



Published in final edited form as:

Clin Microbiol Rev. 2026 June 11; 39(2): e0008525. doi:10.1128/cmr.00085-25.

Contribution of fungal diseases to the U.S. chronic disease burden

Ria R. Ghai¹, Kaitlin Benedict¹, Tom M. Chiller¹, Nancy A. Chow¹, Ian P. Hennessee¹, Sophie Jones¹, Shawn R. Lockhart¹, Meghan Lyman¹, Dallas J. Smith¹, Mitsuru Toda¹, Jeremy A. W. Gold¹

¹Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

SUMMARY

Chronic diseases, defined as conditions that persist for 1 or more years and require ongoing medical attention or impede daily life, represent an urgent public health challenge in the United States. In the last decade, fungal infections have garnered increased attention from public health officials and the media owing to the rapid and global rise of severe and antifungal-resistant infections. It is well-established that certain chronic diseases can increase the risk of invasive fungal infections. However, the inverse relationship—how fungal infections contribute to the development or exacerbation of chronic diseases—is less well studied. In this review, we summarize the current literature on the role of fungal infections in the development of chronic diseases, discussing pathophysiologic mechanisms and examining how chronic conditions can arise from the direct effects and sequelae of fungal infections. In addition, we discuss how the toxic effects of antifungal therapies can also contribute to the development of chronic disease states. Overall, our review highlights the significant yet underexplored role of fungal infections in the burden of chronic disease and emphasizes the need for further research, improved surveillance, increased public and healthcare awareness, and better access to diagnostics and treatments to address this issue.

Keywords

antifungal agents; infectious disease; chronic; fungi; public health; antifungal resistance; diabetes; asthma/allergy; *Candida*; molds

Address correspondence to Ria R. Ghai, RGHai@cdc.gov.

AUTHOR CONTRIBUTIONS

Ria R. Ghai, Conceptualization, Writing – original draft, Writing – review and editing | Kaitlin Benedict, Conceptualization, Supervision, Writing – review and editing | Tom M. Chiller, Writing – review and editing | Ian P. Hennessee, Writing – review and editing | Sophie Jones, Writing – review and editing | Shawn R. Lockhart, Conceptualization, Writing – review and editing | Meghan Lyman, Conceptualization, Writing – review and editing | Dallas J. Smith, Conceptualization, Writing – review and editing | Mitsuru Toda, Conceptualization, Writing – review and editing | Jeremy A. W. Gold, Conceptualization, Supervision, Writing – original draft, Writing – review and editing.

Peer Reviewer Peter G. Pappas, University of Alabama, Tuscaloosa, Alabama, USA

Clinical Microbiology Reviews acknowledges the input of its peer reviewers, who may individually opt for their names to be included in the details for this article or otherwise remain anonymous.

The authors declare no conflict of interest.

INTRODUCTION

Chronic diseases represent an urgent public health challenge. The Centers for Disease Control and Prevention (CDC) defines chronic diseases as conditions that persist for 1 or more years and require ongoing medical attention or impede daily life (1). In the United States, 60% of adults live with at least one chronic disease, while 42% live with two or more (2). These diseases not only adversely affect individual health outcomes but also impose a considerable economic burden, accounting for nearly 90% of the nation's \$4.5 trillion annual healthcare expenditures (1, 3).

Certain chronic diseases can increase the risk of invasive fungal infections. Since many disease-causing fungi are opportunistic, chronic diseases that cause immunosuppression, whether from the disease itself or associated treatments, can predispose people to invasive fungal infections. Patients with cancer, for example, may be immunocompromised for many reasons, including cytotoxic chemotherapy (4). Studies estimate that 5%–15% of patients with acute myeloid leukemia are affected by invasive aspergillosis and invasive candidiasis, with mortality rates of 28%–42% and 23%–40%, respectively (5). Similarly, people with uncontrolled diabetes mellitus are more susceptible to mucormycosis, a rare but life-threatening infection caused by fungi from the order Mucorales. This increased susceptibility occurs because of persistent hyperglycemia, which interferes with innate immune cell activity and function (6). Other chronic diseases that are not broadly immunosuppressive can still increase the risk of fungal infection. For example, chronic obstructive pulmonary disease (COPD), the third leading cause of death worldwide, can cause structural lung damage including cavitations that may facilitate allergic bronchopulmonary aspergillosis and, in a subset of patients, chronic pulmonary aspergillosis (7). In the last decade, fungal infections have garnered increased attention from public health officials and the media owing to the rapid and global rise of severe and antifungal-resistant infections (8).

While some chronic diseases increase the risk and severity of fungal infections, the inverse relationship—how fungal infections contribute to the development or exacerbation of chronic diseases—is poorly understood. This is despite fungal diseases causing an estimated 8 to 49 million years of healthy life lost due to illness, disability, or early death globally (9), suggesting a considerable yet underappreciated burden of chronic disease. In this review, we summarize the current literature on the role of fungal infections in the development of chronic diseases, discussing pathophysiologic mechanisms and examining how these conditions can arise from (i) the direct effects and sequelae of fungal infections, and (ii) the toxicity associated with antifungal therapies. This review does not address how non-infectious exposures to fungi (e.g., fungal sensitization) or their associated mycotoxins may result in chronic disease. By highlighting key research findings and gaps in the relationship between fungal infection and chronic disease, we aim to provide a foundation for future investigations and inform integrated care strategies for at-risk populations.

FUNGAL INFECTIONS CAN RESULT IN CHRONIC DISEASE

Infection-associated chronic conditions are long-term health conditions that are triggered by infectious diseases. Well-known examples include post-treatment Lyme disease syndrome and long COVID (10, 11). Regardless of the causative agent, many patients with infection-associated chronic conditions suffer from symptoms that include fatigue that interferes with daily life, cognitive impairment (brain fog), chronic pain or malaise, immune dysfunction, and sleep problems (12). Despite these conditions being debilitating, they are often under-researched, under-funded, and thus poorly understood by the medical community (13). This is especially true of fungal infections, which are not yet well-recognized as a contributor to infection-associated chronic conditions as compared with bacterial or viral agents.

Nevertheless, more than 1 billion people contract fungal infections globally each year (14). Most infections are relatively mild and self-limiting, resolving with a brief course of antifungal medication or without treatment. However, certain fungal infections can result in a chronically diseased state, either due to persistent infection that requires long-term to lifelong antifungal therapy or to lasting organ damage that necessitates ongoing medical management. Because of underreporting and misdiagnosis, the true prevalence of fungal infections is likely substantially underestimated, and the resultant burden associated with chronic fungal disease is largely unknown (15).

Fungal infections and the subsequent development of chronic diseases are influenced by several factors, including the level of exposure to the pathogen, the pathogen's virulence, and the patient's immune status (Fig. 1). These elements collectively determine not only the likelihood of infection but also the progression of the disease. For example, a well-documented genetic risk factor associated with chronic or recurrent fungal infections is Caspase Recruitment Domain-containing Protein 9 (CARD9) deficiency, which results from autosomal recessive loss-of-function mutations in the CARD9 gene. CARD9 is a crucial adaptor molecule in the innate immune system that transduces signals from pattern recognition receptors—especially C-type lectin receptors such as Dectin-1—following fungal recognition (16, 17). These signaling pathways activate downstream transcription factors like NF- κ B and MAPKs, promoting the production of proinflammatory cytokines and chemokines essential for neutrophil recruitment and antifungal activity (18, 19). Patients with CARD9 deficiency are therefore susceptible not only to acute invasive fungal infections but also to persistent and recurrent fungal infections (20, 21). Overall, impaired signaling in CARD9 deficiency compromises early fungal clearance, which permits pathogens to persist. This persistence might drive repeated cycles of inflammation and tissue injury, potentially contributing to the development of fibrosis, organ dysfunction, and chronic disease states (22). Notably, CARD9 mutations do not impair general immunity but specifically compromise the host's ability to mount effective responses against fungal pathogens, underscoring the importance of innate immune signaling in fungal control and the potential for these mutations to promote chronic diseases.

In the sections below, we explore examples of fungal infections that can cause chronic diseases, organizing our discussion by the affected body systems and including immunologic and epidemiologic reasons for chronic disease.

