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A REVIEW ON CANDIDAEMIA

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INTRODUCTION

Infection plays the important role for human morbidity & mortality. Blood stream infections (BSI) refers to the presence of microorganisms in blood, which are a threat to every organ in the body. All four categories of microbes (bacteria, viruses, fungi and parasites) can cause BSI. Bacteria accounts for the majority of BSI followed by fungi. Among fungi Candida is the most common cause.[1]

Candida is the component of normal flora of human beings. They are seen in oral cavity, GIT, reproductive tract, etc. And they are the yeast-like organisms most commonly isolated from clinical specimens. Candidiasis is a state of the Candida caused ailments. Some of them are oropharyngeal candidiasis, onychomycosis, vulvovaginitis, candidemia, disseminated infection.[2]

Candidemia represents 10% of nosocomial infections in hospitalized patients and is associated with mortality described to be as high as 40%.[3] Underlying immune defect, solid or hematological malignancy, may predispose to candidemia which develops during the clinical course of these conditions in 1.8% of cases.[4]

When Candida invades the bloodstream, the infection becomes systemic and is often deadly. Candida has emerged as the fourth leading cause of bloodstream infection in hospitals in western countries(U.S.). This number is increasing in India also raises issues of concern. Simultaneous recovery of the same species of yeasts from several body sites, including urine is a good indicator of disseminated infection and fungemia.[5]

C. albicans, as the most common cause of candidiasis, is studied more extensively than any other Candida species. Nonetheless, increasing incidence of candidemia caused by non- albicans Candida (NAC) species has also been reported in the latest decade, that led to the rise of NAC investigations.[6] NAC is a heterogeneous group of Candida species with approximately 19 species implicated in human infections. C. tropicalis, C. glabrata, C. krusei and C. parapsilosis are most commonly reported NAC spp.[7]

Different methods such as manual, automated, and molecular methods can be used for identification of Candida species as well as for antifungal susceptibility testing for various species. It has recently been established that 48 hours of incubation for blood cultures may be sufficient to detect 90% of Candida species.[8] Moreover, as is well known, traditional antifungal susceptibility testing of blood cultures positive by microdilution method requires 24 hours more incubation to obtain isolated colonies, and an additional 24 hours to generate MICs for Candida species (about 4 days from the time of sample are needed to obtain an anti- fungal MIC determination). Keeping in mind the high morbidity and mortality in patients associated with these infections, its rapid identification and treatment is necessary.[1]

REVIEW OF LITERATURE

Infections due to fungi belonging to the genus Candida are increasingly reported in recent years. Candida spp. is the only opportunistic fungi that exist both as a commensal and pathogen. It is also unique among mycotic pathogens as it causes a broad spectrum of clinical manifestations ranging from mere mucocutaneous overgrowth to life threatening systemic infections.[9]

The severity of candidiasis is ranges from moderate to fatal and is dependent on the site of infection, virulence of infecting strain and host's immune status. Cutaneous candidiasis is common and can occur in otherwise healthy individual. It is easy to treat with basic hygiene and local treatment.[10] Mucocutaneous and invasive candidiasis is often opportunistic and manifests in patient with either acquired or induced immunosuppressed conditions. Invasive Candida infections are one of major causes of morbidity and mortality in immunocompromised as well as critically ill immunocompetent patients.[11]

Virulence factors of Candida are traits that facilitate colonization and infection of the host cell by the fungus.[12] Many authors define these attributes as "all traits required to establish the disease", "factors that

directly interact with mammalian host cells" or as "a component of pathogen that damage the host". The adhesion of Candida to the host is essential to colonization and establishment of disease. The adhesion to surfaces of medical devices results in raised candidemia and antifungal resistance related to catheter insertion.[13] Secreted aspartyl proteinases (SAPs) are proteins reported to be present in C. albicans, C. parapsilosis and C. guilliermondii.[14] The function of these proteins is to degrade many human proteins at lesion sites, such as albumin, haemoglobin, keratin, and secretory immunoglobulin, and this proteolytic activity is involved with tissue invasion by the fungus.[13] The phenotypic switch meaning transition from yeast to hyphal form is considered the most important virulence factor.[15] At high cell densities, quorum sensing molecule farnesol also promotes hypha formation.[16]

Since yeast seems to be essential for the dissemination of the infection and hyphae contribute to host tissue damage, both morphologies are thought to be important for pathogenicity.[17]

The antigens of Candida species can be divided into two main broad groups; cell wall antigens & cytoplasmic antigens.

