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# Changing Epidemiology of Classical and Emerging Human Fungal Infections: A Review

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**Abstract**

In recent decades, many fungal species have emerged as major causes of human disease. While invasive candidiasis, aspergillosis, and cryptococcosis remain very common, rates of infection by other opportunistic fungal pathogens such as *Histoplasma capsulatum*, *Coccidioides immitis*, *Fusarium* spp. and other yeasts and molds are on the rise. Adding to this bleak picture is the fact that treatment and control measures currently available to us are hardly able to keep up with current trends of morbidity and mortality that associate with common and emerging fungal infections. It is interesting to note the likelihood of emerging fungal pathogens exhibiting significant resistance to standard antifungal therapy is real. Hence, invasive infections due to previously rare fungi such as *Acremonium*, *Scedosporium*, *Paecilomyces*, and *Trichoderma* species are proving difficult to treat. The ever increasing number of hosts with compromised immunity, increased volume of surgeries and invasive medical procedures, limited repertoire of and increased resistance to available antifungals, and better diagnosis and pathogen identification procedures are largely to blame for these alarming trends. Improvements in managing patients with cancer, AIDS, diabetes, and transplantation that are significantly improving patient survival rates are also generously contributing to the pool of patients with compromised immunity. In this article, we review the changing spectrum of invasive mycosis, risk-factors for infections and susceptibility to available antifungals.

***Keywords***: *Aspergillus*, Antifungal Drugs, *Candida*, Compromised Immunity, *Cryptococcus*, *Histoplasma*, Invasive Mycosis.

## 1. Introduction

The incidence of invasive fungal infections (IFIs) and rates of morbidity and mortality due to such infections have all been on the rise over the last three decades (Binder *et al*., 2011; Low *et al*., 2011). Although *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans* are the most common causes of IFIs (Pfaller and Diekema, 2004a), the incidence of infection by *Candida* spp. other than *C. albicans*, *Aspergillus* spp. other than *A. fumigatus*, opportunistic yeast-like fungi (*Trichosporon* spp., *Rhodotorula* spp. and *Geotrichum capitatum* [*Blastoschizomyces capitatus*]), zygomycetes; hyaline molds (*Fusarium*, *Acremonium*, *Scedosporium*, *Paecilomyces*, and *Trichoderma* spp), and a wide variety of dematiaceous fungi are all on the rise (table 1). The emergence of organisms such as *Fusarium* spp., *Histoplasma capsulatum*, *Coccidioides immitis* as significant pathogens has important implications for diagnosis and management. On the one hand, the clinical presentation of infections caused by such pathogens can mimic more common diseases (e.g. aspergillosis). On the other hand, these emerging pathogens are resistant to conventional antifungals making infection management difficult to say the least (Fleming *et al*., 2002; Miceli *et al*., 2011).

**Table 1**. Spectrum of opportunistic human fungal pathogens

| Genus / Group | Species / Members | Genus / Group | Species / Members |
|---|---|---|---|
| *Candida* spp. | *C. albicans*<br>*C. glabrata*<br>*C. gulliermondii*<br>*C. kefyr*<br>*C. krusei*<br>*C. lusitaniae*<br>*C. rugosa*<br>*C. parapsilosis*<br>*C. tropicalis* | Other yeasts | *Cryptococcus neoformans*<br>*Trichosporon* spp<br>*Rhodotorula* spp.<br>*Geotrichum capitatum*<br>*Blastoschizomyces* spp.<br>*Malaseezia* spp.<br>*Saccharomyces* spp. |
| | | Zygomycetes | *Absidia* spp.<br>*Cunninghamella* spp.<br>*Mucor* spp. |
| *Aspergillus* spp. | *A. fumigtus*<br>*A. niger*<br>*A. flavus*<br>*A. terreus* | Dematiaceous molds | *Rhizopus* spp.<br>*Rhizomucor* spp.<br>*Alternaria* spp.<br>*Bipolaris* spp. |
| Other hyaline molds | *Scedosporium* spp.<br>*Fusarium* spp<br>*Acremonium* spp.<br>*Paecilomyces* spp<br>. *Trichoderm* spp.<br>*Scopulariopsis* spp. | | *Curvularia* spp.<br>*Cladophialophora* spp.<br>*Exophiala* spp.<br>*Phialophora* spp. |

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Continuous rise in the number of hosts with compromised immunity (cancer patients, transplant recipients on immunosuppressive therapy, AIDS patients, and diabetics among others) as a result of improved patients management procedures and drugs is partly to blame for this worrying trend (Richardson and Lass-Florl, 2008).

Increased use of antibiotics and immunosuppressive drugs (cyclosporine A, tacrolimus, etc.), hyperalimentation fluids, polyethylene catheters, pressure monitoring devices, heroin abuse, organ transplantation, abdominal surgeries, and prosthetic cardiac valves all disturb host immunity and predispose to opportunistic fungal infections. Lack of preventative measures (vaccines) against all human fungal infections and the limited efficacy of and increased resistance to the few (<15) available antifungal drugs further complicate the issue. Unfortunately, as risk-factors for IFIs continue to increase in type, frequency, and severity, it is likely that the rate of IFI will continue on its upward trend.

Here, we review recent epidemiologic trends of two major groups of human fungal infections. Namely, those caused by yeasts (*Candida* and *Cryptococcus*) and yeast-like fungi (*Trichosporon*, *Rhodotorula*, and *Geotrichum*) and those caused by filamentous molds (*Aspergillus, Scedosporium, Fusarium, Acremonium, Paecilomyces, Trichoderma, Zygomycetes* or *Mucormycetes*, Dematiaceous molds or *Phaeohyphomycetes*, and *Histoplasma*). Published data permitting, the focus in discussing each group will be on the incidence of infection by the pathogen(s), predisposing factors to infection, rates of morbidity and mortality that associate with it, and clinical manifestations.

## 2. Pathogenic Yeasts and Yeast-Like Fungi

### *2.1. Candida Species*

*Candida albicans* and other *Candida* spp. are commonly found in the gastrointestinal tract, oral cavity, and genital areas as harmless commensals. Based on recent studies in healthy individuals, asymptomatic oral carriage of *Candida* spp. occurs in about 24-70% of children and adults with a reduced frequency in babies less than 1 year of age. *C. albicans* represents the majority (38-76%) of isolates identified in both adults and children. The frequency of *C. albicans* varies across different age groups with far greater proportions of isolates identified as *C. albicans* occurring in young babies and the elderly. Higher oral carriage rates are found in HIV positive patients (Liu *et al*., 2008) and diabetics (Abu-Elteen *et al*., 2006).

