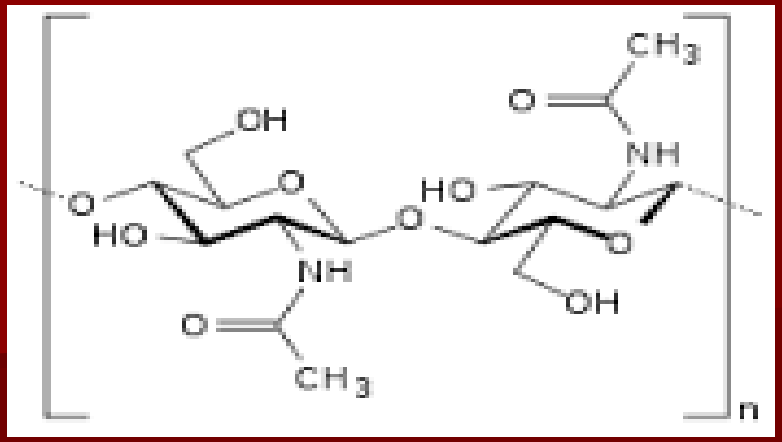
Antifungal Drugs

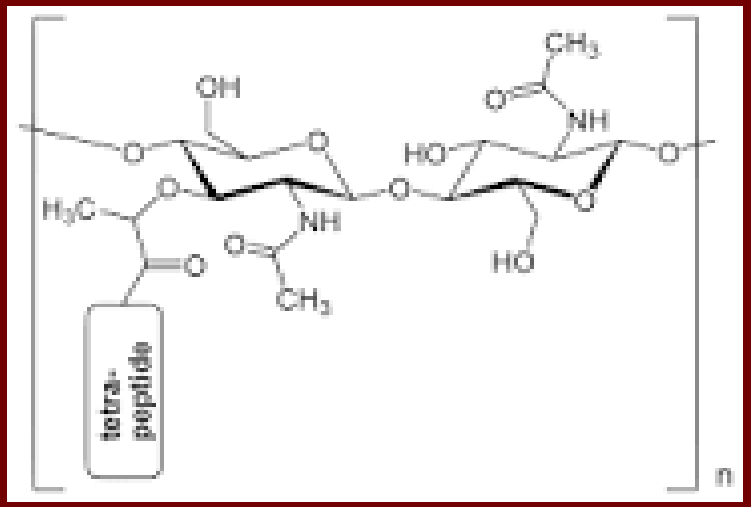
- **Overview**
- **Infectious diseases** caused by **fungi** are ***called mycoses***, and they are often **chronic** in nature. Many common mycotic infections are **superficial** and only involve the **skin** (**cutaneous** mycoses), but fungi may also penetrate the skin, causing ***subcutaneous*** infections. **The fungal infections that are most difficult to treat are the *systemic mycoses*, which are often life-threatening.**

- ***Unlike bacteria***, ***fungi cell walls*** composed largely of ***chitin*** a polymer of ***N-acetylglucosamine*** rather than **peptidoglycan** (a characteristic component of most **bacterial cell walls**).

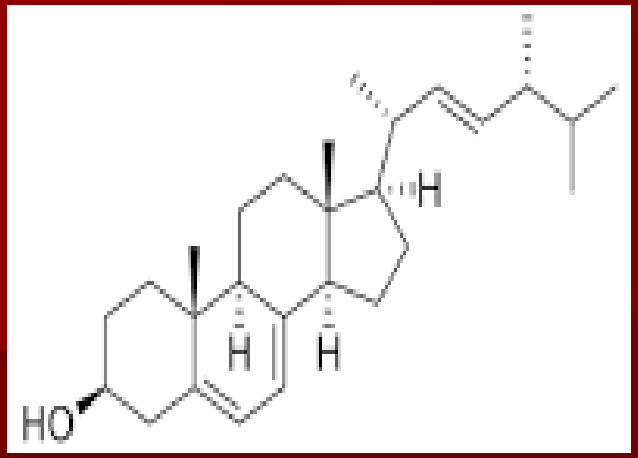
- The ***fungal cell membrane*** contains ***ergosterol*** rather than the **cholesterol** found in **mammalian membranes**. These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections.



