CHAPTER 2

Review of Literature

Incidence of non-albicans Candida over Candida albicans

The incidence of Candida species infection is increasing (Beck-Sague and Jarvis, 1993) along with shift towards non-albicans species (Voss et al., 1997). In last few decades, there have been numerous reports of Candida infections in India (Basu et al., 2003). Candida is most common fungal opportunist and can cause fungal disease (Keye and Magee, 1956). A study by Martin et al. (1937) and Holy and Mc Cobe (1950) on candida that can cause infection in human were C. albicans, C. tropicalis (Kunstadter et al., 1952), C. krusi (Wyckerham, 1957), C. parapsilosis (Skinner, 1947) C. pseudotropicalis (Machinnon et al., 1945). Another study by Pfaller and Diekema, (2007) the trends of species distribution include seventeen different species of Candida as etiologic agents, although 90% of invasive infection due to Candida species are attributed to five species e.g., C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, and C. krusei. Non albicans species of Candida are currently the pathogens most frequently recovered from adults and children in tertiary care medical centers (Pappas et al., 2003)

In last two decades, it has been seen that there is significant increase in the number of reports of systemic and mucosal yeast infection with non albicans
Candida species (Kothavade et al., 2010; Pfäffer et al., 1996; Nguyen et al., 1996). Epidemiological data from the Indian subcontinent showed that 67-90% nosocomial Candidemia were due to non-albicans species of Candida (Kothavade et al., 2010; Kothari and Sagar, 2009). Moreover, a relative decrease in the proportion of infections caused by C. albicans and C. tropicalis and increase in the proportions of infections caused by C. krusei and possibly C. glabrata have been observed, and this shift may be associated with other factors (Abi-Said, 1997).

The comprehensive review of published reports during 1952-1992 showed proportionately higher isolation of non Candida albicans (Wingard, 1995). The rise in the frequency of NAC species has been observed in tertiary care centers in India as well with isolation rates ranging from 52% - 96%. The predominance of C. tropicalis instead of C. glabrata or C. parapsilosis in all age groups under NAC has been reported (Chakraborty et al., 1996).

**Candida species** as normal flora:

*Candida albicans* as well as other non-pathogenic species of candida are common in habitant of oral, respiratory, intestinal tract, genitelia, skin of normal healthy adults (Woods et al., 1957). As a part of normal flora of mouth the Candida species ranges from 30-60% in healthy adults. The vaginal colonization found 13% in women and most commonly by C. albicans and C. glabrata (Scheinfield, 2011).

*Candida species* are unusual cause of urinary tract infection in normal individual as it remain normal flora but with predisposing conditions or in
hospitalized patients it could be the commonest cause of urinary infection (Fisher et al., 2011).

*Candida species* found in approximately 30% of healthy individuals and up to 70% of patients suffering from candidiasis. The high prevalence of these strains implies that they are more successful in colonizing human hosts and in causing disease than other strains (Schmid et al., 1995).

**Candida species: cause of human infection:**

Since early 1980s fungi have evolved as major causes of human disease, especially among immunocompromised and in hospitalized patients. McNeil et al. (2001) published an analysis of trends in infectious disease mortality in United states and found dramatic increase in multiple cause mortality due to mycoses, from 1,557 deaths in 1980 to 6534 deaths in 1997 (Pfaller and Diekema, 2007).

The clinical manifestations of candidiasis are extremely varied, ranging from acute, sub-acute and chronic to episodic infection. *Candida species* can be localized in mouth, throat, skin, scalp, fingers, nails, vagina, bronchi, lungs or gastrointestinal tract or become systemic as in septicemia, endocarditis and meningitis (Skinner, 1947). *Candida albicans* usually isolated from clinical forms of candidiasis. In some of the less common clinical conditions such as endocarditis, other species are frequently isolated (Zimmerman, 1950).

