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Complete List of Authors:	Pana, Zoi-Dorothea ; Johns Hopkins Hospital and Health System, Division of Infectious Diseases Roilides, Emmanuel; Aristotle University School of Medicine, Hippokration General Hospital, , 3rd Department of Paediatrics, Infectious Diseases Unit, Warris, Adilia; University of Aberdeen, MRC Centre for Medical Mycology; Royal Aberdeen Children's Hospital, Medical Pediatrics Groll, Andreas; University Children's Hospital, Pediatric Hematology/Oncology Zaoutis, Theoklis; The Children's Hospital of Philadelphia, Division of Infectious Diseases and the Center for Pediatric Clinical Effectiveness Research ; University of Pennsylvania, Perelman School of Medicine,, Center for Clinical Epidemiology and Biostatistics
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The Epidemiology of Invasive Fungal Disease in Children

Zoi Dorothea Pana; [1] Hospital Epidemiology and Infection Control Department (HEIC), Division of Infectious Diseases, The Johns Hopkins Hospital, Baltimore, USA. [2] 3rd Department of Paediatrics, Infectious Diseases Unit, Aristotle University School of Medicine, Hippokration General Hospital, Thessaloniki, Greece

Emmanuel Roilides; [2] 3rd Department of Paediatrics, Infectious Diseases Unit, Aristotle University School of Medicine, Hippokration General Hospital, Thessaloniki, Greece

Adilia Warris; [3]Aberdeen Fungal Group, MRC Centre for Medical Mycology, Institute of Medical Sciences and the Royal Aberdeen Children's Hospital, University of Aberdeen, UK

Andreas H. Groll; [4]Center for Bone Marrow Transplantation and Department of Paediatric Hematology and Oncology, Infectious Disease Research Program, University Children's Hospital, Muenster, Germany

Theoklis Zaoutis; [5]Division of Infectious Diseases and the Center for Pediatric Clinical Effectiveness Research The Children's Hospital of Philadelphia, Philadelphia, PA, USA; Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA

Contact information: Theoklis Zaoutis, Division of Infectious Diseases; The Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, USA; PA 19104; Phone: 2674265570; email: zaoutis@email.chop.edu

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Abstract

Considerable progress has been made in the prevention, diagnosis and management of pediatric patients with invasive fungal disease (IFD). The reported decreasing trend in the incidence of invasive candidiasis (IC) over the last 15 years in both neonates and children has been encouraging. Nevertheless, a growing population of immunocompromised hosts has increased the number of children at risk for IFD, which continues to be associated with significant morbidity and mortality as well as increased financial burden to the health care system. Therefore, it is important to understand the contemporary epidemiology of IFD. Incidence rates of IFD in children are impacted by geographical, population and time variability. There is an ongoing effort to constantly update the incidence and the species distribution causing IFD among different pediatric populations as a means to target preventative, diagnostic and therapeutic resources to the most appropriate subset of patients. Among children vulnerable to IFD, patients with hematologic malignancies, primary or secondary immunodeficiencies, patients undergoing solid organ or hematopoietic stem cell transplantation, and premature neonates are the major subsets of pediatric patients at risk of developing IFD. This review focuses on fungal disease epidemiology with specific emphasis on the two most common pediatric IFD, IC and invasive aspergillosis (IA).

Introduction

Invasive fungal disease (IFD) is a major cause of morbidity and mortality among immunocompromised and hospitalized pediatric patients [1,2]. There has been a significant increase in pediatric patients at risk of IFD, primarily due to increasing

utilization of immunosuppressive medications across many medical specialties. Simultaneously, there have been advances in the management of IFD via novel fungal diagnostic tests and evidenced-based utilization of antifungal agents for prophylaxis and treatment. Collectively, these factors have altered the epidemiology and outcomes of IFD over the last 15 years [3,4].

The spectrum of pediatric patients vulnerable to IFD is wide and includes children receiving chemotherapy for malignancies, recipients of hematopoietic stem cell (HCT) and solid organ (SOT) transplants, children with primary immunodeficiencies, children receiving immune modulating therapies for autoimmune conditions, and those with acquired immunodeficiency. Beyond these patient groups, neonates and children hospitalized in the intensive care unit, among other groups, are also at risk for IFD [5-10]. The wide range of pediatric populations at risk for IFD makes it challenging to maintain contemporary estimates of epidemiology to guide clinical decision-making.

