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Invasive fungal infections in the paediatric and neonatal population: diagnostics and management issues

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Abstract

Invasive fungal infections in children appear to have increased over the past few decades. Especially neonates and children with primary and secondary immunodeficiencies are at risk. *Candida* and *Aspergillus* spp. are the most commonly isolated organisms. In addition, *Malassezia* may cause systemic infections in newborns and zygomycosis is important because of its rising incidence and high case fatality rate. Timely diagnosis and initiation of appropriate antifungal therapy is imperative for improving outcomes. However, traditional techniques are time-consuming and representative sample material, using invasive procedures, may be difficult to obtain in the paediatric setting. This review provides an overview of the advances in detection and rapid species identification, with a focus on issues relevant in these settings. Subsequently, the current antifungal treatment options for neonates and children are discussed in light of the antifungal spectrum of the available agents and the specific pharmacokinetic properties in different age groups. Although a multitude of newer antifungal compounds have become available within the last decade, further studies are necessary to clearly establish the role for each of these agents among neonates and children.

Keywords: Antifungals, diagnostics, invasive fungal infections, treatment.

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Introduction

Invasive fungal infections in children appear to have increased over the past few decades primarily because there has been an increase in children with primary or secondary immune deficiencies. The growth in this population that is susceptible to fungal infections has been mutlifactorial, as a result of: an increase in neonates surviving preterm delivery, more intense chemotherapy regimens for the treatment of cancer, expanded indications for bone marrow and solid organ transplantation, and improved diagnostic and therapeutic modalities for identifying and treating primary immune deficiencies [1–4].

Among immunosuppressed children, the impact of an invasive fungal infection can be devastating, with a high rate of morbidity and mortality. Timely diagnosis and initiation of appropriate antifungal therapy is imperative for improving outcomes. Fortunately, there have been significant recent advances in the ability to more rapidly identify invasive fungal infections, accompanied by an evolution in the number of available antifungal agents for treatment. We briefly review the epidemiology of more commonly identified invasive fungal infections in children, comment on the important differences with respect to adults, discuss a number of diagnostic laboratory techniques, and summarize the currently available therapeutic options.

Epidemiology

A multitude of fungi have been identified in the setting of human infection [5]. A comprehensive discussion of each of these organisms is beyond the scope of this review. Instead, the focus will remain on *Candida* and *Aspergillus* spp. because they are the most commonly isolated organisms in paediatric invasive fungal infections. *Malassezia* infection and zygomycetes will also be discussed briefly because *Malassezia* may cause systemic infections in newborns and zygomycosis appears to be increasing and has a high case fatality rate.

TABLE 1. Diagnostic and identification tools for the different fungal genera (abbreviations used in the table are spelled out in the footnote)

Genus	M + C	Rapid ID	(1,3)-β-D-glucan	Ag	Ab	Metabolite detection	Comment
Candida	Budding Yeasts ± Pseudomycelium	*C. albicans*: Germ tube test, latex agglutination	Yes	Mannan Ag ELISA (serum)	Anti-mannan Ab ELISA (serum)	Arabinitol (urine, second alternative serum)	Invasive infections in the vast majority of cases are preceded by colonization. ID of the colonizing/invasive isolates may guide choice of pre-emptive/targeted AF treatment
	Pos Blood culture: PNA FISH (*C. albicans*/*C. parapsilosis*, *C. tropicalis*, *C. glabrata*/*C. krusei*	*C. dubliniensis*: germ tube test, latex agglutination					Mannan Ag without simultaneous Ab detection is indicated in neonates
	CHROMagar	*C. glabrata*: RTT *C. krusei*: latex agglutination					DA/DL not optimal for candidaemias caused by *C. krusei* and *C. glabrata*
Malassezia	Lipid dependent (except *M. pachydermatis*)	–	–	–	–	–	Recommended media: Sabouraud + cycloheximide overlaid with sterile olive oil
	Globose cells, round at one end broadly cut in the other						Dixon agar
	Mycelia formed during skin infection						CHROM-Malassezia agar [41]
Aspergillus	Septate hyphae, dichotomous branching	*A. fumigatus* grows at 45°C in contrast to most mould contaminants	Yes	Galactomannan Ag ELISA (serum, plasma, BAL)	Anti-*Aspergillus* Ab (immunediffusion)	–	Sensitivity of GM Ag highest in BAL and in neutropenic patients. False pos: *Bifidobacterium* colonization, *Histoplasma* or *P. marneffei* infection, certain beta lactam antibiotics. Ab relevant in established infections in non-immunocompromised patients
Zygomycetes	Aseptate broad (irregular) hyphae in tissue	ID32C (visual reading)	Not reliably	–	–	–	Broad aseptate hyphae are the characteristic feature. Carbon assimilation pattern using ID32C was recently demonstrated useful in species identification [121]
	Characteristic sporeheads in culture	–	–	–	–	–	

M + C, Microscopy and culture; ID, identification; Ag, Antigen; Ab, Antibody; PNA, peptide nucleotide analogue; FISH, fluorescence *in situ* hybridization; RTT, rapid trehalase test; CSF, cerebrospinal fluid; ELISA, Enzyme Linked Immuno Sorbent Assay; EIA, Enzyme Immuno Assay.