Respiratory disease

Certain pulmonary fungal infections have the potential to develop into chronic disease. A notable example is chronic pulmonary aspergillosis (CPA), a complex chronic lung infection primarily caused by fungi from the *Aspergillus fumigatus* species complex. Unlike invasive aspergillosis, which primarily affects immunocompromised people, CPA typically occurs in immunocompetent people with conditions that compromise lung integrity, including tuberculosis, nontuberculous mycobacterial infections, and COPD, among others (23, 24). CPA symptoms are progressive, starting with cough, hemoptysis, weight loss, and fatigue (Table 1) (25). Cavitory lesions and fibrosing disease tend to progress over time, causing gradual declines in lung function and worsening quality of life and structural lung damage, which can become irreversible. The overall prognosis of CPA is poor; a systematic review and meta-analysis including 79 studies and 8,778 patients found an overall pooled mortality rate of 27%, with 15% at 1 year and 32% at 5 years (26). Medical management is also complicated by comorbidities, complex clinical presentation, toxicity associated with long-term antifungal use, and increasing antifungal resistance (24).

Patients with CPA may exhibit immunological abnormalities that can negatively affect disease progression and outcomes. Approximately 58% of patients with CPA experience lymphocyte depletion (62). Depletion of CD3 cell counts, which occurred in 33% of CPA patients in one study, was associated with multi-cavitory CPA disease, indicating a correlation between T cell depletion and more extensive pulmonary involvement (62). A study that stimulated cytokine production among patients with CPA and healthy volunteers also found that patients with CPA have impaired interferon gamma (IFN- γ) production, which correlated with worse outcomes and increased mortality (63). These results highlight the need for comprehensive immune assessment and management in patients with CPA.

Because *Aspergillus* and other environmental molds are prevalent throughout most indoor and outdoor environments, complete avoidance is impractical for patients at risk of severe infections (64). However, certain strategies might help reduce the risk of exposure and disease development. Healthcare facilities implement strategies to minimize exposure for the most at-risk patients, such as using HEPA filtration and maintaining positive pressure in rooms occupied by patients who have recently undergone hematopoietic stem cell transplantation (65). Immunocompromised patients are encouraged to avoid participating in mold cleanup efforts after natural disasters, as these events can elevate the risk of invasive mold disease. For instance, a surveillance study conducted after Hurricane Harvey in Houston, Texas, revealed a rise in the incidence of invasive mold infections, with an in-hospital all-cause mortality rate of 24.2% among affected patients (66). The growing popularity of inhalational products, such as vaping, raises further concerns regarding mold exposure. A large commercial health insurance study found that cannabis use was associated with a higher prevalence of specific fungal infections, particularly aspergillosis (67). This underscores the current recommendations for certain immunocompromised populations, such as those with solid organ transplants, to avoid smoking cannabis and highlights the need for further research to develop effective strategies for mitigating these risks (68).

Another notable respiratory fungal disease associated with chronic disease is coccidioidomycosis, a condition caused by *Coccidioides* spp. In the United States, cases

of coccidioidomycosis, also known as Valley fever, occur primarily in the Southwestern U.S. states of Arizona and California. National surveillance detected 59,655 cases during 2019–2021 (69), although burden estimates suggest the number of symptomatic cases may be 10 to 18 times higher (70). In approximately 5% of cases, acute infection fails to resolve. Chronic pulmonary coccidioidomycosis develops as necroses and abscesses perpetuate infection, typified by fibrosis and scarring. Often, lung granulomas form, which can vary in size and distribution but are commonly composed of epithelioid cells, multinucleated giant cells, and lymphocytes (71). In chronic *Coccidioides immitis* infections, the lungs have biapical fibronodular lesions with retraction and cavitation, making the chest radiographs distinct from those of acute disease (72). Th2 lymphocytes are believed to be a primary defense against infection; therefore, people with Th2 deficiency or dysfunction are at greater risk of progressing to chronic or disseminated disease (38, 71). Further complicating diagnosis and management, chronic pulmonary coccidioidomycosis can mimic tuberculosis, influenza, or pneumonia, presenting with symptoms like cough, fatigue, headache, joint pain, weakness, and weight loss that can last several months (Table 1) (28, 73). Prolonged systemic symptoms, including low-grade fever and malaise, may persist for months or years following initial infection. In these instances, long-term antifungal therapy is often required to manage the disease and prevent further progression (38).

Like coccidioidomycosis, histoplasmosis, usually caused by *Histoplasma capsulatum* species complex in the United States, is a respiratory fungal disease primarily contracted through inhalation of airborne environmental spores. In the United States, 3,595 histoplasmosis cases were reported to public health surveillance during 2019–2021, primarily in the Eastern region of the country (69). Acute pulmonary histoplasmosis may infect immunocompetent people and typically causes mild illness. Although rare, some acute cases may develop into chronic cavitary pulmonary histoplasmosis, particularly in patients with emphysema (74). Common symptoms include chronic cough, dyspnea, fatigue, fever, hemoptysis, night sweats, and weight loss (Table 1) (74). As the disease progresses, persistent cavitation, development of pulmonary fibrosis, and progressive pulmonary insufficiency are common (32, 75). Clinically, chronic cavitary pulmonary histoplasmosis is difficult to distinguish from pulmonary tuberculosis, which poses a challenge to timely diagnosis and management. The disease is also associated with poor prognosis, perhaps exacerbated by misdiagnosis that delays appropriate treatment (32). In patients who died, average illness duration was 6 years and death resulted from progressive lung cavitation and loss of lung function (32, 76). Most information on chronic cavitary pulmonary histoplasmosis originates from historic case series. Therefore, little is known about present-day prevalence or immunologic mechanisms underlying this disease.

In addition to causing a chronic disease state, some disease-causing fungi, including *Aspergillus* and *Coccidioides*, may also worsen asthma outcomes or predispose people to asthma development. In an age- and sex-matched study, patients with both asthma and coccidioidomycosis had worse asthma outcomes, including more asthma medication, corticosteroid receipt, and healthcare visits than patients with only asthma or only coccidioidomycosis (77). Another study used a large U.S. health insurance claims database to show that 13% of 1,657 patients with coccidioidomycosis received new asthma diagnosis codes or asthma medication within a year, a higher proportion than in comparison cohorts

(78). While the precise mechanism behind this relationship has not been identified, induction of chronic airway inflammation and airway hyperresponsiveness from persistent antigen presence in the pulmonary bronchioles has been suggested (78).

Neurologic disease

Approximately 10%–15% of human pathogenic fungi may infect the central nervous system (CNS) (34, 79). Clinical presentations of neurologic fungal infections can include meningitis, encephalitis, hydrocephalus, cerebral abscesses, and stroke (34). While less common, fungal CNS infections often have poorer prognoses and higher mortality compared with viral and bacterial CNS infections, likely because of the greater prevalence of underlying immunocompromising conditions in patients with fungal CNS infections (34). In a Japanese study of acute meningitis, bacterial and viral meningitis were more common, but mortality from fungal meningitis was higher (21%) than bacterial (0.6%) or viral (9.5%) (80).

Globally, the most common fungal infection of the CNS is cryptococcal meningoencephalitis; a 2020 study estimated 152,000 cases of cryptococcal meningitis and 112,000 cryptococcal-related deaths annually (81). Cryptococcal meningitis is an opportunistic infection in people with advanced HIV disease (AIDS) and causes 19% of AIDS-related mortalities (34, 81). Infection also occurs in patients with immunocompromising conditions other than HIV, including recipients of solid organ transplantations and those with hematologic malignancy (Table 1). While less common, cryptococcal infections caused by *Cryptococcus gatti* in immunocompetent persons have been increasingly common, particularly in the Pacific Northwest of the United States (82). During 1997–2009, non-HIV–related cryptococcal meningitis accounted for one-quarter of cryptococcal meningitis-related hospitalizations and one-third of cryptococcal meningitis-related deaths in the United States (83). Among patients with disseminated cryptococcosis reported to a North American registry, CNS involvement occurred in 84% of patients with HIV infection, 44% of transplant patients, and 28% of immunocompetent patients (84). *Cryptococcus neoformans* exhibits a particular predilection for the CNS, which is in part attributed to secretion of metalloproteases and ureases that facilitate penetration of the blood-brain barrier. Additionally, the production of the virulence factor laccase enables the fungus to utilize neurotransmitters including dopamine, contributing to neuroimmunomodulation. Furthermore, to survive in the nutrient-limited environment of the brain, *C. neoformans* employs mechanisms such as autophagy and the expression of high-affinity sugar transporters (85).