Asymptomatic vaginal carriage of *Candida* spp. is estimated to occur in 21-32% of healthy women, with *C. albicans* representing 20-98% of identified isolates (Ferrer, 2000; Pfaller and Diekema, 2007; Enoch *et al*., 2006; Pirotta and Garland, 2006). Beigi *et.al.*, (2004) found that within a group of women repeatedly screened over 12 months, 30% were never colonized, 70% were colonized on at least one occasion, and 4% were persistently colonized. Higher rates of vaginal carriage have been found in pregnant women, women colonized by *Lactobacillus* spp (Beigi *et al*., 2004; Hamad *et al*., 2006), type I diabetics (de Leon *et al.*, 2002), and post-antibiotic treatment (Pirotta and Garland, 2006). Table 2 gives a brief summary of risk factors for localized and systemic candidiasis in general. It is worth noting that as well as being harmless commensals, *C. albicans* and other *Candida* spp. are opportunistic pathogens capable of causing a wide range of superficial, localized, and/or systemic infections (Pfaller and Diekema, 2007; 2004a).

**Table 2**. General factors predisposing to *Candida* infections

| Factors | Comments | Representative examples |
|---|---|---|
| Immunological factors Neutrophil defect | Presence of abnormally small numbers of neutrophils in the circulating blood, myeloperoxidase deficiency | A cute leukemia, chemotherapy, irradiation |
| T- lymphocyte, mononuclear phagocyte | Certain diseases could lead to a defect in T – lymphocyte mononuclear phagocyte | Auto immune deficiency syndrome (AIDS), Hodgkin's disease, chemotherapy |
| Reticuloendothelial system (RES) | Defect of RES causes impairment in the clearance of infectious particles from the blood; this is due to congenital or surgical causes | Congenital absence or defect of the spleen, splenectomy |
| Chemotherapy and Radiotherapy | Treatment with drugs and/or irradiation that alters the composition of the endogenous microbial flora or suppresses host defenses against infection | Immunosuppressive agents, antineoplastic agents, antibiotics, corticosteroids |
| Interruptes integument | Membrane trauma, burns local occlusion or maceration of tissues | Finger or bone marrow punctures, gastrointestinal (GI) ulcers, catheters. IV needles, wearing dentures |
| Surgical procedures | Introduction of mechanical devices and prostheses into vessels or tissues | Heart valves replacements, tracheostomy respiratory assistance, endoscopies, renal transplant, heart operation, GI or gynecological surgery, blood transfusion |
| Physiological factors | Infectious, idiopathic, congenital, or other debilitating diseases and disorders, Digressions from normal physiological status | Microbial infections, endocrine dysfunctions, defect in cell – mediated immunity Pregnancy , infancy |
| Nutritional factors | Excessof deficiency of food stuff that crate an environment conductive to the development of mucosal candidosis | Carbohydrate – rich diets, vitamin deficiency |

#### *2.1.1. . Superficial Mucosal Infections*

Superficial mucosal lesions (thrush) occur in the oral and vaginal cavities of immunocompetent as well as immunocompromised hosts. Oral candidiasis is common

in infants and the elderly and in cancer patients undergoing chemotherapy to treat hematological malignancies and those undergoing head/neck radiation. It is characterized by white growth on the mucous membranes of the oral cavity that is usually underlined by red areas when the yeast growth is scraped off (MacCallum, 2007).

The majority of isolates associated with oral candidiasis are *C. albicans* (63-84%) (Davies *et al*., 2006). Risk factors associated with oral candidiasis include xerostomia (dry mouth) and denture wearing (Abu-Elteen and Abu-Elteen, 1998; Davies *et al*., 2006), poorly controlled diabetes mellitus (Abu-Elteen *et al*., 2006), and immunosuppression (table 3). The frequency of oral candidiasis, but not oral carriage of *Candida* spp. (Sanchez-Vargas *et al*., 2005), is higher in HIV positive patients with decreased $CD4^+$ T cell count (Liu *et al*., 2006).

**Table 3.** Specific factors predisposing to neonatal, oral and vaginal candidiasis.

| Predisposing factor(s) | Type of candidiasis | | |
|---|---|---|---|
| | Neonatal | Oral | Vaginal |
| Interrupted integument | Birth trauma, catheters | Burns, oral trauma, wearing dentures | |
| Nutritional factors | Malnutrition, breast and bottle feeding | Malabsorption | Malnutrition |
| Chemotherapy and radiotherapy | Antibiotic and steroid therapy (taken by mother of infant after birth) effect (psychophamaceuticals), radiation therapy | Broad spectrum antibiotics, corticosteroids, irradiation, or drugs with xerostomic side | Antibiotic therapy, oral contraceptives |
| Surgical procedures | Resuscitative procedure intubations (especially transplantation and heart surgery), tooth extraction | Parenteral nutrition, convalescence after operations | |
| Other factors | Unsterile delivery, male sex, unhygienic environment, low birth weight, thumb and dummy sucking, | Poor oral hygiene, oral leukoplakia, immunological factors | Environmental factors (humidity and warmth, wearing tight- |

Vulvovaginal candidiasis (VC) represents a real health problem to women of childbearing age worldwide. The majority of cases (>80%) of VC involve colonization by the genitourinary tract commensal *C. albicans* (Pfaller and Diekema, 2007; Enoch *et al*., 2006). Occurrence of VC and recurrent VC has been attributed to compromised immunity and increased levels of estrogen in the reproductive tract milieu (Hamad *et al*., 2004). Symptoms of VC include itching, burning, soreness, and abnormal vaginal discharge. *C. glabrata* is emerging as an important and potentially resistant opportunistic fungal pathogen in VC (Pfaller and Diekema, 2004a). Abu-Elteen (2001) has demonstrated that among the *Candida* spp. *C. glabrata* alone has increased in incidence as a cause of VC in Jordan since 1994. In many geographic regions, *C. glabrata* is becoming a common cause of VC and is gradually showing increased resistant to fluconazole (Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004a; Ray *et al*., 2007).

