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Endemic Mycoses in Immunocompromised Hosts

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Abstract

Endemic mycoses remain a significant cause of morbidity and mortality among immunocompromised patients. As the number of immunosuppressed individuals increases worldwide, the incidence of endemic mycoses is also expected to rise. In immunocompromised patients, endemic mycoses can present in atypical fashion, cause more severe and/or disseminated disease, and result in higher mortality. Despite several noteworthy advances over the past decade, significant challenges remain with regard to the prevention, diagnosis and therapy of endemic mycoses in immunocompromised hosts. This review highlights important developments related to the epidemiology, diagnosis, treatment, and prevention of commonly encountered endemic mycoses. We also discuss emerging topics, knowledge gaps and areas of future research.

Keywords

Endemic fungi; endemic mycoses; *Blastomyces dermatitidis*; *Coccidioides immitis*; *Coccidioides posadasii*; *Histoplasma capsulatum*; *Paracoccidioides brasiliensis*; *Penicillium marneffei*; *Sporothrix schenkii*; immunocompromised; immunosuppressed

INTRODUCTION

The endemic mycoses (blastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, penicilliosis, and sporotrichosis) are caused by a heterogeneous group of fungi that occupy specific ecological niches in the environment and thus have circumscribed geographic ranges (Table 1), are thermally dimorphic, existing as molds in the environment and as yeasts (or spherules) within the human body, and are considered primary pathogens because they cause disease in healthy as well as immunocompromised hosts [1–3]. These pathogens are the cause of significant morbidity and mortality amongst immunocompromised hosts, including patients with hematologic malignancies,

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Compliance with Ethics Guidelines

Conflict of Interest

Trent R. Malcolm and Peter V. Chin-Hong declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

hematopoietic stem cell transplant patients, solid organ transplant recipients, those being treated with tumor necrosis factor (TNF)-alpha inhibitors, and those infected with HIV [4–6]. In many regions, increasing incidence of endemic mycoses correlates with a growing population of immunocompromised hosts [7, 8].

Although there have been noteworthy advances over the past decade, significant challenges remain regarding the prevention, diagnosis and treatment of endemic mycoses in immunocompromised patients. Host factors, including the net state of immunosuppression, and the burden of exposure are essential determinants of the clinical presentation, disease progression and outcome of endemic mycoses in a particular patient. In patients with impaired cellular immunity, endemic mycoses are more likely to manifest as progressive, severe or disseminated disease and tend to have significantly higher mortality (Table) [4, 9–12]. Although timely and reliable diagnosis improves outcomes, infections in immunocompromised hosts are more likely to elude diagnosis due to atypical clinical presentations and suboptimal sensitivities of traditional diagnostic assays [13]. Following diagnosis, immunocompromised patients frequently require prolonged therapy with antifungal agents that may have severe toxicities, profound drug-drug interactions, and rapidly evolving resistance profiles.

Solving these challenges will require the development of new and better prevention strategies, diagnostic technologies and therapeutic approaches. This goal can only be accomplished through a substantial multidisciplinary effort to further our understanding of the molecular biology, genomics, pathogenesis, ecology, and epidemiology of these endemic fungi. The purpose of this review is to highlight important recent advances in the field and to emphasize emerging topics that warrant further study; as such, this review is not intended to be comprehensive. We evaluated the current literature focusing on new advances in the epidemiology, clinical presentation, diagnosis, treatment, and prevention of commonly encountered endemic mycoses.

TRENDS IN THE EPIDEMIOLOGY OF ENDEMIC MYCOSES

The burden of endemic mycoses is increasing in regions throughout the world [7, 14] and will likely continue to rise as the population of immunocompromised hosts expands. Improved understanding of the incidence and epidemiology of endemic mycoses in immunocompromised hosts is needed to facilitate accurate estimation of exposure risk and enhance current prevention and management strategies. Numerous recent retrospective chart review studies have added important new information to our understanding of the risk factors, clinical presentation, emergence, management and outcomes of endemic mycoses in various regions throughout the world. These include reports of high rates of relapse (23%) and overall mortality (30%) among HIV/AIDS patients with disseminated histoplasmosis in Brazil [15], clinical presentation and management of patients that developed coccidioidomycosis while receiving biological response modifiers (BRMs) or disease-modifying anti-rheumatic drugs (DMARDs) for rheumatic diseases [16], and clinical presentation of histoplasmosis and penicilliosis among HIV/AIDS patients in Thailand [17]. In a case series of all published cases of proven *Penicillium marneffei* infection in Mainland China (N=668), Hu et al. [7] report that 87.7% of all cases occurred in HIV-infected

individuals. Although this reported emergence of penicilliosis may reflect an artifactual increase in incidence due to increased disease reporting, this finding underscores the opportunistic nature of endemic fungi in immunocompromised patients.

