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Epidemiology and fungal infection risk factors in patients hospitalized in neonatal and paediatric intensive care units – a multicentre pilot study

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ABSTRACT

Invasive fungal infections are associated with very high mortality and morbidity. Candida sp. is a leading etiological cause of invasive fungal infections (IFI). The aim of this study was to investigate the epidemiology of FI in patients admitted to neonatal and paediatric ICU (NICU and PICU) to investigate risk factors that may contribute to FI development. In this retrospective epidemiologic multicentre pilot study five neonatal and five paediatric intensive care units were included. The data about epidemiology, patient significant clinical data, chronic metabolic disease, surgery, mechanical ventilation, dialysis, central venous catheter, urinary catheter, arterial catheter, total parenteral nutrition, leucopenia, neutropenia, previous antimicrobial therapy or prophylaxis were collected. In this study 25 NICU and 40 PICU patients treated with antifungal drugs during 2014 were enrolled. Among patients with fungal infection from the NICU the most often diagnosis and reason for NICU hospitalization was prematurity. In four NICUs C. albicans was the most common clinically significant fungal isolate. In one NICU C. parapsilosis was the most frequently isolated yeast. From the urine of one NICU patient with urogenital disease C. krusei was isolated. In four of five PICUs C. albicans was the most common cause of fungal infections. C. glabrata and C. krusei were also recorded in PICUs. In one PICU patients with clinically important moulds were recorded – patients with haematological malignancy (Fusarium sp.) and solid organ transplantation (Aspergillus spp). Thus, surveillance of epidemiology, fungal susceptibility and risk factors associated with fungal infection in a prospective multicentre study could be of great value in the future.

Key words: fungal infection, fungal epidemiology, risk factors for FI, paediatric patient, neonatal patient

INTRODUCTION

Invasive fungal infections are opportunistic infections and they are associated with very high mortality and morbidity. Candida sp. is a leading etiological cause of invasive fungal infections (IFI) in adults as well as in children. (1) The incidence of invasive fungal infections has been rising over the past few decades among adults as well as children. Furthermore, most of the invasive candida infections are caused by Candida albicans and Candida parapsilosis but in the past few decades a significant shift towards non-albicans Candida sp. has been documented. Early diagnosis of invasive fungal infection is essential in order to achieve a better outcome for patients. In addition, risk factors for Candida infections have been described for neonatal ICU but with an emphasis on prematurity. Those infections comprise of not only bloodstream, but also urine, peritoneal and CNS infections, but they are not always captured by the diagnostic tools available. Furthermore, as many as 50% of candidemias may not be directly detected, but clinically suspected. It is important to emphasise, that it is well known that the reported incidence rates of IFI between different neonatal settings, or even countries, may be extremely different. Furthermore, up to 16.5% of all neonates having some of the complicated gastrointestinal disease requiring surgical procedure can develop Candida infection. (2) Timely diagnosis of invasive Candida infection still represents a challenge for paediatric intensivists and clinical microbiologist because there are no specific symptoms or signs and associated symptoms can be less well-defined in children than in adults. Published reviews on invasive Candida infections in PICUs have documented the risk factors such as use of the broad spectrum antibiotics, use of catheters and endotracheal tubes, parenteral nutrition, Candida colonization at two or more sites, in addition to factors such as malignancy and haematological disease. Several prediction rules or scoring systems are developed for predicting invasive Candida infections in adult patients, but no such prediction rules exist for the paediatric population admitted to the ICU. Those systems defined for adults cannot be simply extrapolated to a very heterogeneous paediatric population. (3) Epidemiology surveillance, as well as a better understanding of the risk factors, and possibly prediction rule development, could be of great value for paediatric intensivists in order to more easily recognize patients at risk of IFI and to earlier appropriate antifungal therapy introduction and improving patient outcome. Unfortunately, the rising incidence of Candida species with intrin-

sically decreased susceptibility on fluconazole have been described. (4) The aim of this study was to investigate the epidemiology of FI in patients admitted to neonatal and paediatric ICUs and additionally to investigate risk factors that may contribute to FI development.

