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6

The rising threat of fungal diseases and antifungal resistance

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In this briefing document we will explore the fascinating world of fungal diseases and consider the challenges of the rise in levels of antifungal drug resistance.

Fungal diseases

You may think of fungi just as mushrooms in the forest, moulds growing on food, or yeasts that are used to make beer. There are probably over 5 million different species of fungi (yeasts and filamentous fungi) and some of them can infect us and cause serious disease. These are known as fungal pathogens.

Fungi are all around us - in the soil, on the surface of plants, drifting in the air as spores, and even growing on your skin right now. Normally they live harmlessly alongside us but, given the right conditions, they can start to invade our bodies and cause disease.

One of the most well-known fungal diseases is athlete's foot - an itchy rash that commonly grows between the toes. It is caused by a range of microscopic filamentous fungi known as **dermatophytes** that feed off the dead skin cells. Ringworm is another fungal skin infection that creates a red, circular rash with raised edges. Both conditions are quite contagious and can be passed from person to person or even caught from infected animals. A fungus called *Malassezia globosa* is now thought to be the principal cause of dandruff.

Some fungal diseases are more severe and cause life-threatening illnesses (see Figure 1).

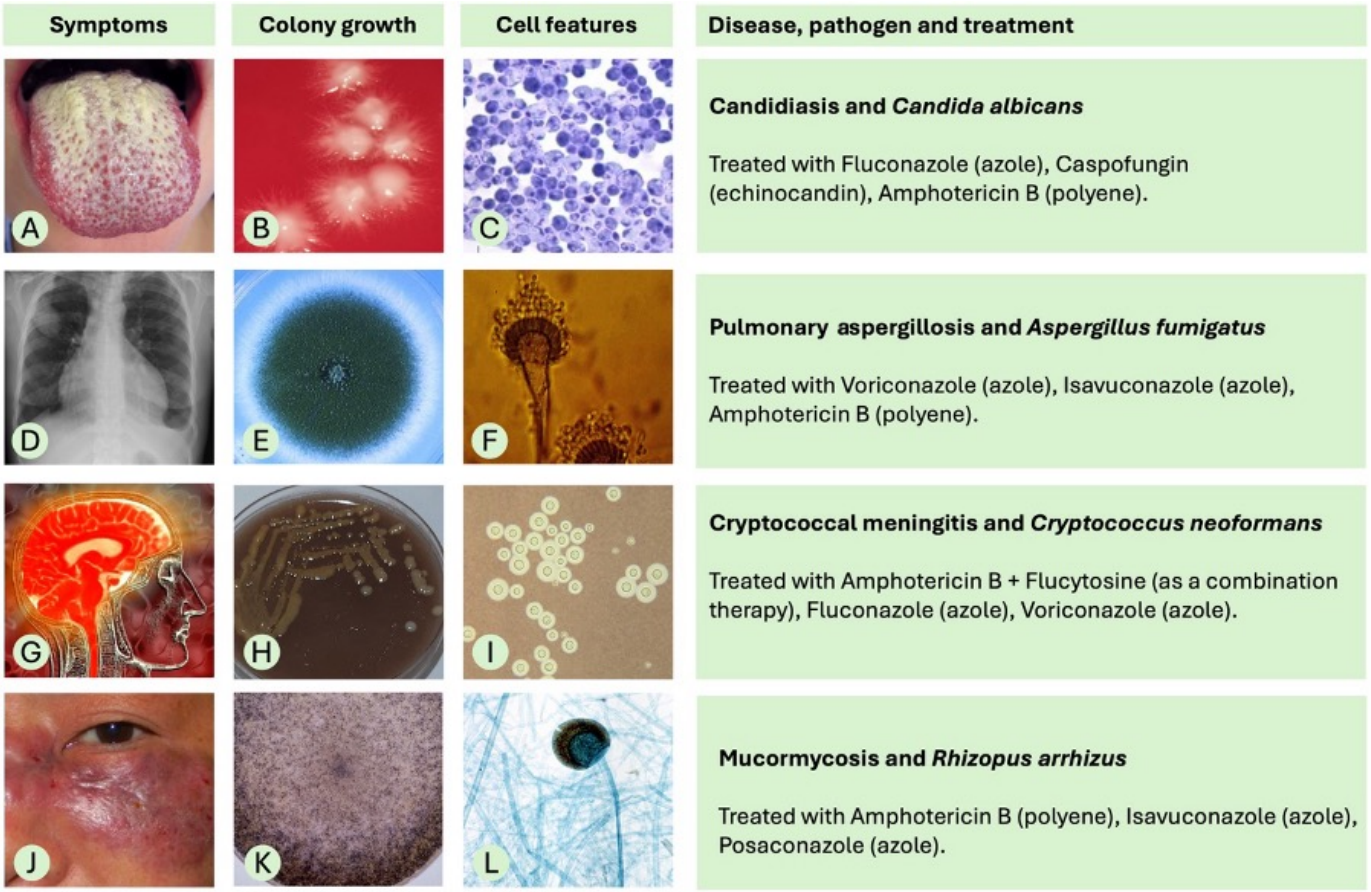

Figure 1: *Examples of important life-threatening fungal diseases that affect human health, highlighting disease symptoms, appearance of fungi grown in the lab on agar plates and key cellular characteristics visible under the microscope.*

Each disease is presented alongside a list of the antifungal drugs most commonly used in their treatment. A-C: Candidiasis and *Candida albicans*. D-F: Pulmonary aspergillosis and *Aspergillus fumigatus*. G-I: Cryptococcal meningitis and *Cryptococcus neoformans*. J-L: Mucormycosis and *Rhizopus arrhizus*.

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Candidiasis and candidaemia - These are yeast infections that can affect the mouth (thrush), vagina, or other moist areas of the body. Nearly everyone has some ***Candida*** yeasts on their skin and inside their guts - which is perfectly normal, but symptomatic infections can occur in people with weakened immune systems. Infection can be restricted to the skin or become invasive and enter the blood stream in immuno-compromised patients, or during surgery. Mortality rates in some patient groups can be very high (>50%).

