Antifungals

Phar 538 Dr. Abdullah Rabba Ref. textbook: Lippincott's Illustrated Reviews: Pharmacology

- Infectious diseases caused by fungi are called mycoses,
- and they are often chronic in nature.
- Mycotic infections may be
  - superficial and involve only the skin (cutaneous mycoses extending into the epidermis), while others
  - may penetrate the skin, causing subcutaneous or systemic infections.
- The characteristics of fungi are so unique and diverse that they are classified in their own kingdom.
- Unlike bacteria, fungi are eukaryotic, with rigid cell walls composed largely of chitin rather than peptidoglycan (a characteristic component of most bacterial cell walls).

- In addition, the fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes.

- These structural characteristics are useful in targeting chemotherapeutic agents against fungal infections

- . Fungal infections are generally resistant to antibiotics, and, conversely, bacteria are resistant to antifungal agents.

- The incidence of fungal infections such as candidemia has been on the rise for the last few decades.

- This is attributed to an increased number of patients with chronic immune suppression due to organ transplantation, cancer chemotherapy, or infection with human immunodeficiency virus (HIV).

- During this same period, new therapeutic options have become available for the treatment of fungal infections.

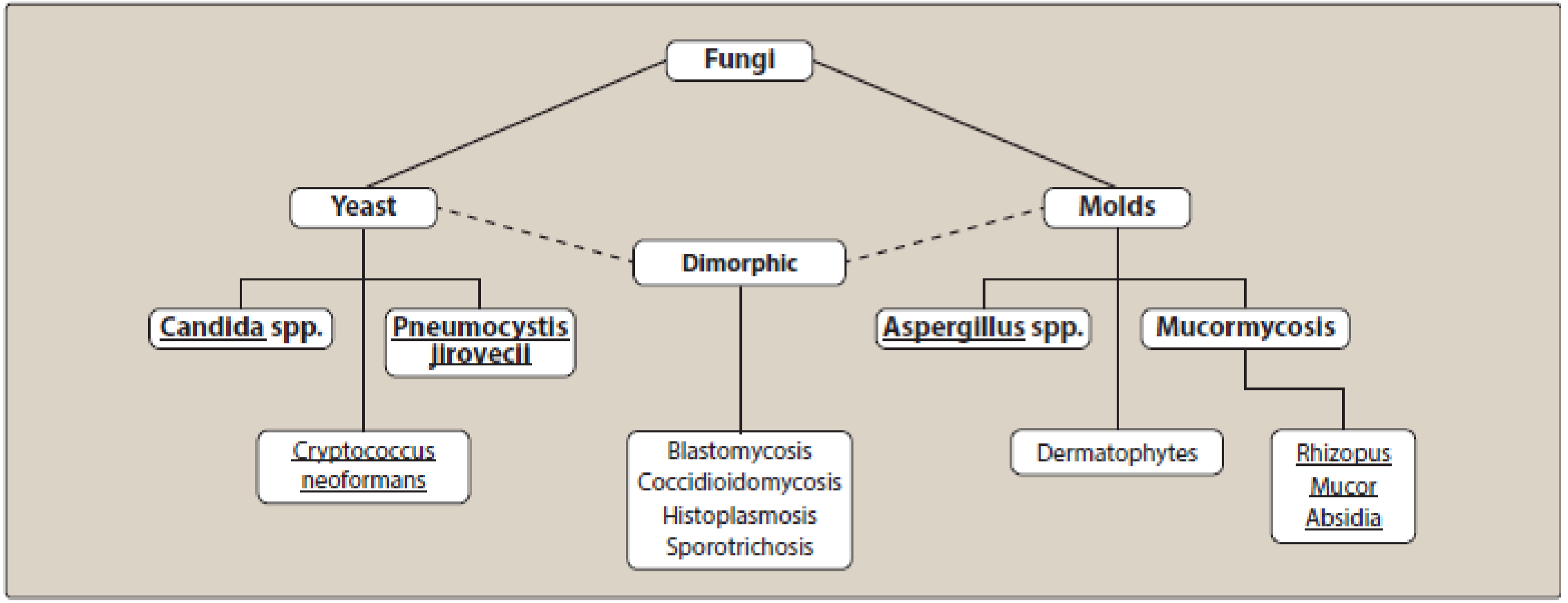
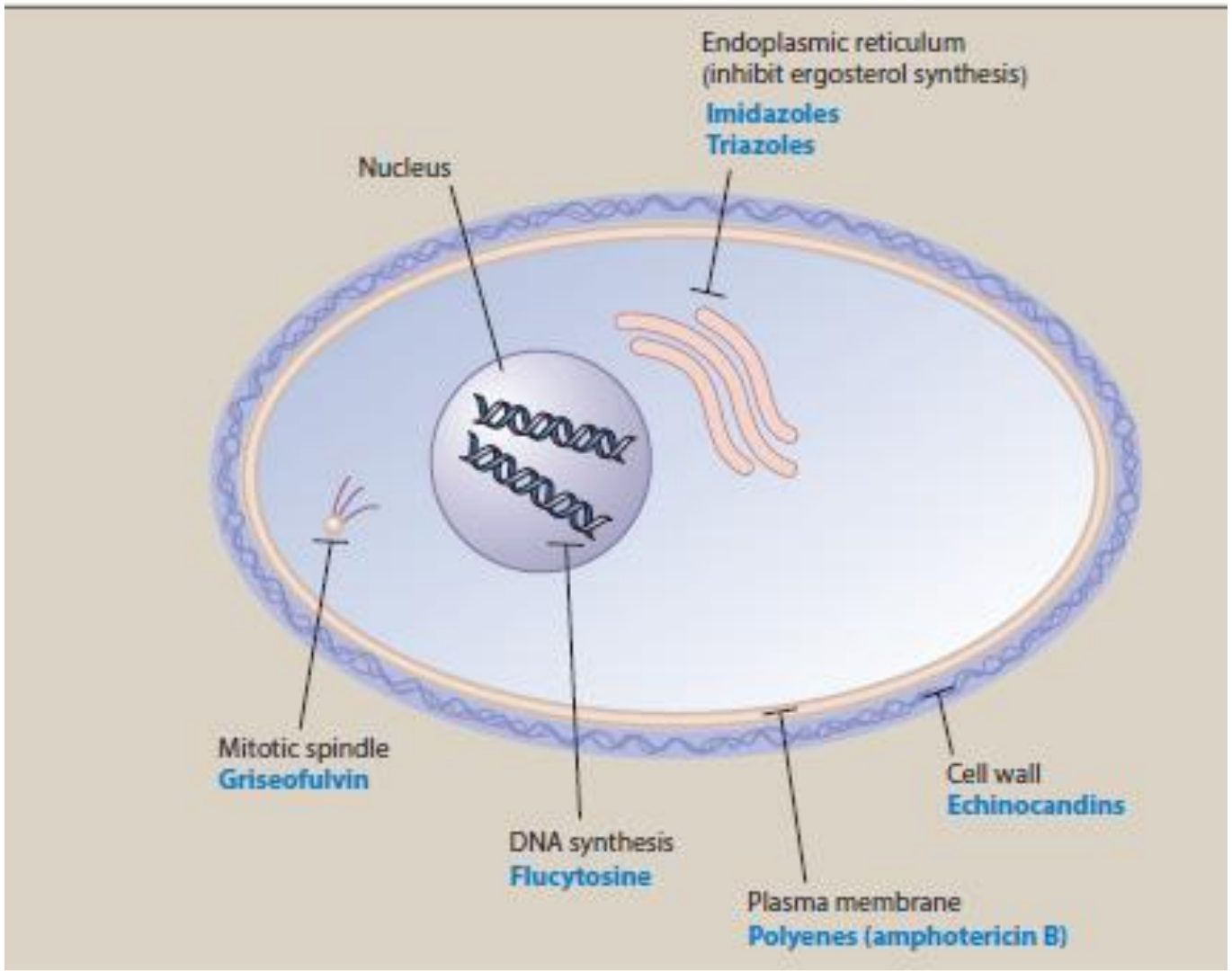


