Dematiaceous Molds

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KEYWORDS

• Dematiaceous molds • Phaeohyphomycosis • Chromoblastomycosis
• Eumycetoma • Fungal meningitis • Opportunistic infections • Emerging molds

KEY POINTS

- Dematiaceous fungi are a heterogenous group of environmental molds characterized by dark pigmentation, distributed worldwide.
- These fungi most commonly cause cutaneous and subcutaneous diseases but can also disseminate and affect the central nervous system, resulting in high morbidity and mortality in both immunocompetent and immunocompromised individuals.
- Effective diagnosis relies on early clinical suspicion, followed by confirmatory mycological, histopathological, or molecular methods.
- Treatment typically involves source control, reducing immunosuppression when applicable, and systemic antifungal therapy, commonly using itraconazole, voriconazole, or posaconazole.
- There is a growing global initiative to raise awareness, enhance surveillance, and advance research in diagnostics and therapeutics for dematiaceous molds.

INTRODUCTION

Dematiaceous fungi are a diverse group of molds commonly found in environments rich in soil or decaying vegetation. Characterized by melanin-like pigments in their cell walls, these fungi exhibit colors ranging from pale brown to black. Over 150 species and 70 genera have been identified.[1] Considered opportunistic fungi—where exposure is common, but disease development is rare—they are medically significant, often affecting vulnerable patient populations with compromised immunity or those with heightened exposure related to socioeconomic factors.

These melanized fungi cause phaeohyphomycosis, a condition that encompasses a wide spectrum of clinical manifestations, including cutaneous, subcutaneous, and systemic diseases. The most commonly implicated genera include *Bipolaris*, *Cladophialophora*, *Exophiala*, and *Alternaria*. Disease can occur in both immunocompetent

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and immunocompromised individuals, with differing pathogenesis, species predilection, and disease manifestations. For example, central nervous system (CNS) infections, though rare, have been reported in individuals with intact immune systems, particularly when the fungi are introduced into sterile spaces via trauma, allowing them to evade the innate immune system.[2,3] Dematiaceous molds also cause cutaneous conditions such as chromoblastomycosis and eumycetoma, which are important neglected tropical diseases (NTDs).[1,4]

This review focuses on clinical syndromes that are significant due to host, microbial, environmental, and iatrogenic factors with outbreak potential. The researchers address the challenges in timely diagnostics and therapeutic approaches due to under-recognition of the disease, variability in diagnostic availability, and the lack of robust evidence-based recommendations given the low disease prevalence. Additionally, the researchers highlight the potential role of newer antifungals in treatment.

EPIDEMIOLOGY

Dematiaceous fungi are a heterogenous group of molds found in soil and plant matter worldwide. Despite their ubiquitous environmental presence, they rarely cause disease. Surveys of outdoor air often detect fungal spores, highlighting common exposure routes through inhalation and minor, often unnoticed, trauma, which is frequently related to occupational activities.[5] Invasive disease caused by these fungi is rare in immunocompetent individuals, with most infections considered opportunistic.[1] The genera most frequently involved in human infections include *Bipolaris*, *Curvularia*, *Exserohilum*, and *Alternaria*.[1]

Recent trends indicate an increasing incidence of dematiaceous fungal diseases.[6–8] A study from a single cancer center in the United States demonstrated a more than 3 fold increase in the incidence of invasive phaeohyphomycosis over 15 years (1993–2008), although the incidence remained low at approximately 3 cases per 100,000 patient-days.[9] Additionally, a comprehensive review of 174 cases of phaeohyphomycosis in China from 1987 to 2021 observed that the number of cases in the past 20 years is approximately 6.6 times higher than 20 years ago.[10] This increase is attributed to a growing number of vulnerable hosts with compromised immunity, as well as improved diagnosis due to heightened disease awareness, advancements in detection techniques, and improved microbiologic and genetic testing.

