Fungal infections

- Fungi are ubiquitous microorganisms that differ from bacteria in their cellular structure, and this makes them naturally resistant to antibacterial agents.

- Fungi are broadly divided into yeasts and moulds. Yeasts are typically round or oval shaped microscopically, grow flat round colonies on culture plates and reproduce by forming buds from their cells.

- Moulds (e.g. *Aspergillus, Mucor) appear as a collection or mass (mycelium) of* individual tubular structures called hyphae that grow by branching and longitudinal extension.

- The most commonly seen yeast, *Candida, occasionally* produces pseudohyphae.

- Humans usually become infected by inhalation of airborne spores or by inoculation into traumatised skin and mucous membrane.

- Microscopical examination and culture of fungi is the mainstay of laboratory diagnosis.

- Appropriate staining of histological sections of affected tissue is helpful in making a diagnosis when culture growth may or may not be positive.

Classification of fungi of medical importance

Group	Examples	Infections caused
Yeast	*Candida* spp.	Oral and vaginal thrush Deep seated: candidaemia, empyema
	Cryptococcus neoformans	Meningitis
	Saccharomyces cervesiae	Rare systemic infection in immunocompromised host
	Malassezia furfur	
Yeast-like	*Geotrichium candidium*	
	Trichosporon beigelii	
Dimorphic fungi	*Blastomyces dermatitidis*	For first three: deep systemic organ involvement, more commonly in the immunocompromised host
	Coccidioides immitis	Deep subcutaneous infection following trauma
	Histoplasma capsulatum	
	Paracoccidioides brasiliensis	
	Sporothrix schenckii	
Moulds 1. Hyaline		
a. Zygomyces	*Rhizopus*	Infections in neutropenic patients and those with diabetic ketoacidosis
	Mucor	
	Absidia	
b. Hyalohyphomycosis	*Aspergillus fumigatus* and other	Systemic infection: invasive pulmonary or central nervous system involvement
	Aspergillus spp.	
	Fusarium	Fusarium keratitis
	Scedosporium apiospermum	Deep infection in immunocompromised host, for example, transplant patients
2. Dermatophytes	*Trichophyton* spp.	For all three: various skin (ringworm) hair and nail infections
	Microsporum spp.	
	Epidermophyton	
3. Dematiaceous	*Alternaria* spp.	Deep tissue infection with granulomas
	Cladophialora spp.	Chromomycosis, mycetomas

Fungal infection:

- It is important to distinguish harmless colonisation with fungi and significant infection, as only the latter would benefit from antifungal treatment.

- More often, fungi are a cause of superficial infections of the skin and mucous membranes.

- In some susceptible hosts whose immune system is heavily compromised, deep-seated infections involving organs like lungs and brain can manifest as ‘difficult to cure’ infections, for example, pulmonary aspergillosis or cryptococcal meningitis.

Antifungal agents

- Topical and systemic antifungal agents are available to treat mucocutaneous candidiasis, various forms of tinea (ringworm) and other dermatophytosis, onychomycosis and deep seated systemic infections (e.g. candidaemia, mucor mycoses, fungal endocarditis, osteomyelitis).

- *Candida is a normal commensal of the human gastro-*Intestinal tract and skin.

- Loss of skin and mucosal integrity or use of broad-spectrum antibiotics which alter normal bacterial flora allow overgrowth of endogenous *Candida.*

Imidazoles:

- *Clotrimazole, miconazole and niridazole are all* used topically in the treatment of vaginal thrush.

- *Miconazole gel is a useful alternative to nystatin* for the treatment of oropharyngeal thrush. The newer imidazoles are well absorbed.

- The first of the orally active agents was *ketoconazole, but* this is associated with severe, even fatal, hepatotoxicity if administered at high doses

- *Fluconazole is used parenterally* for these and other invasive fungal infections, but resistance is common.

- Parenteral *voriconazole may be used for* fluconazole-resistant and life-threatening fungal infections.

- However, it is rather toxic and has very many side-effects, including blurred vision, photophobia and altered visual perception

- ***Itraconazole*** *has a similar activity spectrum* to *voriconazole and is available as oral and IV* infusion formulations.

- The oral liquid form has a much higher bioavailability than the capsules.

- However, even when the oral liquid is used for the prophylaxis of fungal infection in neutropenic patients, serum levels should be monitored to ensure adequate protection.

