization and infection in hospitalized preterm infants: a one-year prospective study. *J. Hosp. Infect*. 48: 193-197.

Hernández-Castro R, Arroyo-Escalante S, Carrillo-Casas EM, et al. (2010). Outbreak of *Candida parapsilosis* in a neonatal intensive care unit: a health care workers source. *Eur. J. Pediatr.* 169: 783-787.

Hinrichsen SL, Falcão E, Vilella TA, Colombo AL, et al. (2008). Candidemia in a tertiary hospital in northeastern Brazil. *Rev. Soc. Bras. Med. Trop.* 41: 394-398.

Huang Lin TY, Leu HS, Wu JL, et al. (1998). Yeast carriage on hands of hospital personnel working in intensive care units. *J. Hosp. Infect.* 39: 47-51.

Kaufman D and Fairchild KD (2004). Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. *Clin. Microbiol. Rev.* 17: 638-680.

Kuzucu C, Durmaz R, Otlu B, Aktas A, et al. (2008). Species distribution, antifungal susceptibility and clonal relatedness of Candida isolates from patients in neonatal and pediatric intensive care units at a medical center in Turkey. *New. Microbiol.* 31: 401-408.

Lupetti A, Tavanti A, Davini P, Ghelardi E, et al. (2002). Horizontal transmission of *Candida parapsilosis* candidemia in a neonatal intensive care unit. *J. Clin. Microbiol.* 40: 2363-2369.

Moudgal V, Little T, Boikov D and Vazquez JA (2005). Multiechinocandin- and multiazole-resistant *Candida parapsilosis* isolates serially obtained during therapy for prosthetic valve endocarditis. *Antimicrob. Agents Chemother*. 49: 767-769.

Neugnot V, Moulin G, Dubreucq E and Bigey F (2002). The lipase/acyltransferase from *Candida parapsilosis*: molecular cloning and characterization of purified recombinant enzymes. *Eur. J. Biochem*. 269: 1734-1745.

Newman TB, Draper D, Puopolo KM, Wi S, et al. (2014). Combining immature and total neutrophil counts to predict early onset sepsis in term and late preterm newborns: use of the I/T2. *Pediatr. Infect. Dis. J.* 33: 798-802.

Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, et al. (2009). Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin. Infect. Dis*. 48: 503-535.

Parm U, Metsvaht T, Sepp E, Ilmoja ML, et al. (2011). Risk factors associated with gut and nasopharyngeal colonization by

common Gram-negative species and yeasts in neonatal intensive care units patients. *Early Hum. Dev*. 87: 391-399.

Pfaller MA, Castanheira M, Messer SA, Moet GJ, et al. (2010). Variation in Candida spp. distribution and antifungal resistance rates among bloodstream infection isolates by patient age: report from the SENTRY Antimicrobial Surveillance Program (2008-2009). *Diagn. Microbiol. Infect. Dis.* 68: 278-283.

Piper L, Smith PB, Hornik CP, Cheifetz IM, et al. (2011). Fluconazole loading dose pharmacokinetics and safety in infants. *Pediatr. Infect. Dis. J.* 30: 375-378.

Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, et al. (2000). Risk factors for candidemia in neonatal intensive care unit patients. The National Epidemiology of Mycosis Survey study group. *Pediatr. Infect. Dis. J.* 19: 319-324.

Singhi S, Rao DS, and Chakrabarti A (2008). *Candida* colonization and candidemia in a pediatric intensive care unit. *Pediatr. Crit. Care. Med*. 9: 91-95.

Trofa D, Gácser A, and Nosanchuk JD (2008). *Candida parapsilosis*, an emerging fungal pathogen. *Clin. Microbiol. Rev*. 21: 606-625.

Uko S, Soghier LM, Vega M, Marsh J, et al. (2006). Targeted short-term fluconazole prophylaxis among very low birth weight and extremely low birth weight infants. *Pediatrics* 117: 1243-1252.

van Asbeck EC, Huang YC, Markham AN, Clemons KV, et al. (2007). *Candida parapsilosis* fungemia in neonates: genotyping results suggest healthcare workers hands as source, and review of published studies. *Mycopathologia* 164: 287-293.

van Asbeck EC, Clemons KV and Stevens DA (2009). *Candida parapsilosis*: a review of its epidemiology, pathogenesis, clinical aspects, typing and antimicrobial susceptibility. *Crit. Rev. Microbiol*. 35: 283-309.

Walsh TJ (2002). Echinocandins - an advance in the primary treatment of invasive candidiasis. *N. Engl. J. Med*. 347: 2070-2072.

Warren DK, Quadir WW, Hollenbeak CS, Elward AM, et al. (2006). Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit. Care Med.* 34: 2243-2244.

Zaoutis TE, Argon J, Chu J, Berlin JA, et al. (2005). The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. *Clin. Infect. Dis.* 41: 1232-1239.