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ORIGINAL ARTICLE

Antibiotic Overuse as a Risk Factor for Candidemia in an Indian Pediatric ICU

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Abstract
Objective To identify risk factors and mycological characteristics of candidemia in Pediatric ICU of a tertiary-care hospital.
Methods Patients were screened for candidemia by blood culture. Recovered isolates were speciated and subjected to antifungal susceptibility testing. For every candidemic patient, three controls were matched for age, underlying diagnosis and period of hospitalization. Premature neonates were also matched for birth-weight. Proportion of cases and controls on specific antibiotics or indwelling devices was compared using Chi-square test, while unpaired t-test was used for comparing the number of antibiotics used and the number of days of antibiotic administration. Concordance between susceptibility testing methods was evaluated using Chi-square test.
Results Significantly wider spectrum of antibiotic coverage was observed among the 28 candidemic patients. While every patient received antibiotic against enteric gram-negative bacilli, antibiotic usage for additional groups of microorganisms was significantly higher among cases. Association of candidemia with increasing use of indwelling devices was also observed. Endogenous colonization was higher in candidemic infants. *Candida albicans* was the commonest species (n=18), followed by *C. tropicalis* (n=7). Fluconazole and ketoconazole resistance was observed in 10.7 % cases.
Conclusions This information on pediatric candidemia could be used to devise locally-tailored strategies for identifying at-risk patients, underline the importance of routine antifungal susceptibility testing and formulate appropriate guidelines for management.

Keywords Pediatric candidemia · Risk factors · Antifungal sensitivity testing

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Introduction

Candida infection, which is being increasingly experienced as a major cause of septicemia in the pediatric intensive care unit (PICU), is often refractory to therapy and associated with high morbidity and mortality [1–3]. The existing literature shows significant differences in the epidemiology of this disease, depending on the type of health-care facility screened and the geographical region surveyed [4]. This underscores the need for monitoring regional trends in the epidemiology, species distribution and antifungal susceptibility profile of pediatric candidemia, since such information holds the key for formulating appropriate prophylactic and treatment guidelines that can lead to the improved management of this condition.

Given the relevance of the issue and considering the fact that data on pediatric candidemia is relatively sparse from the Indian health-care scenario, the present study was conducted to identify the risk factors and to analyze the mycological characteristics of candidemia in the setting of a pediatric ICU in the Himalayan region of North India. The authors

report in this study an interesting association between the spectrum of antimicrobial usage and the occurrence of pediatric candidemia. They also observe that the disc diffusion method of antifungal sensitivity testing is suitable for implementation in the routine workflow of clinical Microbiology laboratories and can be used to guide antifungal treatment in patients with pediatric candidemia.

Material and Methods

This matched case–control study was carried out over a period of 18 mo in the setting of a neonatal and pediatric ICU attached to a 750-bedded tertiary care teaching hospital. A case of candidemia was defined as a patient who had at least one sample of blood culture positive for Candida species. For each case, 3 controls were matched for age, underlying primary condition and period of hospitalization. Premature neonates were also matched for birth weight. The study protocol was approved by the institutional ethics committee. In view of the relative rarity of Candida as a cause of septicemia, compared to bacterial pathogens, the authors decided to adopt a case: control ratio of 1:3, in order to be able to conduct an adequately powered study within the available resources and study duration. They used OpenEpi software for the calculation of sample size, considering two- sided confidence level of 95 %; power of 80 %; expected exposure to additional antibiotics (in excess of the usual coverage from Gram- negative enteric bacilli received by all study participants) among 30 % of controls (based on retrospective survey of hospital records) and an anticipated odds ratio of 3.5. For a case: control ratio of 1:3, they derived an optimum sample size of 28 cases and 82 controls with both Kelsey and Fleiss methods.

Blood culture was done by collecting 2 ml of venous blood at the patient's bedside in Biphasic Brain Heart Infusion (BHI) medium. The culture bottles were incubated for 7 d before being declared negative. Growth on BHI Agar was subcultured on Sabouraud's Dextrose Agar (SDA).

To delineate the role of endogenous colonization in the development of candidemia, skin and mucosal swabs were collected from candidemic and a subset of non-candidemic patients. Swabs were randomly collected from the hands of health care providers to identify environmental source of infection. For skin and mucosal swabs, primary culture was done on SDA.

