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Review Article

Burden and Determinants of Emerging and Re-emerging Fungal Pathogens: Resistance to Antifungal Drugs, Mechanisms, and Future Mitigation Strategies

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A B S T R A C T

Emerging and re-emerging human fungal pathogens are becoming more closely associated, with 13,000,000 morbidity and 1500000 mortality incidences per year. Human fungal pathogens are mainly found in critically ill and immunocompromised patients. Climate change, agricultural activities, occupational hazards, deforestation, migratory trends of people, clay dispersion, decreased immunity of patients, biofilm development, medication tolerance, and resistance to antifungal therapies are all factors that contribute to the emergence of fungal diseases. This document makes recommendations for those who set policy, general population health experts, and other respective bodies to improve the laboratory infrastructure and monitoring, promote innovative and affordable investigations, and execute public health programmes to combat these fungal infections, including preventing the emergence of antifungal medication resistance.

Keywords: Fungal Pathogens, Antifungal Drug Resistance, Antifungal Drug Tolerance, Invasive Fungal Infections, Immunocompromised Patients, Resistance Detection

Introduction

Human fungal pathogens are a serious threat to public health as the cases of illness and deaths due to these pathogens are continuously increasing.[1] Globally, they are responsible for more than 13,000,000 morbidity and 1500000 mortality incidences per year.[2–5] Most often, fungal infections are significantly associated with critically ill and immunosuppressed patients, with increasing mortality rates, despite having historically been associated with severe infections in immunosuppressed individuals and patients who are hospitalised in the critical-care unit.[6] Critically ill and immunocompromised individuals are more susceptible to dimorphic fungi like Histoplasma, Blastomyces, Coccidioides, and Paracoccidioides, as well as fungal pathogens like Cryptococcus, Candida, Aspergillus, and Pneumocystis.[7]

Human fungal infections range from mucocutaneous infections that are not life-threatening to serious invasive infections that affect almost any organ or system of the body.[5,8] Infections of the skin, hair, nails, mucosal surfaces, and allergy symptoms are examples of superficial infections or mycosis caused by primary or opportunistic human fungal pathogens. Fungi also cause internal organ-related invasive infections which may be typically life-threatening. The main risk factor for Pneumocystis pneumonia in HIV patients is a decline in CD4+ lymphocyte activity due to defects in cell-mediated immunity.[2,4,9] Additionally, infectious diseases like influenza,[10–13] COVID-19,[14–16] and tuberculosis,[17–19] as well as chronic conditions or co-morbidities like asthma,[20,21] cirrhosis,[22–24] cancer,[25–27] diabetes,[28–30] cystic fibrosis (CF),[31–33] transplant recipients,[34–36] and chronic obstructive pulmonary disease (COPD)[11,37–39] are the risk factors that complicate fungal infectious diseases. Co-infections with infectious and non-infectious diseases increase hospitalisation day and cost, mortality rates, and antifungal resistance, and decrease treatment options.

Climate change, agricultural activities, occupational hazards, deforestation, migration patterns of people, soil dispersal, decreased patient immunity, enhanced infection detection, and diagnostic examinations are all factors that contribute to the emergence of fungal diseases.[40,41] The increasing incidence of illness and death due to fungal infections is directly associated with antifungal resistance, tolerance to antifungal drugs, and biofilm formation.[1] A partial growth after 24 hours, which can be seen in susceptibility testing and at inhibitory doses of medication, is a sign of antifungal tolerance.[42] Comparatively, resistance to antifungals is the absence of a detectable toxic impact on treating human fungal pathogens. In order to treat fungal infections, only limited classes of antifungals (considering their mode of action) notably polyenes, azoles, echinocandins, allylamines, and flucytosine are available.[43–45] Allylamines are used to treat superficial infections, but the remaining four drug classes are excellent against invasive mycoses. However, beyond their side effects (in terms of their toxicity, spectrum, safety, and pharmacokinetic properties), currently, it is common to see resistance to one or more of the aforementioned clinically prescribed antifungal drugs.[46]

The impact of important fungal pathogens (Pneumocystis jirovecii, Cryptococcus gattii, Candida auris, Histoplasma spp., Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans), as well as the severity of the harm to public health posed by important fungi with high levels of resistance to antimicrobials, is evolving into a global problem. The significant effects of these fungal pathogens may be due to a week-long laboratory infrastructure and monitoring system, investigation and innovative activities, and the implementation of global health initiatives in each country. Consequently, the focus of this review is on clinically significant fungal diseases, risk factors, antifungal resistance, and the significance of preventative and diagnostic measures to safeguard public health.

