Hidden Killers: Human Fungal Infections

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Although fungal infections contribute substantially to human morbidity and mortality, the impact of these diseases on human health is not widely appreciated. Moreover, despite the urgent need for efficient diagnostic tests and safe and effective new drugs and vaccines, research into the pathophysiology of human fungal infections lags behind that of diseases caused by other pathogens. In this Review, we highlight the importance of fungi as human pathogens and discuss the challenges we face in combating the devastating invasive infections caused by these microorganisms, in particular in immunocompromised individuals.

INTRODUCTION

It is widely accepted that fungal pathogens have an enormous influence on plant and animal life. Indeed, a recent report detailed the extraordinary and frightening impact of these pathogens on species extinctions, food security, and ecosystem disturbances (1). In contrast, the effect fungal infections have on human health is not widely recognized (Table 1), and deaths resulting from these infections are often overlooked. For example, the World Health Organization has no program on fungal infection, and most public health agencies—with the singular exception of the U.S. Centers for Disease Control and Prevention (CDC)—conduct little or no mycological surveillance. Most people in their lifetimes will suffer from superficial fungal infections that are generally easy to cure, but millions of individuals worldwide will contract life-threatening invasive infections that are much harder to diagnose and treat (Fig. 1).

Of particular concern is the high rate of mortality associated with invasive fungal infections, which often exceeds 50% despite the availability of several antifungal drugs (Table 1). The purpose of this Review is to estimate, from available scattered data, the disease burden caused by these pathogens; describe the types and impact of fungal infections worldwide; and illustrate the pressing need for more research in this field to facilitate the development of better diagnostic tests and therapies and of as yet unrealized preventative vaccines. Indeed, funding for medical mycology is greatly underrepresented when compared to other infectious diseases, although this may also reflect the number of applications for funding in the area. For example, from the total spent over the last 5 years on immunology and infectious disease research by the Wellcome Trust (a U.K. charitable body), the U.K. Medical Research Council, and the U.S. National Institutes of Health (NIH), only 1.4 to 2.5% was allocated specifically to medical mycology.

FUNGI AND HUMAN DISEASE

Superficial infections of the skin and nails are the most common fungal diseases in humans and affect ~25% (or ~1.7 billion) of the general population worldwide (2). These infections are caused primarily by dermatophytes, which give rise to well-known conditions such as athlete's foot (occurs in 1 in 5 adults), ringworm of the scalp (common in young children and thought to affect 200 million individuals worldwide), and infection of the nails (affects ~10% of the general population worldwide, although this incidence increases with age to ~50% in individuals 70 years and older) (2, 3). The incidence of each particular infection also varies with socioeconomic conditions, geographic region, and cultural habits. Mucosal infections of the oral and genital tracts are also common, especially vulvovaginal candidiasis (or thrush). In fact, 50 to 75% of women in their childbearing years suffer from at least one episode of vulvovaginitis, and 5 to 8% (~75 million women) have at least four episodes annually (4). In world regions with limited health care provision, HIV/AIDS adds nearly 10 million cases of oral thrush and 2 million cases of esophageal fungal infections annually (5). Oral infections are also common in babies and denture wearers, in individuals who use inhaled steroids for asthma, in leukemia and transplant patients, and in people who have had radiotherapy for head and neck cancers. These superficial infections are caused most often by several species of *Candida*, which are the second most numerous agents of fungal infection worldwide.

Invasive fungal infections have an incidence that is much lower than superficial infections, yet invasive diseases are of greater concern because they are associated with unacceptably high mortality rates. Many species of fungi are responsible for these invasive infections, which kill about one and a half million people every year. In fact, at least as many, if not more, people die from the top 10 invasive fungal diseases (Table 1) than from tuberculosis (6) or malaria (7). More than 90% of all reported fungal-related deaths result from species that belong to one of four genera: *Cryptococcus*, *Candida*, *Aspergillus*, and *Pneumocystis*. However, epidemiological data for fungal infections are notoriously poor because fungal infections are often misdiagnosed and coccidioidomycosis (also sometimes called "valley fever") is the only fungal disease that must be reported to the CDC. The statistics presented in Table 1 have been largely extrapolated from the few (mostly geographically localized) studies that have been performed (also see Supplementary Materials) and are undermined by the lack of accurate incidence data from many parts of the developing world. Consequently, our calculations may significantly underestimate the true burden of invasive fungal diseases.

The immune system of healthy individuals has effective mechanisms for preventing fungal infections, and the current incidence of invasive diseases is largely a result of substantial escalations over the last few decades in immunosuppressive infections, such as HIV/AIDS,

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and modern immunosuppressive and invasive medical interventions. For example, the vast majority of patients with cryptococcosis—for which we have comparatively strong epidemiological data, at least from economically developed countries—have quantitative or qualitative defects in cellular immune function, specifically in $CD4^+$ lymphocytes. AIDS is the major risk factor, although individuals who have received immunosuppressive medications, particularly in the setting of solid organ transplantation, are also predisposed. The CDC recently estimated the yearly global burden of cryptococcal meningitis to be nearly 1 million cases, with more than 620,000 deaths in sub-Saharan Africa (8). Mortality rates in AIDS patients are estimated to range from 15 to 20% in the United States and 55 to 70% in Latin America and sub-Saharan Africa, despite treatment (8).