Despite these challenges, a recent increased focus on IFD in the pediatric literature has provided clinicians with reasonable estimates of IFD in at risk populations. *Candida* spp. remain the leading cause of IFD among pediatric patients and are the fourth most common pathogen detected in hospital-acquired pediatric blood stream infections (BSIs) in the United States and Europe [2,11-13]. *Aspergillus* species and organisms from the Mucorales family remain the leading cause of invasive mold disease (IMD). [14,15].

This review summarizes the contemporary literature on the epidemiology of IFD in pediatric patients with malignancies, transplant recipients, children with primary immunodeficiency, and those managed in the pediatric (PICU) and neonatal

intensive care units (NICU). As previously noted, there are other sub-populations of children at risk for IFD, yet as data on IFD epidemiology in these populations are limited they are not included in this discussion. Future investigations are necessary to better define the risk of IFD in these other populations.

Overall IFD Epidemiology

Both candidemia and IA are associated with significant increases in hospital length of stay and an overall in-hospital mortality of 15.8% for pediatric candidemia and 18% for children with IA [12,13]. In an attempt to estimate the attributable financial burden of IFD to the health care system, a cost analysis study revealed that the increase of total hospital charges to treat IC for non-neonatal pediatric patients are $65,058 - $119,474 per episode [12]. Similarly, for children with invasive aspergillosis (IA) the median healthcare cost reached $49,309 per episode [13].

Globally, there are a number of pediatric multicenter studies that have documented the incidence of IC and IA (Table 1) [16-21], as well as the distribution of fungal pathogens in children (Tables 2 and 3). The largest international collaborative studies assessing the incidence of IC and IA in children were conducted by the International Pediatric Fungal Network (IPFN; www.ipfn.org) [14, 22]. A predominance of non-*albicans Candida* spp. in both pediatric (56%) and neonatal (52%) patients were found by the IPFN [22], with similar distribution of *C. albicans* and *C. parapsilosis* as reported in other pediatric studies in Latin America, USA and Europe [23-25]. In particular, a South American surveillance study found *C. albicans* (pediatric 43.8% and neonatal 35.7%) and *C. parapsilosis* (pediatric 27.0% and neonatal 26.3%) prevailed [23]. A higher incidence of *C. parapsilosis* infection both

in neonates (42%) and in pediatric patients (38%) was noticed in an Australian prospective candidemia study revealing a possible difference of geographic *Candida* niches [26]. A European multi-center study to define *Candida* spp. distribution among pediatric patients (EURO-CANDY study) is currently ongoing and led by the European Pediatric Mycology Network (EPMyN) [27].

Epidemiology of invasive mold disease (IMDs) in children revealed that *A. fumigatus* and *A. flavus* are the predominant mold isolated [14]. Beyond *Aspergillus* spp., pathogens from the Mucorales family were the causative agent in 13%, with *Rhizopus* and *Mucor* prevailing [14]. A single centre study reported comparable fungal epidemiology among pediatric patients, with *Aspergillus* spp. accounting for 40% of the IMDs, followed by Mucorales (20%) and *Fusarium* spp. (11%) [28]. Two large international registries (Zygomyco.net and FungiScope™) characterized paediatric-specific data surrounding the underlying fungal epidemiology in mucormycosis., *Rhizopus* spp. predominated (39.7 %), followed by *Lichtheimia* spp. (17.5 %) and *Mucor* spp. (12.7 %) [29].

Invasive fungal disease in pediatric patients with malignancies and hematopoietic stem cell transplantation (HCT) recipients

It is challenging to define the incidence of IFD in children with cancer, as the incidence will vary by chemotherapy regimen and supportive care practices [30, 31]. Furthermore, the criteria for defining and diagnosing IFD have varied over time and application of these definitions varies by study [30-33]. Inconsistencies in IFD diagnostic criteria might impact the true estimate of IFD rates among these patients and therefore make the comparison among different chemotherapy protocol groups

difficult [31]. Despite these challenges, early diagnosis and prompt initiation of effective antifungal therapy remains as one of the important actions necessary for improving IFD outcomes in pediatric patients with malignancies [4, 30,32,33].

