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REVIEW

Invasive Candida infections in the nursery: state of the art

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ABSTRACT

Neonatal sepsis caused by fungi (mainly Candida spp.) causes a huge burden of morbidity and mortality, poor late outcomes, as well as increased hospital costs.

Invasive Candida Infections (ICI) include bloodstream, urine, cerebrospinal, peritoneal infections, infections starting from burns and wounds, or from any other usually sterile site.

Premature neonates are particularly prone to this kind of disease, due to their decreased innate and adaptive immunities, translating into a specific, decreased resistance to candidiasis.

This specific, increased risk for ICI is greatest when gestational age and birth weight are lowest. As the burden of ICI has been increasing over the last years, research efforts have been focused towards identifying key risk factors, effective preventative strategies, and efficacious and well-tolerated antifungal drugs for the neonatal population.

This article summarizes the most remarkable issues in these areas, and features an overview of the current diagnostic, preventative and treatment strategies.

Key words: Candida, neonate, infection, preterm, micafungin, fluconazole

Introduction
The background on neonatal invasive Candida infections

The progress in neonatal care has led to an ever-increasing number of preterm neonates surviving to the most extreme degrees of prematurity, thus in need of aggressive care in neonatal intensive care units (NICUs). (1)

These neonates are affected by a number of innate immunity impairments occurring in the early phases of their extrauterine life, therefore during their stay in the NICU.

Both prematurity and immunity defects determine an enhanced specific risk for development of fungal colonization and systemic infections that are typical for all preterms, being greatest when gestational age and birth weight are lowest.

Overall, most preterm neonates in NICU may feature a number of specific risk factors for fungal colonization and infection.

An impaired activity of the gastric acid barrier, often enhanced by the use of H_2-blockers, decreases the ability of the stomach to stop the passage of pathogens from the upper digestive tract to the gut.

Lack of fresh maternal milk, a frequent occurrence in preterm neonates fed by parenteral nutrition since they have poor ability to tolerate oral feeds, deprives

the infants of important bioactive factors that can provide consistent anti-infective actions. The immaturity of the gut, often associated with an increased permeability of the gut wall, decreases the ability of the infant to defend itself against pathogens at the intestinal level, and –as a result- many of these pathogens may translocate from the gut lumen to the bloodstream.

In addition, loss or paucity of gut commensals such as Bifidobacteria and Lactobacilli, as occurs with prolonged antibiotic treatment, delayed enteral feeding, or nursing in incubators, translates into proliferation of pathogenic microflora and abnormal gut colonization, thus enhancing breakthrough colonization in the gut by many pathogens, including *Candida spp*. (2)

It has been said that invasive Candida infections (ICI) in preterm neonates follow the "90% rule": more than 90% of neonatal ICIs are caused by *Candida spp.* (with only scattered cases attributable to *Aspergillus spp.*), more than 90% occur in premature neonates rather than term, and more than 90% are acquired in the NICU, with only a minority of them originating from vertical transmission. (3)

ICI are severe, and ICI-related mortality is still unacceptably high (up to 30%, compared with some 77% for invasive fungal infections caused by Aspergillus spp.). (4)

Contrary to other high-risk patients, in preterm neonates the risk condition for fungal and Candida infections is destined to vanish as days of stay in the NICU go by.

Availability of mother's fresh milk, and ability of the neonate to tolerate it as he gets older, is critical since maternal fresh milk provides innate defenses that may be helpful to overcome the risky time-window. Moreover, the achievement of the ability of tolerating the withdrawal of central vascular catheters (CVC) removes from these patients the risk of hub colonization, and hence the formation of septic thrombi and biofilms that may be reservoires for systemic spread even after the risky time-window is over.

Of note, suboptimal perinatal bacterial colonization is probably the most important risk factor for Candida invasive infections in preterm neonates. (5-7)

Invasive microorganisms including fungi may be encouraged by the use of antibiotics in the mother before birth and the use of broad spectrum antibiotics in neonates. Sometimes fungal colonization in preterms occurs due to vertical transmission from the mother but, (8) most frequently horizontal transmission occurs within the NICU. (1) This latter modality could particularly explain the great differences in the incidence of fungal infection between European NICUs as there is great variability in terms of antibiotic prescription and overall nursing management.

