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Pediatric Candidemia in the Indian Subcontinent, and in Parts of the Middle East, Africa, and South America

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ABSTRACT

Candidemia is defined as isolation of *Candida* species from at least one blood culture with the presence of symptoms of sepsis. It is the main cause of fungal nosocomial bloodstream infections with its resultant mortality in children ranging from 5% to 71% and sometimes over 80%. A thorough search of the literature in Google, PubMed, Med Facts, using different sets of keywords, viz. candidemia, bloodstream *Candida* infections, neonates, children, developing countries showed that candidemia in neonates and children is caused by a variety of species, viz. *Candida albicans*, *C. auris*, C. *famata, C. glabrata*, *C. guilliermondii, C. krusei*, *C. orthlopsis*, *C. parapsilosis*, and *C. tropicalis*. The predominant etiological agents vary in different countries. Risk factors in most of the reports included prematurity, mechanical ventilation, prolonged use of antibiotic and steroid urinary catheter, hH-2 blockers, neutropenia, leukemia, and malnourishment. The underlying diseases included sepsis, pyogenic meningitis, encephalitis, pneumonia, acute reparatory distress syndrome, chronic liver disease and kidney disease etc. A noteworthy observation in literature is that several investigators employed MALD-TOFE, PCR and molecular methods including DNA sequencing in addition to study of phenotypic features for characterization of *Candida* species. Antifungal therapy in most studies used liposomal amphotericin B, caspofungin, azoles, or combination therapies The epidemiology of pediatric candidemia varies in different countries. Surveillance of candidaemia in different regions is necessary, especially in neonates and children. Rapid and precise detection of *Candida* species isolated from the bloodstream by polymerase chain reaction, restriction fragment length polymorphism technique can help in better management of candidemia. The strategies for prevention of candidemia include improved hand hygiene, optimal catheter placement and care, and prudent hygiene. Prophylactic antifungal therapy is recommended for patients who have not yet been diagnosed with candidemia but are at a high risk of acquiring *Candida* infections.

Keywords: Pediatric candidemia, Indian subcontinent, Middle East, Africa, and South America.

INTRODUCTION:

Candida infections account for approximately 70 to 90% of total invasive fungal infections (IFI) (Delaloye and Calandra, 2014). Global estimates indicated that ~ 750,000 cases of invasive candidiaisis occur annually (Bongomin *et al.,* 2017). Candidemia (blood -stream infection due to *Candida* spp. is the most common clinical presentation of IC and occurs mainly in hospitalized patients with ascribable mortality of 15–35% for adults and 10–15% for neonates (Guinea, 2014). In an update on the epidemiology of invasive fungal infections in the Middle East and North African region, (Osman *et al.,* 2009) have dealt with neonatal and pediatric candidemia in these regions. Candidemia caused by uncommon *Candida* spp with prolonged fungemia and treatment failures is now emerging among hospitalized children (Tsai *et al.,* 2018).

The risk factors for *Candida* infection include prematurity, low birth weight, invasive interventions, prolonged use of antimicrobials, H2 blockers, steroids, prior colonization, total parenteral nutrition, preexisting infection, prolonged use of broad-spectrum antibiotics, immune compromised status, recent surgery, central line dialysis, mechanical ventilation and extended length of stay in the NICU (Bongomin *et al.,* 2017).

DNA-based methods are considered the gold standard for the identification of fungal isolates, but clinical laboratories in resource-constrained countries have limited access to expensive molecular techniques. The definitive diagnosis still is based upon the identification of *Candida* in the blood.

RESULTS:

The brief demographic and clinical features including laboratory investigations and treatment described in the reports from different countries are described below in **Table 1**. It is noteworthy from the reports that investigators from India (Rudhramurhty *et al.,* 2020) used Sanger sequencing targeting internal transcribed spacer (ITS) region of ribosomal DNA, and the ones from Iran (Fattahi *et al.,* 2000) employed PCR-RFLP amplification of ITS1-5.8SrDNA-ITS2 region with pun fungal primers ITS1-ITS4 region in addition to phenotypic study of the isolates on routine mycological media and CHRO Magar.