PATHOGENESIS

The mechanisms by which dematiaceous fungi cause disease, especially in immunocompetent individuals, remain poorly understood. However, melanin production within the fungal cell wall has been shown to be a key virulence factor found in all genera of this group.[11] Melanin is proposed to scavenge-free radicals and hypochlorite produced by phagocytic cells during their oxidative burst, which is necessary for eradicating phagocytosed organisms.[12] Studies in animal models show that disrupting genes involved in melanin production reduces virulence.[13] Furthermore, melanin can reduce the activity of antifungals such as amphotericin B and caspofungin, though not azoles.[14] Additionally, some dematiaceous fungi can develop resistance to antifungals by increasing melanin production.[15]

The melanized cell wall also confers protection against environmental stressors, including ultraviolet irradiation, enzymatic lysis, and extremes of temperature.[16] Thermotolerance, an important virulence factor for fungal pathogenicity, contributes to the dissemination and cerebral localization of several clinically significant neurotropic

molds, including *Cladophialophora bantiana*, *Exophiala dermatitidis*, *Verruconis gallopava* (formerly *Ochroconis gallopava* or *Dactylaria gallopava*), *Cladophialophora modesta*, *Cladophialophora emmonsii,* and *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*).[1,3]

RISK FACTORS

The occurrence of invasive dematiaceous mold disease is influenced by factors that govern microbial exposure burden and/or host immune response (**Table 1**). The most common risk factor identified in a recent comprehensive review from China, which reported on 174 cases of phaeohyphomycosis over the past 35 years, was trauma. This predisposing factor is particularly relevant for individuals in occupations such as agriculture, fishery, forestry, mining, construction, and sanitation.[10] Another Chinese study of 47 cases supports this association with occupational risk, noting a predominance of farmers (57%) and men (57%).[17] Climate also plays a role, with more cases being reported in tropical or subtropical areas.[10]

Conditions that reduce protective host immunity include iatrogenic immunosuppression in the setting of malignancy or organ transplantation, diabetes, corticosteroids use, and malnutrition.[18] Inherited or acquired mutations affecting the interleukin (IL)-17 pathway also increase the risk of fungal infections, including phaeohyphomycosis.[19] For example, caspase recruitment domain-containing protein 9 (CARD9) deficiency disrupts cytokine production following immune cell stimulation with fungal ligands, affecting neutrophil recruitment to infection sites, and impairing IL-17 immunity, leading to impaired antifungal defenses.[20] Similarly, T-helper 17 cell deficiency has been associated with a predisposition to phaeohyphomycosis.[21]

NOTABLE OUTBREAKS

Dematiaceous fungi have become a significant public health concern following a series of outbreaks associated with contaminated medical products. Notably, in 2012,

Table 1
Risk factors for dematiaceous fungal disease

Risk Factor	Description
Immunosuppression	Solid organ and bone marrow transplant recipients, use of immunosuppressive medications (eg, corticosteroids, chemotherapy), secondary fungal disease following respiratory viral outbreaks (eg, influenza, COVID-19)
Underlying Health Conditions	Diabetes, malignancies, malnutrition
Genetic Predisposition	Inherited CARD9 deficiency, Th17 cell deficiency
Trauma	Exposure through minor, unnoticed injuries
Occupational Exposure	Agriculture, fishery, forestry, mining, construction, sanitation
Environmental Factors	Tropical/subtropical climates, climate change
Socioeconomic Factors	Manual labor occupations with more environmental exposure, disease progression due to residence in regions with limited access to expertise and diagnostics
Nosocomial Outbreaks	Incidents related to contaminated medical products and solutions leading to widespread infections

Abbreviations: CARD9, caspase recruitment domain-containing protein 9; COVID-19, coronavirus disease 2019; Th17, T helper 17 cells.

use of methylprednisolone contaminated with *Exserohilum rostratum* for epidural injections led to a multistate fungal meningitis outbreak, resulting in 751 cases of CNS infection and 64 deaths across the United States.[22]

Future outbreaks of fungal disease from environmental contamination of sterile products are likely to occur, as evidenced by historic precedents (**Table 2**) and a recent multinational outbreak of nosocomial meningitis caused by *Fusarium* among immunocompetent individuals who received epidural anesthesia in Mexico.[27]

The coronavirus disease 2019 (COVID-19) pandemic has also heightened awareness of mycoses. The widespread use of corticosteroids in severe COVID-19 cases has been associated with opportunistic fungal diseases, most notably mucormycosis and aspergillosis.[28] Cases of cerebral phaeohyphomycosis caused by *Fonsecaea* and *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*) have also been reported from the Middle East[29,30] and India[31] following use of corticosteroids for COVID-19 in older patients with diabetes.

