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Research Article

CANDIDEMIA IN NEONATES: A CONCERNING THREAT IN NEONATAL INTENSIVE CARE UNITS

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ABSTRACT

Neonatal sepsis is a significant health concern. *Candida* species are the leading cause of invasive fungal infections in neonatal intensive care units, accounting for 9-13% of bloodstream infections in neonates. *Candida albicans* is the most common causative agent, but nonalbicans candidial septicemia is becoming more common due to the increased use of azole drugs. This study aims to isolate and speciate *Candida* from suspected cases of neonatal sepsis, perform antifungal susceptibility testing, and demonstrate biofilm formation. The study involved isolation of *Candida* from neonates with a clinical diagnosis of septicaemia. Gram staining, germ tube test, pigmentation on Chrome *Candida* differential agar, and Dalmau plate culture were used to identify the organisms. Antifungal susceptibility testing was performed according to the Clinical Laboratory Standards Institute (CLSI) guidelines. Biofilm formation was detected by Microtiter Plate method. Out of 469 samples, 54 (11.51%) cases had isolation of *Candida* species. The predominant *Candida* isolates were *Candida tropicalis.* Among all the drugs tested, sensitivity of *Candida* isolates was lowest for fluconazole (70.37%), highest for Caspofungin (100%) and micafungin (100%). The Microtiter Plate Method revealed that 57.41% of the *Candida* isolates had formed biofilms. The study highlights the importance of identifying *Candida* species in neonatal septicemia.

INTRODUCTION

Neonatal period is the first 4 weeks of extrauterine life (Atherton *et al.,* 2004). A significant amount of morbidity and mortality are caused by neonatal sepsis. Clinical symptoms can range from mild infections to severe systemic or localised illness presentations. Origin of the pathogen can be traced to an infection during pregnancy (vertical transmission), from the mother's flora during vaginal delivery or postpartum acquisition from the hospital (Shane *et al.,* 2017). The clinical manifestation of neonatal sepsis depends on the time of exposure, the amount of the inoculum, the infant's immunological state and the virulence of the causative agent. A neonate's immunological immaturity may cause an inadequate response to pathogens. This is particularly true for preterm new-borns, who are more likely to contract infections in hospitals due to their longer hospital stays and requirement for invasive operations.

Candida species are the leading cause of invasive fungal infection in neonatal intensive care unit (NICU) (Wadile *et al.,* 2015). It is the third most common cause of late onset sepsis in NICU patients and accounts for 9-13% of blood stream infections (BSI) in neonates (Juyal *et al.,* 2013). Nosocomial infections are more likely to affect neonates hospitalised to intensive care units. These dangers are connected to their propensity for infections as a result of their immaturity and the invasive medical equipment they require to survive. The rise in *Candida* bloodstream infections over the past ten years has been mostly attributed to the increase in survival rates of new-borns with Very Low Birth Weight (VLBW). Immunocompromised hosts, usage of parenteral antibiotics and corticosteroid use are additional risk factors for candidiasis (Wadile *et al.,* 2015).

Candida albicans was known as most common causative agent till date for neonatal sepsis of fungal origin. Between 50% and 70% of cases of invasive candidiasis were caused by *Candida albicans* (Narain, 2003). On the other hand, current research indicates that nonalbicans candidial septicemia is becoming more common. A rising number of isolates of *Candida tropicalis*, *Candida glabrata*, and *Candida parapsilosis* are found in neonatal septicemia patients. The increased usage of azole drugs suggests an epidemiological shift from *Candida albicans* to non-albicans *Candida* (NAC). These NAC species specifically *Candida krusei* exhibit intrinsic resistance to traditional triazoles like fluconazole and many of them also demonstrate cross-resistance to newer triazoles as *Candida glabrata* (Pahwa *et al.,* 2014; Iwata 1992; Jensen 2016; Arendrup 2013). Recently, *C. auris* has grown to

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represent serious threat in healthcare settings as it has drug resistance to all known antifungal classes including azoles, amphotericin B and echinocandins(Sharma and Kadosh, 2023; Chowdhary *et al.*, 2023). The current study is attempted with a goal to formulate early empirical therapy for neonatal candidemia in our hospital and thus further reduction in morbidity and mortality.

