Original Research Article

Isolation, Identification and Antifungal Susceptibility Testing of *Candida species* from Sepsis Patients from a rural based tertiary care and teaching hospital in Vadodara district, Gujarat

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Abstract

Background: Sepsis is a global problem causing substantial morbidity and mortality to the patients afflicted with it. Moreover sepsis due to fungal infections, especially, the *Candida* infections has increased in the recent times due to increase in patients with immunocompromised conditions. They are the normal commensal of the oral cavity, GIT and the mucosal surfaces in the body as well as the pathogens leading to colonization and also infection**.** Though *Candida* albicans is the most commonly isolated fungal pathogen from clinical samples, gradually *non-albicans Candida species* are becoming predominant pathogens. The increased use of anti-fungal agents for treatment and also for prophylaxis especially in ICU patients has lead to development of resistance against commonly used anti-fungal agents in the treatment like various azoles. Thus this study was carried out to identify different *Candida species* from specimens of clinically diagnosed sepsis patients and their antifungal susceptibility pattern which can be utilized for better management of sepsis patients.

Objectives: The objectives of this study were to isolate and identify the species of *Candida* from different samples of clinically diagnosed sepsis patients and to determine the susceptibility pattern of the *Candida* species isolates against the commonly used anti-fungal agents from the clinical samples of sepsis patients from a rural based tertiary care and teaching hospital.

Materials and methods: A total of 100 *Candida species* were isolated from different samples of clinically diagnosed sepsis patients. These were identified on the basis of gram stain of the samples, colony morphology on Saboraud's Dextrose agar and HiCrome also germ tube and chlamydospore formation. The antifungal susceptibility testing was done according to CLSI M44-A2 for yeasts.

Results: A total of 100 (14.26%) *Candida species* were isolated out of the total 701 isolates from 1136 different samples cultured from clinically diagnosed sepsis patients. Of these, 53% were *C. albicans, 37% C. non-albicans, 6% C. glabrata* and *4% C. tropicalis*. Also 35% were obtained from blood, 20% from catheterized urine, 19% from sputum, 14% from non-catheterized urine, 7% from ET (Endotracheal) tips/secretions and the smaller percentage from other specimens. The antifungal testing showed a higher resistance to most of the antifungal agents tested with 80% towards clotrimazole, 77% to ketoconazole and 63% to fluconazole and 62% towards itraconazole. However, 80% of *Candida species* were susceptible to amphotericin B followed by 33% to fluconazole and 80% were susceptible-dose-dependent to nystatin.

Conclusion: The findings of our study suggest that *Candida species* are an important pathogen causing various infections in our patients leading to sepsis as well as a higher resistance to most of the antifungal agents tested poses a real challenge in the management of patients with sepsis due to *Candida*. Thus routine identification using HiCrome Media and antifungal susceptibility testing by disc diffusion method for yeasts will help in better management of sepsis due to *Candida* infections.

Key words

Candida species, HiCrome, Antifungal susceptibility, Sepsis.

Introduction

Sepsis, a serious clinical condition causes substantial morbidity and mortality amongst the patients globally [1]. *Candida species* are the normal commensal of the oral cavity, GIT and the mucosal surfaces in the body as well as the pathogens leading to colonization and infection. In the recent times incidence of fungal infections has increased with the increased incidence of immunocompromised patients [2]. *Candida* species are frequently isolated from such patients as well as those who are diabetic [3], on immune-suppressants or neutropenic [4] with malignancy undergoing chemotherapy/ radiotherapy [5], long term steroid therapy, long term antibiotic therapy etc. [6]. It has been implicated as a cause of UTI, respiratory infections, septicaemia as well as cutaneous and mucocutaneous infections. The invasive fungal infections often lead to sepsis, severe sepsis and septic shock in critically ill patients in ICU with *Candida species* being the most common cause of fungal sepsis, especially in the hospital acquired infections [7]. More than 17 different *Candida species* are known to be aetiological agents of human infections. Though *Candida albicans* is the most commonly isolated fungal pathogen from clinical samples, gradually *non-albicans Candida species* are becoming predominant pathogens [6]. Moreover, the increased use of anti-fungal agents for treatment and also for prophylaxis especially in ICU patients has lead to development of resistance against commonly used anti-fungal agents in the treatment like various azoles [2, 4, 6]. However the *Candida species* have variable resistance towards various antifungal agents. Thus this study was carried out to identify different *Candida species* from specimens of clinically diagnosed sepsis patients and their antifungal susceptibility pattern which can be utilized for better management of sepsis patients in our set up.

