Chapter 18
What's Old is New: Recognition of New Fungal Pathogens in the Era of Phylogenetics and Changing Taxonomy and Implications for Medical Mycology

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Introduction

Invasive fungal infections are associated with significant morbidity and mortality as these are often difficult to diagnosis and treat. Fungi historically associated with invasive disease in humans include the yeast within the genera *Candida, Cryptococcus,* and *Trichosporon*, the dimorphic fungi *Blastomyces dermatitidis, Coccidioides immitis/posadasii,* and *Histoplasma capsulatum,* and the molds, including limited species within the genera *Aspergillus*, *Fusarium*, and *Scedosporium*, and certain members of the Order *Mucorales.* Over the last two decades, there has been a significant increase in the number of fungal species associated with invasive disease in humans. Factors that have contributed to this increase include an increase in the number of immunocompromised patients at high risk for invasive fungal infections, including HIV-AIDS patients, those receiving immunosuppressive chemotherapy for malignancies, and solid organ transplant recipients, improvements in diagnostic assays and the clinical recognition of patients with risk factors for such infections, as well as improvements in the tools used to identify fungal species. Unfortunately, the recognition of new etiologic agents of invasive mycoses has surpassed the development of new diagnostic assays and treatment strategies against these infections. The increase in the number of etiologic agents of invasive mycoses is also method driven. Taxonomic changes due to phylogenetic analysis have led to the reclassification of many previously recognized fungi. This has led to a concern of nomenclature instability in medical mycology, and the clinical relevance of many of the newly reclassified species is unknown (de Hoog et al.

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2013, 2014). In this chapter, we review the identification of fungi, primarily filamentous organisms, in the clinical setting, and provide examples of known and emerging causes of invasive fungal infections in humans and changes in taxonomy and fungal nomenclature that have occurred and are ongoing.

Fungal Identification in the Clinical Setting

The identification of fungi in the clinical laboratory has historically relied on morphologic characteristics and physiologic traits. The description of the colony appearance and the microscopic features of the organism, including the reproductive structures, has been the hallmark for fungal identification for many years. Certain phenotypic/physiologic traits are also combined with the morphologic features to obtain the identities of fungal isolates. For molds these include, but are not limited to, the ability of the organism to grow at certain temperatures, tolerance to cycloheximide and benomyl, nitrate assimilation, tolerance to different concentrations of sodium chloride, growth on bromcresol purple agar, growth on trichophyton agar, and growth on urea agar (Nelson et al. 1983; Pincus et al. 1988; Kane et al. 1997; Summerbell 1993). Many of these phenotypic/physiologic assays were and still are used to identify the organism to the genus and possibly species level in clinical microbiology and reference mycology laboratories. Identification to the species level is clinically important as it provides the clinician with information that may be useful in the management of patients and help guide antifungal therapy. Indeed, early identification and the initiation of appropriate therapy have been shown to influence patient outcomes while delaying appropriate therapy can be detrimental (Morrell et al. 2005; Greene et al. 2007; Garey et al. 2006; Chamilos et al. 2008). Identification to the species level is important in helping to guide appropriate therapy, as some fungi are intrinsically resistant to certain drugs. Furthermore, some species within the same species complex may have different antifungal susceptibility profiles and this can influence the choice of treatment that is used (Balajee et al. 2005a; Gilgado et al. 2006; Lackner et al. 2012). However, identification by morphologic/physiologic characteristics alone can be time-consuming, and results may not be available in a timely fashion for clinical decisions. Morphologic identification can also be fraught with errors if done by those without proper training and experience. In addition, the morphologic features of fungi may be variable (Balajee et al. 2006, 2007). Different factors can affect these features, including the media used for subculturing and exposure to external stressors, such as antifungal agents prior to recovery from clinical specimens, which can often occur in patient groups at high risk for invasive fungal infections in which empiric or preemptive antifungal therapy is often used.