Epidemiology. The incidence of IFD in children receiving chemotherapy for cancer and those undergoing HCT remains high and is associated with increased morbidity and mortality [30]. Two studies nicely illustrate the changing landscape of IFD within similar cohorts of children with AML [34, 35]. The rate of IFD reached almost 5% using the AML-BFM 93 chemotherapy protocol, while in the same population the IFD incidence decreased to 3% with the more intensified BFM AML 2004 protocol [34, 35]. The lower number of IFD in the BFM AML 2004 study may be partially attributed to the broader administration of antifungal prophylaxis (in >70% of the chemotherapy cycles) with a preference for drugs with anti-mold activity [35]. As a comparator, in a French study including 387 children with AML receiving the ELAM 02 chemotherapy protocol from 2005-2011, the incidence rate of IFD was 6.7% [36]. In the US, a higher incidence of IFD in children with AML enrolled on CCG 2961 protocol by the Children's Cancer Group (CCG) was reported [37]. These differences in IFD incidence have been partially explained by international variations in infection supportive care practices among the BFM and CCG groups for pediatric patients with AML [31]. In particular, BFM centres more frequently provided antifungal prophylaxis compared to Children's Oncology Group centers, including utilization of antifungal agents with anti-mold activity (63.8% *vs* 14.4%) [31].

The inconsistent utilization of antifungal prophylaxis and choice of prophylactic agent also has an impact on reported IFD rates among pediatric patients with malignancies. Without antifungal prophylaxis, mixed population of pediatric patients with malignancies reported rates of IFD between 2.9 - 7.8% [38,39]. In

specific pediatric cancer populations, an IFD rate of 6.1% was observed in patients with promyelocytic AML in a retrospective Canadian study without antifungal prophylaxis and 8.4 % (or IFD incidence of 0.84/1000 person-days) in non-lymphoblastic leukemia patients in an Italian study, respectively [40,41]. In patients receiving antifungal prophylaxis, Watanabe *et al.* reported an IFD rate of 3.8% (6/158 cases) in a mixed population of patients with leukemia and lymphoma receiving oral amphotericin B or intravenous fluconazole [42]. Koyabashi *et al.* in a mixed population of pediatric patients with hematological malignancies or children undergoing HCT receiving antifungal prophylaxis reported an IFD rate of 6.9% (23/334 cases) [43]. By comparison, Kaya *et al.* reported an IFD rate of 13.6% (proven 7.2%) among children with leukemia receiving fluconazole prophylaxis [44].

Candida and *Aspergillus* spp. are the predominant pathogens causing IFD in children with malignancies, while an increasing shift towards other non-*Aspergillus* molds *(Fusarium, Scedosporium* and Mucorales) has recently been observed [3,4, 30, 45]. During a ten year period, the average annual incidence of candidemia among pediatric oncology/HCT patients was 1.25 cases/1000 hospital discharges [45]. Although *C. albicans* is the most frequent species isolated, there is also an increasing trend for non-*albicans Candida* spp. in children with cancer, most frequently *C. parapsilosis* and *C. tropicalis* [22, 30, 45]. *A. fumigatus* is the most common cause of IA in children with hematologic malignancy, followed by *A. flavus* and *A. terreus* [14, 15, 28]. Among non-*Aspergillus* molds, pathogens from the Mucorales family accounted for 13% while all other non-*Aspergillus* and non-Mucorales molds represented 17% of the IFD cases [14].

Outcomes. The overall case-fatality rate of IFDs ranges between 10% and 70%, with higher rates observed in specific subpopulations such as the patients with

disseminated IFD, CNS involvement, or persistent neutropenia [30,41, 43]. Kobayashi *et al.* reported an IFD case fatality rate of 48.2%, and up to 71.4% in patients with lung involvement [43]. For CNS aspergillosis, case-fatality rates before 1990 reached 80%, while after 1990 mortality rates decreased significantly to 39.5% [46]. For IC, overall fatality rates range between 10% and 25%, but can reach close to 50% in patients with ICU admission [30]. In a French study of children with AML, the overall survival at 24 months for children diagnosed with IFD was 72% [36]. The case-fatality rates of IMDs in most studies are between 20% and 50%, increasing to approximately 80% in patients with allogeneic HCT [14, 15, 30, 47]. Pana *et al.* found a case fatality rate of almost 40% for mucormycosis in children suffering from hematological malignancies and 80% for HCT patients [29].