Emerging and Re-emerging Fungal Pathogens

Pneumocystis jirovecii

Pneumocystis jirovecii is a pathogen that is prevalent globally and causes Pneumocystis jirovecii pneumonia (PJP) (Table 1). The populations most vulnerable to this disease are immunocompromised individuals (HIV/ AIDS, cancer, iatrogenic immunosuppression after solid organ transplantation (particularly renal), autoimmune and inflammatory illnesses, and nephritic syndrome).[47–49]

Cryptococcus gattii

The yeast pathogen Cryptococcus gattii, which causes cryptococcosis, is predominantly present in the environment, particularly in the tropical and subtropical regions of the world (Table 1). After spores are inhaled, the human host might become infected. Due to spore inhalation, it primarily affects the respiratory system before easily spreading to the central nervous system (CNS), blood (causing cryptococcaemia), and other body systems.[50,51]

Candida auris

The “invasive candidiasis” may be brought on by the widely common yeast infection caused by Candida auris (Table 1). The human body’s bones, eyes, heart, CNS, blood (causing candidaemia), and internal organs are all infected by C. auris.[52–54]

Histoplasma spp.

Globally dispersed dimorphic fungi called Histoplasma spp. cause an illness known as histoplasmosis by living as mould and yeast-like organisms in the environment (soil, bird and bat droppings, and at body temperature). Lungs are initially impacted, followed by the CNS, blood, and other body systems.[55]

Candida parapsilosis

Invasive candidiasis, which affects the blood (causing candidaemia), heart, CNS, eyes, bones, and internal organs, is caused by the newly discovered, worldwide dispersed Candida parapsilosis yeast (Table 1).[56,57]

Lomentospora prolificans

Lomentospora prolificans is a globally distributed, emerging opportunistic fungal pathogen that causes invasive lomentosporiosis in humans (Table 1). It primarily infects the respiratory system and spreads to the blood, CNS, and other organs.[40,58]

Cryptococcus neoformans

The disease known as cryptococcosis is caused by the opportunistic yeast pathogen Cryptococcus neoformans, which is common in soil and rotting wood habitats (Table 1). When the infection is absorbed from the environment through the respiratory route, it mostly affects the human lungs. From there, it spreads to the CNS and blood, where it causes cryptococcal meningitis and cryptococcaemia, respectively.[59]

Aspergillus fumigatus

An environmental mould called Aspergillus fumigatus can infect people and produce aspergillosis, which can range from an allergic reaction to acute invasive aspergillosis through colonisation and semi-invasive illness (Table 1). It is ubiquitous in nature, easily inhaled from the environment, predominantly affects the respiratory system (e.g., lung) causing pulmonary disease, and disseminates to other systems (e.g., CNS).[60–62]

Candida albicans

Candida albicans is a pathogenic yeast distributed around the world (Table 1). It is a component of the normal human microbiome that lives in the mouth, throat, gut, vagina, and skin. It can cause infections of the mucosae, such as cutaneous candidiasis and oropharyngeal, oesophageal, vulvovaginal, and heart candidiasis, as well as invasive candidiasis, which affects the blood (causing candidaemia), heart, CNS, eyes, bones, and other similar internal organelles.[63]