MATERIALS AND METHODS

In this retrospective epidemiologic multicentre pilot study five neonatal and five paediatric intensive care units were included. The data about epidemiology regarding the species of isolated fungi, susceptibility of fungal isolates (when available) were collected. Furthermore, patient significant clinical data such as, chronic metabolic disease, surgery, mechanical ventilation, dialysis, central venous catheter, urinary catheter, arterial catheter, total parenteral nutrition, leucopenia (<2000/mm3), neutropenia (<400/mm3), previous antimicrobial therapy or prophylaxis were collected. In addition, the data regarding the diagnosis responsible for ICU admission were collected. NICU admission categories were prematurity, low birth weight, respiratory disease, cardiovascular disease, neurological disease, gastrointestinal disease, urogenital disease. PICU admission categories were respiratory disease, cardiovascular disease, neurological disease, gastrointestinal disease, haematological disease, solid organ transplantation. The data regarding the age of the patients hospitalized in PICUs and the mortality of patients with fungal infection in both types of intensive care settings were also collected. The age of the patients from paediatric intensive care units were divided into three categories; 28 days to 12 months, 13 months to six years and seven years to 18 years.

Altogether, in this study 65 patients were enrolled, 25 from NICUs and 40 from PICUs treated with antifungal drugs during 2014.

Due to a small numbers of collected data from patients with fungal infection in both NICUs and PICUs, no statistical methods were performed.

RESULTS

Percentages of patients hospitalised in neonatal intensive care units developing fungal infections were in the range from 0.6% to 6.6%. In four NICUs C. albicans was the most common clinically significant fungal isolate. In one NICU C. parapsilosis was the most frequently isolated yeast. In one institution C. parapsilosis was of the second most frequent fungal isolation. C. tropicalis, C. krusei as well as Saccharomyces cerevisiae were also isolated. In one institution a significant number of Candida remained unidentified to a species level (9). Thirty-seven C. albicans isolates from NICU patients, 8 C. parapsilosis, 1 C. tropicalis, 1 C. krusei, 9 Candida sp were reported. Among patients with fungal infection from NICUs, the most often diagnosis as the reason for NICU hospitalization was prematurity – altogether 14 patients. The most common isolated Candida from those patients was C. albicans, the second most common was C. parapsilosis, and from blood cultures from one patient Sacharomyces cerevisiae was isolated. The second diagnosis of NICU patients with fungal infection was low birth weight, mostly connected with prematurity – 10 patients. The most common isolated Candida from those patients was C. albicans (7), the second most common was C. parapsilosis (6), and from blood cultures from one patient Sacharomyces cerevisiae was isolated. Two patients had respiratory disease and both of them had C. parapsilosis. Neurological disease was recorded in two patients with C. albicans isolated. Gastrointestinal disease was found in 4 NICU patients. C. albicans was the most common (3 patients) and one of the patients had C. parapsilosis. From the urine of one NICU patient with urogenital disease, C. krusei was isolated. The most frequent risk factor associated with C. albicans infection was mechanical ventilation (9 patients), the second was central venous catheter (8 patients), as well as previous antimicrobial therapy (8 patients), previous antifungal therapy (8 patients), then total parenteral nutrition (7 patients), urinary catheter (5 patients), surgery (3 patients), leucopenia (3 patients), neutropenia (3 patients), dialysis (1 patient) and arterial catheter (1 patient). For C. parapsilosis the most often risk factors were mechanical ventilation (8 patients), central venous catheter (8 patients), and total parenteral nutrition (8 patients). On the other hand, in patients with C. parapsilosis previous antimicrobial therapy was documented in 7 patients, urinary catheter in 4 patients, surgery and previous antifungal therapy in 3 patients. Apatient with a C. krusei infection had surgery, mechanical ventilation, central venous catheter, total parenteral nutrition previous antimicrobial and antifungal therapy. An NICU patient with Sacharomyces cerevisiae was on mechanical ventilation, had central venous catheter placed, total parenteral nutrition and was on previous antimicrobial and antifungal therapy. (Table 1) In institution 1 all isolated fungi were C. albicans. Two of those isolates were from blood culture, one from cerebrospinal fluid, tracheal aspirate, central venous catheter and one from respiratory swab. Institution 2 reported 4 isolates from blood culture, 2 C. parapsilosis, one C. albicans and one Saccharomyces cerevisiae. Two C. parapsilosis were isolated from cerebrospinal fluid and one from a central venous catheter in Institution 2. In Institution 4 all isolates were C. albicans and all of them were isolated from urine. Institution 8 reported 4 yeast isolates from blood culture, 3 C. parapsilosis and one C. albicans. One isolate of C. albicans was isolated from a central venous catheter and one C. krusei from a wound swab. In neonatal intensive care units that participated in the study, fungal infections were mostly treated with azoles, than amphotericin B and in one case with echinocandins. One NICU reported C. albicans resistant to fluconazole. The percentage of patients hospitalised in paediatric intensive care units developing fungal infection was different in various institutions ranging from 0.95% to 9.27%. The age of patients in paediatric intensive care units was divided into three categories: 28 days to 12 months (10 patients), 13 months to 6 years (11 patients) and 7 years to 18 years (18 patients). In four of five PICUs C. albicans was the most common isolate and cause of fungal infections. Institution 3 reported that the most common isolates were C. lusitaniae and C. krusei (one isolate of each). Isolates from Institution 1 were all C. albicans. The second most common fungal isolate was different depending on the institution. In Institution 6 the second most common isolatewas C. glabrata followed by C. parapsilosis and C. krusei. In institution 7 the seconf most common isolate reported was Fusarium sp., followed by C. parapsilosis, C. guillermondii, and surprisingly Aspergillus fumigatus was the third most common isolate. The fourth most common isolates in Institution 7 were C. krusei and Aspergillus flavus. Institution 7 was the only PICU that reported moulds as a cause of fungal infection. In Institution 9 C. albicans was the most common isolate,