As reflected above, most of our knowledge on the epidemiology of endemic mycoses stems from case series and single-institution, retrospective surveys. A recently published study from three Midwest US transplant centers described the clinical presentation, diagnosis, treatment and outcomes among 30 solid organ transplant recipients with histoplasmosis (N=22) or blastomycosis (N=8) [4]. Overall, the cumulative incidence of endemic fungal infections in this population was low 0.50% (30/5989), a finding which is consistent with previously reported measurements from single-center studies [4, 18–20]. Although the majority of cases occurred within the first year after transplantation, 20% of cases occurred late, at five or more years following the transplant procedure, confirming that the timing of infection may vary widely in this population. Of note, the authors also noted that there was generally a significant delay between onset of initial symptoms and eventual diagnosis (median time to diagnosis:17 days (range 3–90 days)). This finding, which the authors speculate was likely associated with the non-specific presentation of endemic mycoses and problems associated with available diagnostic testing modalities, highlights common diagnostic challenges which frequently lead to treatment delays. Consistent with previous studies, this multi-center study reports a high rates of disseminated infection (>50%) among solid organ transplant recipients [4].

Although the results above suggest that the incidence of endemic mycoses is low in transplant recipients, the true incidence of endemic mycoses in most immunocompromised patient populations is unknown. This is because there are few longitudinal, population-based estimates. The Transplant-Associated Infection Surveillance Network (TRANSNET) was a large multi-center surveillance study of invasive fungal infections among solid organ and hematopoietic stem cell transplant recipients in the US. To date, this study is the most comprehensive attempt to estimate the burden of fungal infections in immunocompromised hosts [12, 21]. This study reported a 12-month cumulative incidence estimate of 0.2% for endemic fungal infections among solid organ transplant recipients [12]. To date, this study has not provided details on the clinical presentation, diagnosis and treatment of the specific endemic mycoses effecting patients included in TRANSNET.

It is recognized that the endemic mycoses have a relatively limited geographic range. There is little high-quality data on the true geographic ranges of the endemic fungi and much of the data has not been updated with environmental changes that are affecting many parts of the world. Most data on the geographic range of endemic mycoses comes from aggregated case reports or, as in the cases of coccidioidomycosis and histoplasmosis in North America, outdated studies of skin testing for coccidioidin or histoplamsin sensitivity in healthy adults [22]. Given that geographic distribution is a defining factor of an endemic mycosis, the lack of high-quality spatial data on species distribution is surprising and attempts to refine our understanding of the true geographic distribution of most endemic fungi are conspicuously absent in the recent literature. A recently completed study used historical data for all dogs tested for coccidioidomycosis between 1999 and 2009 to estimate the spatial distribution of *Coccidiodes* spp. in Texas [23]. Results from more than 6000 samples of dog sera were

georeferenced to zip code and maps of seropositivity rates were created using standard Bayesian smoothing techniques and kriging (i.e. inference of values for unobserved areas using geostatistical methods). Although the scale of the study is limited and the direct applicability to human infection unknown, this is an important first step toward developing higher resolution maps necessary for estimating geographic variation in human exposure risk to endemic mycoses [23].

To further complicate the issue of endemicity, many immunocompromised patients may have had exposure to endemic mycoses at earlier stages in their lives. Many individuals move from one region to another to obtain additional education, training or work. Furthermore, individuals may have traveled through an endemic region at some point in their lives. As such, careful history of travel and residence should be obtained from all transplant candidates and recipients to determine the risk of infection by an endemic mycosis and to trigger screening for specific endemic mycoses, as appropriate [24].

NEW DIAGNOSTIC TOOLS

Due to high rates of disseminated disease and mortality in immunocompromised patients, timely diagnosis and prompt initiation of appropriate therapy are essential. Multiple diagnostic modalities are currently available, but each has significant limitations. Diagnosis of endemic mycoses may be hampered by a host of factors including low clinical suspicion among practitioners [25], non-specific clinical presentations, inadequate access to appropriate laboratory tests, slow growth rates in culture, reduced seroreactivity among immunocompromised patients [13, 26], and cross-reactivity of antigen testing [27, 28]. The need for more rapid and accurate diagnostic tests has spurred considerable research evaluating the sensitivity and specificity of existing modalities as well as the next generation of tools.