As for diagnosis, blood culture is the gold standard but might not be fully reliable in these particular patients and settings, as its sensitivity is poor, thus translating into frequent negative results that might not correctly represent the true diagnostic picture. Limited sensitivity of blood cultures in neonates depends on inadequate blood volumes collected, transient candidaemic phases, or frequent shedding of the fungal colonies in the biofilms rather than in the bloodstream.

In neonatal ICI, systemic dissemination may occur in every organ, and the risk of central nervous system involvement is higher given the high neonatal permeability of the haemato-encephalic barrier.

Neurodevelopmental sequels are severe and frequent, as they may occur even when the ICI has been properly treated. Poor late outcome is typically associated with *Candida spp.* infections rather than with infections caused by other pathogens. (7)

In view of the above considerations, the best option for decreasing the burden of the disease is to avoid it with specific prophylaxis.

Prevention- current strategies

As mentioned above, prompt diagnosis and effective treatment do not protect preterm neonates in the intensive care unit (ICU) from the risk of late neurodevelopmental impairment in the survivors, (7) thus prevention of Candida infection is the key in these setting of unique patients.

In view of this, improving neonatal management is a key step, and this includes promotion of fresh, human milk feeding, implementation of hygiene measures, cautious CVC management, enhancement of the enteric microbiota composition with the use of specific strains of probiotics, and medical stewardship concerning H_2-blockers and steroid restrictions.

Substantial results in decreasing the rates of ICI have been achieved with the use of fluconazole. This azole may be administered either intravenously or orally, and proved effective in reducing the rates of colonization and infection by 80% in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants. (6) In the literature, more than 2,500 preterm VLBW infants receiving fluconazole have been studied, and no serious adverse effects have been described, thus vouching for substantial safety of this strategy. Adoption of widespread use of prophylactic fluconazol, or at least in the NICUs with highest rates of ICI, would translate into a considerable reduction of the burden of ICI, of the ICI-related hospitalization costs, and (most of all) could deliver increased and better health to thousands of premature infants every year. (6)

A new approach towards reduction of sepsis and necrotizing enterocolitis (NEC) might involve the use of bioactive substances with known anti-infective properties. Lactoferrin is a mammalian milk glycoprotein involved in innate immune host defences, and can reduce the incidence of late-onset sepsis in VLBW infants (9) and of NEC in animal models. The bovine isoform is nearly homologous to the human one. Lactoferrin targets all pathogens, has bifidogenic properties, and enhance maturation of the nascent gut.

In a recent randomized controlled trial, bovine lactoferrin produced a 65% decrease in any-cause Late-Onset Sep-

sis (LOS), and a significant decrease in both surgical and low-stages NEC. (10)

As no adverse effects or intolerances to treatment have been reported to date, the role of lactoferrin in the management of infections and NEC in NICU looks very promising and worthy of future, larger-sized trials to confirm these findings.

Treatment - Current strategies

When prevention has not been performed, or when the goal of prevention has been not achieved, and the preterm neonates faces an ICI, the optimal rescue strategy would be to perform treatment with the most potent antifungal available, in order to minimize the risk of septic foci escaping treatment and disseminating subsequently to organs or cause neurodevelopmental impairments.

It has been said that the best strategy is *"hit fast, hit hard"*, because of the risks inherent to persistence of circulating fungal colonies in the bloodstream, or that fungal septic foci could remain shed in organs or within the biofilms – a risk that absolutely needs to be avoided.

Promptness is the keyword for the treatment of preterm neonatal ICI, and the most correct approach is immediate treatment with documented infection. From retrospective data, this approach has been demonstrated in several studies to improve outcomes.

When detecting candidemia, early removal of a CVC is mandatory since the catheter tip might be colonized and biofilm formation could have occurred. Since fungal colonies nested in biofilms can prevent clearance of infection, the common recommendation is for removal until clearance of candidemia for >3 days documented by daily cultures. At that time reinsertion of a CVC may be considered. It is also important to remember that delayed central catheter removal with candidaemia is associated with worse outcomes and increased mortality. (11)

Of course, maintenance of a CVC is often critical in premature infants, but it is rare that the CVC cannot be removed if needed. If the "loss" of central venous access may indeed result in problems for a critical neonate in whom it may prove impossible to install another CVC, then the usual advice is to quickly remove it and to replace it with another (in another site), provided that at least two bolus-doses of a systemic antifungal have been administered in the meanwhile.

