Mycology is the Study of Fungi (Monera, Protoctista, Fungi, Plantae, Animalia).

Fungi are eukaryotic cells and as such contain nuclei, mitochondria, ER, golgi, 80S ribosomes, etc., bound by a plasma membrane.

Note that fungal cell membranes contain ergosterol rather than cholesterol.

In addition, fungi possess a rigid cell wall containing chitin, glucans and other sugar polymers.
Mycology

Fungi are classified as

• **Yeast**s - round/oval cells that divide by budding

• **Moulds** - tubular structures (hyphae) that grow by longitudinal extension and branching. A mass of hyphae is called a *mycelium*

Diseases Caused by Fungi

Fungal infections in normal healthy adults are confined to conditions such as mucosal candidiasis (e.g., thrush) and dermatophyte (tinea) skin infections (e.g., athlete's foot).

However, in the immunocompromised host, a variety of normally mild or nonpathogenic fungi can cause potentially fatal infections.
Diseases Caused by Fungi

Fungal infections are classified depending on the degree of tissue involvement and mode of entry:

1. **Superficial** - localized to the skin, hair and nails.
2. **Subcutaneous** - infection confined to the dermis, subcutaneous tissue, or adjacent structures.
3. **Systemic** - deep infections of the internal organs.
4. **Opportunistic** - cause infection only in the immunocompromised.

1. Superficial Mycoses

The Dermatophytes

The dermatophytes are not a specific fungus, but rather a short-hand label for three genera of fungi that commonly cause skin disease (*tinea*).

- Epidermophyton spp.  
- Trichophyton spp.  
- Microsporum spp.  
- *tinea capitis*  
- *tinea barbae*  
- *tinea pedis*  
- *tinea cruris*
1. Superficial Mycoses

The Dermatophytes

Tinea pedis
“athletes foot”
Epidermophyton spp.

Tinea capitis
Microsporum spp.

1. Superficial Mycoses

Ringworm, dermatophyte infection (zoophilic)
2. Subcutaneous Mycoses

Subcutaneous infections confined to the dermis, subcutaneous tissue, or adjacent structures; there is no systemic spread.

They tend to be slow in onset and chronic in duration.

These mycoses are rare in the US and are primarily confined to tropical regions (the Americas, South Africa, Australia).

The ease of travel provides the means for unusual fungal infections to be imported into this country.

3. Systemic Mycoses

Systemic mycoses are invasive infections of the internal organs.

The organism typically gains entry via the lungs, GI tract, or through intravenous lines.

Examples include:

- Histoplasmosis
- Coccidiomycosis
- Blastomycosis
Histoplasmosis

Histoplasmosis is caused by *Histoplasma*, a **dimorphic** fungus (grows as a mould at 25°C and as a yeast form at 37°C).

Histoplasma is endemic in the Ohio-Mississippi river basins, where it is found in soil contaminated with bird droppings and bat excrement.

The infection is acquired through inhalation of the mould form and the lungs are thus the most frequently affected site.

Chronic pulmonary infection is frequently associated with preexisting chronic lung diseases (i.e.- emphysema).

All stages of this disease may mimic tuberculosis.

The majority of acute cases (50%-90%) follow a subclinical course (asymptomatic to flu-like Sx).
Histoplasmosis

The spectrum of the disease is wide, however, varying from an acute benign pulmonary infection to a chronic pulmonary infection and even a fatal disseminated disease.

Dissemination and a fatal course are more common in immunocompromised, children less than 2 years, the elderly.

Coccidiomycosis

An infection caused by the dimorphic fungus *Coccidioides immitis*.

The disease is endemic only in regions of the Western Hemisphere (Arizona, California, New Mexico and Texas).

Coccidioidomycosis is acquired from inhalation and an acute respiratory infection occurs 7 to 21 days.

Most patients (50%) are asymptomatic.

Symptoms, when they occur, typically resolve rapidly.
Coccidiomycosis

Occasionally, infection may result in a chronic pulmonary condition and/or disseminate to the meninges, bones, joints, subcutaneous, or cutaneous tissues.

About 25% of patients with disseminated disease have menningitis.

Blastomycosis

A disease caused by the dimorphic fungus *Blastomyces dermatitidis*

It is endemic in the southeastern and south United States.

Infection is acquired via inhalation.

At least 50% of primary infections are asymptomatic.

An acute pulmonary disease indistinguishable from a bacterial pneumonia may occur after 30-45 days post exposure.

Skin lesion following dissemination from the lungs
4. Systemic Mycoses, Opportunistic

Opportunistic fungi are normally of marginal pathogenicity, but can infect the immunocompromised host.

Patients usually have some serious immune or metabolic defect, or have undergone surgery.

Examples include:

Aspergillosis
Candidosis
Cryptococcosis

Candidiasis

**Candidiasis** - an infection caused by a *Candida* spp.

*Candida* is a yeast and is part of the normal flora (commensal) of the skin, mouth, vagina and GI tract.

Antibiotic treatment can alter the normal bacterial flora allowing *Candida* to flourish.