Aims and Objectives

This study aims to isolate *Candida* from suspected cases of neonatal sepsis. An effort is made to perform both speciation and antifungal susceptibility (AFS) testing on all the *Candida* isolates. Demonstration of biofilm formation ability of *Candida* isolates is also done as it is an important virulence factor

MATERIALS AND METHODS

Over the course of ten months, from January 2023 to October 2023, a cross-sectional study was carried out in the department of microbiology at the Government Medical College and Hospital in Nagpur, Maharashtra. The Ethical Committees of our institution approved this studyand informed consent was taken. Candidemia was defined as at least one positive blood culture for *Candida* species in the presence of signs and symptoms of sepsis (Nazir and Masoodi, 2018).

During the sample collection process, all necessary antisepsis measures were taken. Aseptic inoculation of the blood samples (1-2 ml) was performed in paediatric blood culture bottles that held 5-10 ml of Tryptic soy broth. Blood culture bottles were aerobically incubated at 37^0C overnight. Following a 24-hour incubation period, primary subcultures were carried out on Sabouraud Dextrose Agar (SDA), blood agar and MacConkey's agar. A total of 3 subcultures were done to agar plates. Negative report was given after 7 days, if no growth is obtained.

All the *Candida* isolates were subjected to Gram staining and germ tube test using a normal human serum. Preliminary identification was done by colony morphology on chromogenic media (HiCrome, HimediaPvt. Ltd., Mumbai, India) and chlamydospore formation on corn meal agar by Dalmau plate culture. Utilized automated Vitek 2 compact 60 system (BioMerieux India®) using Vitek 2 cards to authenticate the organism's identity.

Antifungal susceptibility (AFS) was done as per Clinical Laboratory Standards Institute (CLSI) M27M44S-Ed3 guidelines by disc diffusion method. On Muller-Hinton agar enriched with 2% glucose and 0.5 µg/ml methylene blue dye (GBM), AFS by disc diffusion was carried out for fluconazole (25µg), voriconazole (1µg), itraconazole (10µg) and amphotericin B (10 µg). The authorised CLSI guidelines were followed in interpreting zone diameters. Based on CLSI-recommended interpretive standards, AFS results for flucytosine, capsofungin, and micafungin were obtained using VITEK two compact systems.

Biofilm formation was performed on a sterile 96-well microtiter plate. A colony of each isolate was inoculated into tubes containing 2 ml of brain heart infusion broth (BHIB) and incubated at 37°C for 24 hours. Using fresh BHIB, all broth cultures were diluted at a ratio of 1:20. Then, 200 µl was added to microtiter plates and incubated for 24 hours at 37°C. Microtiter plates were emptied, rinsed three times with distilled water, and then inverted to blot when the incubation period was over. After that, 200 µl of 1% crystal violet was added to each well, and they were incubated for 15 minutes. Following the incubation period, distilled water was used to rinse the microplates three more times. Next, 200 µl of an 80:20 w/v ethanol: acetone mixture was added to each well, and were read at 450 nm using an ELISA reader, and OD was recorded for each well. Microorganism-free sterile BHIB served as the negative control. By arithmetically averaging the OD of the wells containing sterile BHIB and adding a standard deviation of +2, the cut-off value was established. Positive samples were defined as having an OD greater than the cut-off value, while negative samples were defined as having an optical density lower than the cut-off (Inci *et al.*, 2012).

RESULTS

During the study period, 469 samples from neonates with a clinical diagnosis of septicaemia were received by the Department of Microbiology. Out of total neonates, 220/469 (46.91%) had positive blood cultures. Two of the neonatal samples with culture-positive status exhibited more than one growth. There are 222/469(47.33%) isolates in total as a result. Of them, 54/469 (11.51%) cases revealed the isolation of *Candida* species. There were 21/54(38.89%) female and 33/54(61.11%) male neonates among the cases of neonatal candidiasis (Fig.1). The ratio of male to female was therefore 1.57:1. Compared to early-onset sepsis (EOS), which was represented by 17/54 (31.48%), late-onset sepsis (LOS) 37/54 (68.52%) had a higher isolation rate of *Candida* species. [Fig. 1]

There were 54 *Candida*, 72 gram-positive bacteria and 96 gram-negative bacteria among the 222 isolates [Fig. 2]. The predominant *Candida* isolates were NAC spp, 45/54 (83.33%). *Candida tropicalis* was found to be the most prevalent isolate of all, with 24/54 (44.44%) followed by *Candida albicans* 9/54 (16.67%), *Candida glabrata* 6/54 (11.11%), *Candida krusei* 4/54 (7.41%), and *Candida utilis* 4/54 (7.41%). [Table 1][Fig.3, Fig. 4]