Primary symptoms of cryptococcal meningitis are head and neck pain, but 20% of patients also show altered mental status (34). Convulsions, stroke, paralysis of the lower limbs, photophobia, nausea, vomiting, and disorientation may also occur (Table 1) (34). Without treatment, symptoms can progress to confusion, seizures, reduced levels of consciousness, and eventually coma (85). Intracranial hypertension is a serious complication of cryptococcal meningitis that is associated with poor prognosis. Early detection and treatment, as well as aggressive management of intracranial pressure, can significantly improve odds of survival (86, 87). Among survivors of cryptococcal meningoencephalitis,

studies on long-term outcomes found that 24% of patients reported inability to work 6 months after diagnosis, and 69% of people with HIV and 73% of people without HIV remained cognitively or physically impaired 12 months after diagnosis (87, 88).

Immunologic profiles of patients with cryptococcal meningitis are strongly associated with outcomes. In patients with HIV, a study showed that those who survived had a higher proportion of cryptococcal-specific CD4⁺ memory cells that produced IFN- γ and tumor necrosis factor (TNF) than did patients who died, who predominantly produced inflammatory protein 1 α (89). In patients with HIV who are receiving antiretroviral therapy and in patients without HIV with cryptococcal meningitis, immune system reactions can lead to complications such as post-infectious inflammatory response syndrome. Post-infectious inflammatory response syndrome is characterized by neurological deterioration during treatment, despite effective antifungal therapy and negative cerebrospinal fluid cultures. This condition arises from an exaggerated immune response involving activation of T cells and elevated cytokines like IFN- γ and interleukin-6 (IL), but with ineffective macrophage activation, leading to persistent inflammation and tissue damage. Corticosteroids have been used to manage the syndrome, but their prolonged use poses risks of increased susceptibility to opportunistic infections, prompting research into alternative immunosuppressive treatments. In a retrospective case study of young, immunocompetent patients with cryptococcal meningitis, post-infectious inflammatory response syndrome was identified in 29%, suggesting a likely under-recognized burden of illness that is associated with delayed recovery (90).

Another uncommon but severe fungal infection that leads to neurologic damage is phaeohyphomycosis. This infection is caused by several species of dematiaceous environmental fungi that primarily live in soil and on vegetation. These fungi can enter the body through inhalation or traumatic implantation and are thought to effectively evade host immune defenses due to the presence of melanin, considered a virulence factor, in the fungal cell walls (91). While phaeohyphomycosis has varied clinical manifestations, some causative fungi are neurotropic and can lead to CNS infection with chronic complications such as persistent neurological deficits, hydrocephalus, seizures, cognitive impairment, and, in severe cases, long-term disability or death (34). Phaeohyphomycosis occurs more often in immunocompromised patients, although infections in immunocompetent patients are documented (Table 1) (92). Indeed, in a review of over 100 cases documented globally, more than half of all cases occurred in patients with no known immunodeficiency, and mortality rates were high regardless of immune status (92). Phaeohyphomycosis occurs worldwide and is common in tropical and subtropical regions (37). In the United States, the largest reported outbreak of a healthcare-associated infection was caused by the dematiaceous mold *Exserohilum rostratum*, following injections of contaminated methylprednisolone (93). A total of 753 cases were reported; most patients experienced meningitis that sometimes involved stroke and spinal and paraspinal infections (93). A retrospective cohort study of 440 patients involved in the outbreak found that patients who experienced meningitis and stroke had higher initial mortality rates, but among those who survived, most (87%) were cured by 12 months. In contrast, fewer patients with spinal or paraspinal infections died (3%), but at 12 months, 68% had persistent or worsening pain, and many could not walk without an assistive device (94).

While the immunologic mechanisms associated with disease progression and outcome of phaeohyphomycosis are not extensively studied, impairment of Dectin-1, a C-type lectin receptor that recognizes β -glucans in fungal cell walls and promotes TNF- α - and IL-1 β -mediated macrophage defense, was associated with severe phaeohyphomycosis caused by *Corynespora cassiicola* in 12 of 17 patients (16).

Finally, coccidioidal meningitis, though rare, is a severe and often life-threatening infection that occurs in approximately 1% of all individuals with disseminated disease (95). It is more common among immunosuppressed patients, such as those with HIV/AIDS, solid organ transplants, or hematologic malignancies (Table 1). The disease has a chronic, relapsing course that is nearly always fatal within 2 years if untreated (39, 96). Even with treatment, however, the disease is considered incurable. Therefore, lifelong treatment with high-dose antifungal medications, most often itraconazole or fluconazole, is often required to control progression (95, 97). The long-term effects of coccidioidal meningitis can be substantial. With appropriate treatment, many patients may still require surgical intervention including placement of a ventriculoperitoneal shunt and may experience permanent neurologic sequelae, including cognitive deficits, hearing loss, visual impairment, motor dysfunction, and seizures (96, 98). In one study, high antifungal medication nonadherence rates of 43% were also observed and were associated with multiple shunt failures and rehospitalizations in patients (98), exacerbating the toll associated with an already devastating disease.

Circulatory/cardiac disease

An uncommon but serious complication of fungal infection is endocarditis (i.e., inflammation of the inner lining of the heart chambers and valves). While fungal endocarditis is rare, accounting for 1%–3% of all infective endocarditis cases, it is the most serious of all causes of infectious endocarditis, with mortality estimates that exceed 70% (41). While prevalences are unknown, *Candida* spp. are the most common causative organisms, followed by *Aspergillus* and *Histoplasma* (41, 99). Previous surgery, intravenous drug use, and being immunocompromised are risk factors for disease (Table 1) (99). The long-term effects of fungal endocarditis are poorly understood. One meta-analysis of patients with fungal endocarditis diagnosed from 1965 to 1995 found that of the 162 (60%) patients who survived the initial treatment period, emboli occurred in 25%, and major complications, either from antifungal treatment or the disease itself, occurred in 42% (100).

Gastrointestinal disease

The fungal component of the human gut microbiome, known as the gut mycobiome, has received far less scientific attention compared with the bacterial component, although 66 genera of commensal fungi have been identified as part of healthy gut microflora (101). One study identified that common fungal genera included *Saccharomyces* (present in 89% of the specimens), followed by *Candida* (57%) and *Cladosporium* (42%) (102). Among healthy people, one of the most common commensal species is *Candida albicans* (101). While typically harmless, factors including immunosuppression and antibiotic use, which may imbalance the microflora, can cause *C. albicans* to become pathogenic, manifesting as colonic inflammation and translocation across the digestive intestinal barrier that results in invasive bloodstream infection (103). Associations between *C. albicans* and inflammatory

conditions like Crohn's disease have been demonstrated. For example, studies have shown that people with Crohn's disease are more likely to be colonized by *C. albicans*, and experimental models indicate that colonization can intensify inflammation and promote the production of anti-*Saccharomyces cerevisiae* antibodies, which are commonly found in patients with Crohn's (101, 104, 105). These findings highlight the potential of *C. albicans* overgrowth to disrupt intestinal homeostasis, leading to dysbiosis that contributes to the pathogenesis of chronic gastrointestinal diseases. Overall, however, understanding how perturbations to the mycobiome may affect chronic disease is poorly understood; ongoing advances in metagenomic approaches may help expand this field in the future.

Outside of commensal gastrointestinal fungi, environmental fungi may also result in chronic gastrointestinal disease. Infections with *Histoplasma capsulatum* are among the most common to lead to gastrointestinal involvement, occurring in 70%–90% of patients with progressive disseminated histoplasmosis (42). Risk factors for disseminated disease include AIDS and other immunosuppressing conditions, as well as older age (Table 1) (42). Gastrointestinal histoplasmosis presents in diverse forms, including bleeding, ulceration, perforation, and obstruction, with more severe manifestations and higher rates of gastrointestinal bleeding seen in patients with AIDS. Lesions may mimic malignancy or inflammatory bowel disease, leading to potential misdiagnosis and inappropriate treatment, especially in immunocompromised people (42). Despite these serious manifestations, long-term outcomes can be favorable with appropriate antifungal treatment. In a 15 year institutional review of systemic histoplasmosis, patients treated with amphotericin B followed by itraconazole showed no relapses or deaths, underscoring the importance of timely and prolonged therapy (106).

Finally, *Basidiobolus ranarum* is an environmental saprophytic fungus found in arid climates worldwide. It is now considered an emerging pathogen associated with rare but consequential cases of gastrointestinal basidiobolomycosis (43). A retrospective observational cohort study that concluded in 2010 identified 44 cases worldwide, including 19 in the United States, of which 17 occurred in Arizona. Eighty-two percent of patients were healthy young men; no patients diagnosed with gastrointestinal basidiobolomycosis were immunocompromised. The most common symptom was abdominal pain (Table 1). Most patients (84%) required surgical excision of abdominal masses, and 8 of 41 (20%), including 4 that received no antifungal medication, died of their illness (43).