Although there is evidence to suggest that the sensitivity of widely used diagnostic tests is lower in immunocompromised hosts, this question has not been extensively studied. One recent study evaluated serologic testing for coccidioidomycosis in solid organ transplant recipients [29]. In this retrospective chart review of all solid organ transplant recipients (N=2246) from a single institution between January 1999 and August 2011,27 (1.2%) patients with newly acquired, symptomatic or active coccidioidomycosis were identified. The results of diagnostic tests, including serology results (enzyme immunoassay [EIA], immunodiffusion [ID], and complement fixation [CF]), were tabulated for each patient with proven or probable disease. The positivity of any single serological test ranged from 21% to 56% (EIA IgM 28%, EIA IgG 56%, ID IgM 21%, ID IgG 38%, CF≥1:2 28%), but was 77% for any one positive result among a battery of tests [29]. In addition, positive predictive value increased with repeated testing over time. These findings confirm that, until better tests become available, a multi-faceted approach to diagnostic testing remains necessary in immunocompromised hosts. Unfortunately, the study was unable to estimate true sensitivity and specificity because it did not include patients without disease. Further studies that directly compare the performance of diagnostic modalities in immunocompromised versus immunocompetent hosts are also needed. Given the variability of the diagnostic yield for the various serologic tests, the clinician should familiarize themselves with the sensitivity and

specificity values provided by the reference lab that specimens are sent to. Additionally, given the potential variability in the assays performed as various reference labs, sending specimens to two or more experiences specialized laboratories may increase the diagnostic yield if you suspect an endemic mycosis infection but initial testing is negative.

Antigen detection of serum, respiratory secretion, urine or CSF samples can facilitate the diagnosis of several of the endemic mycoses. There are specific antigen assays for histoplasmosis, blastomycosis and coccidioidomycosis. The yield of these assays is higher in the presence of disseminated infections; detection of urine histoplasma antigen is positive in up to 95% of immunocompromised patients with disseminated infections [28]. There is cross-reactivity of the various endemic-mycosis specific antigen assays; false positive results have been documented with histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, penicilliosis and rarely aspergillus. As a result, additional testing such as direct detection of the endemic mycosis itself is often required. This may be via culture or molecular assay from the infected tissue.

Given the known limitations of conventional diagnostic modalities, discovery of new molecular diagnostic methods is an area of active research and rapid advancement. In recent years, numerous molecular methods have been developed and evaluated to improve the identification of endemic mycoses, including real-time PCR assays for blastomycosis and histoplasmosis [30–32], multiplex PCR for histoplasmosis [33], nested PCR assays for identification of histoplasmosis in HIV-infected patients [34], multiplex suspension array identification of multiple species [35], and PCR identification of sporotrichosis [36]. Parallel efforts to map the genomes of important fungal pathogens continue to inform the rational development of these diagnostic methods. A recently published whole genome transcriptomics analysis of *Histoplasma capsulatum* provides fertile data for further studies of diagnostic and therapeutic targets [37]. Such advancements in genomics and molecular diagnostics have the potential to revolutionize diagnosis of endemic mycoses in immunocompromised patients.

NOVEL THERAPEUTIC AGENTS

Treatment of endemic mycoses in immunocompromised patients has traditionally required prolonged therapy with conventional antifungal agents that have low efficacy, side effects, toxicities, potentially severe drug-drug interactions and antifungal resistance. During the past decade, however, there have been many treatment advances including development of lower-toxicity lipid-based formulations of amphotericin B, development of a new generation of azole antifungals (voriconazole and posaconazole), and updated consensus guidelines for practitioners [10, 38–40]. Despite these noteworthy advances, there is a need for further research and development of additional therapeutic options.

Comparative genomics is an area of active research with significant promise for identifying potential antifungal drug targets. In recent years, the genomes of numerous fungi, including *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracocidioides brasiliensis* and *Histoplasma capsulatum*, have been sequenced in full [41]. This information can used in comparative genomics studies to identify genes which are putatively essential in pathogenic

organisms but absent in the human genome. Employing this strategy, four genes (*trr1*, *rim8*, *kre2*, *erg6*) were recently identified as potential drug targets for the endemic fungi listed above as well as *Candida albicans* and *Cryptococcus neoformans* [41]. Efforts are now underway to virtually screen existing chemical libraries for potential therapeutic agents [41].