The virulence factors contributing to the pathogenicity includes adherence to epithelial and endothelial cells, proteinase production, pseudohyphae formation. *C. albicans* and *C. tropicalis* produce aspartyl proteinase *in vivo*, which is an important factor of pathogenicity. The transformation into the hyphal form is observed during an active infection. It is believed that phospholipase concentrated at the hyphal tip may be related to the greater invasiveness of this form as compared to the yeast form. Moreover, the hyphae being larger than the yeast form are more resistant to phagocytosis and thus morphological change contributes to the increased pathogenic potential of the fungus. Biofilm formation further adds to the pathogenicity of the fungus.

The clinical manifestations of candidiasis are extremely varied, ranging from acute, subacute, chronic and episodic. Involvement may be localized to the mouth, throat, skin, scalp, vagina, fingers, toes, nails, bronchi, lungs or gastrointestinal tract. It may also be systemic as in septicaemia (circulating in the blood and causing damage to blood vessels and sometimes blood cells), endocarditis and meningitis. The pathologic processes evoked are diverse and vary from irritation and inflammation to chronic and acute suppuration or granulomatous response. The diseases include; oral thrush, stomatitis, glossitis, cheilitis, esophagitis, gastritis, vulvovaginitis, balanitis, balanoposthitis, chronic mucocutaneous candidiasis, ocular candidiasis, intertriginous and generalized paronychia and onychomycosis, diaper dermatitis, candidal granuloma, urinary tract infection, endocarditis, pulmonary candidiasis, meningitis, candidemia, dissemination, arthritis, osteomyelitis, endophthalmitis, candidids, eczema, asthma, gastritis, etc.

Oral thrush can mimic bacterial infections like sore throat caused by Staphylococcus aureus, Corynebacterium diphtheriae, leukoplakia, lichen planus and tertiary syphilis. Vaginal candidiasis may be confused with trichomoniasis, bacterial vaginosis and herpes simplex infections. The differential diagnosis of systemic infection must include other mycoses, tuberculosis, neoplasia or chronic bacterial infections. In all these cases fungal culture is essential to confirm or rule out the diagnosis of candidiasis.

The diagnosis of any pathological agent requires high sensitivity and specificity levels, being the microbiological culture the test of choice widely used over time. However, there are different tools other than the microbiological culture, which facilitate the diagnosis. These include smears, biopsies, molecular techniques, and serological tests.

In recent years, the field of laboratory medicine has undergone a sea change from conventional methods to rapid commercial systems and from rapid commercial systems to molecular diagnosis. Although commercial systems and molecular diagnostic methods are rapid and reliable, high cost limits their use.[18] Conventional techniques remain the mainstay of species identification of Candida isolates in most clinical microbiology laboratories.

As compared to rapid commercial kit based system and precise molecular techniques most of diagnostic laboratory still rely on conventional or traditional methods for identification of Candida species. Conventional methods include germ tube test, morphology study and carbohydrate fermentation and assimilation tests.[18]

Most of conventional methods require isolation of Candida on suitable laboratory media. Being non-fastidious in nature, Candida luxuriantly grows on common laboratory media used for isolation of pathogenic bacteria and fungi.[18] Sabouraud's Dextrose Agar (SDA) is widely used media for primary isolation of Candida spp. from clinical specimens.[19] Candida produces creamy, smooth, pasty and convex colonies which may become wrinkled on further incubation.[20] Potato Dextrose Agar (PDA) aids in differentiating between colonies of different yeasts species from the same clinical specimen.[18] Candida grows well on plain blood agar plates. It is frequently isolated in bacterial culture and may be referred to the mycologist for species differentiation. Combination of SDA and brain heart infusion can be also for isolation of Candida spp.

