DISSERTATION SUBMITTED FOR THE MASTER'S DEGREE IN MEDICAL MICROBIOLOGY

TITLE

Candidemia in Immune Compromised Patient in India– Systematic Review

SUBMITTED BY

Shriya Srivastava

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DEPARTMENT OF MICROBIOLOGY INTEGRAL INSTITUTE OF MEDICAL SCIENCES & RESEARCH INTEGRAL UNIVERSITY DASAULI, KURSI ROAD, LUCKNOW-226026, U.P

Candidemia in Immune Compromised Patient in India – Systematic Review

A DISSERTATION Submitted to INTEGRAL UNIVERSITY
In partial fulfilment of the requirements for the award of degree of

Masters of sciences

In

Medical Microbiology

By

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I hereby declare that this dissertation entitles "Candidemia in Immune compromised Patient in India – Systematic Review" is bonafide and genuine research work carried out by me under the guidance of Dr. Mohd. Saquib Assistant Professor, Department of Microbiology and Co-guide Dr. Ausaf Ahmad, Assistant Professor, Department of Microbiology, Integral Institute of Medical Sciences and Research, Lucknow

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This is to certify that research work entitled "**Candidemia In Immune Compromised Patient In India- Systematic Review**" submitted by **Shriya Srivastava, Dr.Mohd Saquib, Dr.Ausaf Ahmad** for ethical approval before the Institutional Ethics Committee IIMS&R.

The above mentioned research work has been approved by Institutional Ethics Committee, IIMS&R with consensus in the meeting held on **19 May 2022**.

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Date: **SHRIYA SRIVASTAVA**

CONTENT

ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ICU	Intensive Care Unit
MDR	Multi Drug Resistance
MIC	Minimum Inhibitory Concentration
PRR	Pattern Recognition Receptor
ROS	Reactive Oxygen Species
RIG 1	Retinoid – Inducible Gene 1 protein
SDD	Susceptible Dose Dependent

INTRODUCTION

Introduction-

The genus *Candida* constitutes of various species of yeast that are present as normal commensals in the human microflora.[1]They are commonly present on skin , throughout gastrointestinal tract and female genital tract. As per observations, due to the commensal nature of candida, they may cause endogenous infection. Across India, *Candida* is the most common invasive mycotic infection.[2] Certain instances of abnormal or increased colonization of *Candida* with associated generalized or local defect in host defenses can lead to diseases termed as **candidiasis**.[1][3]

Super kingdom- Eukaryota

Kingdom- Fungi

Phylum- Duetromyctes

Order- Basidiogenous

Family- Cryptococcaceae

Genera- *Candida*

The *candida* genus comprises of 163 anamorphic species. Out of the 163 species about 13 genera possess teleomorphs. Around, twenty of the species are considered as significant pathogens that cause numerous infections in

human beings. Out of the twenty species, seven are significantly, known opportunistic pathogens. Some of the species are mentioned as follows-:

Candida albicans

Candida tropicalis

Candida krusei

Candida glabrata

Candida auris

Candida haemulonii

Candida guilliermondii

Candida parapsilosis

Candida lusitaniae

Candida kefyr

Candida rugosa

Candida dubliniensis

Candida viswanathi

The range of *candida* infection can vary from mucocutanoeous infection to invasive disease involving various organs and systems.[2] The *candida* infections can be subdivided as follows-:

1) Cutaneous (skin and its appendages),
2) Mucosal (esophageal, oropharyngeal and vulvovaginal) and
3) Systemic manifestation (including candidemia and disseminated candidiasis)

Candidemia is the most common co-infection associated with immune-compromised patients such as individuals suffering from diabetes mellitus, malignancy, organ transplantation recipients, antibiotic therapy and long term hospitalization. [4]

During the last few decades, in various clinical settings, a recent increase has been observed in the incidence of candidemia across the world.[5] As per a study, based in USA on Nosocomial Bloodstream Infections (BSI), *Candida spp* contributes to be the fourth most common cause. Candidemia has become an important cause of mortality and morbidity in certain clinical settings. *Candida* species are responsible for 96% of the opportunistic fungal infection. Invasive candidiasis is not a single clinical condition, but, instead is a disorder with various clinical manifestations that may affect any organ. It is a life threatening condition, with a reported mortality rate up to 38.2%. [6]

Development of invasive candidiasis may occur in both Non-immuno compromised (NIC) and immuno-compromised (IC) individuals. Since, the development of candidemia often occurs in immuno-compromised individuals, so this insinuates the presence of an immuno-deficient state in the individual. Immuno-compromised individuals are referred to as individuals with one or more defects in their normal defense mechanism. Opportunistic infections are caused in individuals with impaired immune system by infectious agents that are a part of normal commensal that normally do not affect a healthy individual.[7] *Candida* attributes to be a common cause of opportunistic fungal infection in immune-compromised patients.[8] The spectrum of affected groups by candidemia ranges from paediatrics to adults. [9] In hospitalized patients, 10% of nosocomial infections are attributed to Candidemia. [10] The various risk factors involved in causing invasive candidiasis include -:

1. Autoimmune deficiency disorder (AIDS)
2. Neutropenia
3. Underlying malignancies
4. Blood and marrow transplantation
5. Administration of parenteral alimentation
6. Myeloproliferative disorder or leukemia

Pathophysiology

The *Candida* spp. transforms from commensalism to opportunistic on disturbance of mucosal microbiota or on immunosuppression conditions, on induction of various associated risk factors. Human invasive infections are associated with certain pre-disposing factors-

1. Immunosuppression-
   i. Genetically caused immunosuppression
   ii. Iatrogenic immunosuppression
2. Over-use or Misuse of broad spectrum of antibiotics
3. Invasion of gastrointestinal and cutaneous barriers by central venous catheters or surgery or chemotherapy. [3]

The antigenic structure of *candida* species is comprised of two main groups-:

i. Cell Wall Antigen
ii. Cytoplasmic Antigen

The *Candida* fungus possesses certain virulence factors that cause opportunistic infections. The virulence factors include -:

- Phenotypic switching: *Candida* can demonstrate phenotypic dimorphism due to its ability to filament and transform its

morphotypes between unicellular yeast cells and pseudohyphae and hyphae. This promotes the ability of fungus to cause invasive disease.

- Toxins and enzymes: *C.albican* secretes various factors that may induce invasive infection. These include candidalysin, phospholipases and aspartyl proteases. Aspartyl proteases and phospholipases activate innate immune response and promote invasion of tissue and damage organs.[12][13] Candidalysin is a cytolytic peptide toxin [14] It induces epithelial cell damage. [3]
- Adhesins: The dissemination of candida spp. into bloodstream is facilitated by adherence and invasion factors [3]
- Complement Receptors

Host immune response

The initial step in development of immune responses is extra-cellular or intra cellular pathogen associated molecular patterns of invading *Candida* spp. The recognition is facilitated through the various soluble and membrane bound pattern recognition receptors (PRR) families of invading *Candida* spp. yeast and hyphae.

The pattern recognition receptors are expressed by myeloid phagocytes. These include retinoid – inducible gene 1 protein (RIG 1) like receptors, toll like

receptors (TLRs) , Nucleotide binding oligomerization domain (NOD) – like receptors, C-type lectin receptors and complement components and receptors.[3]

Candida spp. activates multiprotein intracellular complexes NACHT, LRR and PYD- domains containing protein 10 inflammasomes (NLRP3 and NLRP10).

This results in production of pro-inflammatory cytokines such as IFN γ, Ilβ and IL-17.

The sensing of candida spp. by PRRs initiates complex signalling cascades.

This mediates the production of pro-inflammatory cytokines and chemokines.

This promotes recruitment, phagocytosis and generation of Reactive Oxygen species (ROS) and killing capacity of phagocytes and induces activation of T_H cells responses.[3]

The development of candidemia has been associated with various abnormal physiological conditions involving immuno-suppression in patient such as surgery, central venous access, administration of broad spectrum antibiotics and

in children low birth weight and prematurity . Many cases of *candida* bloodstream infection have been reported from intensive care units (ICU), that includes patients from Neonatal ICUs, Pediatric ICUs (PICUs) and surgical ICUs. In India, the mortality rate associated with candidemia is attributed to be 28% to 71.4%.

A number of studies have reported development of various clinical conditions such as Candidal endocarditis, Hepatosplenic candidiasis, candidal arthritis, candidal infections of eye and fungal peritonitis. [2]

The genus *Candida* is comprised of a heterogenous group of fungal organisms that can grow in the form of yeast. The most prevalent *candida* specie is *Candida albican*, known to affect a variety of groups. But, over a past few decades a recent increase has been observed in number of non-albican candidal bloodstream infection, such as *C.tropicalis*. This variation in the trend of species can be attributed to use of antifungal drugs leading to development of resistance.

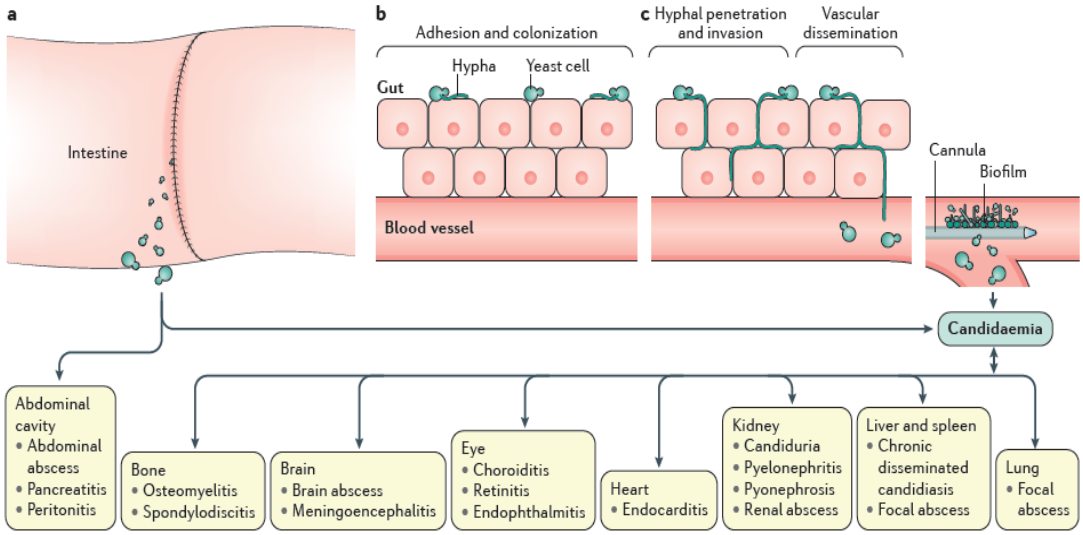


Figure 1 | **Pathogenesis of invasive candidiasis.** *Candida* spp. can be detected on the mucosal surfaces of ~50–70% of healthy humans. **a** | When breaches in the intestinal barriers occur, for example, after gastrointestinal surgery, *Candida* spp. can disseminate to the abdominal cavity directly and invade the bloodstream (candidaemia). **b** | Under normal conditions, the fungus behaves as a commensal organism without causing disease. **c** | Impairment of immune response, among other factors, can promote fungal overgrowth in the gut and candidaemia, which can lead to deep-seated opportunistic infections in various organs (invasive candidiasis).