**Thrush** - a superficial *Candida* infection of the mouth or vagina.
Candidiasis

_Candida_ is the most common cause of opportunistic mycoses worldwide.

_Candida albicans_ is the most pathogenic and most commonly encountered species

Systemic candidiasis is common in the immunocompromised (AIDS, chemotherapy, post-surgery)

Disseminated infections arise from hematogenous spread from the primarily infected locus

Candidiasis

**Oral Thrush**- the white material consists of budding yeast cells and pseudohyphae.

**Mucocutaneous Candidiasis**- granulomatous lesions involving the hands.
Aspergillosis

Aspergillus is a filamentous mould and is a ubiquitous fungus found in nature (soil, plant debris, and indoor air). Aspergillosis is a large spectrum of diseases caused by members of the genus *Aspergillus*.

Colonization of the respiratory tract is common. The organism can infect the lungs, inner ear, sinuses and, rarely, the eye of previously healthy persons.

The three principal entities are:

- allergic bronchopulmonary aspergillosis
- pulmonary aspergilloma
- invasive aspergillosis

Nosocomial occurrence of aspergillosis due to catheters and other devices is also frequently observed.
Pulmonary Aspergilloma

*Aspergillus* spp. may also be local colonizers in previously developed lung cavities due to diseases such as tuberculosis and emphysema (*aspergilloma* or *fungus ball*).

Fruiting body in a lung cavity

Aspergillosis

The clinical manifestation and severity of the disease depends upon the immunologic state of the patient.

Lowered host resistance:
- debilitating disease
- neutropenia
- disruption of normal flora

Almost any organ or system in human body may be involved.
Cryptococcosis

*Cryptococcus* is an encapsulated yeast found world-wide; it is found in pigeon droppings, eucalyptus trees, some fruits and contaminated milk.

*Cryptococcus neoformans* is the only species that is pathogenic to humans.

The primary port of entry is inhalation.

The course of the infection is usually subacute or chronic.

AIDS is the most commonly encountered predisposing factor for development of cryptococcosis.

*Cryptococcus* is neurotropic and the most common clinical presentation is *meningoencephalitis.*
Antifungal Agents

1. Polyene Antifungal Drugs
   These drugs interact with ergosterol in the fungal cell membrane and form pores
   • Amphotericin
   • Nystatin
   • Pimaricin

2. Azole Antifungal Drugs
   These drugs inhibit cytochrome P450’s (C14-demethylase) involved in ergosterol biosynthesis.
   • Fluconazole
   • Itraconazole
   • Ketoconazole

Antifungal Agents

3. Allylamine Antifungal Drugs
   Allylamine drugs inhibit squalene epoxidase, a critical enzyme in the ergosterol biosynthetic pathway.
   • Terbinafine
   • Naftifine

4. Morpholine Antifungal Drugs
   Inhibit the ergosterol biosynthetic pathway at a later step
   • Amorolfine

5. Antimetabolite Antifungal Drugs
   • Flucytosine (5-fluorocytosine) is converted to 5-fluorouracil in fungal cells, which inhibits DNA, RNA and protein synthesis
Antifungal Agents

6. Echinocandin Antifungal Drugs
   Presumably inhibit 1,3-β-glucan synthase.
   1,3-β-glucan is required for fungal cell wall biosynthesis
   • Caspofungin
   • Micafungin
   • Anidulafungin

7. Miscellaneous Antifungal Drugs
   • Griseofulvin inhibits mitotic spindle formation
     required for cell division

Polyene Antifungal Agents

Amphotericin B
was first isolated from
Streptococcus nodosus
in 1955

It is an amphoteric compound
composed of a hydrophilic
polyhydroxyl chain along one
side and a lipophilic polyene hydrocarbon chain on the other.

Amphotericin B is poorly soluble in water.

The drug must be administered intravenously and is
associated with numerous side effects, which may be severe.
Amphotericin B

Amphotericin B preferentially binds to ergosterol, the primary sterol in fungal cell membranes.

This binding disrupts osmotic integrity of the membrane resulting in the loss of intracellular potassium, magnesium, sugars and metabolites.

There are several formulations of Amphotericin B.

The mechanism of action is the same for all of the preparations and is due to the intrinsic antifungal activity of amphotericin B.

Amphotericin B

**Fungizone® (D-AMB)** is the classic amphotericin B formulation and has been available since 1960.

It is a colloidal suspension of amphotericin B with deoxycholate (a bile salt) as a solubilizing agent.

This preparation has a number of toxicities, which has led to the development of alternate lipid carrier formulations.

The major goal of lipid carriers has been to attain a preparation with lower toxicity but similar efficacy as the deoxycholate preparation.
Polyene Antifungal Agents

Nystatin was the first successful antifungal antibiotic to be developed and it is still in general use.

The promise of its broad-spectrum antifungal activity is offset by host toxicity.

It is typically limited to topical use.
Polyene Antifungal Agents

**Pimaricin** (natamycin opthalmic) is used topically to treat superficial mycotic infections of the eye.

It is active against both yeasts and moulds.