Virtually all cases of cryptococcosis are caused by *Cryptococcus neoformans* and the closely related species *Cryptococcus gattii*. *C. neoformans* has a worldwide distribution, particularly in soil and avian habitats. In contrast, *C. gattii* is found in association with trees, and its geographical distribution is more limited. Exposure to *Cryptococcus* mainly occurs after inhalation of airborne organisms into the lungs. In susceptible individuals, both local and systemic spread can occur. However, the fungus has a preference for invading the central nervous system, and most clinical cases present with meningoencephalitis (inflammation of the brain and meninges) (Fig. 1).

Historically, *C. gattii* was found mainly in tropical and subtropical regions of the world and affected people who were not immunocompromised. However, since 1990, human and veterinary cases of *C. gattii*–induced cryptococcosis have been reported with increasing frequency on Vancouver Island, Canada (9), and this outbreak has since spread to mainland British Columbia and Washington and Oregon in the United States. Moreover, a second hypervirulent strain has emerged in Oregon (10). Although *C. gattii* has been isolated from samples of air, soil, and tree debris in outbreak regions, it has been difficult to link specific environmental sources to individual cases. For both outbreaks, most of the patients had little to no underlying immunodeficiency, although one could envisage genetic variation affecting host defense as the cause of disease in a subgroup of the population. Although the numbers of afflicted have thus far been relatively small, the case fatality rate has been high, ranging up to 33% (11). The evolution and rapid geographic expansion of this primary fungal pathogen raise concerns that *C. gattii* infections could emerge as an even greater threat to public health (1). This is underscored by evidence that human activity is contributing to the outbreak by promoting mixing of previously allopatric *C. gattii* lineages (12). Perhaps climate change is promoting a more hospitable habitat for *C. gattii*.

Some fungi normally live, in manageable numbers, on the host epithelial surfaces of most healthy humans, but can initiate life-threatening systemic infections in those who are immunocompromised. *Candida* species are the most common fungal etiological agent of life-threatening invasive infections in patients who (i) are severely immunocompromised, (ii) have endured invasive clinical procedures, or (iii) have experienced major trauma, and treatment requires extended stays in intensive care units. Indeed, *Candida* species are the fourth most common cause of nosocomial (hospital-acquired) bloodstream infections (13), and advanced medical procedures—such as the use of catheters, neonatal intensive care, major gut surgery, or liver transplantation—are predisposing factors to disseminated *Candida* infections. More than a dozen *Candida* species can cause disease, but in almost all patient groups and disease manifestations, *Candida albicans* dominates in terms of incidence (14). The occurrence of disseminated *Candida* infections has been surveyed frequently in the United States and in many European countries, and variable reported incidences ranging from 2.4 (Norway) to 29 cases (Iowa, United States) per 100,000 inhabitants have been published (14–23). A median value of 5.9 per 100,000 inhabitants
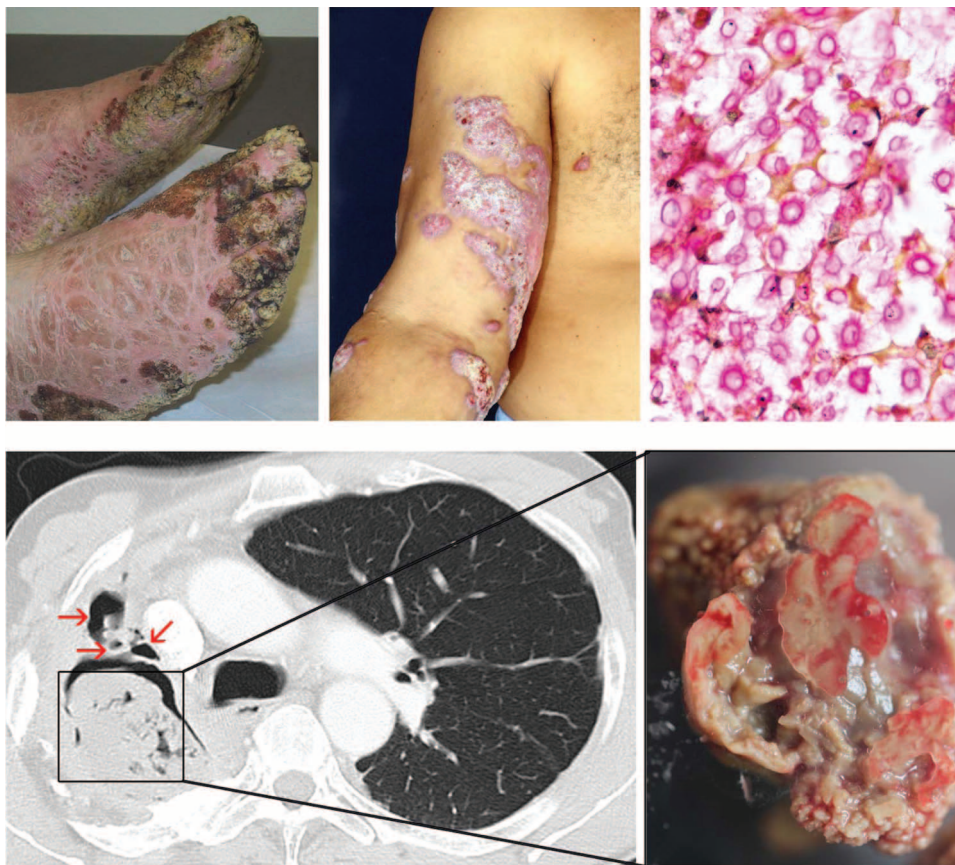
Fig. 1. Remarkable fungal infections. (Top, left to right) Chronic mucocutaneous candidiasis, chromoblastomycosis, and mucicarmine-stained histological section of the cerebellum of an AIDS patient who died from cryptococcal meningoencephalitis (demonstrating an abundance of pink-stained fungi). **(Bottom)** Computed tomography (CT) scan of the lungs of a patient showing a large fungal ball (aspergilloma, black box), which was surgically removed **(right)**. Three smaller cavities are also visible in the CT scan (red arrows), which is typical of chronic pulmonary aspergillosis.