Sensory disease

Some fungal infections can cause vision and hearing decrease or loss, leading to long-term disability. Perhaps the most well-documented example is fungal keratitis, a corneal infection that can result in partial or complete vision loss. Nearly 1 million keratitis-related healthcare visits occur annually in the United States; fungi are the suspected etiology in about 6% of keratitis infections (107). More specific data from the United States are unavailable due to limited surveillance, but global studies estimate that annually, 1–1.5 million people suffer partial or complete vision loss from fungal keratitis, with 8%–11% of these cases resulting in eye removal (44).

Over 100 species of fungi have been identified to cause fungal keratitis, but the most common globally are *Fusarium* and *Aspergillus* (45). Most infections occur through ocular trauma or chronic ocular surface disease; underlying immunodeficiency, contact lens use, and topical corticosteroid use are risk factors for infection and severe disease (Table 1) (107, 108). While the occurrence of fungal keratitis is geographically widespread, outbreaks in developed countries have primarily been reported in association with contact lens contamination. In 2006, a large multi-country outbreak of *Fusarium* keratitis occurred, associated with using a specific brand of contact lens solution. There were 164 confirmed cases in the United States; 55 (34%) patients required corneal transplantation (109).

The relationships between fungal keratitis and underlying immunity have been partly explored. One study found that antimicrobial peptide expression in corneal tissue is increased with active fungal keratitis infection, but profiles differed based on the fungal pathogen. Specifically, *Fusarium* keratitis caused greater expression of human beta-defensin-2, while *Aspergillus* keratitis was typified by LL-37, which are both components of innate immune defense (110). More generally, while immunocompromising conditions can result in more severe infections, overly aggressive immune responses in immunocompetent individuals can lead to excessive corneal inflammation, resulting in stromal damage, scarring, and vision impairment despite effective antifungal treatment (111, 112). Further research study into therapies that eliminate disease-causing fungi while managing inflammation is therefore still necessary (111).

Fungal otitis (otomycosis) causes 10% of all cases of otitis externa (48). While otomycosis may be caused by a variety of fungi, *Aspergillus* and *Candida* species are most commonly associated (48). Infections are most often superficial, but chronic or inadequately treated infections can extend beyond the external canal, resulting in long-term effects on auditory function. These infections may lead to tympanic membrane perforation, canal fibrosis, or ossicular erosion, all of which may contribute to conductive hearing loss and, in some cases, irreversible auditory impairment. Immunocompromised people are at greater risk of otomycosis, and the most serious cases, with perforation of the tympanic membrane, involvement of the middle ear, or the entire temporal bone, are predominantly associated with immunodeficiency conditions (Table 1) (48, 113).

Mucosa, skin, and bone

Cutaneous mycoses of skin, hair, and nails are the most common fungal infections in the United States. Common types include dermatophyte infections (also called tinea infection, athlete's foot, jock itch, or ringworm), caused by dermatophyte fungi, and yeast infections caused by *Candida* species (114). These infections typically thrive in warm, moist areas of the human body such as inguinal folds and can be transmitted through direct contact with infected individuals, animals, or contaminated surfaces (115). Most of these infections are acute and respond to treatment, although in some cases, antifungal resistance is emerging (116). Some, however, require ongoing treatment or management. For example, *Trichophyton indotineae* is a recently emerged dermatophyte that is notable for causing persistent and often extensive skin infections that can last months to years if untreated or undertreated (50, 117). Clinical reports underscore its high rates of terbinafine

resistance, which has contributed to treatment failure and relapse in up to 75% of patients in some studies (50, 118). Chronic dermatophytosis often leads to inflammatory lesions that progressively enlarge and coalesce, triggering epidermal damage (Table 1). Long-standing, untreated lesions may result in permanent scarring and pigmentary changes (119).

Recurrent vulvovaginal candidiasis (RVVC) is another chronic condition that is often characterized by three or more episodes in a year (120, 121). Among U.S. women who had VVC in the past year, approximately 5% had RVVC (122). Long-term antifungal prophylaxis regimens are typically recommended to prevent recurrence but are non-curative; infections typically recur when therapy is ended. Elevated vaginal estrogen levels have been identified as an important predisposing factor, especially in women of reproductive age (53). Risk factors for recurrence include antibacterial use, being of reproductive age, immune dysfunction, impaired glucose tolerance, and prior illness (Table 1) (54). However, 20%–30% of RVVC cases have no clear cause, suggesting a role for *Candida* virulence and host genetics or immune factors in disease susceptibility (54).

The potentially lifelong nature of RVVC extends its effects beyond physical discomfort. RVVC can diminish quality of life, increase healthcare costs, and cause psychological distress (54). In one study of Australian women with RVVC, emergent patient challenges included delays in diagnosis and management, limited health care professional knowledge, lack of healthcare support, and embarrassment, anxiety, and distress stemming from an intimate health condition (123).

Other cutaneous and subcutaneous mycoses can lead to disfigurement and disability over years-long progression. One such example is chromoblastomycosis, a neglected tropical disease that causes chronic skin infection. Infections are rare in the United States, although underdiagnosis and underreporting may contribute to low prevalence estimates (124). Chromoblastomycosis is caused by dematiaceous fungi from several genera, including *Fonsecaea* spp., *Cladophialophora* spp., *Phialophora* spp., and *Rhinocladiella* spp. (125). It is acquired through traumatic inoculation of fungi into the skin, typically due to minor injuries like cuts and splinters (Table 1) (126). Infections are slow-growing and initially present as painless, wart-like lesions. Perhaps for this reason, many people with infections delay seeking healthcare for several months to several years (56). In more severe cases, tissue fibrosis and joint ankylosis have been reported to limit mobility, cause difficulty walking, and impede activities of daily life, including work (Table 1) (56, 57). In one study that followed seven patients with chronic chromoblastomycosis in Brazil, the average duration of infection was 23 years, and all but one required curative amputation after developing squamous cell carcinoma resulting from chronic chromoblastomycosis (127). The relationship between immune factors and chromoblastomycosis is poorly understood, but formation of characteristic thick-walled, single or multicellular clusters of pigmented fungal cells (also known as medlar bodies, muriform cells, or sclerotic bodies), which are highly resistant to immune system attack, contributes substantially to disease chronicity (56).

Another implantation mycosis, eumycetoma, caused by at least 69 species of fungi but commonly from six major genera (*Madurella*, *Falciformispora*, *Trematospheria*,

Curvularia, *Fusarium*, *Exophiala*), is also subcutaneous but can also invade bones, muscles, tendons, and nerves causing functional impairments and disfigurement (Table 1). Like chromoblastomycosis, diagnostic delays for eumycetoma are common, with most patients presenting with advanced disease (128). In advanced disease, patients can suffer from chronic osteomyelitis and joint destruction.

In a cross-sectional study characterizing the disabling consequences of mycetoma in Sudan, 60% of 300 patients had moderate impairment or difficulty, with 40% experiencing challenges walking and 34% reporting significant pain challenging the traditional view of mycetoma as a painless disease (129). More broadly, surgical excision is a common outcome for this infection, and amputations are reported in 39% of cases. Long-term infections may last more than a decade, and recurrence occurs in 32%–47% of cases (130).

Cancer

Cancer is in the top 10 most common chronic diseases in the United States and is the second most common cause of death, resulting in 608,371 deaths in 2021 (131, 132). While genetic mutations and environmental factors are well-established contributors to cancer development, a growing field of research has identified the emergent role of microbial pathogens in carcinogenesis and tumorigenesis. Approximately 20% of cancers, or about 2 million cases per year, arise because of infectious agents, including well-known bacterial pathogens like *Helicobacter pylori* and viral pathogens like hepatitis B and C viruses and human papillomaviruses (133). The contribution of fungi to cancer is less well researched, and the burden has not yet been quantified. Nevertheless, some fungal pathogens might contribute to cancer development and influence severity in many types of cancers.