Table 1: Demographic and brief clinical features of cases of pediatric candidemia in different countries.

Locality, No investigated/ No Positive (%), Study period	***Candida* species as causal agents/ No (% age)**	**Risk factors/ Underlying diseases, and Symptoms**	**Lab methods for isolation & species identification of *Candida***	***In vitro* AFST and treatment**	**Reference**
India					
Delhi 4750 (18.8%) Aged 0-12 yrs Period of study: one year.	*C. parapsilosis* (29.8), *C. tropicalis* (23.4), *C. glabrata* (14.8), *C. krusei* (4.3), *C. auris* (4.3), *C. albicans* (2.1), *C. guilliermondii* (2.1).	Risk factors-prematurity, mechanical ventilation, urinary catheterization, recent surgery, and prolonged antibiotic therapy, hematological disorders, neutropenia, malnourishment, HIV-AIDS, prolonged steroid therapy, previous exposure to antifungals.	43 isolates were re-covered from blood, 2 from peritoneal fluid and 2 each from CSF and pericardial fluid samples inoculated on biphasic medium using BHI agar and broth and incubated at 37^0C for 48 h. Species identification was done phenotypically, a few unusual isolates were identified by DNA Sequencing.	AFST-FLZ resistance was seen in 44.68% cases, & Ampho. While most of *C. albicans* (70%) & *C. parapsilosis* AFST (78.57%) isolates were sensitive to fluconazole, 54.54% among *C. tropicalis* isolates & only 28.6% among *C. glabrata* isolates. Only 54.54% of *C. tropicalis* isolates and 28.6% of *C. glabrata* was sensitive *to* FLZ.	Kumar *et al.,* 2020
Haryana					
Medanta, Gurgaon 20/186 (10.75%) aged 1 month to14 yrs. Consecutively admitted to PICU for severe sepsis.	18 of the children colonized with the same species Risk of Mortality score (95% CI p = .034).	*C tropicalis* (34.2), *C. parapsilosis* (28.8), *C. albicans* (14.4), other species (unidentified) (22.6).	Recovery of *Candida* in blood cultures.		Singhi *et al.,* 2008
Oddisa					
Bhubaneshwar, Odisha, 36//926 (3.88) Study period Jan 2017-Dec. 2019. Aged 1 month-14 yrs.	*C. tropicalis* (44.4), *C. gkabrata* (16,7) *C parapsilosis* (16,7), *C. krusei* (5.6), *C. pelliculosa* (2.8).	Sepsis with MODS-Encephalitis-6, Scrub typhus-5, Pyogenic meningitis-4, Pneumonia with ARDS-3, GB synrome-3, Empyema thoracis-2, one each of Acute pneumonia, complicated malaria with CKD.	Blood samples collected in specific culture bottles, which were then loaded into a fully automatic BacT/Alert 3-D system. Cultures were identified by study of colonial morphology and microscopical features and coloy characters on *Candida* CHROM agar (HiMedia).	Most of the *Candida* isolates were sensitive to Amph. B (94.4%), CLZ (91.67%), VCZ (89%), ITZ (86 %) Lower sensitivity to FLZ (39%) and Nys (53%). *C. pelliculosa* was sensitive to all antifungal agents.	Behera *et al.,* 2020