Table 1.Emerging and Re-emerging Fungal Pathogens

Emerging and Re-emerging Fungal Pathogens	Associated Disease	Affected Organs or Systems	Risk Groups	Treatment Options	Antifungal Resistance Report
Pneumocystis jiroveci[i47–4]*9*	*Pneumocystis jirovecii pneumonia* (PJP)	Lungs	• Nephritic syndrome, cancer, iatrogenic immunosuppression following solid organ transplantation, particularly renal, and HIV/ AIDS	Cotrimoxazole	Unknown
Cryptococcus gatti[i50,5]*1*	Cryptococcosis	Blood (cryptococcaemia), central nervous system (cryptococcal meningitis), lungs, and other bodily components	• Possessing a prior immunosuppression (e.g., oral corticosteroid use, organ dysfunction), being critically ill, immunocompromised, elderly, and possessing these characteristics	Liposomal amphotericin B is combined with flucytosine for severe CNS or pulmonary infections and fluconazole for asymptomatic infections or mild to moderate pulmonary infections	Unknown
Candida auris[52–54]	Invasive candidiasis	Central Nervous System Heart Blood (candidaemia) Other internal organs Eyes Bones	• Cancer patients • Patients with renal impairment • Organ transplant patients	Echinocandins	Known

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Histoplasma spp[5]5	Histoplasmosis	Blood, central nervous system, lungs, and other bodily organs	• People who are immunocompromised and in critical condition, such as HIV, cancer, and organ transplant recipients	No medication (healthy patients) Itraconazole followed by amphotericin B (severe cases) Itraconazole (moderate and chronic cases)	Known
Candida parapsilosis[56,57]	Invasive candidiasis	Blood (candidaemia), heart, central nervous system, eyes, bones and internal organs	• Critically ill and immunocompromised patients (cancer and bone marrow or organ transplant patients)	Echinocandins	Known
Lomentospora prolificans[40,58]	Invasive lomentosporiosis	Blood, central nervous system, various organs, respiratory system, and systemic infections, which are typically fatal	• Critically ill and immunocompromised patients	Voriconazole and terbinafine	Known
Cryptococcus neoformans[59]	Cryptococcosis	Lungs Nervous system (meningitis caused by cryptococcal yeast) Blood (cryptococcaemia)	• HIV • Iatrogenic immunocompr mised • Autoimmune disease • Decompensated liver cirrhosis	Fluconazole Amphotericin B in combination with flucytosine (severe case)	Unknown
Aspergillus fumigatus[60–62]	Invasive aspergillosis	Respiratory system Central nervous system	• Haematological malignancy • Chronic lung disease • Transplantation (both solid and bone marrow) • Corticosteroid therapy • Neutropoenia • Chronic liver disease	Liposomal amphotericin B	Unknown
Candida albicans[63]	Oropharyngeal candidiasis Oesophageal candidiasis Vulvovaginal candidiasis Cutaneous candidiasis Invasive candidiasis	Human microbiota Central nervous system, blood, heart, eyes, bones, and other internal organs	• Terminally ill • immunocompromised patients	Echinocandins	Unknown

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Mechanisms and Effects of Antifungal Medication Resistance

Currently, clinicians prescribe five classes (polyenes, azoles, echinocandins, allylamines, and pyrimidine analogues) of antifungal drugs.[64–66] These antifungal drugs commonly target the ergosterol biosynthesis pathway, the fungal cell wall, or the synthesis of fungal nucleic acids (DNA/ RNA) (Table 2).[67,68] However, along with their side effects, resistance can be seen to one or more of these clinically prescribed antifungal drugs using different survival strategies viz., (i) drug target mutations that reduce their affinity for the drug, (ii) overexpression of the targeted protein by altering the promoter region of the gene, (iii) expression of an efflux system to reduce the drug's concentration inside the fungal cell, (iv) drug degradation, and (v) pleiotropic drug responses (Table 2).[66,69–74] According to studies on the molecular causes of resistance to azole in yeast, the ergosterol biosynthetic pathway, for example, underwent four major changes after the action of azole: (1) a decrease in the affinity for azole for its target, (2) an increase in the number of the azole target, (3) an alteration of the ergosterol biosynthetic pathway, and (4) a reduction in intracellular azole accumulation.[75–77]

Contributing Factors for Emerging Antifungal Resistance

The emergence of novel and resistant infectious diseases in people, plants, and animals is accelerated by host shifts (e.g. human exposure, changing at-risk groups), globalisation, urbanisation, trade, agrochemical use (e.g. fungicides), climate change, increased environmental hotspot areas, change in microbiota and virulence, habitat disruption, and biodiversity loss (Figure 1).[78–80] Due to these factors, new fungal pathogens are able to emerge in human populations by coming into contact with naive hosts in their geographic niches.[78,81] Additionally, the overuse of antifungal agents in agriculture and medicine has caused a worldwide outbreak of drug-resistant fungal pathogens, which has outpaced the development of new antimicrobial therapies.[81] As the effects of anthropogenic environmental modification and climate change are felt by our planet, new fungal pathogens will continue to appear and disappear.