CLINICAL SYNDROMES

For a comprehensive review of clinical syndromes, we refer to other detailed reviews.[1,32] Here, we focus on the main syndromes from a clinician's perspective. While there are no standard therapies for each syndrome, reported approaches are listed in **Table 3**, and more generalized approaches are discussed in a separate therapeutics section.

Superficial and Deep Local Diseases

Dematiaceous fungi most commonly cause superficial diseases, typically resulting from minor traumatic abrasions or environmental exposure. Cutaneous diseases are generally indolent, involving gradually enlarging masses. While these diseases are rarely life-threatening, they can still result in significant morbidity depending on the affected area and response to therapy. Commonly implicated genera in cutaneous and subcutaneous diseases include *Alternaria*, *Exophiala*, *Bipolaris*, and *Phialophora*, which can also cause oculomycosis, rhinosinusitis, and onychomycosis.

Keratitis

Though uncommon, keratitis caused by dematiaceous fungi accounts for 8% to 17% of keratitis cases. The majority of cases occur in tropical regions including India, where traumatic inoculation is implicated in up to 20% to 47% of patients.[36,46] Frequently implicated genera include *Curvularia*, *Bipolaris*, *Exserohilum*, and *Lasiodiplodia*.[1]

Eumycetoma and Chromoblastomycosis

Eumycetoma and chromoblastomycosis are chronic diseases of the skin and subcutaneous tissue, often caused by traumatic inoculation of dematiaceous fungi. Both are classified as NTDs by the World Health Organization (WHO) and have the highest incidence in tropical and subtropical regions, particularly in Africa and Latin America.[47,48]

Eumycetoma is characterized by the formation of granules in the tissue and can be caused by various fungi, such as *Exophiala jeanselmei*, *Leptosphaeria senegalensis*, *Trematosphaeria grisea* (formerly *Madurella grisea*), *Madurella mycetomatis*, and *Medicopsis romeroi* (formerly *Pyrenochaeta romeroi*). Chromoblastomycosis is marked by thick-walled muriform cells with intersecting cross-walls (sclerotic bodies). Commonly involved fungi include *Cladophialophora carrionii*, *Fonsecaea compacta*, *Fonsecaea pedrosoi*, and *Phialophora verrucosa*.

Table 2
Notable outbreaks caused by dematiaceous fungi reported from 2002 to 2016

Year	Location	Fungal Species	Source of Contamination	Number of Cases	Antifungal Therapy Used
2002[23]	North Carolina, United States	*Exophiala dermatitidis*	Contaminated epidural and intraarticular injections	5 (1 death)	Amphotericin B, Voriconazole
2012[24]	Multistate, United States	*Exserohilum rostratum*	Contaminated methylprednisolone injections	751 (64 deaths)	Voriconazole, Amphotericin B, Itraconazole, and Posaconazole[25]
2016[26]	New York City, United States	*Exophiala dermatitidis, Rhodotorula mucilaginosa*	Contaminated intravenous flush solution	17 (3 deaths)	Voriconazole, Posaconazole, Liposomal Amphotericin B

Table 3
Clinical syndromes and therapeutic approaches for diseases caused by dematiaceous fungi