Invasive fungal disease in pediatric solid organ transplant (SOT) recipients

Epidemiology. The true burden of IFD as well as the species distribution following solid organ transplantation has been evaluated in few studies. A US multicenter prospective study (TRANSNET) employing IFD surveillance among mainly adult SOT recipients reported a marginal increase of IFD from 2000-2006, with the highest rates observed among small bowel, lung and liver transplantation, respectively [48]. In an attempt to analyze only the pediatric (SOT) recipient's cases from the TRANSNET database, Knapp K *et al*., reviewed 49 IFD episodes among 41 pediatric SOT recipients (3% of all SOT recipients in the TRANSNET cohort) [49]. The most common organisms detected were *Candida* spp. (78%), followed by *Aspergillus* spp. (8%) [49].

Organ-specific data of IFD in pediatric SOT recipients are limited [50-54]. A study with 98 pediatric liver transplant recipients revealed that 31% presented with *Candida* infections [50]. In a more recently published study, the incidence rate of IC in children undergoing liver transplantation is estimated to be 2.5% (10/397) [51]. Among the 10 IC cases reported, *C. albicans* prevailed (50%), followed by *C. parapsilosis, C. lusitaniae* (20% each) and *C. guillermondii* (10%) [51]. One study dedicated to pediatric heart transplant patients showed that *Candida* infections were 66% of all IFD, followed by IMD at 16% (82% of them attributed to *Aspergillus* spp.) [52]. Among 83 IFD attributed to yeast infections, *C. albicans* was the majority (55%), followed by *C. parapsilosis* (13%), *C. krusei* (4%), *C. glabrata* and *C. tropicalis* (2% each) [52]. Among 22 IFD attributed to mold infections, 18 were caused by *Aspergillus* spp. (82%) followed by zygomycetes (13.6%) and *Exherohilum* spp. (4.5%) [52]. Results from a multi-center US and European study analyzing children undergoing lung transplantation showed that the proven and probable IFD rate reached 10.5% with almost equal distribution of *Candida* and *Aspergillus* spp. [53]. In a single center study with 55 pediatric lung transplant recipients (2002-2007), 11 patients accounted for 14 proven or probable IFD events (20%) [54]. Although pediatric data are lacking, few studies in adult lung transplant recipients, especially for cystic fibrosis patients, have indicated that pre-transplant *Aspergillus* spp. lung colonization could be implicated with the presence of post-transpant bronchiolitis obliterans accociated with *Aspergillus* spp. pulmonary infection [55, 56].

Contemporary data among 548 pediatric SOT recipients between 2000 and 2013 from a single center in the US revealed a low overall IFD incidence of 2.2% (13/584), or 14.3 IFD events per 100,000 patient-days and a decreasing trend over time (accepted article, pending revision, Fisher B). Differences in IFD rates were

reported among organ transplant type and over two time periods. In particular, higher IFD rates were observed for heart/lung recipients (12.5%), lung only(11.4%) and liver (4.7%), compared to kidney and heart (0%). In addition, over the two time periods selected (2000–2006) and (2007–2013), an IFD rate decrease was noted, with a stable number of patients in each period, from 4% (25.5 events per 100,000 patient-days) to 1% (3.9 events per 100,000 patient-days). The number of patients receiving antifungal prophylaxis increased over time from 6% for the first time period to 9% for the second period, which may explain some but likely not all of the decrease in IFD between the two time periods (accepted article, pending revision, Fisher B).

Outcomes. The mortality associated with IFDs varies by type of SOT, type of IFD and time period. In 1999, Gladdy *et al.* reported a 33.3% case fatality rate in pediatric liver transplant recipients with invasive *Candida* infections [50]. On the contrary, in a recently published study, only one of the 10 patients with IC died (mixed infection with *C. parapsilosis* and IA) [51]. In pediatric heart transplant recipients with IFD, the case fatality rate reached almost 50% [52]. More specifically,13/22 patients (59%) with IMD and 43/92 (47%) with yeast infections died [52]. The case fatality rate from the aforementioned cohort of 548 pediatric SOT recipients was 21.4% (3 of 14 pts), including 2 lung recipients and 1 heart/lung recipient (accepted article, pending revision, Fisher B).