Invasive aspergillosis - This disease is caused by inhaling spores of a mould called ***Aspergillus fumigatus***. Infections can spread through the body and impact organs such as the lungs, kidneys or brain. Again, it mostly affects people with weakened immunity. The same fungus can also cause allergic disease - associated with asthma and conditions such as cystic fibrosis.

Cryptococcal meningitis and pneumonia - A potentially life-threatening fungal infection of the brain and spinal cord or lungs that is caused by inhaling ***Cryptococcus*** spores found in soil and pigeon droppings. It's a serious concern for people with weakened immune systems and is a major problem in HIV-infected patients in many parts of the world. Around 200,000 people catch the disease annually, particularly in sub-Saharan Africa, Brazil, Thailand, Malaysia and Papua New Guinea.

Mucormycosis - a devastating group of diseases that have seen a significant increase in incidence reported as a co-infection alongside COVID19 - particularly in South-East Asia. The disease is caused by a range of filamentous moulds and results in major tissue damage and disfigurement - especially around the sinuses, eyes and brain.

While often overlooked compared to bacterial and viral diseases, fungal pathogens represent a major public health burden. Fungi probably cause over 1 billion human infections each year and contribute to over 2 million deaths globally - a staggering toll that exceeds deaths from malaria or breast cancer. New fungal pathogens and diseases which were previously rare or unknown are emerging in patients. These include, eg, *Candida auris*, *Emergomyces*, *Scedosporium / Lomentospora* and Mucormycosis in COVID patients.

How fungi infect and the symptoms they cause

Fungi can infect patients through tiny cuts and openings in the skin, by being inhaled as spores into the lungs, or by being swallowed and entering the digestive tract. Some fungi are able to grow on implanted medical devices, such as catheters, and then infect hospitalised patients.

When fungi infect humans, symptoms can range from mild skin rashes and itching to life-threatening fevers, breathing difficulties and organ failure. Many fungal infections become much more dangerous in people with weakened immune systems, eg, those with HIV/AIDS or cancer patients on chemotherapy. Fungal diseases are also a major challenge to patients with organ transplants because of the need to suppress their immune systems, making them more prone to infection.