Typical Candida colonies, characterized by smooth, creamy and pasty appearance on SDA, were subjected to species identification using standard tests like germ tube test, sugar fermentation test, sugar assimilation test, morphology on Corn Meal Agar and color production on ChromAgar media. The recovered Candida isolates were then subjected to antifungal susceptibility testing by disc diffusion method, using commercially procured antifungal discs (Hi-media) and by broth macro dilution method using commercially procured antifungal powders (Sigma-Aldrich). Standard CLSI guidelines described in documents M- 44A and M27-A2 were followed for the two methods respectively. For interpretation of sensitivity or resistance, zone sizes recommended by disc manufacturers were taken into consideration. Standard ATCC strains, *viz. C. albicans* ATCC 5314 and *C. krusei* ATCC 6258 were used as controls.

Results

This matched case- control study was conducted on 28 candidemic infants, each of whom was matched with 3 controls for age, underlying primary condition and period of hospitalization. Premature neonates were also matched for birth weight. The baseline characteristics of the two groups are depicted in Table 1.

Among the different risk factors analyzed, the authors observed a profound effect of antibiotic usage on the development of candidemia. Although all the patients recruited in the study were on antibiotics, there was a significant difference in the extent of antibiotic coverage between the cases and controls. As shown in Fig. 1, the candidemic cases received antibiotic coverage for a wider spectrum of microorganisms, compared to the controls (χ^2=18.735; df =5; p 0.005). While every recruited patient received antibiotic coverage against gram negative enteric bacilli, prescription of extra antibiotics for additional groups of microorganisms was significantly higher among the candidemic infants (85 % *vs.* 44.4 %; χ^2= 9.741; p 0.008). Antibiotic coverage against gram-positive cocci, in addition to gram-negative enteric bacilli, was also significantly higher among the cases, compared to the controls (χ^2=7.515; p 0.011). Use of antibiotics with specific antipseudomonal action was, however, not significantly higher among the cases (χ^2=2.467; p 0.190). The average number of antibiotics received by the candidemic patients (3.1 *vs.* 2.6; p 0.097; unpaired t test) and the duration of antibiotic therapy (7.5 *vs.* 6.4 d; p 0.187; unpaired t test) were also not significantly different compared to the controls.

The authors also observed a significant increase in the occurrence of candidemia with the increasing number of indwelling devices used. While three types of devices were used in the recruited infants; use of indwelling devices other than IV canula, *viz.* nasogastric tube and endotracheal tube, posed significantly higher risk for the development of candidemia than the use of IV canula alone (p 0.0007).

The authors then examined the association of candida colonization with the development of candidemia. While 14 of the 24 candidemic patients screened (58.3 %) were colonized at one or more sites, the same was observed in 8 of the 30 non-candidemic patients (26.7 %) (p 0.018). At all the sites screened for colonization, *viz.* oropharyngeal mucosa, rectal

Table 1 Baseline characteristics of cases and controls

Characteristic	Cases (n =28)	Controls (n =84)	p value	95 % CI
Age (mo) (Mean±SD)	0.9±1.6	0.6±1.2	0.475	−0.5-1.0
Male gender (%)	21 (75)	59 (70.2)	0.629	
Gestational age (wk) (Mean±SD)	36±3.6	35.9±3.5	0.936	−1.75-1.9
Cesarean delivery (%)	10 (35.7)	32 (38.1)	0.821	
Birth weight (kg) (Mean±SD)	2.0±.6	2.1±.7	0.356	−.55-0.2
Primary condition (%)				
Septicemia	14 (50)	42 (50)		
Respiratory distress syndrome	4 (14.3)	12 (14.3)		
Congenital heart disease	3 (10.7)	9 (10.7)		
Necrotizing enterocolitis	1 (3.6)	3 (3.6)		
Pneumonia	4 (14.3)	12 (14.3)		
Birth asphyxia	2 (7.1)	6 (7.1)		
Period of hospitalization (days) (Mean±SD)	7.5±2.3	6.5±3.2	0.239	−0.63-2.5
Hemoglobin level (%)	15.3±3	15.7±2.5	0.523	−1.9-0.9
Total WBC count (cells/cu.mm) (Mean ± SD)	18659±15615	17108±9708	0.610	−4482-7585
Differential count (%) (Mean ± SD)				
Neutrophil	56.2±19.5	55.0±19.2	0.811	−8.8-11.3
Lymphocyte	35.4±18.9	36.3±18.4	0.845	−10.6-8.7
Monocyte	0.6±1.7	0.3±0.9	0.387	−0.3-0.9
Eosinophil	1.4±1.8	1.5±1.8	0.894	−1-0.9
C- reactive protein	26.7±36.6	18.7±26.9	0.308	−7.5-23.5

mucosa, axilla and groin, colonization was significantly higher among the candidemic infants, compared to the controls. The rectal mucosa was the commonest site of colonization in both the study groups (Table 2). To look for possible exogenous source of Candida infection, the authors performed surveillance culture of hand swabs of randomly