Invasive fungal disease in primary immunodeficiencies (PID) pediatric patients

Epidemiology. Among all PID, the epidemiology of IFD has been most clearly defined for chronic granulomatous disease (CGD), an inborn error of the phagocyte NADPH oxidase complex. While children with CGD are at risk for a wide

range of yeast and mold pathogens, *Aspergillus* spp. and *Candida* spp. are most common [5, 57-64]. Among 155 CGD patients in a French study from 1976-2008, 42.6% (66/155) developed at least one IFD [58]. In particular, IMDs represented 61.3% (49/80) of all IFD events. *Aspergillus* spp. accounted for 65.3% of these IMDs (32/49), with *A. fumigatus* (28.5%) and *A. nidulans* (22.4%) being the most common *Aspergillus* spp. [58]. Notably, itraconazole prophylaxis had a significant impact on IFD incidence [58].

Another congenital immunodeficiency associated with an increased susceptibility to IFD is Hyper-IgE syndrome (HIES) (i.e. Job's syndrome) [5,65]. Invasive pulmonary aspergillosis occurs in almost 20% of these patients almost exclusively secondary to presence of pneumatocysts and bronchectasis due to recurrent bacterial infections and due to impaired local STAT3-dependent lung epithelial immunity [65,66]. While rare, dissemination to the CNS in these patients has been occasionally reported [65, 67]. A recent literature review reported 16 HIES cases with rare endemic/dimorphic fungi such as *Coccidioides*, *Cryptococcus* and *Histoplasma*, underscoring the vulnerability of this patient group to a wide range of fungal pathogens [66].

The caspase recruitment domain-containing protein 9 (CARD9) represents an essential molecule for the production of T-helper cells producing interleukin-17 pathway. CARD9 deficiency is a PID with impaired *Candida* spp. killing [67-69]. Although large enough cohorts are not available to define the true incidence and case fatality rates of IFD in these patients, a case series report suggests that the GI tract and in particular CNS are common anatomical locations for *Candida* infection [69]. Other important anatomic locations are the bone and eye [70]. A subsequent case series

found that CARD9 deficient patients can also suffer from isolated IA in the CNS and GI-tract [71].

Outcomes. The overall IFD case fatality rate for CGD reached 17% in one study, with a reported reduction of mortality over time from 43% (1985–1990) to 6% (1991-2009) [62]. The decrease in mortality for CGD patients over the last 15 years has been attributed to high clinical awareness but also to the implementation of itraconazole prophylaxis [58,62,64]. Nevertheless, IA remains a major cause of death for CGD patients [64]. In HIES, a 17% IFD case fatality rate has been reported [65].

Invasive fungal disease in PICU patients

Children in PICUs represent a heterogeneous pediatric population with a well-documented increased risk for developing IFD due to a unique combination of critical and complex clinical conditions, including prolonged need of hospitalization, frequent invasive interventions, and the presence of foreign devices, such as catheters and endotracheal tubes [72]. The predominant cause of IFD in the PICU is IC, while IA is mainly observed in children with underlying hematological malignancies admitted to the PICU.

Epidemiology. The incidence of IC and the *Candida* spp. distribution vary among different PICUs and among different time periods. These differences may reflect specific institution peculiarities associated with differences in critical care practices, differences in geographical niches of *Candida* spp., and the expansion of antifungal prophylactic regimens. For example, from 2005-2009 the incidence of IC among seven PICUs in Greece ranged from 0-14.1 cases/1000 admissions with a median incidence of 6.4 cases/1000 admissions [73]. Comparable incidences have

been reported from Spain with 6.9 cases/1000 admissions during a two-year period (1996-1998) [74]. Slightly lower incidences were found in a study from the US with 3.5 cases/1000 admissions reported during 1997–2004 [75], similar to the results from Egypt (3 cases/1000 inpatient-days) [76]. Over a 10-year-period, the incidence of IC in PICU patients in a single center study in Germany was 0.59/1000 hospital discharges (95% CI, 0.02–1.09) [45]. A more recent update from Spain for the period 2008-2009 reported an incidence of 4.22 cases/100 PICU admissions [77].