Courtesy- Pappas, P. G., Lionakis, M. S., Arendrup, M. C., Ostrosky-Zeichner, L., & Kullberg, B. J. (2018). Invasive candidiasis. *Nature reviews. Disease primers*, *4*, 18026. https://doi.org/10.1038/nrdp.2018.26

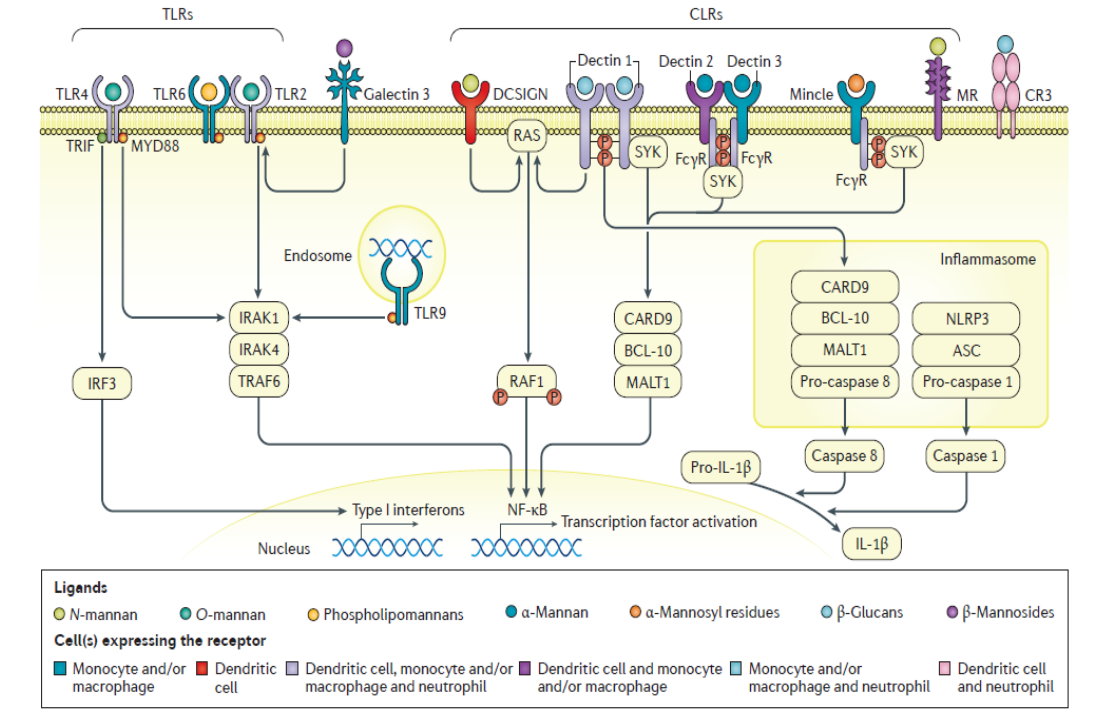


Figure 2 |Recognition of *Candida* spp. by pattern recognition receptors of myeloid phagocytes

Courtesy- Pappas, P. G., Lionakis, M. S., Arendrup, M. C., Ostrosky-Zeichner, L., & Kullberg, B. J. (2018). Invasive candidiasis. *Nature reviews. Disease primers*, *4*, 18026. https://doi.org/10.1038/nrdp.2018.26

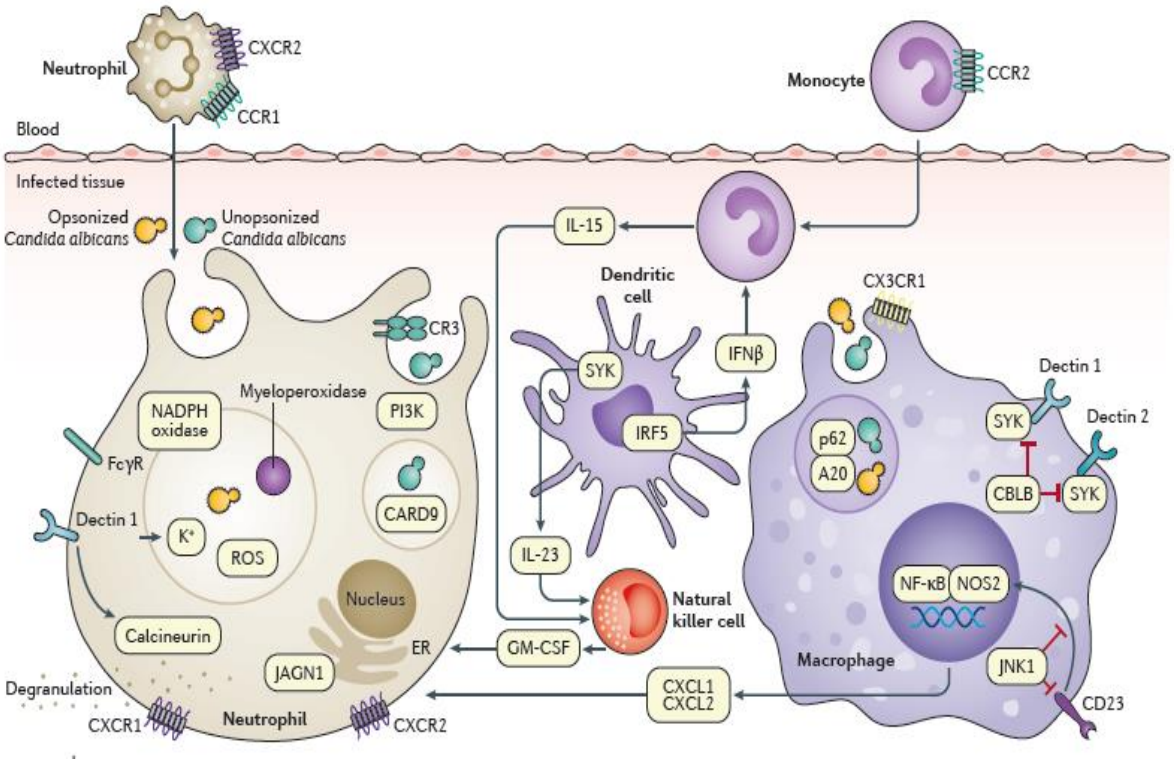


Figure 3 | **Effector mechanisms of myeloid phagocytes for control of invading *Candida* spp. in infected tissue**

Courtesy- Pappas, P. G., Lionakis, M. S., Arendrup, M. C., Ostrosky-Zeichner, L., & Kullberg, B. J. (2018). Invasive candidiasis. *Nature reviews. Disease primers*, *4*, 18026. https://doi.org/10.1038/nrdp.2018.26

The laboratory diagnosis of *candida* is done by standard protocols including –

I. Direct Microscopic Examination
II. Germ tube formation
III. Chlamydospore Production
IV. Sugar Fermentation and Assimilation Test
V. Culture Method

The various culture methods used for growth of *Candida* are as follows-:

Sabourad's Dextrose Agar (SDA)

Brain Heart Infusion Broth (BHI broth)

Tetrazolium Reduction Medium

Corn Meal Agar (CMA)

CHROMagar

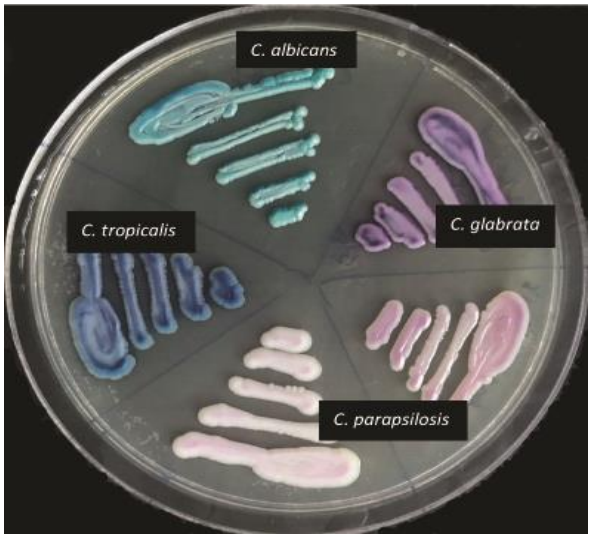


Fig 4. Demonstration of various *Candida species* on Hi Media Chromagar.

1) *C.albicans* 2) *C.glabrata*
2) *C.tropicalis* 4) *C.parapsilosis*

Courtesy- Jain,S.Swain,B.Kabi,S.(2020).*Comparison of Manual and Automated Method for Speciation and Antifungal Susceptibility of Candida Species Causing Blood Stream Infection in Critically ill Patients*,J Clin of Diagn Res. *14*(5), DC04-DC07. https://www.doi.org/10.7860/JCDR/2020/4364

Various *Candida* specie with variety of growths on different Culture medias				
Candida specie	SDA	SD broth	CMA	CHROMagar
C. albicans	Pasty and smooth		Large thick walled, terminal chlamydospore	Light green to bluish green
C. tropicalis	Cream colored to off-white , glistening to dull, soft, smooth or wrinkled with mycelial fringe	Thin pellicle on top	Blastospores formation singly or in small groups. Fir tree appearance	White to pale pink[15]
C.krusei	Flat , dull and dry	Thick pellicle on top		Pinkish to purplish colored colonies
C. parapsilosis	Creamy and lacy pattern. Blastospore production singly or in small clusters along psuedohyphae			Cream – colored colonies
C. glabrata (only species to not show pseudohyphae production)	Glistening, smooth, cream colored			Pink to purple
C. kefyr	Colonies are creamy , smooth			
C. quilliermondi	Colonies are thin flat, glossy cream to pink , glistening, smooth or dull , wrinkled			
C.dubliniesis	Colony growth shows phenotypic similarity with *C.albicans*			Dark green colonies

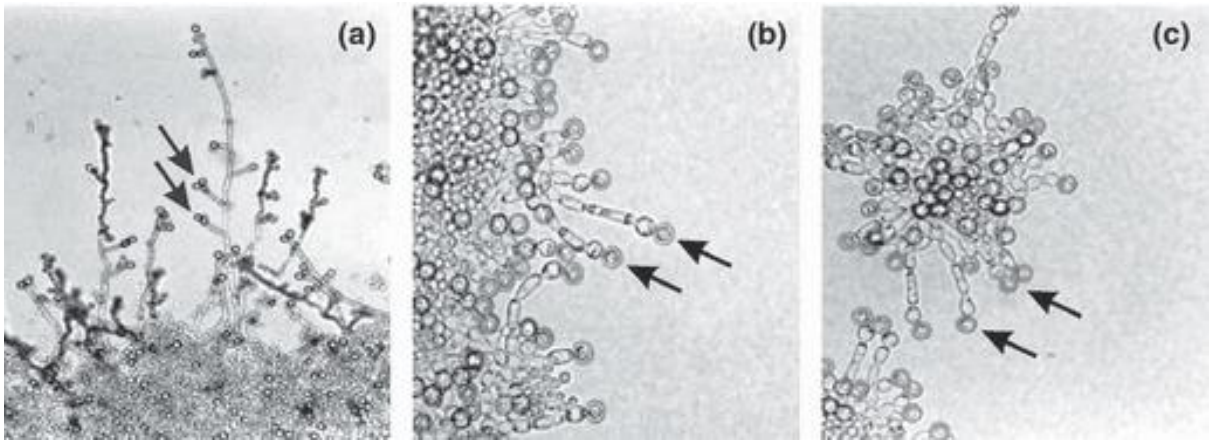


Figure 5: Morphology of *C. albicans* and *C. dubliniensis* chlamydospores. (a) Example of a *C. dubliniensis* strain demonstrating occasional triplet or pairs of chlamydospores (arrows), on the ends of short, hyper branching hyphae. (b) Example of a *C. albicans* strain demonstrating a single terminal chlamydospore arising from a suspensor cell (arrow), (c) Example of a *C. dubliniensis* strain showing almost identical single terminal chlamydospores (arrow) to that in (b).