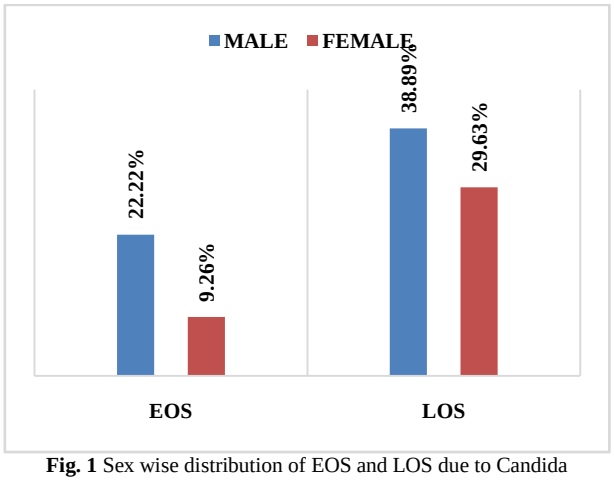

Fig. 1 Sex wise distribution of EOS and LOS due to Candida

Risk factors

Following a correlation analysis between our results for candidemia and related risk variables, the current study found that Low Birth Weight (LBW) and prematurity were the most common risk factors followed by prolonged intravenous antibiotic therapy, prolonged central venous line and ventilator support [Table 2]

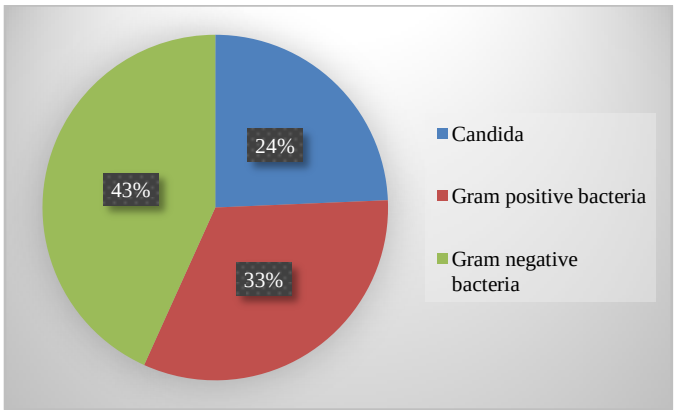

Fig. 2 Distribution of microorganisms isolated from neonatal septicemia cases

Table 1 *Candida* species isolated from neonatal septicemia cases

***Candida* species isolated (n=54)**	**Number of isolates (%)**
○ *Candida tropicalis*	24(10.81%)
○ *Candida albicans*	9(4.06%)
○ *Candida glabrata*	6(2.70%)
○ *Candida krusei*	4(1.80%)
○ *Candida utilis*	4(1.80%)
○ *Candida guilliermondii*	3(1.35%)
○ *Candida parapsilosis*	2(0.90%)
○ *Candida lusitaniae*	1(0.45%)
○ *Candida kefyr*	1(0.45%)

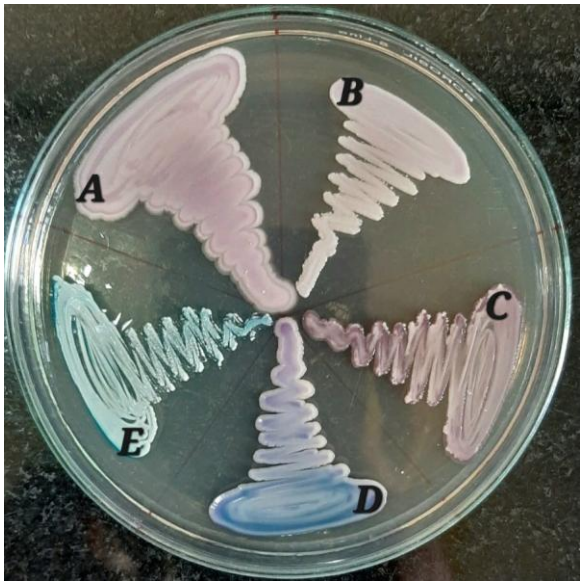

Fig. 3 Growth of different species of *Candida* on CHROMagar plate- A. *Candida krusei*, B. *Candida parapsilosis*, C. *Candida glabrata*, D. *Candida tropicalis*, E. *Candida albicans*