*2.1.2. Bloodstream Infections or Candidemia*

Bloodstream infections by *Candida* spp. (candidemia) is the fourth leading cause of nosocomial bloodstream infections (BSI) in the United States (Pfaller and Diekema, 2004a; 2007, Wisplinghoff *et al*., 2004). The annual incidence of *Candida* associated BSIs have been reported at 6-23 cases/100,000 Americans (Clark and Hajjeh, 2004; Pfaller *et al*., 2006), and 2.5-11 cases/100 000 Europeans (Tortorano *et al*., 2006). In recent years, it has been noted that a gradual increase in the incidence of BSIs is taking place (Bougnuox *et al*., 2008; Vardakaz *et al*., 2009; Chow *et al*., 2008). More than 17 different *Candida* spp. have been identified as etiologic agents of BSIs. However, 95% or so of all *Candida* BSIs are caused by four *Candida* spp.; namely, *C. albicans, C. glabrata, C. parapsilosis,* and *C. tropicalis* (Hajjeh *et al*., 2004; Pfaller and Diekema, 2004b). The remaining 5% of *Candida* BSIs are caused by *C. krusei, C. lusitaniae, C. guilliermondii, C. dubliniensis,* and *C. rugosa* among others (Bassetti *et al*., 2009; Fridkin *et al*., 2006; Peman *et al*., 2008). *C. albicans* is the lead cause of BSIs as it accounts for 42-100% of cases depending on the patient group. For example, frequency ratio of *C. albicans* to non-*albicans Candida* in patients with hematological malignancies was about ½ that in patients with solid tumors (Tortorano *et al*., 2006; Pasqualotto *et al*., 2006). Although epidemiologic data reflects significant differences between countries with regard to *Candida* spp. distribution in general, *C. albicans* continues to be the most commonly encountered *Candida* spp. in Europe and the United States. The second most commonly encountered *Candida* spp. in Southern Europe and in France, Germany, and the UK are *C. glabrata* and *C. parapsilosis* respectively (Hajjeh *et al*., 2004; Almirante *et al*., 2005). *C. parapsilosis* occurs with high frequency in premature neonates and in patients with vascular catheters (Almirante *et al*., 2005; Arendrup *et al*., 2005). *C. glabrata* infections are rare in infants and children but occur with high frequency in the elderly (Pfaller *et al*., 2006; Hajjeh *et al*., 2004; Malani *et al*., 2005). *C. tropicalis* is an important cause of invasive diseases in patients with hematological malignancy (Pfaller and Diekema, 2004 a). With the increasing use of fluconazole as an anti-candidiasis agent in the USA, the emergence of *C. glabrata* and *C. krusei* has been reported (Pfaller and Diekema, 2004 a, Malani *et al*., 2005; Shao *et al*., 2007). In contrast, the frequency of *C. glabrata* as a cause of BSIs has decreased in Europe from 12.3 % to 8.8% and in Latin America from 10.2% to 4.7% (Hope *et al*., 2002). But overall, the frequency of non-*albicans Candida* spp. as causative agents of BSIs continues to rise (Pfaller *et al*., 2006; Clark and Hajjeh, 2004).

The majority of patients who develop candidemia are intensive care unit (ICU) patients and those undergoing abdominal surgery. Other patient groups at risk of candidemia are cancer patients (solid tumor or hematological malignancies), premature babies (<1 kg birth weight), patients on steroids therapy (MacCallum,

2007), and patients with catheters and other invasive medical devices. According to one study, 14% of screened central venous catheter (CVC) tips were positive mainly for coagulase-negative *Staphylococcus* spp. followed by *C. albicans* (Hammarskjold *et al*., 2006). It should be noted that for critically-ill patients, several risk factors may be present in, or apply to, the same patient.

*2.2. Cryptococcus Species*

Cryptococcal infections occur with a near worldwide distribution in immunosuppressed hosts. They are the second most common cause of opportunistic fungal infections in AIDS patients. The incidence of infections caused by the encapsulated yeast *Cryptococcus neoformans* (*C. neoformans*) has risen markedly over the last 20 years (Bicanic and Harrison, 2004). Infections occur through inhalation of small diameter (<10 mm) yeast like organisms which enter small respiratory passages and become mostly dormant for a time (Bicanic and Harrison, 2004; Subramanian and Mathai, 2005) before reactivating in the lungs and/or lymph nodes. Clinical manifestations of infection can range from asymptomatic colonization of the respiratory tract to a widespread dissemination depending on host immune factors, inoculum, and degree of virulence (Mitchell and Perfect, 1995). As dissemination occurs, the central nervous system (CNS) is commonly involved. The basal meninges of the brain are preferentially affected causing thickening with subsequent invasion of the deeper brain tissues. In the meninges, the organism appears to be suspended in a mucoid-like material that is derived from the capsule (Mitchell and Perfect, 1995).

*Cryptococcus neoformans* is a basidomycete that normally grows as saprophytic haploid-budding yeast. Opposite mating types of *C. neoformans* do exist and the pathogen can undergo sexual reproduction and meiosis to produce spore. The yeast is spherical-oval in shape and is 5-10 µm in diameter. *C. neoformans* strains manifest antigenic differences that allow them to be grouped into five different serotypes (A, B, C, D, and an AD hybrid) as well as different varieties. *C. neoformans* var. *neoformans* includes serotypes D and AD while var. *grubii* includes serotype A and var. *gattii* includes serotypes B and C. *C. neoformans* var *neoformans* and var. *grubii* are responsible for the majority of clinical infections in immunocompromised host while var. g*attii* causes disease primarily in immunocompetent hosts (Fraser *et al*., 2005; Morrow and Fraser, 2009).

*Cryptococcus neoformans* has a number of virulence factors that enable it to survive and replicate in humans (Casadevall *et al*., 2003), especially in cases where T-cell immunity is compromised. Fungal capsule , which is anti-phagocytic and down-regulates cellular and humoral immune responses when shed into host tissues, and laccase and melanin, which interfere with oxidative killing by phagocytes, are among the prevalent virulence factors (Mitchell and Perfect, 1995). Production of melanin from 1-dopa by the enzyme laccase may account for the predilection of the organism for CNS. *C. neoformans* is both an intracellular and an extracellular pathogen; it can survive and replicate within acidic macrophage phagolysosomes (Levitz *et al*., 1999). A host site with abundant carbon dioxide concentration favors capsule bioformation (Subramanian and Mathai, 2005). While *C. neoformans* lives in soil and organic matter containing pigeon and bird excreta, *C. gattii* is found primarily in tropical and subtropical regions and has been associated with several spp. of eucalyptus trees an causes infection in immunocompetent hosts.