Syndrome	Common Genera	Risk Factors	Therapeutic Consideration
Superficial and Deep Local Infections	*Alternaria, Bipolaris, Exophiala, Phialophora*	Trauma, immunocompromised status	Itraconazole or voriconazole; surgical debridement if necessary; cryotherapy, laser, heat and photodynamic therapy[33–35]
Keratitis	*Alternaria, Curvularia, Exserohilum, Bipolaris*	Trauma, tropical regions	Topical agents (eg, 5% natamycin and amphotericin B with or without topical azoles), oral azoles in severe and refractory cases; possible surgical intervention[36,37]
Eumycetoma	*Exophiala jeanselmei, Madurella mycetomatis, Medicopsis romeroi*	Tropical, subtropical regions, low socioeconomic status, manual workers	Long-term antifungal therapy (eg, itraconazole, voriconazole, or posaconazole, in combination with terbinafine or flucytosine), surgical excision in advanced cases[35,38]
Chromoblastomycosis	*Cladophialophora carrionii, Fonsecaea compacta, Fonsecaea pedrosoi, Phialophora verrucosa*	Tropical and subtropical climates, poverty, agricultural workers[39]	Itraconazole, terbinafine, posaconazole; surgical excision, cryotherapy[40]
Allergic Fungal Sinusitis	*Bipolaris, Curvularia, Exserohilum, Alternaria*	Atopic patients, immunocompetent	Corticosteroids, antifungal therapy (eg, itraconazole)[41]
Pulmonary Infection	Exophiala, Chaetomium, Verruconis	Immunocompromised	Voriconazole, liposomal amphotericin B
CNS infection	*Cladophialophora bantiana, Rhinocladiella mackenziei, Exophiala dermatitidis, Exophiala asiatica*	Immunocompetent and immunocompromised	Voriconazole, posaconazole, or amphotericin B; combination therapy with triazole plus an echinocandin plus flucytosine; surgical excision of abscesses, reversal of immunosuppression[42]
Disseminated infection	*Lomentospora prolificans, Bipolaris spicifera, Exophiala dermatitidis*	Immunocompromising conditions (malignancy, organ transplant), diabetes, asthma[32]	Liposomal amphotericin B, itraconazole, voriconazole, or posaconazole; reduction in immunosuppression. For Lomentospora infections, combination therapy (eg, voriconazole plus terbinafine)[34,43–45]

Allergic Fungal Sinusitis

Dematiaceous molds can cause hypersensitivity reactions without invasive disease, especially in immunocompetent, atopic-prone patients. The main genera implicated are *Bipolaris* and *Curvularia*.[49] The burden of allergic cases attributed to these molds exceeds that linked to *Aspergillus* species.[50]

A notable syndrome is allergic bronchopulmonary mycosis (ABPM), characterized by severe hyperimmune responses to molds in the lower airways and elevated immunoglobulin E (IgE) levels.[51] ABPM cases have been linked to non-*Aspergillus* species such as *Curvularia* and *Bipolaris*. Fewer than 200 cases have been reported worldwide, but this may be an underestimation due to under-recognition by medical providers and a lack of serologic testing.

Pneumonia

Pulmonary disease can arise from direct inoculation or as an end-organ manifestation of disseminated disease.[32,52] Colonization with dematiaceous fungi prior to transplantation has been linked with subsequent pneumonia in lung transplant patients.[52] Pulmonary involvement is even more common in stem cell transplant recipients compared to those who received solid organ transplant.[7]

Central Nervous System Disease

CNS diseases caused by melanized fungi are rare but cause significant morbidity, with mortality rates exceeding 70% regardless of immune status.[2,53] These infections can arise from extension from adjacent paranasal sinuses, penetrating head trauma, contaminated wounds, and hematogenous spread from an initial pulmonary focus.[54]

A review of 101 cases of culture-proven primary CNS phaeohyphomycosis from 1966 to 2022 reported that *C bantiana* and *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*) were frequently isolated species.[2] Other causative fungi include *E dermatitidis* (formerly *Wangiella dermatitidis*), *V gallopava* (formerly *O gallopava*), *F pedrosoi*, and *Bipolaris spicifera* (formerly *Drechslera spicifera*). Brain abscess was the primary clinical manifestation, and more than half of the cases occurred in individuals without known immunodeficiencies.