Although genomic studies may ultimately extend the frontier of antifungal therapeutics, important efforts are also ongoing to refine treatment strategies using existing agents. Based on evidence that quinolone antibiotics may also have antifungal activity, the *in vitro* interaction between ciprofloxacin and amphotericin B, itraconazole, voriconazole and caspofungin against *H. capsulatum* and *C. posadasii* has recently been studied [42]. With the exception of ciprofloxacin and voriconazole against *H. capsulatum* in yeast form, most tested combinations of ciprofloxacin and antifungal drugs resulted in significant minimum inhibitory concentration (MIC) reductions against both species. The *in vitro* inhibitory effect of farnesol against *C. posadasii* in combination with antifungal agents was also recent tested and farnesol was associated with significantly decreases in the MICs for itraconazole and voriconazole and acts synergistically with amphotericin B and caspofungin [43]. Although studies of these combinations in patients are needed, these data highlight the potential for synergistic combination antimicrobial therapy as a promising adjuvant in cases of disseminated or refractory mycoses.

NEW PREVENTION STRATEGIES

Given the limitations in existing therapeutic agents and treatment protocols, improved strategies for the prevention of fungal infections are needed. In recent years, significant effort has been dedicated to the development of vaccines for blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis [44–51]. Although numerous experimental vaccines hold promise, there are currently no anti-fungal vaccines in clinical trials or approved for human use [52].

Development of vaccines suitable for use in immunocompromised hosts is particularly problematic given the difficulty of inducing immunity in the absence of a normal immune response. A recent mouse model of vaccination against blastomycosis demonstrated that functional memory $CD8^+$ T cells are maintained for at least six months in the absence of $CD4^+$ T cells [53, 54]. Another study found that immunity against blastomycosis in this model is likely mediated by IL-17-dependent signaling of neutrophils [53]. Taken together, these two recent studies demonstrate the potential for $CD8^+$–mediated vaccines in patients with low $CD4^+$ counts, such as transplant recipients, but considerable research is needed to translate these findings to a human vaccine.

EMERGING TOPICS

Although a rare complication, infectious diseases transmitted from donor tissues are increasingly recognized as a significant cause of morbidity and mortality among solid organ transplant recipients [24, 55]. Reports of such donor-derived transmission events, including transmission of endemic mycoses, have increased in recent years [55]. Recently, multiple reports of donor-derived coccidioidomycosis have garnered attention. Disseminated

coccidioidomycosis was documented in three solid organ transplant recipients that received organs from a single organ donor [56]. The donor was a 52-year old homeless woman from an endemic region that was found disoriented on the street and later discovered to have had previously unrecognized meningeal coccidioidomycosis. Two of the three recipients died as a result of the infection; the third recovered after receiving appropriate therapy. In a second, similar report, three of five organ recipients from a single donor in a non-endemic region developed *Coccidioides* infection, resulting in one fatality [25].

Such unfortunate outcomes highlight the difficulty of diagnosing donor-derived endemic mycoses in immunocompromised patients, particularly in non-endemic regions. In these areas, diagnosis may be delayed due inadequate access to diagnostic testing, lack of routine screening in potential donors and recipients [56], and low index of suspicion [25]. Timely diagnosis may also be hampered by the low sensitivity of serologic testing in immunocompromised patients [29] and the inherent delays associated with awaiting definitive cultures [25].

In light of these challenges, multiple authors have underscored the importance of obtaining a detailed travel history in potential organ recipients and donors in order to adequately evaluate for potential exposure to *Coccidioides* spp. [57–59]. Although it is more difficult to obtain a detailed travel and medical history in deceased organ donors, efforts should be made to obtain this history from next of kin at the time of organ procurement [57]. Additionally, such fatalities due to donor-derived coccidioidomycosis have also led to calls for routine screening of potential organ recipients and donors [56, 59]. However, available serologic tests lack sensitivity for use as routine screening tools and are not reliable for distinguishing active infection from previous exposure [60]. At present, some institutions in endemic regions routinely screen living organ donors for *Coccidioides* spp. infection but there is no standard policy for screening of deceased donors [60]. Similarly, without more accurate estimates of the incidence of donor-transmitted coccidioidomycosis, it is not possible to make evidence-based decisions regarding use of prophylactic antifungal treatment in organ recipients [61].

