

Emerging Fungal Infections: New Species, New Names, and Antifungal Resistance

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BACKGROUND: Infections caused by fungi can be important causes of morbidity and mortality in certain patient populations, including those who are highly immunocompromised or critically ill. Invasive mycoses can be caused by well-known species, as well as emerging pathogens, including those that are resistant to clinically available antifungals.

CONTENT: This review highlights emerging fungal infections, including newly described species, such as *Candida auris*, and those that having undergone taxonomic classification and were previously known by other names, including *Blastomyces* and *Emergomyces* species, members of the *Rasamsonia argillacea* species complex, *Sporothrix brasiliensis*, and *Trichophyton indotinae*. Antifungal resistance also is highlighted in several of these emerging species, as well as in the well-known opportunistic pathogen *Aspergillus fumigatus*. Finally, the increased recognition and importance of fungal co-infections with respiratory pathogens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is discussed.

SUMMARY: Both clinicians and clinical microbiology laboratories should remain vi

gilant regarding emerging fungal infections. These may be difficult both to diagnose and treat due to the lack of experience of clinicians and laboratory personnel with these organisms and the infections they may cause. Many of these fungal infections have been associated with poor clinical outcomes, either due to inappropriate therapy or the development of antifungal resistance.

Introduction

Invasive fungal infections remain challenging to clinicians, especially in critically ill patients and those who are immunocompromised, either due to disease or immunosuppressive agents. Currently, it is estimated that there may be between 1.5 million to 5 million fungal species, of which at least 300 are associated with infections in humans (1). However, the number of fungi associated with infections in humans, animals, and plants is increasing with the emergence of new pathogenic fungi and our increased understanding of fungal taxonomy due to advances in molecular techniques and phylogenetic analyses. In addition, resistance to clinically available antifungals has increased in many well-known pathogens, and recently there has been a greater recognition of the importance of fungal co-infections with other microbes, including respiratory pathogens, which often lead to poor patient outcomes. This review will discuss emerging fungal infections, including those caused by newly reclassified species, the development of antifungal resistance in certain pathogens, and our increased understanding of fungal co-infections in patients with viral pneumonia. Examples of emerging fungal pathogens are shown in Fig. 1.

Candida Infections and *Candida auris*

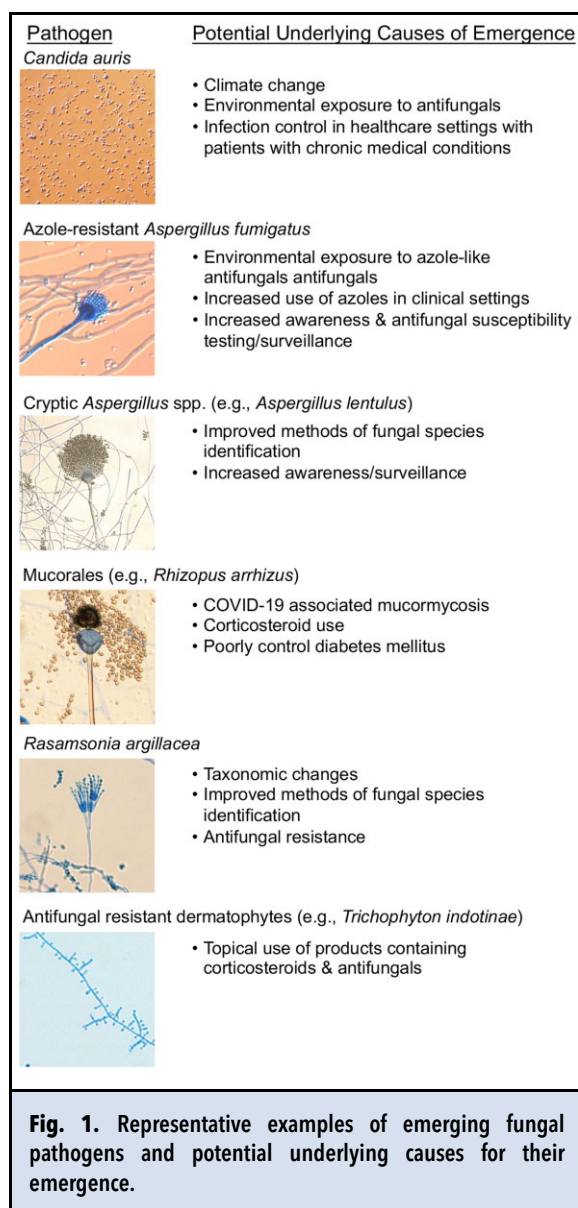
Candida species are common causes of invasive infections in patients with healthcare exposure, including bloodstream infections, which are associated with substantial morbidity and mortality (2). Although *C. albicans* is the most common species associated with invasive infections at many institutions, non-*albicans* species, including *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*, have emerged worldwide with higher rates of antifungal resistance, especially to fluconazole, an agent that is relatively inexpensive and well-tolerated and consequently has frequently been used to treat these infections (3). One species that has recently garnered attention in both the lay press and the medical literature is *Candida auris*. This is a relatively new species that was described in 2009, first isolated from the external ear canal of a patient in Japan (4), with the first invasive infections described in patients in South Korea in 2011 (5). This species has now emerged as a pathogen of substantial concern and has quickly spread to at least 47

