

**Mycology** is the study of fungi.

Fungi include: **yeasts, molds** – they cause **mycoses** (fungal infections).

1. are eukaryotic
2. have a rigid cell wall
3. are chemoheterotrophs (organisms that require organic compounds for both carbon and energy sources)
4. obtain their nutrients by absorption
5. obtain nutrients as saprophytes, organisms that live off of decaying matter, or as parasites that live off of living matter.

### Reproduction of yeasts

1. Yeasts reproduce **asexually** by a process called budding. A bud is formed on the outer surface of the parent cell as the nucleus divides. One nucleus migrates into the elongating bud. Cell wall material forms between the bud and the parent cell and the bud breaks away. A few yeasts, such as *Candida albicans*, also produce clusters of asexual reproductive spores called **blastoconidia** (blastospores) and thick-walled survival spores called **chlamydoconidia** (chlamydospores).

2. Yeasts can also reproduce **sexually** by means of sexual spores called **ascospores** which result from the fusion of the nuclei from two cells followed by meiosis. Sexual reproduction is much less common than asexual reproduction but does allow for genetic recombination.

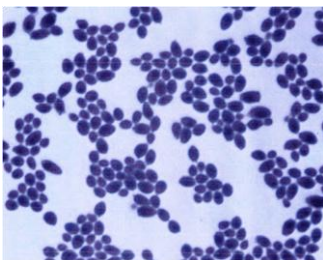


Blastoconidia and chlamydoconidia of *Candida* spp.

### Yeast infections

***Candida albicans*** is found as normal flora on the mucous membranes and in the gastrointestinal tract but is usually held in check by:

- a) normal flora bacteria
- b) normal body defenses



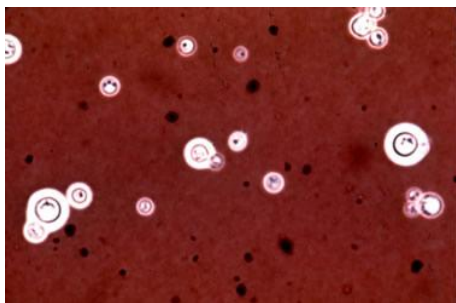
*Candida* stains with Gram technique – it appears as GP budding cells

*Candida* can cause a variety of opportunistic infections in people who are debilitated, immunosuppressed, or have received prolonged antibacterial therapy. Women who are diabetic, pregnant, taking oral contraceptives, or having menopause are also more prone to vaginitis. These conditions alter the sugar concentration and pH of the vagina making it more favorable for the growth of *Candida*. People

who are immunosuppressed frequently develop thrush, vaginitis, and sometimes disseminated infections. Any Candida infection is called **candidiasis**. Candida most commonly causes **vaginitis**, thrush, **balanitis**, and **cutaneous infections**. Less commonly, Candida can infect the **lungs, blood, heart, and meninges**, especially in the compromised or immunosuppressed host. Candida causes about 10% of all cases of septicemia.

### **Cryptococcus neoformans**

A lesser known but often more serious pathogenic yeast is **Cryptococcus neoformans**. Like many fungi, this yeast can also reproduce sexually. It appears as an oval yeast and forms buds with a thin neck, and is surrounded by a thick **capsule**. It does not produce pseudohyphae and chlamydo spores. The capsule enables the yeast to **resist phagocytic engulfment**. Cryptococcus infections are usually mild or subclinical but, when symptomatic, usually begin in the lungs after inhalation of the yeast in dried bird feces. It is typically associated with pigeon and chicken droppings and soil contaminated with these droppings. Cryptococcus, found in soil, actively grows in the bird feces but does not grow in the bird itself. Usually the infection does not proceed beyond this pulmonary stage. In the immunosuppressed host however, it may spread through the blood to the meninges and other body areas, often causing cryptococcal meningoencephalitis. Any disease by this yeast is usually called **cryptococcosis**. Dissemination of the pulmonary infection can result in a very severe and often fatal **cryptococcal meningoencephalitis**. Cutaneous and visceral infections are also found. Although exposure to the organism is probably common, large outbreaks are rare, indicating that an immunosuppressed host is usually required for the development of severe disease.



Cryptococcus – note thick capsule surrounding the yeast cells

### **Pneumocystis jiroveci**

Pneumocystis jiroveci (former name Pneumocystis carinii) is thought to be transmitted from person to person by the respiratory route and is almost always asymptomatic. However, in persons with **highly depressed immune responses**, such as people with leukemias or infected with the HIV, P. jiroveci can cause an often lethal pneumonia called **PCP (Pneumocystis pneumonia)**.