The introduction of molecular and proteomic tools, such as DNA sequence analysis and matrix-assisted light desorption ionization time-of-flight (MALDI-TOF), a relatively new diagnostic tool in the clinical microbiology laboratory, has dramatically changed how fungi are identified. These methods can reduce the amount of

Table 18.1 DNA targets used for molecular sequence identification of fungi and examples of genera these targets may be used to identify

Targets	Genera
Internal transcribed spacer (ITS)	All genera
28S rDNA large subunit (D1/D2)	All genera
Beta-tubulin / Calmodulin	*Aspergillus*
Calmodulin	*Scedosporium*
Translation elongation factor	*Fusarium*
RNA polymerase	*Penicillium*
Glyceraldehyde-3-phosphate dehydrogenase	*Curvularia*

time needed to determine the identity of an organism and reduce errors associated with morphologic variability. However, these methods have their own limitations and have not eliminated the need for the morphologic evaluation of fungi in the clinical laboratory. For both DNA sequence and protein spectrum analysis, the results that are obtained must be compared to those deposited in databases from known organisms in order for an identity to be obtained. For fungi, publicly available databases for DNA sequence comparisons are available, including those at the National Center for Biotechnology Information (GenBank; www.ncbi.nlm.nih.gov/genbank/), the Centraalbureau voor Schimmelcultures Fungal Biodiversity Centre in the Netherlands (CBS-KNAW; www.cbs.knaw.nl), the International Society of Human and Animal Mycology ITS database (ISHAM; its.mycologylab.org), and the Fusarium-ID database (http://isolate.fusariumdb.org). Reference laboratories or clinical microbiology laboratories may also have their own databases. The use of sequence results can be extremely useful when compared with credible deposits. However, not all fungal deposits within databases have been confirmed to be from accurately identified organisms (Bridge et al. 2003; Deckert et al. 2002; Crous 2002). This can lead to erroneous results and the misidentification of the cultured specimen. In addition, the choice of the target sequence can be critical for the proper identification of fungi. Although the internal transcribed spacer region (ITS) has been put forth as a universal barcode for the identification of fungi (Schoch et al. 2012; Seifert 2009; Petti 2007), this target cannot be used alone to discriminate between closely related fungi. Several other DNA targets may be used to identify fungi in the clinical setting (Table 18.1), and the choice of targets is dependent on the organism. Thus, an assessment of the morphology of the organism prior to sequence analysis can provide useful information as to what DNA targets to use for identification.

Changes in Fungal Nomenclature

Under Article 59 of the International Code for Botanical Nomenclature, polymorphic fungi were allowed to have multiple names. These names described either the sexual (teleomorph) or asexual (anamorph) stages of the organism's life cycle. The

dual nomenclature system served a purpose when fungal identification was based upon the observed morphologic features. However, it became obsolete with the introduction of molecular tools into the field of mycology (de Hoog et al. 2014; Hawksworth 2011). Under the newly named International Code of Nomenclature of algae, fungi, and plants, the dual nomenclature system under Article 59 is abolished, and as of January 1, 2013, all fungi are now to have only one correct name (Norvell 2011). Regardless of the life history stage of the type, all legitimate fungal names are now to be treated equally for the purpose of establishing priority. While the abandonment of the dual nomenclature system was an important first step, mycologists are now charged with implementing this change and contributing to the production of lists of accepted and suppressed names for fungi.

The abandonment of the dual nomenclature system and the increased use of molecular tools have implications for the field of medical mycology. Phylogenetic studies have demonstrated that fungi are much more molecularly diverse than previously recognized, and this has led to an increase in the number of clinically recognized fungi, as new species have been described and other pathogens have been reclassified (de Hoog et al. 2013). Some examples of recent nomenclature changes that have occurred for clinically relevant fungi are shown in Table 18.2. However, molecular diversity does not necessarily equate to clinical diversity, and the true clinical relevance of newly discovered species or newly reclassified organisms may be unknown. It has been suggested that this increase in recognized fungal species, combined with the abandonment of the dual nomenclature system, may be compromising the stability of the nomenclature of medically important fungi (de Hoog et al. 2013, 2014). Potentially detrimental aspects may be the confusion of clinicians who do not closely follow taxonomic changes but are responsible for the care of patients and the impediment of navigating the literature to find clinically useful