allows an estimate (24) of the annual global incidence of *Candida* bloodstream infections at ~400,000 cases, with the most occurring in economically developed regions of the world. Crude and attributable mortality rates of 42 and 27%, respectively, are very high even in comparison to the most aggressive types of bacterial and viral sepsis (25).

Continuous lung exposure to *Aspergillus* species translates into the common occurrence of invasive infections in individuals with impaired immune function, in particular those with lower than normal numbers of neutrophils, solid organ transplant recipients, and patients on immunosuppressive therapies, such as high-dose corticosteroids. An emerging risk group includes patients with chronic obstructive pulmonary disease (COPD; also called emphysema). These opportunistic infections are caused primarily by *Aspergillus fumigatus* and *Aspergillus flavus*, spore-producing species that are found worldwide and are common in the environment.

Aspergillus infections also cause a gradual destructive disease in the lung called chronic pulmonary aspergillosis (Fig. 1), which complicates numerous pulmonary disorders including tuberculosis, COPD, and the systemic inflammatory disease sarcoidosis (26). It is estimated that more than 200,000 cases of invasive aspergillosis occur each year, including more than 10% of patients with acute leukemia, bone marrow and other transplant patients (>105,000 cases), and 1.3% of COPD patients admitted to the hospital (60,000 confirmed cases) (27, 28). However, because of underdiagnosis, these estimates likely represent only 50 to 65% of actual existing cases (29). Invasive aspergillosis carries an overall 50% mortality rate even if diagnosed and treated, but if the diagnosis is missed or delayed, then it is nearly 100% fatal. Certain patient groups do especially poorly (>75% mortality), notably those with COPD, those in intensive care units, mismatched hematopoietic stem cell transplant recipients, and those with brain infections (29). Chronic pulmonary aspergillosis is estimated to affect more than 3 million people worldwide and is especially common in patients with underlying lung diseases, including asthma, and has an at least 15% mortality in the first 6 months after diagnosis (equating to at least 450,000 deaths worldwide), often as a result of massive pulmonary hemorrhage (30, 31).

A. fumigatus is also a ubiquitous aeroallergen. Globally, millions of susceptible individuals develop pulmonary and nasal allergies to *A. fumigatus* and other airborne fungal particles. Severe asthma is linked to fungal allergy and *A. fumigatus* colonization (or infection) of the airway, principally in adults, but also in children (32–34). Severe asthma with fungal sensitization is thought to affect between 3.25 million and 13 million adults worldwide and to contribute to the 100,000 people who die from asthma annually (29). Allergic bronchopulmonary aspergillosis is a discrete allergic syndrome estimated to affect more than 4 million people with asthma and cystic fibrosis worldwide (35, 36), whereas allergic fungal rhinosinusitis affects ~1.3% of those with chronic rhinitis, ~12 million people (29).

Another common respiratory opportunistic pathogen is *Pneumocystis jirovecii*, which causes *P. jirovecii* pneumonia (PJP or PCP) in individuals with impaired immunity, especially those suffering from HIV/AIDS; in fact, PCP is an AIDS-defining disease (37). Other groups at risk include individuals with hematological malignancies, transplant patients, and individuals on prolonged immunosuppressive therapy, such as corticosteroids or methotrexate. *Pneumocystis* is thought to have coevolved with its mammalian host, with gradual differentiation into host-specific species and probable loss of its ability to survive independently. Transmission occurs via aerosols from patients with pneumonia or from early-life contact with family or community members who carry the organism in their lungs (38). Methods for culturing *Pneumocystis* in the laboratory have yet to be established, hindering its study.

Because of diagnostic inadequacies, the worldwide incidence of PCP is unclear, but it is likely to exceed 400,000 cases per year with mortality rates higher than 13% (that is, more than 52,000 deaths per year) and possibly as high as 80% (39, 40). These numbers were extrapolated

Table 1. Statistics of the 10 most significant invasive fungal infections.

Disease (most common species)	Location	Estimated life-threatening infections/ year at that location*	Mortality rates (% in infected populations)*
Opportunistic invasive mycoses			
Aspergillosis (*Aspergillus fumigatus*)	Worldwide	>200,000	30–95
Candidiasis (*Candida albicans*)	Worldwide	>400,000	46–75
Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	>1,000,000	20–70
Mucormycosis (*Rhizopus oryzae*)	Worldwide	>10,000	30–90
Pneumocystis (*Pneumocystis jirovecii*)	Worldwide	>400,000	20–80
Endemic dimorphic mycoses*†			
Blastomycosis (*Blastomyces dermatitidis*)	Midwestern and Atlantic United States	~3,000	<2–68
Coccidioidomycosis (*Coccidioides immitis*)	Southwestern United States	~25,000	<1–70
Histoplasmosis (*Histoplasma capsulatum*)	Midwestern United States	~25,000	28–50
Paracoccidioidomycosis (*Paracoccidioides brasiliensis*)	Brazil	~4,000	5–27
Penicilliosis (*Penicillium marneffei*)	Southeast Asia	>8,000	2–75