Among immunocompromised individuals, most cases occur in solid organ transplant recipients,[55] patients with malignancies,[56] or those living with human immunodeficiency virus and substance-use disorder.[57] *V gallopava*, a neurotropic dematiaceous mold, causes pulmonary and CNS infections in immunocompromised individuals.[58] In a study of transplant recipients, the CNS was involved in 50% of patients with *V gallopava* infection, often resulting in poor outcomes.[59] CNS disease related to contaminated glucocorticoids or other injectable solutions is discussed separately earlier.

Disseminated Disease

Disseminated disease caused by dematiaceous fungi is uncommon and mainly affects immunocompromised individuals. A review of 72 cases of disseminated disease found that 76% had immune dysfunction, with 18% being transplant recipients.[32] Eosinophilia was observed in 11% of cases. Blood cultures were positive in over half of the cases, with most identified as *Lomentospora prolificans* (previously *Scedosporium prolificans*), which has a case fatality rate exceeding 70%.

In a review of 162 cases of *L prolificans*, all individuals with disseminated disease had underlying immune dysfunction, most commonly from a hematological malignancy (80%). Blood cultures were positive in 70% of those with disseminated disease.[43,60] Neutropenia, fever, and cerebral symptoms were predictive of disseminated disease,[60]

and malignancy, fungemia, and CNS and lung involvement were predictive of poor clinical outcomes.[43] *Scedosporium* and *Lomentospora* infections account for 25% of all non-*Aspergillus* mold infections in organ transplant recipients.[61]

L prolificans is inherently resistant to all currently approved antifungal drugs, presenting a significant therapeutic challenge.[62] No antifungal regimens, including multiple combination therapies, have been shown to improve survival in disseminated infection.[32,60] Recognizing this challenge, *L prolificans* is categorized as a medically important fungus in the medium priority group on the 2022 WHO fungal priority pathogen list.

DISEASES IN RECIPIENTS WITH ORGAN TRANSPLANT

Solid organ transplant recipients (SOTRs) are particularly at risk for dematiaceous fungal infections due to their net state of immunosuppression. Within the Transplant Associated Infection Surveillance Network database, a large multicenter prospective cohort study of invasive fungal diseases in solid organ and stem cell transplant recipients, phaeohyphomycosis accounted for 2.6% of all invasive fungal diseases.[7] These diseases typically occurred in the late posttransplant period and presented with a wide range of clinical manifestations, predominantly involving the skin and the respiratory tract. Similarly, in a retrospective study of 3441 SOTRs followed at a single US health care center from 1988 to 2009, 27 developed phaeohyphomycosis of which 89% had manifestations limited to the skin.[6]

Cutaneous lesions often have a predilection for the lower extremities and a nodular appearance on examination, which correlates with granulomatous findings on histopathology. Dematiaceous fungal disease should be considered in the differential diagnosis of any chronic skin lesions in SOTRs with low threshold for skin biopsy.[63] Visceral diseases involving the lungs, brain, and bloodstream are much less common.[1]

Alternaria and *Exophiala* species are associated with skin, soft tissue, or joint diseases, while *V gallopava* has been linked to systemic invasive diseases, including brain abscesses. Mortality rates depend on underlying comorbidities and extent of disease; overall mortality is 7% for these diseases but can increase to 32% to 87% in disseminated disease.[64] **Table 4** summarizes key studies of SOTRs with dematiaceous fungal diseases.

DIAGNOSIS

The approach to diagnosis relies heavily on a high index of clinical suspicion along with appropriate mycological investigation.[35,67] The traditional foundation of dematiaceous fungi identification is the observation of colony and microscopic morphology in conjunction with physiologic characteristics. All dematiaceous molds are pigmented, spanning a wide range of colors. The specific coloration can also vary based on environmental conditions.[1] Under light microscopy, dematiaceous molds demonstrate hyphae associated with distinct structures (eg, ascomata, perithecia, ascospores, and conidia), enabling genus and sometimes species level identification.[1] Physiologic characteristics may also assist in further separating various genera/species; biochemical profiling for dematiaceous fungi may utilize the differential growth on cycloheximide and salt-containing media, urease and nitrite production, and carbohydrate utilization.[1]