The objectives of this study were to isolate and identify the species of *Candida* from different samples of clinically diagnosed sepsis patients and to determine the susceptibility pattern of the *Candida species* isolates against the commonly

used anti-fungal agents from the clinical samples of sepsis patients from our setup in a rural area.

Materials and methods

A total of 100 *Candida* isolates were obtained from 1136 different samples cultured from clinically diagnosed sepsis patients with the following inclusion criteria:

Inclusion Criteria [1]

Adult patients (age >18 years) and having 2 or more of the following:

a. Body temperature: >38^{0}C or <36^{0}C
b. Tachypnea: >20 breaths/minute
c. Tachycardia: Heart rate>90 beats/minute
d. Leuckocyte count: >12,000/µl or <4, 000/ µl

Thus the specimens whose Gram stained smears showed presence of any yeast cells or yeast-like cells with budding and with or without pseudohyphae were processed for fungal culture and inoculated on Sabourad's Dextrose Agar (SDA). Plates were incubated aerobically at 37^{0}C for 24 hours. The colonies of *Candida species* were obtained after overnight incubation. The colonies were identified by colony morphology on SDA, colony colour on HiCrome Media, germ tube test and chlamydospore formation as follows [8]:

Thus colonies of white, creamy white or yellow-white with smooth, pasty consistency on SDA after overnight incubation were considered as suggestive of yeast or yeast-like fungi. In addition the presence of pseudohyphae in yeasts from direct specimen or colony was suggestive of infection with *Candida species.* The gram stain of the colonies was also performed. Well isolated colonies suggestive of *Candida species* from SDA were picked up with the sterile inoculating loop and streaked onto HiCrome medium (from HiMedia) for species identification. Different species of *Candida* grow with different coloured colonies on this medium. The colonies were identified according to colour and interpreted as shown in the **Table - 1** and **Figure - 1, 2**.

Table - 1: Interpretation of the colour of the colonies [9, 10, 11].

Colour of the colony	Species Identified
Light green	*Candida albicans*
Cream to White	*Candida glabrata*
Purple, fuzzy	*Candida krusei*
Blue purple and Bluish green	*Candida tropicalis*

Figure - 1: Colonies of *Candida* species on HiCrome.

Figure - 2: Colonies of *Candida* species on SDA.

Those which could not be identified as one of the species as mentioned in the **Table - 1**, were labelled as *Candida non-albicans*.

In addition to the colour of the colonies on HiCrome, a germ tube test and observation of chlamydospore formation on cornmeal agar were carried out for identification of *Candida albicans*. For germ tube test, a well isolated colony from SDA was emulsified in 0.5 ml of human serum using sterile straight wire. The test tubes were incubated at 35^0C and no longer than 2 hours. A drop of serum sample was placed on a clean, grease free slide and a coverslip was placed over it. This slide was then observed first under 10X and then under 40X objective lens of microscope for the presence of germ tubes. Germ tube is a filamentous extension from yeast cell without constriction at the neck (true germ tube) and is seen in *C. albicans*. For inoculation of corn meal agar, 3 parallel cuts about 1 cm apart were made on the surface of the agar holding the sterile straight wire at about 45^0 angle. A cover slip was placed over the inoculated areas. The plates were then incubated for 24-48 hours at 30^0 C. The cover slips were then observed under the microscope for chlamydospore [8].

Antifungal Susceptibility Testing [12, 13, 14]
Antifungal Susceptibility test was carried out for *Candida species* according to CLSI guidelines for testing anti-fungal agents for yeasts [12]. In order to carry out antifungal susceptibility testing, an inoculum of 0.5McFarland was prepared from a well isolated colony from SDA. A lawn culture was made on Mueller-Hinton Agar + Glucose-Methylene-Blue (GMB) medium from the above inoculum using a sterile swab. The GMB was prepared according to the method described in CLSI-M44-A2. Thus MHA was prepared first (according to the manufacturer's instructions) and to this 2% of glucose and 0.5 µg/ml methylene blue were added [12]. A hexadisc (Hexa-Antimyco-01/HX104 from HiMedia) containing Amphotericin B (100 units), Clotrimazole (10 µg), Fluconazole (25 µg), Itraconazole (10 µg), Ketoconazole (10 µg) and Nystatin (100 units) was used. The plates were then incubated at 37^0C for 24 hours. Zones of inhibition for antifungal agents used for *Candida species* were measured (**Figure - 3**) and interpreted according to the Mahmoudabadi AZ, et al. [14]. For Amphotericin B and Clotrimazole, the zones were interpreted according to the manufacturer's manual [13].