Figure 42.2
Common pathogenic organisms of Kingdom Fungi.


Endoplasmic reticulum
(inhibit ergosterol synthesis)
Imidazoles
Triazoles
Nucleus
Mitotic spindle
Griseofulvin
DNA synthesis
Flucytosine
Plasma membrane
Polyenes (amphotericin B)
Cell wall
Echinocandins

II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

A. Amphotericin B

- *Amphotericin B* is a naturally occurring polyene antifungal produced by Streptomyces nodosus.

- In spite of its toxic potential, *amphotericin B* remains the drug of choice for the treatment of several life-threatening mycoses.

- **1. Mechanism of action:**
- *Amphotericin B* binds to ergosterol in the plasma membranes of sensitive fungal cells.

- There, it forms pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antifungal and the sterol

- The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.

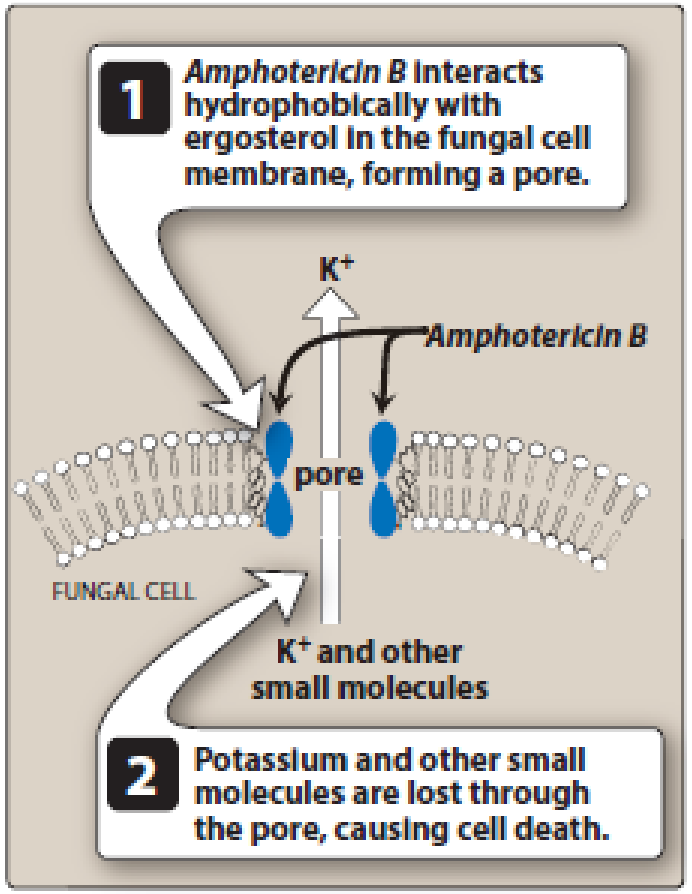


Figure 42.4
Model of a pore formed by *amphotericin B* in the lipid bilayer membrane.

- **2. 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
  - many strains of Aspergillus.
  - [Note: *Amphotericin B* is also used in the treatment of the protozoal infection leishmaniasis.]

- **3. Resistance:**

- Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.

- **4. Pharmacokinetics:**
- *Amphotericin B* is administered by slow, intravenous (IV) infusion

- *Amphotericin B* is insoluble in water and must be coformulated with either sodium deoxycholate (conventional) or a variety of artificial lipids to form liposomes.

- The liposomal preparations have the primary advantage of reduced renal and infusion toxicity.

- However, due to high cost, liposomal preparations are reserved mainly as salvage therapy for patients who cannot tolerate conventional *amphotericin B.*

- *Amphotericin B* is extensively bound to plasma proteins and is distributed throughout the body.

- Inflammation favors penetration into various body fluids, but little of the drug is found in the CSF, vitreous humor, or amniotic fluid. However, *amphotericin B* does cross the placenta.

- Low levels of the drug and its metabolites appear in the urine over a long period of time, and some are also eliminated via the bile.

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

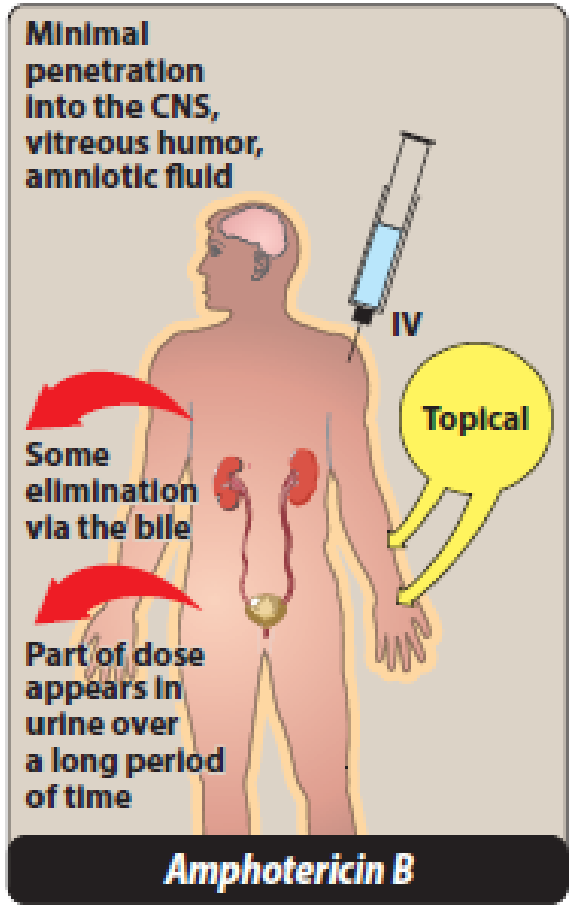


Figure 42.5
Administration and fate of *amphotericin B*. CNS = central nervous system.