Table 2.Antifungal Drug Resistance Mechanisms of Human Fungal Pathogens

Antifungal Classes	Effect on Microbial Cells	Mechanism of Action	Resistance Mechanisms
Polyenes	Fungicidal	▪ Alteration of membrane function by binding to ergosterol	• Reduction of ergosterol concentration in the cell membrane due to defects in the ERG3 or ERG6 gene
Azoles	Fungistatic	▪ Alteration of ergosterol biosynthesis by blocking 1, 4-α-lanosterol demethylase	• Drug efflux by multi-drug transporters (ABC transporters) • Decrease in drug affinity through mutation in Erg11p or over expression of ERG11 gene
Echinocandins	Fungistatic or fungicidal	▪ Alteration of cell wall biosynthesis by inhibiting 1,3-β-D glucan synthase	• Mutation in Fks1 and Fks2 binding units
Allylamines	Fungistatic	▪ Inhibition of ergosterol bio-synthesis by inhibiting squalene epoxidase	• Interference from multidrug transporters • Mutations in the squalene epoxidase gene
Pyrimidine analogues	Fungicidal	▪ Inhibition of nucleic acids (RNA and DNA) synthesis	• Mutation in cytosine permease and deaminase

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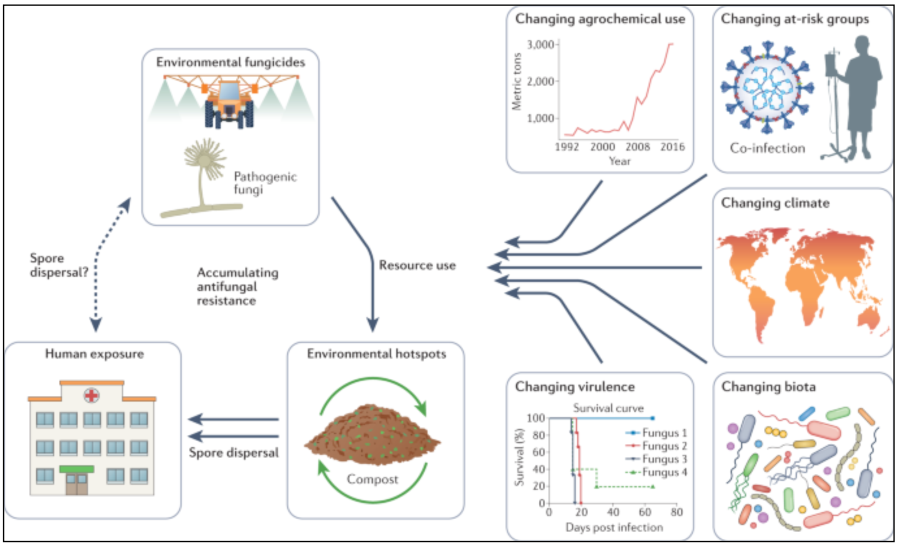

Figure 1.Contributing Factors for Emerging Antifungal Resistance[43]