Chronic oropharyngeal candidiasis has occurred as a complication of inhaling steroids therapy for respiratory diseases (Milne and Crompton, 1974). Thrush of the newborn is commonly associated with mother having vaginal
*candida* infection (Kozinn et al., 1958). A cream white to grey pseudomembrane covers the tongue, palate, buccal mucosa and other oral surfaces. The distribution is discreate, confluent or patchy (Jha et al., 2006; Sharma et al., 1965).

Esophageal cadidiasis is often an extension of lesions from the oral cavity, especially in thrush of new born (Lederer and Todd, 1949). In adults *candida* infection of a oesophagus is associated with antibiotic therapy, corticosteroids, diabetes, AIDS (Klein et al., 1984). Other than *C. albicans*, it can be caused by *C. glabrata, C. tropicalis, and C. krusei* (Pankhurst, 2011)

The term pulmonary candidiasis has extensively been used to indicate superficial *candida* infection of cavities, persistent presence of *candida* in bronchial secretion. Invasive pulmonary candidiasis has been found in many adult cases (Oblath, 1951), in children (Joshi and Wang, 1923), and in neonates (Linhartova and Chung, 1963). Various *Candida species* have been isolated from sputum and throat swabs of healthy person from 20-38 percent (Sharp, 1954). Prevalence of *Candida species* in chronic respiratory disease is reported to vary from 23-77 percent. These have been reported to cause chronic bronchitis, allergic asthma and pneumonitis. Invasive lung infection by *Candida species* is rare in immunocompetant subjects. The diagnosis of pulmonary candidiasis is difficult and need good clinical correlation to ascertain the clinical significance of the isolates. A study by Jha et al.,(2006) shown the main risk factors associated with pulmonary candidiasis are chronic obstructive pulmonary disease, smoking, tuberculosis, malnutrition, malignancy, diabetes mellitus, HIV infections and prolonged use of antibiotics.
The clinical bronchopulmonary candidiasis was first described by Castellani (1914) among tea plantation workers in Ceylon. The first well documented case of bronchopulmonary candidiasis was described by Lewis in the year 1933 (Gupta et al., 1996). Bronchopulmonary candidiasis have been reported in renal transplant cases (Riffkind et al., 1967), acute leukemia (Mirsky and Cuttner, 1972), compromised host (Preisler et al., 1969) tuberculosis (Baum, 1960). A prospective study by Phukan et al., (2000) in Assam showed 76% C. albicans and 24% non albicans Candida association in bronchopulmonary candidiasis.

*Candida* invasion of stomach wall is very rare event and usually occurs during the final stages of disseminated disease (Katzenstein and Maksem, 1979). The patient with hematopoietic malignancies and with solid malignancies had GIT candidiasis at autopsy (Parker et al., 1976).

Invasion of blood stream and viscera occurs secondary to primary focus on mucosal surface in most instances (Zimmerman, 1955). Iatrogenic factors like intravenous catheterization and intravenous fluid therapy has been reported as the cause of blood invasion (Publio et al., 1970; Kobza et al., 1976). *Candida species* is reported as the fourth leading cause of nosocomial blood stream infection in the USA, the reports also supports an increase in Candidemia in Europe, Australia and India (Adhikary and Joshi, 2011).

Epidemiological studies have demonstrated a continuing increase in the prevalence of vulvovaginal candidiasis (Verghese et al., 2001). *Candida* vaginites is one of the most frequently encountered form of superficial candidiasis. It has been seen that vulvovaginal candidiasis caused by *Candida albicans* as well non-
*albicans* Candida species of candida is quite prevalent in women of childbearing age (Jindal et al., 2007). The disease is characterized by presence of a thick yellow milky discharge and patches of gray white pseudomamranes are seen on the vaginal mucosa (Hopwood et al., 1984). It usually arises due to alterations in the normal physiological state of host and is a common detection in for example, poorly controlled diabetes (Steinberg, 1958), antibiotic therapy (Mc Govern et al., 1953, Steinberg, 1958 ), in women taking oral contraceptives (Morris and Morris, 1967; Corbishelly, 1977) and in pregnancy (Pandya et al., 1958). Antibiotics are known to destroy the normal protective flora and help in colonization with *Candida*.

