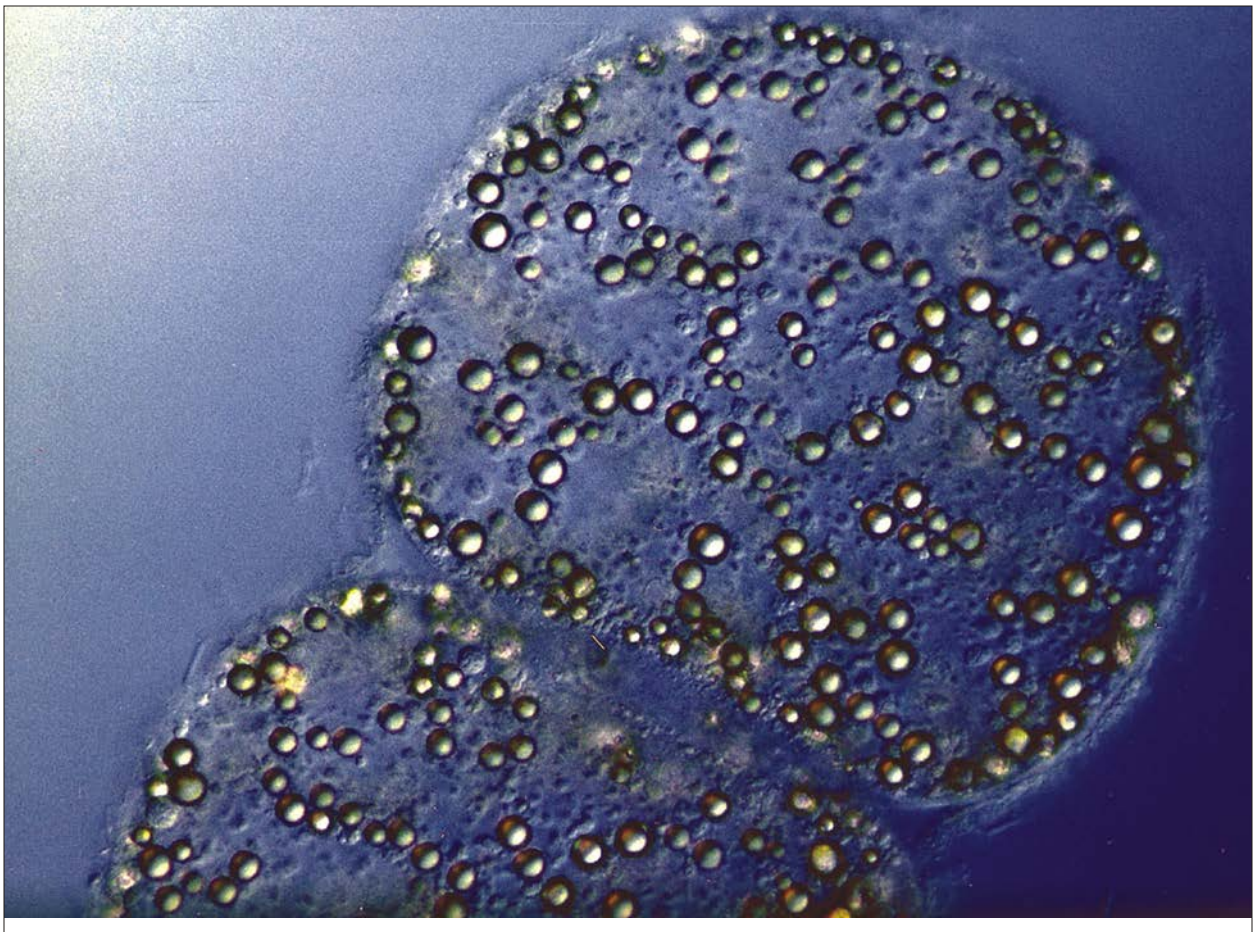

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A Comprehensive Review of the Occurrence and Management of Systemic Candidiasis as an Opportunistic Infection

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ABSTRACT

Candidiasis is a fungal infection which is prone to occur in people with immunosuppression due to debilitating diseases and nosocomial causes. The epidemiology of *Candida* fungal infections is on the rise and it is a common cause of systemic infections. Even though bloodstream infection in on the decline, the number of risk factors which could eventually lead to candidiasis has been increasing steadily They include immunosuppression due to chemotherapy or corticosteroid therapy, diabetes mellitus, low birth weight in neonates, broad spectrum antibiotics, long term catheterization, haemodialysis and parenteral nutrition. However, it has generally been observed that 3 main groups of patients are associated with candidiasis, namely those with neutropenic cancer, organ or stem cell transplant patients and those undergoing intensive care procedures. Discussion of surveillances and reports will be useful to improve our understanding of the importance of systemic *Candida* infections and to facilitate the prioritization of the investigation as well as the prevention efforts.