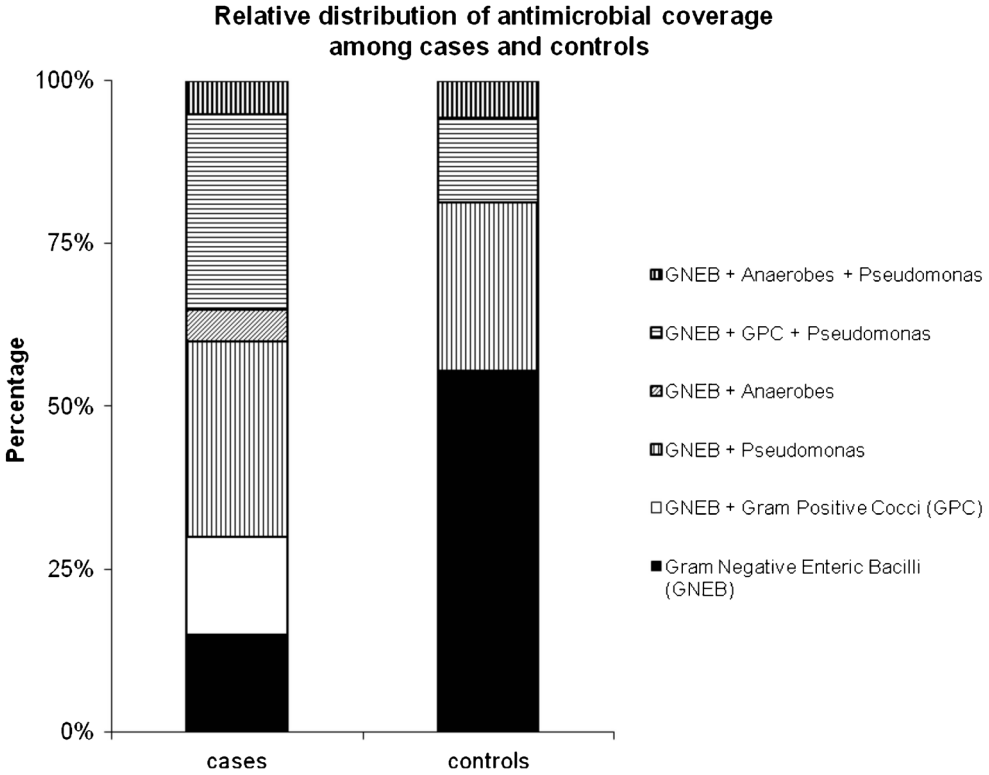

Fig. 1 Relative proportion of cases and controls on various antibiotic regimens. Every patient, in both the populations, received antibiotic coverage against enteric Gram- negative bacilli. However, Gram-positive coverage was significantly commoner among the cases

Table 2 Comparison of risk factors between cases and controls

Characteristic	Cases (n =28)	Controls (n =84)	p value
No. of antibiotics administered (Mean ± SD)	3.1±1.2	2.6±1.0	0.097
Antibiotic classes			
Penicillins	6 (20.8)	7 (8.7)	0.06
Vancomycin	4 (12.5)	7 (8.7)	0.36
Fluoroquinolones	4 (12.5)	4 (4.3)	0.09
Beta-lacatmase inhibitor	8 (29.2)	20 (23.9)	0.61
Carbapenems	2 (8.3)	4 (4.3)	0.63
Anti-Pseudomonal Penicillin	5 (16.6)	9 (10.9)	0.32
Polymixin B	2 (8.3)	2 (2.2)	0.23
Metronidazole	2 (8.3)	4 (4.3)	0.62
Chloramphenicol	5 (16.6)	7 (8.7)	0.15
Indwelling devices			
IV canula alone	7 (25)	52 (61.9)	0.0007
IV canula + endotracheal tube	14 (50)	22 (26.2)	0.019
IV canula + nasogastric tube	8 (28.6)	10 (11.9)	0.037
IV canula + other devices	21 (75)	32 (38.1)	0.0007
Endogenous colonization[a]			
Total no. of colonized patients	14 (58.3)	8 (26.7)	0.018
Oropharynx	10 (41.7)	4 (13.3)	0.018
Rectum	12 (50)	6 (20)	0.02
Axilla	6 (25)	2 (6.7)	0.059
Groin	8 (33.3)	3 (10)	0.034

[a] Figures based on screening of 24 candidemic and 30 non-candidemic patients

selected health- care workers at quarterly intervals throughout the study period. Of the 60 hand swabs examined, none yielded the growth of any Candida isolate.