On a larger scale, international efforts are underway to better understand the epidemiology of donor-derived disease transmission and implement policies intended to mitigate the risk of such unexpected infectious disease transmissions [24, 55, 62, 63]. In the United States, the Organ Procurement and Transplantation Network (OPTN) requires notification of the organ procurement organization any time that a transplant program has knowledge or substantial concern that a transmissible disease in an organ recipient may be of donor origin [63]. Such notification is intended to enable expert panel evaluation of potential donor-derived transmission events, permit timely diagnosis and treatment of infection in other patients that received organs from the same donor, and facilitate improved epidemiological study of such events [55, 63]. OPTN also mandates routine screening of potential donors for certain pathogens, including HIV, HBV, HCV, syphilis, human T-lymphotropic virus, CMV and EBV [55]. However, routine screening for fungal infections is not required currently by OPTN policy in the United States. The American Society of Transplantation (AST) Infectious Disease Community of Practice recently developed detailed guidelines to help the community understand the optimal donor evaluation to prevent donor-derived fungal

infection transmissions and to optimally manage them in organ transplant recipients when they do occur [24].

CONCLUSION

In recent years, considerable progress has been made toward improving our understanding of endemic mycoses on multiple fronts. These range from fungal genomics to international epidemiology. The rapidly evolving fields of molecular biology and comparative genomics have the potential to revolutionize diagnostic technologies and therapeutic agents and basic science advances in the development of new antifungal agents and new vaccines continue to progress at a rapid pace. In addition, in the digital age, practitioners will soon be able to harness datasets encompassing information on host and pathogen genetics, host immune status, geographic distribution of pathogens, and environmental risk factors to estimate the risk of infection for individual patients. Such individualized risk modeling will play a critical role in guiding rational selection of antifungal prophylaxis and treatment regimes for immunocompromised hosts. However, to realize this goal, further research is needed to characterize the true geographic distribution and incidence of endemic mycoses throughout the world.

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Table 1

Geographic distribution and clinical presentation of endemic mycoses.

Endemic Mycoses	Organism(s)	Geographic Distribution	Clinical Presentation		References
			Immunocompetent Hosts	Immunocompromised Hosts	
Blastomycosis	*Blastomyces dermatitidis*	North America; principally within the Mississippi River basin, Ohio River basin, Great Lakes region and Southeastern USA.	Generally subclinical or self-limiting pulmonary infection. Uncommon severe pneumonia and extrapulmonary infection.	Relatively uncommon, but presents with severe pneumonia and/or extrapulmonary dissemination frequently involving skin, bones, joints, genitourinary system and CNS.	[3, 6]
Coccidioidomycosis	*Coccidioides immitis* *Coccidioides posadasii*	Arid and semi-arid regions within the Southwestern USA, northern Mexico and Brazil.	Generally subclinical (~60% asymptomatic) or self-limiting pulmonary infection. Rare chronic or extrapulmonary infection.	Up to 30–50% with extrapulmonary dissemination, frequently involving skin, bones, and meninges.	[2, 3, 64]
Histoplasmosis	*Histoplasma capsulatum*	Temperate zones worldwide; principally Mississippi and Ohio River basins of the USA, Central America, Southeast Asia and the Mediterranean.	Generally asymptomatic (~90%) or self-limiting pulmonary infection. Rare severe or extrapulmonary infection.	Severe pneumonia and/or extrapulmonary dissemination frequently involving the gastrointestinal tract, adrenal glands, and skin. Uncommon severe CNS manifestations.	[2, 39, 40]
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*	Regions of Central and South America; principally Brazil, Argentina, Uruguay, Paraguay, Peru, Venezuela, Colombia and Ecuador.	Generally asymptomatic pulmonary infection which may progress to chronic (>90%) or acute/subacute disease. Commonly disseminates to mucosa, skin, adrenal glands and CNS.	Infrequently reported among immunocompromised hosts, but more likely to be associated with disseminated disease and relapse.	[65]
Penicilliosis	*Penicillium marneffei*	Tropical Asia; principally Thailand, Vietnam, Taiwan, Northwestern India, and Southern China.	Generally asymptomatic pulmonary infection. Rare extrapulmonary dissemination.	Chronic disseminated disease with cutaneous lesions and lymphadenopathy.	[7]
Sporotrichosis	*Sporothrix schenkii* species complex	Tropical and temperate regions; principally Japan, India, Mexico, Brazil, Uruguay, USA and Peru.	Cutaneous nodules and ulceration. Uncommon pulmonary infection. Rare visceral dissemination.	Osteoarticular, pulmonary, mucosal, disseminated, and systemic infections. Widespread cutaneous ulceration.	[66]