Figure - 3: Antifungal Susceptibility Testing of *Candida* species.

Results

A total of 14.26% isolates of *Candida* species were obtained from 1136 different samples cultured from clinically diagnosed sepsis patients yielding 701 bacterial and fungal isolates altogether. The distribution of different fungal isolates is as shown in the **Chart - A**. Thus the most frequent isolate was *C. albicans* (53%), followed by *C. non-albicans* (37%), *C.glabrata* (6%) and *C. tropicalis* (4%).

The **Chart - B** shows the number & types of specimens from which these *Candida* species were obtained. Thus most frequently these were isolated from blood (35%) followed by catheterized urine (20%), sputum (19%), non-catheterized urine (14%), ET tips/secretions (7%) and also in small percentages from other samples as shown in the chart. The overall susceptibility pattern of the antifungal agents tested is as shown in the **Chart - C**.

Chart - A: Type & Percentage of *Candida* species isolated and identified.

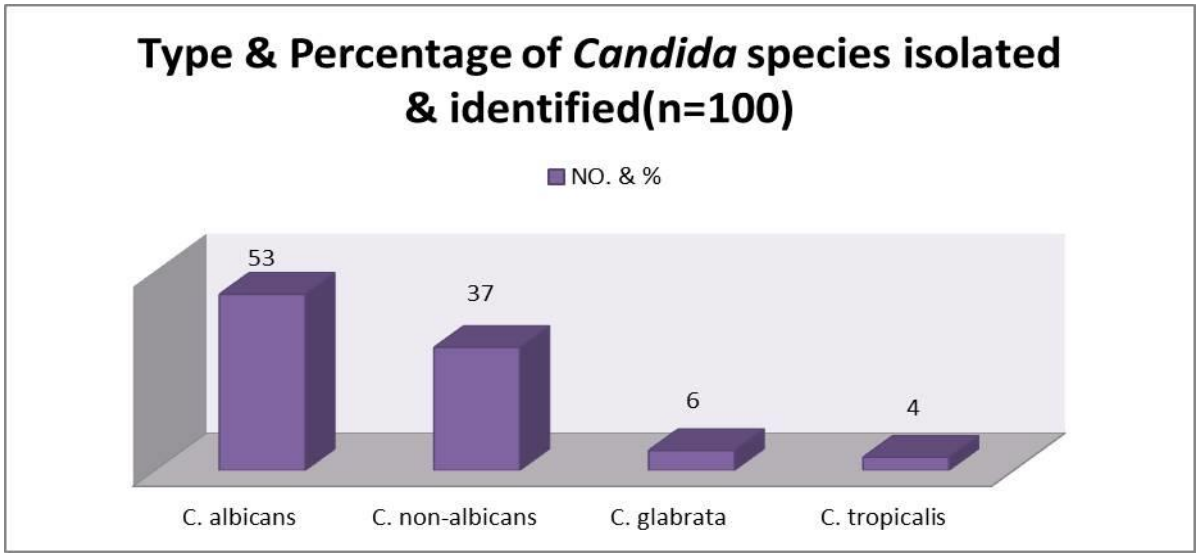


Chart - B: Distribution of *Candida species* amongst different samples (n=100).