- **5. Adverse effects:**
- ***Amphotericin B has a low therapeutic index.***

- ***The*** total adult daily dose of the conventional formulation should not exceed 1.5 mg/kg/d, whereas lipid formulations have been given safely in doses up to 10 mg/kg/d.

- Toxic manifestations are outlined below

- **a. Fever and chills:**
- **These occur most commonly 1 to 3 hours** after starting the IV administration but usually subside with repeated administration of the drug.

- Premedication with a corticosteroid or an antipyretic helps to prevent this problem.

- **b. Renal impairment:**
- **Despite the low levels of the drug excreted** in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function.

- Serum creatinine may increase, creatinine clearance can decrease, and potassium and magnesium are lost.

- Renal function usually returns with discontinuation of the drug, but residual damage is likely at high doses.

- Azotemia is exacerbated by other nephrotoxic drugs, such as aminoglycosides, *cyclosporine, pentamidine, and vancomycin,* although adequate hydration can decrease its severity.

- To minimize nephrotoxicity, sodium loading with infusions of normal saline and the lipid-based *amphotericin B products can* be used.

- **c. Hypotension:**
- **A shock-like fall in blood pressure accompanied** by hypokalemia may occur, requiring potassium supplementation.

- Care must be exercised in patients taking *digoxin and* other drugs that can cause potassium fluctuations.

- **d. Thrombophlebitis: Adding *heparin to the infusion can alleviate***
- this problem.

- **c. Hypotension:**
- **A shock-like fall in blood pressure accompanied** by hypokalemia may occur, requiring potassium supplementation.

- Care must be exercised in patients taking *digoxin and*
- other drugs that can cause potassium fluctuations.

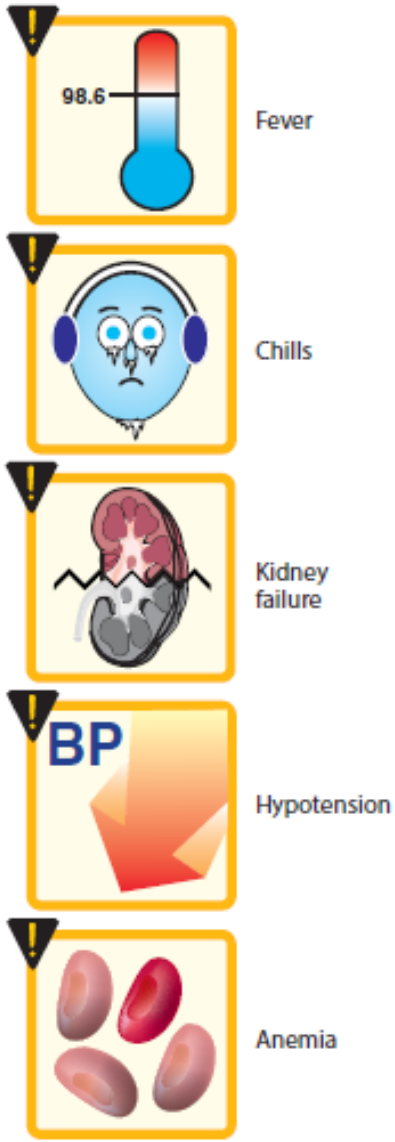


Figure 42.6
Adverse effects of *amphotericin B.*

B. Antimetabolite antifungals

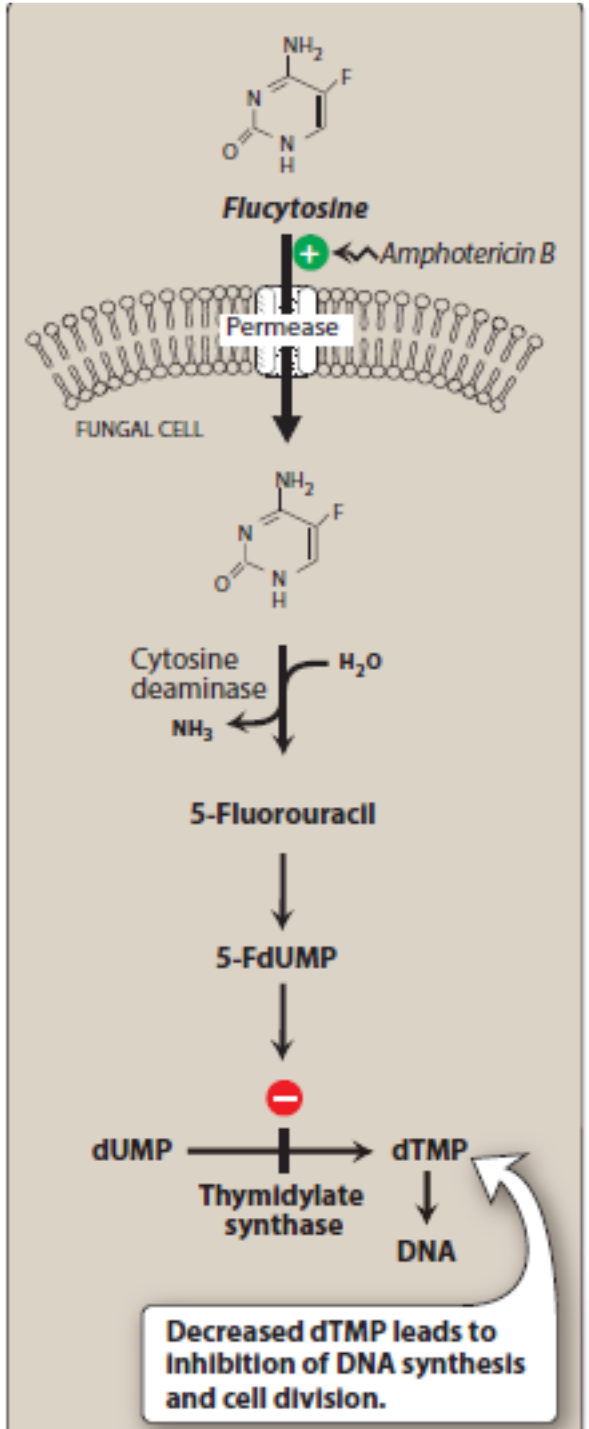
- *Flucytosine [floo-SYE-toe-seen] (5-FC) is a synthetic pyrimidine antimetabolite* that is often used in combination with *amphotericin B*.