Courtesy- Candida albicans or Candida dubliniensis? - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Morphology-of-C-albicans-and-C-dubliniensis-chlamydospores-a-Example-of-a-C_fig8_26743523

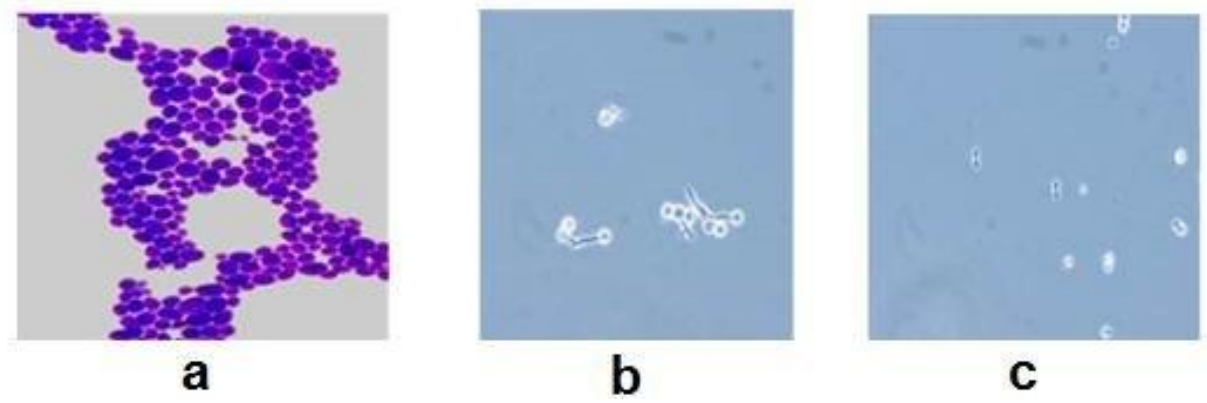


Figure 6| Microscopy of *Candida* species (a) Gram's staining (b) Germ tube test positive showing lateral tubes from *Candida* cells (c) Germ tube negative showing budding yeast cells.

Courtesy- Aslam A, Akhtar N, Hasan F, Shah AA (2015). Prevalence and in vitro Antifungal Susceptibility Pattern of Candida species in a Tertiary Care Hospital. Pakistan Journal of Zoology 04/2015; 47(2):335-342. - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Microscopy-of-Candida-species-a-Grams-staining-b-Germ-tube-positive-showing-lateral_fig1_284167224

The presence of candidemia with symptoms and signs of sepsis such as presence of fever with a temperature more than or upto 38º C, tachycardia, tachypnea and leucocytosis, and other manifestations such as respiratory distress or shock, either at the time of blood sample collection or anytime within 72 hours of it is termed as Symptomatic candidemia. Candidemia is confirmed by the presence of clinical illness with at least one positive blood culture.[16] The various risk factors associated with candidemia include underlying malignancy, Acquired immunodeficiency syndrome, prolonged ICU and hospital stay, debility, use of antibiotics and corticosteroids, administration of parenteral alimentation , diabetes , neutropenia , respiratory illness , renal diseases, central venous catheterization and azotemia. [11][2][17] The source of *candida* blood stream infection has been proposed to be Endogenous source such as gastrointestinal tract or Exogenous source such as skin flora. [17]

On increase in length of hospitalization, there is increase in invasive procedure. The administration of broad spectrum antibiotics leads to suppression of endogenous Gastro-intestinal flora. This causes decrease in incidences of bacterial infections and induces colonization of various mucosal surfaces with fungi. This results in development of invasive fungal infections. Mechanical ventilation is an invasive procedure that can cause colonization of airways with various organisms such as *Candida*. [17] In catherised patients, candida infection is facilitated due to the ability of devices to breach protective barriers of normal

flora.[18] *Candida* infection involves effects on extreme age groups such as neonates and old age. A clinical condition in a neonate presenting isolation of pure growth of *Candida* species from at least one positive blood culture with presence of associated clinical manifestations in the first 4 weeks of birth is termed as Neonatal Candidemia. The presence of *Candida* species attributes to be 9-13% of all blood isolates. [19] In neonates the factors involved also include prematurity and low birth weight conditions.**[20]** The other clinical manifestations associated with neonatal candidemia include thrombocytopenia, hemodynamic instability, temperature instability, hyperglycemia, respiratory distress and feeding intolerance. [19] The clinical presentation of candidemia is similar to that of sepsis syndrome due to which differentiating between the two conditions and the diagnosis only on the basis of sign and symptoms is difficult.[21]

In a recent study the incidence of candidemia was reported to be about 6.9 per 1000 ICU patients. These cases were associated with administration of antifungal therapy in 7.5% of ICU patients. [22] [23] The risk of development of candidemia is higher among the patients admitted in Surgical ICUs. The increase in mortality rate associated with candidemia has been observed of about 20-49%.[24][25] The induction of intravascular catheters is also an important associated pre-disposing factor. The materials used in intravascular catheters provide a site of adherence for *candida* species that provide a potential source of infection to the patient.[26] In case of malignancy and cancer

chemotherapy , on receiving treatment the patients normal flora is supressed, due to which opportunistic pathogen become active leading to development of infection. Malignancy also involves extended period of hospital stay and use of antimicrobials. Candiduria has been associated with development of candidemia in about 10% of cases.[27] A patient associated with multiple co-morbid factors is more prone to development of candidemia. In an ICU setting, a patient may be associated with many such risk factors, which make it difficult to accurately predict the actual cause. Organ transplantation is another risk factor that attributes to development of candidemia. Complications related to transplantations can be caused when the host's immune response recognises the organ as foreign, induces immune response leading to immune-suppresion in the individual.

Patients with lack of gastrointestinal absorption are provided with total parenteral nutrition. These parenteral nutrition being nutritive facilitate *Candida* growth within.[17]

The trends in *candida* species as the causative agent of candiemia have been changing over the years. A variety of *candida* species have developed as fatal pathogenic organisms, with development of more species over the years. The causative agents of infection have been attributed to be most commonly as *C.auris, C.albicans, C.parapsilosis, C.glabrata , C.krusei and C.tropicalis.*

The most commonly used antifungal agent for treatment of candidemia includes azole group. Fluconazole is the most significantly used antifungal, being

available in both intravenous and oral formulation. It is available at a low cost in comparison to other antifungal agents. Other antifungals include itraconazole, voriconazole, polyenes and echinocandins. Polyenes include amphotericin B that has a cidal action on various *candida* species. Echinocandins include caspofungin and micafungin that have demonstrated to be efficient in treatment.[17]

REVIEW OF LITERATURE

Review of Literature

Over the decades *Candida* infection are increasing causing significant increase in the morbidity and mortality rate. The isolation of *Candida* species from blood cultures is defined as Candidemia.[2] Candidemia, is widely prevalent as a hospital-acquired infection.[17] A systematic study done across India based on Intensive Care Unit (ICU) acquired candidemia, demonstrated association of 6.51cases per 1000 ICU admissions. In ICU the observed duration of onset of Candidemia was 8 days. The majority of cases, comprising of 93.6% of patients experienced only a single episode of infection. More than one episode of infection was experienced by 6.4% of cases. While 0.5% cases demonstrated infection with two different *Candida* species. The spread of *Candida* species causing candidemia varied to a great extent. The most prevalent specie was *C.tropicalis,* comprising of 41.6% of cases. *C.albicans* comprised of 20.9% of cases and 10.9% by *C.parapsilosis*. 92.8% of cases were caused by eight species while 22 other, less common species attributed to occurrence of 7.2% cases. Out of the 27 ICUs taken under study, from 19 ICUs 5.2% of *C.auris* were isolated, emerging as the multi-drug resistant species.**[2]** Another study showed that 6.9% cases suffered from Candidemia in a total of 101 patients. The variety of species observed included 42.8% of *C.albicans* , 14.2% each of *C.parapsilosis, C.tropicalis* , *C.famata* and *C.catenulata* .[17]

In a study the isolates demonstrated a sensitivity of 46.6% towards all the antifungals. The resistance demonstrated against various antifungals includes 2.1% towards amphotericin B, 11.8% towards azoles and 6.9% towards echinocandin. 1.9% isolates appeared to be multi-drug resistant (MDR), including 0.3% isolates as pan-resistant (to all antifungals classes). The commonly isolated MDR were *C.krusei* , *C.tropicalis* and *C.auris*. [2]

In various studies, it is observed that various risk factors associated with candidemia include respiratory illness, renal diseases, malignancy, surgery, central venous catheterization patients and use of broad spectrum antibiotics.

A study showed 25.0% of patients with underlying respiratory illness. This included 32.9% pneumonia cases, 17.9% acute respiratory distress syndrome and 15.4% chronic obstructive pulmonary disease. 22.9% of the patients were associated with underlying renal disease, these included cases with majorly acute (61.2%) and chronic (30.1%) renal failure. 12.8% cases associated with malignancy included solid organ malignancy , hematological malignancy , gastrointestinal malignancy and intraperitoneal malignancy. 37.3% patients with surgical procedures were observed . Central venous catheterization patients showed 74.0% of cases associated with *Candida*. Development of candidemia occurring due to broad spectrum antibiotics accounted for 93.0% of cases.[2] In another study patients were also observed with underlying conditions as follows 42.8% cases with ischemic stroke, 14.2% each of tetanus, intracerebral

haematoma, chronic obstructive airway disease and AIDS with cryptococcal meningitis. The patients had some more associated clinical conditions such as 28.5% were diabetic. All individuals were associated with central venous catheterization, receiving parenteral nutrition, broad-spectrum antibiotics and mechanical ventilation. In candidemic patients the average duration of hospitalization was 28.29 days. A mortality of 71.4% of total diagnosed with candidemia was determined.[17]

Based on several studies, over the past decades yeasts have significantly developed as a cause of nosocomial infection. This can be ascribed to the increase in immuno-compromised patients. A study in Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow from a total of 4871 Bloodstream infections, 0.43% *Candida* cases were detected. The study observed increase in isolation of non- *albican Candida* species. The specie trends observed 33.3% of *C.tropicalis*, 9.5% of *C.parapsilosis* and *C.glabrata* each, 4.76% of *C.lusitaniae*, *C.krusei* and *C.guilliermondii* each. The rate of number of candidemia per 1000 admissions was 1.61**.** The predisposing factors included 47.6% gastrointestinal diseases, 19% hematological diseases, 9.5% of renal diseases, 9.5% immunological dysfunction. The probable predisposing factors included use of broad spectrum antibiotics, 42.9%, gastro-intestinal surgery and protein energy malnutrition 23.8% each, neutropenia attributed to

14.3% and central venous line to 4.8%. The highest incidence of candidemia was observed to be in surgical ICU patients accounting to 0.82% of cases.[28]

A retrospective study from South India revealed that the causative agent of 74% of candidemia cases to be non-*albicans Candida*. The isolates included 39.7% of *C.tropicalis*, 26.4% of *C.albicans*, 5.8% of *C.lipolytica* , 4.4% *C.famata*, *C.parapsilosis* and *C.pelliculosa* each, 2.9% of *C.guilliermondii*, 1.4% of *C.lusitaniae* and *C.sphaeria* each. However 8.8% of *Candida* spp. could not be speciated. The study demonstrated a mortality rate of 37%. The pre-disposing factors related to candidemia included 49% cases from ICU, 19% in malignancy patients, 42% of surgery cases and 65% of patients receiving broad spectrum antibiotics.[5] A retrospective study was done in a Tertiary Care Centre to determine the *candida* species distribution and candidemia associated risk factors over a period of 5 years.[16] In this study, 6% of the total samples were positive for candidemia. The observed *candida* species included *C.parapsilosis* 36.6%, *C.tropicalis* 28.3%, *C.albicans* 18.3%, *C.glabrata* 15.0%, *C.guilliermondi* 0.16% and *C.krusei* 0.83%. The mortality rate over the period of 5 years was attributed to be 63.4%. The pre-disposing factors involved, included prior use of antibiotics for 71.2% cases, urinary catheters for 55.6%, central venous catheter 37.5%, post- operative 41.8%, miscellaneous factors including gastric probe, parenteral nutrition and pre- maturity 16%. In 5% of strains, dose dependent susceptibility was observed against fluconazole,

which included 2 isolates of *C. glabrata* and 1 of *C. parapsilosis*. Resistance was observed in 11.7% isolates that included only *C. glabrata*.[16]