*Most of these figures are estimates based on available data, and the logic behind these estimates can be found in the text and in the Supplementary Materials. †Endemic dimorphic mycoses can occur at many locations throughout the world. However, data for most of those locations are severely limited. For these mycoses, we have estimated the infections per year and the mortality at a specific location, where the most data are available.

from clinical data gathered in the United States, where PCP occurs in AIDS patients on antiretroviral therapy at a rate of 3 infections per 100 person-years (*41*). With 1.2 million AIDS patients (*42*), we estimate that there are ~36,000 cases of PCP each year in the United States. The combined population of HIV-infected individuals in other economically developed countries is three times the size of that in the United States, suggesting that ~108,000 cases of PCP occur each year in the developed world. The population of HIV-infected people in the developing world is more than six times that of the economically developed countries; these individuals often do not have ready access to antiretroviral drugs, which means that they continue to be immunocompromised and less able to fight *Pneumocystis* infections. In Africa, for example, the number of AIDS-related deaths is estimated to be ~1.3 million each year. Because hospitalizations driven by *Pneumocystis* infection are estimated to be 11% or higher in these patients, we calculate that there are more than 143,000 new cases of PCP each year (*43–45*). Together, these data allow us to estimate that at least 400,000 new cases of PCP arise worldwide every year. Furthermore,

Pneumocystis may also contribute to the deterioration of COPD and thus to the annual 3 million deaths globally that are attributed to this disease (*46*, *47*).

Fungi also contribute to several other notable diseases, including infection-related blindness and the debilitating and disfiguring chronic subcutaneous infections. Fungal keratitides (infections of the cornea) are notable for their frequency (~1 million new fungal eye infections annually worldwide) and their contribution to blindness, particularly in Asia and Africa (*48*). The subcutaneous mycoses are generally uncommon and include chromoblastomycosis (Fig. 1), sporotrichosis, Madura foot (eumycetoma), and the fortunately rare entomophthoramycosis.

INFECTION AND IMMUNITY

The increased prevalence of fungal infections has stimulated one branch of fungi-related human disease research: investigations into the protective and nonprotective mechanisms of antifungal immune responses in the
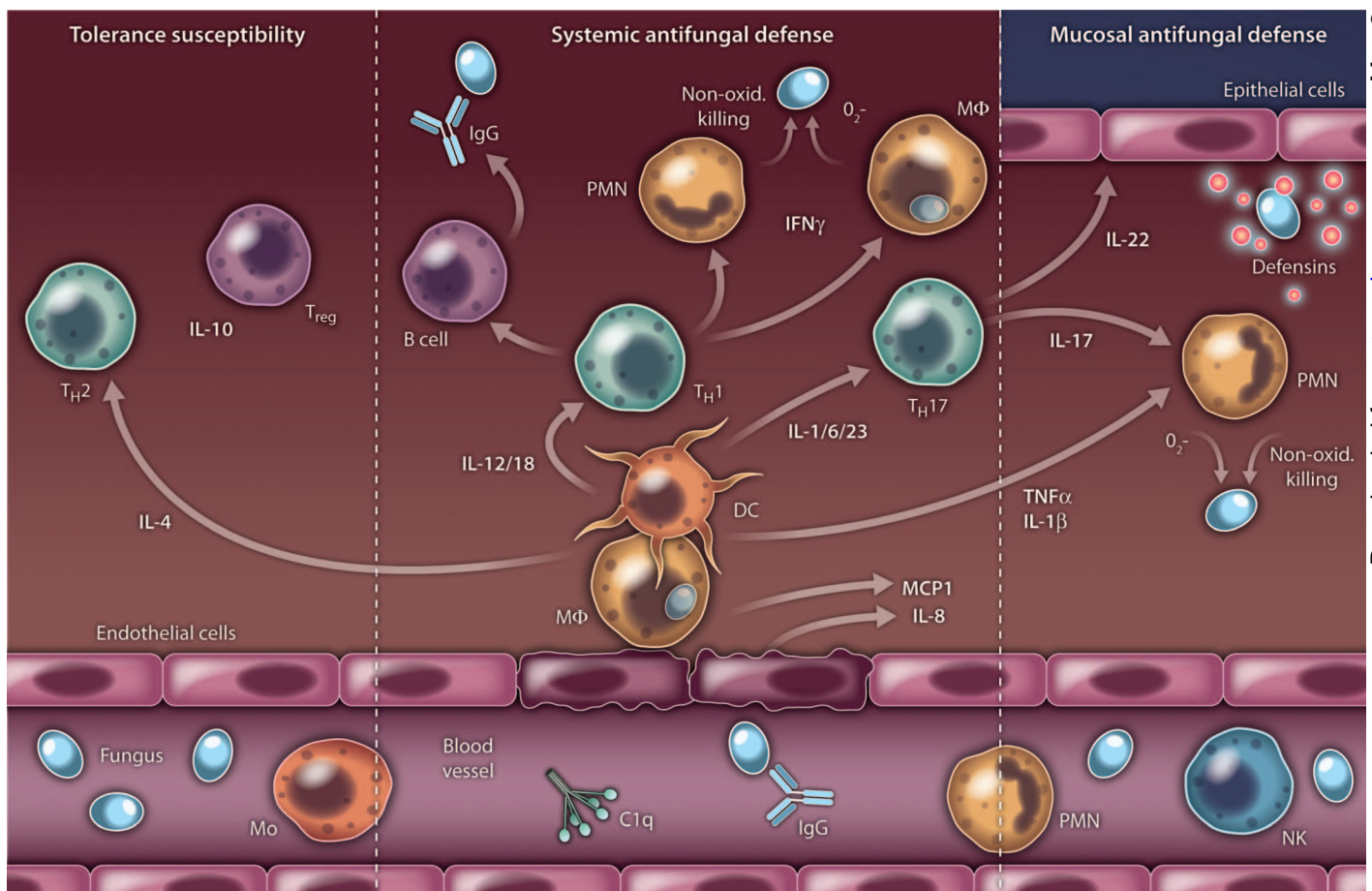
Fig. 2. Host defense mechanisms. In the human host, fungal infections are fought by both humoral (complement, antibodies) and cellular (phagocytes, T cells) immune mechanisms. Protective mechanisms in both systemic and mucosal antifungal immunity are based on chemotaxis and activation of neutrophils, monocytes/macrophages, and, in the case of mucosal immunity, epithelial cells, by chemokines and cytokines released by macrophages and proinflammatory T_H1 and T_H17 cells. In contrast, T_H2 and some other regulatory T lymphocytes (under the control of modulatory mechanisms such as indoleamine 2,3-dioxygenase) release anti-inflammatory cytokines that provide the tolerance mechanisms necessary to balance inflammation and tissue damage. However, when activated inappropriately or too strongly, the anti-inflammatory T_H2 and other regulatory T cell responses can down-regulate antifungal immunity and increase susceptibility to infection. CREDIT: C. BICKEL/*SCIENCE TRANSLATIONAL MEDICINE*