- *This* combination of drugs is administered for the treatment of systemic mycoses and for meningitis caused by
  - C. neoformans and
  - C. albicans.

- **1. Mechanism of action:**
- ***5-FC enters the fungal cell via a cytosine specific*** permease, an enzyme not found in mammalian cells.

- It is subsequently converted to a series of compounds, including *5-fluorouracil and 5-fluorodeoxyuridine 5'-**monophosphate, which*** disrupt nucleic acid and protein synthesis.

- [Note: *Amphotericin B increases cell permeability, allowing more 5-FC to* penetrate the cell and leading to synergistic effects.]


Flucytosine
Amphotericin B
Permease
FUNGAL CELL
Cytosine deaminase
H_2O
NH_3
5-Fluorouracil
5-FdUMP
dUMP
Thymidylate synthase
dTMP
DNA
Decreased dTMP leads to inhibition of DNA synthesis and cell division.

- **2. Antifungal spectrum:**
- ***5-FC is fungistatic.***

- It is effective in combination with *itraconazole for treating chromoblastomycosis (causes* skin and subcutaneous infections) and

- in combination with *amphotericin B for treating candidiasis and cryptococcosis.*

- *Flucytosine can also be used for Candida urinary tract infections* when *fluconazole is not appropriate; however, resistance can* occur with repeated use.

- **3. Resistance:**
- **Resistance due to decreased levels of any of the** enzymes in the conversion of *5-FC to 5-fluorouracil (5-FU) and* beyond or from increased synthesis of cytosine can develop during therapy.

- This is the primary reason that *5-FC is not used as a* single antimycotic drug.

- The rate of emergence of resistant fungal cells is lower with a combination of *5-FC plus a second antifungal* agent than it is with *5-FC alone.*

- **4. Pharmacokinetics:**
- ***5-FC is well absorbed by the oral route.***

- ***It distributes*** throughout the body water and penetrates well into the CSF.

- *5-FU is detectable in patients and is probably the result of metabolism* of *5-FC by intestinal bacteria.*

- *Excretion of both the parent drug* and its minimal metabolites is by glomerular filtration, and the dose must be adjusted in patients with compromised renal function.

- **5. Adverse effects:**
- ***5-FC causes reversible neutropenia, thrombocytopenia,*** and dose-related bone marrow depression.

- Caution must be exercised in patients undergoing radiation or chemotherapy with drugs that depress bone marrow.

- Reversible hepatic dysfunction with elevation of serum transaminases and alkaline phosphatase may occur.

- Gastrointestinal disturbances (nausea, vomiting, and diarrhea) are common, and severe enterocolitis may also occur.

C. Azole antifungals

- Azole antifungals are made up of two different classes of drugs—
  - imidazoles and
  - triazoles.

- Although these drugs have similar mechanisms of action and spectra of activity,
- their pharmacokinetics and therapeutic uses vary significantly.

- In general, imidazoles are given topically for cutaneous infections, whereas

- triazoles are given systemically for the treatment or prophylaxis of cutaneous and systemic fungal infections.

- [Note: Imidazole antifungals are discussed in the section on agents for cutaneous mycotic infections.] The

- triazole antifungals include
  - *fluconazole,*
  - *itraconazole,*
  - *posaconazole, and*
  - *voriconazole.*
- Imidazoles include
  - *butoconazole*
  - *clotrimazole,*
  - *econazole*
  - *ketoconazole*
  - *miconazole*
  - *oxiconazole*
  - *sertaconazole*
  - *sulconazole*
  - *terconazole*
  - *tioconazole*

- **1. Mechanism of action:**
- **Azoles are predominantly fungistatic.**

- **They** inhibit C-14 α-demethylase (a cytochrome P450 [CYP450] enzyme), thereby blocking the demethylation of lanosterol to ergosterol, the principal sterol of fungal membranes .

- The inhibition of ergosterol biosynthesis disrupts membrane structure and function,which, in turn, inhibits fungal cell growth.

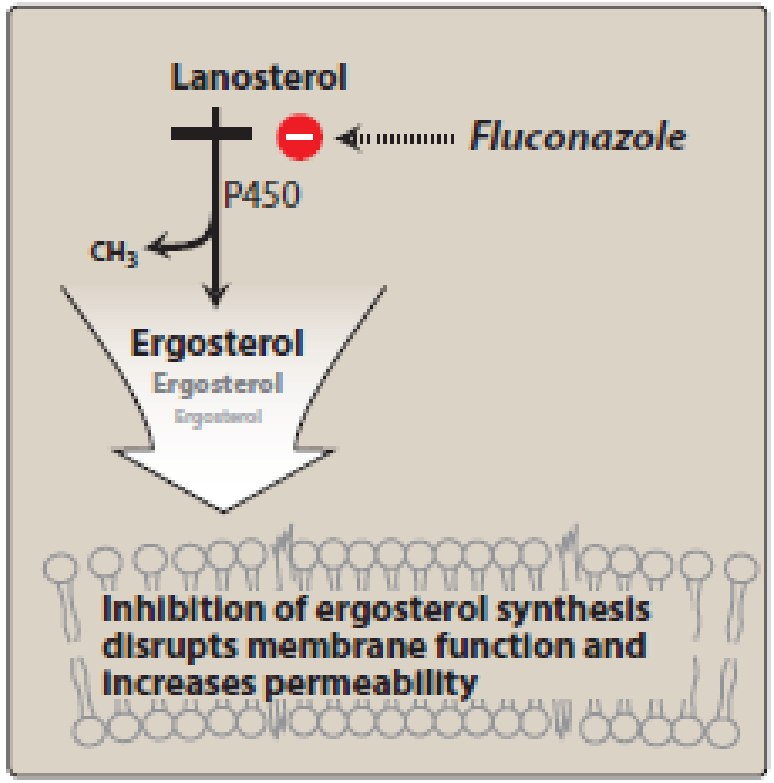


Figure 42.8
Mode of action of azole antifungals.

- **2. Resistance:**
- **Resistance to azole antifungals is becoming a significant** clinical problem, particularly with protracted therapy required in immunocompromised patients, such as those who have advanced HIV infection or bone marrow transplant.

- Mechanisms of resistance include mutations in the C-14 α-demethylase gene that lead to decreased azole binding.

- Additionally, some strains of fungi have developed efflux pumps that pump the azole out of the cell.

- **3. Drug interactions:**
- **All azoles inhibit the hepatic CYP450 3A4** isoenzyme to varying degrees.

- Patients on concomitant medications that are substrates for this isoenzyme may have increased concentrations and risk for toxicity.

- Several azoles, including *itraconazole* and *voriconazole, are metabolized by CYP450 3A4 and* other CYP450 isoenzymes.