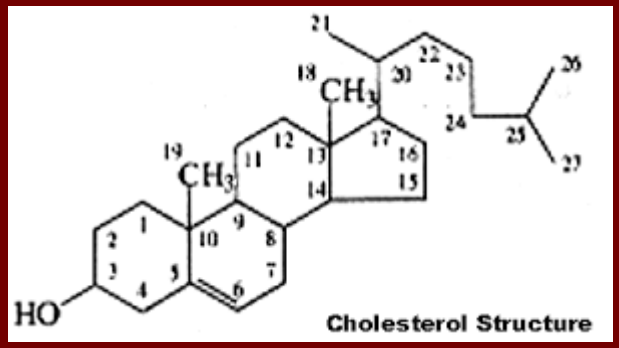
- **(C8H13O5N)n = Hexosamines = CHITIN**



- **Peptidoglycan**



- ***ergosterol***



- **cholesterol**

- **Fungal infections** are generally **resistant to antibiotics** used in the treatment of bacterial infections, and **conversely**, **bacteria are resistant to the antifungal agents**. The last two decades have seen a rise in the incidence of fungal infections so that **candidemia** is the fourth most common cause of **septicemia.**

- **Mycoses** can be further defined into fungi that are **yeasts or molds.**
- The terms ***yeast form*** **reproduce by budding (** التبرعم**).**
- **Yeasts include , Examp:** ***Candida*** **,** ***Cryptococcus*** المُسْتَخْفِيَةُ ….,. The pathogenic species of *Candida* include ***C. albicans,*** *C. krusei*, *C. parapsilosis*, ***C. tropicalis,*** *C. lusitaniae*, *C. glabrata* (*Torulopsis glabrata*), *C. guilliermondii*, *C. pseudotropicalis*, and *C. dubliniensis*.

- **Molds are composed of hyphae (خيط).**
- **Molds** include **Aspergillus** and the agents of **mucormycosis** فُطَار عَفَنِيّ.
- ***Aspergillus fumigatus*** is the **most pathogenic** of the **molds** and the most common of that species to cause invasive disease.
- **Other species of aspergillus include *A. flavus*, *A. terreus*, and *A. niger*.**

- The **dimorphic** fungi are capable of producing both **hyphal** and **yeast like** forms **depending on temperature.**
- They typically grow as **yeasts at body temperature** and as ***molds at room temperature.***
- The **dimorphic** fungi include the agents of **histoplasmosis, blastomycosis, sporotrichosis** داءُ الشَّعْرِيَّاتِ المُبَوَّغَة , **coccidiomycosis, paracoccidioidomycosis, and chromoblastomycosis** فُطارٌ اصْطِباغِيّ
-

- This **increased** incidence of **fungal infections** is associated with greater numbers of individuals who are **on :**
- **Chronic immune suppression following organ transplant,**
- **Undergoing chemotherapy for myelogenous and solid tumors**, or
- **Infected with the human immunodeficiency virus (HIV).**

- **The five major pathogens that cause endemic mycoses are :**
- **(1)** ***Coccidioides immitis,*** الكُرَوانِيَّةُ اللَّدودَة
- **(2)** ***Histoplasma capsulatum,*** النَّوسَجَةُ المُغَمَّدَةُ
- **(3)** ***Blastomyces dermatitidis*** البُرْعُمِيَّةُ المُلْهِبَةُ للجِلْد
- **(4) Aspergillosis** الرشاشيات
- **(5) Candidiasis** المبيضات

- ANTIFUNGAL DRUGS
- 1- SUBCUTANEOUS & SYSTEMIC MYCOSES
- Amphotericin B
- Flucytosine
- Ketoconazole
- Fluconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Echinocandins : Caspofungin, micafungin, and anidulafungin.

- **ANTIFUNGAL DRUGS**
- **2- CUTANEOUS MYCOSES**
- Naftifine
- Griseofulvin
- **Nystatin**
- Miconazole
- Clotrimazole
- Butoconazole
- Terconazole
- Econazole.

Aspergillosis

Aspergillosis, the most common invasive mold infection worldwide, caused by Approximately 150 species include *A. fumigatus, A. flavus, A. niger, A. terreus*, and *A. nidulans*. *A. fumigatus is* the predominant species causing invasive aspergillosis. *A. fumigatus* is the *most rapidly growing* species and *has very small spore size,* allowing *deep penetration into the lungs.*

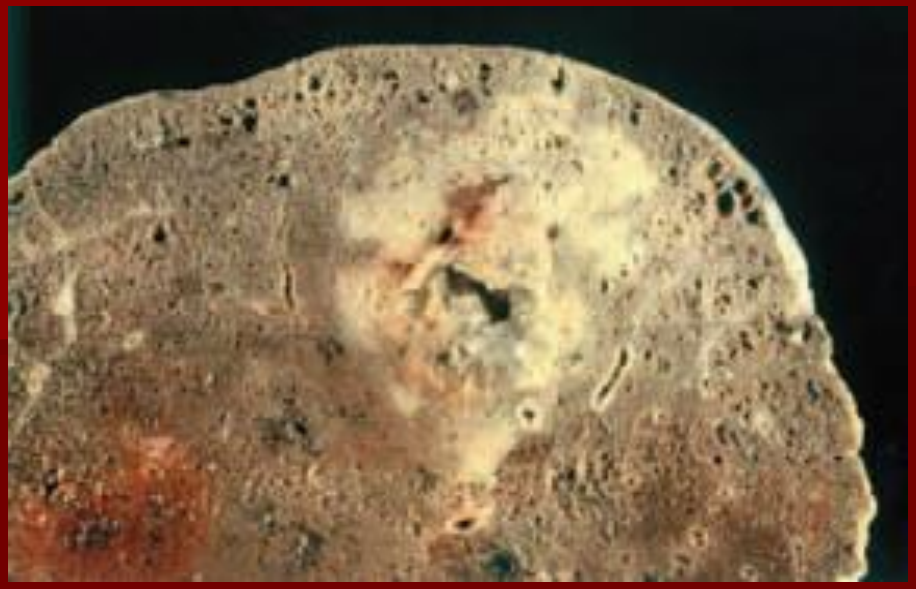
Macrophage and neutrophils are the primary host defenses against *Aspergillus* in the lungs.

