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 (Pfaffler 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

<table>
<thead>
<tr>
<th>Genus / Group</th>
<th>Species / Members</th>
<th>Genus / Species / Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida spp.</td>
<td>C. albicans</td>
<td>Other yeasts</td>
</tr>
<tr>
<td></td>
<td>C. glabrata</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td></td>
<td>C. guilliermondii</td>
<td>Trichosporon spp</td>
</tr>
<tr>
<td></td>
<td>C. kessel</td>
<td>Rhodotorula spp.</td>
</tr>
<tr>
<td></td>
<td>C. lusex</td>
<td>Geotrichum</td>
</tr>
<tr>
<td></td>
<td>C. rugosa</td>
<td>capitatum</td>
</tr>
<tr>
<td></td>
<td>C. panax</td>
<td>Blastoschizomyces capitatus</td>
</tr>
<tr>
<td></td>
<td>C. tropica</td>
<td>Zygomyces</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus spp</td>
<td>A. fumigatus</td>
<td>Dematiaceous molds</td>
</tr>
<tr>
<td></td>
<td>A. niger</td>
<td>Rhizopus spp</td>
</tr>
<tr>
<td></td>
<td>A. farus</td>
<td>Rhizomucor spp</td>
</tr>
<tr>
<td></td>
<td>A. terreus</td>
<td>Bipolaris spp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other hyaline molds</td>
<td>Scedosporum spp</td>
<td>Cerdosporiella spp</td>
</tr>
<tr>
<td></td>
<td>Fusarium spp</td>
<td>Euphaelia spp</td>
</tr>
<tr>
<td></td>
<td>Acremonium spp</td>
<td>Pichia phaffii</td>
</tr>
<tr>
<td></td>
<td>Paecilomyces spp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trichoderma spp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scopulariopsis spp</td>
<td></td>
</tr>
</tbody>
</table>

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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 patient 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, Paecilomyces, Trichoderma, Zygomycetes or Mucoromycetes, 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., 2004). 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; Pfaffer 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>
<thead>
<tr>
<th>Factors</th>
<th>Comments</th>
<th>Representative examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological factors</td>
<td>Neutrophil defect</td>
<td>Presence of abnormally small numbers of neutrophils in the circulating blood, myeloperoxidase deficiency</td>
</tr>
<tr>
<td>T- lymphocyte, mononuclear phagocyte</td>
<td>Certain diseases could lead to a defect in T- lymphocyte mononuclear phagocyte</td>
<td>Auto immune deficiency syndrome (AIDS), Hodgkin’s disease, chemotherapy</td>
</tr>
<tr>
<td>Reticuloendothelial system (RES)</td>
<td>Defect of RES causes impairment in the clearance of infectious particles from the blood; this is due to congenital or surgical causes</td>
<td>Congenital absence or defect of the spleen, splenectomy</td>
</tr>
<tr>
<td>Chemotherapy and Radiotherapy</td>
<td>Treatment with drugs and/or irradiation that alters the composition of the endogenous microbial flora or suppresses host defenses against infection</td>
<td>Immunosuppressive agents, antineoplastic agents, antibiotics, corticosteroids</td>
</tr>
<tr>
<td>Intermittent integument</td>
<td>Membrane trauma, burns local occlusion or maceration of tissues</td>
<td>Finger or bone marrow punctures, gastrointestinal (GI) ulcers, catheters, IV needles, wearing dentures</td>
</tr>
<tr>
<td>Surgical procedures</td>
<td>Introduction of mechanical devices and prostheses into vessels or tissues</td>
<td>Heart valves replacements, tracheostomy respiratory assistance, endoscopies, renal transplant, heart operation, GI or gynecological surgery, blood transfusion</td>
</tr>
<tr>
<td>Physiological factors</td>
<td>Infectious, idiopathic, congenital, or other debilitating diseases and disorders, Digressions from normal physiological status</td>
<td>Microbial infections, endocrine dysfunctions, defect in cell – mediated immunity Pregnancy, infancy</td>
</tr>
<tr>
<td>Nutritional factors</td>
<td>Excesses of deficiency of food stuff that create an environment conducive to the development of mucosal candidosis</td>
<td>Carbohydrate – rich diets, vitamin deficiency</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Predisposing factors(s)</th>
<th>Type of candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit</td>
<td>Neonatal, Oral</td>
</tr>
<tr>
<td>Birth trauma, cecumuses</td>
<td>Oral, vaginal</td>
</tr>
<tr>
<td>Malnutrition, breast and bottle feeding</td>
<td>Malabsorption, Malnutrition</td>
</tr>
<tr>
<td>Chemotherapy and radiotherapy</td>
<td>Antibiotic and steroid therapy, Broad spectrum Antibiotic, therapy, in infants after birth, oral effect, with xenotomic side</td>
</tr>
<tr>
<td>Surgical procedures</td>
<td>Parenteral nutrition, corvallence after operations</td>
</tr>
<tr>
<td>Uterine delivery, male sex, unlygenic environment, low birth weight, thumb and dummy sucking</td>
<td>Poor oral hygiene, oral leukoplakia, factors, immunological factors, humidity and factors, warmth, varying light</td>
</tr>
</tbody>
</table>

