**Antifungal Drugs**

1. **OVERVIEW**

Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature.1 Some mycotic infections are superficial and some involve the skin (cutaneous mycoses extending into the epidermis), 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 are eukaryotic. They have rigid 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. 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 such that candidemia is a significant cause of septicemia. This increased incidence of fungal infections is associated with greater numbers of patients with chronic immune suppression following organ transplant, from undergoing chemotherapy for myelogenous and solid tumors, or from the human immunodeficiency virus (HIV). During this same period, there have been significant changes in the therapeutic options available to the clinician, including new azoles and echinocandins. Figure 35.1 lists clinically useful agents for subcutaneous and systemic mycoses as well as cutaneous mycoses.

**II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS**

1. **Amphotericin B**

Amphotericin [am-foe-TER-i-sin] B is a naturally occurring polyene macrolide antibiotic produced by Streptomyces nodosus. 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 nonlipid formula- tion) has undergone several formulation improvements to reduce the incidence of side effects, particularly nephrotoxicity.] The drug is also sometimes used in combination with flucytosine to achieve more rapid sterilization of the cerebrospinal fluid (CSF).

1. **Mechanism of action**: Several amphotericin B molecules bind to ergosterol in the plasma membranes of sensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol (Figure 35.2). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death. [Note: Because the polyene antibiotics bind preferentially to ergosterol rather than to cholesterol (the sterol found in mammalian membranes) a relative (but not absolute) specificity is conferred.]

2. **Antifungal spectrum**: Amphotericin B is either fungicidal or fungi- static, 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, intra- venous (IV) infusion (Figure 35.3). Amphotericin B is insoluble in water, and injectable preparations require the addition of sodium deoxycholate, which produces a soluble colloidal dispersion. The more dangerous intrathecal route is sometimes chosen for the treatment of meningitis caused by fungi that are sensitive to the drug. Amphotericin B has also been formulated with a variety of artificial lipids that form liposomes. The three amphotericin B lipid formulations marketed in the United States are AMPHOTEC, ABELCET, and AMBISOME. For example, the simplest and smallest of the liposome preparations, AMBISOME, is produced by the incorporation of amphotericin B into a single liposomal bilayer composed of phospholipids and cholesterol (Figure 35.4). These liposomal preparations have the primary advantage of reduced renal and infusion toxicity. However, because of their high cost, liposomal preparations are reserved mainly as salvage therapy for those individuals who cannot tolerate conventional amphotericin B. Amphotericin B is extensively bound to plasma proteins and is distributed through- out the body, becoming highly tissue bound. Inflammation favors penetration into various body fluids, but little of the drug is found in the cerebrospinal fluid (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 compromised hepatic function, but when conventional amphotericin B causes renal dysfunction, the total daily dose is decreased by 50 percent. To minimize nephrotoxicity, alternatives including sodium loading with infusions of nor- mal saline and the lipid-based amphotericin B products are used.

5. **Adverse effects**: Amphotericin B has a low therapeutic index. The total adult daily dose should not exceed 1.5 mg/kg. Small test doses may be administered to assess the degree of negative responses, such as anaphylaxis or convulsions. Other toxic manifestations include the following (Figure 35.5).

a. **Fever and chills**: These occur most commonly 1 to 3 hours after starting the IV administration, but they 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. Creatinine clearance can drop, and potassium and magnesium are lost. [Note: Nephrotoxicity may be potentiated by sodium depletion. A bolus infusion of normal saline before and after amphotericin B infusion may reduce the incidence of drug-induced nephrotoxicity.] Normal renal function usually returns with suspension of the drug, but residual damage is likely at high doses. Azotemia (elevated blood urea) is exacerbated by other nephrotoxic drugs, such as aminoglycosides, cyclosporine, and pentamidine, although adequate hydration can decrease its severity.

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.

d. **Anemia**: Normochromic, normocytic anemia caused by a reversible suppression of erythrocyte production may occur. This may be exacerbated in patients infected with HIV who are taking zidovudine.

e. **Neurologic effects**: Intrathecal administration can cause a variety of serious neurologic problems.

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

**B.** **Flucytosine**

Flucytosine [fl oo-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 Cryptococcus neoformans and Candida albicans. 1. Mechanism of action: 5-FC enters fungal cells via a cytosine- specific permease, which is an enzyme not found in mammalian cells. 5-FC is then converted by a series of steps to 5-fl uorodeoxyuridine 5’-monophosphate. This false nucleotide inhibits thymidy- late synthase, thereby depriving the organism of thymidylic acid, an essential DNA component (Figure 35.6). The unnatural mononucleotide is further metabolized to a trinucleotide (5-fl uorodeoxyuridine 5’-triphosphate) and is incorporated into fungal RNA, where it disrupts nucleic acid and protein synthesis. [Note: Amphotericin B increases cell permeability, allowing more 5-FC to penetrate the cell. Thus, 5-FC and amphotericin B are synergistic (Figure 35.7).]