In another study from a Level I Trauma Center of the total blood cultures 2.1% isolates were *Candida spp*. In the candidemia patients the mean duration of hospital stay was observed to be 39.1 days. 27.6% candidemia cases were observed per 1000 admissions. The ICU cases that suffered from candidemia attributed to 76.40%. The risk factors involved included broad spectrum antibiotics to be 100%, multiple blood transfusion 95.5%, mechanical ventilation 94.4%, CVC insertion 94.4% , hyperglycaemia 24.7% and steroid therapy 18.0% of the total cases. The variety of *candida* species ranges from *C.tropicalis* 39.0%, *C.albicans* 14.7%, *C.parapsilosis* 22.1%, *C.glabrata* 5.9% and *C.rugosa* 18.4%. The total non – *albican* candida species constituted to be 80% of isolates. The antifungal susceptibilty test demonstrated resistance to be 5.9% of the isolates. While the SDD for fluconazole was about 8.1%. Against voriconazole, amphotericin B and flucytosine all the isolates demonstrated complete susceptibility. While against fluconazole the isolates demonstrated the following resistant pattern. *C.albican* was not resistant towards fluconazole. *C.tropicalis* was 1.9% resistant, *C.parapsilosis* was 6.7 %, *C.glabrata* was 12.5% and *C.rugosa* was 16.0 %. The total resistance was observed to be 5.9%.[29]

A study conducted in a Pediatric ICU demonstrated 4.3% of candidemia cases of the total patients admitted. The number of cases significantly included of 50% of infants to be less than 1 year old. The clinical manifestations demonstrated by the patients included 75% as symptomatic and 25% as asymptomatic. The pre-disposing factors included 87.5% cases due to broad spectrum antibiotics, 87.5% due to intravenous catheters, 9.37% were on immunosuppressive therapy and 30% because of endotracheal intubation and ventilation. The *candida spp.* isolated included 1.6% *C.glabrata*, 6.3% *C.krusei*, 14.1% of *C.guillermondii*, 29.7% of *C.albicans* and 48.4% *C.tropicalis*. In the medical setting 70% of cases were accounted by Non-*albicans candida***.**[30]

A study conducted in an Indian Trauma Care Center setting presented isolation of 212 Candida species isolates. The most commonly isolated *Candida* species was *C.tropicalis* about 39% of cases, *C.parapsilosis* 20%, *C.albicans* 14%, *C.glabrata* 11%, *C.rugosa* 9%, *C.hemulonii* 3%, *C.guilliermondii* 2%, *C.famata* 1.5% and *C.lusitaniae* 0.5%. The 3.3% of isolates demonstrated resistance towards fluconazole and amphotericin B each. The number of candidemia episodes that were observed concluded to 14.95 incidences per 1000 admissions. The association of candidemia was demonstrated in 64.96%. The associated risk factor included 96.2% of catherised patients. Total parenteral nutrition condition associated with candidemia was observed in 23.6% cases. All patients clinical conditions were associated with use of broad

spectrum antibiotics.[31] A retrospective study observed the isolation of 3.4% *Candida* isolates from the total blood samples received in the laboratory setting, over a period of 5 months. The study significantly observed involvement of age as a risk factor. The affected age group included 47.89% patients to be of age group below 1 month, 25.35% cases of infants and 14.08% of children up to 5 year. 85.91% of Non *albican candida* isolates were obtained that included 35.21% *C.tropicalis* and 21.13% *C.glabrata*. Only 14.08% of *C.albicans* isolates were observed, 9.86% of *C.krusei* and *C.pelliculosa* each, 4.23% of *C.parapsilosis* and *C.gulliermondii* each. Only 1.4% of *C.utilis* isolates were obtained. The 71 isolates observed an overall resistance of 11.27% towards fluconazole.[32]

In a study from a Tertiary Care Hospital, Maharashtra 3.45% incidences of candidemia were obtained from total Blood stream infection cases. The specie variety observed was 34.48% of *C.tropicalis*, 27.58% of *C.parapsilosis*, 10.34% of *C.albicans* and *C.krusei* each, 68.96% of *C.haemulonii*, 34.48% of *C.famata*, *C.lusitaniae* and *C.rugosa* each. In the study the mortality rate ascribed to be 24%. The antifungal susceptibility test was done for fluconazole and amphotericin B. The resistance demonstrated against fluconazole was 40% by *C.tropicalis*, 12.5% by *C.parapsilosis*, 66.66% by *C.krusei* and 100% by *C.haemulonii*. The resistance demonstrated against amphotericin B was 10% by *C. tropicalis*, 33.33% by *C.albicans* and *C.krusei*. While against caspofungin, flucytosine and voriconazole all isolates were sensitive.[33]

In a Tertiary Care Centre 1.31% of Candidemia cases were observed of the total blood samples received. The numbers of cases were majorly contributed by pediatric patients about 63.5%, while 36.5% cases developed in adults. The commonly isolated species included mostly 40.1% of *C.tropicalis* , 15.2% of *C.albicans* , 13.1% *C.pelliculosa* , 6.6% of *C.krusei* , 4.7% of *C.parapsilosis* , 4.6% of *C.guilliermondii*, 3.2% of *C.glabrata*, 1.2% of *C.auris*, 1.09% of *C.orthopsilosis*, 0.67% of *C.lambica* , 0.5% of *C.fabianii*, 0.11% of *C.intermedia* and *C. metapsilosis* each, 0.08% of *C. vishwanathii* , 0.05% of *C. sake*, 0.02% of *C. carpophila* , *C. catenulata* , *C.duobushaemulonii* ,*C. inconspicua* , *C. pseudohaemulonii* and *C. sorbosa* each.[34]

A study from South India demonstrated 20.39% prevalence of Candidemia cases of the total neonatal septicemia cases. The *Candida* species obtained included 26.92% of *C.albicans*, 36.53% *C. tropicalis*, 19.23% *C.glabrata*, 7.69% *C.parapsilosis*, 3.84% of *C.guillermondii* and 1.92% *C.krusei*. The associated risk factors included prolonged intravenous antibiotics in 100% cases, low birth weight in 61.53%, prolonged central venous line in 40.38%, prematurity in 30.76%, ventilator support in 23.07% and corticosteroid therapy in 17.3% of cases. *C.albicans* demonstrated 100% sensitivity towards flucytosine, fluconazole and voriconazole, while a 5% resistance was demonstrated against itraconazole. *C.tropicalis* demonstrated a resistance of 8%

towards flucytosine, 44% towards itraconazole, 9% towards fluconazole and 0.5% towards voriconazole. *C.glabrata* demonstrated 100% sensitivity towards flucytosine, 79% towards itraconazole, 37.5% towards fluconazole and 15.5% towards voriconazole. *C.parapsilosis* presented 91.5% resistance towards flucytosine, 34.4% towards itraconazole, 32.2% towards fluconazole and 9.4% towards voriconazole. *C.guillermondii* demonstrated 100% sensitive towards flucytosine and voriconazole, while 47% resistance towards itraconazole and 31% towards fluconazole. *C.krusei* demonstrates 89.2% resistance towards flucytosine, 100% resistance towards itraconazole and fluconazole , while 100% sensitivity towards voriconazole. The MIC of less than 1µg/ml demonstrated against amphotericin B was about 100 for *C.albicans, C.tropicalis, C.glabrata*, *C.parapsilosis* and *C.guillermondii*. While only *C. krusei* demonstrated 88.8% of MIC against amphotericin B.[35]

An observational study done to observe the epidemiology and antifungal susceptibility of *Candida* species demonstrated 4.03% of isolation of *Candida* species of the total Blood stream infections over a study period of 5 years. The species identified included 48.57% of *C.albicans* while 51.42% were Non *albicans Candida* species. The Non *albicans Candida* species included 24.28% *C.tropicalis* , 8.57% *C.haemulonii,* 5.71% *C.glabrata* , 2.86% *C.pelliculosa,* 4.29% *C.sake*, 2.86% *C.rugosa and C.famata* each. The species were further subjected to antifungal susceptibility test towards flucytosine, fluconazole, itraconazole and voriconazole. *C.tropicalis* was 8% resistance towards

flucytosine, 9% towards fluconazole, 44% towards itraconazole, 4.5% for voriconazole. *C.glabrata* was 100% susceptible towards flucytosine while demonstrated resistance of 37.5% towards fluconazole, 79% towards itraconazole, 15.5% for voriconazole. *C.parapsilosis* was 8.5% resistant towards flucytosine 32.2% towards fluconazole 34.4% towards itraconazole and 9.4% towards voriconazole. *C.guillermondi* was 100% susceptible towards flucytosine and voriconazole, resistance demonstrated was 31% towards fluconazole, 47% towards itroconazole. *C.krusei* was 100% resistant towards fluconazole and itraconazole, 89.2% towards flucytosine but 100% sensitive towards voriconazole. The Non *albicans Candida* report to be more resistant towards azole antifungals.[36] A prospective study observed 58.01% of positive culture bottles. 32.5% candidemia cases were observed. The species isolated were 82.85% of non-albicans *Candida*, while *C. albicans* were about 17.5% cases. *C. tropicalis* was about 13.8% of isolates. *C. krusei* was 4.8%, *C. parapsilosis* 3.2%, *C. guilliermondii* 2.8%, and *C. dubliniensis* 2.0%. The antifungal resistance in *C.albicans* was observed to be 42% against fluconazole, 28% against flucytosine and 14% against amphotericin B. *C.tropicalis* resistance was about 49% against fluconazole, 42% against flucytosine and 10% against amphotericin B. *C.parapsilosis* demonstrated resistance 12% towards fluconazole, 12% against flucytosine and 12% against amphotericin B. *C.krusei* demonstrated a resistance of 50% of fluconazole, 35% against flucytosine and 16% against amphotericin B. *C. guilliermondii* demonstrated a resistance of 14

% of fluconazole, 14% against flucytosine and 100% sensitivity against amphotericin B . All species were completely sensitive towards voriconazole and capsofungin. The associated risk factors included preterm birth for 78.5%, low birth weight for 73.7%, prolonged IV antibiotics for 72.5%, ventilator support for 56.2%, prolonged central venous line for 50% cases.[37]

A Tertiary Care Center demonstrated in a prospective study 59 Candidemia cases. The associated risk factors involved age significantly, involving 44% of infants and 23.7% of more than or up to 40 years of age. The surgery involvements such as gastrointestinal, cardiac or neurosurgery constituted to up to 37.4%. The species identified in the isolations included *C. tropicalis* 35.6%, *C. parapsilosis* 28.8%, *C. pelliculosa* 11.9%, *C. glabrata* 11.9%, *C.albicans* 3.4%, *C. guillermondii* 3.4% and *C. pseudotropicalis* 3.4%. The mortality rate determined in the study was about 16.9% significantly affecting the age group above and up to 40 years of age.[38] Another study in a Tertiary Care Hospital setting demonstrated a presence of 80 candidemia cases over a period of one year. The various *candida* species demonstrated the presence of 27.5% *C.albicans* and 72.5% of non *albicans candida*. The predominantly present non *albican candida* species included *C. tropicalis* 15%, *C. glabrata* 27.5%, *C. krusei* 16.25% , *C. stellatoides* 5%, *C.guilliermondii* 3.5%, *C. parapsilosis* 2.5% and *C. dubliniensis* 2.5%.