Table 18.2 Examples of changes in fungal nomenclature of clinically relevant fungi

New species name	Previous species name	Invasive disease
Curvularia spicifera	*Bipolaris spicifera*	Fungal sinusitis, cerebral phaeohyphomycosis
Curvularia hawaiiensis	*Bipolaris hawaiiensis*	
Curvularia australiensis	*Bipolaris australiensis*	
Lichtheimia corymbifera	*Absidia corymbifera*	Mucormycosis
Lomentospora prolificans	*Scedosporium prolificans*	Pulmonary infection (scedosporiosis)
Rasamsonia argillacea	*Geosmithia argillacea*	Pulmonary infection
Sarocladium kiliense	*Acremonium kiliense*	Mycetoma, keratitis in immunocompetent hosts, invasive infections in immunocompromised individuals
Talaromyces marneffei	*Penicillium marneffei*	Disseminated infection in HIV+ individuals
Verruconis gallopava	*Ochroconis gallopava*	Cerebral phaeohyphomycosis

information about fungal pathogens and invasive mycoses due to confusion about the name of the organism or the diseases the fungi cause. Thus, it has been proposed that in clinical practice medical mycologists be allowed to follow taxonomic changes and implement these more gradually (de Hoog et al. 2013). At the species level, once the clinical relevance of molecular sibling species is determined, novel nomenclature could be adopted. However, until such evidence becomes available, cryptic species can be referred to as species complexes in medical practice. A potential drawback of this approach is the hindrance of gaining knowledge about the clinicopathology of a particular organism. In order to establish a body of literature necessary to gain an understanding of the clinical relevance of a particular fungal species in relation to disease and its response to therapy, the true identity of the infecting organism must be known. The rate at which such knowledge is accumulated may be slowed if such similar species are lumped into species complexes without further delineation.

Examples of Clinically Relevant/Emerging Fungi and Changes in Fungal Taxonomy and Nomenclature

Invasive Aspergillosis and Aspergillus *Section* Fumigati

Invasive aspergillosis is a major invasive fungal infection and significant cause of morbidity and mortality in immunocompromised hosts. Groups at highest risk for the development of invasive aspergillosis include highly immunocompromised individuals. Such groups have historically included solid organ transplant recipients, those undergoing hematopoietic stem cell transplantation, and patients receiving highly immunosuppressive chemotherapies (Wiederhold et al. 2003). Results from the PATH Alliance Registry from 2004 to 2007, which collects information on patients with invasive fungal infections at medical centers in the USA, demonstrated that invasive aspergillosis was the most frequent invasive fungal infections in patients undergoing hematopoietic stem cell transplantation ahead of invasive candidiasis, mucormycosis, and other invasive fungal infections (Neofytos et al. 2009). Allogeneic stem cell transplant recipients who receive prolonged course of corticosteroids for the treatment of graft versus host disease are at further risk for invasive aspergillosis (Wiederhold et al. 2003; Baddley et al. 2010; Kontoyiannis et al. 2010). Of the solid organ transplant recipients, individuals who receive lung or dual heart/lung transplants are at higher risk for invasive pulmonary aspergillosis as the primary route of entry into the body is via inhalation into the lungs (Minari et al. 2002). Although pulmonary involvement is a major component of invasive aspergillosis due to the route of entry into the body via the lungs, dissemination to other organs can occur, as invasive disease has been reported in all organ systems. The mortality rate of this disease is exceptionally high with dissemination to the central nervous system in the setting of continued immunosuppression. In addition

to these patient populations, invasive aspergillosis has also become more important in critically ill patients not traditionally considered at high risk, including those with acute chronic obstructive pulmonary disease and those receiving corticosteroids (Meersseman et al. 2004; Garnacho-Montero et al. 2005). Chronic pulmonary aspergillosis is also a significant problem in patients with structure damage to the lungs, such as those who have had tuberculosis or sarcoidosis (Smith and Denning 2011; Denning 2001). The prevalence of chronic pulmonary aspergillosis is estimated to be approximately 3 million patients worldwide (Denning et al. 2011, 2013a, b). Treatment of these patients often involves prolonged courses of azole therapy, which predisposes individuals to the adverse effects and drug interactions associated with these agents and the potential development of drug-resistant organisms (Howard et al. 2009).