Richards *et al.* reported that almost 10% of bloodstream infections in US PICUs were attributed to *Candida* spp. [78], while a study in Israel reported that 14.4% of bloodstream infections in PICUs were candidemia [79]. *C. albicans* remains the leading cause of IC in the PICU, with an increasing trend of non-*albicans Candida* spp. worldwide. In Europe, *C. albicans* prevails, with a percentage ranging between 37.6 to 55.5% comparable to US studies reporting a 46% of IC caused by *C. albicans*. [73,75-77, 80]. *C. parapsilosis* is the second leading etiology of IC at approximately 20%. The high percentage of *C. parapsilosis* isolated in the PICU emphasizes the need of implementing further infection control bundle measures, as its origin is mainly exogenous either through horizontal transmission or adherence to foreign devices (such as catheters and other devices) [75]. Other *Candida* spp. account for 10-15% of the isolates, most prominently with *C. tropicalis, C. glabrata, C. krusei* and *C. lusitaniae*. Differences in the distribution of these species among different PICUs have been associated with local practices and therefore it is necessary to learn a center's local epidemiology.

Outcomes. The case fatality rate of IC in the PICU is difficult to estimate due to the high clinical complexity and severity of underlying conditions. Zaoutis *et al.* compared the case fatality rates in children with IC and controls in the PICU and

found a statistically significant higher rate of death in children with IC (44% *v*s 14%; OR: 4.22; CI: 2.35, 7.60) [75]. The same group observed a prolonged median PICU- and hospital- length of stay for children with IC (35 and 46 days, respectively) [75]. Hegazi *et al.* found a similar case fatality rate in PICU patients (42.4%), while the case fatality rate from candidemia was estimated to be 16.7%, similar to the 18.2% reported by Vogiatzi *et al.* [73,76].

The impact of species-specific mortality among children in the PICU has been evaluated, however, results are conflicting. In another study, children with candidemia due to non-*albicans Candida* spp. were twice as likely to die than children with *C. albicans* [80]. On the contrary, other studies found no significant difference between different *Candida* spp. and case fatality rates [72,75]. In one study, the main species associated with higher mortality were *C. glabrata, C. krusei* and *C. tropicalis*, and this was felt to be most likely due to decreased susceptibility and/or resistant to fluconazole among *C. glabrata* and *C. krusei* [72].

Invasive fungal disease in NICU patients

A significant increase in the incidence of IC was initially reported during the 1990s temporally associated with increased survival rates of premature very low birth-weight (VLBW) neonates, while in the last 15 years there has been an overall decrease in neonatal IC within European countries and the US [16,17,20,21, 81-84]. The cause of this decrease is likely multifactorial and has been correlated with prophylactic use of fluconazole and with infection control bundle measures eliminating catheter-related bloodstream infections [17, 84].

Epidemiology. In a large cohort study including 6956 VLBW neonates, *C. albicans* was the third most common pathogen causing late onset sepsis (6%) [85]. Results from a multicenter study (19 centers in the US) among extreme low birth-weight (ELBW) neonates showed a significant variability in the incidence of IC among different centers (2-28%) [86]. Aliaga *et al.* was among the first to report a significant decrease of neonatal IC, dropping from 3.6 per 1000 infants in 1997 to 1.4 per 1000 infants in 2010 in the US [84]. Similar decreases have now been reported in a number of smaller European studies [16,19]. In a UK study, a lower median age of diagnosis was reported for *C. albicans* (11 days) and *C. glabrata* (9 days) compared to other species such as *C. parapsilosis* (18 days), *C. tropicalis* (20 days) and *C. lusitaniae* (23 days) in infants < 90 days of age [16]. Irrespective of the age of diagnosis, *C. albican*s remains the most frequent *Candida* spp. associated with neonatal IC, followed by *C. parapsilosis, and C. tropicalis; C. glabrata* and *C. krusei* are less frequently encountered [87-89]. The incidence of *C. parapsilosis* infections in NICU patients is rather stable when comparing the time period before 2000 (33.5%) and after 2000 (27%) [90].