A wet mount preparation should always be performed first when growth yeast like organism is seen on culture medium. is is essential to differentiate between yeast and

bacterial growth. Examination of wet preparation also reveals size, shape, number of buds and pattern of attachment of bud to the yeast cell. Gram stain used for bacteria also demonstrates Candida. Candida appears as gram positive. Large size, presence of bud and pseudohyphae makes yeast cell very distinctive in gram stained smear. Germ tube test is the most widely used conventional technique for identification of Candida spp. Among Candida spp. of medical importance, C. albicans and C. dubliniensis produce germ tubes. In addition to these species, C. africana is also germ tube positive isolate.[21]

Certain Candida spp. like C. albicans, C. dubliniensis and C. tropicalis (few strains) produce chlamydospores on nutritionally deficient media. Chlamydospore formation test is less subjective but more time consuming than germ tube technique.[22] The pattern of growth on corn meal agar (CMA) can be used for speciation of Candida isolates. Morphological features of some medically important Candida spp. on CMA is shown in table 1.

Table 1: Morphological features of medically important Candida species on corn meal agar.[23]

Candida spp.	**Morphological feature on corn meal agar**
C. albicans	Elongated pseudohyphae with grape-like clusters of blastoconidia at the septa. Chlamydospores are present at the end of the hyphae or their short, lateral branches.
C. tropicalis	Abundant branched pseudhyphae composed of elongated cells. Blastoconidia are seen singly or in small groups along mycelia and show characteristic "**pine forest arrangement**". True hyphae present in some strains and chlamydospores are produced, especially on initial inoculation.
C. parapsilosis	Pseudohyphae are long, thin and branched. Single or small clusters blastospores seen along the pseudomycelia. Large, mycelia elements, called giant cells is the characteristic feature.
C. guilliermondii	Abundant or sparse, very fine and short pseudohyphae. Small blastoconidia seen in small chains or in clusters. Absence of terminal chylamydospores.
C. krusei	Long, slender, straight cells showing tree-like branching and chains of blastoconidia arises from the point between cells resembling **"crossed matchsticks".**
C. kefyr	Abundant production of pseudohyphae. Cells are elongated and fall apart and lie parallel, like **"logs in a stream"**.
C. dubliniensis	Production of true hyphae on CMA helps to distinguish this species from *C. albicans*. Abundant chlamydospores often in clusters or contiguous pairs on the true hyphae. Presence of solitary or cluster of blastoconidia is an important characteristic feature.
C. glabrata	Formerly classified as "*Torulopsis glabrata*". Absence of hyphae or pseudohyphae is the characteristic feature.
C. lusitaniae	Ovoid yeast cells arranged in pairs and chains. Abundant branched pseudohyphae may be seen. Pseudohyphae are curved. Some strains have rudimentary to no pseudohyphae.
C. rugosa	Pseudohyphae well developed with abundant blastospores at internodes.

The ability of Candida spp. to assimilate a particular carbohydrate as the sole carbon source has been used identification.[18] Carbohydrate assimilation test is simple and cost effective conventional method for speciation of Candida isolate. Carbohydrate assimilation pattern of some medically important Candida spp. is shown in table 2.

Table 2: Carbohydrate assimilation pattern of *Candida* spp.[23]

Organisms	**Assimilation**											
	Dextrose	Maltose	Sucrose	Lactose	Galactose	Melibiose	Cellobiose	Inositol	Xylose	Raffinose	Trehalose	Dulcitol
C. albicans	+	+	+	-	+	-	-	-	+	-	+	-
C. glabrata	+	-	-	-	-	-	-	-	-	-	+	-
C. parapsilosis	+	+	+	-	+	-	-	-	+	-	+	-
C. tropicalis	+	+	+	-	+	-	+	-	+	-	+	-
C. kefyr	+	-	+	+	+	-	+	-	+	+	-	-
C. krusei	+	-	-	-	-	-	-	-	-	-	-	-
C. lipolytica	+	-	-	-	-	-	-	-	-	-	-	-
C. guilliermondii	+	+	+	-	+	+	+	-	+	+	+	+
C. rugosa	+	-	-	-	-	-	-	-	+	-	-	-
C. viswanatii	+	+	V	-	+	-	+	-	+	-	+	-
C. dubliniensis	+	+	+	V	+	-	-	-	-	-	+	-

† '+' positive, '-'negative, 'V' variable.