### **Molds Morphology**

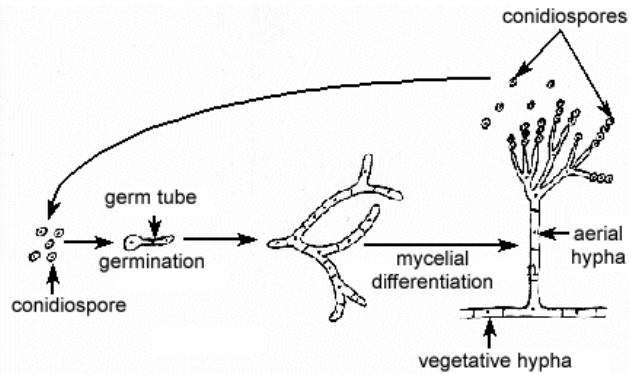
1. Molds are multinucleated, filamentous fungi composed of **hyphae**. A hypha is a branching tubular structure which is usually divided into cell-like units by crosswalls called **septa**. The total mass of hyphae is termed a **mycelium**. The portion of the mycelium that anchors the mold and absorbs nutrients is called the **vegetative mycelium**, composed of vegetative hyphae; the portion that produces asexual reproductive spores is the **aerial mycelium**, composed of aerial hyphae.
2. Molds have typical eukaryotic structures.
3. Molds have a cell wall usually composed of chitin, sometimes cellulose, and occasionally both.

4. Molds are obligate aerobes, that is, they grow only in the presence of oxygen.

5. Molds grow by elongation at apical tips of their hyphae and thus are able to penetrate the surfaces on which they begin growing.

### Reproduction of Molds

1. Molds reproduce primarily by means of **asexual reproductive spores**. These include the following:
  - a. **conidiospores** (conidia) are spores borne externally on an aerial hypha called a conidiophore
  - b. **sporangiospores** are spores borne in a sac or sporangium on an aerial hypha called a sporangiophore;
  - c. **arthrospores** are spores produced by fragmentation of a vegetative hypha.



2. Molds may also reproduce **sexually** by sexual spores such as ascospores and zygospores but this is not common.

### Pathogenic Molds:

1. **Dermatophytes**. The dermatophytes are a group of molds that cause **superficial cutaneous mycoses of the hair, skin, and nails** and utilize the protein **keratin**, that is found in hair, skin, and nails, as a **nitrogen and energy source**. Infections are commonly referred to as ringworm or tinea infections and include tinea capitis, tinea barbae, tinea corporis, tinea cruris, tinea unguium, and tinea pedis. The three most common dermatophytes are **Microsporum, Trichophyton, and Epidermophyton**. They produce characteristic asexual reproductive spores called **macroconidia and microconidia**. Another mold that commonly infects the skin is **Malassezia furfur** that causes tinea versicolor.

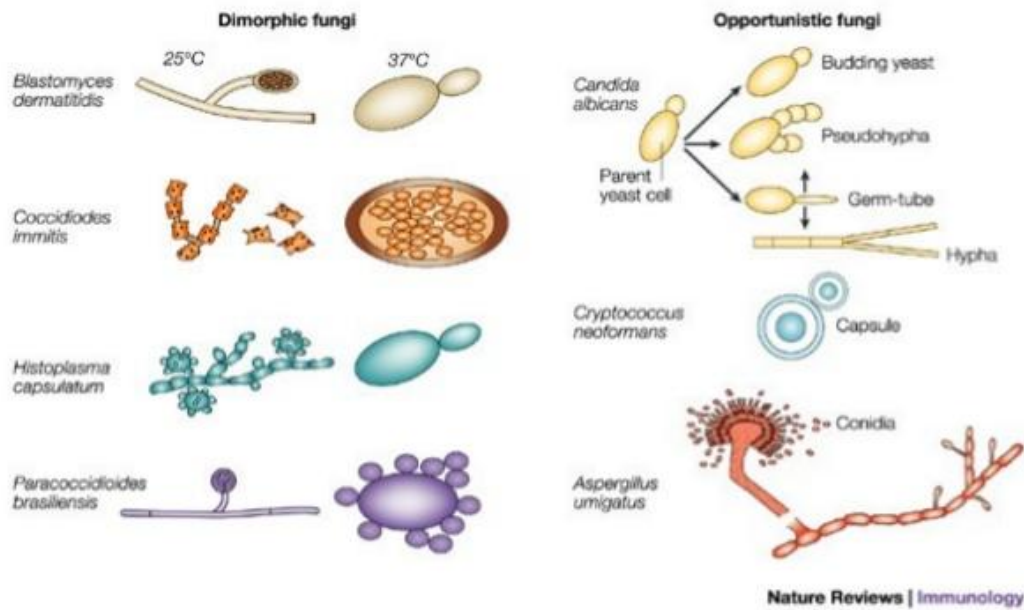
2. **Dimorphic fungi**. Dimorphic fungi may exhibit **two different growth forms**. Outside the body they grow as a **mold**, producing hyphae and asexual reproductive spores, but in the body they grow in a **non-mycelial form**. These infections appear as **systemic mycoses** and usually begin by inhaling spores from the mold form. After germination in the **lungs**, the fungus grows in a non-mycelial form.