One of the most challenging aspects of this disease is the ability to make a timely and accurate diagnosis. The diagnosis of invasive aspergillosis involves the incorporation of clinical, radiological, serological, and histopathological findings. Although studies have demonstrated the usefulness of radiographic studies, such as chest computed tomography, in patients with risk factors for invasive aspergillosis, the images obtained cannot conclusively rule in or rule out this fungal infection as other pulmonary fungal infections can show similar signs (Walsh et al. 2008). Rapid diagnosis of this disease has focused on the detection of surrogate markers of infection, including components of the cell wall within normally sterile biologic fluids. One particular strategy that is clinically used is the detection of galactomannan, a component of the cell wall released during growth of the organism (Latge et al. 1994). A commercially available assay, the Platelia *Aspergillus* ELISA kit (Bio-Rad), uses a rat monoclonal antibody (EB-A2) directed against tetra (1 → 5)-β-D-galactofuranoside, the immunodominant epitope in galactomannan (Stynen et al. 1992, 1995; Morelle et al. 2005). This assay has proven to be useful for the diagnosis of invasive aspergillosis with a high specificity (≥85 %) in patients with hematologic malignancies at high risk for this opportunistic disease (Pfeiffer et al. 2006). The detection of galactomannan using this assay now fulfills part of the diagnostic criteria for probable invasive aspergillosis (Walsh et al. 2008). Other assays that are clinically used to detect invasive fungal infections detect another component of the cell wall of many pathogenic fungi, (1 → 3)-β-D-glucan. The chromogenic assay available for clinical use (Fungitell, Associates of Cape Cod) is based on the activation of the horseshoe crab coagulation cascade and uses amebocyte enzymes from *Limulus polyphemus* (Fungitell 2008). The prompt diagnosis of invasive aspergillosis, including the use of these surrogate diagnostic markers, can have significant effects on patient outcomes. Early diagnosis and initiation of antifungal therapy have been shown to reduce mortality in patients with invasive fungal infections including invasive aspergillosis (Greene et al. 2007; Garey et al. 2006; Caillot et al. 1997). This has led to the strategy of preemptive therapy in which antifungal agents are initiated upon the first signs of a potential infection as suggested by high-resolution computer tomography and serial screening of surrogate markers. However, these assays are not without their limitations. (1 → 3)-β-D-glucan is a pan-fungal target, since many clinically relevant species contain this polysaccharide

within their cell walls (Odabasi et al. 2006). Thus, a positive result can be seen in patients with infections caused by a variety of fungi including *Aspergillus*, *Candida*, *Fusarium*, *Acremonium*, *Trichosporon*, *Sporothrix*, *Histoplasma*, *Coccidioides*, and *Blastomyces* (Odabasi et al. 2006; Senn et al. 2008; Pickering et al. 2005; Ostrosky-Zeichner et al. 2005). In addition, several substances can result in false-positive test results, primarily due to glucan content. This can occur in patients receiving hemodialysis with cellulose membranes, those receiving immunoglobulin products and albumin, as well as following serous exposure to gauze, which can occur in surgical patients (Odabasi et al. 2004, 2006). Thus, while a positive assay result does provide evidence of an invasive mycosis, it does provide information on the causative organism, which is important for making decisions regarding appropriate therapy. The galactomannan assay is more specific for *Aspergillus* than those for (1 → 3)-β-D-glucan. However, the sensitivity of serum galactomannan may be reduced in patients with antifungal exposure with a high degree of variability among different patient populations (Marr et al. 2005). While the specificity of this assay is consistently above 85 %, the sensitivity may vary considerably between patient populations with rates reported in the literature ranging from 29 to 100 % (Pfeiffer et al. 2006; Verweij 2005). Furthermore, reports of cross-reactivity with this assay have been reported with other fungi, including *Fusarium* and *Trichosporon* species (Fekkar et al. 2009; Mikulska et al. 2012; Tortorano et al. 2012). The galactomannan assay also will not provide information on the species of *Aspergillus* that is causing infection, which is also important for making treatment decision in patients with invasive aspergillosis. For example, the galactomannan assay is not able to distinguish between *A. fumigatus* and *A. terreus*, the latter demonstrating resistance to amphotericin B, a widely used antifungal agent (Steinbach et al. 2004).