In the absence of or to provide complementary information to culture-based methods, histopathological detection directly from biopsy samples leverages the ability Gomori methenamine-silver and periodic acid-Schiff stains to enhance visualization of fungal cell walls and highlight local tissue inflammation (**Fig. 1**).[68] Black-colored

Table 4
Key studies of dematiaceous fungal diseases in organ transplant recipients

Study	Population	Median Months Posttransplant	Common Disease	Mortality
Singh et al,[65] 1997	34 SOT (50% kidney, 24% liver, 24% heart)	22	Cutaneous (79%), disseminated (21%)	Cutaneous (7%), disseminated (57%)
Schieffelin, et al,[6] 2014	27 SOT (41% kidney, 33% heart, 11% lung), 1988–2009	20	Cutaneous (89%), pulmonary (4%), CNS (4%), disseminated (4%)	7% due to disseminated disease
McCarty et al,[7] 2015	30 SOT (53% lung, 20% kidney, 10% heart), 26 SCT (43% allogeneic, 8% autologous), 2001–2005	23 (SOT), 3 (SCT)	Disseminated (55%) Cutaneous disease more common in SOT vs SCT; pulmonary disease more common in SCT vs SOT	25% overall, 42% SCT, 10% SOT
Radcliffe et al,[64] 2022	94 SOT (44% kidney in EU, 91% kidney in non-EU), 2011–2022	18	Mostly localized to skin, disseminated (22%)	5% overall
Lo Porto et al,[66] 2023	201 SOT (61% kidney, 10% liver, 13% heart, 12% lung), 1973–2022	31	Cutaneous (73%), CNS (11%), disseminated (11%)	7% overall, 32% among disseminated disease

Abbreviations: CNS, central nervous system; EU, European Union; SCT, stem cell transplant; SOT, solid organ transplant.

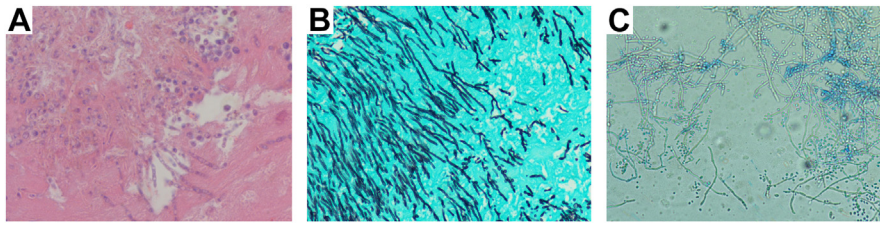

Fig. 1. Visualization of fungal elements in heart valve tissue identified from culture as *Exophiala dermatitidis*. (*A*) Hematoxylin and eosin (H&E) stain, 40X magnification. (*B*) Grocott's methenamine silver (GMS) stain, 40X magnification. (*C*) Tease preparation, 40X magnification. (*Courtesy of* Phyu M. Thwe, PhD and Selin Kurt, MD, Department of Pathology, Montefiore Medical Center, Bronx, New York.)

granules of melanin pigment, which lend dematiaceous fungi the moniker "black mold," may be discernible, particularly in tissues with visible pigmentation. If pigmentation is not apparent on direct visualization, Fontana–Masson staining can be used to detect melanin.[68] The presence of melanin, however, is not pathognomonic for dematiaceous mold as other fungal genera (eg, *Aspergillus* and *Mucorales*) can also produce melanin.