Antifungal susceptibility pattern

Among all the drug tested, sensitivity of *Candida* isolates was lowest for Fluconazole (70.37%) and highest for Caspofungin (100%) and micafungin (100%). *Candida albicans* had lowest sensitivity to Fluconazole (77.78%) and itraconazole (77.78%). Most prevalent NAC, *Candida tropicalis* has lowest sensitivity to Fluconazole (62.5%), but it has high level of sensitivity to Voriconazole, Ampotericin B, Flucytosine, Caspofungin and Micafungin.The result of antifungal susceptibility of different *Candida* spp. is shown in Table 3

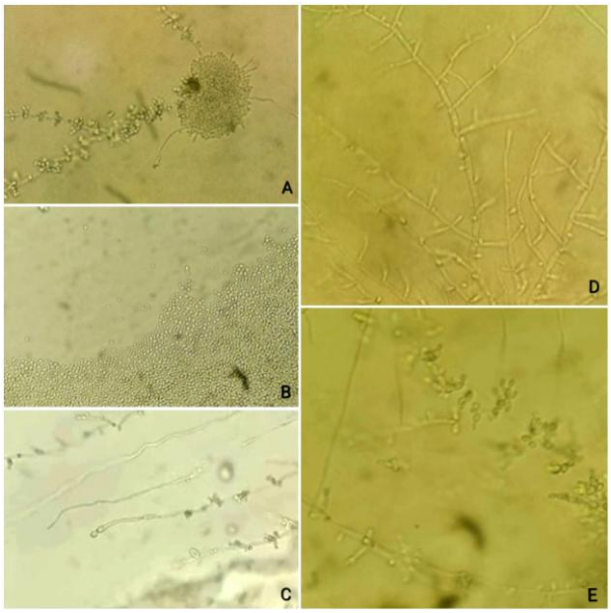

Fig.4 Dalmau plate culture on Corn Meal agar- A.*Candida guilliermondii*, B. *Candida glabrata*, C. *Candida albicans*, D. *Candida parapsilosis*, E. *Candida tropicalis*

Table 2 Potential risk factors for candidemia in neonates (n=54)

Underlying risk factors	**n (%)**
Low birth weight	43 (79.63%)
Prematurity	41 (75.93%)
Prolonged IV antibiotics	38 (70.37%)
Prolonged central venous line	32 (59.56%)
Ventilator support	29 (53.70%)

IV = Intravenous

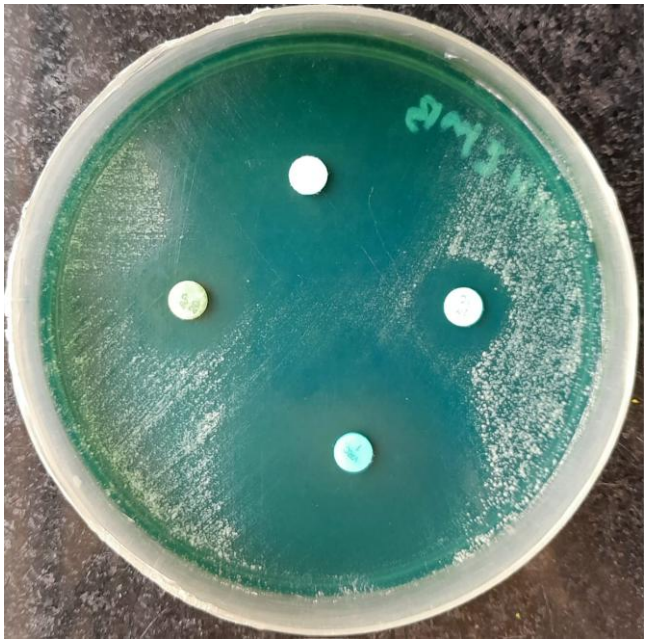

Fig. 5 Antifungal susceptibility testing by Disc diffusion method

Biofilm formation

The Microtiter Plate Method revealed that 31 (57.41%) of the 54 candida isolates had formed biofilms. Of the nine isolates of *Candida albicans*, five (55.56%) strains produced biofilms. Out of the 45 NAC isolates, 26 (57.78%) produced biofilm. [Table 4]