Although there are over 200 individual *Aspergillus* species, common causes of invasive aspergillosis in humans include *A. fumigatus*, *A. flavus, A. niger, A. nidulans,* and *A. terreus*. Of these, *A. fumigatus* is the major etiologic agent of invasive disease at most institutions (Morgan et al. 2005). This species is usually readily distinguishable from the other common causes of aspergillosis based on its morphology (Balajee et al. 2006, 2007). However, the morphology of *A. fumigatus* is unstable and by phylogenetic analysis several distinct species are now recognized within the section *Fumigati* (Sugui et al. 2014). Currently, this section consists of 51 phylogenetically separate species, 15 of which have been reported to cause clinical disease in humans (Sugui et al. 2014). These include *A. felis*, *A. fumigatiaffinis*, *A. fumigatus*, *A. fumisynnematus*, *A. lentulus*, *A. novofumigatus*, *A. parafelis*, *A. pseudofelis*, *A. pseudoviridinutans*, *A. viridinutans*, *A. fischeri*, *A. hiratsukae*, *A. laciniosus*, *A. thermomutatus*, and *A. udagawae*. Infections that have been reported caused by these species include invasive pulmonary aspergillosis, osteomyelitis, peritonitis, cerebral aspergillosis, and invasive otitis (Balajee et al. 2005b; Matsumoto et al. 2002; Jarv et al. 2004; Zbinden et al. 2012; Ghebremedhin et al. 2009).

Species identification within this section is a multifaceted approach, requiring morphologic, physiologic, and molecular sequence results. Although the morphology and phenotypic features within this section are variable, some members are not easily distinguished from *A. fumigatus* without the use of molecular sequencing.

The ITS region, although recognized as the universal barcode for fungi, is not capable of discriminating between members of section *Fumigati* (Samson et al. 2014). For this purpose, sequencing of the beta-tubulin region is recommended. Thus, here is the potential for misidentification of members of this section in clinical laboratories that do not routinely use sequence analysis for identification. The need for correct identification of the species causing infection is important since several species within this section are refractory to antifungal therapy and may cause more chronic infections than *A. fumigatus* (Zbinden et al. 2012; Barrs et al. 2013; Vinh et al. 2009a). These include *A. lentulus*, *A. felis*, *A. parafelis*, *A. pseudofelis*, *A. pseudoviridinutans*, *N. pseudofischeri*, and *N. udagawae* (Balajee et al. 2005a; Sugui et al. 2010, 2014; Vinh et al. 2009b; Khare et al. 2014). Clinical failures have occurred in patients treated with antifungals for infections caused by these species that were misidentified as *A. fumigatus* (Balajee et al. 2005a, b, 2007; Zbinden et al. 2012; Vinh et al. 2009a; Khare et al. 2014).