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countries on several continents (5), with earlier reports of sporadic infections now being replaced by nosocomial outbreaks involving larger groups of patients. *Candida auris* is now endemic in South Africa and India accounting for 15% and between 5% and 30% of reported candidemia figures, respectively, in these countries (5, 6). An early study of 54 patients with invasive disease found candidemia in 61% with a mortality rate of 59% (7), while other studies have reported mortality rates between 30% and 60% (6). Many of the patients with invasive disease are elderly or have multiple comorbidities, including tracheostomies and the need for ventilator

support. In addition, the majority of isolates are resistant to fluconazole and many are multidrug resistant.

The exact origin of *C. auris* remains unknown, and no animal reservoir has been identified. Recently, isolates have been cultured from samples taken from the tropical marine ecosystem around the isolated Andaman Islands in the Indian Ocean, including a salt marsh area without human activity and a beach (8), which suggests an environmental source. Other have suggested that its emergence and spread may be multifactorial, including factors associated with healthcare (e.g., poor infection control practices in patients with multiple comorbidities), climate change and adaptations by the organism in response to rising temperatures and increased exposure to antimicrobials in the environment, and increased human contact with its natural niche (9).

Genomically, *C. auris* has been separated into 5 geographic clades, including: Clade I (South Asian clade), Clade II (East Asian clade), Clade III (African clade), Clade IV (South American clade), and Clade V (Iranian clade) (5). By whole genome sequencing, each clade differs by >10 000 single nucleotide polymorphisms (SNPs), while far fewer SNPs (range <16 to >70) were identified within each clade (7). The high number of SNPs between the clades and the low number within each clade suggests simultaneous emergence in multiple locations rather than a clonal source. Interestingly, there appear to be clade-specific antifungal resistance patterns with the majority of isolates in Clades I and III being fluconazole resistant, while those in Clade II are susceptible to antifungals. In the US approximately 90% of isolates are fluconazole resistant, 30% are resistant to amphotericin B, and 5% are also resistant to the echinocandins, which are currently the drugs of choice for the treatment of invasive infections (6). Acquired resistance to the echinocandins has also been documented in patients receiving treatment with this class of antifungals (6), and up to 4% of isolates to date have been resistant to at least one member of all clinically available antifungal classes (5).

In addition to invasive infections, *C. auris* frequently colonizes the axilla, groin, nares, respiratory tract, and urinary tract of patients, and the colonization rates are significantly higher in skilled nursing facilities caring for ventilated patients compared to facilities without ventilator support (5). Unfortunately, infections have been reported to develop in between 5% to 10% of colonized patients (5). This species has also been found on numerous objects within patient rooms and can also colonize healthcare workers (5, 6). Commonly used disinfectants in healthcare settings, including quaternary ammonium compounds, have limited activity against *C. auris* and are unable to eradicate the biofilms formed by this species (5, 6), allowing it to persist for several weeks on different moist or dry abiotic surfaces,

including linen, temperature probes, and blood pressure cuffs (10). For clinical microbiology laboratories, *C. auris* has been difficult to identify, as this organism may be misidentified as other yeast species when commonly used biochemical assays and automated systems are used (11). Although antifungal susceptibility testing is often performed on clinical strains as part of routine clinical diagnostic testing, no clinical breakpoints have been formally established to classify isolates as susceptible or resistant. The US Centers for Disease Control and Prevention has provided general guidance for classifying isolates as resistant to fluconazole, amphotericin B, and the echinocandins (12).