- Therefore, concomitant use of potent CYP450 inhibitors (for example, *ritonavir) and inducers (for example, rifampin) can lead to increased adverse effects or clinical failure of* these azoles, respectively.

- **4. Contraindications:**

- **Azoles are considered teratogenic, and they** should be avoided in pregnancy unless the potential benefit outweighs the risk to the fetus.

D. Fluconazole

- *Fluconazole was the first member of the triazole* class of antifungal agents.

It is the least active of all triazoles, with most of its spectrum limited to yeasts and some dimorphic fungi.

- It has no role in the treatment of aspergillosis or zygomycosis.

- It is highly active against Cryptococcus neoformans and certain species of Candida, including C. albicans and C. parapsilosis.

- Resistance is a concern, however, with other species, including C. krusei and C. glabrata.

Fluconazole is used for prophylaxis against invasive fungal infections in recipients of bone marrow transplants.

- It also is the drug of choice for Cryptococcus neoformans after induction therapy with *amphotericin B and flucytosine and is used for the treatment of* candidemia and coccidioidomycosis.

- *Fluconazole is effective against* most forms of mucocutaneous candidiasis.

- It is commonly used as a single-dose oral treatment for vulvovaginal candidiasis.

- *Fluconazole* is available in oral or IV dosage formulations.

- It is well absorbed after oral administration and distributes widely to body fluids and tissues.
- The majority of the drug is excreted unchanged via the urine, and doses must be reduced in patients with renal dysfunction.
- The most common adverse effects with *fluconazole are nausea, vomiting,* headache, and skin rashes.
- Hepatotoxicity can also occur, and the drug should be used with caution in patients with liver dysfunction.

E. Itraconazole

- *Itraconazole [it-ra-KON-a-zole] is a synthetic triazole that has a broad* antifungal spectrum compared to *fluconazole.*
- *Itraconazole is the* drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis.
- It is rarely used for treatment of infections due to Candida and Aspergillus species because of the availability of newer and more effective agents.
- *Itraconazole is* available in two oral dosage forms, a capsule and an oral solution.

- The oral capsule should be taken with food, and ideally an acidic beverage, to increase absorption.

- In contrast, the solution should be taken on an empty stomach, as food decreases the absorption.

- The drug distributes well in most tissues, including bone and adipose tissues.

- *Itraconazole is extensively metabolized by the liver, and the* drug and inactive metabolites are excreted in the feces and urine.

- Adverse effects include nausea, vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache.

- Hepatotoxicity can also occur, especially when given with other drugs that affect the liver.

- *Itraconazole has a negative inotropic* effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

F. Posaconazole

- *Posaconazole* [poe-sa-KONE-a-zole], a synthetic triazole, is a broadspectrum antifungal structurally similar to *itraconazole.*
- It is available as an oral suspension, oral tablet, or IV formulation.
- *Posaconazole* is commonly used for the treatment and prophylaxis of invasive Candida and Aspergillus infections in severely immunocompromised patients.
- Due to its broad spectrum of activity, *posaconazole* is also used in the treatment of invasive fungal infections caused by Scedosporium and Zygomycetes.
- *Posaconazole* has a low oral bioavailability and should be given with food.
- Even though *posaconazole* has a long half-life, the suspension is usually given in divided doses throughout the day due to saturable absorption in the gut, whereas the tablet is given once daily.

- Unlike other azoles, *posaconazole* is not metabolized in the liver by CYP450 but is eliminated via glucuronidation.
- The most common adverse effects include gastrointestinal disturbances (nausea, vomiting, and diarrhea) and headaches.
- Like other azoles, *posaconazole* can cause an elevation in serum hepatic transaminases.
- Drugs that affect the gastric pH (for example, proton pump inhibitors) may decrease the absorption of oral *posaconazole* and should be avoided if possible.
- Due to its potent inhibition of CYP3A4, concomitant use of *posaconazole* with a number of agents (for example, ergot alkaloids, *atorvastatin*, *citalopram*, *risperidone, pimozide,* and *quinidine*) is contraindicated.

G. Voriconazole

- *Voriconazole [vor-i-KON-a-zole], a synthetic triazole related to fluconazole,* has the advantage of being a broad-spectrum antifungal agent that is available in both IV and oral dosage forms.
- *Voriconazole* has replaced *amphotericin B as the drug of choice for invasive aspergillosis.*
- It is also approved for treatment of invasive candidiasis, as well as serious infections caused by Scedosporium and Fusarium species.
- *Voriconazole has high oral bioavailability and penetrates* into tissues well.
- Elimination is primarily by metabolism through the CYP450 enzymes.
- *Voriconazole displays nonlinear kinetics, which* can be affected by drug interactions and pharmacogenetic variability, particularly CYP450 2C19 polymorphisms.

- Adverse effects are similar to those of the other azoles; however, high trough concentrations are associated with visual and auditory hallucinations and an increased incidence of hepatotoxicity.

- *Voriconazole is not only a* substrate but also an inhibitor of CYP2C19, 2C9, and 3A4 isoenzymes.

- Inhibitors and inducers of these enzymes may impact levels of *voriconazole, leading to toxicity or clinical failure, respectively.*

- *In* addition, drugs that are substrates of these enzymes are impacted by *voriconazole .*

- *Due to significant interactions, use* of *voriconazole is contraindicated with many drugs (for example, rifampin, rifabutin, carbamazepine, and the herb St. John's wort).*