Candida albicans, a dimorphic commensal fungus found on the skin and gut surface, is a well-known cause of mucosal and invasive infections, particularly among immunocompromised people. Recent observational research suggests that invasive candidiasis may also be associated with oral, gastric, and colorectal cancers through multiple mechanisms, including (i) producing carcinogenic acetaldehyde, (ii) damaging the mucosal epithelium, and (iii) triggering chronic inflammation that contributes to tumor metastasis (Table 2) (134, 135). Links between *C. albicans* and oral cancer are the best studied. In one case-control study, the presence of oral *Candida* and genotypic diversity of *C. albicans* were significantly higher in patients with oral cancer compared with those who were oral cancer-free (136, 137). In a study of gastrointestinal cancer, gastric fungal imbalances were observed in patients with gastrointestinal cancer that were characterized by lower species richness and overall enrichment of *Candida albicans*, suggesting this fungus may mediate gastrointestinal cancer by suppressing fungal diversity and promoting cancer pathogenesis (138). While mechanistically dissimilar to *C. albicans*, chronic chromoblastomycosis can also undergo malignant transformation that develops into squamous cell carcinoma (Table 2) (127, 139).

Recently, a study found *Malassezia* spp., a common genus of commensal skin fungus, was associated with acceleration of pancreatic ductal adenocarcinoma, a cancer with poor prognosis. Researchers found that pancreatic ductal adenocarcinoma tumors were 3,000-fold higher in fungal content than normal pancreatic tissue and were markedly enriched by

Malassezia. Ablating all fungi present using the antifungal amphotericin B protected against tumor growth, and repopulating tumors with *Malassezia*, but not *Candida*, *Saccharomyces*, or *Aspergillus*, accelerated oncogenesis in mouse models (143). However, a reanalysis of this study's data suggested that evidence was insufficient to support the hypothesis that the pancreatic or gut mycobiome promoted pancreatic cancer development in humans. The authors of the reanalysis highlighted the challenges of studying low-biomass samples and called for standardized microbiome research methodologies to improve study reproducibility (146). In another study, one species of *Malassezia*, *M. globosa*, was shown to be associated with breast tumors and to promote tumorigenesis through a defined mechanism of growth factor upregulation that results in poorer rates of survival in breast cancer patients (Table 2) (144).

Fungal infections may not only contribute to the development of cancer but, in some instances, have also been shown to exacerbate cancer progression and worsen severity. In one study, living and transcriptionally active *Candida* species were discovered at gastrointestinal tumor sites. Their presence was predictive of both metastatic disease and decreased likelihood of survival (147). In another study, *C. albicans* was shown to participate in oral squamous cell carcinoma progression by stimulating the production of matrix metalloproteinases, oncometabolites, protumor signaling pathways, and overexpression of prognostic marker genes associated with metastatic events (148).

Despite growing observational and *in vitro* evidence supporting the contribution of fungi to the development and exacerbation of cancer, many aspects of these relationships are still poorly understood. Additional studies to elucidate the mechanistic processes and to understand the contribution of fungal infections relative to other causes of cancer are needed. A more comprehensive understanding of these interactions will be essential for developing targeted interventions, including those that use fungi as biomarkers of carcinogenesis, to improve patient outcomes.

TOXICITY ASSOCIATED WITH ANTIFUNGAL USE CAN LEAD TO CHRONIC DISEASES

Antifungal medications are prescribed to treat fungal infections or as prophylaxis for high-risk patients, like those undergoing chemotherapy or organ transplants. At least partly because of the greater biological similarity between fungal cells and human cells, antifungals generally exhibit greater toxicity and require longer courses of administration than antibiotics. While antifungals are essential for treating fungal infections, they can cause substantial side effects. Adverse effects associated with antifungals can result in chronic conditions, sometimes shortly after administration, and sometimes when prescribed for use over months or years. In some instances, such as with coccidioidal meningitis or severe pulmonary histoplasmosis, treatment may be required for years or for the patient's entire lifetime (40). Therefore, while some adverse effects resulting in chronic conditions may resolve after antifungal discontinuation, patients may still deal with their consequences for prolonged periods of time.

Currently, four main classes of antifungal drugs exist for treating invasive infections: azoles, polyenes, echinocandins, and pyrimidine analogs (5-fluorocytosine). Below, we outline the adverse effects commonly associated with various antifungal drugs prescribed within each class.

Azoles

Azoles work by blocking the biosynthesis of ergosterol, a critical component of fungal cell membranes. Systemic azoles, including fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole, are often used as prophylaxis or treatment against invasive fungal infections (Table 3). Some azoles, including fluconazole at prolonged high doses, may be associated with congenital birth defects. Therefore, long-term or high-dose administration, particularly in the first trimester of pregnancy, is not generally recommended (149).

One of the most well-studied adverse effects associated with azole use is hepatotoxicity or drug-induced liver injury, which can arise directly from the drug or its toxic metabolites (Table 3) (150). The frequency of liver injury associated with azole antifungals varies by agent. Voriconazole, for example, presents a high risk of hepatotoxicity, with up to 12% of patients needing to cease therapy due to liver-related adverse effects (151). Since 2013, the U.S. Food and Drug Administration has also limited the use of one azole, systemic ketoconazole, to situations where alternative therapies are unavailable or not tolerated, warning that the drug may cause severe liver and adrenal injuries (Table 3) (149, 152). Azole-associated hepatotoxicity may occur at any time after azole therapy begins but is common within the first month. Liver damage is generally reversible following dosage reduction or discontinuation of therapy (152, 153). Despite the detrimental effects of hepatotoxicity, mechanisms of action are not well understood, and correlations with the development of toxicity are conflicting (153, 154).

Patients on triazole antifungals, primarily voriconazole and itraconazole, are also at an increased risk of developing peripheral neuropathies (Table 3) (155). Symptoms of peripheral neuropathy may include numbness and tingling in the extremities, as well as feet and leg weakness. Peripheral neuropathies may start days or weeks after treatment initiation and may occur even when therapeutic drug levels are below the maximum target (155). While peripheral neuropathies may resolve when triazole medication is discontinued, one study found persistent hand numbness was irreversible in 2 out of 10 patients (155). Additionally, vinca alkaloids (for cancer treatment) or calcineurin inhibitors (for immunosuppression) may increase the risk of peripheral neuropathies when used concurrently with azoles. In a study of 27 lung transplant patients being treated for *Aspergillus* colonization or infection, nine developed painful neuromuscular disorders that included muscular pain/weakness, numbness, and sensory loss 2 weeks to >1 year after initiation of voriconazole. Peripheral neuropathies may still manifest without neuropathy-inducing medications with triazole administration, although the mechanism for toxicity is poorly understood (153).

Some adverse effects are specific to particular azoles. Some systemic azoles, for example, including ketoconazole, itraconazole, and posaconazole, may interfere with

human steroidogenesis via off-target inhibition of adrenal CYP enzymes. Rare but clinically significant endocrine effects have been reported, including adrenal insufficiency, hypokalemia, and salt-retaining (pseudohyperaldosteronism) syndromes (Table 3) (153, 156, 157).

Long-term voriconazole therapy is also associated with several well-known adverse effects. Aside from hepatotoxicity (described above), other common adverse effects include visual disturbances, which occur in 19%–30% of patients, and phototoxicity (Table 3). In one retrospective study of 430 children in the United States, phototoxicity occurred in 20% of all children and 47% of those treated for 6 months or longer (158, 159). Phototoxicity is now also a recognized factor associated with skin cancer, one of voriconazole's most worrisome long-term events. In a 2 year retrospective cohort study of lung transplant recipients, exposure to voriconazole was associated with a 2.6-fold increased risk of squamous cell carcinoma; this risk increased by 6% in 60 day increments when 200 mg was administered twice daily (160). The precise mechanism for carcinogenesis is not well-defined. However, the mechanism of voriconazole-associated skin cancer development is unique, showing that voriconazole metabolites are phototoxic and initiate tumorigenesis, while voriconazole itself upregulates COX-2, a pivotal enzyme in promoting UV-associated tumors in an aryl hydrocarbon receptor-dependent manner (161).

Despite the aforementioned adverse effects, voriconazole is still a useful drug due to its ability to penetrate the blood-brain barrier, allowing circulation in the vitreous body, aqueous humor, and cerebrospinal fluid. CNS penetration may also lead to neurologic adverse events. In a prospective study of voriconazole toxicity in 72 patients, 17% experienced visual or auditory hallucinations (162). Similarly, analysis of the French Pharmacovigilance Database identified neurologic disturbances among the most common adverse effects of voriconazole, comprising 14% of all reported (163).