Corticosteroids can substantially impair the functions of macrophages and neutrophils.

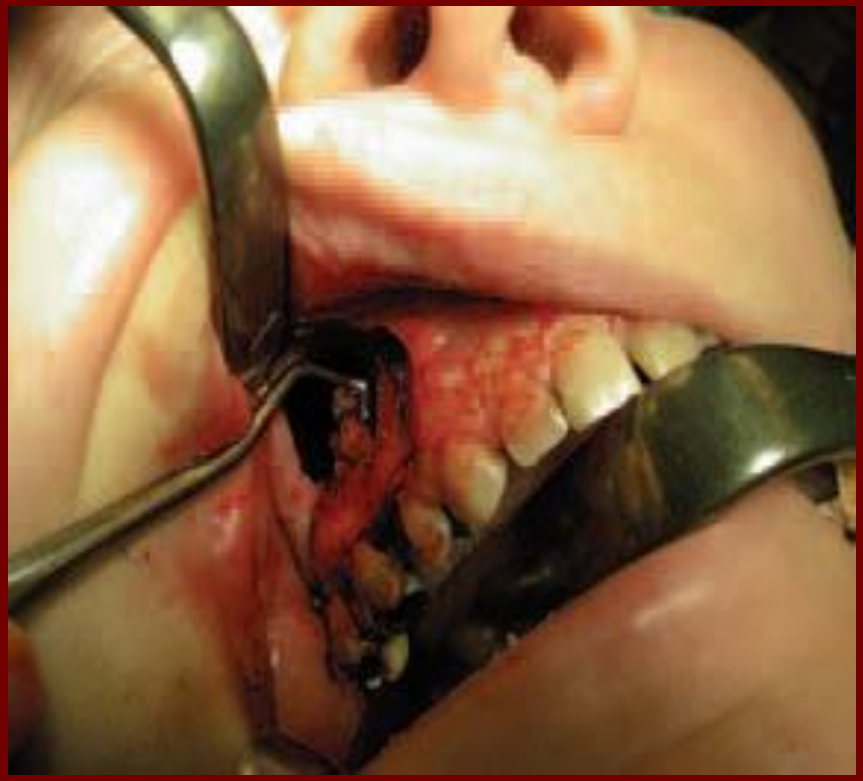
T-cell function is thought to be important in the more chronic forms of invasive aspergillosis.

- **Acute Pulmonary**
- **Acute invasive pulmonary aspergillosis occurs primarily in immunocompromised hosts. Early symptoms may consist of dry cough with fever and nonspecific chest pain. Hemoptysis can occur with focal disease without warning and can be life threatening. More commonly, the clinical presentation of acute pulmonary aspergillosis in *immunocompromised hosts* is one of *unremitting fever* and the development of *lung infiltrates* despite broad-spectrum antibacterial therapy.**

- **Chronic Pulmonary**
- **Chronic invasive aspergillosis occurs less frequently than acute aspergillosis. Affected patients commonly have underlying conditions such as AIDS, chronic granulomatous disease, diabetes mellitus, alcoholism, and corticosteroid use.**
- **They include chronic productive cough, mild to moderate hemoptysis, low-grade fever, malaise, and weight loss.**