followed by C. parapsilosis as the second most common, and the third most common isolates were isolates from the blood culture reported as a blastoconidiae candida without identification and Candida sp. without identification to a species level. (Figure 1) By far the most common diagnosis in patients hospitalized in PICUs developing yeast infection was neurological disease (13 patients). Altogether, C. albicans were the most frequently isolated from patients with yeast infection regardless of diagnosis that was the reason for PICU hospitalisation. Gastrointestinal diseases were on the second place (7 patients) and on the third place were haematological diseases (6 patients). The next place are respiratory diseases (4 patients) and solid organ transplantation (4 patients) followed by cardiovascular diseases (3 patients). (Table 2)

In PICU patients the most common risk factor was previous antimicrobial therapy (38 patients), followed by mechanical ventilation (35 patients) and central venous catheter placement. The next risk factor was the presence of the urinary catheter (33 patients) followed by total parenteral nutrition (31 patients). In about half of the patients (16) surgery as well as arterial catheter (13 patients) and previous antifungal therapy (12 patients) was reported. Neutropenia (9 patients), leucopenia (8 patients), dialysis (6 patients) and chronic metabolic disease was present much less often. (Table 2) Blood culture is by far the most predominant specimen as well as one of the most important from which yeasts were isolated in PICUs (14 patients). Other primarily sterile specimens were seldom represented, only one isolate from cerebrospinal fluid, one isolate from central venous catheter and one from VP shunt. On the other hand, tracheal aspirate was on the second place with 7 isolates followed by urine (5 isolates). The third place share respiratory swabs, stool and drainage with similar number of isolates. PICU patients with clinically important moulds which were treated, were diagnosed with haematological malignancy for Fusarium sp. and solid organ transplantation for Aspergillus spp. All Fusarium sp. (3 patients) were isolated from blood culture. Aspergillus fumigatus (2 patients) were isolated from tracheal aspirates and one patient had Aspergillus flavus in drainage. The most frequent age of patients hospitalized in PICUs with fungal infection was from 7 to 18 years, almost half of the patients were from age group 28 days to 12 months and 13 months to 6 years. In PICUs enrolled in the study fungal infections were mostly treated with azoles and amphotericin B and in about half of the cases echinocandins. One Institution reported two C. albicans isolates intermediately susceptible to fluconazole. C. krusei in one institution was surprisingly reported as in vitro susceptible to fluconazole, although it is considered intrinsically resistant to fluconazole.