*C. neoformans* is neurotropic and most patients with cryptococcal meningitis suffer from defective cellular immunity. The infection is seen most frequently in association with lymphomas, AIDS, transplant recipients, and patients on corticosteroid therapy (Khawcharoenporn *et al*., 2007 a). In the 1980s (the age of AIDS), cryptococcosis emerged as an important opportunistic infection occurring in 5-10% of AIDS patients in the US, Europe, and Australia (Bicanic and Harrison, 2004). With increased use of fluconazole for oral candidiasis and the advent of highly active antiretroviral therapy (HAART) in the mid-1990s, the annual incidence of cryptococcosis has markedly decreased in the developed countries. For example, in Atlanta/Georgia in the US, the incidence of cryptococcosis dropped from 66 cases/1000 AIDS patients in 1993 to only 7 cases/1000 in 2000 (Mirzak *et al*., 2003). In a recent review of cryptococcal infections in HIV-negative patients, splenectomy was reported to be a risk factor in 3% of cases (Qazzafi *et al*., 2007). Other groups at risk of cryptococcosis are organ transplant recipients on immunosuppressive therapy and patients with sarcoidosis or lymphoproliferative disorders. In a cohort of 306 HIV-negative patients with cryptococcosis, the predisposing conditions were steroids (28%), organ transplantation (18%), chronic organ failure (Liver, kidney, lung)(18%), malignancy (18%) and rheumatological diseases (13%) (Pappas, *et al*., 2001); in 22% of patients in the study group no predisposing factor was identified.

Traditionally, non-*neoformans* cryptococci have been regarded as saprophytes and rarely reported as human pathogens (Khawcharoenporn *et al*., 2007b). However, the incidence of infection due to such organisms has increased over the last few decades with *Cryptococcus albidus* being responsible for 80% of reported cases. Impaired cell-mediated immunity is an important risk factor for non-*neoformans* cryptococcal infections and prior azole prophylaxis accounts for increased incidence of resistance being noted. *Cryptococcus gattii* causes disease in immunocompetent hosts in a geographically restricted area in Australia (Richardson and Lass-Florl, 2008; Bicanic and Harrison, 2004). Recently, invasive C. gattii infections in immunocompetent hosts have been reported in Western Canada, mainly Vancouver Island (Lindberg *et al*., 2007) and the North West region of the USA. The organism, which is thought to thrive only in tropical regions, has been recovered in some temperate climate zone countries.

*2.3. Pathogenic Yeast–Like fungi*

The frequency of invasive mycoses due to rare and emerging opportunistic yeast-like fungi has increased significantly over the last two decades (Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004a; Walsh *et al*., 2004). Such organisms may occupy environmental niches, found in food and water, or exist as normal human microflora. The list of opportunistic yeast-like fungi is long; hence, this discussion will be limited to three genera

that pose particular medical problems. Namely, *Trichosporon*, *Rhodotorula*, and *Geotrichum capitatum* (*G. capitatum* or *Blastoschizomyces capitatum* as it is commonly known) (Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004a; Konotoyiannis *et al*., 2004; Girmenia *et al*., 2005; Makela *et al*., 2003).

*2.3.1. Trichosporon Species*

*Trichosporon* is a genus of basidiomycetous yeasts that inhabits the soil and colonizes human skin and GI tract (Li *et al*., 2005). Previously, all pathogenic members of the genus *Trichosporon* were regarded as members of a single species (*Trichosporon beigelii*). More recently however, with biochemical and morphologic differences within the genus being increasingly appreciated, *T. beigelii* has been regrouped into several distinct species. Greater than eight of which have the potential to cause human disease; namely, *T. asahii, T. inkin, T. asteroids, T. cutaneum, T. mucoides, T. ovoides, T. pullulans*, and more recently *T. loubieri* (Li *et al*., 2005). While *T. asahii* and *T. mucoides* cause deep invasive and disseminated infections, *T. asteroids* and *T. cutaneum* cause superficial skin infections, *T. ovoides* causes white piedra of the scalp, and *T. inkin* causes white piedra of the pubic hair (Walsh et al., 2004; Flemming *et al*., 2002; Middelhoven, 2003; Marty *et al*., 2003). *T. faecale* was isolated from the skin of a patient with tinea pedis in Germany (Hahner *et al*., 2008) and *T.loubieri* has been associated with mycosis in patients with adult polycystic kidney disease (Padhye *et al*., 2003). *T. mycotoxinivorans* is a newly recognized human respiratory pathogen with high predilection for patients with cystic fibrosis (Hicket *et al*., 2009). Additionally, *T. montevideense* and *T. domesticum* have also been implicated in summer-type hypersensitivity pneumonitis (Nishiura *et al*., 1997; Sugita *et al*., 1998).

Risk factors for infection include immunosuppression, disruption of mucosal integrity, and CVCs. Neutropenic cancer patients on cytotoxic therapy are among the high risk groups of developing trichosporonosis. Furthermore, it has been reported that 63% of 287 *Trichosporon* cases had an underlying hematological malignancy (Girmenia *et al*., 2005) suggesting that hematological malignancies represent a major risk factor for trichosporonosis. In contrast, disseminated trichosporonosis is less common in patients with solid-organ transplants (SOT), AIDS, or burns, and in premature babies.

Overall rates of mortality due to infections by *Trichosporon* spp are high; they range between 60-80% (Walsh *et al*., 2004; Flemming *et al*., 2002). However, recent improvement in diagnosis, treatment, and prevention measures are bringing these rates down.

*2.3.2. Rhodotorula Species*

*Rhodotorula* spp. are yeast-like fungi that belong to the family *Cryptococcaceae*, sub-family *Rhodotorulodea*. These encapsulated basidiomycetes are being increasingly recognized as important human pathogens (Lo Re, *el al*, 2003; Thakur *et al*., 2007; De Almeida *et al*., 2008; Baradkar and Kumar, 2008; Shinde *et al*., 2008; Hsueh *et al*., 2003; Fung *et al*., 2008; Riedel *et al*., 2007; Zaas *et al*., 2003). Many species of the genus *Rhodotorula* have been described. *R. rubra, R. glutinis, R. mucilaginosa*, and *R. minuta* have been implicated as causes of meningitis, endocarditis, ventriculitis, peritonitis, fungemia, CVC-related infections, and keratitis (De Almeida *et al.*, 2008; Baradkar and Kumar, 2008; Shinde *et al*., 2008; Hsueh *et al*., 2003; Fung *et al.*, 2008; Riedel *et al*., 2007; Zaas *et al*., 2003). They exist as commensals on the skin, nails, and mucous membranes (Pfaller and Diekema, 2004a; Richardson and Lass-Florl, 2008). While *Rhodotorula* strains appear to be less virulent than the more common yeast pathogens (*Candida* and *Cryptococcus neoformans*), *Rhodotorula* infections have been associated with a crude mortality rate of up to 15% (De Almeida *et al*., 2008). They can also cause sepsis and other life-threatening complications (Pfaller and Diekema, 2004a; Richardson and Lass-Florl, 2008). Risk factors include CVC and malignancies (Pfaller and Diekema, 2004a). De Almeida *et al*. (2008) and Tuon *et al.* (2007) reported that in 88 cases of CVC-related fungemia due to *Rhodotorula* spp, all but one patient had an underlying disease state; most commonly cancer (78.4%). *R. mucilaginosa* was the species most frequently recovered (75%) followed by *R. glutinis* (6%). *Rhodotorula* BSIs can be successfully managed with line removal, antifungal therapy, or combinations of both.