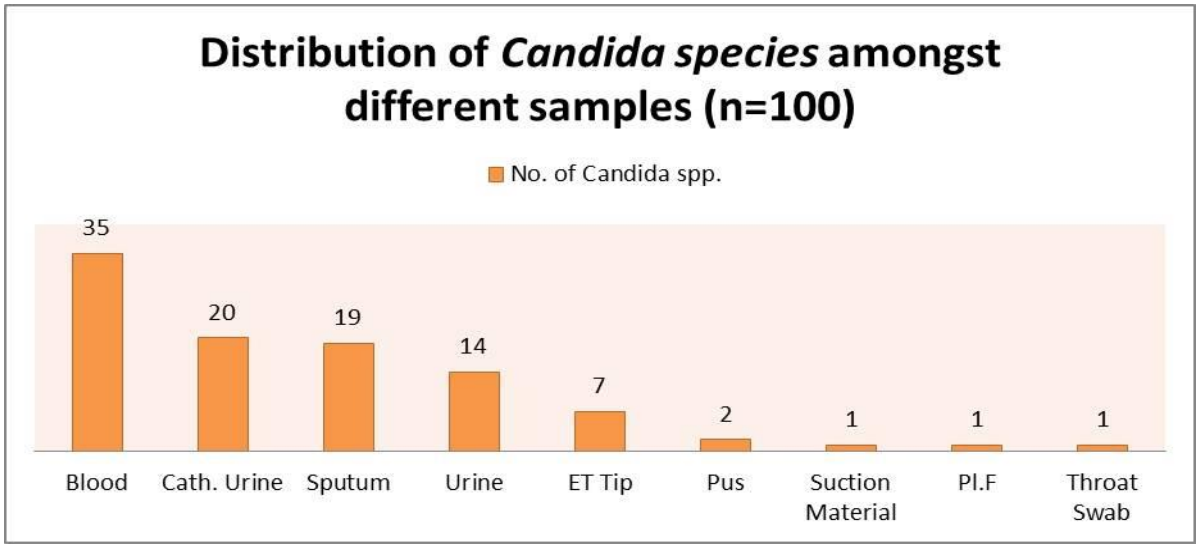
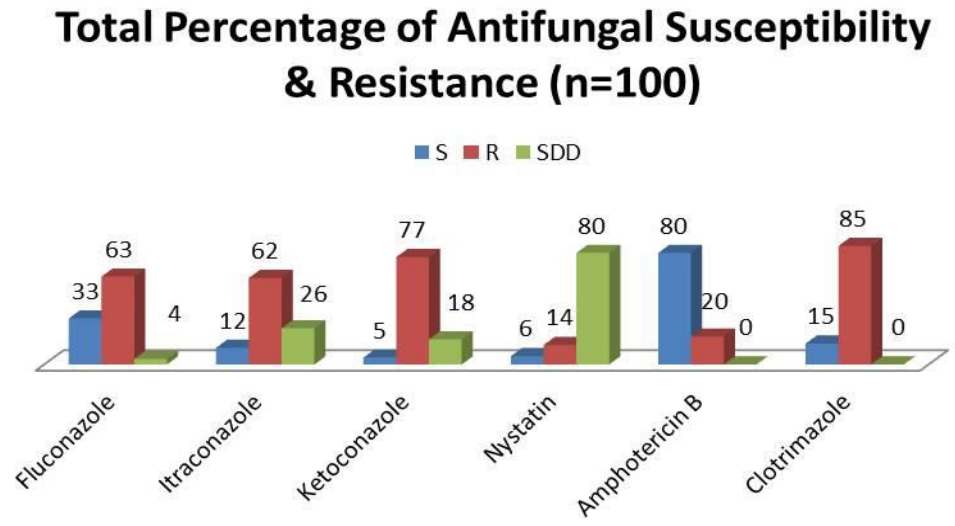


Chart - C: Total Percentage of Antifungal Susceptibility and Resistance (n=100).



Susceptibility to Fluconazole:

Of the isolates tested 33%, 63% and 4% were susceptible, resistant and dose dependent respectively. The maximum resistance was exhibited by *C. albicans* followed by *C. non-albicans, C. tropicalis* and least by *C.glabrata.*

Susceptibility to Itraconazole:

As shown in the **Chart - C** 62%, 26% and 12% were resistant, dose dependent and susceptible to Itraconazole respectively. The maximum resistance was shown by *C. albicans* followed by *C. tropicalis* and least but almost equally by *C.non-albicans* and *C.glabrata*.

Susceptibility to Ketoconazole:

It showed that 77%, 18% and 5% were resistant, dose dependent and susceptible to Ketoconazole respectively. The maximum yet equally the dose dependence was shown by *C. glabrata* and *C. tropicalis* followed by *C. non-albicans* and least by *C. albicans*, which also showed a maximum resistance.

Susceptibility to Nystatin:

Of the total isolates 80%, 14% and 6% were dose dependent, resistant and susceptible to Nystatin respectively. The maximum dose dependence was shown by *C. albicans, C. glabrata, C. non-albicans* and finally *C. tropicalis*.

Susceptibility to Amphotericin B:

It shows that 80% and 20% were susceptible and resistant respectively. The SDD could not be reported for this category as the interpretation was not available for this category from either the guidelines or the literature. The maximum resistance was shown by *C. tropicalis* followed *C. glabrata, C. non-albicans* and least by *C. albicans*.