Invasive aspergillosis of the lung

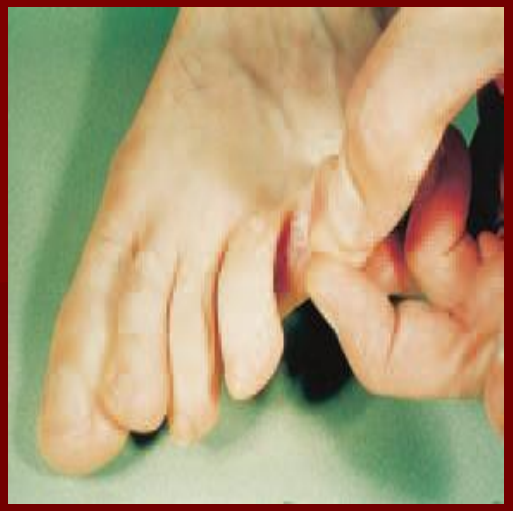


Aspergilloma in the maxillary sinus

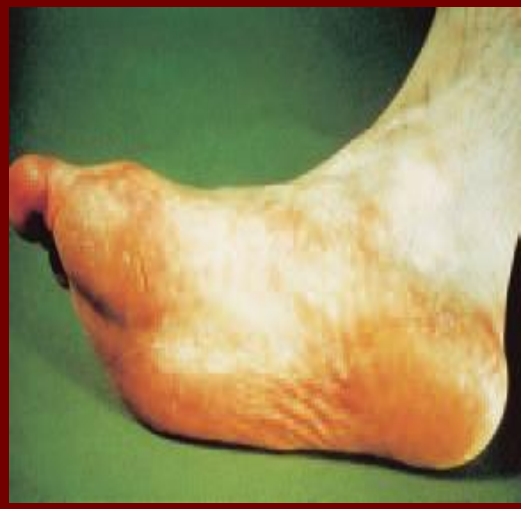
Management

- **Acute invasive pulmonary aspergillosis**
- • **Amphotericin B:** 1.0–1.5 mg/kg/day, to a total dose of at least 25 mg/kg (1 month) (DW5%).
- • **Itraconazole: 600 mg/day for 4-7 days** then **200 mg twice daily (3 months).**
- • **Caspofungin:** 70 mg/day until patient stabilizes.
- • **Voriconazole: 6 mg/kg, IV b.i.d. on day 1** followed by **4 mg/kg,IV b.i.d. until patient stabilizes**, **then 200 mg/day, b.i.d, orally.**

Dermatophytosis
Tinea pedis سعفة القدم



Interdigital tinea pedis due to *Trichophyton rubrum*.



Moccasin form of tinea pedis.

Definition

Dermatophyte infection of the feet.

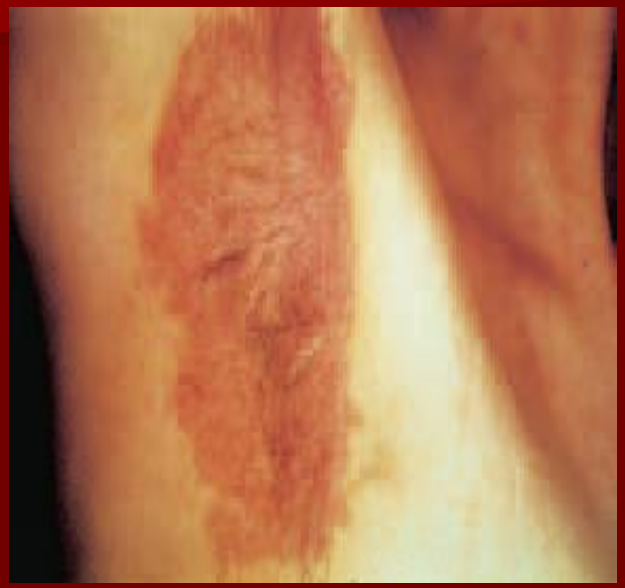
Causal organisms and habitat

- ***Trichophyton rubrum*** الشَّعْرَوِيَّةُ الحَمْراء is the most common cause.

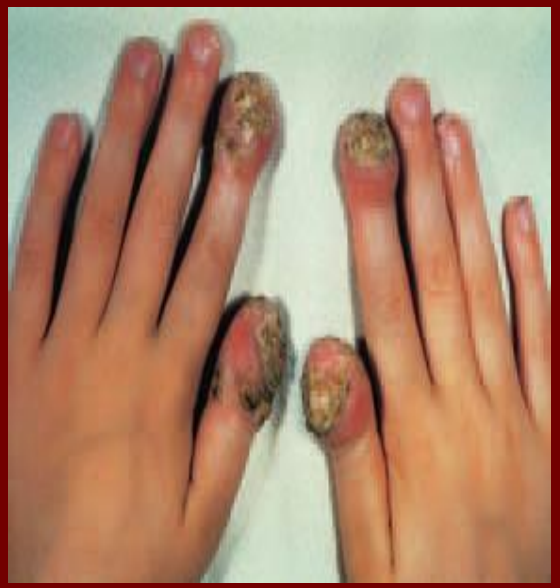
- **Management**
- This condition seldom resolves if untreated. However, it often responds to :
- **Topical treatment : with an azole (clotrimazole, econazole, miconazole, sulconazole), naftifine or terbinafine morning and evening for 2–4 weeks.**
- **Oral therapy**, if indicated, includes these alternatives:
- • **itraconazole:** 200 – 400 mg/day for 1 week.
- • **terbinafine:** 250 mg/day for 2– 6 weeks.