Eighteen of the 28 candidemic infants (64.28 %) were infected with *Candida albicans*, followed by 7 infants with *C. tropicalis* (25 %), 2 with *C. glabrata* (7.14 %) and 1 with *C. parapsilosis* (3.57 %). Comparing the distribution of risk factors, the authors observed a significant association of non-albicans candidemia with preterm infants and higher number of indwelling devices. Metronidazole usage was also observed more commonly among infants with non-albicans Candida infections.

In the index study authors observed no resistance to Nystatin and Amphotericin B among the recovered isolates. Clotrimazole was the least effective antifungal agent, while Fluconazole and Ketoconazole resistance was observed among 10.7 % of the isolates. No difference in azole resistance was observed between the *C. albicans* and non-albicans isolates. The authors also evaluated the MICs of all the isolates against Amphotericin B, Fluconazole and Ketoconazole by broth macrodilution method and examined its concordance with the disc diffusion method. While they observed 100 % agreement between the two methods for Amphotericin B, the same was found to be 95.8 % and 91.7 % respectively for Fluconazole and Ketoconazole. There was discrepancy in one *C. parapsilosis* isolate, which was found to be sensitive to Fluconazole by the disc diffusion method and demonstrated dose- dependent susceptibility to Fluconazole by broth macrodilution method. Similarly, one isolate each of *C. albicans* and *C. tropicalis* were found to be resistant to Ketoconazole by the former method, while they showed dose-dependent susceptibility by the latter (Table 3).

Discussion

In this study authors observed that the risk of candidemia in an Indian pediatric ICU increases significantly with increasing spectrum of antibiotic coverage, increase in the number of indwelling devices and is associated with concomitant endogenous colonization. They observed that *C. albicans* was the predominant species involved in these episodes and fluconazole and ketoconazole resistance was observed among a sizable fraction of both *C. albicans* and non-albicans isolates. They also observed that the results of the disc diffusion method for antifungal sensitivity testing show significant concordance with the more labor- intensive broth macrodilution method.

Unlike countries where antibiotic usage is generally restricted and prescription of antibiotics is regulated by specific policies, the situation is very different in India where antibiotics are freely available across-the-counter, guiding policies

Table 3 Results of antifungal sensitivity testing in the recovered isolates

Name of species	No.	Method of antifungal sensitivity testing	No. of resistant isolates (%)				
			Fu	Kt	Cc	Ny	AmB
C. albicans	18	Broth macrodilution	1(5.6)	0	ND	ND	0
		Disc diffusion	1 (5.6)	1 (5.6) ^	9 (50)	0	0
C. tropicalis	7	Broth macrodilution	1 (14.3)	0	ND	ND	0
		Disc diffusion	1 (14.3)	1 (14.3) ^	6 (85.7)	0	0
C. glabrata	2	Broth macrodilution	1 (50)	1 (50)	ND	ND	0
		Disc diffusion	1 (50)	1 (50)	2 (100)	0	0
C. parapsilosis	1	Broth macrodilution	0	0	ND	ND	0
		Disc diffusion	0	0	1 (100)	0	0

Fu Fluconazole; *Kt* Ketoconazole; *Cc* Clotrimazole; *Ny* Nystatin; *AmB* Amphotericin B; *ND* Not Done

^These isolates demonstrated dose-dependent susceptibility to the corresponding antifungal agent by broth-macrodilution method

on antibiotic usage are not available, wide variability is observed in the choice of antibiotics between treating clinicians and antibiotics are often used to compensate for poor infection-control practices. While such uncontrolled use and misuse of antibiotics is known to be responsible for the growing menace of antibiotic resistance among bacterial pathogens, it could also account for the increasing incidence of pediatric candidemia, as has been observed in the present study.