Table 3 Antifungal susceptibility pattern of Candida isolates

***Candida*spp**	**Fluconazole n (%)**	**Itraconazole n (%)**	**Voriconazole n (%)**	**AmpotericinB n (%)**	**Flucytosine n (%)**	**Caspofungin n (%)**	**Micafungin n (%)**
C. tropicalis (n=24)	15(62.5)	18(75)	24(100)	24(100)	24(100)	24 (100)	24(100)
C. albicans (n=9)	7(77.78)	7(77.78)	8(88.89)	9(100)	9(100)	9(100)	9(100)
C. glabrata (n=6)	5(83.33)	5(83.33)	6(100)	6(100)	5(83.33)	6(100)	6(100)
C.krusei (n=4)	IR	2(50)	4(100)	4(100)	3(75)	4(100)	4(100)
C.utilis (n=4)	4(100)	4(100)	4(100)	4(100)	0(0)	4(100)	4(100)
C.*guilliermondii* (n=3)	3(100)	3(100)	3(100)	3(100)	3(100)	3(100)	3(100)
C.parapsilosis (n=2)	2(100)	2(100)	2(100)	2(100)	1(50)	2(100)	2(100)
C. lusitaniae (n=1)	1(100)	1(100)	1(100)	0(0)	1(100)	1(100)	1(100)
C. kefyr (n=1)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)
Total (n=54)	38(70.37)	43(79.63)	53(98.15)	53(98.15)	47(87.04)	54(100)	54(100)

Table 4 Biofilm formation by various Candida species

***Candida* species (number of isolates)**	**Biofilm Positive n (%)**	**Biofilm Negative n (%)**
Candida tropicalis (24)	14 (58.33)	10 (41.67)
Candida albicans (9)	5 (55.56)	4 (44.44)
Candida glabrata (6)	4 (66.67)	2 (33.33)
Candida krusei (4)	4 (100)	-
Candida utilis (4)	-	4 (100)
Candida guilliermondii (3)	1 (33.33)	2 (66.67)
Candida parapsilosis(2)	2 (100)	-
Candida lusitaniae(1)	1 (100)	-
Candida kefyr (1)	-	1 (100)
TOTAL (54)	31 (57.41)	23 (42.59)

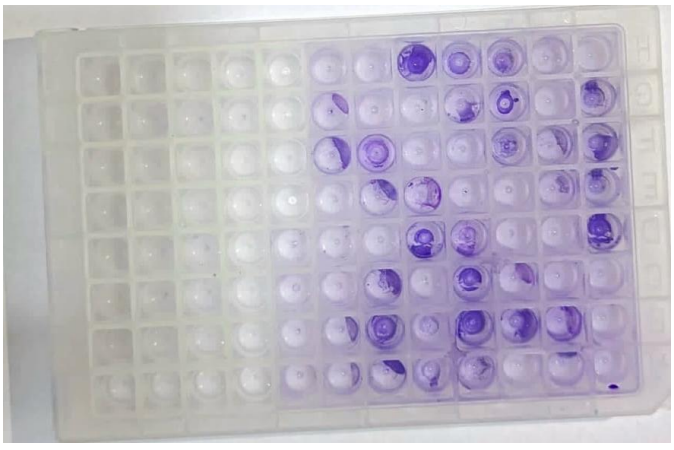

Fig. 6 Biofilm formation by Microtiter Plate Method

DISSCUSSION

Candidemia is a significant cause of mortality and morbidity in neonates admitted in the neonatal intensive care units (NICUs) (Sardana *et al.,* 2012).Immunocompromised hosts, early fungal gastrointestinal tract colonisation, a propensity for invasive fungal dermatitis, and the use of parenteral antibiotics and corticosteroids are additional risk factors linked to candidiasis (Baley, 1991).

In the present study, *Candida* isolation rate among cases of neonatal septicaemia is 11.51%. This finding is comparable to 13.64% of Agarwal *et al* (2004) but slightly less in comparison to 16.4% of Roy *et al* (1993).A noteworthy feature of our study was the emergence of NAC (83.33%) as a major cause of neonatal candidemia. Our findings are supported by other studies such as Xess *et al* (2007), Baradkar *et al* (2008), Kapila *et al* (2016); from different regions of India that have documented predominance of NAC over *C. albicans* in neonatal septicaemia.