*2.3.3. Geotrichum capitatum*

*Geotrichum capitatum (*formerly known as *Trichosporon capitatum* or *Blastoschizomyces capitatus*) is an uncommon, but frequently fatal, cause of IFIs in immunocompromised patients, particularly those with hematological malignancies (Pfaller and Diekema, 2004a; Richardson and Lass-Florl, 2008; Girmenia *et al*., 2005; Bouza and Munoz, 2004; Martino *et al*., 2004). It is widely distributed in nature and may be found as part of the normal skin flora. In a retrospective multicentre study from Italy, the incidence of *G. capitatum* infections among patients with acute leukemia was reported at 0.5% with a 55.7% crude mortality rate (Girmenia *et al*., 2005). Infection of neutropenic patients with *G. capitatum* presents in a manner similar to that of *Trichosporon* infections; i.e., frequent breakthrough infection (36% of episodes), frequent fungemia with multi-organ (including brain) dissemination, and a mortality rate of 60-80% (Martino *et al*., 2004); blood cultures are usually positive. As with *Trichosporon* infections, chronic disseminated *G. capitatum* infections may be seen upon resolution of neutropenia.

## 3. Pathogenic Filamentous Fungi

*3.1. Aspergillus Species*

Although the genus *Aspergillus* contains approximately 175 species, only *A. fumigatus, A. flavus, A. terreus, A. niger* and *A. nidulans* are associated with human disease (Pfaller and Diekema, 2004 a; Richardson and Lass-Florl, 2008; Maschmeyer *et al*., 2007). The conidia or spores are easily released into the atmosphere to reach the lung alveoli (Richardson and Lass-Florl, 2008); breathed air is a major route of transmission. Invasive aspergillosis (IA) occurs almost exclusively in immunocompromised individuals. Infections have frequently been described in patients with hematological malignancies, SOT recipients, and patients undergoing chronic intermittent hemodialysis

(IA in the later case has been linked mainly to *Aspergillus* spp-contaminated hospital ventilation systems). Over the last 10 years, *A. fumigatus* has become the most prevalent airborne fungal pathogen accounting for >90% of human fungal infections (Maschmeyer *et al*., 2007; Singh and Paterson, 2005; Denning, 1998; Rosenhagen *et al*., 2009). IA is currently responsible for approximately 30% of fungal infections in patients dying of cancer; it also occurs in 10-25% of all leukemia patients where post-treatment mortality rate is 80-90% (Rosenhagen *et al*., 2009; Denning, 1995; Verweij and Denning, 1997).

Risk factors for IA include prolonged and profound neutropenia, high-grade graft- versus-host diseases (GVHD), use of corticosteroids, age >40 years, and receipt of stem cells from HLA-mismatched donors (Shao *et al*., 2007; Nivoix *et al*., 2008; Marr *et al*., 2002) (table 4). Aspergillosis remains particularly common in hematopoietic stem cell transplant (HSCT) recipients and patients with advanced AIDS. It is also emerging as a serious outcome of immunosuppression, especially that rendered by new and more effective generations of immunosuppressives like infliximab (Pfaller *et al*., 2006; Patterson, 2005). Rates of *Aspergillus* infection in HSCT recipients and in SOT recipients have been reported at 2-26% and 1-15% respectively. Rates of mortality in transplant recipients due to IA range between 74-92%. Some have suggested that about 9-17% of deaths that occur in transplant recipients during the first year can be attributed to IA (Singh and Paterson, 2005). Pagano *et al*. (2007) have reported that IA rate of infection in 3000 transplant recipients was 2.8% (91 cases) and that the mortality rate within this subgroup was about 72%. Other studies have reported higher incidence; a Spanish study (Martino, *et al*., 2002) reported a rate of infection of 8.1%. Recent US series (Upton *et al*., 2007) have put IA-related mortality rates at 2.5%.

Globally speaking, the incidence of IA is about 1.4%; it is somewhat higher in lung transplant recipients (3%), heart transplant recipients (2.4%) (Gavalda *et al*., 2005), and liver transplant recipients (1.5-10%) (Rosenhagen *et al*., 2009). In general terms, IA is associated with high rates of mortality, which exceeds 50% according to many reports (Pfaller *et al*., 2006; Shao *et al*., 2002; Nivoix *et al*., 2008). Higher mortality rates were noted in HSCT recipients compared with SOT recipients (68% vs 41%) and in neutropenic patients compared with non-neutropenic counterparts (89% vs. 60%) (Cornillet *et al*., 2006). Aspergillosis is also emerging as a serious form of mycosis in the ICU; it has been reported that the incidence of aspergillosis in the ICU is 2.7-58 cases/1000 admissions with a mortality rate of 75-95% (Meersseman *et al*., 2007). Most infected patients present chronic obstructive pulmonary disease and receive high-dose corticosteroids (Meersseman *et al*., 2007).

Infections by non-*fumigatus Aspergillus* spp. are becoming increasingly common as well (Shao *et al*., 2002; Singh and Paterson, 2005). This is especially true with regard to infections caused by *A. terreus* (Meersseman *et al*., 2007; Howard *et al*., 2009; Steinbach *et al*., 2004; Lass- Florl *et al*., 2005), which has been recently recognized as a cause of frequently lethal infections and which tends to be resistant to amphotericin B (Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004a). In some cases, hospital-born *A. flavus* infections are becoming more common than those caused by *A. fumigatus*; the reason(s) for this trend are not readily apparent (Hedayati *et al*., 2007). Common clinical syndromes that associate with *A. flavus* infections include chronic granulomatous sinusitis, keratitis, cutaneous aspergillosis, wound infections, and osteomyelitis (Shao *et al*., 2002; Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004a). Additionally, *A. flavus* produces aflatoxin, which is an extremely toxic and potent hepatocarcinogen. Infections caused by a recently recognized spp. of *Aspergillus* (*A. lentulus*) have been reported (Balajee *et al*., 2006; Ando *et al*., 2008). Recent studies have shown that new triazoles like voriconazole and posaconazole are more effective than fluconazole in preventing and treating IA cases in HSCT recipients or those with GVHD (Shao *et al*., 2002; Richardson and Lass-Florl, 2008; Abu-Elteen and Hamad, 2007).