Antifungal treatments and resistance

For a long time we have had a small number of antifungal medications that have been used quite effectively to treat fungal infections, from simple athlete's foot creams (containing terbinafine, clotrimazole and miconazole), medicated shampoos (containing ketoconazole, selenium sulfide or zinc pyrithione), to powerful injected drugs used to treat life-threatening fungal diseases in hospitals (eg, fluconazole, itraconazole, amphotericin B and caspofungin) - see Figure 2. But now, fungi are becoming increasingly resistant to many of our antifungal drugs.

Figure 2. *Antifungal medications are used in clinical settings (in hospitals, on prescription and over-the-counter) and also used as fungicides in agriculture.* **A.** Life-threatening infections may be treated with intravenous antifungal drugs. **B.** A diverse range of antifungal drugs are available including azoles (fluconazole, itraconazole, voriconazole, miconazole, ketoconazole), polyenes (amphotericin), echinocandins (caspofungin), pyrimidine analogs (flucytosine) and allylamines (terbinafine, naftidine, butenafine). **C.** Over-the-counter medications suitable for treating minor/irritating skin infections (thrush/athlete's foot) are often available without prescription so in many ways their use is unsupervised. **D.** Azole antifungal drugs are used both in medicine and to control diseases in crops. **E.** Widespread application of fungicides exposes environmental isolates of fungi that can cause human disease to different classes of antifungal drugs, leading to resistance in clinical isolates.

Image sources:
A: https://upload.wikimedia.org/wikipedia/commons/0/0d/ICU_IV_1.jpg
B: https://upload.wikimedia.org/wikipedia/commons/d/d1/Les_m%C3%A9dicaments_en_pharmacie.jpg
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E: https://commons.wikimedia.org/wiki/File:Tractor_Fertilize_Field_Pesticide_And_Insecticide.jpg

Just as bacteria can become resistant to antibiotics, fungi can evolve resistance mechanisms that make our drugs less effective at stopping or killing them. For example, some fungi have mutated to produce strains that pump antifungal drugs back out of their cells before they can act. Other fungal pathogens have found ways to neutralise the drugs and break them down, or have mutations that alter the targets of the drug inside the cell making them less effective. The rise of antifungal resistance is making many common and serious fungal infections harder to treat. For invasive aspergillosis infections that spread through the body, over 30% are now resistant to at least one major antifungal drug.

Here are just three examples of antifungal drugs that now have reduced effectiveness due to the emergence of antifungal drug resistance.

1. **Fluconazole** is a very widely-used azole antifungal drug that is losing effectiveness against several *Candida* species in healthcare settings. Resistance rates as high as 30-40% have been reported for infections by the fungus *Nakaseomyces glabratus* (formerly known as *Candida glabrata*).

2. **Itraconazole** is another azole drug commonly used to treat aspergillosis. However, itraconazole resistance in *Aspergillus fumigatus* strains is increasing, with resistance rates that are over 20% documented in some regions.

3. **Amphotericin B** is one of the oldest and still much-relied upon antifungal medications. Emerging resistance to it has been detected in strains of *Candida albicans* and *C. auris*, *Aspergillus fumigatus*, *Cryptococcus neoformans* and many other fungal pathogens, severely limiting treatment options.

The rise of resistance to these key antifungal drugs, which span different drug classes (see Figure 3), is extremely concerning. It leaves healthcare providers with fewer effective choices to treat potentially lethal invasive fungal infections, especially in immunocompromised patients.

This resistance crisis is being driven by the overuse and misuse of antifungal medications, as well as poor protocols preventing the spread of resistant strains in hospitals. One major issue is that the same antifungal compounds are often licensed for use in an agricultural *and* healthcare setting - meaning that fungal pathogens acquired from the environment have often been exposed to antifungal drugs before they cause infections in patients. Antifungal agents are also often included in unregulated cosmetic products. Pharmaceutical companies have also been slow to invest in developing brand new types of antifungal drugs because of the high costs of development.

If antifungal resistance keeps increasing and spreading unchecked, we could find that we have almost no effective treatments for deadly fungal infections that can strike people with weakened immunity. This alarming possibility is pushing researchers to investigate new antifungal medications.