The associated pre-disposing factors included extremes of age, various system disorders such as nervous system or gastrointestinal, prematurity or low birth weight in neonates, use of antimicrobials, use of catheters, diabetes, AIDS, surgeries and various other factors. Of the total cases, 81.25% of patients were admitted in ICU including both neonates and adults. In neonates 95% of cases involved Vascular access devices as a pre-disposing factor, 70% involved prematurity, 65% involved low birth weight, 25% involved prior antimicrobial therapy, in 20% use of corticosteroids, systemic disorders were present in 20% of cases, recent surgeries in 10% and respiratory disorders in 5% cases. In adults the use of catheters was significantly involved such as intravenous catheters up to 96.67% cases, urinary catheter for 45% and central venous catheter in 30% cases. Malignancy was involved in 18.33% cases while AIDS in only 1% cases. The prior use of antimicrobial therapy was involved in 70% cases. The mortality rate of about 20% was observed. [39]

A prospective study demonstrated pure growth of 34.65% of *Candida* species of the total blood samples in infants admitted to the hospital. The candida species identified included 25% of *Candida parapsilosis,* 21.97% of *C. tropicalis,* 19.70% of *C. albicans,* 14.39% of *C. glabrata* and 10.61% of *C. krusei.* While 8.33% of the isolates represented unidentified *Candida* species. The associated co-morbidity factors involved included 73.49% of prematurity cases, 67.42% of low birth weight cases, 61.36% of Broad spectrum antibiotic use, 64.39% cases of use of indwelling catheters, 55.30% cases of total parenteral nutrition,

49.24% cases of ventilator support and 32.58% of prolonged hyperalimentation cases. The study involved demonstration of antifungal susceptibility profile for the isolated *candida* species against the following antifungals Fluconazole, Itraconazole and Amphotericin-B. The total overall antifungal resistance determined was of 34.09% for fluconazole, 27.27% for itraconazole and 3.79% for Amphotericin-B. The crude mortality observed due to candidemia was of about 34.85%.[40]

The blood culture positive rate of 37.88% was demonstrated in the study in a neonatal ICU setting. The positive rate for *Candida* isolates was detected to be of 9.93%. The study illustrated the predominance of Non *albican candida* species of about 78.12%. The percentage of isolates included *C. tropicalis* for 43.75%, *C. albicans* for 21.87%, *C. glabrata* for 18.75%, *C. parapsilosis* for 12.5% and *C. krusei* for 3.12% of cases. The associated pre-disposing factors demonstrated include low birth weight for 93.75%, prolonged use of intravenous antibiotics for 87.5%, prolonged use of central venous line for 68.75%, prematurity for 62.5% and ventilator support in 37.5% of cases. The antifungal sensitivity pattern was determined against voriconazole, micafungin , fluconazole, caspofungin, amphotericin B and flucytosine. The resistance demonstrated against amphotericin B was about 5% in all isolates. The resistance against fluconazole was about 7% for *C.tropicalis,* 33% for *C.glabrata,* 43% for *C.albicans* and 100% for *C.krusei. C.parapsilosis* was 100% sensitive towards fluconazole. All non *albican candida* were 100%

sensitive to casponfungin, while *C.albican* was 14% sensitive towards caspofungin. All isolates demonstrated 5% resistance towards Amphotericin B.[41]

A study was done on neonatal septicemia to demonstrate the trends of various *Candida* species and their antifungal susceptibility patterns. The rate of *candida* isolation was determined to be 8.1%. The isolated *Candida* specie isolates included 61.19% of *C. tropicalis,* 19.40% of *C. albicans,* 11.94% of *C. glabrata,* 5.97% of *C. parapsilosis* and 1.49% of *C. guillermondii.* The Non *albican* species can be concluded up to 80.59% of the *Candida* isolates. The antimicrobial susceptibility test was determined for the *Candida* species isolates against fluconazole by Disk diffusion and minimum inhibitory concentration (MIC) method. By the Disk diffusion method the resistance observed was about 1% by *C. tropicalis* and 5% by *C. glabrata.* While sensitivity of about 100% was demonstrated by *C. albicans, C. parapsilosis and C. guillermondii.* The neonates mean age was about 3.8 days. The associated manifestations were determined to be low birth weight with prophylactic antibiotics use in 100% of cases, presence of central venous line in 71% cases, 40% involved prematurity, 31.2% involved perinatal asphyxia, 27.8% jaundice , meconium aspiration in 10.8% and 1.49% involved HIV condition .The crude mortality rate was 50.1%. [42] A retrospective study done in East India demonstrated 15% yield of *candida* isolates of the total blood samples collected. The range of candida species isolated was highly variable. The isolation rate included *C.albicans* 27% ,

C.tropicalis 24.5%, *C.krusei* 14%, *C.parapsilosis* 8.5%, *C.pelliculosa* 8%, 1.5% of *C.famata*, *C.glabrata* and *C.utilis* each, 2% of *C.guilliermondii* , 9% of *C.haemulonii* , 0.5% of *C.inconspicua*, *C.lusitaniae* , *C.magnoliae* , *C.spherica* and *C.sake* each . The strains showed varied resistance towards the antifungals amphotericin B, flucytosine, fluconazole, micafungin and caspofungin.[43]

In a study the author demonstrated 7.43% of isolation rate of *Candida* infection of the total blood cultures received. The isolated *Candida* species included 70.8% of *C.tropicalis*, 20.8% of *C.albicans* and 8.3% of *C.krusei* . The associated clinical manifestations were attributed to be intravenous devices and gastrointestinal tract colonization. Further, the resistance of the isolated *Candida* species was demonstrated towards antifungals including fluconazole, itraconazole and amphotericin B. The *C.tropicalis* isolates were 21.2%

resistant to fluconazole, 4.5% were resistant to itraconazole, and 0.4% were resistant to amphotericin B. While *C.albicans* was 18.3% resistant to fluconazole, 3.6% were resistant to amphotericin B and 2.4% were resistant to itraconazole. [44] A retrospective analysis showed the presence of certain pre-disposing factors in the hospitalised children diagnosed with Candidemia including 35% of cases with antimicrobial therapy, 31.25% with bacterial sepsis, 8.75% with gastrointestinal surgery, 7.5% with various gastrointestinal diseases, 6.25% with skin lesions and 2.5% with necrotizing enterocolitis. The prevalence of *candida* isolates was observed to be 57.14% of the total blood

samples. The isolated *Candida* species included 35% *C.tropicalis*, 20% *C.albicans*, 17.5% *C.glabrata*, 15% *C.krusei*, 5% *C.parapsilosis* and 7.5% *C.guilliermondii.* The antifungal susceptibility pattern was obtained of the all isolated *Candida* species towards fluconazole, which was about 4% resistance towards the antifungal.[45]

Isolation of 96 *Candida* isolates was done in an ICU setting. The most common isolate recovered was 78.1% of *C. albicans*, 15.7% of *C. tropicalis*, 6.5% of *C. glabrata*. On the recovered isolates an antifungal susceptibility was performed by the Disk Diffusion Method against fluconazole, ketoconazole, itraconazole, clotrimazole, nystatin and amphotericin B. The resistance rate determined for *C.albicans* was 20.6% towards fluconazole, 33.3% towards ketoconazole, 4.8% towards itraconazole and 1.6% against clotrimazole. *C. tropicalis* demonstrated 50% of resistance towards fluconazole, 83.3% towards ketoconazole, 75% towards itraconazole and 25% towards clotrimazole. While *C.glabrata* was 100% resistant towards fluconazole, ketoconazole, itraconazole and clotrimazole. Also, the three *candida* species were 100% sensitive towards nystatin and amphotericin B. Overall, 26% of all *candida* isolates were resistant towards fluconazole and 38.5% towards ketoconazole, 18.7% to itraconazole and 10.4% to clotrimazole. The associated co-morbid factor included usage of antibiotics in up to 31.25% cases, IV cannula in 21.87% cases, hospital stay of more than 7 days was observed in 25% cases, 9.37% of cases were associated

with chronic renal failure and induction of urinary catheter each, 6.25% of cancer chemotherapy cases, 5.20% of diabetes and anaemia each. [46] A five year study of candedimia cases demonstrated the presence 114 *Candida* species. These identified species included 39.4% of *C. tropicalis*, 17.5% of *C. auris,* 14% as *C. albicans*, 11.4% as *C. parapsilosis.* 5.2% as *C. glabrata* , 0.87% of *C. orthopsilosis*, *C. lusitanae, C. metapsilosis*, , and *C. utilis* each.[47]

A study based in a Pediatric ICU setting demonstrated 28 candidemia patients. The *candida* isolates included 64.28% of *C.albicans* , 25% of *C.tropicalis* , 7.14% of *C.glabrata* and 3.57% of *C. parapsilosis*. The antifungal susceptibility of the strains was studied by disk diffusion method and broth macrodilution method for fluconazole, ketoconazole, clotrimazole, nystatin and amphotericin B. This demonstrated a resistance by *C.albicans* about 5.6% against fluconazole by both disk diffusion method and broth macrodilution method. For ketoconazole there was a 5.6% resistance by the disk diffusion method while no resistance by the broth macrodilution method. Against clotrimazole 50% resistance was deduced by the disk diffusion method. *C.tropicalis* was 14.3% resistant against fluconazole by both disk diffusion method and broth macrodilution method. By the disk diffusion method was 14.3% resistant against ketoconazole and 85.7% against clotrimazole, while 100% sensitive against nystatin. *C.glabrata* was 50% resistant by both methods against ketoconazole and also fluconazole. However, *C.glabrata* and *C.parapsilosis* were 100% resistant towards clotrimazole by the disk diffusion

method. All the isolates were completely sensitive towards amphotericin B. The risk factors involved significantly demonstrated the association of antibiotic usage with development of candidemia in all cases. The association of candida colonisation was about 58.3% in cases. Also, the increase in number of cases was observed on increase in usage of indwelling devices. [48]

AIMS AND OBJECTIVE

Aim –

To evaluate the epidemiology of invasive Candida infection in immuno-compromised patient taking various risk factors into consideration.

Objective-

To perform a systematic review of candidemia in Indian scenario taking following points into consideration:

a) Candida species involved in the invasive candida infection?

b) Risk factors which contribute significantly in Candidemia .

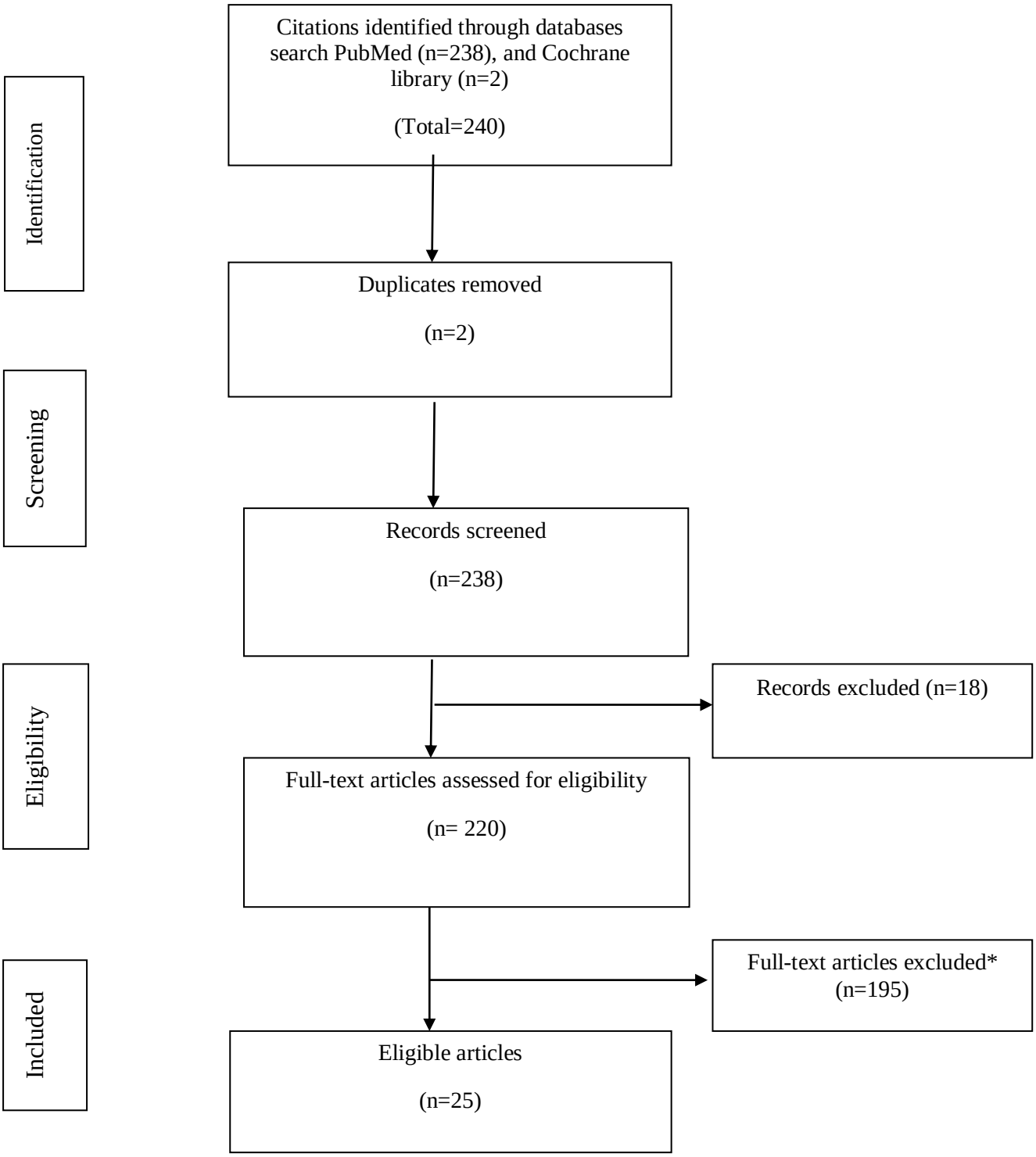
c) Has Antifungal Prophylaxis decreased the incidence of disseminated Candidiasis infection .

d) Morbidity and mortality associated with different Candida spp.

e) Preventive measures to decrease the incidence of Candidemia.