**Table 4.** Co-morbid conditions for aspergillosis and mold infections in high-risk patients

| Hematological malignancies | Organ transplant patients |
|---|---|
| Leukaemia | Lung, Liver, heart, renal |
| Myelodysplastic syndrome | Acute and chronic rejection |
| Stem – cell transplant | Steroids |
| GvHD[a] (acute and chronic) | Haemodialysis |
| Prolonged neutropenia | Tacrolimus |
| Induction chemotherapy | Renal failure |
| Fungal colonization | Cytomegalo virus (CMV) |
| Local epidemiology | Re – transplantation |
| Steroid prophylaxis | Splenectomy |
| Neutrophil dysfunction | Alemutuzumab |
| Cytotoxic drugs | Local epidemiology |
| Infliximab | Diabetic ketoacidosis [b] |
| Alemtuzumab | Iron overload [b] |
| T- cell depletes stem – cell products | Diabetes mellitus [b] |
| CD34-selected stem cell products | Deferoxamine therapy [b] |
| Diabetic ketoacidosis [b] | skin breakdown [b] |
| Iron overload [b] | |
| Diabetes mellitus[b] | |
| Deferoxamine therapy [b] | |
| Skin breakdown [b] | |

[a]GvHD, Graft vs. host disease.
[b]Relates to mucormycosis

### 3.2. Filamentous Fungi-Beyond Aspergillus

Other genera of filamentous fungi such as *Scedosporium* spp., *Fusarium* spp., *Paecilomyces* spp., dematiaceous fungi (e.g. *Alternaria* spp.), and the mucorales group (*Mucor* spp., *Rhizopus* spp., *Rhizomucor* spp., *Absidia* spp., and *Cunninghamella* spp.) are currently recognized as emerging opportunistic human pathogens (Shao *et al*., 2002; Richardson and Lass-Florl, 2008; Cortez *et al*., 2008; Nucci and Anaissie, 2007). Infections due to these opportunistic molds are usually marked by poor responses to antifungal therapy, *in vitro* resistance to most available antifungals, and an overall poor outcome with excessive mortality.

#### 3.2.1. Scedosporium Species

Within the genus *Scedosporium*, *Scedosporium apiospermum* (teleomorph, *Pseudallescheria boydii*) and *S. prolificans* are ubiquitous filamentous fungi that live in soil, sewage, and polluted waters. Scedosporiosis represents a broad spectrum of clinical diseases caused by agents of the genus *Scedosporium*. Infections caused by these organisms can be localized, extend to the surrounding tissues, or disseminate to distant organs. The range of diseases caused by these fungi is broad, ranging from transient colonization of the respiratory tract to saprophytic involvement of abnormal airways, allergic bronchopulmonary reaction, and invasive localized disease. These infections occur mainly in the skin and soft tissues but could extend to tendons, ligaments, and bone (mycetoma). Septic arthritis, osteomyelitis, lymphocutaneous syndrome, pneumonia, endocarditis, peritonitis, chorioretinitis, and endophthalmitis are possible outcomes. In individuals who experience near-drowning accidents, *P. boydii* and *S. apiospermum* should always be considered in the differential diagnosis of any post-accident infections, especially if pneumonia or brain abscess ensues. *Scedosporium apiospermum* and *S. prolificans*, represent two medically-important antifungal-resistant opportunistic pathogens. *S. apiospermum* causes mycetoma and deep-seated infections (e.g. CNS abscesses) and could disseminate in neutropenic bone marrow transplant (BMT) recipients and immunosuppressed individuals; crude mortality rate is about 55% (Cortez *et al*., 2008, Mellinghoff *et al*., 2002; Nesky *et al*., 2000; Perlroth *et al*., 2007). *S. prolificans* causes bone and soft tissue infections in immunocompetent individuals and deeply invasive and disseminated infections in immunocompromised patients with a crude mortality rate of 90% (Perlroth *et al*., 2007). Surgical resection remains the only definitive therapy for *S. prolificans* infections (Walsh *et al*., 2004; Cortez *et al*., 2008).

#### 3.2.2. Fusarium Species

Like *Aspergillus, Fusarium* spp. are fungi with hyaline-branched septated hyphae (Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004 a; Cuenca-Estrella *et al*., 2008; Caston-Osorio *et al*., 2008; Nucci and Anaissie, 2007). Of all filamentous fungi, *Fusarium* spp. remain the second most common cause of invasive disease in immunosuppressed patients (Nucci, and Anaissie, 2007). Besides classical risk factors (neutropenia, GVHD, and immunosuppression), recent findings suggest that hospital water systems may play a significant role in the transmission of these pathogens (Nucci and Anaissie, 2007; Dignani and Anaissie, 2004; Anaissie *et al*., 2001). Furthermore, fusariosis frequency is higher in patients with hematological malignancies and in HSCT recipients (Nucci and Anaissie, 2007; Dignani and Anaissie, 2004). Clinical manifestations of fusariosis are more often characterized by cutaneous involvement and fungemia than those of *Aspergillus* spp. However, fusariosis cannot be always distinguished from IA with high enough confidence on the basis of clinical manifestations alone (Nucci and Anaissie, 2002). Typical presentation of disseminated fusariosis includes positive blood culture (up to 75%) and the appearance of multiple purpuric cutaneous nodules with central necrosis (Nucci and Anaissie, 2007; Nucci *et al.*, 2004; Dignani and Anaissie, 2004; Walsh *et al*., 2004). Infections by *Fusarium* spp. usually associate with high mortality that is due in part to high rates of resistance to available antifungals.

#### 3.2.3. Acremonium

*Acremonium* spp. are becoming increasingly recognized as opportunistic fungal pathogens. Major predisposing factors for infection include prolonged corticosteroid therapy, splenectomy, and bone marrow transplantation with subsequent tacrolimus-dependent immunosuppression (Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004a). Following entry through penetrating injuries, they can cause foot mycetomas and corneal infections even in immunocompetent hosts. Greater than 35 cases of *Acremonium*-related infections have been described in adults (Schinabeck and Ghannoum, 2003) and >15 cases (excluding mycetoma and keratitis) have been documented in children (Miyakis *et al*., 2006). Among *Acremonium* spp., *A. strictum* is the most commonly identified species in children and adults. The presence of adventitious forms of *A. strictum* provides a mechanism for hematological spread and dissemination. Fungemias caused by *A. strictum* has been reported mainly in neutropenic patients (Schinabeck and Ghannoum, 2003).