human host (Fig. 2). One prominent breakthrough was an appreciation of the importance of innate-immune Toll-like receptors (TLRs) in antimicrobial host defense. TLRs were originally identified in fruit flies as essential components for the development of resistance to infection with *Aspergillus* (and later, other fungi). The discovery of TLRs as key players in human innate immunity brought these so-called pattern recognition receptors (PRRs) to the attention of the entire scientific community and Nobel prizes in Medicine to scientists Jules Hoffman and Bruce Beutler in 2011. Fungal recognition by the innate immune system also led to the discovery of another class of mammalian PRRs, the C-type lectin receptors (CLR), as well as the identification of new intracellular signaling pathways modulated by CLRs (*49*). It turns out that there are hundreds of CLRs but only 11 TLRs encoded by the human genome. So it is not surprising that CLRs are now recognized to play a predominant role in antifungal immunity (*50*). In humans, deficiencies and polymorphisms in both PRR systems were subsequently found to cause susceptibility to a range of fungal infections (*51*).

Our understanding of adaptive immunity has also benefited from the research on antifungal host defense. Although scientists had functionally divided the diverse population of immune-regulatory CD4$^+$ T helper (T$_H$) cells in humans into T$_H$1 cells (critical for protective antifungal immunity) and T$_H$2 cells (generally nonprotective during fungal infections), T$_H$17 cells were identified only recently in the context of autoimmune diseases. T$_H$17 cells are now recognized to play essential roles in protective antifungal immunity at mucosal surfaces such as in the lungs and mouth. Indeed, genetic defects in T$_H$17 responses render patients susceptible to chronic mucosal fungal infections, such as occurs in hyperimmunoglobulin E syndrome, which results from mutations in the gene (*STAT3*) that encodes the signal transducer and activator of transcription 3 (STAT3) protein (*52*), or in autosomal dominant chronic mucocutaneous candidiasis, caused by mutations in the *STAT1* gene (*53*, *54*) (Fig. 1). However, unlike for other pathogens, the broader identification of factors that contribute to fungal susceptibility—for example, through genome-wide association studies—has been hampered by the lack of large patient cohorts.