a) **Coccidioides immitis** causes coccidioidomycosis. *C. immitis* produces **hyphae and arthrospores** when it grows **in arid soil** but grows as **endosporeulating spherules** (a spherule filled with yeast-like spores) **in the lung**.

b) **Histoplasma capsulatum** causes histoplasmosis. *H. capsulatum* produces **hyphae and tuberculate macroconidia in soil contaminated with bird or bat droppings** but grows as an **encapsulated yeast in the lungs**.

c) **Blastomyces dermatitidis** causes blastomycosis. *B. dermatitidis* produces **hyphae and conidiospores in soil contaminated with bird droppings** but grows as a thick-walled **yeast in the body**. These infections usually remains localized in the lungs, but in rare cases may spread throughout the body.

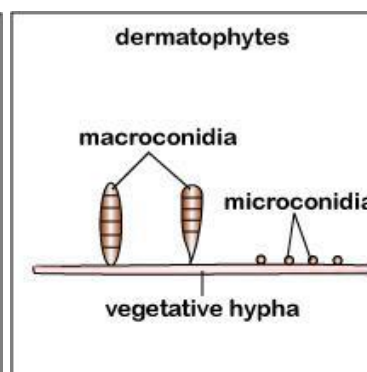
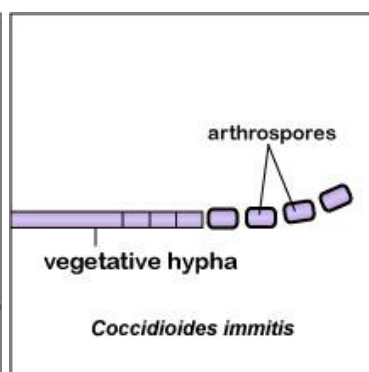
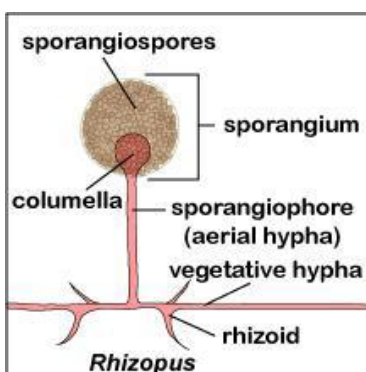
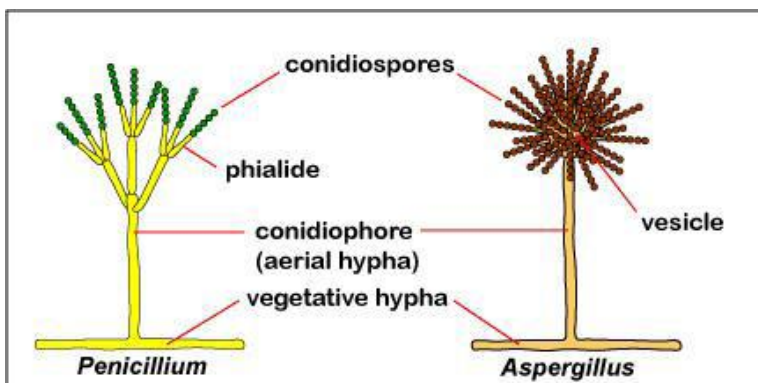
# Systemic Mycoses (Dimorphic fungi)