Outcomes. Despite a decreasing incidence, neonatal IC is associated with a high case fatality rate with an overall estimate of about 20% and increasing to 50% in extremely low birth weight (ELBW) infants. Increased mortality and long term neurodevelopmental abnormalities have been associated with neonatal IC, and in particular with the occurrence of hematogenous *Candida* meniningoencephalitis (HCME) [86,91,92]. Almost 50% of the infants surviving neonatal IC will have long-term neurodevelopmental deficits [91-95]. Additional poor prognostic factors for neonatal IC outcome include the early onset of IC, delayed catheter removal and delayed initiation of antifungal therapy [96-98]. A recently published meta-analysis in

2016 showed that fluconazole prophylaxis in ELBW infants not only contributed to a significant reduction of IC but also to a reduction in case fatality rates [99].

Conclusion

There is an ongoing global effort to constantly update our knowledge on the incidence and distribution of pathogens causing pediatric IFD. Continuing and actually expanding this effort is necessary to better understand the changing incidence and outcomes of IFD and to identify emerging at risk populations. Local monitoring of the epidemiology is also necessary to understand the burden of IFD at the institutional level. These data are of utmost importance to tailor preventive measures, to focus resources on the most susceptible hosts and to implement institution-based infection control strategies. Although the spectrum of children vulnerable to IFD is wide, the majority of cases are inclusive of the patient populations reviewed in detail above. Recent studies on the epidemiology of *Candida* infections suggest a decrease in the infection rates in the last decade. The reason for this decline is not exactly known but often attributed to the utilization of antifungal prophylaxis and improved infection control practices. A gradual shift from *C. albicans* to non-*albicans Candida* has also been recorded, while a stable incidence of IA was observed. Mortality rates remain high depending on the fungal pathogen isolated and underlying condition of the pediatric patient. Future work is needed to improve diagnostic capabilities to better understand the epidemiology of these infections and to allow for earlier initiation of appropriate therapeutic interventions that will result in improved survival from these devastating infections.

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Table 1. Incidence of Invasive Candidiasis and Invasive Aspergillosis from contemporary multicenter pediatric studies

Author [ref]	IFD incidence	Time period	Cases (N)	Mortality	Type of study	Comments
	Invasive Candidiasis (IC)					
Zaoutis *et al*. [12]	4.3 /10. 000 pediatric admissions	2000	1118	15.8%	Multicenter US study (KID 2000) & (NIS 2000)	Analysis showed an absolute 10.0% increase in mortality attributable IC
Oeser *et al.* [16]	15.2/10.000 person-years	2000-2009	1473	NR	Multicenter EU study (England & Wales)	Decrease in IC incidence after 2007: 2.09/100. 000 (2007) *versus* 1.53/100. 000 (2009) Difference in IC incidence among age groups: Highest in <1 year old patients (11.0/100.000) and lowest in 10-14 year old patients: (0.47/100. 000)
Blyth *et al.* [26]	4.6/10.000 admissions 4.39/100. 000 population (neonates) 0.92/100 000 population (children)	2001-2004	1005	10% children 22% neonates	Multicenter study in Australia	
Fisher *et al.* [17]	2.46/10. 000 inpatient days (2003) 0.77/10. 000 inpatient days (2011)	2003-2011	4456	14%	Multicenter US study	Decrease in IC incidence:72% for pediatric and 91% for neonatal cases Mortality varied: 17.3% (2003) *versus* 11.6% (2011)
Santolaya *et al.* [23]	8.1/10.000 pediatric admissions	2008-2010	302	28%	Multicenter study in Latin America	
Cleveland *et al.* [19]	ATL: 13.3/ 100. 000 person-years BTM: 26.2 / 100. 000 person-years	2008-2011	1863	29% 28%	Multicenter US study population-based surveillance	Significant decrease of IC for both pediatric and <1 year of age groups.
Cleveland *et al.* [18]	19/ 10.000 person-years (children) 33.8/ 100. 000 person-years (neonates) * mixed population children and adults (children N=121; <1 yr N=113)	2008-2013	3848*	NR	Multicenter US study population-based surveillance	Baltimore: Decrease in IC incidence in neonatal but not in pediatric patients: Reported increase 17% (2.0/100.000 in 2008 to 2.4/100,000 in 2013); Atlanta: the decline was greatest for persons aged <1 year: reported decrease 60% (41.7/100,000 in 2008 to 16.6/ 100.000 in 2013)