Chandigarh 39/47 (82.97) Aged 0-18 years Study period: January 1-31 December.	*C. krusei* (21.3%) (11.85), *C. tropicalis* (10.86), *C. albicans* (5.80), *C. pelliculosa* (3.83).	Predisposing factors-Gastrointestinal disease, previous antibiotics especially carbapenems. Observed among patients with candidemia due to *C. tropicalis* did not have any association with that due to *C. krusei.* Examination of 40 environmental samples, viz bed railing, washbasins, taps, medicine trolley and ventilator, & 24 HCW revealed clonality between blood & environmental isolates indicating cross-transmission of *C. krusei.*	Blood samples were inoculated into BD BAC-TEC blood culture bottles BD BACTEC^{TM} 9240, and incubated. Loopfuls of positive cultures were inculated on blood agar and SDA and incubated at 37 ^{0}C for 24 h. *Candida* species were identified by phenotyping methods and MALD-TOFEL A few isolates were subjected to molecular identification for confirmation by Sanger sequencing targeting internal transcribed spacer (ITS) region of ribosomal DNA.	AFST-Only 8.6%. 4.8% and 6.1% of the isolates tested had MIC of ≤ 1 mg/L against caspofungin, micafungin and anidulafungin respectively. All isolates had MIC of ≤ 0.5 mg/L against ITZ, VCZ and PSZ except for two isolates which showed MIC of ≤ 2 mg/L mg/L against VCZ. Treatment of the cases is not mentioned.	Rudramurthy *et al.*, 2020 to Kaur *et al.*, 2020
Pakistan					
Karachi 34 children Study period: January 2006-May 2009 Age range (2-14) years.	*C. albicans* (20.0) *C. tropicalis* (17.0), *C. parapsilosis* (18.5).	Risk factors-increased use of cephalosporins (COR 4.14, 95 % CI 1.52–11. 26) and decreased use of BLICs and vancomycin total parental nutrition. Most children acquired infections nosocomially with use of venous catheters, ventilators and abdominal and pleural cavity drains.	Species identification was based on conventional phenotypic characteristics: production of a germ tube, morphology on BBL on conventional phenotypic characteristics: production of a germ tube, morphology on BBL BiGGY Agar (BD), growth with cycloheximide, urease production. Identi-fication was also confirmed using either a Luminex multi analyze profiling assay with ITS 2 target or DNA sequencing.	AFST and treatment is not mentioned.	Farooqi *et al.*, 2013
Bangladesh					
Dacca Out of 100 cases of candiedmia, 21 were due to *C. auris.* Period of study not mentioned.	*Candida* species 70 isolates not identified.	Twenty-one isolates identified as *C. auris.*	Identification of *Candida* isolates as *C. auris* was done by growth characters, and biochemical characteristics, and further confirmed by PCR and sequencing ITS1 and ITS2 targeting the con-served regions of 5.85 rRNA.	AFST by DD, and MIC method Out of 21 *C. auris* isolates, 17 (81. 0%), 7 (33. 3%) and 3 (14.3%) were sensitive Ampho. B, FLZ and VCZ respectively. 14 isolates were FLZ resistant. Treatment not mentioned.	Dutta *et al.*, 2019
Qatar					
Doha- 35 cases of neonatal candidemia detected during the study period: Jan 2004, Dec. 2010.	*C. albicans* (30.2), *C. glabrata* (22.5%), *C. tropicalis* (17.9), & *C. orthoolopsis* (17.9), other species (8.3).	All *Candida* isolates were recovered by blood culture and identified phenotypically. Identification was confirmed by ethanol-formic acid extraction protocol.	AFST- 2.2% of *C. albicans*, 6.5% of C. glabrata, 35.2% of *C. tropicalis,* (n 5; 6.5%), *C. tropicalis*, 5.5% of *C. parapsilosis* demonstrated Ampho B. MIC above the ECV.	Treatment and outcome of patients is not mentioned.	Taj-Aldeen *et al.*, 2014
Oman					
Muscat-Study of 2 pediatric cases of *C. aurisfungemia* detected during 2016-19. Both were male children, one aged 0.5 yr. and the other 2 yrs.	One of the cases was neutropenic.	Identification was done by MALD-TOF and confirmed by ITS-rDNA sequencing. Microsatellite typing revealed that the isolates belonged to South Asian Clade 1.	AFST-The isolates were susceptible to VCZ and Ampho. B but were resistant to FLZ.	The child aged 0.5 yr was treated for 15 days, and the one aged 2 yrs for 16 days.	Moshin *et al.*, 2020