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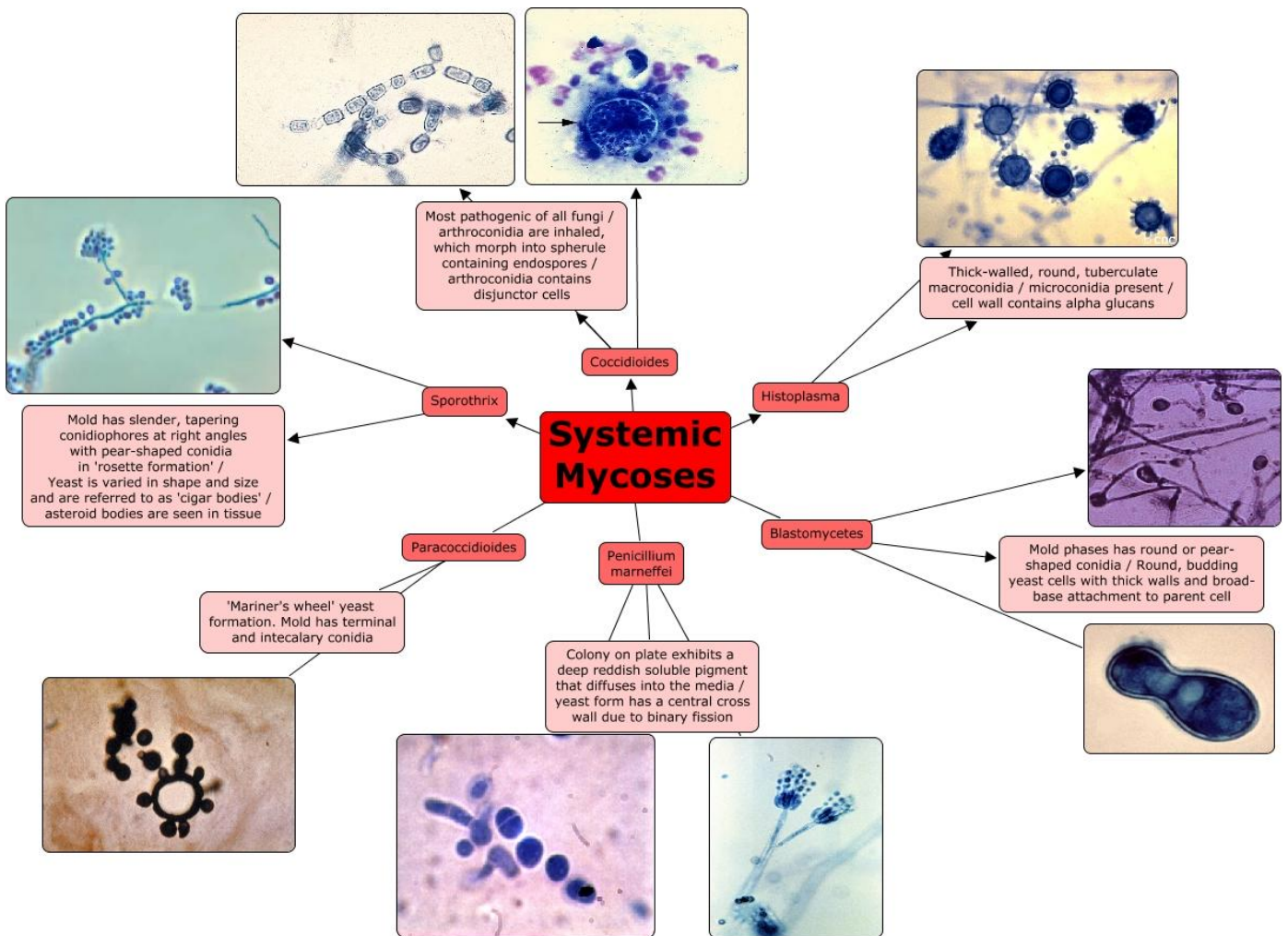
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**3. Opportunistic molds.** Certain molds once considered as non-pathogenic have recently become a fairly common cause of opportunistic lung and wound infections in the debilitated or immunosuppressed host. These include the common molds *Aspergillus* and Zygomycetes family (*Rhizopus*, *Mucor*, *Absidia*).