A variety of chromogenic media are available for speciation of Candida isolates. Improved isolation rate, rapid identification and differentiation of poly-fungal populations in clinical samples are prominent advantages of chromogenic media. CHROMagar Candida is a commercially available selective and differential media for isolation and identification of Candida spp. is medium contains chromogenic (hexosaminidase) substrates that react with species-specific enzymes secreted by yeast cells, resulting in development contrasting colored colonies. C. albicans produce leaf-green colored colonies, C. tropicalis colonies are dark blue-grey with a purple halo and C. krusei forms pink colonies with whitish border. On CHROMagar, NAC spp. like C. famata, C. guilliermondii, C. kefyr, C. lusitaniae, C. norvegenesis and C. parapsilosis produce colonies of variable shades of ivory, lavender and pink indistinguishable from each other.[18] C. glabrata colonies appear as a dark violet colored and can be differentiated from the pink and white colours produced by other species. C. rugosa produces distinct small, dry colonies of a brilliant blue colour with distinctive pale or white

border.[24] Colonies of other species are entire and smooth and colony color ranges from white to dark pink.[18]

In addition, tests can be performed for isolation and identification using urease test, resistance to cycloheximide, fermentation of sugars, carrot-potatoes agar, among others. Currently, commercial automated systems allow the identification of yeast in a short time (<15 h), with time reduction in the diagnosis.[25]

Like the aforementioned techniques, molecular tests will have diagnostic value when invasive candidiasis is suspected. These tools allow a quick diagnosis (<7 h); however, the cost is much higher. Some of the most used molecular techniques are PCR-REA, PCR-LiPA, PCRsn, multiplex PCR, nested PCR, PCR-SB, PCR-rt., among others.[26] MALDI-TOF MS is also currently used for its detection with higher sensitivity and specificity.

It is important to note that a positive result for Candida culture does not always confirm the diagnosis of Candida infection, since this microorganism is considered normal biota in some parts of the body. To achieve a proper diagnosis of candidiasis, the patient's signs and symptoms must be taken into account, in addition to the laboratory results. If the culture comes from biopsy or is a blood culture, the positive result confirms the diagnosis of invasive candidiasis. On the other hand, a negative result for the culture of Candida is of greater diagnostic value since it allows to discard the infection by this yeast.[27]

Broadly speaking, the pharmacological treatment comprises three antifungal groups: amphotericin B-based preparations, azoles antifungals, and echinocandins. In the past years, management of infections caused by different species of Candida has undergone various changes. In 2016, the Infectious Disease Society of America (IDSA) reference guides were updated, and the appropriate use of echinocandins (caspofungin, micafungin, and anidulafungin) was included, as well as the incorporation of expanded-spectrum azoles, and lipid formulation of amphotericin B.

Although C. albicans is the most common cause of mycoses in hospitalized patients, the rate of candidaemia caused by C. non albicans spp. is increasing.[28] Among these candidiasis, C. glabrata and C. krusei are com- mon (15-25% of bloodstream Candida isolates worldwide) and difficult to treat because of their reduced susceptibility to common antifungal agents.[29] C. krusei is innately resistant to fluconazole, in addition to intrinsic resistance nearly about 20% strains of C. glabrata can acquire resistance during course of therapy.[30] C. tropicalis is generally considered as a fluconazole-susceptible species however, recent studies have documented emergence of fluconazole resistance in this NAC spp.[31] C. parapsilosis is reported to have high minimum inhibitory concentration to echinocandins, the recent addition to antifungal arsenal.[32] Candida auris has emerged as an important nosocomial pathogen which is highly drug resistant.[1] Thus, the rate of fungal infections and the different susceptibility to antifungal drugs among different species of Candida highlight the importance of an accurate species identification and above all a rapid anti- fungal MIC determination.[33]

