EDITORIAL

The Confrontation of Fungal Sepsis in Neonates

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Present day neonatal care has enhanced survival of extremely low birth weight babies but augmented the requirement for multiple invasive modus operandi intensifying the curse of healthcare-associated infections. Escalation in incidence of fungal sepsis is one of the inevitable effects of such advancement. A favorable outcome in neonates with fungal septicemia depends on timely clinical suspicion and institution of appropriate antifungal therapy, identification of end organ damage, and close follow-up. It thus becomes imperative for neonatologists to recognize babies at highest risk for fungemia. The risk factors for acquiring fungal sepsis have been extensively studied. Mortality associated is distressingly high, and it is imperative to be acquainted with risk factors for poor outcome.

Candida has emerged to be one of the most common causes of neonatal fungemia, and accounts for up to 13% of such infections with most of the surveillance studies reporting a rising trend [1]. It ranks fourth in the United States and seventh in Europe among the causes of nosocomial blood stream infection [2,3]. *Candida albicans* is the third most common cause of neonatal late onset sepsis in infants whose birth weight is less than 1500 g, as demonstrated by a multicenter study from the National Institute of Child Health and Human Development Neonatal Research Network [4]. An illustration from the National Nosocomial Infection Surveillance points out that the occurrence of these hospital-acquired pathogens is greatest in extremely low birth weight infants (birth weight <1000g) [5].

Until recently, *C. albicans* was by far the predominant species in most countries, responsible for 60% of all cases of candidemia. However, recently several countries around the world have witnessed a change in the epidemiology of Candida infections, characterized by a progressive shift from a predominance of *C. albicans* to non-albicans Candida species notably *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. guilliermondii* and *C. glabrata*. Evidence suggests a role for increasing use of azole antifungals in this epidemiological shift. Some of these non-albicans Candida species (*e.g.*, *C. glabrata* and *C. krusei*) exhibit intrinsic resistance to traditional triazole agents like fluconazole, and may also demonstrate cross-resistance to newer triazoles [6]. This makes it imperative to perform both speciation and antifungal susceptibility testing of all yeasts from patients with invasive candidiasis. Due to considerable regional inconsistency, local epidemiological awareness is paramount in the successful management of such Candidia infections.

A comparatively newer species, *Candida auris*, is being increasingly reported from many Indian states since its first report from Japan in 2009. From India, *C. auris* was first reported from northern India. Since then, this has emerged as an important challenge in the management of patients due to its outbreak potential, multidrug resistance and associated high mortality. It is underreported because it is commonly misidentified in the routine diagnostic laboratories as *C. haemulonii* or *C. famata* by commercial identification systems. Sequencing of the Internal transcribed spacer (ITS) region and the D1/D2 region of the large subunit (28S) of the ribosomal DNA or even Matrix assisted laser desorption ionization – time of flight (MALDI-TOF) mass spectrometry can confirm the identity of this oval yeast, which does not form pseudohyphae/germ tube, and fails to grow in the presence of 0.01% or 0.1% cyclohexamide, but can grow at 42^0C, and ferment maltose [7]. Even identification of *C. haemulonii* is difficult as it is phenotypically very similar to *C. famata* and *C. guilliermondii* [8].

The research paper by Basu, *et al.* [9] published in this issue of *Indian Pediatrics* evaluates the local epidemiology of neonatal candidemia in and around city of Varanasi in India. As their study came across non-albicans Candida species in nearly double the number of *C. albicans* candidemia, the authors have very nicely estimated the predictors of such an outcome. Identification and prevention of such risk factors in

susceptible neonates can significantly improve outcome of neonates with fungal sepsis. The authors have been able to characterize phenotypically 82 out of 114 isolates of Candida to the species level. Although phenotypic or commercially available rapid detection systems may be useful for clinicians, they often lack reproducibility. MALDI-TOF biotyper is an exception, which, as well as DNA sequencing correctly identifies Candida up to the species level. Hence, molecular methods though expensive, but reproducible and reliable, should be adopted by tertiary care hospitals for monitoring and surveillance of important hospital-associated bugs.

Antifungal susceptibility is very essential for effective treatment and the authors have also done susceptibility testing of their Candida isolates by disc diffusion test. Minimum inhibitory concentration (MIC) determination as per Clinical and Laboratory Standards Institute (CLSI) M27-A3 guidelines may be more reliable in such circumstances as also increasing the number of antifungals to include newer azoles (like ravuconazole, posaconazole) and echinocandins, as often some isolates are multidrug resistant (resistant across two antifungal classes). For echinocandins, disk diffusion is not recommended by CLSI. As breakpoint MICs for some newer Candida species is still not defined by CLSI M_{27}-A3, breakpoint suggested for yeast in CLSI M_{27}-S4 can be used for such interpretations.

The knowledge of possible source of such fungimea is imperative for future preventive strategies. As most of the surveillance studies report a rising trend in neonatal candidemia over the years, the authors could possibly have done a trend analysis to evaluate any such inclination. This is equally essential for scrutinizing surveillance programs and policy formulation.

To conclude, candidemia in the neonates is a challenging condition not only for the clinicians but also for the microbiologists. Risk factor identification along with speciation and drug susceptibility testing is crucial for timely management of such neonates.

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