## Mycoses:

- A. **Superficial** affects outermost layers e.g. hair shaft, dead layer of epidermis. These infections are caused by e.g. *Trichosporon* spp., *Malassezia furfur*. Examples of infections include: Athlete's foot, pityriasis. These mycoses arise from external environment or endogenous flora (e.g. *Malassezia*) – **exogenous or endogenous**
- B. **Cutaneous** affects deeper layers e.g. deeper parts of epidermis, hair, nail. These infections are commonly caused by **dermatophytes** (*Trichophyton*, *Epidermophyton* and *Microsporum* genera) keratophilic fungi that produce enzyme keratinase. Example of the infection is tinea (ringworm). These mycoses may be transmitted from human-to-human through direct contact with infected tissues or subjects (e.g. floor, hairbrush, shoes, sleepers) or inoculation into skin – **exogenous or endogenous** (candidiasis of the skin or nails; or oral thrush)
- C. **Subcutaneous** affects subcutaneous tissue, connective tissue, muscle and fascia. ***Sporothrix schenckii*** is a common agent of subcutaneous mycoses ('rose gardener's disease'). These infections are acquired by thorn prick, contamination of open wounds from the external environment (inoculation into the skin) – **exogenous**
- D. **Systemic** – these mycoses are further divided into primary and opportunistic.
  - i) **Systemic primary** are caused by primary pathogenic fungi: **dimorphic fungi** (*Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides* sp.) – they are endemic and spread through respiratory route (inhalation of spores present in the soil; in the lungs the spores differentiate into yeast, hence dimorphic fungi), thus most common clinical manifestation is pneumonia (acute or chronic, similar to TB), but disseminated infections may occur. In some cases e.g. blastomycosis skin may be involved. However, most of these infections are asymptomatic or present as a self-limited flu-like syndrome. They are **exogenous** and are not communicable.
  - ii) **Systemic opportunistic** are caused by **endogenous** yeast *Candida* spp. or **exogenous** fungi present in the environment e.g. *Cryptococcus neoformans*, molds such as *Aspergillus*, *Zygomycetes*, *Pseudoallesheria* or *Pneumocystis jiroveci*. Opportunistic mycoses develop in severely immunocompromised patients and mostly take the disseminated form involving brain, lungs, heart, spleen, liver, kidneys and other organs and systems.
- E. **Allergic mycoses** affects lungs or sinuses. After inhalation of fungal spores or mycotoxins patients may have chronic asthma or sinusitis.



•**Dermatophytosis:**

Ringworm infections are the commonest of all mycoses.

Ringworm is often referred to clinically as Tinea. Dermatophytosis: =Tinea = Ringworm infection.

•Infection of the skin, hair or nails caused by a group of keratinophilic fungi, called dermatophytes.

•Dermatophytes : are a group of fungi that infect the superficial keratinized portion of the body- skin, hair, nails without spread into the deeper skin

•Dermatophytosis is caused by 17 species of microsporium, 22species of Trichophyton, or by Epidermophyton Floccosum.

- ❖Microsporium: Hair, skin
- ❖Epidermophyton: Skin, nail
- ❖Trichophyton: Hair, skin, nail



Tinea capitis (Ringworm of the scalp)

ADAM

## Fungal Pathogenicity

As with the bacteria, fungal virulence factors can be divided into two categories: virulence factors that promote fungal colonization of the host and virulence factors that damage the host.

**A. Virulence Factors that Promote Fungal Colonization** of the host include the ability to:

1. contact host cells
2. adhere to host cells and resist physical removal
3. invade host cells
4. compete for nutrients
5. resist innate immune defenses such as phagocytosis and complement
6. evade adaptive immune defenses

**Examples of Virulence Factors that Promote Fungal Colonization:**

1. **A compromised immune system is the primary predisposing factor for serious fungal infections.**
2. As with bacteria, the ability to **adhere** to host cells with cell wall adhesions seems to play a role in fungal virulence.
3. Some fungi produce **capsules** allowing them to **resist phagocytic engulfment**, such as the yeast **Cryptococcus neoformans** and the yeast form of **Histoplasma capsulatum**.
4. **Candida albicans** stimulates the production of a cytokine called **GM-CSF** (granulocyte-macrophage colony stimulating factor) and this cytokine can **suppress the production of complement by monocytes and macrophages**. This may decrease the production of the opsonin C3b as well as the complement proteins that enhance chemotaxis of phagocytes.
5. Some fungi are **more resistant to phagocytic destruction**, e.g., *Candida albicans*, *Histoplasma capsulatum*, and *Coccidioides immitis*. For example, it is much harder for phagocytes to engulf *Candida albicans* when it is in its hyphal form.
6. There is evidence that when the yeast form of *Candida* enters the blood it activates genes allowing it to **switch from its budding form to its hyphal form**. In addition, when engulfed by macrophages, it starts producing the **tubular germ tubes which penetrate the membrane of the macrophage thus causing its death**.
7. The yeast **Cryptococcus neoformans** inhibits the productions of the cytokines **TNF-alpha and interleukin-12 (IL-12) while stimulating the production of Interleukin-10 (IL-10)**. TNF and IL-12 activate macrophages while IL-10 suppresses their activation. **As a result, macrophages are not activated**. Macrophage activation is needed in order to kill the organism that have been engulfed.
8. Factors such as body temperature, osmotic stress, oxidative stress, and certain human hormones activate a dimorphism-regulating histidine kinase enzyme in **dimorphic molds**, such as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*, causing them to **switch from their avirulent mold form to their virulent yeast form**. It also triggers the yeast *Candida albicans* to **switch from its yeast form to its more virulent hyphal form**.