When a positive result from blood cultures is not available, decision on whether to institute or not a specific antifungal treatment should be based on a comprehensive assessment of the clinical picture, of the laboratory markers, and of the ecological pre-existing situation. (12)

The use of fungal colonization information may often aid in decision making regarding empirical therapy. Empirical therapy for 48-72 hours while awaiting culture results in symptomatic high risk patients is often used to deliver early, appropriate therapy to these vulnerable hosts. (13)

Some indentified risk factors that can be combined with clinical symptoms of infection include: <27 weeks gestation, exposure to 3rd or 4th generation cephalosporin or carbapenems in the previous 7 days, new onset thrombocytopenia, and/or with symptoms of sepsis despite 48 hours of antibacterial treatment. While empiric therapy is often advocated, little data is available and it has not been subjected to rigorous controlled trials.

Mention has already been made of the non-total reliability of blood cultures and the fact that as many as 72 hr may be needed to secure the growth of Candida. A delay of this kind is obviously unacceptable in the management of the patients. (14)

Prompt, empirical treatment is imperative for non-immunocompetent subjects such as preterm neonates, since Candida-associated mortality is as high as 38% and rises to 50% in those who start antifungal therapy more than two days after the first positive blood culture. (15)

It is useful to underline once more that –either in the case of targeted treatment or of empirical treatment - the preferable antifungal drugs must have significant activity against biofilms, as well as activity against *C. glabrata*, *C. tropicalis* and *C. krusei*, i.e. the species that may survive prophylactic fluconazole

Historically, the first options in the treatment of neonatal ICI have been –and currently are- fluconazole and amphotericin B. Indeed, their use in neonates is hampered by lack of sufficient pharmacokinetic data (PK) which gives rise to a risk of inappropriate response to treatment. Moreover, these two drugs carry limitations both in efficacy and in putative toxicity.

Fluconazole is poorly active against some *Candida spp.* strains that are quite frequently retrieved from neonates (e.g., *C. glabrata* and *C. krusei*). In addition, it is not reasonable to use such an azole for treatment in all cases in which it has already been used for prophylaxis: if prophylactic fluconazole failed, it is highly unlikely that therapeutic fluconazole can work. Or –at the very least – it is not appropriate to run this risk, since a "wait-and-see" approach is not correct in such a severe disease. (16)

On the other hand, amphotericin B would be a reasonable first-choice option as empirical treatment for a VLBW neonate with clinical deterioration and signs of sepsis who does not respond to the optimum antibiotic empirical treatment. (2)

However, in spite of some reassuring data, (17) amphotericin B has some renal and bone marrow toxicity that has never been subjected to well-designed, prospective safety trials in neonates.

Recently, new therapeutic alternatives have drawn the neonatologists' attention. The Echinocandins (Caspofungin, Micafungin, Anidulafungin) are a new class of antifungal drugs with characteristics that might better meet the needs of this particular population of patients. These products are broad-spectrum antifungal agents that have been shown effective for treatment of invasive aspergillosis, oesophageal candidiasis and other invasive *Candida*

infections in adults, and (for Micafungin) in children including infants. (18) Moreover, their safety profile is reported as more favourable than conventional or liposomal amphotericin B, with less drug-related adverse events, less infusion-related events, and less nephrotoxicity. Recent new data confirmed this overall good safety profile for Micafungin. (19,20) Echinocandins have therefore become an attractive option for first-line treatment in all paediatric and neonatal patients affected by Candida and/or Aspergillus systemic infections, and – as a matter of fact - Micafungin is, as-of-today, the only antifungal drug authorized for neonatal use by the EMA – European medicines agency. (21)

Conclusion

Management and prevention of neonatal ICI is a challenge for every neonatologist.

Specific education and skills are required to properly address diagnostics, use of laboratory information, and choice of the correct antifungals, timing and duration of treatment.

Nonetheless, most ICI could be avoided if only prophylaxis with fluconazole could be instituted in every high-risk neonate, or neonatal setting.

Clearly, advocacy for such objectives needs to become inherent to the mission and to the ethical approach of all neonatologists and neonatal nurses.

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