- **Cutaneous candidosis, Definition**
- Cutaneous candidosis is a ***yeast*** infection of the skin caused by members of the genus ***Candida***. Infection of the proximal nail fold known as ***Candida paronychia*** داحِس
- (التهاب ما حول الظفر) may lead to nail infection.
- **Causal organisms and habitat**
- • Most commonly caused by *Candida albicans* then *C. tropicalis* ; other species are occasionally implicated: Normal flora of the **skin, mouth, intestinal tract and vagina**.

- **Mucosal and cutaneous infections**
- **Cutaneous candidosis**

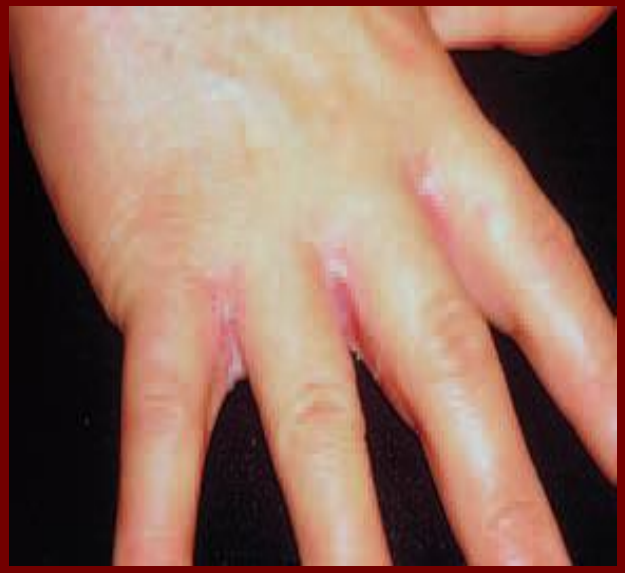


Candida *albicans* infection of axilla.

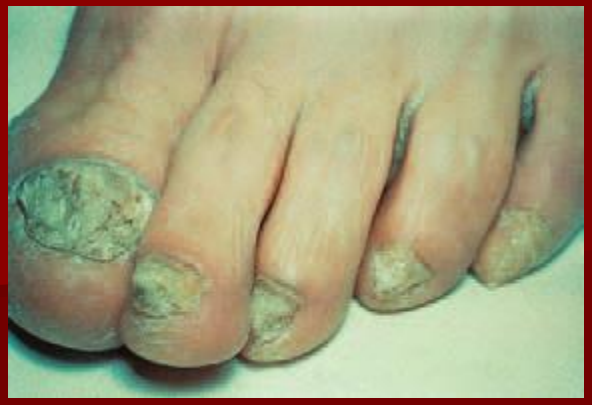


Chronic mucocutaneous **candidosis**.

Candida granuloma of the forehead and angular cheilitis associated with chronic mucocutaneous candidosis due to congenital defects in cell-mediated immunity.

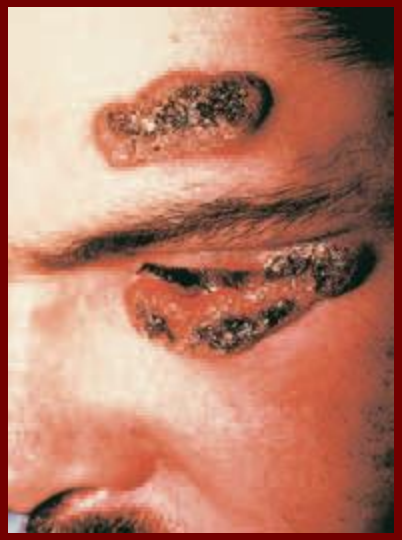


Interdigital candidosis caused by *Candida albicans*.



Tinea unguium due to *Trichophyton rubrum*

Superficial white onchomycosis.



Cutaneous blastomycosis

Chronic cutaneous coccidioidomycosis showing granulomatous lesions on face, neck and chin.

- **Management:**
- **Topical therapy:** with **azole** agents, **nystatin** and **naftifine**, should be **used twice daily until 1–2 weeks after clearing.**
- **Oral agents:** are indicated for folliculitis, nail involvement, extensive lesions and in the immunocompromised:
- • **itraconazole 200 mg/day or fluconazole 100 mg/day, 2-4 weeks.**

Additional steroid or antibacterial therapy may be indicated.