Iran					
Isfahan Study 16/36 (44.4%) Study period: Oct. 2013 to Jan. 2015.	*C. albicans* (68.7%), *C. glab rata* (25.0), *C. parapsilosis* (6.2).	Risk factors-7 children had cancer, 4 ileus. 2 diabetes, and one each had cerebral tumor hear failure, and kidney trans-plantation. 14 (87.5%) had nonspecific symp-toms including fever, chills, pain. Nausea, vomiting, and 2 child-ren (12.5%) were asymptomatic.	Phenotypic identification of blood culture *Candida* isolates on CHROM agar *Candida* (Paris, France) and confirm ation by PCR-RFLP of ITS1-5.8SrDNA-ITS2 region in addition to phenotypic study of the isolates on routine mycological media and CHROMagar.	Not done.	Jabari *et al.*, 2016
Tehran 42/75 (84%) aged 6-12 yrs (Males -12, F-30). Period of study: 2017-2018.	*C. parapsilosis* (59.52) *C. albicans* 26.19), *C. tropica-lis* (9.52), *C. glabrata* (4.76).	Identification of *Candida* spp was done PCR-RFLP method. The *Candida albicans* Complex and *Candida parapsilosis.* Complex were differentiated by *HWP1* gene amplific-ation and PCR-RFLP with *NlaIII* restriction enzyme respectively.	Isolation of *Candida* was done by inoculating blood samples into aerobic culture medium bottles, which were. incubated for 5 days The isolates were purified by sub-culturing on Blood agar and CHRO Magar, Definitive identification was confirmed by the PCR- RFLP approach.	AFST and treatment is not mentioned.	Fattahi *et al.*, 2020
A set of 50 *C. para-psilosis* and six *C. orthopsilosis* isolates from 42 and five candidemic pediatric patients, respectively, hospitalized in Tehran, 2014–2017.	*C. paraopsilosis* (89.4), and *C. orthopsilosis* (10.6).	Risk factors-exposure to Vancomycin and 3rd generation cephalos-porin's, CVC. TPN. Underlying conditions premature birth and metabolic disease.	AFLP fingerprinting and microsatellite typing and analysis for nucleotide polymorphism by *FSKI* and *ERG11* sequencing APPLP-fingerprinting grouped isolates in two main clusters.	Not mentioned.	Hare *et al.*, 2022
Turkey					
Samsun 51 pediatric cases aged ≤ 18 yrs. detected during June 2007-June 2009.	*C. albicans* (18.4), *C. parapsilosis* (10.6), *C. tropi-calis* (7.4).	Samples were process-sed in automated blood culture system. The isolates were identified phenotypically on SDA, cornmeal Tween 80 agar and confirmed by using API ID 32 yeast identification system.	Predisposing factors-The underlying diseases-AMC, PN. VC, UC, ETE surgery. Trach-eotomy trauma. Prolonged ICU stay. Underlying diseases-Prematurity, malignancy, in-fection, hereditary syndromes, vascular disease, & others.	AFST and treatment are not mentioned.	Brinci *et al.*, 2011
South Africa					
Gauteng and Wes-tern Cape provinces-1478 neonates (≤28 days of age), 806 infants (29 days to <12 months), 589 children (1–11 yrs.), & 123 adolescents (12–17 yrs.) Study period: 2012-17	*C. parapsilosis* (42.0), *C. albicans* (33.0), *C. glab-rata* (6.0), C. *auris* (3.0), *C. tropicalis* (3.0)	Risk factors-very low birth premature Infants.	The isolates were identified phenotypically and identify-cation was confirmed Vitek-2 system or the matrix-assisted laser desorption/ionization time-of-flight mass spectro-metry flex analysis system.	AFST0 broth micro-dilu-tion panels containing Al-amar blue MICs of amp-hotericin B were deter-mined by Etest. 35% of isolates were resistant to FLZ. All isolates of *C. auris* were susceptible to Amph. B & 90% were resistant to FLZ. Treat-ment is not mentioned.	Shuping *et al.*, 2021
Nigeria					
Ibadan, Oyo State 17/25 (68%) child-ren less than 1 yr. old diagnosed as cases of candied-mia during the study period: September 2008-August 2009.	*C. tropicalis* (24.0), *C. parapsilosis* (16. 0), *C. albicans* (4.0), (1.0) each of *C. albicans* & *C. albicans* & *C. tropicalis* mixed infection.	Risk factors- very low birth weight and premature infants.	10 milliliter or each blood specimen inoculated into BACTEC blood culture bottle and incubated at 37 °C using a BACTEC 9050 blood culture system. Cultures showing yeast cells were phenoty-pically identified on SDA and con-firmed by API 20C AUX.	AFST-tested for sensiti-vity in RPMI broth in microtiter plates incubi-ted at 35 ^{0}C for 24-48 hrs. All isolates of Can-dida spp were susceptible to fluconazole (MIC < 8 mg/mL). Treatment is not mentioned.	Oladele *et al.*, 2014