**2. Antifungal spectrum**: 5-FC is fungistatic. It is effective in combi- nation with itraconazole for treating chromoblastomycosis and in combination with amphotericin B for treating candidiasis and cryptococcosis.

**3. Resistance**: Resistance due to decreased levels of any of the enzymes in the conversion of 5-FC to 5-fl uorouracil (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 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, such as nausea, vomiting, and diarrhea, are common, and severe enterocolitis may also occur. [Note: Some of these adverse effects may be related to 5-FU formed by intestinal organisms from 5-FC.]

**C. Ketoconazole** Ketoconazole [kee-toe-KON-a-zole] was the first orally active azole avail- able for the treatment of systemic mycoses. 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 (Figure 35.8). This inhibition disrupts membrane structure and function, which, in turn, inhibits fungal cell growth. [Note: Unfortunately, as is often the case for the initial member of a class of drugs, the selectivity of ketoconazole toward its target is not as precise as those of later azoles. For example, in addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production. In addition, ketoconazole inhibits CYP450-dependent hepatic drug-metabolizing enzymes.]

**2. Antifungal spectrum**: Oral ketoconazole is active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but not aspergillus species. Itraconazole has largely replaced ketocon- azole in the treatment of most mycoses because of its broader spectrum, greater potency, and fewer adverse effects. As a second-line drug, oral ketoconazole is a less-expensive alternative for the treatment of mucocutaneous candidiasis. However, strains of several fun- gal species that are resistant to ketoconazole have been identifi ed. Topical ketoconazole is used to treat tinea corporis, tinea cruris, and tinea pedis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton fl occosum. Also, topical ketocon- azole is used to treat tinea versicolor caused by Malassezia furfur, cutaneous candidiasis caused by Candida species. It is also used topically in the treatment of seborrheic dermatitis and dandruff .

**3. Resistance**: This is becoming a significant clinical problem, particularly in the protracted therapy required for those with advanced HIV infection. Identifi ed mechanisms of resistance include mutations in the C-14 α-demethylase gene, which cause decreased azole binding. Additionally, some strains of fungi have developed the ability to pump the azole out of the cell.

**4. Pharmacokinetics**: When ketoconazole is administered orally (Figure 35.9), it requires gastric acid for dissolution and is absorbed through the intestinal mucosa. Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H2-histamine– receptor blockers and proton-pump inhibitors, impair absorption. Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria. Ketoconazole is extensively bound to plasma proteins. Although penetration into tissues is limited, it is effective in the treatment of histoplasmosis in lung, bone, skin, and soft tissues. The drug does not enter the CSF. Extensive metabolism occurs in the liver, and excretion is primarily through the bile. Levels of parent drug in the urine are too low to be eff ective against mycotic infections of the urinary tract.

**5. Adverse effects**: In addition to allergies, dose-dependent gastro- intestinal disturbances, including nausea, anorexia, and vomiting, are the most common adverse eff ects of ketoconazole treatment. Endocrine effects, such as gynecomastia, decreased libido, impotence, and menstrual irregularities, result from the blocking of androgen and adrenal steroid synthesis by ketoconazole. Transient increases in serum transaminases occur in 2 to 10 percent of patients receiving ketoconazole. Frank hepatitis occurs rarely, but requires immediate cessation of ketoconazole treatment. [Note: Ketoconazole may accumulate in patients with hepatic dysfunction. Plasma concentrations of the drug should be monitored in these individuals.]

**6. Drug interactions and contraindications**: By inhibiting CYP450, ketoconazole can potentiate the toxicities of drugs such as cyclosporine, phenytoin, triazolam, and warfarin, among others (Figure 35.10). Rifampin, an inducer of the CYP450 system, can shorten the duration of action of ketoconazole and the other azoles. Drugs that decrease gastric acidity, such as H2-receptor blockers, ant- acids, proton-pump inhibitors, and sucralfate, can decrease absorp- tion of ketoconazole. 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 (Figure 35.11). Finally, ketoconazole is teratogenic in animals, and it should not be given during pregnancy.