Candidemia in hospitalized patients especially in ICU patients is emerging as a significant problem worldwide. The change in epidemiology and pattern of antifungal susceptibility of Candida infection has made identification of aetiological agent compulsory along with its antifungal susceptibility. Various risk factors have attributed to this increase in Candidemia in the hospital settings. The increase in resistance to antifungal agents among Candida isolates has resulted in increased mortality and morbidity. Prevention of risk factors in Candidemia patients with early removal of central line, timely fungal culture, Candida speciation and antifungal susceptibility are necessary for appropriate treatment and better outcome.

DISCUSSION

The prevalence of Candida species in bloodstream infections (BSIs)has increased worldwide in the last three decades. In the United States, a seven yearlong study has reported Candida species to be the 4th most common cause of BSI in hospitals.[3] Lot of variation in the prevalence and incidence of Candidemia have been reported from India. A study from SGPGI, Lucknow ranked Candida species as 8th among all isolates causing BSI with incidence rate of 1.61%.[34] A five-year study from All India Institute of Medical Sciences (AIIMS), New Delhi found a prevalence of 6% for Candida Species in BSI.[35] A study conducted in Maulana Azad Medical College (MAMC), New Delhi found the incidence rate of Candidemia to be 6.9%.[36]

Candidaemia is associated with one of the highest rates of mortality of all (BSIs). Crude mortality rates of 67% were reported for BSI due to Candida spp, compared to BSI due to Enterobacter spp (53%), Pseudomonas aeruginosa (47%), or Staphylococcus aureus (24%).[37] Inadequate empirical antifungal treatment[38], or even a delay of initiation of adequate antifungal therapy in patients with candidaemia)[39], is associated with a high risk of mortality and prolonged hospital stay.

More than 90% of the invasive infections due to Candida are attributed to five Species - C. Albicans, C. Glabrata, C. Parapsilosis, C. Tropicalis and C. Krusei. However, the list of new species of Candida isolated from clinical specimens continues to grow every year.[40] C. albicans has been earlier recognized as the most frequently identified yeast in blood cultures. However, more recent studies have shown a decreasing frequency of C albicans candidemia, while the frequencies of C. glabrata and C. krusei candidemia have remained stable and those of C. parapsilosis and C. tropicalis are increasing.[41] C.

tropicalis was found to be the most common isolates from Candidemia pts by (Shivprakash et al., 2007) (35.6%) and (Adhikary et al., 2011) (39.7%) respectively.[42,43] Xess et al., from AIIMS, New Delhi also found C. tropicalis to be the most common species of Candida in blood isolates (35.3%).[35] Since the first report of ear-canal infection by C. auris in Japan in 2009, candidaemia due to this yeast has been reported with a large number of cases from India.[44]

Antifungal susceptibility testing of NAC in various studies shows higher resistance to most of the antifungals when compared with C. albicans. Among the NAC, C. glabrata shows high resistance to most of the antifungals, especially to amphotericin B.[45,46,47,48] The antifungal resistance is an emerging problem. In these cases, appropriate treatment can be decided on the basis of species identification.[49] Fluconazole and the other triazoles have less activity against species of Candida such as C. krusei and C. glabrata. The emerging trend of resistance to fluconazole and other triazoles among Candida isolates from BSI has made echinocandins very important.[50] Even as per CDC, to date, there are no established minimum inhibitory concentrations (MICs) breakpoints for susceptibility testing of C. auris. [5]

As per CDC, to date, there are no established minimum inhibitory concentrations (MICs) breakpoints for susceptibility testing of C. auris.[51]

In conclusion, the contribution of C. albicans and NAC species in Candida infections is changing from the past in different areas, and epidemiological data show the increasing trend of NAC infections worldwide. Due to the increasing of antifungal resistance of Candida species and the elevating number of immunosuppressed patients, so it is essential to provide new effective strategies for treatment of this fungal infection. As NAC species have various virulence factors and antifungal susceptibility profile, thus precise molecular identification can help us to reach to these advantageous strategies.

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