**Predisposing factors in association of candidal infection:**

Neumerous predisposing conditions contribute to the increase in the fungal infections (Fridkin and Jarvis, 1996). The expanding population with immunocompromised condition due to mucosal and cutaneous barrier disruption, dysfunction of neutrophills or cell mediated immunity, metabolic dysfunction, or old age, any of these may be the cause of infection (Davis et al., 2007). The population based survey made by CDC during 1992-1993, which showed increasing incidence of invasive candidiasis. (Pfaller and Diekema, 2007). Poor oral hygiene, tobacco smoking and the use of contraceptive pills were recorded as possible risk factors for development of ora lesions (Shaheen and Taha, 2006).

Several studies have shown the increase in trend of bloodstream infection with *C. glabrata*. It is well documented in several studies that incidence of infection by *C. glabrata* associated with older age and exposure of fluconazole.
Capoor et al. (2005) reported increased risk of dying in older adults (age >60 years) is due to infection with *C. glabrata* and also focused most common risk factors for *C. glabrata* in blood stream were use of broad-spectrum antibiotic, central venous catheters, receipt of parenteral nutrition and longer stay in an ICU.

Lin et al. (2005) found that use of piperacillin–tazobactam and vancomycin was found to be significantly associated with nosocomial blood stream infection due to *C. glabrata*.

*C. parapsilosis* and *C. tropicalis* are also found in association with blood non albicans candidiasis. *C. parapsilosis* has the ability to form biofilm on catheter or other implanted devices. It is also known for causing infections in neonates. *C. tropicalis* is an important pathogen in patients with neutropenia and with hematologic malignancies. *C. krusei* was also found to be associated with hematologic malignancies (Pfaller and Diekema, 2007).

Biofilms are the microbial communities found to attach and encase in a matrix of exopolymeric material and contribute in the development of clinical infection. *Candida* contributes to the formation of extensive biofilm on catheter and other prosthetic devices and consider as one of the most important risk factor for the development of Candidemia in patients (Vinitha and Ballal, 2007). Catheter related blood stream infection is life threatening and is associated with significant medical cost (Marcia et al., 2006).

*C. guillermondii* and *C. rugosa* although uncommon species but are associated with hospital acquired infection and found to have decreased susceptibility against fluconazole.
A study by Capoor et al., (2005) showed that the combination of suppressed host defense and exposure of multiple risk factors are responsible for the Candidal infection. There is significant change of distribution of infection by non-albicans Candida species than C. albicans. The spectrum of canidiasis has changed with emergence of non-albicans Candida and significantly acquired antifungal resistance. Multiple predisposing factors contribute exposure, as well as colonization followed by infection in high risk group. In their study 48% C tropicalis followed by C. parapsilosis 27.4%, C. albicans 22.5%, one C. glabrata and one C. krusei isolated from the total number of samples. The data of antifungal susceptibility test suggested that routine susceptibility testing is desirable for clinical decision making and surveillance of emerging antifungal resistance.