Although we have made significant advances in our understanding of the underlying mechanisms of protective immunity, particularly to invasive infections with *Aspergillus*, *Candida*, and *Cryptococcus*, there remains much to be learned. For example, there are still no antifungal vaccines, and we know little about the immunopathological processes of the common noninvasive fungal infections, such as recurrent vulvovaginal candidiasis or dermatophytosis. Moreover, little is known about immunity to most other fungal
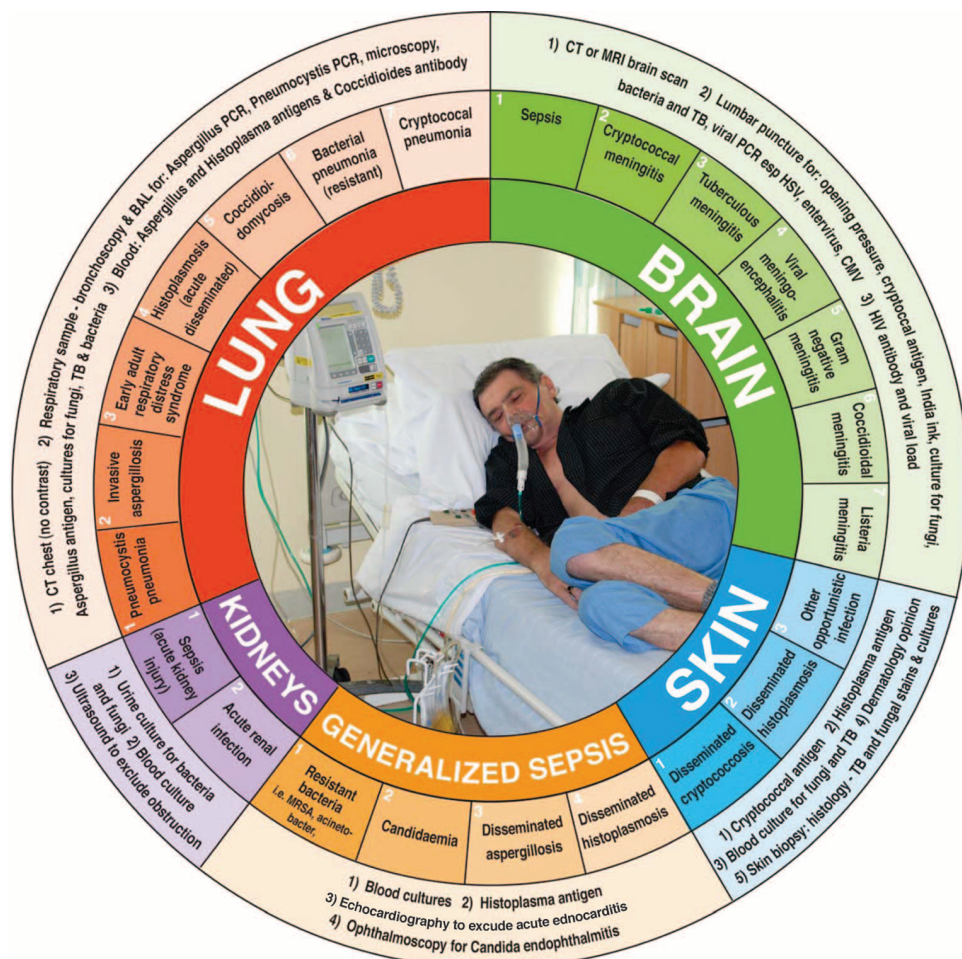

Fig. 3. Diagnostic dilemma. A representative clinical scenario that demonstrates the magnitude of problems associated with the diagnosis of fungal infections with current diagnostic tools. The figure shows the diagnostic considerations, starting with the organ that may be involved (inner circle), the most likely diagnoses (middle circle), and the testing required to rule in or out each of these diagnoses (outer circle). Certain features of the illness make some diagnoses much more or less likely, in particular, the patient's travel history and skin papule, whereas other abnormalities are nonspecific. The patient is a 53-year-old man (photograph displayed unaltered, with permission from patient) admitted after having been increasingly unwell for 10 days despite administration of oral antibiotics. He has a previous history of pneumonia (2 years earlier), is a 30–pack per year smoker, and takes 15 mg of prednisolone (a corticosteroid) and 50 mg of azathioprine (an immunosuppressive agent) for interstitial lung disease. He has traveled extensively in the United States, southern Europe, and the Middle East. On admission, he had a fever of 38.3°C, was slightly confused but fully conscious, had oxygen saturations of 94%, had a blood pressure of 95/60 (low), had a new nonulcerated dark papule on his right lower arm 1 cm across, and had nonspecific general wheezing in his chest. He had a slightly raised white blood cell count with neutrophilia, a raised serum creatinine indicative of significantly impaired renal function, and negative blood cultures. Nine months earlier, an HIV antibody test had been performed for employment purposes and was negative. His chest radiograph showed slightly increased haziness bilaterally and showed no improvement after 36 hours of treatment with broad-spectrum antibiotics. PHOTO CREDIT: G. WHITEHURST

pathogens, especially emerging pathogens (such as the less-common filamentous fungi) and endemic diseases in developing countries such as paracoccidioidomycosis. The potential role of fungal pathogens in the immune pathology of inflammatory and autoimmune diseases—for example, Crohn's disease, sarcoidosis, colitis (55), and arthritis—also requires attention by scientists.

CLINICAL ARSENAL

One of the greatest challenges in the field is the shortcomings in current techniques of diagnosing invasive fungal diseases (a typical clinical scenario is shown in Fig. 3). Culturing the organism is insensitive and slow; for example, a blood culture has a sensitivity of ~50% for invasive candidiasis and 0% for invasive aspergillosis. Although the identification of some infections is relatively straightforward—such as the detection of cryptococcal antigens in the blood and cerebrospinal fluid using a new point of care dipstick test (56)—the available diagnostics (polymerase chain reaction–based assays, fungal antigen detection, radiography, and x-ray CT scans) for most fungal infections suffer from a lack of specificity, sensitivity, or both and are unaffordable in developing countries.

A revealing example of the pervasive bottlenecks is the diagnosis of invasive aspergillosis, in which serum testing for fungal galactomannan is about 80% sensitive for the detection of this disease in neutropenic patients who are not taking itraconazole, voriconazole, and posaconazole—a therapeutic regimen called antimould prophylaxis—but only about 20% sensitive if the patients are taking these drugs (57). This diagnostic measure is even less efficient in intensive care or solid organ transplant patients (58). Chronic pulmonary aspergillosis, on the other hand, is often confused with tuberculosis both radiologically and clinically. Although the diagnosis of chronic pulmonary aspergillosis is theoretically uncomplicated, with detection of circulating anti-*Aspergillus* antibodies as a main diagnostic tool, antibody detection itself is far from standardized, with few commercial suppliers and a lack of consensus among clinicians on performance characteristics. These complexities, combined with subtle clinical presentations, often result in delayed diagnosis and compromise clinical care. Robust and simple diagnostics along with better screening methodologies are urgently needed.