Scedosporiosis and Pseudallescheria/Scedosporium

Another group of fungi recognized to cause invasive infections for which there has been significant taxonomic change is the genus *Scedosporium*. Members of this genus are ubiquitous ascomycetes found in soil, polluted water, sewage, and manure and are capable of causing many different types of infections in humans (Cortez et al. 2008; Walsh et al. 2004; Guarro et al. 2006). Invasive infections have been reported primarily in immunocompromised hosts, and these fungi are recognized as the second most common fungal colonizers in cystic fibrosis patients behind *Aspergillus* species (Blyth et al. 2010). Because the route of entry is similar to that of *Aspergillus* species, *Scedosporium* species can cause sinopulmonary disease that is difficult to distinguish from disease caused by *Aspergillus* and other molds that may be more amendable to antifungal therapy (Walsh et al. 2004; Bouza and Munoz 2004). Such infections can be especially devastating in lung transplant recipients (Johnson et al. 2014), and because these fungi can so adversely affect patient outcomes, colonization of the lungs may be a contraindication to lung transplantation (Raj and Frost 2002; Morio et al. 2010). *Scedosporium* species have also been recognized as causes of breakthrough infections in persistently neutropenic and/or lymphopenic patients receiving antifungal therapy (Lamaris et al. 2006; Nucci 2003). In patients whose immune system fails to recover disseminated infections may occur, which portends a poor prognosis. Infections can also occur in immunocompetent individuals. Near-drowning victims can develop pulmonary infections with dissemination to the brain, which are difficult to treat and associated with significant morbidity and mortality (Guarro et al. 2006; Buzina et al. 2006; Nakamura et al. 2013). Mycetomas, chronic, tumor-like infections of subcutaneous tissue and contiguous bone with draining sinuses, can also occur in otherwise healthy hosts secondary to traumatic inoculation (Cortez et al. 2008; Walsh et al. 2004; Guarro et al. 2006).

Over the last decade, the taxonomy of *Scedosporium* has changed markedly. Due to the ability to develop sexual structures on route culture media, members of this genus were identified by clinical microbiology laboratories as *Pseudallescheria boydii* when the teleomorph was present and as *Scedosporium apiospermum* when only the anamorph was found. However, with the use of molecular phylogeny it was subsequently determined that *P. boydii* (anamorph *Scedosporium boydii*) and *Pseudallescheria apiosperma* (anamorph *S. apiospermum)* were indeed separate species (Gilgado et al. 2008, 2010). Other species that have been discovered through the use of molecular phylogenetics, but which are morphologically identical to these sibling species, include *S. aurantiacum, P. minutispora, P. desertorum,* and *S. dehoogii* (Gilgado et al. 2005, 2008; Lackner et al. 2014a). Recently, due to the abolishment of Article 59 of the Code of Botanical Nomenclature of algae, fungi, and plants, it has been proposed that *Pseudallescheria* should be treated as a synonym of *Scedosporium* and that *Scedosporium* be given precedence as it is the oldest valid generic name (Lackner et al. 2014a). The morphologically distinct species *Scedosporium prolificans*, which in contrast to other members of the *Scedosporium* genus, is a phaeoid mold with inflated versus tubular conidiogenous cells and has been renamed *Lomentospora prolificans* based on significant phylogenetic differences (Lackner et al. 2014a). The distinction between this species and *Scedosporium* species is clinically relevant, as *L. prolificans* is highly resistant to multiple antifungal agents (Lackner et al. 2012, 2014b; Cortez et al. 2008; Walsh et al. 2004; Lewis et al. 2005; Wiederhold and Lewis 2009), and infections caused by this organism are extremely difficult to treat and are associated with poor patient outcomes (Cortez et al. 2008).

For the members of the genus *Scedosporium,* it has been suggested that for the routine identification in clinical microbiology laboratories, these fungi might be identified as members of the *Scedosporium apiospermum* complex since the sibling species *S. apiospermum* and *S. boydii* are without medically relevant differences (Lackner et al. 2014a). However, there is some evidence that differentiation among the members of this complex may be clinically important, and differences in antifungal susceptibility have been reported among these species. For example, *S. apiospermum* isolates have been reported to be less susceptible to posaconazole than those of *S. boydii* (Lackner et al. 2012). In addition, several studies that have evaluated the in vitro potency of clinically available antifungals have demonstrated that *S. aurantiacum* isolates are resistant to these agents with the exception of the triazole voriconazole (Lackner et al. 2012, 2014b; Tintelnot et al. 2009; Alastruey-Izquierdo et al. 2007), which is currently the drug of choice for the treatment of infections caused by *Scedosporium* species (Tortorano et al. 2014). Since many of the *S. aurantiacum* isolates included in these studies have been of clinical origin, this may be of clinical significance. Some of the species within this genus do have reduced susceptibility to voriconazole, including *S. dehoogii*, and the recently renamed *Lomentospora prolificans* (formerly *S. prolificans*), mentioned earlier, which is resistant to all clinically available antifungals (Lackner et al. 2012). While the clinical relevance of reduced susceptibility to antifungal agents is not fully understood, with the exception of the resistance observed with *L. prolificans*, fur-