Blood stream infection (BSI) with Candida is the forth important cause of nosocomial infection and third most common cause of intensive care infection. Approximately 95%-97% of all Candida-associated BSIs are caused by five species: C. albicans, C. glabrata, C. parapsilosis, C. tropicalis and C. krusei (Pfaller et al., 2006). BSI with Candia species are an important cause of morbidity and mortality in hospitalized patients (Warnock, 2007, Gudlaugsson et al., 2003). There is increasing proportion of non-albicans Candida infection over C. albicans (Shivaprakasha et al., 2007). A study by Chow et al. (2008) where medical and surgical ICU patients were investigated for BSI along with the various multiple underlying parameters and well differentiated the cause of etiology. The authors stated the increased risk of BSI due to non-albicans Candida independently associated with duration of Central venous catheter (CVC), number of days of fluconazole exposure. Fluconazole exposure is the potential risk factor for the
development of candidemia with non albicans candidiasis. Multifactorial causes are associated with the effect of fluconazole on different candida species. It has been reported that effect of fluconazole is limited on biofilm. C. tropicalis and C. parapsilosis frequently encountered in biofilm and there is discrepancy between the in vitro susceptibility of fluconazole and in vivo clinical response to fluconazole. However, there may be factors which are independently associated with an increased risk of candidemia due to non-albicans candida compared with C. albicans candidemia (Chow et al., 2008).

According to National nosocomial infection surveillance (NNIS ), US data shows that 87% of primary blood stream infections occurred in patients with a central line and in ICU approximately 80,000 catheter related blood stream infections occur each year and result in upto 20,000 deaths (Erna et al., 2004).

Alarmingly, the incidence of nosocomial Candidemia has risen sharply in recent years particularly in critical care units. At the same time there has been an important shift in the type of Candida infections away from the C. albicans to more resistant non-albicans species (David and Snydman, 2003, Rani et al., 2002). Hospital acquired candidiasis or nosocomial candidiasis is a problem in populations such as neonate patients in intensive care unit (ICU) and patients with burn and malignant disease (Emmuanuel et al., 2003). In the healthcare setting the mechanism of cross infection include direct patient to patient transmission; transmission from colonized and infected person to a recipient via third person, often a health care worker; transmission from a colonized or infected person to another individual via a medical device; and more or less simultaneous
transmission to two or more patients from a common source such as contaminated intravenous infusion. In most reports it has been found that outbreak in ICU with Candidal infection is due to the cross infection from the hands of the health care workers (Malcolm and Devid, 2003). Another study shows highest incidence of candidemia in patients in surgical ICU (SICU) and highest mortality rate (100%). Similar results were observed by the National Epidemiology of Mycoses Survey (NEMIS) group who reported the nosocomial blood stream infection in SICU and neonatal SICU. Fungal infection rate observed by the The National Nosocomial Infection Surveillance System (NNISS) from 1986-1990 was high in burn/trauma, cardiac, surgery, oncology, high risk nursery and general surgery services (Beck Sague and Jarvis, 1993).

*Candida species* is an important nosocomial pathogen in the new born population, particularly among preterm and in neonatal intensive care unit (Roilides et al., 2003; Zaoutis et al., 2005). Colonization of the neonatal skin and gastrointestinal tract is the first step in the pathogenesis of invasive candidiasis. This has been attributed to the improvement in technology, life support system, relative immunodeficiencies in the preterm, prevalence of hand carriage of *Candida* in health care provider, ability of *candida* to survive on environmental surfaces and colonization of maternal vagina (Mendiratta et al.; 2006).

Hospital acquired urinary tract infection is a commonest nosocomial infection and accounts for 35-45% of nosocomial infection. Variety of risk factors associated with aetiopathogenesis of hospital acquired urinary tract infection. Per urethral catheter is identified, worldwide, as the single most important predisposing
factor for the hospital acquired urinary tract infection. The improperly maintained catheter may serve as a portal of entry for the pathogens. The pathogens enter during the time of catheter insertion or later by intraluminal or transurethral spread. A prospective study by Umesh S. Kamat et al., (2009) done in 498 patients showed almost 11% of the organisms were *Candida albicans* and was in pure isolates in all the instances. Among newborn infants especially those born before term, most candiduria reflects Candidemia (Fisher, 2011)

A study by Kumar and Batra (2000) Hospital personnel carry pathogenic yeast on their hands in both clinical and non clinical settings. The frequency of yeast carriage on the hands of the nursing staffs was determined by broth wash technique. The nosocomial *candida* infection may be due to the transmission of yeast from the hands of the healthcare worker. Hospital environment along with the hand carriers of *Candida* play one of the most important roles in the spread of hospital acquired infection by the yeast (Pfaller, 1996).