Table 1. Diagnosis and risk factors of patients admitted to Neonatal ICUs (intensive care units) and developed fungal infection (candida)

	C. albicans (Patients No)	**C. parapsilosis (Patients No)**	**C. krusei (Patients No)**	**Saccharomyces cerevisiae (Patients No)**
Prematuritiy	7	6		1
Low birth weight	4	5		1
Respiratory disease		2		
Cardiovascular disease				
Neurological disease	2			
Gastrointestinal disease	3	1		
Urogenital disease			1	
Surgery	4	3	1	
Mechanical ventilation	9	8	1	1
Dialysis	1			
Central venous catheter	8	8	1	1
Urinary catheter	5	4		
Arterial catheter	1			
Total parenteral nutrition	7	8	1	1
Leucopenia (<2000/mm3)	3			
Neutropenia (<400/mm3)	3			
Previous antimicrobial therapy	8	7	1	1
Previous antifugal therapy	3	3	1	1

Table 2. Diagnosis and risk factors of patients admitted to Paediatric ICUs and developed fungal infection (candida)

	C. a (Patients No)	C. pp (Patients No)	C. lus (Patients No)	C. g (Patients No)	C. guill (Patients No)	C. k (Patients No)	Blast (Patients No)	Candida sp. (Patients No)	Total (Patients No)
Respiratory disease									4
Infection	4								
Surgery									
Cardiovascular disease	3								5
Infection			1						
Surgery			1						
Neurological disease	6	2			1		1	1	13
Infection	1								
Surgery	1								
Gastrointestinal disease	1								7
Infection	2	2				1			
Surgery	1								
Haematological disease									6
Infection	3	1		1	1				
Solid organ transplantation									4
Infection	3								
Surgery						1			
Chronic metabolic disease	1								
Surgery	10	2		1			2		1
Mechanical ventilation	23	5	1	1	1		2	1	1
Dialysis	5	1							
Central venous catheter	22	5	1	1	2		2	1	1
Urinary catheter	22	5	1	1			2	1	1
Arterial catheter	8	2					1	1	1
Total parenteral nutrition	19	5	1	1	1		2	1	1
Leucopenia (<2000/mm3)	5	1		1	1				
Neutropenia (<400/mm3)	6	1		1	1				
Previous antimicrobial therapy	26	4	1	1	2		2	1	1
Previous antifugal therapy	7	1	1	1			2		

C.a. - C. albicans
Cpp - C. parapsilosis
Cg - C. glabrata
C.k. - C. krusei
C. lus . - C. lusitaniae
C. gull - C. guillermondii
BK – blastoconidiae