#### 3.2.4. Paecilomyces

*Paecilomyces* are cosmopolitan filamentous fungi that inhabit the soil, decaying plants, and food products. Member species are usually considered as contaminants; however, some can cause infection in humans and animals. The genus *Paecilomyces* contains several species including the emerging pathogens *P. lilacinus* and *P. variotii* (Richardson and Lass-Florl, 2008; Pfaller and Diekema, 2004a; Pastor and Guarro, 2006). *P. lilacinus* tends to cause devastating oculomycosis and other severe human infections (Pastor and Guarro, 2006). It usually shows low susceptibility to conventional antifungals and variable susceptibility to novel triazoles *in vitro*. Around 120 cases of human *P. lilacinus* infections have been reported between 1964 and 2004. Most of which were oculomycosis (51.3%) and cutaneous and subcutaneous infections (35.3%); the rest (13.4%) were miscellaneous infections. Direct cutaneous inoculation can lead to infections that involve a variety of human organ systems. Pulmonary and cutaneous infections, cellulitis, onychomycosis, otitis media, endocarditis, osteomyelitis,

and catheter-related fungemia have all been reported (Pastor and Guarro, 2006). Peritonitis and sinusitis are the most common infections caused by *P. variotii*.

Different infections are usually associated with varying sets of predisposing factors. In that, while oculomycosis associates with lens implantation, cutaneous and subcutaneous infections occur in SOT and BMT recipients, neutropenic and immunodeficient hosts, and patients undergoing surgery. Infections in apparently immunocompetent hosts have also been reported. The following reported case is cited to serve as an illustration of the predisposition to, infection by, and manifestation and diagnosis of *P. lilacinus* infections. A male of 56 years of age presented with a 2-month history of painful erythematous nodules over the right knee 12 months after receiving a liver transplant. Several biopsies yielded a mold that was initially (phenotypically) identified as a *Penicillium*, subsequent molecular sequence analysis however determined the etiologic agents to be *P. lilacinus*. Skin and soft tissue infections were the most common presentation (Pastor and Guarro, 2006; van Schooneveld *et al*., 2008; Pfaller and Diekema, 2004a). Surgical debridement combined with drug therapy or correction of the predisposing factor(s) is usually required for measurable improvement.

*3.2.5. Trichoderma*

*Trichoderma* spp. have traditionally been employed in the biotechnology industry as sources of enzymes and antibiotics. They have also been used in agriculture as plant growth promoters and biofungicides. However, mounting epidemiological data suggests that these previously nonpathogenic spp., are emerging as important opportunistic pathogens in immunocompromised patients and in patients undergoing peritoneal dialysis (Pfaller and Diekema, 2004a; Richardson and Lass-Florl, 2008). It is now recognized that fatal disseminated disease due to *Trichoderma longibrachiatum* occurs in patients with hematologic malignancies and in BMT or SOT transplant recipients (Chouaki *et al*., 2002).

*3.3. Mucormycosis*

Mucormycosis (formerly zygomycosis) is the term used to describe a group of frequently lethal mold infections that have a predilection for diabetic patients, patients on steroid therapy, and severely immunocompromised hosts (such as HSCT recipients) (Bitar *et al*., 2009; Spellberg *et al*., 2005; Chayakulkeeree *et al*., 2006). The majority of human infections are due to fungi that mostly belong to the genera (or principal species) *Rhizopus* (*R. arrhizus*), *Mucor* (*M. circinelloides*), *Rhizomucor* (*R. pusillus*), *Cunninghamella* (*C. bertholletiae*), and *Absidia* (*A. corymbifera*). Despite the emergence of mucormycosis as a significant cause of mycosis, it remains much less frequent than other (more common) forms like invasive aspergillosis. The incidence figures are difficult to collect as few national studies have been undertaken; however, the annual incidence rate of 1.7 cases/million is the estimated figure in the US (Pfaller and Diekema, 2004a; Richardson and Lass-Florl, 2008; Bitar *et al*., 2009, Spellberg *et al*., 2005; Chayakulkeeree *et al*., 2006). Mucormycosis are generally acute and rapidly progressive with mortality rates of 70-100% (Gonzalez *et al*., 2002). The molds that cause entomophthoramycosis (*Conidiobolus* spp. and *Basidiobolus* spp) also belong to the class Zygomycetes. They principally cause nasal, facial, and other subcutaneous infections, which may become persistent but rarely disseminate. Such infections are rarely encountered outside of West Africa, India, and Central and South America (Pfaller and Diekema, 2004a; Richardson and Lass-Florl, 2008; Spellberg *et al*., 2005; Chayakulkeeree *et al*., 2006).

Inhaled infectious spores may establish an infection in the sinuses; less common routes of acquisition include the intestinal tract (by ingestion) or the skin (through breaches). The fact that mucormycosis is less common than IA suggests that these pathogens possess fewer (and/or milder) virulence factors (Spellberg *et al*., 2005; Chayakulkeeree *et al*., 2006). A review of 929 cases of mucormycosis reported in the literature up to 2004 has indicated that a majority of the cases associate with type 2 diabetes mellitus, a sizable portion associate with unknown risk factors, and a minority of cases associate with malignancy (Roden *et al*. (2005). That said, the number of cases that associate with malignancy, HSCT, and intravenous drug abuse has been on the rise for over three decades. Rhinocerebral mucormycosis was more commonly associated with diabetes, whereas pulmonary infection occurred more often in those with malignancy. Multivariate analysis revealed that independent risk factors for increased mortality include disseminated infection with *Cunninghamella* spp. as the causative agent and renal failure. Antifungal therapy and surgery were independently associated with decreased mortality risks (Rogers, 2008).

In a retrospective review of 15 patients with mucormycosis diagnosed at a non-oncology tertiary referral centre between 1999 and 2004 (Sims and Ostrosky-Zeichner, 2007), it was found that 9/16 episodes were associated with diabetes mellitus, whereas trauma, vascular disease, steroid therapy, and neutropenia constituted the rest of contributory conditions. Ten episodes were due to *Rhizopus* spp. and six were due to *Mucor* spp. Common sites of infection include wounds, rhinocerebrum, and pulmonary and peritoneal areas. The noticeably significant increase in the incidence of mucormycosis between 2000 and 2003 coincided with increased use of voriconazole; hence the possible link between drug overuse and predisposition to mucormycosis (Trifilio *et al*., 2007; Almyroudis *et al*., 2007).