Mexico					
Mexico City Retrospective study 2012-17 to identify cases of invasive candidiasis due to *C. guilliermondii* Complex.	15 patients identified aged ≥17 yrs.	The underlying diseases- CHD (40%), hematological disorders (26%) Risk factors-indwelling catheter, CVC, and h/o BSAT.		All patients with hematological disorders received prophylactic FLZ. AFT included FLZ (40%), CF (27%), Amph. B (20%), FLZ+ CP (13%).	Castillo-Bejarano *et al.*, 2020
Brazil					
São Paulo 13 Pediatric cases detected during the period: Jan 2009-July 2017.	*C. parapsilosis* (76.9%) *C. krusei* (15.4%), *C. rugosa* (7.7%). Micro-satellite typing of *C. parapsilosisisol* at Barrientosyes.	Underlying diseases- Septic shock in 5 cases, CVC-associated infections in 7 cases, lung infiltrates in 8 cases, and heaptic nodules in 2 cases. Risk factors- All had received BSAT, 10 had mucositis and 7 had been TPN.	Blood cultures were collected in Bactec® pediatric or aerobic bottles and incubated for 5 days. Positive cultures were purified by subcultures on Sheep BA and identified by Vitek MS, MALDI-TOF mass spectrometry.	AFST-by using CLSI broth micro-dilution method. All patients under-went prophylactic antifungal therapy with MF in 13 cases, and in 3 cases each with FLZ, ITZ, and 1 with VCZ.	Barrientos *et al.*, 2021

It is noteworthy from the reports that investigators from India (Rudhramurhty *et al.,* 2020) used Sanger sequencing targeting internal transcribed spacer (ITS) region of ribosomal DNA, and the ones from Iran (Fattahi *et al.,* 2000) employed PCR-RFLP amplification of ITS1-5. 8SrDNA-ITS2 region with pun fungal primers ITS1-ITS4 region in addition to phenotypic study of the isolates on routine mycological media and CHRO Magar.

Abbreviations

NUPE- Neonatal unit of paediatric emergency, HCW -Health care workers, FAFLP-Fluorescent amplified fragment length polymorphism, ITS- Internal Transcribed spaces, ECV-Epidemiological cut off value, MIC-Minimum inhibitory concentration, CLSI-Clinical laboratory standards institute, EC-Echinocandins, MF-Micafungin, BA-Blood agar, CHD-Congenital heart disease, and BSAT-Broad-spectrum antibiotic therapy

CONCLUSION:

Given the high mortality rate and the difficulties encountered in administering early and effective antifungal therapy, better methods of prevention will decrease candidemia-associated mortality more effectively than will advances in therapy. The strategies for prevention of candidemia include improved hand hygiene, optimal catheter placement and care, and prudent hygiene Guinea, (2014). For hand washing, both alcohol nosocomial candidemia Guinea, (2014). For hand washing, both alcohol *Candida* species on the hands of health care workers. The role of prophylactic or empirical therapy in preventing candiedmia or decreasing mortality rate associated with it is not clear. Because of the high mortality associated with the more delayed therapy in candidemia especially in neutropenic patients, empirical therapy with anti-fungal drugs is usually advocated for such patients. Prophylactic antifungal therapy is recommended for patients and those who do not have the suggestive symptoms but are at a high risk of acquiring *Candida* infections. The regional surveillance of the pediatric patients at highest risk and the pattern of causative agents of candidemia in order to develop guidelines for better management of this fatal infection are emphasized.

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CONFLICTS OF INTEREST:

The author has no conflict of interest with any individual or organization.

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