Azole Antifungal Agents

**Azoles** have five-membered organic rings that contain either two (imidazole) or three nitrogen molecules (triazoles)

These agents are thought to inhibit cytochrome P450 14α-demethylase (P45014DM).

This enzyme is in the sterol biosynthesis pathway and converts lanosterol to ergosterol.
Imidazole Antifungal Agents

Clotrimazole (lozenges)

Miconazole

Ketoconazole (PO)

Triazole Antifungal Agents

fluconazole
PO, injection

itraconazole
PO, injection

voriconazole
PO, injection

posaconazole
**Allylamine Antifungal Agents**

*Terbinafine*, a synthetic antifungal agent.

Terbinafine inhibits squalene epoxidase

This enzyme is part of the fungal sterol biosynthetic pathway required to synthesize ergosterol.

Terbinafine is mainly effective on dermatophytes (topical or PO)

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**Allylamine Antifungal Agents**

*Naftifine* also inhibits squalene epoxidase

Naftifine is a topical agent used to treat:

- athlete's foot (ringworm of the foot; tinea pedis)
- jock itch (ringworm of the groin; tinea cruris)
- ringworm of the body (tinea corporis)
**Antifungal Agents**

**Antimetabolites**

**Flucytosine** (5-fluorocytosine) is an analog of cytosine.

It is activated by deamination within the fungal cells to 5-fluorouracil. (mammalian cells do not have the enzyme)

It is converted to 5-FU-triphosphate, which interferes with fungal DNA, RNA and protein synthesis.

**Echinozandins**

These agents block the synthesis of a major fungal cell wall component, 1,3-\(\beta\)-glucan.

The presumed target is 1,3-\(\beta\)-glucan synthetase.
**Echinocandins**

Caspofungin  
(Micafungin  
*parenteral*)  

Micafungin  

Anidulafungin

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**Miscellaneous Agents**

**Griseofulvin** is an antifungal agent first isolated from a *Penicillium* spp. in 1939.

The drug is insoluble in water.

Griseofulvin inhibits fungal mitosis by disrupting the mitotic spindle through interaction with polymerized microtubules.

Griseofulvin is mainly effective on dermatophytes.
**Antifungal Agents**

**Pneumocystis**

*Pneumocystis jiroveci* (formerly *P. carinii*) was previously considered a protozoan, but is in fact a fungus.

It is commonly found in the environment and in the lungs of healthy humans and other animals.

Pneumocystis is a commensal of many animals and human infection is commonly derived from dogs.

Airborne transmission of this low-virulence organism leads to a dormant, asymptomatic infection.

*P. jiroveci* is a common cause of pneumonia in immunocompromised patients and is a major cause of opportunistic infections, morbidity and mortality in AIDS patients.
Pneumocystis- Life Cycle

Three distinct morphological stages:

• **Trophozoites** (trophic forms)- uninucleate ameboid-like cells. This form adheres to alveolar walls and probably multiply by binary fission.

• Sporocyte- intermediate between trophozoites and cysts.

• **Cyst**- double cell wall. Probably the most immunogenic stage. Mature cysts contain 6 to 8 intracystic bodies (spores).

![Cysts obtained by bronchiolar lavage](image-url)
Pneumocystis - Transmission

After inhalation, mature cysts reach the alveoli where they rupture and release intracystic bodies.

The haploid bodies fuse forming diploid trophozoites that develop into cysts. (sexual replication)

Binary fission (asexual replication) of the trophozoites also occurs, which is thought to be the primary mode of replication in the lung.

The organism multiplies slowly but extensively in the lungs, which progressively fills the alveoli with a foamy exudate consisting of clusters of Pneumocystis jiroveci, degenerated cells, host proteins, and few alveolar macrophages.

Pneumocystis - Clinical Presentation

• Dyspnea, SOB
• Cyanosis
• Non-productive cough
• Fever

• Chest radiography demonstrates bilateral infiltrates

• Extrapulmonary lesions occur in < 3% of patients
  • lymph nodes
  • spleen
  • liver
  • bone marrow

Increasing pulmonary involvement leads to death in untreated patients
**Pneumocystis- Diagnosis and Treatment**

**Diagnosis**
- Clinical Sx
- Chest Radiograph
- Identification of organisms in bronchopulmonary secretions (sputum/bronchoalveolar lavage)

**Treatment**
- TMP-SMX, 21 days HIV, 14 days non-HIV
- Dapsone plus trimethoprim
- Pentamidine (inhalation, parenteral)
- Trimetrexate (parenteral)

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**Pneumocystis- Drugs**

Sulfonamides and Trimethoprim are often co-administered

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PABA \xrightarrow{dihydropterolic acid synthetase} \text{Dihydrofolic Acid} \xrightarrow{dihydrofolate reductase} \text{Tetrahydrofollic Acid} \rightarrow \text{Purines DNA}
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This combination synergistically acts at two steps in the biosynthetic pathway.