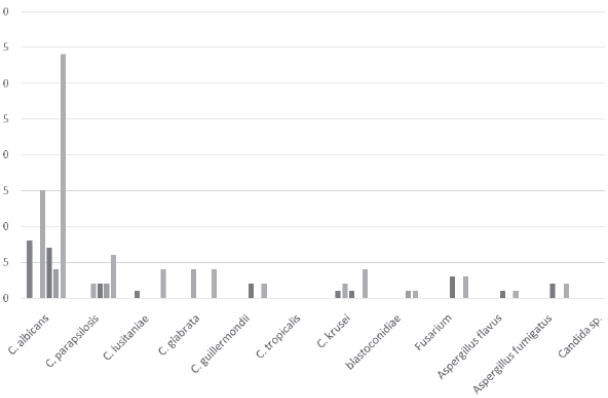

Figure 1 . Fungal infection epidemiology in PICUs

DISCUSSION

The majority of published studies on fungal infections primarily deal with adult ICU patients and the differences in epidemiology, fungal species causing infection, management, and the outcome of fungal infection between adults and children diminish the possibility of extrapolation of the conclusions to children. (5) Thus, the surveillance of epidemiology, as well as susceptibility of fungal isolates in NICUs and PICUs in various institutions, is very important for the early recognition and better management of patients with fungal infection. The percentages of patients hospitalised in NICUs developing fungal infections was different in various institution probably due to different approaches to prophylaxis, a different proportion of surgical population admitted, possibly related to the feeding practice, as well as different microbiological laboratory possibilities considering methods and the mycological experience. In our study, one isolate of C. albicans was found resistant to fluconazole, which is considered very rare (up to 5%) in the literature. (6) In neonatal intensive care settings and from the majority of institutions that participated in this study, C. albicans is the most common fungi causing fungal infection, followed by C. parapsilosis, as previously described. Unfortunately, isolates such as C. krusei are emerging, and those isolates cannot be treated with fluconazole because of their intrinsic resistance to fluconazole. A case of a premature baby with repeated Saccharomyces cerevisiae isolate from blood cultures is very interesting. The baby was not receiving probiotics and the origin of the isolate needs to be investigated. It has been documented in NICU patients that even prompt antifungal therapy does not prevent neurodevelopment sequelae in the most immature neonates. (7) Accurate data on the colonisation of NICU patients are very important because the literature has consistently shown that differently colonised patients have various odds of developing an invasive disease. (3) Early and effective prophylaxis is therefore very important. (8) It is well known that true incidence of fungal infection (even in neonatal patients) is not known and it may be higher than thought. (3) In our study, at the NICU institutions most patients were premature and had low birth weight, but other diagnosis were neurological or gastrointestinal diseases. One patient with urogenital disorder developed fungal infection caused by C. krusei after treatment with fluconazole of C. albicans infection. It is important to emphasize, that the incidence of invasive candida infection is greater in children than in adults. (9) Previous studies have suggested a rise in incidence of infections caused by non-albicans species, probably because of widespread use of fluconazole propylaxsis. (10) The results of our study showed a similar shift towards non-albicans Candida, but also mould infections in one PICU. In our study, C. albicans is still the most frequently isolated yeast as an etiologic agent of fungal infection followed by C. parapsilosis, but a special concern represents Candida isolates such as C. krusei and C. glabrata with its resistance to fluconazole, and C. lusitaniae with resistance to amphotericin. One institution reported one isolate from blood culture as blastoconidiae. Microbiological laboratory probably did not succeed to identify this isolate, although it is very important to identify the fungal isolate to the species level because of intrinsic resistance of some fungi to antifungal drugs and different interpretation of in vitro susceptibility, but sometimes identification is not simple and requires some special equipment beside experience. Furthermore, in this study the percentage of fungal infections in paediatric patients shows huge differences from institution to institution. The reasons are different pathology and different diagnostic possibilities between different mycology laboratories. Our data show that fungal infections are 2 times more frequent in the age group 7 to 18 years than in groups 28 days – 12 months and 13 months to 6 years. In paediatric intensive care settings enrolled in this study, the broader spectrums of diagnosis were documented when compared to neonatal intensive care units, and surprisingly neurological diseases were the most common.. Those patients are mainly hospitalised in the PICU for a long time, are mechanically ventilated, receiving total parenteral nutrition, being treated with broad spectrum antibiotics and often have several artificial medical devices and that could be the reason for increased incidence of fungal infection. In our study, the prevalence of fungal infections was highest in the patients with concomitant haematological, gastrointestinal and cardiovascular diseases, and the lowest among patients with solid organ transplantation. Such findings perhaps can be explained with effective antifungal prophylaxis introduced in patients with solid organ transplantation. Most of the fungal infections from our study were treated with azoles, then amphotericin B and echinocandins, but there are significant difference between institutions probably due to various patients' co-morbidities because empiric therapy with fluconazole should not be used in critically ill patients with sepsis or septic

shock. (11) In our study in a single PICU moulds (Fusarium sp. and Aspergillus sp.) were isolated. It is important to emphasize, that moulds are emerging pathogens in the ICU setting, and not just in haematological patients but also in non-neutropenic patients. (12) Thus, surveillance of epidemiology as well as susceptibility of fungal isolates and further surveillance of various risk factors and conditions associated with fungal infections in a prospective multicentre study could be of great value in order to improve the outcome of neonatal and paediatric patients.

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