- ***General Treatment Guidelines***
- **1. Polyene antifungals : Amphotericin B, Nystatin, Natamycin and rimocidin**
- **2. Azoles : Imidazole, triazole, thiazole**
- **2.1 Imidazoles : Clotrimazol, Econazol, Ketoconazol, Sertaconazol, Omoconazol and Oxiconazol**

  2.2 Triazoles: Fluconazol, Itraconazol, Posaconazol, Voriconazol and Terconazol

  2.3 Thiazoles : Abafangin

General Treatment Guidelines

- **3. Allylamines : Amorolifin, Naftifine and Terbinafine**
- **4. Echinocandins : Micafungin, Caspofungin, Anidulafungin**
- **5. Others : Grisofulvin, Benzoic Acid, Flucytosine.**

The *first three antifungal* classes target *fungal cell membranes* by interacting with or *inhibiting* *ergosterol*.

The echinocandins uniquely target *fungal cell wall* (by inhibiting 1,3-β-D-glucan synthesis for the fungal **cell wall), chitin .**

- **Amphotericin B**
- In spite of its **toxic potential**, amphotericin B is the **drug of choice for the treatment of life-threatening, systemic mycoses**. **[**Note: **Conventional amphotericin (amphotericin B deoxycholate,** the non lipid formulation) has undergone several formulation improvements to reduce the incidence of side effects, **particularly nephrotoxicity.]** The drug is also sometimes used in **combination** with **flucytosine** so that lower (**less toxic**) levels of amphotericin B are possible.

- Antifungal spectrum: Amphotericin B is either **fungicidal or fungistatic**, **depending on: the organism *and the* concentration of the drug**. It is effective **against** a wide range of fungi, including **Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis and Moderate or severe aspergillosis.**
- **Resistance: Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.**

- **Pharmacokinetics:** Amphotericin B is administered by **slow, intravenous infusion**. Amphotericin B is ***insoluble*** in water, and ***injectable preparations require the addition of sodium deoxycholate***, which produces a ***soluble colloidal dispersion***.

- The simplest and smallest of the liposome preparations, AmBisome®,.
- These **liposomal** preparations **have the primary advantage of reduced renal and infusion toxicity.**

- Amphotericin B is **extensively bound to plasma proteins** and is **distributed throughout the body, becoming highly tissue bound**.
- **Amphotericin B does cross the placenta.**
- **Amphotericin B is Poorly crossing BBB.**
- **Blood-Brain Barrier (BBB).**
- **Metabolized in liver.**
- **Terminal half-life of up to 15 days.**

- **Dosage adjustment is not required in** patients with **compromised hepatic function**, ***but when renal dysfunction*** **is due to the use of conventional amphotericin B, the total daily** ***dose is decreased by 50% .***

- **Adverse reactions**: **Amphotericin B has a low therapeutic index**.
- **A total adult daily dose should not exceed 1.5 mg/kg**. Small test doses are usually administered to assess the degree of a patient's negative responses, **such as anaphylaxis or convulsions.**
  Other toxic manifestations include the following:

- **Fever and chills: Premedication** with a **corticosteroid or an antipyretic** helps to prevent this problem.
- **Renal impairment:** Despite the low levels of the drug excreted in the urine, patients may exhibit a **decrease in GFR and renal tubular function. Creatinine clearance can drop, and *potassium and magnesium are lost.***
- ***Azotemia*:** (elevated blood urea) is **exacerbated** by other **nephrotoxic drugs, *such as*** *aminoglycosides, cyclosporine, or pentamidine,* **although adequate hydration can decrease its severity.**

- **Hypotension: accompanied by hypokalemia, *requiring potassium supplementation.* Care** must be exercised **in patients taking digoxin.**

- **Anemia:** This may be exacerbated in **patients infected with HIV who are taking zidovudine.**

- **Thrombophlebitis (التهاب الوريد الخثري):** Adding **heparin** to the infusion can **alleviate** this problem.

- **Interactions**
- **Flucytosine : Toxicity of flucytosine is increased** and allows a lower dose of amphotericin B. **Amphotericin B may also facilitate entry of flucystosine into the fungal cell.**
- **Diuretics or cisplatin : Increased renal toxicity and increased risk of hypokalemia**
- **Corticosteroids : Increased risk of hypokalemia.**

- **Interactions**
- **Aminoglycosides : Increased risk of serious renal damage**, monitor kidney function closely.
- **Ganciclovir, Tenofovir, and Adefovir :**
- **hematological** and **renal** side-effects **of amphotericin B are increased.**
- **Transfusion of leukocytes :** Risk of **pulmonale damage occurs**. Space the intervals between the application of amphotericin B and the transfusion, and monitor pulmonary function.