Contemporary diagnostics utilize modern molecular techniques and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) as adjunctive methods to obtain species-level identification. Next-generation sequencing and polymerase chain reaction (PCR)-based sequencing allow identification of dematiaceous fungi to genus level or below based on unique genetic "barcodes," most commonly the internal transcribed spacer or large subunit region of ribosomal DNA.[69] Other DNA-based methods primarily used in research include PCR assays, denaturing gradient gel electrophoresis, and microarray systems. MALDI-TOF MS holds significant promise as a method of rapid detection of these molds; however, identification is limited by the reference spectra within a database, which may not be available for less common dematiaceous fungi.[70]

Interpretation of these diagnostic data must be contextualized within the clinical presentation and requires a high degree of clinical suspicion. Dematiaceous fungi can transiently reside on body surfaces and are common culture contaminants given their ubiquitous distribution in the environment[1]; proven or probable disease requires evidence of tissue invasion or isolation from sterile sites.[71] There are unfortunately no serologic or antigen-based tests to facilitate discrimination of invasive disease.

TREATMENT

The cornerstone of management is source control, either alone in the case of limited cutaneous infection or in combination with antifungal treatment in the case of deep and/or disseminated disease.[34,35] Other adjunctive measures include modifying the degree of immunosuppression when applicable and considering immunotherapy options such as transfused leukocytes,[72] colony-stimulating factors, interferons, and interleukins, although these remain mostly investigational at this time.[54] When antifungal therapy is indicated; however, there is no clear consensus on the optimal agent or appropriate duration of therapy, nor is there an established correlation between in vitro minimum inhibitory concentrations and patient outcomes, which hinders the determination of antifungal susceptibility. Without any clinical trials to guide management, guidelines rely on a combination of in vitro, animal model, and small-scale observational studies informed by expert opinion.[34,35]

The greatest clinical experience is with oral itraconazole and voriconazole, supported by the most consistent in vitro activity against dematiaceous fungi. Voriconazole may be considered for CNS infections as it achieves better cerebrospinal fluid levels.[73] Posaconazole and isavuconazole are considered reasonable alternatives and/or salvage regimens.[34,35] Fluconazole, however, has minimal efficacy,[35] and ketoconazole is often associated with treatment toxicity at the doses and duration necessary to achieve cure.[35] Amphotericin B is a common alternative regimen, which is generally efficacious against dematiaceous molds although treatment failures are seen in scedosporiosis and lomentosporiosis.[34]

In cases of disseminated or refractory disease, combination therapy with an azole and amphotericin B is often considered.[34,35] There are also in vitro data and anecdotal in vivo evidence to support use of other systemic antifungals, such as terbinafine and flucytosine, in combination with azoles.[1,44,74] Treatment duration is dictated by clinical response and often requires months of antifungal therapy.

In the future, novel antifungal agents may provide additional treatment options for dematiaceous molds. Fosmanogepix, a Gwt1 enzyme inhibitor, shows the broadest in vitro activity against rare molds.[75] Ibrexafungerp,[76] a first-in-class triterpenoid, and olorofim,[77–80] a new dihydroorotate dehydrogenase enzyme inhibitor, also demonstrate selective efficacy among the dematiaceous fungi. Opelconazole, an inhaled triazole, and rezafungin, an echinocandin, have not been studied for this indication.

CHALLENGES IN DIAGNOSING AND TREATING DEMATIACEOUS FUNGAL DISEASES

Epidemiologic Challenges

The epidemiology of rare molds remains poorly elucidated, with scare incidence and prevalence data to define the geographic and demographic variations in disease burden. These molds are often underdiagnosed due to under-recognition by medical providers and limited availability of existing diagnostics.[10] A review of 174 phaeohyphomycosis cases reported in China over the past 35 years revealed a misdiagnosis rate as high as 74%, with nearly 19% resulting in poor quality of life due to disability, disfigurements, and blindness.[10]

Additionally, surveillance for antifungal resistance in dematiaceous mold remains limited, although data of resistant isolates in a single-center study in Malaysia[81] and in other types of fungi[82,83] suggest that antifungal resistance is emerging as a public health challenge. With the ubiquitous use of antifungal prophylaxis in specific immunocompromised populations, there has also been a noticeable shift toward breakthrough infections with non-*Aspergillus* molds, including those that are intrinsically azole resistant and difficult-to-treat.[83]