Susceptibility to Clotrimazole:

Here also no SDD could be reported but 85% and 15% resistance and susceptibility were seen against Clotrimazole respectively. The maximum resistance was shown by *C. albicans* followed equally by *C. non-albicans* and *C. glabrata* and least by *C. tropicalis*.

Discussion

A total of 14.26% isolates of *Candida species* were obtained from 1136 different samples cultured from sepsis patients yielding 701 bacterial and fungal isolates altogether. All these were obtained from patients who fulfilled the inclusion criteria for defining sepsis and thus all the isolates were considered to be significant here rather than contamination. Of the total 100 *Candida species* isolated, the most common isolate was C. albicans (53%) followed by C.non-albicans (37%), C. glabrata (6%) and C. tropicalis (4%). In a multicentric one year study conducted in 27 ICUs of India for determining incidence of candidemia by Chakraborti A, et al. [15] found an incidence of 6.51 cases/1000 ICU admissions with the highest burden from ICUs of North India contributing 8.95 cases/1000 ICU admissions. Tak V, et al. [16] report candidemia incidence of 7.76 cases/1000 ICU admissions whereas Dewan E, et al. [17] report 10% candidemia in patients with hematological malignancies. Delaloye J and Calandra T [7] in their review article mention *Candida species* as the fourth most common blood stream isolate accounting for 10% to 15% of hospital acquired fungal sepsis and 5% of all cases of severe sepsis and septic shock. It accounts for 8 to 10% of blood stream infections in the United States and about 2-3% in Europe. Sonawane J, et al. [18] from Mumbai and Gupta S [19] from New Delhi, North India report 7.14% and 3.31% isolates of *Candida spp*. from blood cultures. Of the total 35 isolates obtained from blood, *C. albicans* was the most common isolate 42.86% (15/35) followed by *C. non-albicans*, 40% (14/35), *C. glabrata*, 11.43% (4/35) and *C. tropicalis*, 5.71% (2/35). Our findings are similar to the findings reported in a laboratory based surveillance study carried out across Asia by Tan BH, et al. [20] which reports *C. albicans* as the most common cause of candidemia with the similar percentage of prevalence.

The **Table - 2** shows the comparison of different studies in relation to *Candida* species and **Table - 3** shows comparison in relation to antifungal susceptibility.

Table - 2: Comparison of studies in relation to *Candida* species.

Reference	**Place of Study**	***Candida* species (%)**
Guzman AJ, et al. 2011 [21]	USA	*Candida non-albicans* (74%) *C. albicans* (26%)
Giri S, et al. 2013 (JPGM) [22]	Chennai, Tamil Nadu	*C. tropicalis* (74.35%) *C. albicans* (10.26%) *C. parapsilosis* (7.69%) *C. krusei* (5.13%) *C. glabrata* (2.56%)
Tak V, et al. 2014 [16]	New Delhi	*C. tropicalis* (38.7%) *C. parapsilosis* (20.3%) *C. albicans* (13.7%) *C. glabrata* (11.4%) *C. rugosa* (9.4%) *C. hemulonii* (2.8%) *C. guilliermondi* (1.8%) *C. famata* (1.4%) *C. lusitaniae* (0.47%)
Chakraborti A, 2014 [15]	27 ICUs across India	*C. tropicalis* (41.6%) *C. albicans* (20.9%) *C. parapsilosis* (10.9%) *C. glabrata* (7.08%) *C. auris* (5.66%) *C. rugosa* (3.15%) *C. krusei* (1.74%) *C. guilliermondi* (1.74%)
Dewan E, et al. 2015 [17]	Uttarakhand, India	*C. tropicalis* (46.67%) *C. ablicans* (26.7%) *C. glabrata* (6.7%) *C. parapsilosis* (6.7%) *C. krusei* (6.7%) *C. dublinensis* (6.7%)
Tan BH, et al. 2015 [20]	25 hospitals across Asia	*C. albicans* (41.3%) *C. tropicalis* (25.45) *C. glabrata* (13.9%) *C. parapsilosis* (12.1%)

In our study a total of 34% of *Candida* species were isolated from urine samples which may have lead to candidemia in these patients. Of these total 34 isolates, 20 (58.82%) were obtained from urine samples of catheterized patients. Giri S, et al. [22] report urinary catheters in 53.90% patients as a predisposing factor for candidemia while Xess, et al. [23] report it in 55.6% patients. Moreover in a review article, Giri S [24] quotes that as many as 10% of candiduria cases are significantly associated with development of candidemia. Mahmoudabadi AZ, et al. [14] report 62.3%, 26.8% and 4.3% C. *albicans*, *C. glabrata* and *C. tropicalis* from urine of 92 patients with candiduria. Besides 35% from blood and 34% from urine culture *Candida species* were also isolated from sputum (19%), non-catheterized urine (14%) and ET

tips/secretions (7%), pleural fluid, suction material and throat swab suggesting that these sites would have been the source of *Candida* infection leading to sepsis in these patients. Guzman AJ, et al. [21] report 27% and 51% rate of isolation of *Candida species* from urine, sputum and catheter-related samples of septic shock and no-shock group of patients respectively.