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 (Pfaffer 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 (Pfaffer and Diekema, 2004a; Almirante et al., 2009). It has been reported (Pfaffer and Diekema, 2004; Ray et al., 2007). 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 (Pfaffer 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 (Pfaffer and Diekema, 2004). 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 (Pfaffer and Diekema, 2004; 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. is increasing as a cause of BSIs continues to rise (Pfaffer 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,
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 meningae 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. gattii 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; Pfäffer 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; Pfäffer 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 beigeli*). More recently however, with biochemical and morphologic differences within the genus being increasingly appreciated, *T. beigeli* has been regrouped into several distinct species. Greater than eight species have been recognized, including *T. asahii, T. inkin, T. asteroidis, 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. asteroidis 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; Fleming et al., 2002; Middelhoven, 2003; Marty et al., 2003). *T. faecale* was isolated from the skin of a patient with tinea pedis in Germany (Hahnner et al., 2008) and *T. loubieri* has been associated with mycosis in patients with adult polycystic kidney disease (Padyte 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; Fleming 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, et 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 (Pfäffer 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 (Pfäffer and Diekema, 2004a; Richardson and Lass-Florl, 2008). Risk factors include CVC and malignancies (Pfäffer 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 capitatum*) is an uncommon, but frequently fatal, cause of IFIs in immunocompromised patients, particularly those with hematological malignancies (Pfäffer 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 (Pfäffer and Diekema, 2004a; 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.
which tends to be resistant to amphotericin B (Richardson 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., 2002; 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 (Pfaffer 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 2.7-5.8 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-Flör, 2008; Pfaffer 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-Flör, 2008; Pfaffer 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-Flör, 2008; Abu-Elteen and Hamad, 2007).

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

<table>
<thead>
<tr>
<th>Hematological malignancies</th>
<th>Organ transplant patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td>Lung, Liver, heart, renal</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>Acute and chronic rejection</td>
</tr>
<tr>
<td>Stem – cell transplant</td>
<td>Haemodialysis</td>
</tr>
<tr>
<td>GVHD* (acute and chronic)</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Prolonged neutropenia</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Induction</td>
<td>Re – transplantation</td>
</tr>
<tr>
<td>Fungal colonization</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Local epidemiology</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Steroid epideioloogy</td>
<td>Diabetic ketoacidosis b</td>
</tr>
<tr>
<td>Steroid prophylaxis</td>
<td>Iron overload b</td>
</tr>
<tr>
<td>Neutrophil dysfunction</td>
<td>Diabetes mellitus b</td>
</tr>
<tr>
<td>Fungal Infections</td>
<td>Deferoxamine therapy b</td>
</tr>
<tr>
<td>Local epidemiology</td>
<td>Skin breakdown b</td>
</tr>
<tr>
<td>T- cell depletes stem – cell products</td>
<td></td>
</tr>
<tr>
<td>CD34-selected stem cell products</td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis b</td>
<td>Iron overload b</td>
</tr>
<tr>
<td>Diabetes mellitus b</td>
<td>Deferoxamine therapy b</td>
</tr>
<tr>
<td>Skin breakdown b</td>
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</tbody>
</table>

*GVHD, Graft vs. host disease.
*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, lymphohematogenous disease, pneumonia, endocarditis, peritonitis, chorioptic 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-invasive 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; Pfäffler 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; Pfäffler 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 (Miyakos 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; Pfäffler 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. varioti*.

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; Pfäffler 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 (Pfäffler 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; Chayakulkheeere 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 fungal infection, 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 (Pfäffler and Diekema, 2004a; Richardson and Lass-Florl, 2008; Bitar et al., 2009, Spellberg et al., 2005; Chayakulkheeere 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 (Pfäffler and Diekema, 2004a; Richardson and Lass-Florl, 2008; Spellberg et al., 2005; Chayakulkheeere 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; Chayakulkheeere 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 (Trifilò 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 (Pfäffler 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 obovoides, 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. fargiminosum represents a third variety that is recognized as an equine pathogen (Kaufman, 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 (Kaufman, 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 (Kaufman, 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) (Kaufman, 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 (Kaufman, 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) (Kaufman, 2007; 2009).

### Table 5: A tentative tally of the common risk factors for disseminated histoplasmosis

<table>
<thead>
<tr>
<th>Risk factor</th>
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</thead>
<tbody>
<tr>
<td>Age (infants)</td>
</tr>
<tr>
<td>AIDS</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
</tr>
<tr>
<td>Solid organ transplant</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplant</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Tumor necrosis factor antagonists</td>
</tr>
<tr>
<td>Congenital T-cell deficiencies</td>
</tr>
<tr>
<td>Gamma interferon receptor deficiency</td>
</tr>
<tr>
<td>Hyperimmunoglobulin M syndrome</td>
</tr>
</tbody>
</table>

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 non-pathogenic are emerging as serious pathogens. Coccidioidomycosis (Cox and Magee, 2004), paracoccidioidomycosis (Travassos et al., 2007), blastomycosis, and unusual fungal and pseudofungal infections (Pfaffer and Dickena, 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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