The bottom line

You may have thought fungi were just a nuisance causing athlete's foot or mould on food, but there's an entire hidden kingdom of fungi that can lead to serious and life-threatening infections in humans. Fortunately, we currently have medications to treat many of these fungal diseases, but rising resistance threatens to make some of these remedies obsolete.

Confronting the escalating dangers of fungal diseases and antifungal resistance, the World Health Organization has published a Fungal Priority Pathogens List that outlines a three-pronged strategy to tackle this key issue. Firstly, increase the monitoring and detection capabilities for fungal infections through enhanced clinical surveillance measures. Secondly, prioritise funding and resources for research and development of new initiatives aimed at the discovery of novel antifungal treatments and advanced diagnostic tools. Thirdly, strengthen public health initiatives and awareness to educate the global population about the growing threats posed by fungal pathogens and drug-resistant strains.

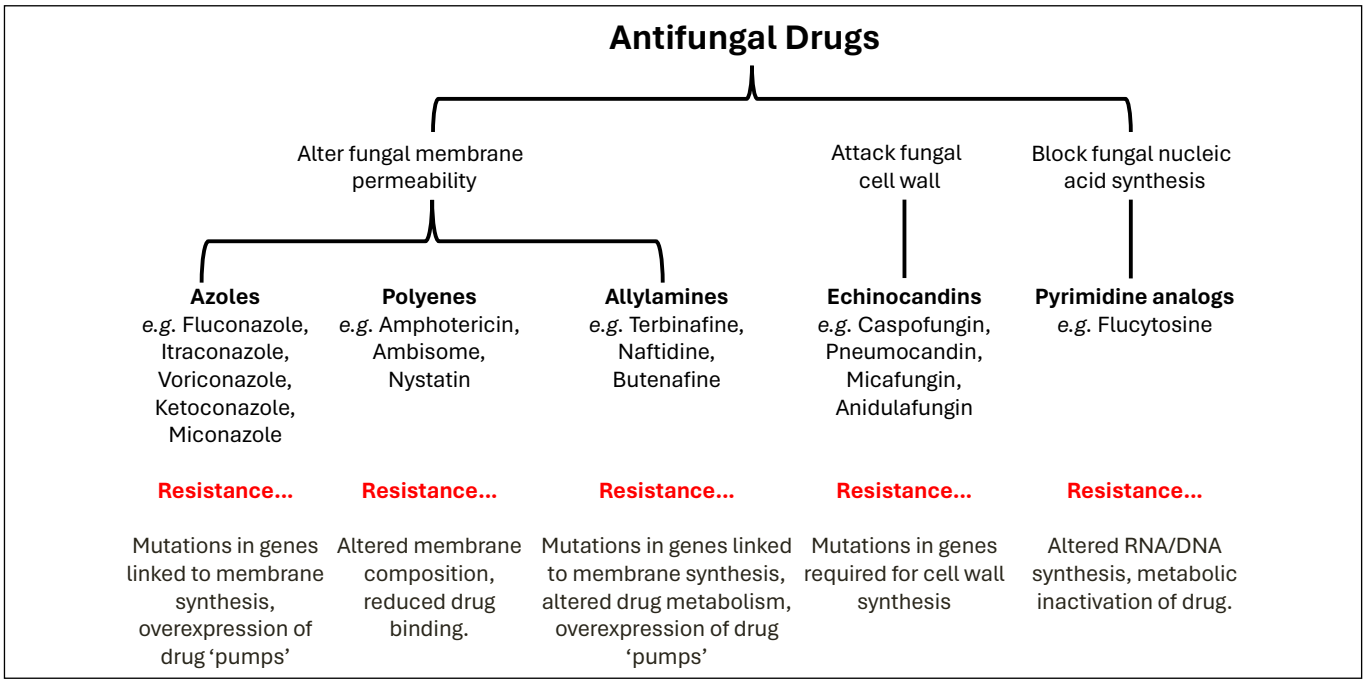

Figure 3. *Major classes of antifungal drug used in medicine and some common resistance mechanisms.*
Note that some azole antifungals (such as tebuconazole) are widely used in agriculture to control fungal diseases in crops, terbinafine is sometimes used as a seed treatment in agriculture and Amphotericin B is also used in agriculture for post-harvest treatment of fruits and vegetables to prevent spoilage during storage and transportation.