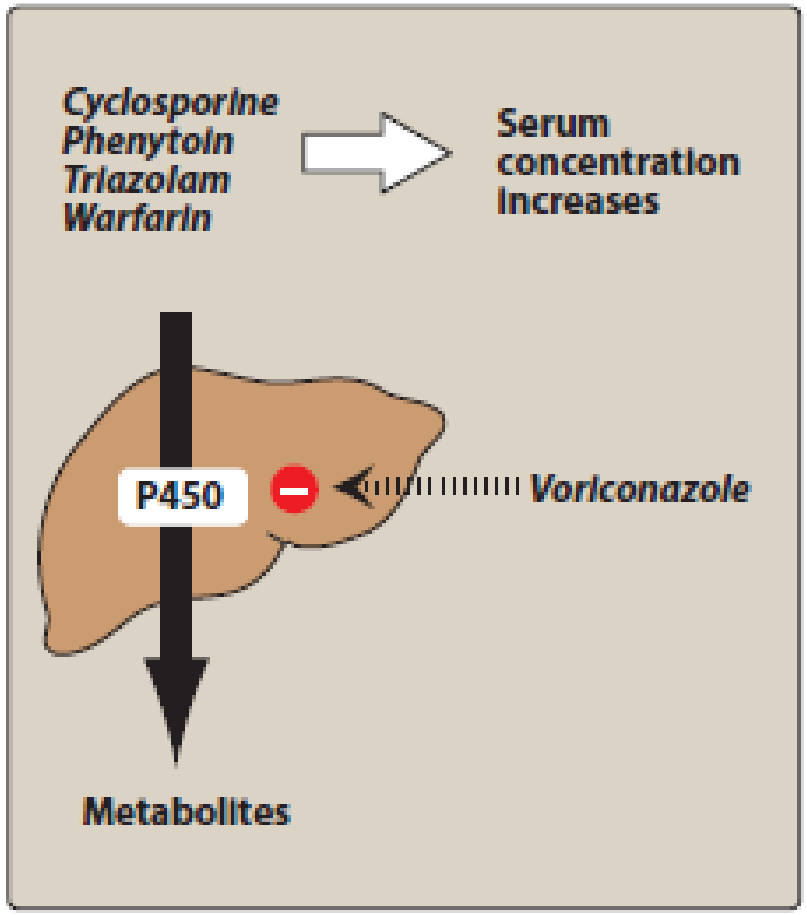


Figure 42.9
By inhibiting cytochrome P450, *voriconazole* can potentiate the toxicities of other drugs.

	FLUCONAZOLE	ITRACONAZOLE	VORICONAZOLE	POSACONAZOLE
SPECTRUM OF ACTIVITY	+	++	+++	++++
ROUTE(S) OF ADMINISTRATION	Oral, IV	Oral	Oral, IV	Oral, IV
ORAL BIOAVAILABILITY (%)	95	55 (solution)	96	Variable
DRUG LEVELS AFFECTED BY FOOD OR GASTRIC PH	No	Yes	No	Yes
PROTEIN BINDING (%)	10	99	58	99
PRIMARY ROUTE OF ELIMINATION	Renal	Hepatic CYP3A4	Hepatic CYP2C19, 2C9, 3A4	Hepatic Glucuronidation
CYTOCHROME P450 ENZYMES INHIBITED	CYP3A4, 2C9, 2C19	CYP3A4, 2C9	CYP2C19, 2C9, 3A4	CYP3A4
HALF-LIFE ($t_{1/2}$)	25 hours	30–40 hours	Dose Dependent	20–66 hours
CSF PENETRATION	Yes	No	Yes	Yes
RENAL EXCRETION OF ACTIVE DRUG (%)	> 90	< 2	< 2	< 2
TDM RECOMMENDED (RATIONALE)	No	Yes (Efficacy)	Yes (Efficacy and Safety)	Yes (Efficacy)

INTERACTING DRUG	DRUG	EFFECT ON DRUG EXPOSURE	MAIN CLINICAL CONSEQUENCE OF INTERACTION
Amiodarone, dronedarone, citalopram, pimozide, quinidine	*Itraconazole, fluconazole, voriconazole, posaconazole**	↑ exposure to interacting drugs	QT interval prolongation with risk of torsades de pointes
Carbamazepine	*Voriconazole*	↓ exposure to *voriconazole*	Treatment failure of *voriconazole*
Efavirenz	*Voriconazole*	↓ exposure to *voriconazole*	Treatment failure of *voriconazole*
		↑ exposure to *efavirenz*	Risk of *efavirenz* toxicity
Ergot alkaloids	*Itraconazole, fluconazole, voriconazole, posaconazole**	↑ exposure to ergot alkaloid	Ergotism
Lovastatin, simvastatin	*Itraconazole, voriconazole, posaconazole*	↑ exposure to HMG-CoA reductase inhibitor	Risk of rhabdomyolysis
Midazolam, triazolam	*Itraconazole, voriconazole, posaconazole*	↑ exposure to benzodiazepine	Sleepiness
Phenytoin	*Voriconazole, posaconazole*	↓ exposure to *voriconazole, posaconazole*	Treatment failure
		↑ exposure to *phenytoin*	Nystagmus, ataxia
Rifabutin	*Voriconazole, posaconazole*	↓ exposure to *voriconazole*	Treatment failure of *voriconazole*
		↑ exposure to *rifabutin*	Uveitis
Rifampicin (rifampin)	*Voriconazole, posaconazole*	↓ exposure to *voriconazole*	Treatment failure of *voriconazole*
High-dose *ritonavir* (400 mg twice daily)	*Voriconazole*	↓ exposure to *voriconazole*	Treatment failure of *voriconazole*
Vincristine, vinblastine	*Itraconazole, voriconazole, posaconazole*	↑ exposure to vinca alkaloids	Neurotoxicity
Sirolimus	*Voriconazole, posaconazole*	↑ exposure to *sirolimus*	Risk of *sirolimus* toxicity

H. Echinocandins

- 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.
- ***Caspofungin, micafungin, and anidulafungin*** *are available for* IV administration once daily.
- The echinocandins have potent activity against Aspergillus and most Candida species, including those species resistant to azoles.
- However, they have minimal activity against other fungi. All three agents are well tolerated, with the most common adverse effects being fever, rash, nausea, and phlebitis at the infusion site.
- They can also cause a histamine-like reaction (flushing) when infused too rapidly.

- **1. Caspofungin:**
- the first member of the echinocandin class of antifungal drugs.

- a first-line option for patients with invasive candidiasis, including candidemia, and a second-line option for invasive aspergillosis in patients who have failed or cannot tolerate *amphotericin B* or an azole.

- Dose adjustment is warranted with moderate hepatic dysfunction.

- Concomitant administration of *caspofungin* with certain CYP450 enzyme inducers (for example, *rifampin*) may require an increase in the daily dose.

- *Caspofungin* should not be coadministered with *cyclosporine* due to a high incidence of elevated hepatic transaminases with concurrent use

- **2. Micafungin and anidulafungin:**
- are newer members of the echinocandin class of antifungal drugs.
- are first-line options for the treatment of invasive candidiasis, including candidemia.
- *Micafungin* and *anidulafungin* do not need to be adjusted in renal impairment or mild to moderate hepatic dysfunction.
- *Anidulafungin* can be administered in severe hepatic dysfunction, but *micafungin* has not been studied in this condition.
- These agents are not substrates for CYP450enzymes and do not have any associated drug interactions.

III. DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS

- Mold-like fungi that cause cutaneous infections are called dermatophytes or tinea.
- Tinea infections are classified by the affected site (for example, tinea pedis, which refers to an infection of the feet).
- Common dermatomycoses, such as tinea infections that appear as rings or round red patches with clear centers, are often referred to as "ringworm."
- The three different fungi that cause the majority of cutaneous infections are
  - Trichophyton,
  - Microsporum, and
  - Epidermophyton.

A. Squalene epoxidase inhibitors

- These agents act by inhibiting squalene epoxidase, thereby blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane (Figure 42.12).

- Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.