Voriconazole is also known to cause skeletal issues including periostitis (i.e., inflammation of the periosteum, connective tissue enveloping bones) and exostoses (i.e., bone spurs) in 5%–10% of patients on long-term therapy (Table 3) (153, 164). Typically, patients present with diffuse bone pain and elevated plasma fluoride, resulting from voriconazole's three fluorine atoms and elevated alkaline phosphatase levels that resolve 2–5 months after treatment discontinuation (164). Bone pain is a complication largely isolated to voriconazole; in a comparative study that examined fluoride levels and bone pain among patients provided azoles, 3 of 20 patients receiving voriconazole had clinically significant skeletal diseases, which were not observed in the other 12 patients receiving other azoles or the control group (165). Thus, the long-term use of voriconazole is a critical consideration in children, who have relatively larger surfaces of bone crystallites and may accumulate fluoride more rapidly (153).

Although less common than with voriconazole, itraconazole use is also associated with several severe side effects beyond hepatotoxicity. A 2001 study that used data from the Food and Drug Administration's (FDA) Adverse Event Reporting System identified that, while rare, this antifungal is also associated with congestive heart failure, identifying 58 suggestive cases between 1992 and 2001 (166). Consequently, the FDA issued a black-box

warning associating itraconazole with ventricular dysfunction, now known to be associated with decreases in heart contractility and left ventricle ejection fraction (Table 3) (167). The mechanism for this event is unknown, but appears dose-dependent, with increased risk in patients whose doses exceed 400 mg/day (168). While adverse effects are typically reversible, continued cardiac dysfunction, in some instances resulting in the need for heart transplants, has been documented (169). In one single-center retrospective study examining cardiac toxicities associated with itraconazole, stopping itraconazole therapy or decreasing dose resulted in complete resolution of cardiac dysfunction in 54% of patients, partial resolution in 30%, and failure to resolve in 13% (168). Similarly, fluconazole has been associated with a potentially fatal arrhythmia known as torsades de pointes (Table 3). This adverse effect is primarily attributed to inhibition of the cardiac human ether-à-go-go-related gene (hERG) potassium channels, which are crucial for cardiac repolarization. By impeding these channels, fluconazole can delay ventricular repolarization, leading to QT interval prolongation and increasing the risk of torsades de pointes (170).

Fluconazole is commonly prescribed and is typically associated with fewer severe adverse effects than voriconazole and itraconazole. In a single-center retrospective study assessing the long-term tolerability of fluconazole, adverse effects occurred in 52% (94) of patients, irrespective of therapeutic drug levels. The most common adverse effects included xerosis (17%), alopecia (16%), and fatigue (11%), which decreased patient willingness to accept long-term therapy (171, 172).

Posaconazole is generally well tolerated for long-term use, although adverse effects have been reported. In clinical trials involving patients with refractory invasive fungal infections, treatment-related adverse effects occurred in 38% of participants, with nausea (8%) and vomiting (6%) being the most common (Table 3). Serious adverse effects were observed in 8% of patients, including low rates of corrected QT interval prolongation (1%) and elevated hepatic enzymes (2%). Importantly, the incidence of these adverse effects did not increase with therapy extending beyond 6 months (173). However, elevated serum posaconazole concentrations ($\geq 3,000$ ng/mL) have been linked to increased adverse drug reactions, including hypokalemia, hypertension, and pseudohyperaldosteronism (174). Therapeutic drug monitoring is recommended to mitigate these risks.

Isavuconazole is a newer second-generation triazole that is effective against various yeasts and molds, with a relatively favorable side effect profile compared with voriconazole (175). Common side effects include gastrointestinal symptoms, and liver enzyme monitoring is recommended because of the potential for hepatotoxicity, which is rarer with isavuconazole compared with other triazoles (Table 3) (176). Isavuconazole serves as an important alternative option for treating invasive aspergillosis and mucormycosis; however, its high cost and insurance barriers might pose obstacles to its use in clinical practice (175, 177).

Polyenes

Polyenes work by binding to ergosterol, a key structural component of fungal cell membranes, to form extramembranous aggregates that extract ergosterol from lipid bilayers. This increases membrane permeability, which causes leakage of potassium and other molecules in cells (178, 179).

Amphotericin B has been a cornerstone in treating severe systemic fungal infections for over 5 decades due to its broad activity and potency, especially for fungal strains that are resistant to newer azole therapies. However, its use is limited by several frequent adverse effects (Table 3). In a study that assessed antifungal tolerability as an odds ratio of the number of study withdrawals due to adverse effects, amphotericin B had the highest risk of withdrawal, 3.2 times higher than placebo (180).

The most common adverse effect of amphotericin B is nephrotoxicity, which can have long-term debilitating effects (Table 3). The nephrotoxic effects of amphotericin B are primarily due to two mechanisms: direct damage to kidney cells and alterations in renal blood flow. Firstly, amphotericin B binds to sterols in cell membranes, including cholesterol in human kidney cells, leading to increased membrane permeability and direct tubular injury. This results in the leakage of essential ions and molecules, impairing the kidneys' ability to concentrate urine and maintain electrolyte balance. Secondly, the drug induces vasoconstriction of the renal arterioles, reducing blood flow to the kidneys and leading to decreased glomerular filtration rate. This reduction in glomerular filtration rate contributes to azotemia, characterized by elevated levels of nitrogenous waste products in the blood. Patients undergoing amphotericin B therapy may experience a range of renal complications, including acute kidney injury, renal tubular acidosis, and electrolyte imbalances such as hypokalemia and hypomagnesemia. These disturbances can lead to symptoms like muscle weakness, cardiac arrhythmias, and metabolic acidosis. In some cases, the renal impairment may be irreversible, especially in patients receiving high cumulative doses of the drug, leading to chronic kidney disease or end-stage renal disease requiring long-term dialysis or kidney transplantation (181). Research is ongoing to investigate other formulations and derivatives of amphotericin B to reduce side effects, for example, a new renal-sparing structural amphotericin B derivative and an oral lipid nanocrystal formulation (182, 183).

In a 9 year retrospective analysis of amphotericin B deoxycholate-associated nephrotoxicity, 139 (28%) adult patients experienced renal toxicity, and 12% experienced moderate-to-severe nephrotoxicity that occasionally required hemodialysis (184). These rates may be higher in immunocompromised populations. Among patients with hematologic malignancies, for example, nephrotoxicity from amphotericin B deoxycholate was observed in 36%. Among patients who experienced nephrotoxicity, 10% progressed to stage 3 renal failure (185).

Liposomal amphotericin B, while more costly, has been developed to mitigate the nephrotoxicity commonly associated with conventional amphotericin B formulations. Encapsulating the drug within liposomes reduces accumulation in the kidneys, decreasing renal toxicity. A systematic review and meta-analysis demonstrated that liposomal formulations are associated with substantially lower nephrotoxicity compared to conventional amphotericin B (185). Additionally, liposomal amphotericin B does not contain deoxycholate, a component known to cause direct renal tubular toxicity, further contributing to its improved renal safety profile. Liposomal amphotericin B may also reduce the occurrence of severe nephrotoxicity, with one study finding severe nephrotoxicity in 11.5% of patients receiving amphotericin B-deoxycholate and 2.4% in patients receiving liposomal

amphotericin B. In this study, liposomal amphotericin B was also a protective factor for mortality (186).

While liposomal amphotericin B is generally more well-tolerated than amphotericin B-deoxycholate, it may still cause comparable additional adverse effects at high frequency, although reactions may be less severe (187). Infusion-related reactions are among the most common and include fever, chills, and rigors (Table 3). Electrolyte disturbances, particularly hypokalemia, are also observed with liposomal amphotericin B therapy. A study involving pediatric patients found that hypokalemia occurred in 55.4% of treatment episodes, typically manifesting around day 10 of therapy (188). In adults, another study found that patients still frequently developed anemia, thrombocytopenia, hepatotoxicity, nephrotoxicity, and hypokalemia (189). Therefore, while liposomal amphotericin B offers a better safety profile than conventional amphotericin B, vigilant monitoring and supportive management are still required during therapy.

Echinocandins

Echinocandins, including anidulafungin, caspofungin, micafungin, and rezafungin, work by compromising the integrity of fungal cell walls through the disruption of glucan synthesis via the inhibition of the 1,3- β -D-glucan synthase enzyme (180). Perhaps because no similar target molecule exists in humans, echinocandins are generally considered to be the safest and most well-tolerated systemic antifungal agents (180). However, one network meta-analysis showed that while micafungin was associated with lower risks of elevated liver enzymes and hypokalemia than azoles and polyenes, it was linked to 5.8 times greater incidence of bilirubin elevation. Micafungin and caspofungin were also found to pose the highest risk of skin and subcutaneous tissue disorders of all antifungals (180), including rare instances of severe skin diseases such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme (Table 3) (190, 191).