Polyenes:

- Examples of these are *amphotericin and nystatin,* which damage the fungal cell membrane to cause cytoplasmic leakage.

- They are not absorbed orally and may be administered as lozenges or mouthwashes for treating oropharyngeal thrush.

- For vaginal thrush, *nystatin is administered as a* pessary, but has largely been replaced by the imidazoles.

- *Amphotericin is administered parenterally for* serious systemic fungal or yeast infections, but may cause severe renal damage, even at low doses, and also severe neurological side-effects, including deafness and convulsions.

- Liposomal formulations are somewhat more effective and less toxic than the original sodium deoxycholate complex for IV use.

- However, nephrotoxicity may still be a problem. They are very expensive compared to the sodium deoxycholate complex.

- Fungal infections of the scalp and nails respond well to oral *griseofulvin, which accumulates in* those tissues, although this may need to be administered continuously for up to 6 months, possibly 12 months for infection of the toenails.

- In the treatment of systemic candidiasis, *amphotericin may be used in combination with flucytosine, an antimetabolite of cytosine that has* no action on the true filamentous fungi.

- *Flucytosine may cause serious blood and hepatic* disorders, so careful monitoring is required.

- *Caspofungin is the first of a new class of antifungal* agents, the **echinocandins, which interfere** with fungal cell wall synthesis through their action against 1,3-beta-D-glycan synthase.

- These agents appear to be less toxic than *amphotericin* and may be used to treat invasive candidiasis and aspergillosis.

- *Caspofungin is also used for the* empiric treatment of suspected fungal infections in neutropenic patients. However, it may cause hepatic damage and blood dyscrasias.

- Patients with diabetes and steroid users, whether inhaled or oral, are also prone to infections.

- Dysphagia due to candidal oesophagitis presents in patients with AIDS and cancer.

- Dermatophytosis, or tinea, is a condition caused by three genera of dermatophyte fungi: *Trichophyton, Epidermophyton* and *Microsporum.*

- *Unlike Candida, these are moulds which* have a predilection for keratinised tissue such as skin, nail and hair.

- The main oral antifungals used for dermatophytosis are terbinafine, itraconazole and fluconazole.

- Griseofulvin is an alternative treatment for tinea capitis.

Pityriasis versicolor

- This is a common superficial skin infection caused by a yeast-like fungus, *Malassezia furfur. The organism is a member of the normal* skin flora and lives only on the skin because it has a growth requirement for medium-chain fatty acids present in sebum.

- The condition usually appears as patches scattered over the trunk, neck and shoulders. These patches produce scales and may be pigmented in light-skinned individuals, appearing light brown in colour.

- Pityriasis versicolor is treated with topical terbinafine cream or a topical imidazole cream such as clotrimazole, econazole or miconazole.

- In severe cases, oral itraconazole (200 mg once daily for 7 days) may be given. Treatment of seborrhoeic dermatitis and folliculitis is undertaken with topical azole creams and 1% hydrocortisone.

Deep-seated fungal infections:

- Fungi that cause superficial infections can also cause deepseated infection in immunocompromised patients with leukaemia and lymphoma and those in the post-transplant period of immunosuppression.

- A breach in the body's mechanical barriers may predispose to fungal infection.

- For example, fungal infection of the urinary tract occurs most commonly in catheterised patients who have received broadspectrum antibiotics, while total parenteral nutrition (TPN) is strongly associated with fungaemia, sometimes with unusual fungi such as *Malassezia furfur.*

Conditions predisposing to systemic or deep-seated fungal infection

Infection	Predisposing conditions
Systemic candidiasis	Neutropenia from any cause (disease or treatment) Use of broad-spectrum antibiotics which eliminate the normal body flora Indwelling intravenous cannulae, especially when used for total parenteral nutrition Haematological malignancy and HSCT Solid organ transplantation AIDS (particularly associated with severe mucocutaneous infection) Intravenous drug abuse Cardiac surgery and heart valve replacement, leading to *Candida* endocarditis Gastro-intestinal tract surgery Oesophagectomy leak leading to pleural space infection (empyema)
Aspergillosis	Neutropenia from any cause, especially if severe and prolonged Acute leukaemia Solid organ transplantation (mainly lungs) Chronic granulomatous disease of childhood (defect in neutrophil function) Pre-existing lung disease (usually leads to aspergillomas; fungus balls form in the lung rather than invasive or disseminated infection)
Cryptococcosis	AIDS Systemic therapy with corticosteroids Renal transplantation Hodgkin's disease and other lymphomas Sarcoidosis Collagen vascular diseases
Zygomycosis	Diabetic hyperglycaemic ketoacidosis (leading to rhinocerebral infection) Severe, prolonged neutropenia Burns (leading to cutaneous infection)

HSCT, hematopoietic stem cell transplantation.