Unfortunately, there are now several reports of *C. auris* co-infections in critically ill patients with COVID-19. In one intensive care unit (ICU) setting in New Delhi, India, between April and July 2020, candidemia was diagnosed in 15 of 596 (2.5%) patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, of which 10 were due to *C. auris* (13). Most patients were elderly with chronic underlying comorbidities, including hypertension, diabetes mellitus, and chronic kidney or liver disease. Candidemia developed between 10 to 42 days post admission, and the fatality rate among those with *C. auris* candidemia was 60%. Similar outbreaks have been documented in other ICU settings in other countries, including the US, China, Mexico, and Lebanon, to name a few (14–16). In one report, improper use of personal protective equipment, and improper disinfection of shared medical equipment and hand hygiene were considered as likely contributors to *C. auris* transmission (14).

Aspergillosis Including Azole-Resistant *Aspergillus* and Co-Infections with Viral Pneumonia

Aspergillus species are important causes of invasive and chronic infections that typically involve the lungs, although dissemination to other organs can occur. Highly immunocompromised patients are one of the groups recognized as being at greatest risk for invasive disease, including those receiving highly immunosuppressive chemotherapies, those undergoing hematopoietic stem cell transplantation, and individuals receiving prolonged courses of high-dose corticosteroids for graft-versus-host disease (17). Of solid organ transplant recipients those who have received lung transplants are at higher risk, as the primary route of entry of *Aspergillus* is through inhalation into the lungs (18). *Aspergillus* spp. are also now increasingly recognized as important causes of mycoses in critically ill patients that traditionally have not been considered at high risk, including those with acute

chronic obstructive pulmonary disease (19, 20). In individuals with structural damage to the lungs, including those with tuberculosis or sarcoidosis, chronic pulmonary aspergillosis can occur, and studies have estimated that the prevalence of chronic pulmonary aspergillosis at approximately 3 million people worldwide (21, 22).

There is growing concern regarding increasing rates of azole resistance in *Aspergillus* species, particularly *A. fumigatus*, as the treatment of these infections is heavily reliant upon this class of antifungals. Historically, azole resistance in *Aspergillus* has arisen in patients with chronic azole exposure, and was first reported in the late 1990s in patients who were treated with itraconazole (23). Over the last two decades, several studies have reported increased rates of azole resistance in *A. fumigatus*, primarily in Europe, with rates as high as 28% reported in one center that cares for patients with chronic pulmonary aspergillosis who often receive long-term azole therapy (24). In the US, azole-resistant *A. fumigatus* may occur in 3.5% to 5% of clinical isolates (25). Mechanisms of azole resistance in *A. fumigatus* include point mutations within the *CYP51A* gene, which encodes the enzyme responsible for the last step in the ergosterol biosynthetic pathway, Cyp51A, and these can occur clinically with chronic azole exposure (26). However, for resistance to develop, clinical exposure to azoles is not necessary, as resistance has also been documented with environmental exposure to azole-like compounds used in agriculture and other settings (27–29). Indeed, invasive aspergillosis due to azole-resistant *A. fumigatus* has been described in azole-naïve patients (28, 29), which has now been documented worldwide (30, 31). In these isolates, point mutations in the *CYP51A* gene are accompanied by base pair tandem repeats within the promoter region of this gene leading to its increased expression (32, 33). The most prevalent of the environmental exposure mechanisms of resistance include TR₃₄/L98H, which results in pan-azole resistance, and TR₄₆/Y121F/T289A, which primarily affects voriconazole and isavuconazole. Isolates harboring such mutations have now been documented, including those cultured from patients and from environmental sources, in numerous countries around the world (23, 34). Recently, numerous mechanisms of azole resistance that are not *CYP51A* mediated have also been described. Examples include overexpression of efflux pumps, gain-of-function mutations in transcription factors, and mutations within *HMG1*, which encodes HMG-CoA reductase, a rate-limiting enzyme in the ergosterol biosynthetic pathway (35–37). Treatment options against azole-resistant infections are currently limited and usually consist of a lipid formulation of amphotericin B, which is problematic given the nephrotoxicity that can occur with prolonged administration and the need for intravenous access.