Key words: Systemic candidiasis, *Candida albicans*, immunosuppression

INTRODUCTION

The incidence of systemic *Candida* infection has changed during the last few years. The frequency of the disease has increased and the population of patients at risk has expanded to include patients with solid organ and Hematopoietic Stem Cell Transplantation (HSCT), receipt of immunosuppressive therapy, Human Immunodeficiency Virus (HIV) infection, premature birth, advanced age, surgery and cancer (Chakravarthi *et al*., 2010a). Moreover, the etiology of invasive mycoses has also changed. In the 1980s, yeasts (mainly *Candida albicans*) were the most frequent causative agents of invasive fungal infections. Despite of its benefits, medical development has led to a susceptible population with suppressed immunological defenses against fungal infection.

These factors heighten the risk for many invasive fungal infections, including candidiasis, aspergillosis, cryptococcosis and mucormycosis (Ruping *et al*., 2008). Epidemic of HIV is a major factor that has contributed to a remarkable increase in the frequency of invasive candidiasis. Before the extensive use of Highly Active Antiretroviral Therapy (HAART) in developed countries, 80% of HIV-infected patients developed mucosal candidiasis, while others developed cryptococcosis, pneumocystosis and other lethal mycoses, for example, penicilliosis (Fidel, 2006). Candidiasis, a main cause of death in patients with leukemia and solid organ transplants or recipients of stem cell,

is currently observed more frequently among patients in intensive care units (ICUs). The species of *Candida* causing infection are more diverse. *C. albicans* is the most frequent pathogen followed by *C. glabrata*, *C. tropicalis* and *C. parapsilosis* (Edmond *et al.*, 1999).

Systemic *Candida* infections: Bloodstream infection by *Candida* species (candidemia) is the most frequent clinical manifestation of invasive candidiasis and is a significant cause of morbidity and mortality in hospitalized patients. *Candida* species are the fourth most widespread cause of hospital-acquired bloodstream infections in the United States (Wisplinghoff *et al.*, 2004), with a frequency of 1.5 cases per 10,000 patients days (Hajjeh *et al.*, 2004). In a comparable European study the frequency is slightly lower, at 0.5-0.7 cases per 10,000 patients days (Richet *et al.*, 2002; Marchetti *et al.*, 2004).

Currently, the highest reported incidence of healthcare related candidemia (3.7 cases per 10,000 patients days) comes from an eleven-center sentinel observation plan in Brazil (Colombo *et al.*, 2006). While the reasons for this high rate of infection are not obvious, several factors could be involved, including the availability of less resources for medical care and training programs, difficulties in the achievement of infection control programs in hospitals of developing countries, limited numbers of health-care staffs and less effective practices of antifungal drug treatment in high-risk patients. Candidemia is usually connected with infection outside of bloodstream. In numerous patients the yeast spreads from the gastrointestinal tract to other organs and this helps to elucidate why *Candida* septicaemia infection is similar to a devastating disease. In the United States, the mortality rate for candidemia in medical centers from 1997 to 2001 was 49% (Gudlaugsson *et al.*, 2003), which was 11% higher than that detected in the same hospital from 1983 to 1986 (Wey *et al.*, 1988).

Analysis of the epidemiological researches that evaluates the varying incidence of *Candida* bloodstream infection over time is complicated. However, it is necessary to find important dissimilarities in the results coming from various countries or various centers. Most cases of *Candida* infection result from *Candida albicans*, which is an opportunistic fungus as it does not induce disease in immunocompetent individuals but only in those with impaired host immune defenses. Its infection is generally classified into superficial and deep. It commonly infects the nails, skin and mucous membranes, especially the oropharynx, vagina, oesophagus and gastrointestinal tract. Occasionally, the fungus invade the bloodstream and spread to other deep structure organs in the body such as kidneys, lungs, brain or other structures, causing systemic candidiasis (Chakravarthi *et al.*, 2010b).