Material and Method

METHODOLOGY



*Full text was not available

Studies involving countries other than India.

Studies including cases of clinical manifestation associated with *Candida* other than candidemia such as candiduria or invasive candidiasis.

Studies including only specific *candida* species.

Studies associated with biofilm formation

Studies including only a particular clinical manifestation with candida such as HIV or COVID 19

Studies including evaluation of *candida* scoring systems.

The study includes peer- reviewed full text Indian studies published between 2000 to 2021 that provide information regarding epidemiology, clinical manifestation and risk factors . The search and selection of articles is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[49] The method of study involved search of various articles using the Boolean operators on various websites such as PubMed, Google scholar and Cochrane Library. Boolean operators include use of terms AND, OR, NOT, NOR or AND NOT as conjunctions to combine or exclude keywords in a search. This proved to be more helpful in obtaining more precise and accurate articles ideal for the analysis. The search strategy included use of particular keywords such as – Candidemia, Immunocompromised and India. Moreover the selection of other articles was also done by doing search through the reference section of the already selected articles. The study comprises of various research articles, original articles and review articles based on the topic.

RESULT

RESULT

On the basis of our study we deduce that the increasing immuno-compromised state in patients in association with ICU admissions and presence of co-morbidity indicates the development of *candida* as a potential opportunistic pathogen.

Based on our findings we conclude that the candidemia is now being predominantly caused by non-*albicans Candida*. The following graphs demonstrate the trends in *candida* species observed in the various studies.

The highest isolation rate has been observed of *C.tropicalis* in most studies. This indicates the change in the trend of infection causing *candida* specie, which was previously identified to be *C.albican* as pre-dominant. The other species that demonstrated a high isolation rate in most of the studies included *C.hemulonii, C.famata, C.parapsilosis , C.lusitaniae , C.glabrata* and *C.rugosa*.

Based on graph 1 the highest isolation rate has been observed of *C.tropicalis* in most studies. Followed by *C.albicans , C.parapsilosis, C.glabrata ,C.rugosa* and *C. hemulonii*. The isolation of other species that were previously not considered to be very significant were also observed such as *C.auris, C.lipolytica, C.krusei, C. utilis and C.guilliermondii*.

Based on graph 2 *C.albicans* have a significant isolation rate in few studies. However, the progressively increasing isolation rate of *C. hemulonii* and *C.albican* indicates there emergence as a significantly pathogenic species.

The spread of candidemia has predominantly affected the pediatric age group. A notable number of researches have been held to identify this emerging clinical condition. Based on our findings as depicted in graph 3, we deduce that most vividly affecting *candida* species among the pediatric age group to be *C.tropicalis* in most of the studies. *C.albicans* is yet significantly present in the isolates. The emerging specie among the pediatrics notably includes *C.parapsilosis* and *C.glabrata*. These isolates attribute to be of most concern. The other species include *C.utilis, C.krusei* and *C.guilliermondii*. However, graph 4 demonstrates presence of higher isolates of *C.albicans,* yet the second most dominant specie was *C.albicans*. The *candida* species included *C.glabrata, C.parapsilosis* and *C.krusei*.

The overall findings establish that while *C.albicans* has been the cause of most infection over the decades, but *C.tropicalis* has evolved notably over the years to emerge as significant *candida* specie. Thus, the observed emergence of Non *albican candida* specie is a major concern. These species have appeared to be highly virulent and possess a high resistance towards antifungal agents. The cause of resistance among the non *albicans* can be inherent.

In most of the studies the authors have demonstrated the antifungal susceptibility of most of the *Candida* isolates against the various commonly used antifungals such as azole groups and polyenes. Among the antifungals fluconazole is the commonly manifested antifungal for treatment of *candida*, due to which high rate of resistance has been developed in the various isolates. The highest rate of resistance has been observed towards fluconazole in the various studies. The progressive rate of resistance development even among the other isolates and other antifungals can prove to be fatal for the treatment strategies advised at present.

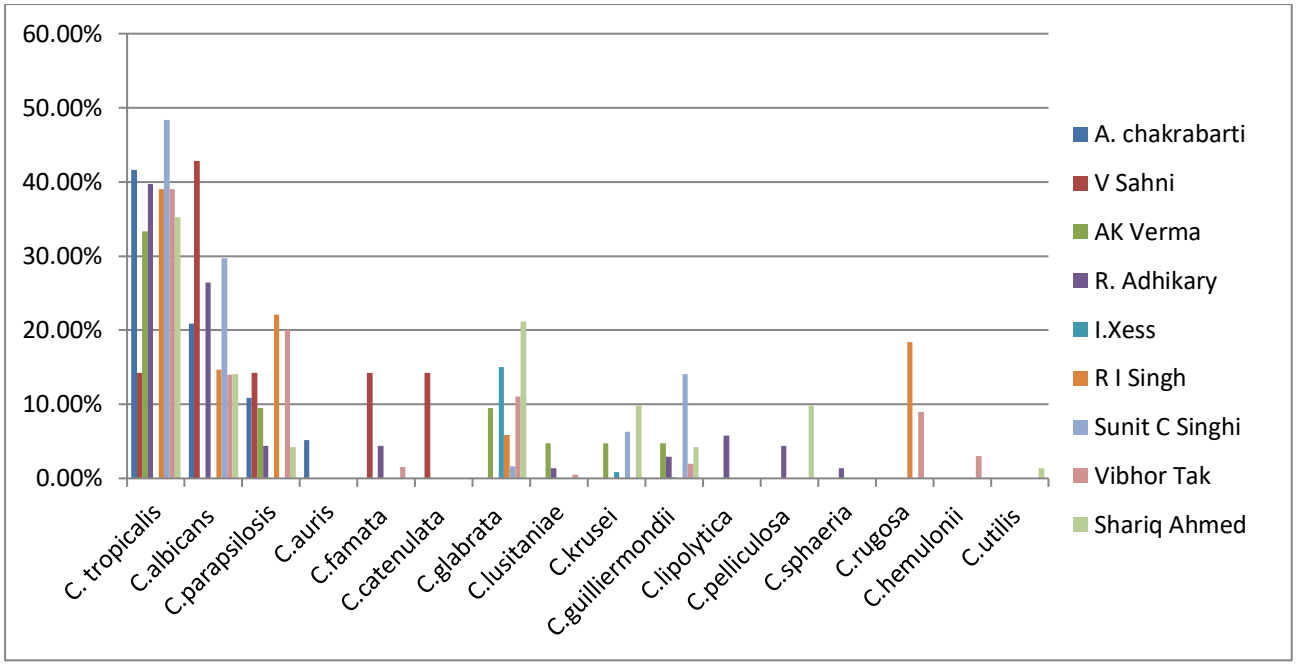
On the basis of our study, we deduce that the increasing immuno-compromised state in patients in association with ICU admissions and presence of co-morbidity indicates the development of *Candida* as a potential oppurtunitic pathogen. Most of the studies demonstrated the isolation of candidemia cases from hospital setting, in which ICUs were most involved. The ICU setting range include Critical ICU, Surgical ICU, Pediatric ICU and Neonates ICU. The infection was also reported to be progressively affecting individuals of older age groups i.e. of more than 60years. The induction of invasive medical instruments such as catheters was also a commonly present risk factor. Patients with malignancy and those subjected to therapy are significantly associated with *candida* infection such as candidemia.

In association with neonates and pediatrics candidemia is a significant cause of mortality and morbidity. Candidemia is wide spread among neonates and pediatrics admitted in ICU, particularly among those with premature birth or low birth weight. Most studies presented a large proportion of cases from Pediatric ICUs. Based on the Graph 5 we deduce that candidemia is highly associated with the young age group, as the most affected patients indicate to be neonates and pediatric. The most commonly associated predisposing factor is prematurity, low birth weight, prolong antibiotics use and catheters. Based on Graph 6 the other commonly associated factors also include malignancy, surgery and organ transplantation. We infer based on all the data that candidemia is associated with causing high mortality.

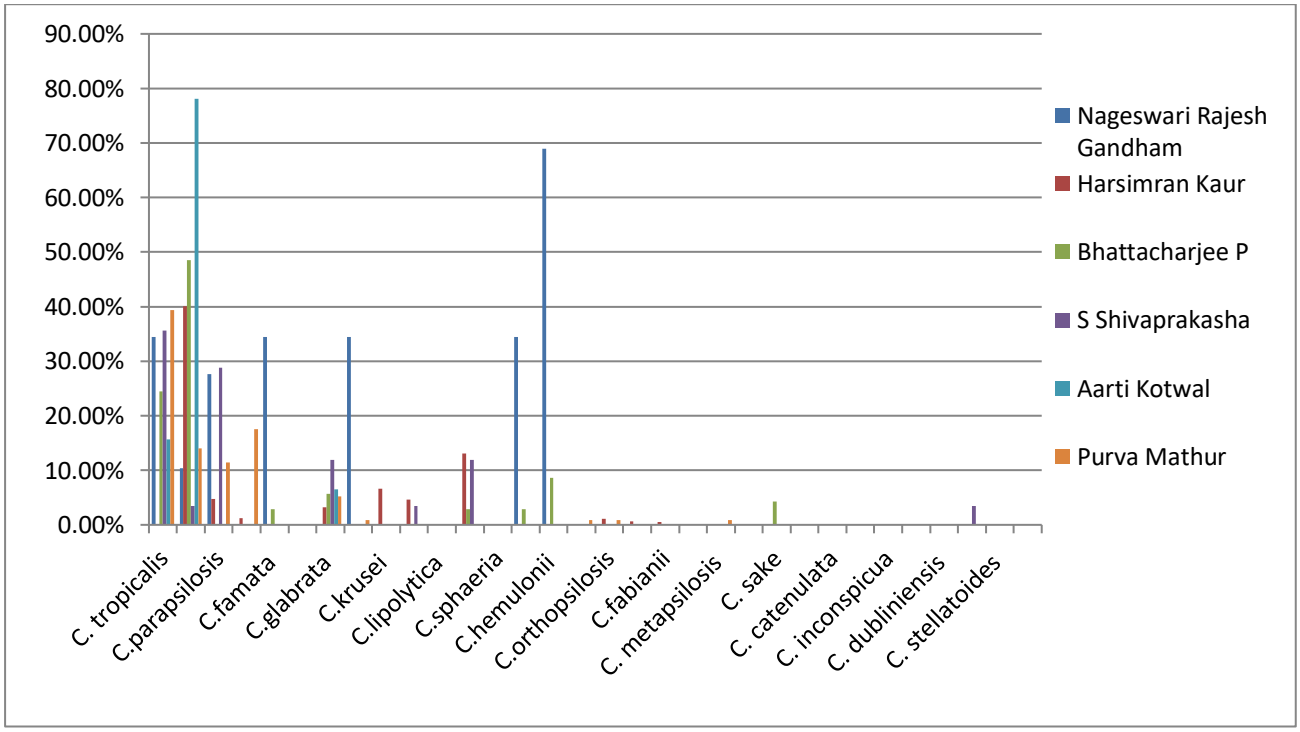
Author, year [Ref.]	Duration of Data Collection	Country, City	Setting	Design	Population	Ascertainment Method	Tested Sample	Positive	Prev. (%)
A.K. Verma et al, 2002[28]	1/2000-6/2001	India	Hospital based	Prospective	Patients in wards of various surgical and non-surgical units, and surgical intensive care unit (SICU)	Patients who developed suspected nosocomial BSI	4871	21	0.43%
Arunaloke Chakrabarti et al,2005[2]	4/2011-9/2012	India	ICU based	Prospective, multicentric, observational study	ICU setting	Patients who contracted ICU-acquired candidemia	215,112	1,400	0.65%
V Sahni et al, 2005 [17]	6 MONTHS	India	ICU based	Prospective	ICU setting	ICU-acquired candidemia	101	7	6.9%
R Adhikary et al , 2011 [5]	1/2009-12/2010	India	Quaternary care multi super-specialty hospital	Retrospective	Patients within hospital setting	NA	NA	55	NA
I. Xess et al, 2007 [16]	1/2001-12/2005	India	Tertiary Care Centre	retrospective study		NA	7,297	439	6%
Rohit Inder Singh et al, 2011 [29]	4 /2008–12/2009	India	Level I trauma centre	Prospective laboratory-based surveillance study	Patients admitted	NA	3225	89	2.1%
Sunit C. Singhi et al, 2004 [30]	3/1993 - 12/1996	India	Pediatric intensive care unit of a tertiary care teaching and referral hospital	Retrospective cohort study	Patients admitted	Patients who developed candidemia	1,450	64	4.3%