**Candida and HIV/AIDS:**

Due to low absolute CD4 counts there is progressive immunosuppression in HIV infection. The oral health status of a HIV infected patients may reveal important information regarding the immune status of a individual and it is about 64-80% cases of HIV/AIDS in India (Patel et al., 2011). The most common HIV-related oral disorder is oral candidiasis which occurs in 17–43% cases with HIV infection and in more than 90% of cases with AIDS. *Candida albicans* found to be associate with four forms of infection: Pseudomembranous candidiasis, hyperplastic candidiasis, erythematous candidiasis and angular cheilitis.
Pseudomembranous candidiasis is characterized by creamy white curd-like plaques on the buccal mucosa, tongue or other oral mucosal surface, which can be removed by scraping and that can lead to red or bleeding underlying surface, where in hyperplastic candidiasis white plaques can be seen which cannot removed by scraping. Erythematous candidiasis presents red macular lesions. In angular cheilitis, there is cracking, peeling or ulceration of the corners of mouth (Shetti et al., 2011; Baradkar and Kumar, 2009). Although *C. albicans* continues to be present in most yeast carriage from oral mucosa of HIV-infected patients, but there is immerging trend of non-*albicans* Candida (Nweze and Ogbonnaya, 2011).

Oral candidiasis is early oral manifestation of AIDS and reliable prognostic indication of this disease (Samaranayake and Hoimstrup, 1989). Oral candidiasis is perhaps the most frequent opportunistic infection associated with HIV disease and AIDS (Pfaller et al., 1996). It has been estimated that between 11-96% of HIV infected individual develop oral candidiasis during their disease span (Samaranayake and Hoimstrup, 1989). Chronic orpharyngeal and esophageal candidiasis has also been noted as a first sign of clinical AIDS (Klein et al., 1984).

HIV/AIDS has become a global crisis and impaired cellular immunity due to HIV infection place the infected person with at risk of opportunistic infections, thrush or oral candidiasis is the most common mucosal infection. The appearance of an opportunistic disease may be the first manifestation of HIV infection. When CD4*T* cell count falls to <200/μL the patient was at high risk for opportunistic infection (Anthony, 2008).
Oropharyngeal candidiasis is another opportunistic infection found to be in association with immunocompromised HIV/AIDS patients being most widely reported in India (Banerjee, 2005).

**Clinical importance of antifungal susceptibility testing:**

Fluconazole is well established as well as first line management option for both localized and systemic Candidiasis. It is having well known efficacy and safety profile and is suitable for use in children, elderly and patients with impaired immunity, (Martin, 1999). The decrease in susceptibility of *Candida* isolates to fluconazole is a matter of concern although voriconazole, amphotericin B show good efficacy (Adhikary, 2011). Other azole like ketoconazole and itraconazole is used orally. And for systemic lesions intravenous infusion of amphotericin B is indicated (Chender, 2009). HIV infected patients may have higher frequencies of amphotericin B resistant non- *albicans* Candida isolates, on the other hand some studies also shown low resistance or no resistance for amphotericin B (Satana et al., 2010). Presence of *Candida* sp. as colonizers may not always be producers of Candidemia which often tempts the clinicians to start antifungal empirically and persistence or a <50% decrease in clinical signs and symptoms following a seven day treatment course is referred as Fluconazole resistance by the clinicians (Saha et al., 2008). Selection of optimal antifungal therapeutic strategy is becoming increasingly complex and it is often complicated further by concerns of emerging antifungal resistance. Routine antifungal testing by disc diffusion is simple and is very alluring method for the use in the clinical laboratory. The results are available in real time (i.e., 24hrs) and inventive efforts to integrate this form of antifungal testing into the workflow of the clinical laboratory are ongoing (Pfaller et al., 2006).