Several studies have reported an association between the occurrence of candidemia and the use of broad- spectrum antibiotics, particularly third generation cephalosporins [4–8]. Since all the patients recruited in this study were receiving antibiotic coverage against gram-negative enteric bacilli with a combination of third generation cephalosporins and aminoglycosides, the authors could not delineate the specific role of these antibiotics in the development of candidemia. Interestingly, however, use of vancomycin for gram-positive coverage and metronidazole for anaerobic coverage was significantly higher among the cases. Similar to authors' observations, MacDonald et al. have also reported a trend towards more-prolonged use of vancomycin in hospitalized children developing candidemia [3]. Though the authors observed no statistically significant difference in the use of anti-pseudomonal penicillins, fourth generation cephalosporins, beta-lactam and beta-lactamase inhibitor combinations and carbapenems between the cases and controls, the association of individual classes of antibiotics with the occurrence of candidemia needs to be examined in a more elaborate study. This would prove useful for identifying patients at higher risk for pediatric candidemia in situations like present where every hospitalized patient is put under antibiotic coverage. The mechanism by which these antibiotics influence the development of candidemia also needs to be elucidated.

Previous studies have also reported association of candidemia with the presence of indwelling vascular devices, particularly central venous catheters [3, 7, 9–12]. Since all the patients recruited in this study had IV canula inserted and none had central venous catheter, the authors could not assess the role of these devices in the development of candidemia. They did not, however, have the data to look for a difference in the number of catheter- days between cases and controls. Nevertheless, their observation regarding the increasing incidence of candidemia with the use of other indwelling devices, like nasogastric tube and enotracheal tube, is significant for future infection-control surveillance.

The authors observed endogenous colonization in 58.3 % of the screened candidemic patients and failed to detect any exogenous source of candidemia in the hands of health-care workers. One of the limitations of the index study was that the environmental surveillance was limited in scope, as it did not include probable sources like ventilator tubing, latex gloves, bandages, IV catheters, IV solutions, *etc.* However the index data is in concordance with previous studies, which suggest that candidemia usually originates from an endogenous source [8, 13] and isolation from hospital sources and staff skin is usually linked with nosocomial epidemic outbreaks [10, 14–17].

C. albicans is usually the predominant species reported from pediatric patients, as has been observed in the index study [7, 11, 18–20]. This is in contrast to many studies conducted in adult candidemia [21–24], where non- albicans species have been found to outnumber *C. albicans* isolates. The species-distribution of non- albicans isolates is characterized by marked geographical variation, with *C. glabrata* being the commonest non-albicans species isolated worldwide [21, 24–27]. However, studies from India, Singapore and Taiwan have reported *C. tropicalis* to be the commonest non-albicans Candida [28–30] similar to the index findings.

Unlike antibacterial susceptibility testing, antifungal susceptibility testing is not a routine practice in most clinical laboratories and an empirical approach is usually followed in

prescribing this class of drugs. In a previous study on candidemia occurring in adult ICU patients of authors' hospital, fluconazole resistance of 17.3 % was observed among *C. albicans* isolates and 26 % among Candida isolates of all species, using the disc-diffusion method [31]. Following this alarming observation, the authors planned to conduct a similar study in pediatric patients and to corroborate the findings of disc-diffusion method with the broth-macrodilution method. The index results suggest that the prevalence of antifungal resistance is markedly lower in pediatric patients, compared to adult patients, and the two methods demonstrate significant inter-test agreement. However, isolates found resistant by the disc-diffusion method might be re-tested by the broth macrodilution technique for confirmation. This observation is of significance since reliable results obtained in a less laborious test, like the disc-diffusion technique, offers a scope of implementing this method in clinical laboratories for routine performance of antifungal sensitivity testing, similar to the practice adopted for bacterial isolates.

The index study suffers from several limitations. The newer antifungals like voriconazole, posaconazole, caspofungin, *etc.*, which have not been included in the present study, should also be tested for efficacy against the resistant isolates. Moreover, correlation needs to be explored between the results of antifungal sensitivity testing and the clinical response to antifungal treatment. Secondly, molecular studies to demonstrate the relatedness between colonizing and bloodstream isolates were not performed.

This observational study, aimed at characterizing the epidemiological and mycological profile of candidemia in the setting of a typical Indian pediatric ICU, could assist the clinical fraternity in adopting locally relevant prophylactic and treatment guidelines for the improved management of this condition.

Contributions CA: Manuscript preparation, literature search, clinical and experimental studies, data acquisition; DB: Concepts, manuscript editing, data and statistical analysis; AG: Clinical studies; BSC: Experimental studies. DB will act as guarantor for this paper.

Conflict of Interest None.

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