Vibhor Tak et al, 2014 [31]	1/2009 – 7/ 2012	India	Tertiary care Trauma Center of India	Prospective	Patients admitted	Patients who developed candidemia	212	157	64..96 %
Shariq Ahmed et al, 2021 [32]	5 months May 2019 to October 2019	India	Tertiary Care Center	Retrospective, observational	Samples received in microbiology laboratory	Patients with suspected BSI.	2084	71	3.41%
Nageswari Rajesh Gandham et al, 2016 [33]	1-year	India	Tertiary Care Hospital	Prospective	Patients admitted	Suspected cases of septicemias from CCUs	839	225	3.45%
Harsimran Kaur et al, 2020 [34]	1/ 1999 - 12/2018	India	Tertiary Care Centre	Retrospective study	Patients admitted		602,963	7927	1.31%
M. S. Srinivas Rao et al, 2014 [35]	1 year	India	Tertiary care institution	Prospective study	Patients admitted	Patients admitted in NICU	255	52	20.39 %
Bhattacharje e P et al, 2016 [36]	1/2011- 3/ 2015	India	Tertiary care hospital	Retrospective, observational	Patients admitted	Patients who developed candidemia	1735	70	4.03%
Asifa Nazir et al, 2018 [37]	1/2016 - 12/2016	India	Intensive Care Unit of teaching hospital	Prospective observational study	Patients admitted	Suspected cases of septicemias	246	80	32.5%
S Shivaprakas ha et al, 2007 [38]	One and half years	India	Tertiary care hospital	Prospective	Patients admitted	Patients who developed candidemia	59	42	71.2%
Barnini Banerjee et al, 2015 [39]	One year	India	Tertiary care hospital	Prospective	Patients admitted	Patients who developed candidemia	NA	80	NA
Deepak Juyal et al, 2013 [40]	1/2012 – 12/2012	India	Tertiary care	Prospective study	Patients admitted	Neonates who developed candidemia	381	132	34.65 %
Mamta Lamba et al, 2019 [41]	5/2014 - 6/2015	India	Tertiary care hospital	Prospective study	Patients admitted	Patients suspected of neonatal sepsis	322	32	9.93%

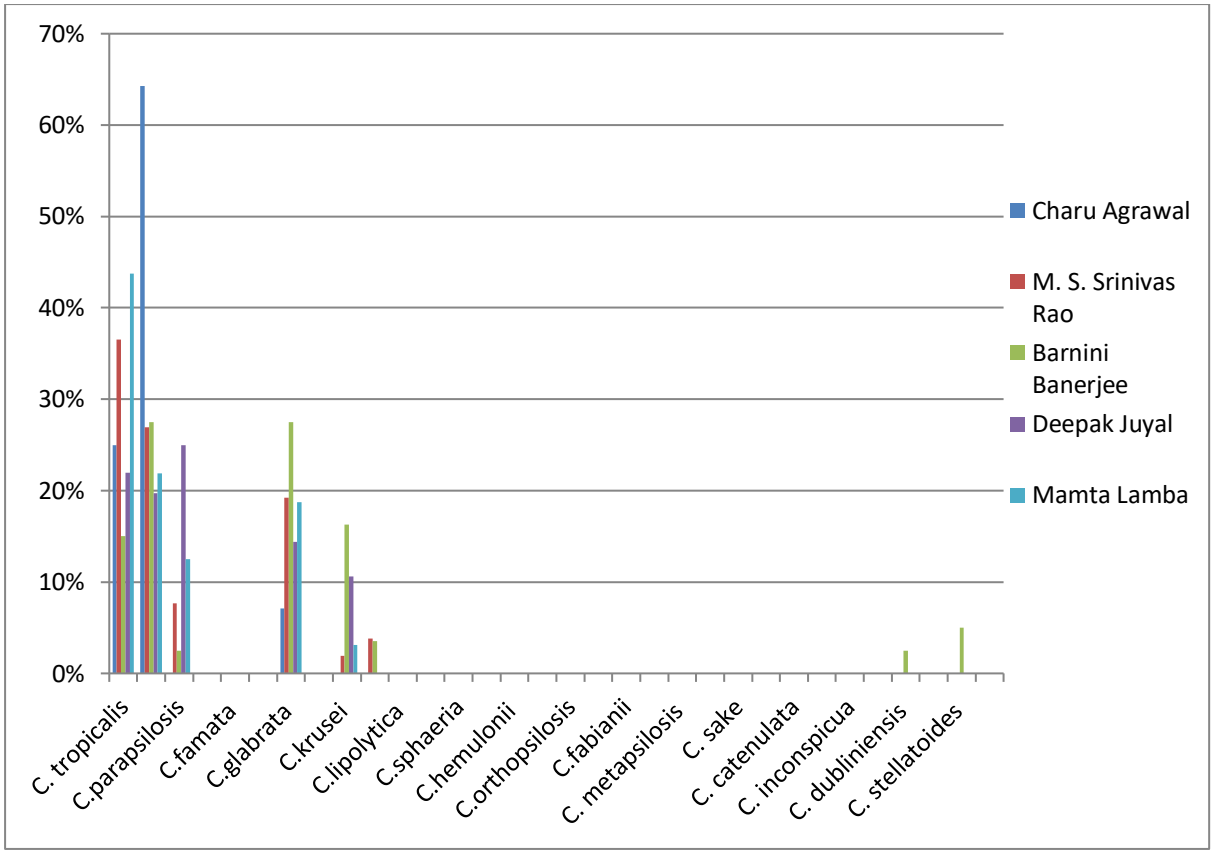
Nidhi Goel et al, 2009 [42]	6/2008-12/ 2008	India	Tertiary care	Prospective study	Patients admitted	Patients suspected of neonatal sepsis	825	61	8.1%
Mandira Chakraborty et al, 2021 [43]	1/2015-10/2018	India	Tertiary care hospital	Retrospective	Patients admitted	Patients who developed candidemia	1280	192	15%
Avijit Kumar Awasthi et al, 2011 [44]	1/2006 – 2/ 2007	India	Tertiary care hospital	Nested case–control study	Patients admitted	Patients suspected of neonatal sepsis	323	24	7.43%
Rumpa Saha et al, 2008 [45]	1/2004-12/2005	India	Tertiary care hospital	Retrospective	Patients admitted	Patients suspected of neonatal sepsis	140	80	57.14 %
Aarti Kotwal et al, 2011 [46]	18 months	India	ICU based	Observational study	Patients admitted	ICU-acquired candidemia	NA	41	45%
Purva Mathur et al,2018 [47]	2012 to 2017	India	Indian Trauma Center	NA	Patients admitted	Patients who developed candidemia	NA	114	NA
Charu Agrawal et al, 2014 [48]	18 months	India	Tertiary-care hospital.	Case- control study	Patients admitted	Pediatric ICU patients acquired candidemia	NA	28	NA



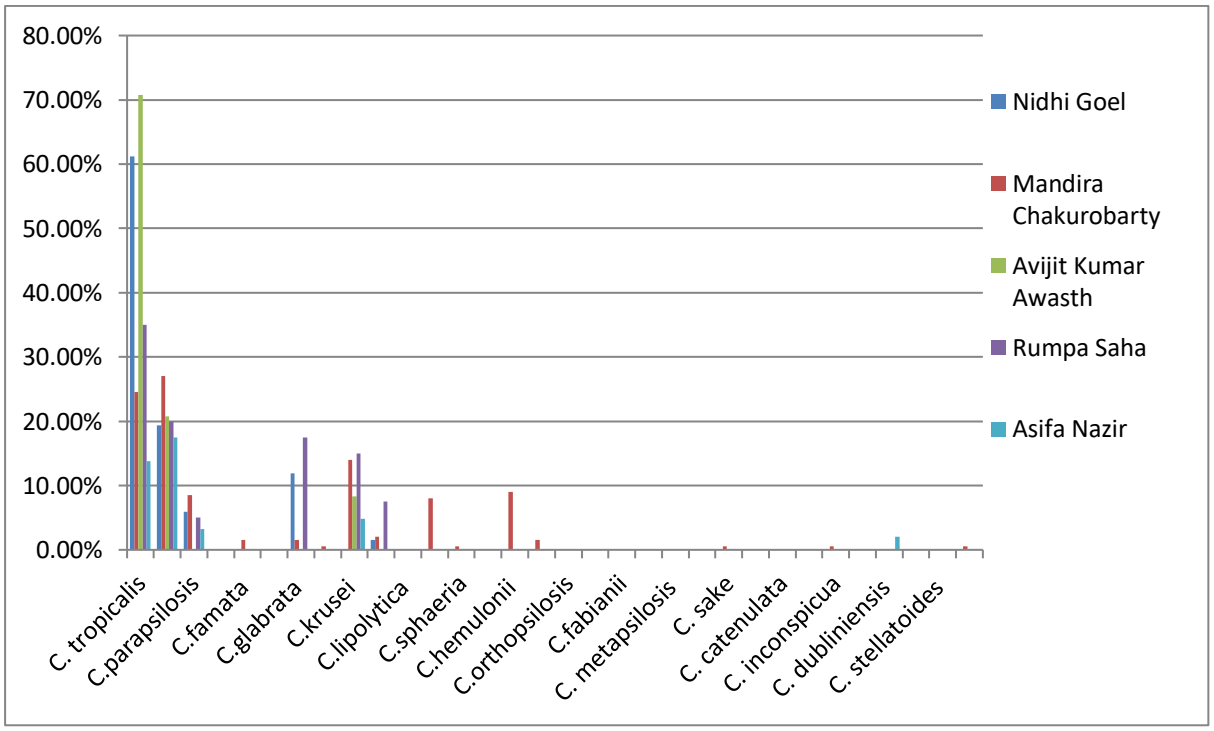
Graph 1: Trends of *candida* species in various studies