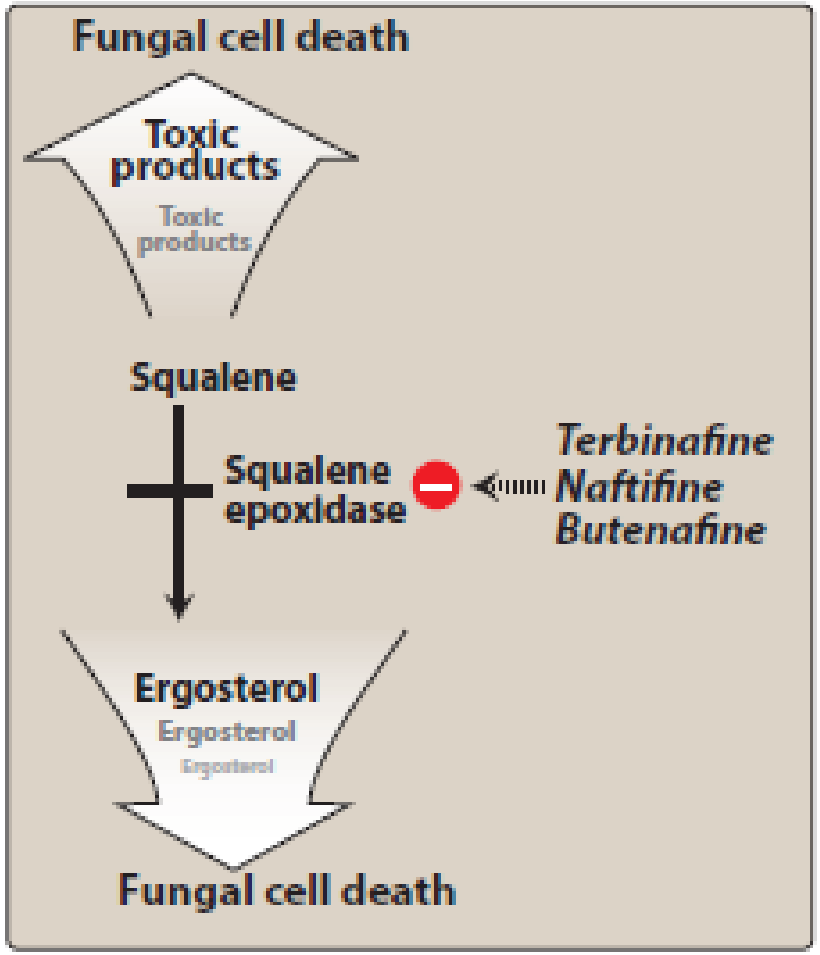


Figure 42.12
Mode of action of squalene epoxidase inhibitors.

1. Terbinafine:

- Oral *terbinafine* [TER-bin-a-feen] is the drug of choice for treating dermatophyte onychomycoses (fungal infections of nails).
- It is better tolerated, requires a shorter duration of therapy, and is more effective than either *itraconazole* or *griseofulvin.*
- Therapy is prolonged (usually about 3 months) but considerably shorter than that with *griseofulvin.*
- Oral *terbinafine* may also be used for tinea capitis (infection of the scalp).
- [Note: Oral antifungal therapy (*griseofulvin*, *terbinafine*, *itraconazole*) is needed for tinea capitis. Topical antifungals are ineffective.]
- Topical *terbinafine* (1% cream, gel or solution) is used to treat tinea pedis, tinea corporis , and tinea cruris (infection of the groin).
- Duration of treatment is usually 1 week.

- **b. Pharmacokinetics:**
- *Terbinafine* is available for oral and topical administration, although its bioavailability is only 40% due to first-pass metabolism.
- *Terbinafine* is highly protein bound and is deposited in the skin, nails, and adipose tissue.
- A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues.
- Oral *terbinafine* is extensively metabolized by several CYP450 isoenzymes and is excreted mainly via the urine .
- The drug should be avoided in patients with moderate to severe renal impairment or hepatic dysfunction.

- **c. Adverse effects:**
- Common adverse effects of *terbinafine* include gastrointestinal disturbances (diarrhea, dyspepsia, and nausea), headache, and rash.

- Taste and visual disturbances have been reported, as well as

- transient elevations in serum hepatic transaminases.

- *Terbinafine* is an inhibitor of the CYP450 2D6 isoenzyme, and concomitant use with substrates of that isoenzyme may result in an increased risk of adverse effects with those agents.

2. Naftifine:

- *Naftifine* [NAF-ti-feen] is active against Trichophyton, Microsporum, and Epidermophyton.

- *Naftifine* 1% cream and gelare used for topical treatment of tinea corporis, tinea cruris, and
- tinea pedis. Duration of treatment is usually 2 weeks.

3. Butenafine:

- ***Butenafine [byoo-TEN-a-feen]***
- ***is active against*** Trichophyton rubrum, Epidermophyton, and Malassezia.

- Like *naftifine, butenafine 1% cream is used for topical treatment of* tinea infections.

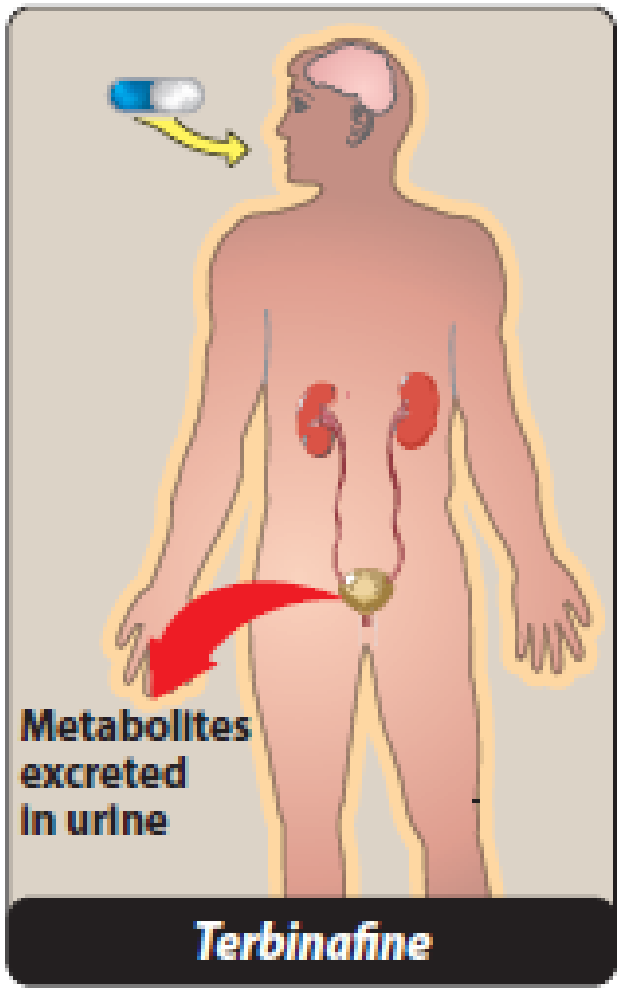


Figure 42.13
Administration and fate of *terbinafine*.