	Invasive Aspergillosis (IA)					
Zaoutis *et al.* [13]	437/100. 000 (0.4%) hospitalized immunocompromised children	2000	666	18%	Multicenter US study	Children with IA had a significantly higher mortality and longer median length of hospital stay (16 days) than immunocompromised children without IA (3 days)

Table 2. Distribution of *Candida* spp. causing IFD among pediatric patients from multicenter studies between 2000-2017

Author [ref]	Invasive Candidiasis (IC) Fungal species distribution		Time period	Cases (N)	Mortality	Type of study
	Candida albicans N (%)	**Non-*albicans* *Candida* spp.** N (%) (three most frequently reported)				
Oeser *et al* [16]	815 (55.3)	*C parapsilosis* 320 (21.7) *C glabrata* 60 (4.1) *other* 153 (10.4)	2000-2009	1473	NR	Multicenter EU study (England & Wales)
Blyth *et al.* [26]	47 (43.9)	*C parapsilosis* 41 (38.3) *C glabrata* 3 (2.8) *C krusei* 2 (1.9) *C tropicalis* 2 (1.9) *C orthopsilosis* 2 (1.9)	2001-2004	80 pediatric	NR	Multicenter study in Australia
Blyth *et al.* [26]	13 (39.4)	*C parapsilosis* 14 (42.4) *C glabrata* 3 (9.1) *C tropicalis* 1 (3.0)	2001-2004	24 neonatal	NR	Multicenter study in Australia
Steinbach *et al.* [22]	87 (44)	*C. parapsilosis* 45 (22) *C. glabrata* 21 (11) *C. lusitaniae* 8 (4)	2007-2011	196 pediatric	19%	Multicenter US & EU study (IPFN)
Steinbach *et al.* [22]	12 (48)	*C. parapsilosis* 7 (28) *C. glabrata* 1 (4) Other 6 (24)	2007-2011	25 neonatal	8%	Multicenter US & EU study (IPFN)
Santolaya *et al.* [23]	115 (38.1)	*C. parapsilosis* 80 (26.5) *C. tropicalis* 44 (14.6) *C. guilliermondii* 31 (10.3)	2008-2010	302 pediatric	28%	Multicenter study in Latin America

IPFN: International Pediatric Fungal Network

NR: not reported

Table 3. Distribution of *Aspergillus* spp. causing IFD among pediatric patients from multicenter studies between 2000-2017

Author [ref]	Invasive mold Diseases (IMDs) Fungal species distribution		Time period	Cases (N)	Mortality	Type of study
	***Aspergillus* spp.** N (%)	**Non-*Aspergillus* Molds** N (%)				
Burgos *et al.* [15]	*A. fumigatus* 67 (52.8) *A. flavus* 20 (15.7) *A. terreus* 6 (4.7) *A. niger* 6 (4.7)	NR	2000-2005	139 IA	*A. fumigatus* 38 (52) *A. flavus* 11 (15)	Multicenter EU study
Pana *et al.* [29]	NR	*Rhizopus* spp. (39.7) *Lichtheimia* spp. (17.5) *Mucor* spp. (12.7)	2005-2014	63 MC	33%	Multicenter study (Fungiscope & zygomyco.net)
Wattier *et al.* [14]	*A. fumigatus* 26 (20) *A flavus* 7 (5) *A. niger* 6 (5)	Mucormycoses 17 (13) *Rhizopus* spp 9 (7) *Mucor* spp 3 (2) Other mold 22 (17) *Curvularia* spp 4 (3) *Exserohilum* spp 4 (3) *Fusarium* spp 4 (3)	2007-2011	131 IMIS: 98 IA 17 MC	IMIs 39 (30) IA 30 (31) MC 6 (35)	Multicenter EU and US study (IPFN)

IA: Invasive Aspergillosis

IMIs: Invasive Mold infections

MC: Mucorales infections

NR: Not reported