In the Netherlands, the incidence rate of candidemia among hospitalized patients rose from 0.37 to 0.72 cases per 10.000 patient days between 1987 and 1995 (Voss *et al.*, 1996). But in Switzerland, the rate remains approximately permanent between 1991 and 2000 (median incidence: 0.5 cases per 10,000 patient days) (Fidel, 2006). In the past years, the main groups at risk for serious *Candida* diseases were cases that were neutropenic, had received transplants, or had been treated with cytotoxic or corticosteroids drugs. At present, the patients who are in the ICU are the most susceptible to show severe *Candida* infections. The most high risk patients are those who have a central venous catheter, are receiving parenteral nutrition or are on broad-spectrum antibiotics and have high Acute Physiology and chronic health evaluation scores (Pappas *et al.*, 2003; Rangel-Frausto *et al.*, 1999; Michalpopulos *et al.*, 2003). The fourth most frequent cause of nosocomial systemic infection among ICU patients is *Candida* species. Moreover, these yeasts are the third most widespread cause of nosocomial bloodstream infections (Alimirante *et al.*, 2005).

Aetiologic agents: There are now approximately 200 species of *Candida*, but only a few have been involved in human infection. Ninety percent of all *Candida* bloodstream infection globally have been caused by five species: *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* (Hajjeh *et al*., 2004; Arendrup *et al*., 2005; Takakura *et al*., 2004). The remaining diseases have been caused by several other *Candida*, including *C. dubliniensis*, *C. famata*, *C. guilliermondii*, *C. lusitaniae*, *C. norvegnesis*, *C. pelliculosa*and *C. rugosa* (Takakura *et al*., 2004; Sandven *et al*., 2006). Though these species are unusual causes of candidiasis, some of them are recognized to happen in nosocomial clusters, or display innate, or even obtained resistance to antifungal drugs (Colombo *et al*., 2003; Masala *et al*., 2003).

Candida albicans remains the predominant cause of candidemia worldwide. While the exact mechanism leading to candidiasis is not known, the initiation and progression of candidiasis can be viewed as an imbalance in the host-pathogen relationship in favour of infecting fungus (Chakravarthi *et al*., 2010c). The frequency of systemic candidiasis which is recovered from blood samples varies according to geographical setting and demographics of the population studied. Broad use of fluconazole for treatment of HIV-infected cases with persistent oropharyngeal candidiasis resulted in the selection of *Candida* species essentially less sensitive to azoles in the early 1990s. The azole-drug resistant strains in these patients emerged because of acquisition of resistance with previously sensitive strains of *C. albicans* (Sanglard and Odds, 2002). This occurrence has led to the concern that extensive fluconazole use in broader patient populations could cause related selections for species and strains that possess inherent or acquired azole resistance. Nevertheless, the frequency of fluconazole resistance among *C. albicans* bloodstream isolate, gathered in population-based and sentinel surveillance programs worldwide, stays insignificant (Hajjeh *et al*., 2004; Alimirante *et al*., 2005; Colombo *et al*., 2006).

A new trend noted in numerous hospitals is an enhancement in the frequency of *C. glabrata* as serious *Candida* infections (Baddley *et al*., 2001; Malani *et al*., 2001). There are some reasons for this increase, including the living habitat, age and type of the patients and use of fluconazole. *C. glabrata* is usually noted in persons older than 60 years (Malani *et al*., 2001) and in patients who have leukemia or received a stem cell transplant and those who are associated with increasing use of fluconazole (Marr *et al*., 2000). The significance of this epidemiologic trend is that *C. glabrata* is frequently resistant to fluconazole, the drug used most often for the treatment of candidemia.

Though candidemia is the main type of invasive candidiasis, broad visceral invasion with *Candida* can happen by persistently negative blood cultures. Almost all organs can be infected, although the kidneys, eyes, liver, spleen and brain are most frequently involved. Signs of invasive infection that ought to be clinically diagnosed are endophthalmitis or chorioretinitis as well as the emergence of painless skin lesions.

Based on the results from few studies, candidiasis appears more severe in experimentally induced breast cancer. These studies also open more lines of thought into various aspects of cancers and immunosuppression as a whole. Immunosuppression from effect of cancer increases susceptibility to systemic candidiasis. The development of this form of systemic candidiasis further breaks down the host defence and permit severe and early metastases. This study also throws a light to encourage autopsy in humans who die of immunosuppression to establish opportunistic infection (tissue diagnosis). This may indicate the need for early screening of cancer patients for candida infection and prompt treatment where that is established (Chakravarthi *et al*., 2010d; Choo *et al*., 2010).

Treatment: The patients with confirmed candidemia or invasive candidiasis must be treated with an antifungal drug (Pappas *et al*., 2004). The elevated rate of spreading to main organs, once *Candida* obtains entrance to the bloodstream, offers the basis for this approach. There are primarily two goals in the treatment of candidiasis, interference with *Candida* proliferation in the body and the reduction of the factors providing favourable environment for growth of *Candida*. Several antifungal drugs are available for the treatment of candidiasis. These consist of fluconazole, voriconazole, caspofungin, amphotricin B and lipid formulations of amphotricin B. Studies confirm that fluconazole, caspofungin and voriconazole are as valuable as amphotricin B deoxycholate in the treatment of candidemia (Mora-Duarte *et al*., 2002).