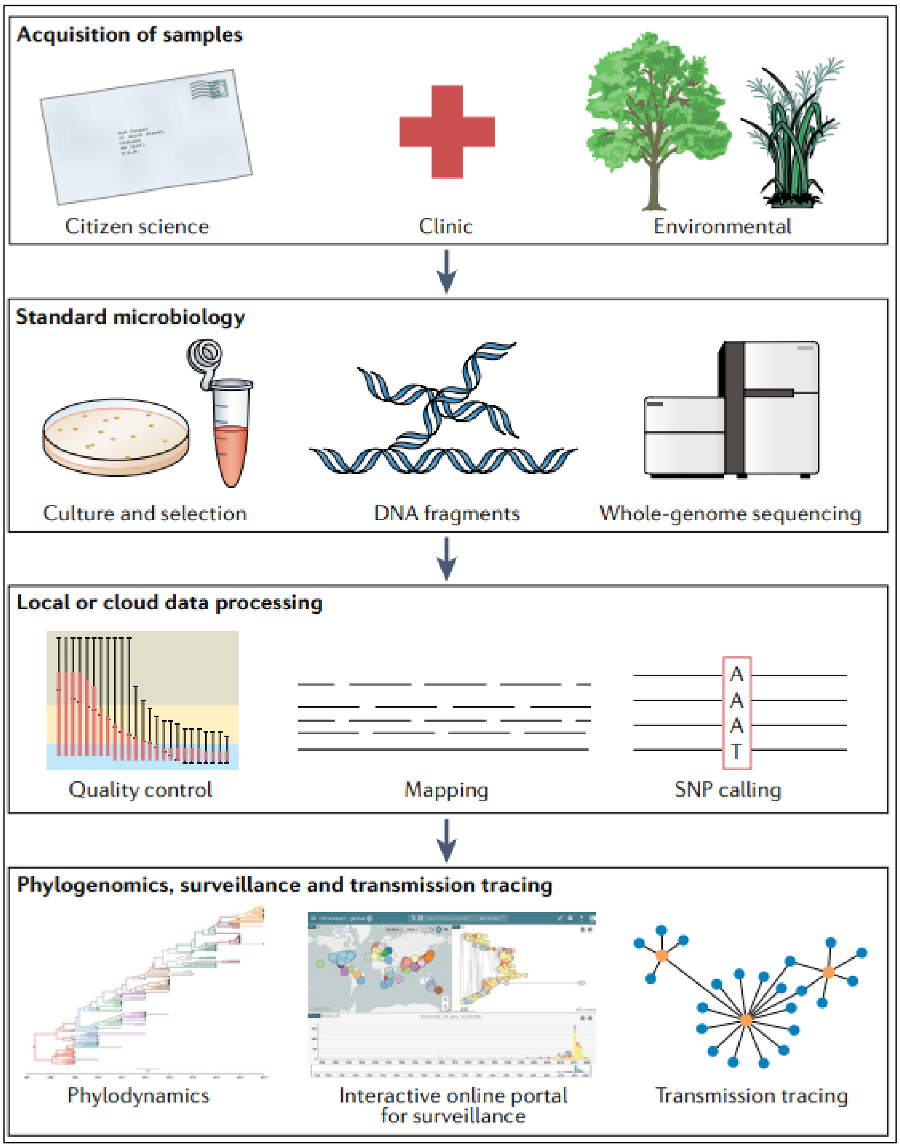

Figure 2.Resistance Detection, Tracking, and Surveillance[43]

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Resistance Detection, Combat, and Surveillance

Fungal samples can be obtained from the environment or medical facilities, as well as by interacting with the public as "citizen scientists".[82] From these materials, traditional, known microbiology techniques can cultivate and select isolates that are prepared for genomic DNA extraction. These DNA fragments are employed to create a sequencing library for whole-genome sequencing (WGS). There are numerous technologies for sequencing that can produce both long-read and short-read sequence data. Before mapping to a reference genome, raw sequencing data needs to be quality controlled, either locally or using cloud computing. High-confidence single-nucleotide polymorphisms (SNPs) can be used to deduce the evolutionary origins of alleles linked to drug resistance. Tracing transmission episodes is made possible by phylodynamic inference and the creation of interactive internet portals (such as Nextstrain[83] or Microreact[84]) that are accessible to academicians and physicians (Figure 2).

Concluding Remarks

Fungal infections are a growing global public health concern, particularly among critically ill and immunosuppressed patients. Anthropologic environmental factors contribute to the global expansion of both the incidence and geographic range of fungal infections. Fungal diseases are a neglected and growing threat to global health, made worse by the rapid establishment of antifungal resistance and the lack of access to effective diagnoses and treatment options. Despite growing concern, fungal infections receive little funding and attention, have limited access to high-quality diagnostics and treatments, and lack high-quality data on the frequency of fungal diseases. This study provides suggestions for policymakers, public health professionals, and other stakeholders to enhance the response to these fungal diseases, along with preventing the spread of antifungal drug resistance.

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