



Recovery from serious fungal infections should be realisable for everyone

Fungal infections are neglected by social and political communities. However, they affect more than a billion people, resulting in approximately 11.5 million life-threatening infections and more than 1.5 million deaths annually.^{1,2} There have been enormous advances in fungal diagnostics and antifungal drug development over the past 20 years, but most of the world's population has not yet benefited from these advances. *The Lancet Infectious Diseases Fungal Infections Series* brings readers up to date on fungal infections and addresses how fungal infection management can be integrated into health systems in low-income and middle-income countries (LMICs).

Many medical specialties see patients with fungal infections, including general practitioners (eg, cutaneous, thrush), paediatricians (almost all infections), dermatologists (eg, cutaneous, sporotrichosis), ophthalmologists (fungal keratitis), oncologists and haematologists (candidiasis and invasive mould infections), intensive-care-unit practitioners (candidiasis and aspergillosis), internal medicine and AIDS physicians (eg, cryptococcosis, histoplasmosis, pneumocystis pneumonia), ear, nose, and throat surgeons (external otitis, fungal rhinosinusitis), and respiratory physicians (all forms of aspergillosis and fungal asthma), which complicates provision of holistic education about fungal infections. In countries with developed health systems, fungal infections are diagnosed and treated, although many are still missed and only identified at autopsy.^{3,5} However, in LMICs the absence of diagnostic tools and antifungal drugs, plus insufficient training of health-care staff, ensures that the mortality and morbidity of fungal infections remains unacceptably high. Kneale and colleagues⁶ highlighted many country differences in antifungal drug availability and price in 2015. Amphotericin B is not available to a population of 481 million, and where it is available the price varies from less than US\$1 per day to \$171 per day. Flucytosine is unavailable to more than 2.9 billion people in more than 70% of the countries investigated. Conversely, the situation was better for azole drugs. Fluconazole was licensed in 88.6% of the countries surveyed, with a daily price variation (750–800 mg) of less than \$1 to \$31. Itraconazole was unavailable to more than 78 million people, with a daily price variation of less than \$1 to \$102.⁶ Fluconazole has been on

WHO's Essential Medicines List for many years, amphotericin B and flucytosine were listed in 2013, and itraconazole and voriconazole were added in 2017.⁷

Cutaneous infections—the most common group of fungal diseases—do not threaten life but often lead to substantial social stigma. Most serious fungal infections demand high-level medical skill, affect all body systems, are usually camouflaged by other well known diseases, and kill more patients with AIDS than tuberculosis or bacterial infection. Cryptococcal meningitis, pneumocystis pneumonia, and disseminated histoplasmosis are always lethal unless diagnosed and treated early and correctly.⁸ Andrew H Limper and colleagues⁹ review the opportunistic infections associated with advanced HIV that kill millions of people each year.

Fungal infections also compromise cancer outcomes. Intensive care, renal dialysis, major gastrointestinal surgery, hyperalimentation, sepsis, and pancreatitis are all linked to hospital-acquired fungal infections, with mortality rates of around 50%. A L Colombo and colleagues¹⁰ review the new risk assessment, diagnostic strategies, and therapeutic approaches for candida and invasive mould infections.

Fungal outbreaks affect a wide diversity of populations, and are caused by many different fungal pathogens from various sources. Kaitlin Benedict and colleagues¹¹ review community-acquired and health-care-associated outbreaks, highlighting the challenges that arise during investigations.

Chronic pulmonary aspergillosis complicates many pulmonary conditions and might be misdiagnosed as tuberculosis. Fungal asthma is poorly controlled and affects millions of people with asthma. Aspergillus sensitisation in chronic obstructive pulmonary disease is associated with poor lung function and hospital admission with fatal invasive infection.¹² David W Denning and Arunaloke Chakrabarti¹³ summarise knowledge of pulmonary fungal infections in non-immunocompromised people.

In many rural communities, especially in tropical areas, fungal disease is linked to poverty (mycetoma, chromoblastomycosis, phaeohiphomyces, sporotrichosis, and fungal keratitis). Furthermore, globally there are areas

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where fungal infections are endemic and affect healthy people, including histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, and *Talaromyces marneffeii* infection. Flavio Queiroz-Telles and colleagues¹⁴ review neglected fungal infections (only mycetoma and chromoblastomycosis are recognised as neglected by the WHO).

Fungal infection does not escape the global emergency of antimicrobial resistance. David S Perlin and colleagues¹⁵ review this situation, especially the global spread of azole-resistant *Aspergillus* spp of environmental origin and the rise of multidrug-resistant *Candida glabrata* and *Candida auris*, and address antifungal stewardship.

Because current antifungal drugs are imperfect, new approaches are vital, including those that support patients' host defences. Adjunctive host-directed therapy could be an option to improve outcomes for patients. Darius Armstrong-James and colleagues¹⁶ discuss the value of such novel therapeutic strategies as viable adjuncts to antifungal therapy.

Finally, Donald C Cole and colleagues¹⁷ describe the deficiencies of health-care systems regarding fungal diseases. Using examples, they recommend integration of diagnostics and clinical expertise into existing HIV, tuberculosis, diabetes, chronic respiratory disease, and blindness health programmes. A better provision of enhanced laboratory capacity to detect fungal diseases, and procurement and distribution of low-cost, high quality antifungal drugs, are basic measures that should be implemented in LMICs. Public health mycology needs strengthening.¹⁸

The Global Action Fund for Fungal Infections (GAFFI) is supporting a new model for reducing illness and death due to fungal infection in Guatemala, in association with a local non-governmental organisation (Asociación de Salud Integral), which operates one of the largest comprehensive HIV units in Guatemala.¹⁹ The programme is based on an existing microbiology laboratory, a linked clinical service with fungal infections proficiency, and a national network of 14 HIV centres. GAFFI is funding and providing technical expertise to provide a comprehensive non-culture-based diagnostic service. This new toolkit, combined with a focused education programme for health professionals, is allowing rapid diagnosis of fungal infections. So far, 90% of HIV units in Guatemala have had advanced training in fungal infections in AIDS, a

central reference laboratory has been equipped with rapid diagnostic equipment, and techniques and response times for test results have been reduced from more than 1 week to 72 h (or less). Rapid non-culture-based tests, fast sample transport, advanced clinical training, and internet ordering and results delivery are together transforming care across Guatemala. GAFFI's pioneering project in Guatemala paves the way for other regions and countries.

GAFFI has called for 95% of the world's population to have access to fungal disease diagnostics and treatment by 2025 (95–95 by 2025).¹ An aspect of this call is provision of reference laboratories in every country in the world, and provision of a critical mass of expertise and a complete portfolio of diagnostic tests. By scaling up the model in Guatemala, and related models across the globe, we are confident that patients with fungal infections will be properly diagnosed and treated. Involvement of governmental health-care systems, academia, industry, and the public is essential to stimulate the economic, political, and scientific measures needed to develop a network of health professionals trained in fungal infection management, equipped laboratories with rapid diagnostic techniques, and availability of antifungal drugs to treat at affordable prices in LMICs.

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