Fluconazole is the preferred treatment of candidemia. Fluconazole is effective against most species of *Candida*. It has been revealed to be as useful as amphotricin B in nonneutropenic patients. Nevertheless, fluconazole has restricted activity against *C. glabrata* and is not effective against *C. krusei*. Combination therapy may be used to cope with treatment failures (Barchiesi *et al*., 2007; Huang *et al*., 2008). Doctors should become aware of the most frequent species of *Candida* causing bloodstream invasive infection at their centers. Vascular catheter removal enhances the clearance of *Candida* from the blood (Rex *et al*., 1995). Daily blood culture is required to confirm that the problem of fungemia is resolved and treatment must continue for two weeks following the date of the primary negative blood culture.

Laboratory diagnosis: The disease is very difficult to diagnose because some of the aetiologic agents of disease are also commonly observed in healthy people. As a result, laboratories have an important role in detection of diseases and identification of aetiologic agents of them. In addition, they can help with the selection and the monitoring of antifungal therapy. Information that is essential for laboratory workers is as follows; the clinical history of patients, occupation, the source of the samples, any prior treatment with antifungal, anti-microbial and immunosuppressive drugs, the method by which the samples were collected and types of transport medium. The patients must not take any antifungal drugs three days before sampling. For urinary sampling, 10 ml of midstream or catheter specimens should be collected in a sterile test tube. Cerebrospinal fluid (CSF) samples provide good specimens for patients with candida meningitis. CSF is usually collected by a clinician using a routine lumbar puncture technique. In candidemia, 20 mL of blood from adults or 1-5 mL from children is collected and directly inoculated into the blood culture medium (Biphasic medium). Suitable specimens for respiratory candidiasis are early morning sputum and bronchial washing collected in a sterile screw-cap container. The samples should be digested by KOH or N-acetyl cysteine or pancratein before preparing smears and cultures. Another method for sampling from candidiasis is biopsy from organs.

Direct examination of specimens and observation of fungal elements in clinical materials is a very important part of laboratory diagnosis. As a result, a correct report can help the clinician prescribe suitable treatment. Furthermore, in acute diseases, such as *Candida* meningitis and systemic candidiasis in AIDS patients, rapid direct microscopy can play a very important role in suitable treatment. For liquid specimens, such as urine, saliva, sputum and CSF, firstly, centrifuge and then microscope slides can be prepared from their sediments. The microscope slides should be stained by Gram, Giemsa or methylene blue stains. Tissue sections should be stained using Periodic Acid Schiff, Grocott's methenamine silver or Gram stain. Ovoid yeast cells, budding cells (3-7 μm in diameter), true hyphae, pseudohyphae or both are the morphological forms of *Candida* species that are usually seen in clinical materials. Positive direct microscopy from a biopsy or a sterile site,

such as blood, CSF and vitreous and joint fluid, are significant, whether of yeast or pseudohyphae. The presence of mycelial forms of *Candida* in direct microscopy is as a diagnostic marker for candidiasis; however, when *C. glabrata* is the etiologic agent of disease, pseudohyphae is not be observed in smears (Talwar *et al*., 1990).

All clinical materials are cultured on the suitable culture medium. There are a number of culture media for isolation of *Candida* species from clinical materials but the selective medium most often used is Sabouraud's Dextrose Agar (SDA) with chloramphenicol or other anti-bacterial agents. Many species of *Candida* (*C. krusei, C. parapsilosis* and *C. tropicalis*) are sensitive to cycloheximide, which is why media with cycloheximide should not be for isolation of *Candida* species. CHROMagar Candida is a new medium that is used for isolation and identification of some clinically important *Candida* species. The incubation temperature for cultures is 30-37°C for 24-72 h (Pappas *et al*., 2003).

CONCLUSION

Systemic candidiasis is seen as a cause of opportunistic infection with increased incidence in the past few years. This expected increase reflects several factors, such as changes in hosts at risk and progress in diagnostic methods. The appearance of *Candida* with variable susceptibilities to antifungal agents emphasizes the clinical importance of establishing fungal diagnoses. Changes in hosts sensitive to *Candida* infection, diagnostic approaches, practice patterns and probable changes in climatic influences, will possibly continue to affect the incidence for years to come.

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