Table - 3: Comparison of studies in relation to antifungal susceptibility and resistance pattern.

Reference	Place of Study	Resistance Pattern (%)	Susceptible Pattern (%)
Guzman AJ, et al. 2011 [21]	USA	Not Reported	Not Reported
Giri S, et al. 2013 (JPGM) [22]	Chennai, Tamil Nadu	Fluconazole (30.8) Ketoconazole (12.8) Amphotericin B (0)	Fluconazole (69.2) Ketoconazole (87.2) Amphotericin B (100)
Tak V, et al. 2014 [16]	New Delhi	Fluconazole (3.3) Amphotericin B (3.3) Flucytosine (0) Voriconazole (0)	Fluconazole (93.9) Amphotericin B (93.9) Flucytosine (0) Voriconazole (0)
Chakraborti A, 2014 [15]	27 ICUs across India	Fluconazole (6.2) Itraconazole (1.2) Voriconazole (5.6) Amphotericin B (2.1) Anidulafungin (1.7) Caspofungin (5.6) Micafungin (1.7)	Fluconazole (82.8) Itraconazole (89.5) Voriconazole (71.5) Amphotericin B (97.9) Anidulafungin (96.7) Caspofungin (84.3) Micafungin (96.1)
Dewan E, et al. 2015 [17]	Uttarakhand, India	Fluconazole (20) Clotrimazole (20) Voriconazole (13.4) Flucytosine (100) Nystatin (66.67) Amphotericin B (26.67)	Fluconazole (80) Clotrimazole (80) Voriconazole (86.66) Flucytosine (0) Nystatin (33.33) Amphotericin B (73.33)
Tan BH, et al. 2015 [20]	25 hospitals across Asia	Not Reported	Not Reported
Present Study, 2017*	Gujarat, India	Fluconazole (63) Itraconazole (62) Ketoconazole (77) Nystatin (14) Amphotericin B (20) Clotrimazole (85)	Fluconazole (33) Itraconazole (12) Ketoconazole (05) Nystatin (06) Amphotericin B (80) Clotrimazole (15)

*It represents overall percentage of all 100 isolates; and also SDD percentage is not compared here for any of the studies.

Also we found HiCrome media and disc diffusion method for antifungal susceptibility testing to be cost effective, convenient and useful methods for identification of *Candida species* and determining susceptibility and resistance to antifungal agents respectively on daily basis in our laboratory. Other authors too have found HiCrome to be equally good when compared to CHROME agar, Nested PCR and standard

biochemical methods for identification of *Candida species* [9, 10, 11].

Overall, the difference in the prevalence, of *Candida species*, the types of *Candida species* and the antifungal susceptibility and resistance patterns, may be due to the difference in the geographical locations; the clinical settings i.e. only ICU or hospital; patient demographics i.e. only patients with certain conditions, adult or pediatric; number of and types of samples processed; different media/methods used for isolation and identification like automated vs. conventional/semi-automated; different numbers of *Candida spp.* identified and tested for antifungal agents as well as different types of antifungal agents tested in different studies. Most of the studies have taken into account only those *Candida species* which cause candidemia, but in our study we have studied all the *Candida* species isolated from all different samples of sepsis patients to identify the source of infection in them. Also most of the studies from developed countries and those from premier institutes in India are equipped with automated systems for culture which are useful in increasing the yield of *Candida species*, especially, from blood samples, identification to the species level and determination of susceptibility pattern through MIC values of antifungal agents tested.

Conclusion

Candida species are important pathogens causing various infections leading to sepsis in our patients. Also we found HiCrome media and disc diffusion method for antifungal susceptibility testing to be cost effective, convenient and useful methods for identification of *Candida species* and for determining susceptibility/resistance to antifungal agents respectively and using these routinely in our laboratory will help determine the prevalence of *Candida* infections along with their susceptibility pattern in our setup which in turn will help in better management of sepsis patients as well as all other patients with *Candida* infections.

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