B. Griseofulvin

- *Griseofulvin [gris-ee-oh-FUL-vin] causes disruption of the mitotic* spindle and inhibition of fungal mitosis .
- It has been largely replaced by oral *terbinafine for the treatment of onychomycosis,* although it is still used for dermatophytosis of the scalp and hair.
- *Griseofulvin is fungistatic and requires a long duration of treatment* (for example, 6 to 12 months for onychomycosis).
- Duration of therapy is dependent on the rate of replacement of healthy skin and nails.

- Ultrafine crystalline preparations are absorbed adequately from the gastrointestinal tract, and absorption is enhanced by high-fat meals.

- The drug concentrates in skin, hair, nails, and adipose tissue.

- *Griseofulvin induces hepatic CYP450 activity, which increases the* rate of metabolism of a number of drugs, including anticoagulants.

- The use of *griseofulvin is contraindicated in pregnancy and patients* with.

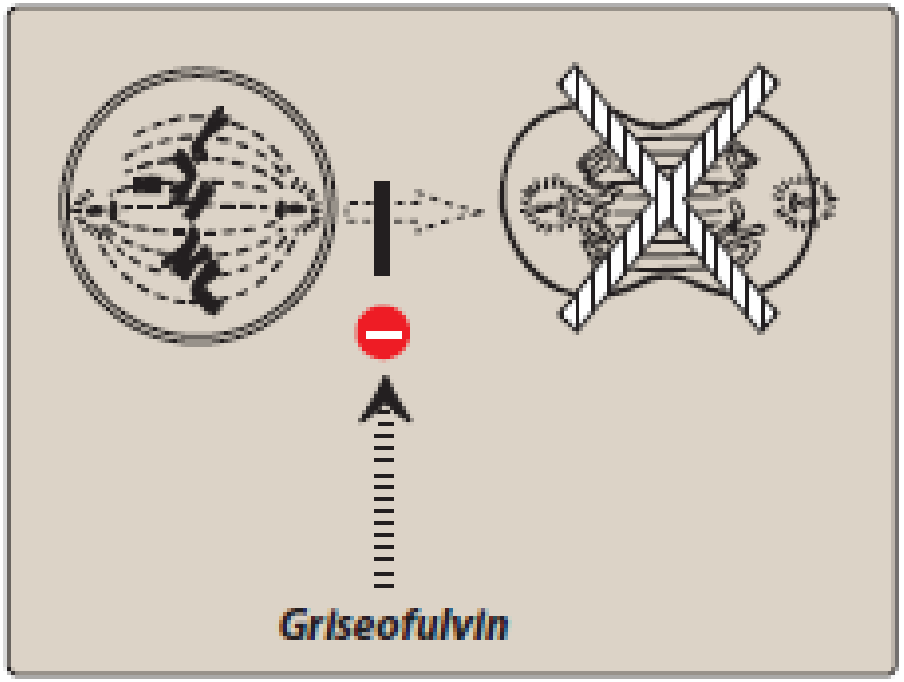


Figure 42.14
Inhibition of mitosis by *griseofulvin*.

C. Nystatin

- *Nystatin [nye-STAT-in] is a polyene antifungal, and its structure,* chemistry, mechanism of action, and resistance profile resemble those of *amphotericin B*.

- *It is used for the treatment of cutaneous* and oral Candida infections.

- The drug is negligibly absorbed from the gastrointestinal tract, and it is not used parenterally due to systemic toxicity (acute infusion-related adverse effects and nephrotoxicity).

- It is administered as an
  - oral agent ("swish and swallow" or "swish and spit") for the treatment of oropharyngeal candidiasis (thrush),
  - intravaginally for vulvovaginal candidiasis, or
  - topically for cutaneous candidiasis.

- Imidazoles include
  - *butoconazole*
  - *clotrimazole,*
  - *econazole*
  - *ketoconazole*
  - *miconazole*
  - *oxiconazole*
  - *sertaconazole*
  - *sulconazole*
  - *terconazole*
  - *tioconazole*

D. Imidazoles

- they have a wide range of activity against Epidermophyton, Microsporum, Trichophyton, Candida, and Malassezia, depending on the agent.

- The topical imidazoles have a variety of uses, including
  - tinea corporis,
  - tinea cruris,
  - tinea pedis, and
- oropharyngeal and vulvovaginal candidiasis.

- Topical use is associated with contact dermatitis, vulvar irritation, and edema.

- *Clotrimazole is also available as a troche* (lozenge), and *miconazole is available as a buccal tablet for the treatment* of thrush.

- Oral *ketoconazole has historically been used for the* treatment of systemic fungal infections but is rarely used today due to the risk for severe liver injury, adrenal insufficiency, and adverse drug interactions.

E. Ciclopirox

- *inhibits the transport of essential elements* in the fungal cell, disrupting the synthesis of DNA, RNA, and proteins.

- *Ciclopirox is active against Trichophyton, Epidermophyton,* Microsporum, Candida, and Malassezia.

- It is available in a number of formulations. *Ciclopirox 1% shampoo is used for treatment* of seborrheic dermatitis.

- Tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor may be treated with the 0.77% cream, gel, or suspension.

F. Tolnaftate

- distorts the hyphae and stunts mycelial growth in susceptible fungi.

- *Tolnaftate* is active against Epidermophyton, Microsporum, and Malassezia furfur. [Note: *Tolnaftate* is not effective
- against Candida.]

- *Tolnaftate* is used to treat tinea pedis, tinea cruris, and tinea corporis. It is available as a 1% solution, cream, and powder.

Which of the following antifungal agents is MOST likely to cause renal insufficiency?

- A. Fluconazole.
- B. Amphotericin B.
- C. Itraconazole.
- D. Posaconazole.

- A 55-year-old female presents to the hospital with
- shortness of breath, fever, and malaise. She has a history
- of breast cancer, which was diagnosed 3 months ago,
- and has been treated with chemotherapy. Her chest x-ray
- shows possible pneumonia, and respiratory cultures are
- positive for Aspergillus fumigatus. Which of the following
- is the MOST appropriate choice for treatment?
- A. Voriconazole.
- B. Fluconazole.
- C. Flucytosine.
- D. Ketoconazole.

- Which of the following antifungal agents should be avoided
- in patients with evidence of ventricular dysfunction?
- A. Micafungin.
- B. Itraconazole.
- C. Terbinafine.
- D. Posaconazole.