## B. Virulence Factors that Damage the Host

1. As fungi grow in the body, they can **secrete enzymes to digest cells**. These include proteases, phospholipases, and elastases. In response to both the fungus and to cell injury, **cytokines are released**. This leads to an inflammatory response and extracellular killing by phagocytes that causes **further destruction of host tissues**, e.g. yeast cell wall components **activate the alternative complement pathway and the lectin pathway**, defense pathways that play a variety of roles in body defense.

2. Many molds secrete **mycotoxins**, especially when growing on grains, nuts and beans. These toxins may cause a variety of effects in humans and animals if ingested including loss of muscle coordination, weight loss, and tremors. Some mycotoxins are mutagenic and carcinogenic. Aflatoxins, produced by certain *Aspergillus* species, are especially carcinogenic. A mold called *Stachybotrys chartarum* is a mycotoxin producer that has been implicated as a potential serious problem in homes and buildings as one of the causes of "sick building syndrome." Mycotoxin symptoms in humans include dermatitis, inflammation of mucous membranes, cough, fever, headache, and fatigue.

## Chemotherapeutic Control of Fungi

1. One antibiotic, **griseofulvin** (Fulvicin, Grifulvin, Gris-PEG), **interferes with nuclear division by preventing the aggregation of microtubules needed for mitosis in superficial mycelial fungi**. It is used only for severe dermatophyte infections.

2. The antimetabolites **trimethoprim + sulfamethoxazole, trimetrexate, atovaquone, and flucytosine interfere with normal nucleic acid synthesis**. Trimethoprim/sulfamethoxazole (Septra, Bactrim), atovaquone (Mepron), and trimetrexate (Neutrexin) are used to treat *P. jirovecii* pneumonia. Flucytosine (Ancobon) is used for more serious *Candida* infections.

3. Polyene antibiotics such as **amphotericin B, pimaricin, and nystatin** are fungicidal drugs that **bind to ergosterol in the fungal cytoplasmic membrane thus altering its structure and function and causing leakage of cellular needs**. Nystatin (Mycostatin) is used to treat superficial *Candida* infections (thrush, vaginitis, cutaneous infections), amphotericin B (Abelcet, Fungizone) is used for systemic *Candida* infections, *Cryptococcus* infections, and dimorphic fungal infections.

4. The azole derivative antibiotics such as **clotrimazole, miconazole, itraconazole, fluconazole, and ketoconazole**, are fungistatic drugs used to treat many fungal infections. They **interfere with ergosterol biosynthesis and thus alter the structure of the cytoplasmic membrane as well as the function of several membrane-bound enzymes** like those involved in nutrient transport and chitin synthesis. Clotrimazole (Lotramin, Mycelex), miconazole (Monistat), and econazole (Spectazole) are used to treat superficial *Candida* and dermatophyte infections; oxiconazole (Oxistat) and sulconazole (Exelderm) are used for dermatophyte infections; butaconazole (Femstat-3), terconazole (Terazole), and tioconazole (Vagistat-1) are used for *Candida* vaginitis; ketoconazole (Nizoral) and itraconazole (Sporanox) are used for systemic *Candida*, *Cryptococcus*, and dimorphic fungal infections; and fluconazole (Diflucan) is used for *Candida* infections.

5. **Naftifine** (Naftin) and **terbinafine** (Lamisil) are allylamines that **block synthesis of ergosterol** as does the topical thiocarbonate **tolnaftate**. They are used to treat dermatophyte infections.