Image source: Mark Ramsdale

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That's why medical mycologists, who study these important fungal diseases, are racing to understand the biology of the key fungal pathogens and develop new generations of diagnostics and antifungal treatments. Fungi themselves may also contain the answers, as many are sources of beneficial compounds that may be used to combat disease.

To find out more about fungal diseases, why not have a go at the "Hands-on" activity below or visit some of the key websites listed at the end that provide additional information about "**the rising threat of fungal diseases and antifungal resistance**".

More information and key websites:

1. Denning, D. W. Global incidence and mortality of severe fungal disease. Lancet Infect. Dis. https://doi.org/10.1016/S1473-3099(23)00692-8 (2024).

2. Fisher, M.C., Denning, D.W. The WHO fungal priority pathogens list as a game-changer. *Nat Rev Microbiol* **21**, 211- 212 (2023). https://doi.org/10.1038/s41579-023-00861-x

3. WHO: WHO fungal priority pathogens list to guide research, development and public health action https://www.who.int/publications/i/item/9789240060241 (2022).

4. https://thefungalthreat.com/ A website run by the MRC-Centre for Medical Mycology, University of Exeter that promotes a better understanding of the challenge of fungal infections.

5. https://gaffi.org/ Global Action for Fungal Infections (GAFFI) - a website dedicated to promoting the vision of a world without fungal death.

6. https://www.cdc.gov/fungal/index.html Centre for Disease Control (CDC). A comprehensive and accessible website looking at fungi, fungal diseases and issues such as antifungal drug resistance.

Hands-on activity - Antifungal Drug Product Audit

1. Visit a local pharmacy, chemist or supermarket and undertake a survey of the antifungal products available on the shelves. Look at foot creams and medicated shampoos. Using Google, undertake a survey of the antifungal products that can be bought online. Make a list of the different antifungal compounds used (common ones include clotrimazole, miconazole, terbinafine, selenium sulphide, zinc pyrithione).
2. Carry out some research on how each of those antifungal compounds works to kill or inhibit fungal growth. Try to identify which drug classes or families they belong to based on their chemical structures.
3. See if you can find any information on documented resistance to each of those antifungal drugs by different fungal pathogens. Consider how the use of these compounds might affect our ability to control infections in patients with life-threatening fungal disease such as aspergillosis or candidaemia.

Additional class-room activities teachers/students can undertake to improve their knowledge of human fungal pathogens and antifungal drug resistance

1. **Fungal Infection Case Study**
   Research a specific case of an invasive or life-threatening fungal infection covered in hospital, medical or scientific reports. Maybe a high-profile case that has made the news.

   Summarise details including the type of fungus involved, how the infection could have arisen, the key symptoms, the patient populations most at risk, and what antifungal medications can be used to treat it.

2. **Antibiotic vs Antifungal Resistance**
   We hear a lot about antibiotic resistance, but not as much about antifungal resistance. Make a comparison table listing the mechanisms that allow bacteria to become resistant to antibiotics versus how fungi are able to develop resistance to antifungal drugs.

   Consider reasons why the development of new antibiotics has outpaced new antifungal drugs and speculate about the reasons for the difference. Discuss the respective medical and social impacts of antibiotic vs antifungal resistance.

3. **Antifungal drug resistance and the one health policy**
   In a group discuss how the overuse or misuse of fungicides in agriculture could potentially contribute to the development of antifungal drug resistance in human fungal pathogens. Encourage students to consider factors such as cross-resistance, genetic mutations and the potential for horizontal gene transfer between environmental and human fungal strains.

   Finally, have each group present their findings and propose strategies to mitigate the risk of antifungal resistance arising from agricultural practices. This could include suggestions for responsible use of fungicides, rotation of different antifungal classes and the development of new antifungal agents with novel modes of action. Consider the role of regulation in setting aside certain classes for agricultural or clinical use.

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