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Epidemiology of invasive fungal infections in neonates and children

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Abstract

Invasive fungal infections are major causes of morbidity and mortality in neonates and in both immunocompromised and immunocompetent children. Although these infections have been well characterized in adults, the incidence and analysis of risk factors, diagnostic tools, treatments and outcomes have not been well described for large cohorts of paediatric or neonatal patients. Paediatric exclusion has limited our knowledge of the epidemiology and pathophysiology of paediatric fungal disease, and has also resulted in a paucity of data regarding the safety and efficacy of paediatric antifungal therapy. Previous paediatric cooperative models in other disciplines have successfully advanced our understanding and treatments of childhood diseases, but in the past there has not been a similar organization for paediatric invasive fungal infections. Although there are numerous other reviews outlining the differences in paediatric antifungal dosing pharmacokinetics, there are only smaller epidemiological reports depicting the exact distribution and outcomes of paediatric invasive fungal infections treated with these antifungals. This review will highlight some of the available epidemiological data on paediatric invasive fungal infections.

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Introduction

Epidemiology is at the heart of medicine. Detailed epidemiology allows us to understand which patients will become sick and why, letting us determine who is at risk for developing disease and therefore better direct our diagnostic and therapeutic efforts as well as more accurately predict prognosis. Invasive fungal infections are major causes of morbidity and mortality in both the expanding immunocompromised and the immunocompetent patient populations [1]. As contemporary medicine advances the treatment of life-threatening conditions such as malignancies, organ transplantation, and autoimmune disorders, invasive fungal infections have become a major complication. *Candida* species constitute the fourth most common pathogen isolated in nosocomial bloodstream infections [2]. Cryptococcal meningitis caused by *Cryptococcus neoformans* and *Cryptococcus gattii* is the most common cause of fungal central nervous system infection in the world today, primarily producing disease in immunocompromised patients, but also causing disease in apparently normal hosts [3]. The incidence of invasive aspergillosis (IA) caused by *Aspergillus fumigatus* has increased three-fold in the last decade [4], and IA mortality has correspondingly risen by over 300% [5]. The Infectious Diseases Society of America listed *A. fumigatus* as one of only six infectious pathogens for which a substantive treatment breakthrough is urgently needed [6].

Effective treatments for invasive fungal infection-associated morbidity and mortality are often lacking. Treatment for invasive candidiasis and cryptococcal meningitis has an approximately 70% success rate, but generally only in the healthiest patients [7,8]. Current therapy for IA has a disappointing 40–50% treatment success rate [9,10]. The poor therapeutic outcomes of invasive fungal infections, coupled with expensive underlying endeavours such as transplantation and intensive-care unit management, mean that both the human and the financial costs of invasive fungal infections are exceedingly high. The burden of invasive fungal infections on the healthcare system is staggering, with conservative estimates of $2.6 billion annually in the USA alone [11]. In many major medical centres, antifungals currently comprise

the largest proportion of overall anti-infective expenditure [12].

This review will focus on some of the epidemiology of paediatric invasive fungal infections, information that we can use to guide current diagnosis as well as design future therapeutic trials in the field. The focus will be on the major invasive fungal infections, IA and invasive candidiasis in children and neonates. Although many aspects of risk factors and treatment algorithms learned over the last several decades from adult patients can be employed in children, there are some unique nuances in children that are outlined for the practising clinician.

Paediatric and Neonatal Epidemiological Factors

Autopsy data demonstrate that IA has surpassed invasive candidiasis as the most frequent invasive fungal infection in some tertiary medical centres [13–18]. The treatment success rate with IA remains approximately 50%, despite newer antifungals now being available [9]. Despite the increasing incidence and continued dismal outcomes, the majority of information on IA epidemiology, diagnosis, treatment and outcome has been obtained from studies conducted almost solely on adult patients. Each clinical trial for IA has purposefully excluded children, and some have enrolled a small number of patients older than 12 years. There have been several previous paediatric IA epidemiology reports, but most were only single-centre studies and conducted prior to the availability of many newer antifungals and diagnostic strategies. Similarly, although IA has been shown to be the most deadly of the frequently occurring invasive fungal infections [19], invasive candidiasis is generally known as the most common invasive fungal infection among immunocompromised patients. However, although there are have been great strides in understanding the high-risk groups and outcome data in adult patients with candidiasis, children have been neglected in large-scale analyses.

The largest multicentre, prospective analysis of paediatric IA included 139 contemporary cases from six US medical centres [20] in the setting of newer diagnostic and therapeutic tools. The mean age of patients was 9.9 years, and the majority of the patients had an underlying malignancy. An equal number of patients had underlying malignancy not treated with haematopoietic stem cell transplantation (HSCT) or an underlying disorder treated with HSCT. Most patients had numerous immunosuppressive risk factors in the 30 days prior to diagnosis of IA, including neutropenia (Absolute neutrophil count (ANC) <500/mm^3) for ≥3 days in 59% of the patients, and in approximately 30% of these the neutropenia lasted for ≥30 days (overall mean 18.9 days). Concomitant infections consisted of 124 episodes of bacterial, viral and other fungal infections among 65.5% of the patients, of which bacterial infections accounted for approximately half of all the concomitant infections.

A second paediatric IA study was a prospective, 5-year observational study in 346 paediatric cancer patients receiving intense chemotherapy for newly diagnosed or recurrent malignancy at the University Hospital of Frankfurt [21]. During the 5-year period, there were 13 cases of IA, and all cases occurred in patients with haematological malignancy; the highest rates were seen in patients with acute myelogenous leukaemia (AML) and relapsed acute lymphocytic leukaemia (ALL). This study only looked at patients with malignancies and found a higher predominance of IA in those patients with leukaemia than in those with solid tumours. Similarly, a recent single-centre review from France [22] found 24 cases from 1986 to 2000, and the greatest incidence of disease was in acute myeloblastic leukaemia (5.35%) and leukaemic relapse (4%), with survival being only 12.5%.

The largest analysis of high-risk immunocompromised paediatric patients with and without IA found staggering differences in mortality resulting from IA [23]. Among the common paediatric malignancies, overall mortality from AML (3%) and from ALL (1%) was quite low. However, when children with these malignancies also developed IA, their mortality escalated to 20% and 21%, respectively. This equated to relative risks of mortality of 5.0 in AML patients and 14.9 in ALL patients, altering paediatric malignancies with high cure rates to diseases with substantial mortality resulting from IA.

A 49-hospital paediatric study found that *Candida* species constituted the fourth most common cause of bloodstream infection (9%) in children less than 16 years old, following coagulase-negative *Staphylococcus* (43%), enterococci (9%), and *Staphylococcus aureus* (9%) [24]. The limited data available show that the *Candida* species infecting children appear to differ from those causing adult infections. For instance, whereas *Candida albicans* is the most frequently isolated *Candida* species in both adult and paediatric patients, *Candida parapsilosis* is clearly the second leading species in paediatric patients, whereas *Candida glabrata* follows in adult patients [25]. Another study showed similar results, indicating that the percentage of candidaemia caused by *C. parapsilosis* was higher among children <1 year of age (17%) than in all other age groups (6%). Additionally, the percentage caused by *C. glabrata* again steadily increased with age [26]. In addition to *Candida* infections in immunocompromised children, it is becoming increasingly more common to see immunocompetent children with candidaemia—resulting from either