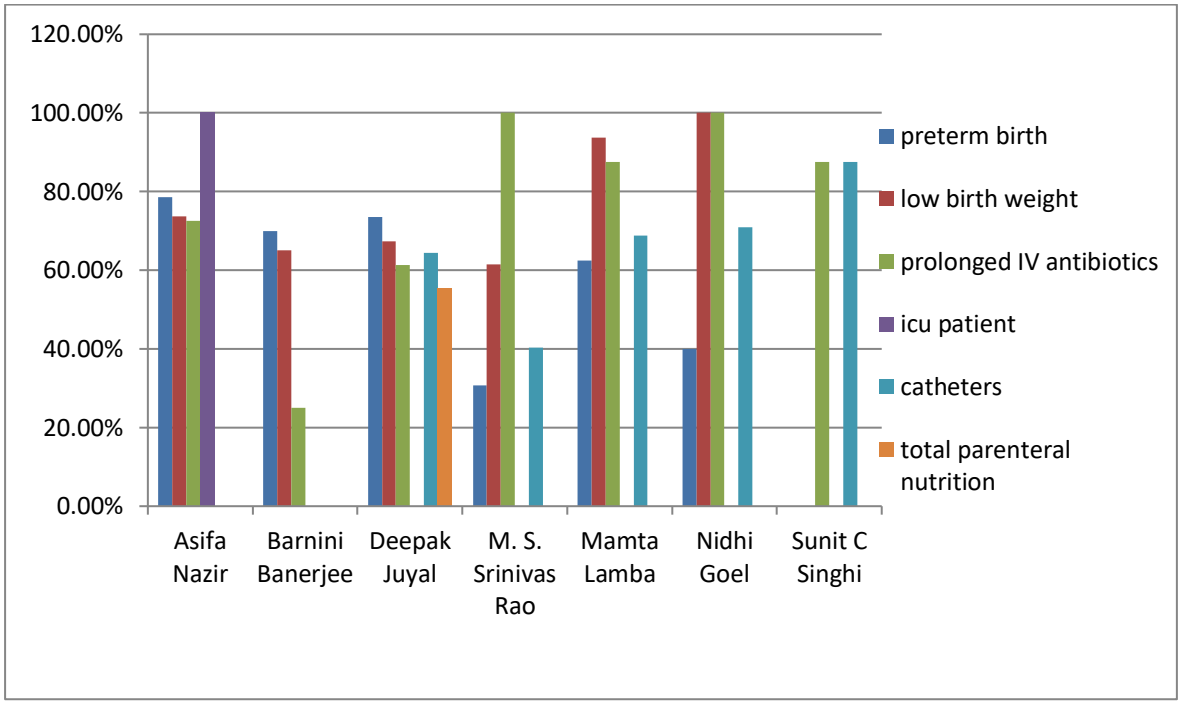
Graph 2: Trends of *candida* species in various studies



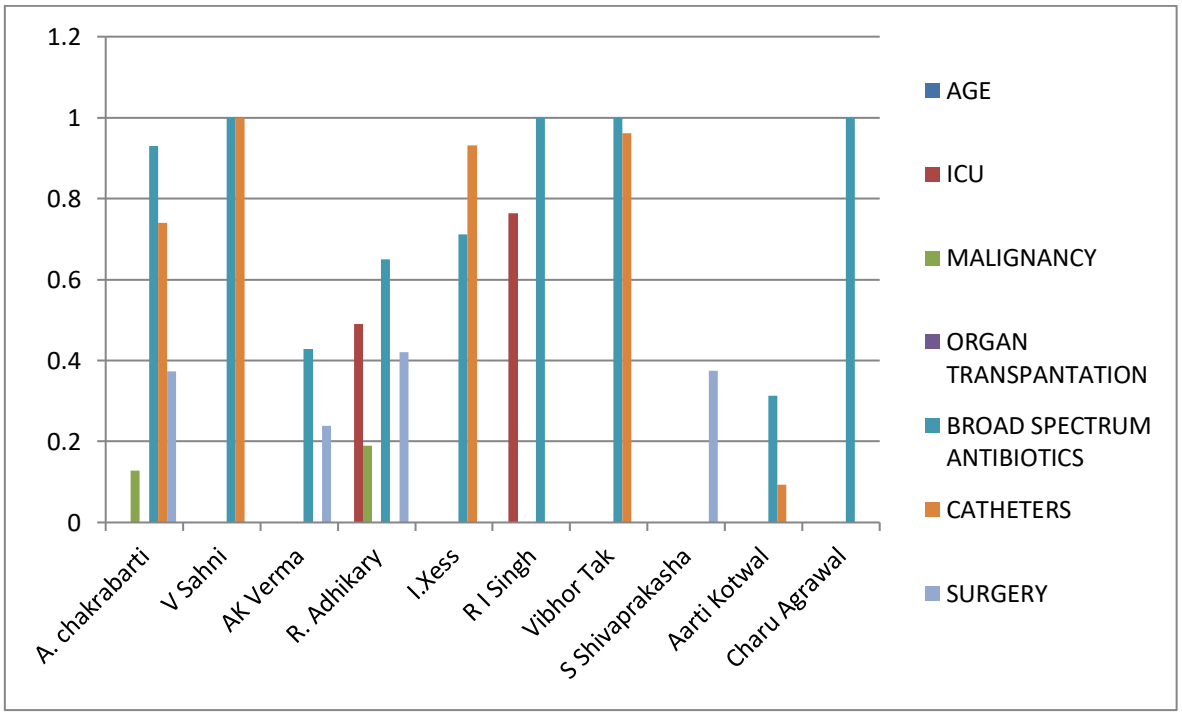
Graph 3: Trends of *candida* species demonstrated in Pediatric ICU in various studies



Graph 4: Trends of *candida* species demonstrated in Pediatric ICU in various studies



Graph 5: COMMONLY ASSOCIATED RISK FACTORS AMONG THE PEDIATRIC GROUP



Graph 6: COMMONLY ASSOCIATED RISK FACTORS

DISCUSSION

DISCUSSION

The *Candida* fungi have evolved significantly from a normal commensal to a pathogenic organism. This process of evolution has been very dynamic and interesting. Based on our analysis we conclude that previously Candidemia was majorly caused by the *Candida albican* species. But over the years, a distinctive increase has been observed in emergence of Non *albican candida* species and even certain unidentified *candida* species. This emergence in the non-significant *candida* species can be attributed to increase in ICU admissions and long durations of stay in ICU, immuno-compromised and immuno-supressed state in patients.

The unnecessary and excessive use of antifungals has also contributed to emergence of Non *albican candida* species infection. Also, certain *candida species* have been observed to possess inherent resistance to antifungal agents. Based on our findings, we also document that there has been an increase in resistance towards fluconazole among the previously susceptible *candida* species such as *C.albicans ,C.lusitaniae , C.tropicalis* and *C.dubliniensis*. This has been associated with widespread use of fluconazole as the first line antifungal therapy drug. The various antifungals that are administered for the use of treatment of *Candida* include mostly azole group such as itraconazole, fluconazole or other polyenes such as amphotericin B and nystatin.

The use of broad spectrum antibiotics causes decrease in protective bacteria presence and promotes the fungal growth. The prolonged duration of ICU admission is a significant cause of mortality due to candedimia in patients. The admission of patients in hospitals for a pro-longed period of time, particularly in those who have an over exposure to antibiotics, presence of single or multiple invasive medical procedures or parentral nutrition have been significantly diagnosed with Blood stream infection. In the pediatric age group *Candida* has been associated with causing high rate of crude mortality and attributable mortality.

CONCLUSION

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To conclude, our study highlights that candidemia is causing a drastic effect on the health system. The overuse of antifungal agents should be strictly limited, observing the development of resistance in the *candida* species towards the various antifungal groups or else, the scarcity of antifungals can lead to decrease in availability of treatment strategy. A complete observation is required to understand the response developed in the various species against the antifungals.

The extremes of age group are much affected by fungemia, especially including neonates with immune-supressed states such as low birth weight, premature status or any associated clinical conditions such as AIDS, diabetes, surgeries and systemic disorders. This extensive spread of infection requires formulation and implementation of Infection Control Strategy. A strategy that focuses exclusively on prevention from infection and therapeutic measures for treatment of candidemia . The limited availability of antifungals necessitates the devising of an antifungal policy. To prevent the emergence of resistance species as an organized study using Antibiotic susceptibility testing.

The high prevalence of candidemia in patients admitted in ICUs also presents the spread of *Candida* as a Hospital Acquired Infection. Thus, simple measures are advised to prevent their spread in the hospital environment such as hand

washing and proper septic measures. These various measures can prove to be very effective to prevent *Candida* caused epidemiology and outbreaks.

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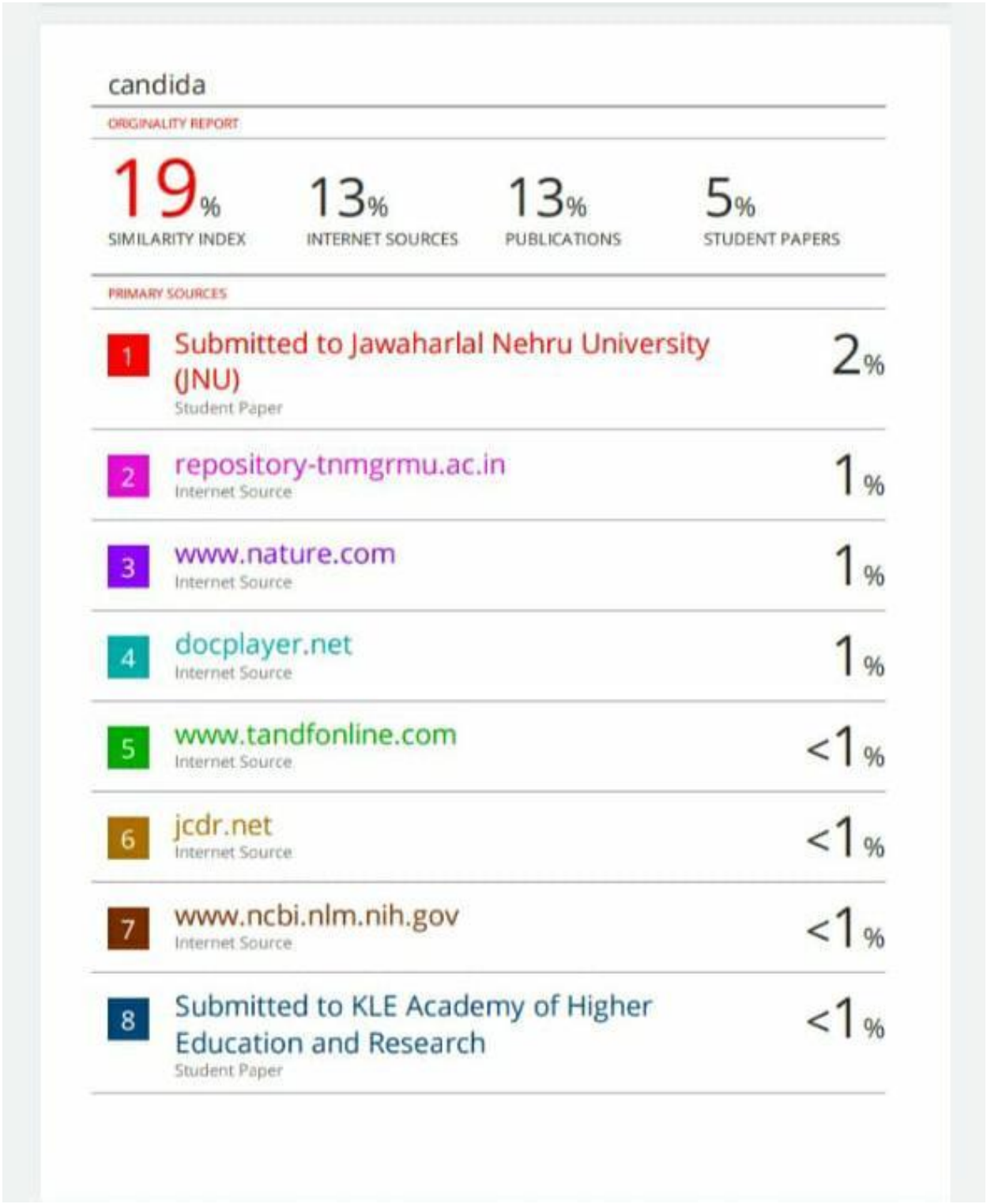

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