Both acute and chronic forms of aspergillosis are most often caused by a handful of species, including *A. fumigatus*, *A. flavus*, *A. nidulans*, *A. niger*, and *A. terreus*, with *A. fumigatus* being the most prevalent species at many institutions (17, 38). However, there are over 200 individual species within this genus, and surveillance studies in the US and Spain have reported rates of cryptic species, such as *A. lentulus*, *A. udagawae*, *A. tubingensis*, and *A. calidoustus*, higher than previously appreciated among clinical isolates (11% to 14.5%) (39, 40). This is important as several cryptic species have reduced susceptibility to different antifungals, and many have been associated with invasive disease in both humans and animals.

Recently, co-infections with respiratory viruses and *Aspergillus* have come into focus. Although an association between severe influenza and invasive pulmonary aspergillosis was described decades ago, we are now gaining a better understanding of influenza associated pulmonary aspergillosis (IAPA). In one retrospective, multicenter cohort study conducted in tertiary care ICUs in Belgium and the Netherlands, invasive pulmonary aspergillosis was diagnosed in 83 (19%) of 432 patients admitted with influenza a median of 3 days post ICU admission (41). In contrast, invasive pulmonary aspergillosis occurred in only 16 (5%) of 315 patients in the control group, which included those with severe community-acquired pneumonia but without influenza. The 90-day mortality was 51% in patients with IAPA compared to 28% in those with influenza but without invasive aspergillosis. Influenza was independently associated with invasive pulmonary aspergillosis, as was corticosteroid use. Interestingly, 43% of those with IAPA would not have been classified as having proven or probable invasive pulmonary aspergillosis per European Organisation for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria, as many in the influenza cohort lacked host factors since they were non-immunocompromised. It should be noted that not all studies have reported high IAPA rates, with one institution in Canada reporting an incidence of 7.2% over a 5-year period from 2014 to 2019 (42). Virus-induced anatomical and/or immunological changes are likely involved in the development of IAPA, and invasive *Aspergillus* tracheobronchitis (IATB) is an important manifestation of invasive aspergillosis in those with severe viral pneumonia. Plaques in the trachea and bronchi are observed due to epithelial erosion caused by viral replication, possibly providing a portal of entry for *Aspergillus* to cause invasive airway disease (43).

Invasive pulmonary aspergillosis has also recently been reported with COVID-19 disease (termed COVID-19-associated pulmonary aspergillosis, or CAPA). Studies have reported incidence rates of CAPA of between 1% to

33% in intubated patients (44–47), and overall mortality rates ranged from 44% to 74% (43). In contrast, mortality in similar patients with COVID-19 but without CAPA were between 19% to 39% (43). Similar to IAPA, corticosteroid use was also associated with CAPA, which in contrast with cases of influenza is recommended in patients with severe COVID-19 disease who are intubated or require supplemental oxygen (48). In addition, many patients with CAPA do not meet EORTC/MSG criteria for proven or probable invasive aspergillosis since they lacked host factors. However, some question whether CAPA represents a distinct entity and the clinical relevance of *Aspergillus* colonization in intubated patients with severe COVID-19 (47, 49).

Mucormycosis and COVID-19

Similar to invasive aspergillosis, mucormycosis is a well-known type of fungal infection. However, the incidence of this highly aggressive and destructive invasive mycosis has increased in several countries due to increases in the numbers of patients at risk, which includes those with poorly controlled diabetes mellitus, patients with profound neutropenia or other forms of immunosuppression, including the use of corticosteroids, and those suffering from major burns or through traumatic inoculation (50). The main route of infection is the inhalation of spores, which leads to pulmonary or rhino-orbital cerebral mucormycosis. Other forms of mucormycosis, including gastrointestinal disease which can occur following ingestion of these fungi, and cutaneous mucormycosis, which has been documented following traumatic inoculation of fungal elements, can also occur (50). Although *Rhizopus* species are the most common causes of mucormycosis, invasive disease can be caused by numerous species, including members of the genera *Apophysomyces*, *Cunninghamella*, *Lichtheimia*, *Mucor*, *Rhizomucor*, *Saksenaia*, and *Syncephalastrum*. The pathogenesis of mucormycosis is characterized by tissue invasion, hemorrhagic infarction, angioinvasion, and subsequent thrombosis leading to tissue necrosis (50). Even with appropriate treatment, mucormycosis is often associated with substantial morbidity and mortality.