Rise in Vulnerable Populations

Although dematiaceous molds are rarely pathogenic, the at-risk population is growing due to the development and expansion of novel immunomodulating therapies, including small molecule kinase inhibitors, immune checkpoint inhibitors, and chimeric antigen receptor T cells. Despite the rising incidence of opportunistic fungal diseases, which are associated with significant morbidity and mortality, awareness of and surveillance for dematiaceous molds remain limited.[84–86]

Impact of Climate Change

Climate change is a critical driver of changes in the epidemiology of invasive fungal diseases.[87] Global shifts in temperature and weather patterns enhance microbial adaptability to stressors, increase virulence, and extend the geographic range of

microbes. Dematiaceous molds, which predominantly reside in soil and plant environments in tropical and subtropical climates, are being exposed to these selective pressures.[88,89]

Socioeconomically vulnerable groups are often disproportionally impacted by the effects of climate change, which can drive outbreaks and increase spread of fungal organisms.[88,90] Dematiaceous mold infections are already associated with occupational exposures linked to low-income status or residence in under-resourced regions. NTDs like chromoblastomycosis and eumycetoma are likely to experience shifts in their etiologic agents and geographic distribution due to climate change[88,89] and primarily affect impoverished populations.[39,91] Mycology expertise and advanced diagnostic capabilities, however, are typically concentrated in major academic centers, creating disparities in diagnosis and treatment.[92]

Global Efforts and Initiatives

The WHO's inclusion of chromoblastomycosis and eumycetoma as NTDs,[93] the addition of eumycetoma causative agents and *L prolificans* to the 2022 fungal priority pathogen list, and initiatives like the "One World—One Guideline" highlight the increasing recognition and commitment of various national and international societies to address the challenges posed by emerging fungal diseases.[34,94–96] Given the infeasibility of conducting traditional clinical trials for these rare conditions, novel study designs are necessary to generate evidence for therapeutics.[97] Funding will be a crucial component in this response, particularly for rare and neglected diseases where it is often negligible.[98]

SUMMARY

Dematiaceous fungi pose a risk to both immunocompetent and immunocompromised individuals, primarily causing superficial and subcutaneous diseases but also leading to systemic diseases with significant morbidity and mortality. The incidence of dematiaceous mold diseases continues to grow in part due to medical advancements in immunotherapy, global increases in predisposing comorbidities such as diabetes, and greater recognition of viral-associated fungal infections during the recent pandemic. Additionally, historic outbreaks from contaminated solutions injected into sterile spaces are alarming and raise concerns about potential recurrences.

Significant challenges persist in the clinical care of vulnerable populations with dematiaceous mold diseases, including misdiagnosis or delayed diagnosis and limited therapeutic evidence to guide management, largely due to the rarity of the disease. Climate change-driven shifts in fungal distribution and increasing selective pressure for azole-resistant molds further exacerbate these challenges. These issues highlight the urgent need for a global effort to enhance awareness, surveillance, and research into diagnostics and therapeutics for dematiaceous mold diseases.

CLINICS CARE POINTS

- Maintain high clinical suspicion for diseases caused by rare fungi, such as dematiaceous molds, in the appropriate clinical context, particularly in immunocompromised individuals or those with significant environmental exposure factors.
- Progressive skin lesions, often resulting from unnoticed trauma, on the extremities of immunocompromised individuals should be biopsied for histopathology and culture.

- To treat most of the disease syndromes caused by dematiaceous molds, itraconazole, voriconazole, and posaconazole are commonly used. Voriconazole is preferred for cases involving the CNS.
- Over half of CNS diseases caused by dematiaceous molds occur in immunocompetent individuals, most commonly involving *C bantiana*. This infection should be considered in the differential diagnosis in the appropriate clinical setting when common microbes have been ruled out.
- Molds have been implicated in historic fungal meningitis outbreaks related to the use of contaminated medical products, such as injectable steroids. Most treatment experience involves voriconazole and posaconazole.
- Emerging evidence suggests a possible role for newer antifungals such as fosmanogepix and ibrexafungerp, which have shown in vitro efficacy against dematiaceous molds.

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DISCLOSURE

The authors have nothing to disclose.

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