ther insights into the clinicopathology of infections caused by different *Scedosporium* species may be difficult to ascertain if these fungi are routinely lumped into a species complex.

Mucormycosis and the Order Mucorales

Pathogenic fungi of the Order *Mucorales* are capable of causing invasive infections termed mucormycosis. Organisms that have been associated with infections in humans include members of the genera *Rhizopus*, *Rhizomucor*, *Mucor*, *Cunninghamella*, *Lichtheimia* (formerly *Absidia*), *Saksenaea*, and *Apophysomyces* (Kontoyiannis and Lewis 2006; Mendoza et al. 2014; Kwon-Chung 2012; Petrikkos et al. 2012). Mucormycosis is a highly aggressive angioinvasive fungal infection that primarily occurs in immunocompromised hosts, including solid organ transplant recipients, hematopoietic stem cell transplant recipients, and hematologic malignancy patients receiving immunosuppressive chemotherapy (Kontoyiannis and Lewis 2006; Petrikkos et al. 2012). In addition, diabetic patients with poorly controlled disease have also been shown to be at risk for infections caused by members of the Order *Mucorales*. Mucormycosis has also been reported in otherwise healthy individuals following traumatic inoculation (Hospenthal et al. 2011; Neblett Fanfair et al. 2012). Infections caused by these fungi include rhino-orbital and rhino-cerebral disease, pulmonary, gastrointestinal, and cutaneous infections. Disseminated infections can also occur and are associated with high mortality rates (Kontoyiannis and Lewis 2006; Petrikkos et al. 2012). Aggressive treatment is needed in patients with mucormycosis, and this often involves multiple modalities including high-dose antifungal therapy and surgery when possible to remove infected and necrotic tissue (Kontoyiannis and Lewis 2006). However, in the setting of continued immunosuppression, clinical outcomes may be poor even with aggressive treatment. Furthermore, these species are also resistant to several antifungals, including voriconazole, the azole frequently used to treat other invasive mold infections such as invasive aspergillosis and scedosporiosis, and the echinocandins (Kontoyiannis and Lewis 2006; Almyroudis et al. 2007).

The name used to describe an infectious disease caused by members of the Order *Mucorales* has also been subject to change. In 1885, the first well-documented case was published by the German pathologist Paltauf, who used the term mycosis mucorina to describe a systemic infection with rhino-cerebral and gastrointestinal involvement (Kwon-Chung 2012; Paltauf 1885). The use of mucormycosis as the disease name was first used by Baker to describe an infection caused by members of the Order *Mucorales* in the 1950s (Baker 1956, 1957). Ajello et al. subsequently proposed the term zygomycosis to include infections caused by species from two separate orders: (1) *Mucorales*, including infections caused by species within the genera *Rhizomucor*, *Rhizopus*, *Mucor*, *Lichtheimia* (*Absidia*), *Apophysomyces*, and *Saksenaea*, and (2) *Entomophthorales*, due to *Conidiobolus* and *Basidiobolus* species (Ajello et al. 1976). Until recently, zygomycosis was the term frequently used

synonymously in the clinical literature with mucormycosis to describe infections caused by members of the Order *Mucorales*, in animal models of invasive infections caused by them, as well as in vitro antifungal susceptibility results against these organisms. However, there are major differences between species classified in the Orders *Entomophthorales* and *Mucorales*, including morphologic and epidemiologic differences, and in the types of infections that they cause (Mendoza et al. 2014; Petrikkos et al. 2012). While the pathogenic species within *Mucorales* cause acute invasive infections in immunocompromised hosts, chronic subcutaneous infections are often caused by the *Entomophthorales* and can often occur in immunocompetent individuals (Mendoza et al. 2014; Kwon-Chung 2012). In addition, the phylum *Zygomycota* has been eliminated, as it was found to be polyphyletic and had also not been validly described (Hibbett et al. 2007). Thus, mucormycosis and entomophthoromycosis have again been put forth as the proper terms used to describe infections caused by these different groups of fungi (Kwon-Chung 1994).