- **Azole = Imidazole = Ketoconazole**
- ***First orally active azole*** available for the ***treatment of systemic mycosis.***
- **Mechanism of action**: Fungistatic.
- They **inhibit C-14 α-demethylase** , thus **blocking** the **demethylation** of **lanosterol** to **ergosterol** the principal **sterol of fungal membranes.**

- **Antifungal spectrum**: Ketoconazole is active against many fungi, including : **Histoplasma, Blastomyces, Candida, and Coccidioides**, ***but not aspergillus species.***
- **Resistance**: This **is** becoming a significant **clinical problem**, particularly in the protracted therapy required for those **with** advanced **HIV infection.**

- **Pharmacokinetics:**
- **Only orally.** It requires **gastric acid** for dissolution and is **absorbed through the gastric mucosa.**
- **Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria**.
- It is **extensively bound to plasma proteins**.
- **Penetration into tissues is limited.**
- **It *does not enter the CSF*.**
- **Extensive metabolism** occurs in the **liver,** and **excretion** is primarily through the **bile.**

- **Adverse effects**:
- In addition to **allergies**, **dose-dependent gastrointestinal disturbances**, including **nausea, anorexia, abdominal pain and vomiting**, are the most common adverse effects of ketoconazole treatment.
- ***Dose reductions*** should be considered in patients ***with severe liver disease.***

- **Drug interactions and contraindications:**
- **By inhibiting CYP3A4, CYP1A2, CYP2C9 ketoconazole** can **potentiate** the **toxicities** of **drugs** such as:
- **cyclosporine, phenytoin, tolbutamide, Buspirone, Calcium channel blockers, glimepiride, glipizide, losartan, montelukast, nateglinide, warfarin, zafirlukast and warfarin, Sildenafil, Tadalafil.**

- **Drug interactions and contraindications:**
- **Rifampin**, an **inducer** of CYP450 system, can **shorten** the **duration** of **action** of **ketoconazole and the other azoles.**
- **CONTRAINDICATIONS :** co administration with **ergot** derivatives or **cisapride** is contraindicated due to risk of **potentially fatal cardiac arrhythmias.**

Ketoconazole and amphotericin B should not be used together, because the decrease in ergosterol in the fungal membrane reduces the fungicidal action of amphotericin B **.**

Finally, ketoconazole is **teratogenic** in animals, **and it should not be given during pregnancy (C).**

DOSAGE FORMS

- **Aerosol, topical [foam] : 2% (50 g, 100 g)**
- **Cream, topical : 2% (15 g, 30 g, 60 g)**
- **Gel, topical : 2% (15 g) [contains dehydrated alcohol 34%]**
- **Shampoo, topical: 1% (120 mL), 2% (120 mL)**
- **Tablet : 200 mg (LFTs monitoring)**

- **Azole = Triazole = Fluconazole**
- **Fluconazole** is ***clinically important*** because of its **lack of the endocrine side effects of ketoconazole and its excellent penetrability into the CSF of both normal and inflamed meninges.** Fluconazole is employed ***prophylactically,*** with some success, for reducing fungal infections in recipients ***of bone marrow transplants.***

- **Mechanism of action: Like Ketoconazole**
- Fluconazole is effective against all forms of **mucocutaneous candidiasis.**
- Fluconazole is **administered orally or intravenously.** Its **absorption is excellent** and, **unlike that of ketoconazole, *is not dependent on gastric acidity.***
- **Binding to plasma proteins is minimal.**

- The drug **is excreted via the kidney**, ***and doses must be reduced in patients with compromised renal function.***

- **Concentrations** measured in the **urine, tears, and skin are approximately 10 times the plasma concentration, only 10% of elimination is due to metabolism**, the remainder being **excreted** in **urine** and **sweat.**

- Fluconazole **has no endocrinologic effects**, because it ***does not inhibit the CYP450 system*** responsible for the synthesis of androgens.
- Fluconazole **is secreted in human milk** at **concentrations similar to plasma.**
- Fluconazole therapy **has been associated with QT interval prolongation.**

- **Side effects: Nausea, vomiting, and rashes. Hepatitis is rare.**
- **Fluconazole is teratogenic, as are other azoles, and should not be used in pregnancy (C).**

- **A dosage of 500–600 mg/day** may be used **for systemic or severe infections**, and, in **urgent infections** such as meningitis caused by yeast, **800 mg/day have been used. Pediatric doses are measured at 6 –12 mg/kg/day.**

- **Azole = Triazole = Voriconazole**
- It is available for **IV** administration and **orally** administration and is approximately **0.95 bioavailable.**
- **Voriconazole is approved for the *treatment of invasive aspergillosis* and seems to have replaced amphotericin B as the treatment of choice for this indication.**

- **Voriconazole penetrates tissues well, including the CNS. *Elimination* is primarily by *metabolism* through the CYP450 2C19, 2C9, and 3A4 enzymes.**
- **One unique problem is a transient visual disturbance that occurs within 30 minutes of dosing.**
- **DOSAGE FORMS**
- **Injection, powder for reconstitution: 200 mg,**
- **Powder for oral suspension: 200 mg/5ml,**
- **Tablet: 50 mg, 200 mg.**

- **ADVERSE REACTIONS**
- **Hallucinations**, Fever , chills , headache
- **Hypokalemia**
- Nausea , vomiting , abdominal pain .