Recently, there have also been numerous reports of mucormycosis in patients with SARS-Cov-2 infection, termed COVID-19-associated mucormycosis (CAM) (51–55). CAM has been documented in several countries, and many of these infections were identified during the second COVID-19 surge that occurred in India in the winter and spring of 2021 (52–55), with many of these patients suffering from rhino-orbital cerebral mycosis. Risk factors for CAM include poorly controlled diabetes mellitus and the use of systemic corticosteroids (52, 54, 55). In one large retrospective, observational study in India with COVID-19-associated rhino-orbital

cerebral mycosis, 87% of patients had received corticosteroids, and 78% were diabetic (52). Fifty-six percent of patients developed rhino-orbital cerebral mucormycosis within 14 days of the onset of COVID-19, but delayed manifestations were observed after 14 days in 44%. The mortality rate in patients with CAM in a large series that included 2826 patients was 14%, but this may underestimate the true mortality due to the short follow-up period in this study (mean 14.4 days) (52). These infections are associated with substantial morbidity, as vision loss often occurs in survivors of rhino-orbital cerebral disease (52, 55). The high incidence of CAM in India has been suggested to be due potentially to the injudicious use of corticosteroids

combined with the high prevalence of diabetes mellitus within its population (56).

Changes in Fungal Taxonomy and Recognition of Mycoses Due to New Species

There are many examples of fungi that are newly recognized as distinct species due to changes in fungal taxonomy brought on by phylogenetic analysis. Several of these are also now considered emerging pathogens, either due to increased awareness secondary to advances in diagnostic assays or concern due to antifungal resistance (Table 1). One new group of fungi that are increasingly recognized as potential pathogens in humans

Table 1. Examples of other newly recognized or reclassified fungal species of clinical significance, including some with resistance to antifungals.

Current name/classification	Previous name/classification	Clinical relevance
<i>Blastomyces helicus</i>	<i>Emmonsia helica</i>	<ul style="list-style-type: none"> Atypical and disseminated blastomycosis in immunocompromised humans and companion animals [Schwartz et al. (57)]. Cases reported in western states and provinces of US and Canada.
<ul style="list-style-type: none"> <i>Emergomyces</i> species <i>Emergomyces africanus</i> <i>E. canadensis</i> <i>E. europaeus</i> <i>E. orientalis</i> <i>E. pasteurianus</i> 	<i>Emmonsia</i> -like species	<ul style="list-style-type: none"> Disseminated infections in patients with advanced-HIV/AIDS [Kenyon et al. (58)]. Systemic infections in other immunocompromised patients [Schwartz et al. (59) and Spallone et al. (60)].
<i>Rasamsonia argillacea</i> species complex	<i>Geosmithia</i> species	<ul style="list-style-type: none"> Invasive disease in those with chronic granulomatous disease and hematologic malignancies, and colonization in cystic fibrosis patients [Houbraken et al. (61)]. Intrinsic resistance to voriconazole and isavuconazole [Houbraken et al. (61) and Steinmann et al. (62)]. Often misidentified as <i>Penicillium</i> or <i>Paecilomyces</i>.
<i>Sporothrix brasiliensis</i>	<i>Sporothrix schenckii</i>	Zoonotic transmission can occur with outbreaks in humans reported due to infected cats [Barros et al. (63) and Brandolt et al. (64)].
<i>Trichophyton indotineae</i>	<i>Trichophyton mentagrophytes</i> species complex (<i>T. interdigitale</i>)	Outbreaks of dermatophytosis with emerging resistance to terbinafine, fluconazole, and griseofulvin in patients in Northern India, leading to clinical failures in the treatment of tinea corporis/cruris infections [Singh et al., Tang et al., and Kano et al. (65-67)].

are the members of the *Rasamsonia argillacea* species complex. Previously classified as *Geosmithia*, members of this complex, which includes *R. argillacea*, *R. eburnean*, *R. piperina*, and *R. aerogroticola*, are commonly misidentified as *Penicillium* or *Paecilomyces* species by morphologic characteristics alone (61). Members of this species complex can cause invasive disease in those with chronic granulomatous disease and hematologic malignancies and chronic colonization of the respiratory tract in cystic fibrosis patients (61). Invasive disease has also been documented in cystic fibrosis patients undergoing lung transplants, and poor outcomes may result when inappropriate antifungal therapy is used due to being misidentified as another species, as members of the *Rasamsonia argillacea* species complex are intrinsically resistant to voriconazole and isavuconazole (62, 68).