5-Fluorocytosine

5-Fluorocytosine is a nucleoside analog that works by interfering with fungal cell nucleic acid synthesis (192). It is primarily involved in treating certain forms of invasive candidiasis and cryptococcosis. Bone marrow suppression, including leukopenia and thrombocytopenia, is the primary concerning side effect (Table 3). The incidence of grade IV neutropenia was relatively low (4.4%) in recent trials using a dose of 100 mg/kg/day (193). In addition, hepatotoxicity, gastrointestinal intolerance, and renal impairment have been observed at high doses (192).

CONCLUSIONS AND FUTURE DIRECTIONS

The intersection of fungal infections and chronic diseases remains an understudied area, particularly regarding how fungal infections contribute to the development of chronic disease states. In the United States, the burden of chronic disease in persons aged ≥ 50 years is projected to double from 2020 to 2050 (194). Concurrently, the incidence of fungal disease is also rising, likely due to a growing population of immunocompromised patients and environmental changes (195).

Despite a growing recognition of the physical burden posed by fungal infections and associated treatment, the mental health and wellness aspects of disease remain understudied or absent in the literature. Failure to address these psychosocial dimensions results in an incomplete understanding of the true burden these illnesses impose. Studies that incorporate assessment of mental health effects are therefore urgently needed. Additionally, incorporating mental health considerations into clinician management of chronic fungal diseases and their therapies is essential to improving patient outcomes.

Additional future research could aim to clarify the mechanisms by which fungi contribute to chronic disease states. Further, estimates of the true burden of fungal diseases could be enhanced by incorporating quality of life measures and the long-term development of chronic conditions into fungal disease surveillance efforts and clinical studies. Finally, enhancing education and awareness of fungal infections among the public and healthcare providers, increasing access to testing and rapid diagnostics, ensuring access to treatment, and improving living conditions could help mitigate the burden of fungal infections and their subsequent contribution to chronic diseases.

ACKNOWLEDGMENTS

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control (CDC). Furthermore, the use of any product names, trade names, images, or commercial sources is for identification purposes only, and does not imply endorsement or government sanction by the U.S. Department of Health and Human Services.

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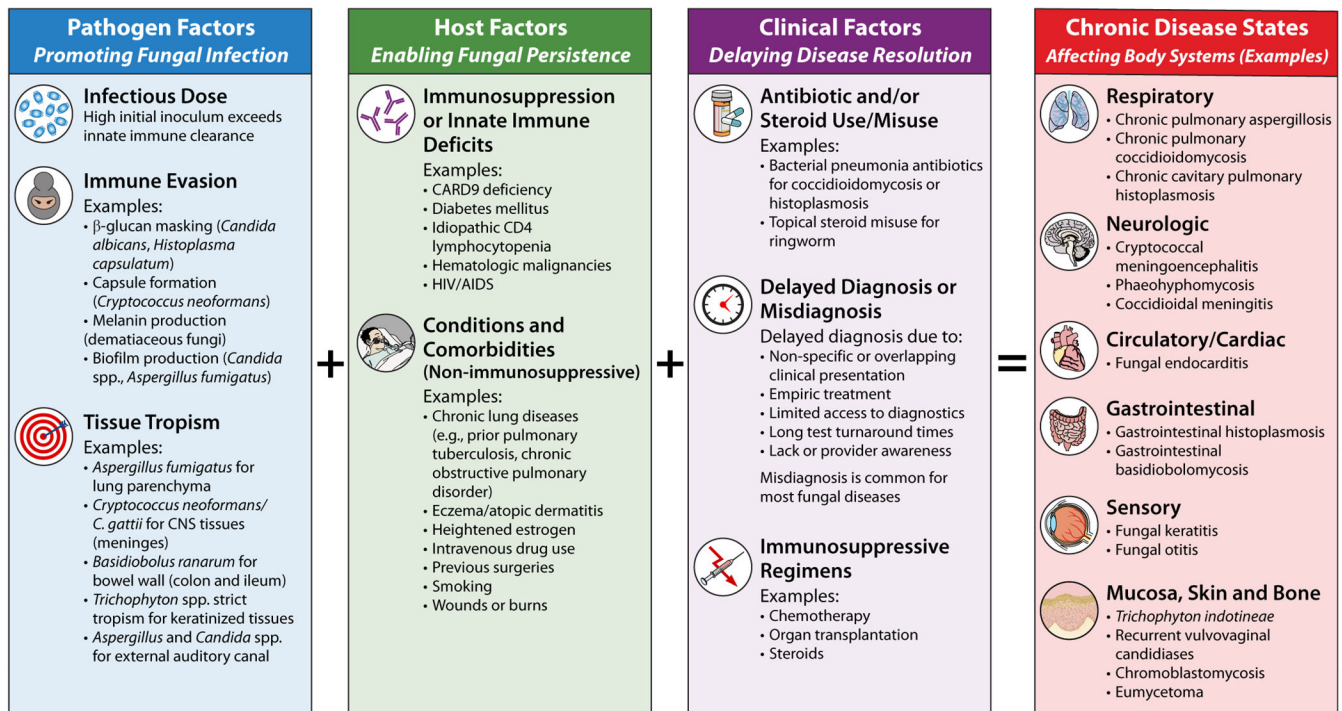
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**FIG 1.**

Factors contributing to chronic disease states associated with fungal infections: pathogen factors (i.e., organism-specific characteristics of disease-causing fungi), host factors (i.e., intrinsic biological characteristics of an infected organism), and clinical factors (external healthcare- and diagnosis-related elements) may all contribute to an increased likelihood of fungal infection resulting in a chronic disease state.

TABLE 1

Fungal diseases with potential to cause chronic conditions by body system: etiologic agents, risk factors and predisposing conditions, and typical clinical presentation

Body system	Chronic disease	Fungal agent	Risk factors and conditions	Typical clinical presentation	Reference(s)
Respiratory	Chronic pulmonary aspergillosis	<i>Aspergillus fumigatus</i> species complex (and other <i>Aspergillus</i> spp.)	• Pre-existing structural lung disease: • Pulmonary tuberculosis • Nontuberculous mycobacterial infections • COPD/emphysema • Bronchiectasis • Prior pulmonary cavities	• Chronic productive cough • Fatigue • Hemoptysis • Weight loss	(23-25, 27)
	Chronic pulmonary coccidioidomycosis	<i>Coccidioides immitis/C. posadasii</i>	• Diabetes mellitus • Immunosuppression • Male sex • Occupational/environmental exposure • Older age • Pre-existing structural lung disease: • COPD • Pulmonary tuberculosis • Smoking	• Chronic cough • Fatigue • Headache • Joint pain • Night sweats • Pulmonary nodules/cavities • Weakness • Weight loss	
	Chronic pulmonary histoplasmosis	<i>Histoplasma capsulatum</i>	• Male sex • Older age • Pre-existing structural lung disease: • COPD • Pulmonary tuberculosis • Smoking • TNF-α inhibitors • Immunosuppression	• Chronic cough • Dyspnea • Hemoptysis • Night sweats • Weight loss	
Neurologic	Cryptococcal meningoencephalitis	<i>Cryptococcus neoformans</i> and <i>C. gattii</i>	• HIV/AIDS • Other immunosuppression: • Solid organ transplant • Glucocorticoid use • Hematologic malignancies • Liver disease • Renal insufficiency	• Subacute-chronic headache • Neck stiffness/pain • Altered mental status/confusion/disorientation • Convulsions • Fever (variable) • Nausea and vomiting • Signs of elevated intracranial pressure (visual changes, papilledema)	(34-36)
	Phaeohyphomycosis	Dematiaceous fungi (many [70+] genera)	• Traumatic injury • Immunosuppression: • Chronic use of catheters • Corticosteroids • Diabetes mellitus • Hematologic malignancy • Rheumatoid arthritis • Solid organ transplant	• Subcutaneous or cutaneous cysts, nodules, abscesses, or lesions, often on extremities, after trauma • Altered mental status • Headache • Fever • Nausea and vomiting	
	Coccidioidal meningitis	<i>Coccidioides</i> spp. (<i>C. immitis/C. posadasii</i>)	• Occupational/environmental exposure • Immunosuppression: • HIV/AIDS • Solid organ transplants • Hematologic malignancies	• Persistent headache • Altered mental status • Cranial nerve palsies • Hydrocephalus • Meningismus	