- **CONTRAINDICATIONS** :
- Hypersensitivity to voriconazole or any component of the formulation.
- coadministration with barbiturates (long acting), carbamazepine, ergot alkaloids, rifampin, rifabutin.

- **DRUG INTERACTIONS :**
- **Calcium channel blockers: Serum levels** may be **increased**, including felodipine, nifedipine, and verapamil).
- **Omeprazole:** Voriconazole may **increase** omeprazole serum levels. In patients taking **≥ 40 mg** of omeprazole per day, **dose** of omeprazole **should be reduced by half.**
- **Warfarin:** Anticoagulant effects may be **increased**; monitor INR.

- **Echinocandins :**
- **Caspofungin, micafungin, and anidulafungin.**
- Echinocandins interfere with the synthesis of the **fungal cell wall** by **inhibiting the synthesis of β(1,3)-D-glucan**, leading to lysis and cell death. This **drug's** spectrum is **limited to Aspergillus and Candida species.**
- ***Caspofungin is not active by the oral route.***
- **DOSAGE FORMS**
- **Injection, powder for reconstitution: 50 - 70 mg.**

- ***Elimination*** **is approximately equal between the *urinary and fecal routes.***

- **Adverse effects** include **fever, rash, nausea, and phlebitis**.
- **Caspofungin *should not be* coadministered with cyclosporine.**

- **Caspofungin** is a **second-line antifungal** for those who **have failed or cannot tolerate amphotericin B or an azole**.

- **Allylamines-thiocarbamates**
- (**terbinafine hydrochloride** and **naftifine hydrochloride**) **are reversible noncompetitive inhibitors of the fungal enzyme sequalene monooxygenase (sequalene 2,3-epoxidase),** which **converts squalene to lanosterol.**
- This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell.

- **Allylamines - thiocarbamates**

- **Terbinafine**
- Terbinafine is the **drug of choice for treating dermatophytosis and, especially, onychomycosis (fungal infections of nails).** It is better tolerated, **requires shorter duration of therapy**, **and is more effective than either itraconazole or griseofulvin.**

- **Antifungal spectrum**: Antifungal activity is limited to **dermatophytes and Candida albicans**. **Therapy is prolonged usually about 3 months.**
- **Pharmacokinetics** : **Terbinafine is orally active**, although its **bioavailability is only 0.4 due to first-pass metabolism.**
- **It is greater than 99 percent bound to plasma proteins. It is deposited in the skin, nails, and fat.**

- **Terbinafine accumulates in breast milk** and, therefore, **should not be given to nursing mothers.**
- **A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues.**
- **Terbinafine** is ***extensively metabolized*** prior to urinary excretion.

- **Side effects**: are gastrointestinal disturbances ***(diarrhea, dyspepsia, and nausea), headache, and rash***. **Taste and visual disturbances have been reported *as well as transient elevations in serum liver enzyme levels***.
- Although terbinafine is extensively metabolized, there **does not seem** to be a significant **risk** of **reduced clearance of other drugs**.
- **Rifampin decreases blood levels of terbinafine, whereas cimetidine increases blood levels of terbinafine.**

- **Dosage reductions** are **required with *renal or hepatic* insufficiency**.

- **Oral terbinafine is generally well tolerated but *occasionally causes gastric distress and liver enzyme elevation.***

- **ALLYLAMINES**
- **Naftifine hydrochloride (*Naftin*) is available for *topical* use *only* in the treatment of cutaneous dermatophyte and *Candida* infections.**

- Sources http://en.wikipedia.org/wiki/Antifungal
- http://www.lamisil.com/
- http://www.tinactin.com/
- http://en.wikipedia.org/wiki/Griseofulvin
- http://www.journals.uchicago.edu/CID/journal/issues/v30n4/990666/990666.text.html?erFrom=-48603785169359057 51Guest
- http://en.wikipedia.org/wiki/Nystatin
- http://inventors.about.com/library/inventors/blnystatin.htm

- **WWW sites**
- Please note that this list is by no means exhaustive!
- **Fungal infections, general**
- http://www.clinical-mycology.com
- http://fungus.utmb.edu/mycology
- http://www.doctorfungus.org/
- http://www.medicalmycology.org/
- http://www.medsche.wisc.edu/medmicro/myco/mycology.htm
- http://www.fungalforum.com
- **Specific infections**
- http://www.aspergillus.man.ac.uk
- http://www.genolist.pasteur.fr/CandidaDB
- http://www.panix.com/~candida/
- http://alces.med.umn.edu/Candida.html