Condition/organism	Common clinical presentations
Candidiasis (*Candida albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, other *Candida* species)	Fungaemia Colonisation of intravenous cannulae Pneumonia Meningitis Bone and joint infections Endocarditis Endophthalmitis Peritonitis in chronic ambulatory peritoneal dialysis
Aspergillosis (*Aspergillus fumigatus*, *A. flavus*, other *Aspergillus* species)	Invasive pulmonary aspergillosis Disseminated aspergillosis Aspergilloma Endocarditis
Cryptococcosis (*Cryptococcus neoformans*)	Meningitis Pneumonia Cutaneous infection
Zygomycosis (various species of the genera *Rhizopus*, *Mucor*, *Absidia*)	Rhinocerebral infection Pulmonary mucormycosis Surgical wound and burns infection
Malassezia furfur	Cutaneous infection (especially in burns patients) Fungaemia associated with total parenteral nutrition

Clinical presentation of systemic fungal infection

Condition	Clinical presentation
Fungaemia (the presence of fungi in the bloodstream), usually due to *Candida* species	Fever, low blood pressure and sometimes other features of septic shock, especially in neutropenic patients Relatively low-grade fungaemias such as those associated with colonised intravenous cannulae often present only with fever Disseminated infection to multiple organ systems is quite common with *Candida* species, leading to central nervous system disease, endocarditis, endophthalmitis, skin infections, renal disease, bone and joint infection
Pneumonia, most frequently due to *Aspergillus* species	Fever, chest pain and cough which may be non-productive. May progress rapidly, especially with *Aspergillus* infection, to severe respiratory distress, necrosis of the lung and pulmonary haemorrhage Formation of fungal balls in pre-existing lung cavities with or without invasion
Meningitis and other central nervous system infection	*Candida* infection may present as a typical meningitis, although it is often more insidious. Aspergillosis is associated with headache, confusion and focal neurological signs due to the presence of brain infarcts. Cryptococcosis most frequently presents as a chronic, insidious meningitis with headache and alteration in mental state
Mucormycosis	Angioinvasive. The most common presentation of mucormycosis is rhinocerebral infection. Initially an infection of the sinuses, it then spreads locally to the palate, orbit and eventually into the brain, leading to encephalitis Pulmonary disease can present as fungal balls radiologically with symptoms of haemoptysis

Side effects of antifungal agents

Drug	Side effects
Griseofulvin	Mild: headache, gastro-intestinal side effects. Hypersensitivity reactions such as skin rashes, including photosensitivity Moderate: exacerbation of acute intermittent porphyria; rarely, precipitation of systemic lupus erythematosus. Contraindicated in both acute porphyria, systemic lupus erythematosus, pregnancy and severe liver disease
Terbinafine	Usually mild: nausea, abdominal pain; allergic skin reactions; loss and disturbance of sense of taste. Not recommended in patients with liver disease
Amphotericin	Immediate reactions (during infusion) include headache, pyrexia, rigors, nausea, vomiting, hypotension; occasionally, there can be severe thrombophlebitis after the infusion Nephrotoxicity and hypokalaemia Anaemia due to reduced erythropoiesis Peripheral neuropathy (rare) Cardiac failure (exacerbated by hypokalaemia due to nephrotoxicity) Immunomodulation (the drug can both enhance and inhibit some immunological functions)
Flucytosine	Mild: gastro-intestinal side effects (nausea, vomiting). Occasional skin rashes Moderate: myelosuppression (dose related), hepatotoxicity
Fluconazole	Mild: nausea, vomiting and occasional skin rashes; occasionally, elevated liver enzymes (reversible) Moderate or severe: rarely, hepatotoxicity and severe cutaneous reactions, especially in AIDS patients
Itraconazole	Mild: nausea and abdominal pain; occasional skin rashes Moderate or severe: rarely, hepatotoxicity
Voriconazole	Similar to fluconazole and itraconazole Mild: reversible visual disturbances occur in about 30% patients
Caspofungin	Mild: gastro-intestinal side effects; occasional skin rashes