Body system	Chronic disease	Fungal agent	Risk factors and conditions	Typical clinical presentation	Reference(s)
Circulatory/ Cardiac	Fungal endocarditis	<i>Candida</i> spp. (e.g., <i>C. albicans</i> , <i>C. parapsilosis</i>), <i>Aspergillus</i> spp., <i>Histoplasma</i> spp., other disease-causing fungi	• Prosthetic valves • Prior cardiac surgery • Intravenous drug use • Indwelling central catheters • Immunosuppression • Male sex	• Nausea and vomiting • Signs of elevated intracranial pressure (visual changes, papilledema) • Chills • Chest pain • Diaphoresis • Dyspnea • Embolic phenomenon • Fatigue • Fever • Malaise • Persistent fungemia • Progressive heart failure • Orthopnea • Weight loss	(41)
Gastrointestinal	Gastrointestinal histoplasmosis	<i>Histoplasma capsulatum</i>	• Immunosuppression: • HIV/AIDS • Idiopathic CD4 lymphocytopenia • TNF-α inhibitors • Older age	• Abdominal pain • Diarrhea • Gastrointestinal bleeding • Fever • Weight loss	(42)
	Gastrointestinal basidiobolomycosis	<i>Basidiobolus ranarum</i>	• Unknown	• Abdominal pain • Abdominal mass • Diarrhea • Fever • Weight loss	(43)
Sensory	Fungal keratitis	Filamentous fungi (most commonly <i>Fusarium</i> and <i>Aspergillus</i>); <i>Candida</i> spp.; 100+ other species	• Ocular trauma • Chronic ocular surface disease • Immunosuppression • Corticosteroid use • Contact lens use	• Eye pain/discomfort • Eye discharge • Blurred/decreased vision • Photophobia	(44-47)
	Fungal otitis	<i>Aspergillus</i> and <i>Candida</i> spp. Most common	• Prior ear procedures or trauma • Swimming • Immunosuppression: • Diabetes • HIV/AIDS • Steroid eyedrop use • Chemotherapy and malignancy	• Otalgia • Otorrhea • Hearing loss • Aural fullness • Tinnitus • Itching	(48, 49)
Mucosa, skin and bone	Chronic dermatophytosis	<i>Trichophyton indotineae</i> and other <i>Trichophyton</i> spp.	• Topical steroid misuse • Immunosuppression: • Diabetes • HIV/AIDS • Solid organ transplantation • Atopic dermatitis • Hot/humid climates • Obesity	• Chronic or relapsing pruritic plaques • Annular, erythematous lesions with central clearing and active scaly borders • Large area rash involvement • Lichenification/hyperpigmentation	(50-52)
	Recurrent vulvovaginal candidiasis (RVVC)	<i>Candida albicans</i> and non- <i>albicans Candida</i> spp.	• May be idiopathic • Antibiotic use • Estrogenized state (reproductive age, exogenous estrogen)	• Three or more episodes of VVC in a year • Itching/pruritus of vulva/vagina • Burning, soreness, irritation of vulvovaginal area • Vulvar erythema	(53-55)

Body system	Chronic disease	Fungal agent	Risk factors and conditions	Typical clinical presentation	Reference(s)
	Chromoblastomycosis	Dematiaceous fungi (70+ genera)	• Immunosuppression • Diabetes/impaired glucose tolerance • Occupational/environmental exposure • Traumatic injury • Male sex • Adult age range	• Thick, white, clumpy vaginal discharge • Dyspareunia • Dysuria • Papular skin lesions, often on extremities (early presentation) • Itching • Lesion types: nodular, plaque-type, tumoral, cicatricial, and verrucous	(56-58)
	Eumycetoma	Six major genera (<i>Madurella</i> , <i>Falciformispora</i> , <i>Trematosphaeria</i> , <i>Curvularia</i> , <i>Fusarium</i> , <i>Exophiala</i>); at least 69 species	• Living in endemic, arid, or semi-arid regions (the “mycetoma belt”) • Occupational/environmental exposure • Male sex • Walking barefoot	• Subcutaneous mass (often painless; often on foot) • Serous or purulent fluid discharge • Black grain discharge • Progressive subcutaneous fibrosis and tumor-like deformity • Late bone involvement/osteomyelitis	(59-61)

TABLE 2

Fungal diseases associated with cancer development or progression: proposed mechanisms and strength of evidence

Cancer type	Fungal disease/agent	Proposed mechanisms	Type and strength of evidence	References
Oral squamous cell carcinoma (SCC); gastric cancer; colorectal cancer	<i>Candida albicans</i>	• Acetaldehyde production (carcinogenic) • Epithelial barrier damage • Chronic inflammation leading to protumor signaling	• More evidence for oral SCC. Human observational studies and mechanistic support from <i>in vitro</i> models	(136, 140)
Squamous cell carcinoma	Chromoblastomycosis	• Chronic inflammation and longstanding epithelial injury and scarring over years leading to malignant transformation	• Limited to case reports but well-documented	(127, 139, 141, 142)
Pancreatic ductal adenocarcinoma; breast cancer	<i>Malassezia</i> spp.	• Tumor mycobiome enrichment leading to activation of complement and tumor-promoting inflammatory pathways; growth-factor pathway upregulation	• Emerging/primarily preclinical; preclinical evidence (mouse models) and human tumor sequencing showing enrichment	(143-145)

TABLE 3
Summary of primary antifungal classes, mechanisms of action, common adverse effects, and notable characteristics

Drug class	Mechanism of action	Key drugs	Common or class-wide adverse effects	Summary of notable drug-specific toxicities and clinical considerations
Azoles (triazoles and imidazoles)	Inhibit ergosterol biosynthesis by blocking CYP450-dependent 14- α -demethylase	- Fluconazole - Itraconazole - Voriconazole - Posaconazole - Isavuconazole - Ketoconazole (restricted use)	- Hepatotoxicity (variable by agent) - GI symptoms - QT prolongation (some agents)	- Fluconazole: low hepatotoxicity; common adverse effects are xerosis, alopecia, and fatigue; QT prolongation leading to torsades de pointes; avoid long-term/high-dose use in first trimester pregnancy - Itraconazole: low hepatotoxicity; FDA black-box warning for congestive heart failure (dose-dependent); CYP3A4 inhibition; peripheral neuropathies; endocrine effects - Voriconazole: high hepatotoxicity; peripheral neuropathies; visual disturbances/hallucinations; phototoxicity; increased risk of skin cancer; bone pain, perioritis, and exostoses; despite toxicities, strong CNS penetration - Posaconazole: generally well tolerated with common adverse effects being nausea and vomiting; QT interval prolongation; elevated serum concentration linked to hypokalemia, hypertension, and pseudohyperaldosteronism that requires therapeutic drug monitoring - Isavuconazole: fewer hepatic and neurologic toxicities; common adverse effects include gastrointestinal symptoms; high cost - Ketoconazole: severe hepatotoxicity and adrenal toxicity (restricted use)
Polyenes	Bind ergosterol, increasing membrane permeability	- Amphotericin B deoxycholate - Liposomal amphotericin B	- Nephrotoxicity resulting in: - Acute kidney injury - Renal tubular acidosis - Electrolyte disturbances - Hypokalemia - Hypomagnesemia - Infusion-related reactions: - Fever - Chills - Rigors	- Amphotericin B deoxycholate: high risk of nephrotoxicity. - Liposomal amphotericin B: significantly less nephrotoxic but still causes hypokalemia, anemia, hepatotoxicity; more costly.
Echinocandins	Inhibit 1,3- β -D-glucan synthase, disrupting fungal cell wall synthesis	- Caspofungin - Micafungin - Anidulafungin - Rezafungin	- Generally safest systemic antifungal - Mild liver enzyme elevation - GI symptoms	- Caspofungin and micafungin: rare instances of severe skin diseases: - Stevens-Johnson syndrome - Toxic epidermal necrolysis - Erythema multiforme - Micafungin: bilirubin elevation
5-Fluorocytosine	Pyrimidine analog that inhibits fungal nucleic acid synthesis	5-Fluorocytosine	- Bone marrow suppression - GI intolerance - Hepatotoxicity - Renal impairment (dose dependent)	Use in combination therapy to avoid rapid antifungal resistance.