Another fungal infection that may be caused by several newly described species is that of sporotrichosis. Sporotrichosis primarily occurs following minor trauma resulting in subcutaneous inoculation of the fungi, with infections being localized to subcutaneous tissues with extension through the lymphatic system (63). Inhalation of conidia can also occur resulting in pulmonary sporotrichosis and disseminated disease. Based on phylogenetic analysis, several species in addition to *Sporothrix schenckii* are now recognized, including *S. brasiliensis*, *S. globosa*, *S. mexicana*, *S. albicans*, *S. inflata*, and *S. luriei* (69). Species most commonly associated with human disease include *S. schenckii*, *S. globosa*, and *S. brasiliensis*. Zoonotic transmission can also occur, and outbreaks of sporotrichosis caused by *S. brasiliensis* and spread by infected cats have occurred in humans in different parts of Brazil, including Sao Paulo and Rio de Janeiro (64), with cases reported as far as Argentina (70).

Within the family Ajellomycetaceae there are several fungal pathogens capable of causing infections in humans, including members of the genera *Blastomyces*, *Histoplasma*, *Paracoccidioides*, and the recently described *Emergomyces*. First described as *Emmonsia*-like species in an outbreak of disseminated fungal infections primarily in HIV-positive individuals in South Africa (58), *Emergomyces* was reclassified as a new genus in 2017 (71), which consists of separate species, including *E. africanus*, *E. canadensis*, *E. europaeus*, *E. orientalis*, and *E. pasteurianus* (59, 60). Systemic infections in immunocompromised individuals have now been reported in several countries on different continents (60).

Blastomycosis is an endemic fungal infection that occurs in the US and Canada in areas around the Mississippi and Ohio river basins, those bordering the Great Lakes, and along the St. Lawrence River. In these regions blastomycosis is caused by *B. dermatitidis*, and to a lesser extent by the cryptic species *B. gilchristii*.

Several species of *Emmonsia* have now been reclassified into the genus *Blastomyces*, including *B. helicus* (previously *E. belica*), which causes atypical and disseminated blastomycosis in humans, primarily in immunocompromised individuals, and animals (57). Unlike *B. dermatitidis*, this species has been found in the western states and provinces of the US and Canada. Other new *Blastomyces* species capable of causing disease in humans have also been described in different parts of Africa and the Middle East, including *B. percursus* and *B. emzantsi* (72, 73).

Recently, there have been reports of outbreaks of dermatophytosis in southern Asia caused by *Trichophyton* isolates with elevated virulence and resistance to the commonly used antifungal terbinafine. These isolates have been associated with extensive infections of the trunk and groin areas, frequent relapses, and treatment failures. By molecular analysis, clinical isolates cultured from patients in northern India with these infections have fallen into *Trichophyton mentagrophytes* genotype VIII, which is now known as *T. indotinea* (65–67). In one study that performed antifungal susceptibility testing on 129 isolates collected over a 5-year period from northern India, 36% were considered to be resistant to terbinafine (minimum inhibitory concentration [MIC] range 4 to >32 µg/ml), 39.5% were resistant to fluconazole (MIC range 32 to >64 µg/ml), and 95% had elevated griseofulvin MICs (>2 µg/ml) (65). In each of the terbinafine-resistant isolates the amino acid substitutions L393F and F397L caused by mutations in the squalene epoxidase gene previously shown to confer resistance to this antifungal were found. Interestingly, these outbreaks and the shift from *T. rubrum* to *T. mentagrophytes* species complex isolates as the causative agent have coincided with the wide availability of topical corticosteroid creams, either alone, or combined with antifungals, including miconazole, clotrimazole, and terbinafine (66). Other reports have also documented terbinafine resistance in *Trichophyton* isolates, including members of the *T. mentagrophytes* species complex as well as in *T. rubrum* and *T. tonsurans* (65).

Conclusion

Over the last several years, there have been numerous reports of emerging fungal infections, many of which may be difficult to diagnose and treat and are associated with substantial morbidity and mortality in at-risk patient populations. Clinicians and clinical microbiology laboratories should remain vigilant toward these emerging fungal infections as well as the development of antifungal resistance, which can occur in both well-known pathogens and newly described fungal species. In addition, consideration should also be given to the emergence of fungal co-infections with other microbes,

including those caused by respiratory viruses, such as influenza and SARS-CoV-2. Some of these emerging fungal infections and those that cause co-infections with respiratory viruses have been associated with corticosteroid use.

Nonstandard Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CAPA, COVID-19-associated pulmonary aspergillosis; CAM, COVID-19-associated mucormycosis.

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