In the present study, *Candida tropicalis* (44.44%) was found to be the most prevalent *Candida* isolate followed by *Candida albicans* (16.67%), *Candida glabrata* (11.11%), *Candida krusei* (7.41%), *Candida utilis* (7.41%), *Candida guilliermondii (5.56%)* and *Candida parapsilosis* (3.70%). Similarly, ina study by Nazir and Masoodi (2018), *C. tropicalis* (13.8%) was the most common species followed by *C. albicans* (5.6%), *Candida krusei* (4.8%), *C. parapsilosis* (3.2%), *C. guilliermondii* (2.8%), and *C. dubliniensis* (2.0%). But the findings of Fairchild *et al* (2002) revealed *Candida albicans* (71%) as the most common species followed by *C. glabrata* (15%) and *C. parapsilosis* (14%).

Early colonisation by *Candida albicans* (within 72 hours of birth) and frequent colonisation following vaginal delivery are indicative of a vertical mode of transmission. However, infections with other species of *Candida* usually happen later in the course, usually from the hands of healthcare professionals, suggesting horizontal transmission (Ananthaiah

et al., 2019). Widespread use of broad-spectrum antibiotics, mucosal immunity loss, colonisation, LBW, and length of hospital stay are among the risk factors (Fraser *et al.,* 1992; Gupta et al, 2001). The most frequent related risk factors found in neonates with candidemia in our study were low birth weight (79.63%) and preterm delivery (75.93%). In Lamba *et al* (2021), most common risk factor was low birth weight (93.75%) which is consistence with our study.

In the present study, sensitivity of *Candida* isolates was lowest for Fluconazole (70.37%) and highest for Caspofungin (100%) and micafungin (100%). Sensitivity of *Candida* isolates to Itraconazole, Amphotericin B and voriconazole are 79.63%, 98.15% and 98.15% respectively. Antifungal susceptibility testing in Goel *et al* (2009) revealed that all the *Candida* isolates except *C. glabrata* were 100% sensitive to fluconazole, though, three isolates of *C. tropicalis* were found to be in the Susceptible Dose Dependant (SDD) range with MIC 16 mg/ml, when tested by broth micro-dilution MIC method. Antifungal susceptibility in Lamba *et al* (2021) showed 100% sensitivity to voriconazole and Micafungin, while sensitivity to fluconazole was lowest which is comparable to our study. *Candida albicans* had lowest sensitivity to Fluconazole (77.78%) and itraconazole (77.78%). All isolates of *Candida albicans* were sensitive to Amphotericin B, Caspofungin and Micafungin.According to Lamba *et al* (2021), only 57% *Candida albicans* were sensitive to fluconazole and only 86% sensitive to caspofungin which is low in comparison to this study.Most prevalent NAC, *Candida tropicalis* has lowest sensitivity to Fluconazole (62.5%), but it has high level of sensitivity to Voriconazole, Ampotericin B, Caspofungin and Micafungin. In the study by Baghdadi *et al* (2016), it was found that 58.4%and 58.4% of *C. tropicalis* were sensitive to fluconazole and voriconazole, respectively and were highly susceptible to caspofungin and amphotericin B (100%, 83.3%) which is comparable to our study.

One of the main virulence factors of Candida is the biofilm formation, and because of their extreme antifungal resistance, biofilms of *Candida* are very challenging to eradicate (Seneviratne *et al.,* 2008). The present study showed biofilm production in 57.41% of *Candida* isolates which is in line with the findings of Pannanusorn *et al* (2013). This study observed that 55.56% of *Candida albicans* produced biofilm, which is marginally lower than the 61.1% published by Girish Kumar and Menon (2006).Among the NAC studied for biofilm production in the present study, 100% of *C. parapsilosis* and *C. krusei* showed biofilm formation, followed by *C.glabrata*(66.67%) and *C. tropicalis* (58.33%). The current study revealed that NAC produced biofilms more frequently than *C. albicans*. This conclusion contradicts a previous study by Kuhn *et al* (2002) that claimed pathogenic *Candida albicans* had a higher propensity to form biofilms than NAC species like *Candida parapsilosis.* But the findings of the current study go in accordance with findings of Marak and Dhanashree (2018).

CONCLUSION

The current study emphasises the clinical significance of *Candida* speciation in neonatal candidemia. The incidence of neonatal fungal sepsis secondary to NAC is increasing when compared to *Candida albicans*, with the most common NAC species being *Candida tropicalis*. The AFS pattern of the *Candida* isolates in the NICU will assist the clinician in choosing the best empirical antifungal therapy for suspected candedimia cases of neonatal sepsis. In addition, ongoing surveillance of candidemia is required to track alterations in the epidemiological characteristics and susceptibility to antifungals, as well as to formulate the antimicrobial policy of the hospital to strengthen the antibiotic stewardship programme.

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