Although antifungal treatments for invasive fungal infections have increased substantially in the past decade, when these drugs are prescribed, patient outcomes are similarly disappointing. Compared to other pathogens, fungi are evolutionarily close to humans, which lim-
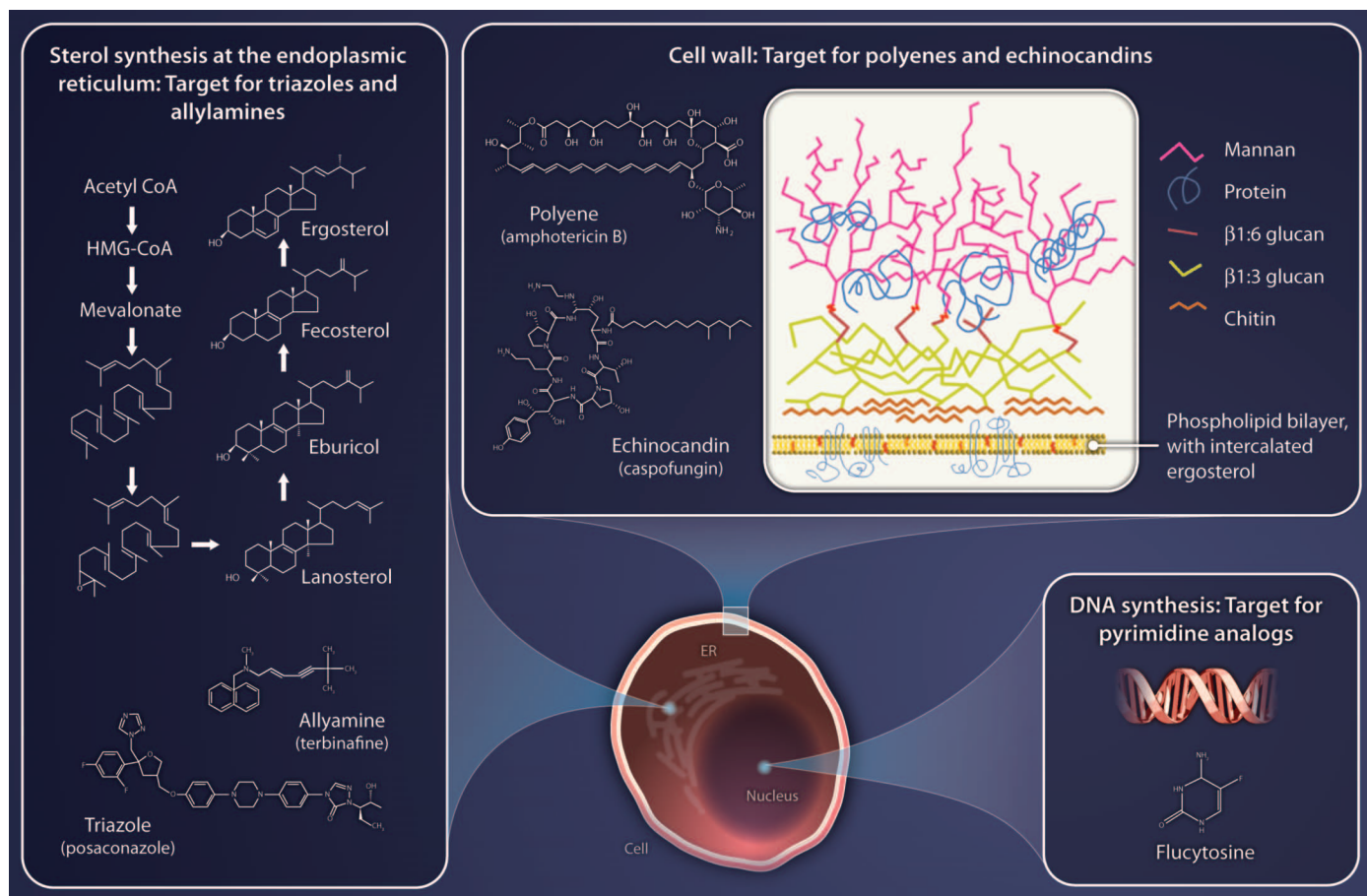
Fig. 4. Paucity of targets and therapeutics. Representation of the fungal cell pinpointing the pathogen components targeted by the various classes of antifungal drugs currently in clinical use. The structures of representative drugs are also shown. Adapted from (74) with permission. CREDIT: C. BICKEL/*SCIENCE TRANSLATIONAL MEDICINE*

its the scope of drug discovery and development. The global antifungal drug market was worth $9.8 billion in 2009 (59). The structural classes and targets of antifungal agents currently in clinical use are illustrated in Fig. 4. The introduction of the echinocandins (the only new class of drug licensed within the last 10 years) and the third-generation triazoles (voriconazole and posaconazole), in particular, has improved therapeutic options for many fungal diseases (60). Yet, antifungal drugs have had modest success in reducing the high mortality rates associated with invasive diseases. This is due, in large part, to the lack of early and directed antifungal therapy caused by the delays in disease diagnosis and fungal identification. These drugs also suffer from restrictions in route of administration, spectrum of activity, and bioavailability in target tissues (such as the brain) (61).