Phylogenetic studies within the Order *Mucorales* have resulted in several name changes in pathogenic species. Some examples of these include *Lichtheimia corymbifera* (formerly *Absidia corymbifera*), *Mucor circinelloides* f. *janssenii* (formerly *Mucor velutinosus*), *Mucor ardhlaengiktus* (formerly *Mucor ellipsoideus*), and *Mucor irregularis* (formerly *Rhizomucor variabilis*) (Walther et al. 2013; Alastruey-Izquierdo et al. 2010). Some clinical laboratories that do not routinely use sequence analysis for identification of fungi attempt to discriminate between species within the genera *Rhizopus* and *Mucor* by the presence or absence of rhizoids. However, these morphologic features are not specific to *Rhizopus* species and can be found in several *Mucor* species, including the clinically relevant species *M. circinelloides*. There is also some controversy regarding the name of one of the most prevalent causes of mucormycosis, *Rhizopus arrhizus* or *Rhizopus oryzae.* Although the names are synonymous, some have suggested that *R. arrhizus* is the correct species name since it was used previous to that of *R. oryzae* (1892 vs. 1895) (Dolatabadi et al. 2014). The name that is used may be of consequence as *R. oryzae* is more frequently used in the medical literature, and there is some suggestion that there may be differences in in vitro potency between the triazoles isavuconazole and posaconazole (Verweij et al. 2009; Gonzalez 2009; Thompson and Wiederhold 2010; Chowdhary et al. 2014). This is significant as both agents can be orally administered, thus possibly avoiding the need for long-term intravenous therapy with the nephrotoxic agent amphotericin B in patients with mucormycosis caused by this species. There is also some controversy as to whether or not the similar species *Rhizopus delemar* is a separate species or a variety of *R. arrhizus.* By molecular analysis using ITS alone and with multiple loci, several authors had demonstrated that *R. delemar* is indeed a phylogenetically distinct species (Dolatabadi et al. 2014; Abe et al. 2006, 2007). In addition, phenotypically *R. delemar* lacks the ldhA gene and is unable to produce lactic acid and instead forms fumaric and malic acid, while *R. arrhizus* contains two genes for lactate dehydrogenase and is therefore able to produce lactic acid (Abe et al. 2007; Saito et al. 2004). The genome sequence of a *R. delemar* strain previously classified as *R. oryzae* that was obtained from a fatal case of mucormycosis is also available (http://www.ncbi.nlm.nih.gov/

bioproject/13066) (Ma et al. 2009). However, zygospore formation has been reported in crosses between *R. delemar* and *R. arrhizus* strains, which has led some to suggest that these are the same species, even though the viability of the progeny could not be demonstrated (Dolatabadi et al. 2014). It is currently unknown if there is a clinical difference between *R. delemar* and *R. arrhizus.*

Conclusion

The introduction of molecular tools for the identification and classification of fungi has led to significant changes in fungal taxonomy and nomenclature. These changes have major implications for the field of medical mycology, which may be both beneficial and detrimental in the clinical setting. The correct identification of the species that is causing infection is important and can help guide therapy and ensure the use of appropriate antifungal agents. However, the rapid changes in fungal taxonomy may also lead to nomenclature instability in the clinical setting, and there is concern that this may impede access to clinically relevant literature. The changes in taxonomy and nomenclature are also currently outpacing our understanding of the clinical significance of newly classified cryptic species as well as how to effectively manage patients with infections caused by these organisms.

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