*3.4. Dematiaceous molds (Phaeohyphomycosis)*

The long and taxonomically-diverse list of infections caused by dematiaceous (pigmented thick-walled) fungi are grouped under phaeohyphomycosis. Dematiaceous molds are characterized by the presence of a pale brown-dark melanin-like pigment in the cell wall. They may cause a variety of cutaneous and subcutaneous infections in immunocompetent hosts and invasive or disseminated infections in immunocompetent and immunocompromised hosts (Pfaller and Diekema, 2004a; Richardson and Lass-Florl, 2008; Caston-Osorio *et al*., 2008; Negroni *et al*., 2004; Revankar *et al*., 2004). The number of dematiaceous molds being reported as etiologic agents of phaeohyphomycosis is growing; several of which target the nervous system (Caston-Osorio *et al*., 2008;

Walsh *et al*., 2004; Revankar *et al*., 2004); hence the descriptive name "neurotropic fungi". Common neurotropic fungi include *Cladophialophora bantiana*, *Bipolaris spicifera*, *Exophiala* spp., *Wangiella dermatitidis*, *Ramichloridium obovoideum*, and *Chaetomium atrobrunneum* (Revankar *et al*., 2004). Brain abscess is the most common CNS presentation. However, *Bipolaris* spp. and *Exerohilum rostratum* infections may initially present as sinusitis to then extend into the CNS (Revankar *et al*., 2004; Yehia *et al*., 2004).

*3.5. Histoplasmosis*

Histoplasmosis or Darling's disease is pulmonary mycosis caused by the soil-inhabiting dimorphic fungus *Histoplasma capsulatum*. There are two varieties of *H. capsulatum* that are pathogenic to humans; *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*. *H. capsulatum* var. *farciminosum* represents a third variety that is recognized as an equine pathogen (Kauffman, 2007; 2009). Although *H. capsulatum* var. *capsulatum* occurs in many different parts of the world, it is most commonly encountered in North and Central America and in Europe (Kauffman, 2007; 2009). *H. capsulatum* var. *duboisii* occurs in Africa; cases that have been reported in Europe were related to Africans visiting Europe for treatment purposes. In the United States, *H. capsulatum* is endemic in the Mississippi and the Ohio River valleys. It also exists in localized foci in many Middle Eastern countries. Soil containing large amounts of bird or bat guano supports the growth of these molds (Kauffman, 2009).

Humans acquire *H. capsulatum* infections during occupational or recreational activities in areas where the pathogen is highly endemic (disrupted soil, accumulated dirt and guano in old buildings and bridges, or in caves where bats roost) (Kauffman, 2007; 2009). Most individuals with histoplasmosis are asymptomatic; symptomatic episodes manifest within 3-17 days after exposure. Most affected individuals have clinically silent manifestations and show no apparent ill effects (Kauffman, 2007; 2009). The acute phase is characterized by non-specific respiratory (cough or flu-like) symptoms. Chest X-ray findings are unremarkable in 40–70% of cases. In some cases, chronic histoplasmosis may resemble tuberculosis; disseminated histoplasmosis affects multiple organ systems and is often fatal unless treated. Severe infections can cause hepatosplenomegaly, lymphadenopathy, and adrenal enlargement. Leakage from scar tissues left on the retina following ocular histoplasmosis damages the retina and could result in loss of vision. Immunosuppressed patients and those unable to develop effective cell-mediated immunity against the organism are likely to manifest symptomatic disease during acute/disseminated episodes (table 5) (Kauffman, 2007; 2009).

**Table 5.** A tentative tally of the common risk factors for disseminated histoplasmosis

| Risk factor |
|---|
| Age (infants) |
| AIDS |
| Hematologic malignancies |
| Solid organ transplant |
| Hematopoietic stem cell transplant |
| Immunosuppressive agents |
| Corticosteroids |
| Tumor necrosis factor antagonists |
| Congenital T-cell deficiencies |
| Gamma interferon receptor deficiency |
| Hyperimmunoglobulin M syndrome |

## 4. Recent Advances in Fungal Species Identification

Correct and timely identification of fungal clinical isolates is an essential component in the management of patients with invasive fungal infections; this is particularly true for the immunocompromised and the critically-ill. Recent advances in fungal genomics is helping in this regard as PCR-based identification of clinical isolates is proving to be far superior as compared to conventional biochemical identification panels (e.g. API-20C-AUX, VITEK ID-YST, and so on). Pyrosequencing is a relatively inexpensive, extremely rapid DNA sequencing method that uses novel chemistry to sequence short (>70-bp) fragments within pre-selected regions of the genome in question (Borman *et al*., 2010; Montero *et al*., 2009). Several studies suggest that pyrosequencing could be a very productive approach for the identification of medically important yeasts (Boyanton *et al*., 2008; Gharizadeh *et al*., 2004; Montero *et al*., 2008). Pyrosequencing of a short segment within the internal transcribed spacer 2 region (ITS2) was shown capable of accurately distinguishing *C. glabrata* from its close genetic relative *C. nivariensis* (Borman *et al*., 2008b). ITS2 pyrosequencing has also been reported capable of discriminating between *C. parapsilosis*, *C. orthopsilosis*, and *C. metapsilosis* (Borman *et al*., 2009). Another promising target region for comparative pyrosequencing of various *Candida* species is the D1-D2 segment of the nuclear 28S large rRNA gene (Andrew *et al*., 2008b; Borman *et al*., 2010). The utility of pyrosequencing in large-scale comparative studies aiming at distinguishing closely-related and disparate pathogenic fungi and at identifying rare yeast species has been demonstrated (Ghannoum *et al*., 2010; Borman *et al*., 2010; Montero *et al*., 2009). Employing a pyrosequencing approach, Ghannoum and co-workers (2010) were able to characterize the profile of the oral microbiome (mycobiome) in healthy subjects. The mycobiome characterized in their study consisted of 85 different fungal genera and 101 different fungal species.

## 5. Conclusion

Common human fungal infections are on the rise and fungal species that have been classically labeled as mildly-pathogenic or nonpathogenic are emerging as serious pathogens. Coccidioidomycosis (Cox and Magee, 2004), paracoccidioidomycosis (Travassos *et al*., 2007), blastomycosis, and unusual fungal and pseudofungal infections (Pfaller and Diekema, 2005) are cases in point. This trend is strongly associated with improvements in disease management, improvements in the diagnosis of infections and infectious diseases, overuse/misuse of antifungals and antibiotics, and resistance to existing antifungal drugs. It is also aided by increased resistance to and limited efficacy of existing antifungal drugs. Slow progress in developing more effective and safer antifungals and the striking lack of fungal vaccines are not helping either. Therefore, use of definitive diagnostic procedures, rational application of available antifungals, and prudent management of patients at risk are the more imperative.

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