Further complications include toxicity, undesirable drug interactions, and the emergence of drug resistance. For example, interactions with statins, corticosteroids, and other drugs greatly limit the use of the triazoles. Because there is substantial interindividual variation in drug absorption and clearance, therapeutic drug monitoring (measuring drug concentrations in the blood at defined times after dosing) is required for optimum efficacy and to avoid toxicity (61). Although drug resistance has been less of a problem than with other classes of pathogens, a trend of increasing resistance to azoles has been reported for *Aspergillus* and partly blamed on environmental fungicide use (62). All of these factors and the high cost of antifungal therapies exacerbate the problem in resource-limited settings, where mortality rates are consequently much higher. Although combinations of existing drugs may yet prove to be more efficacious than single-drug therapy, new and cheaper drugs are desperately needed that are rapidly fungicidal and that overcome the various deficiencies listed above. Unfortunately, there are currently only a few antifungal drugs in preclinical development because very few companies are developing antimicrobials of any type, selective antifungal drug targets are lacking, and these drugs are not predicted to give a large enough financial return to attract Big Pharma. For infections that result from failures in immune function, cure may be improved if the immune deficit remits; thus, adjunctive immunotherapy is added to the antimycotic drug regimen, and drug treatment is continued for a long enough period to completely resolve the infection. However, this multipronged approach also has significant drawbacks. For example, concomitant treatment with antiretroviral drugs of patients with AIDS-related cryptococcosis can cause life-threatening central nervous system inflammation as a result of immune reconstitution inflammatory syndrome (63). For some infections, such as chronic pulmonary aspergillosis and coccidioidal meningitis, cure is rarely possible. Here, drug treatment is partially successful in controlling symptoms and in minimizing progression, but treatment usually needs to be lifelong to prevent relapse of the disease (64, 65). For asthma patients with fungal sensitization, antifungal therapy can help ameliorate disease (66, 67).

Antifungal prophylaxis with drugs can provide protection to susceptible individuals, although this is not always economically or medically justified, especially if the perceived risk is low. Furthermore, this approach is only partially protective and can, in certain cases, be contraindicated (68). Having a better understanding of who is at risk would greatly facilitate targeted prophylaxis and implementation of other prophylactic therapeutic measures such as protection with air filtration in hospitals. There is, however, a nearly complete lack of genetic and other prognostic biomarkers that would allow identification of these high-risk individuals. Validation of genetic and other risk factors for fungal diseases could transform the current practice of antifungal prophylaxis and empirical therapy as well as surveillance strategies.

The ideal solution would be to prevent fungal infection through vaccination, but currently, there are no vaccines in clinical use for any fungal pathogen. Advances in our understanding of antifungal immunity have led to the development of several vaccines against a number of fungal pathogens, and some have been shown to be effective in animal models (69). However, few have been translated to clinical trials because of lack of funding and difficulties in conducting efficacy trials in an era in which the highest-risk individuals routinely receive antifungal prophylaxis (70). In addition, two formidable scientific challenges will need to be overcome if protective vaccines against the invasive mycoses are to become a reality. First, many of the persons in high-risk vaccine target populations are immunocompromised. Vaccination responses are diminished in these patients, and the use of live vaccines is generally contraindicated. Second, antigen-specific T cell responses are paramount to protecting against natural infection with many of the fungi, such as *C. neoformans* and *P. jirovecii*. However, most currently licensed vaccines work by eliciting protective antibody responses (71). Advances in vaccinology, including the use of new adjuvants that promote T cell responses and elicit stronger responses in immunocompromised patients, are needed to overcome these barriers. However, for persons with AIDS who have severely depressed $CD4^+$ T cell counts, the most viable strategy may be to bypass "natural immunity" and induce protective responses by $CD8^+$ T cells or antibodies because these arms of the immune system remain relatively intact (72).

OUTLOOK

Despite the multifaceted importance of medical mycology, the study of fungal infections has lagged behind that of other pathogens, and lethal mycoses continue to undo the good work done in the treatment of cancers, intensive care patients, and severely immunocompromised individuals. Public health understanding of the impact of fungal disease in both the hospital and the community is limited.

So what is to be done? Perhaps most critical is to raise the general awareness of the significance of fungi as human pathogens. To understand the true scale of the problem, we need to gather better-defined and accurate epidemiological data. We also need to determine the socioeconomic impact of these diseases to mobilize investment in this research area, and stimulate scientific interest in tackling the huge challenges that we face in combating these diseases.

Three areas require immediate attention. First, better and more rapid diagnostics need to be developed to allow quicker implementation of appropriate therapeutics. Development of such tools would have an immediate impact on mortality rates and would also facilitate the gathering of more accurate epidemiological data. Second, we need safer and more effective antifungal drugs and to translate our growing knowledge of antifungal immunity into novel immunotherapeutic strategies, especially for the treatment of immunocompromised individuals. Indeed, there are already encouraging data that such approaches are possible, such as using adjunctive interferon-γ immunotherapy in the treatment of HIV-associated cryptococcal meningitis (73). Third, we need to get antifungal vaccines into clinical trials. Some vaccines may ultimately be of benefit not only for invasive infections but also for widespread superficial infections, such as vaginal candidiasis. Attainment of any one of these goals would have a substantial impact in reducing the global burden and negative impact of fungal infections.

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