**D. Fluconazole**

Fluconazole [floo-KON-a-zole] is a member of the triazole class of anti- fungal products. It 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. It inhibits the synthesis of fungal membrane ergosterol in the same manner as ketoconazole and is the drug of choice for Cryptococcus neoformans after therapy with amphotericin B, for most candidemias, and for coccidioidomycosis. Fluconazole is effective against most forms of mucocutaneous candidiasis. [Note: Treatment failures due to resistance have been reported in some HIV- infected patients.] Fluconazole is administered orally or intravenously. For the treatment of vaginal candidiasis, the dose is 150 mg as a single oral dose. Its absorption is excellent and, unlike that of ketoconazole, is not dependent on gastric acidity. Binding to plasma proteins is mini- mal. Unlike ketoconazole, fluconazole is poorly metabolized. The drug is excreted via the kidney, and doses must be reduced in patients with compromised renal function. The adverse effects caused by fluconazole treatment are less of a problem than those with ketoconazole. Fluconazole has no endocrinologic effects because it does not inhibit the CYP450 system responsible for the synthesis of androgens. However, it can inhibit the P450 cytochromes that metabolize other drugs listed in Figure 35.10. Nausea, vomiting, and rashes are a problem. There is a caution for patients with liver dysfunction. Fluconazole is teratogenic, as are other azoles, and should not be used in pregnancy. E. Itraconazole Itraconazole [it-ra-KON-a-zole] is an antifungal agent with a broad anti- fungal spectrum. Like fluconazole, it is a synthetic triazole and also lacks the endocrinologic side effects of ketoconazole. Its mechanism of action is the same as that of the other triazoles. Itraconazole is the drug of choice for the treatment of blastomycosis, sporotrichosis, paracoc- cidioidomycosis, and histoplasmosis. Unlike ketoconazole, it is effective in acquired immunodeficiency syndrome–associated histoplasmosis. Itraconazole is well absorbed orally, but it requires acid for dissolution. Food increases the bioavailability of some preparations. The drug is extensively bound to plasma proteins and distributes well throughout most tissues, including bone and adipose tissues. However, therapeu- tic concentrations are not attained in the CSF. Like ketoconazole, itraconazole is extensively metabolized by the liver, but it does not inhibit androgen synthesis. Its major metabolite, hydroxyitraconazole, is bio- logically active, with a similar antifungal spectrum. Little of the parent drug appears in the urine, eliminating the need for dose reduction with renal failure. Adverse effects include nausea and vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache. Itraconazole should be avoided in pregnancy. Itraconazole inhibits the metabolism of many drugs, including oral anticoagulants, statins, and quinidine. Inducers of the CYP450 system increase the metabolism of itraconazole. The capsules should not be taken by patients with evidence of ventricular dysfunction, such as congestive heart failure (CHF) or a history of CHF.

**F. Voriconazole**

Voriconazole [vor-i-KON-a-zole], a triazole, has the advantage of being a broad-spectrum antifungal agent. It is available for both IV and oral administration and is approximately 96 percent bioavailable. Voriconazole is approved for the treatment of invasive aspergillosis and has replaced amphotericin B as the treatment of choice for this indication. Voriconazole is also approved for treatment of serious infections caused by Scedosporium apiospermum and Fusarium species. Voriconazole pen- etrates tissues well, including the CNS. Elimination is primarily by metabolism through the CYP450 2C19, 2C9, and 3A4 enzymes. The significant number of drug interactions due to its metabolism through the various hepatic enzymes may limit its use. Side effects are similar to those of the other azoles. High trough concentrations are associated with visual and auditory hallucinations.

**G. Posaconazole**

Posaconazole [poe-sa-KONE-a-zole], a triazole, is a new oral, broad- spectrum antifungal agent with a chemical structure similar to that of itraconazole. It was approved in 2006 to prevent Candida and Aspergillus infections in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis. Due to its spectrum of activity, posaconazole could possibly be used in the treatment of fungal infections caused by Mucor species and other zygomycetes. To date, amphotericin B formulations are the only other antifungal agents available for treatment of zygomycete infections. Overall, posaconazole is relatively well tolerated. The most common side effects observed were gastrointestinal issues (nausea, vomiting, diarrhea, and abdominal pain) and headaches. Like other azoles, posaconazole can cause an elevation of the liver function tests, causing elevated serum levels of hepatic transaminases. Additionally, in patients who are receiving concomitant cyclosporine or tacrolimus for management of transplant rejection, rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been report- ed. Due to its inhibition of CYP450 3A4 enzymes, posaconazole may increase the effect and toxicity of many drugs, including cyclosporine, tacrolimus, and sirolumus. Concomitant use of posaconazole with ergot alkaloids, pimozide, and quinidine is contraindicated. To be effective, posaconazole must be administered with a high fat meal. Posaconazole may be given two or four times daily for a total daily dose of 800 mg.

**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 adminstration once daily. Micafungin does not require a loading dose.

**1. Caspofungin**: Caspofungin [kas-poh-FUN-jin] is the first approved member of the echinocandins class of antifungal drugs. Caspofungin has activity against Aspergillus and most Candida species, including those species resistant to azoles. Adverse effects include fever, rash, nausea, and phlebitis. Flushing occurs, which is probably due to the release of histamine from mast cells. The dose of caspofungin does not need to be adjusted in renal impairment but is warranted with moderate hepatic dysfunction. Concomitant administration of caspofungin with CYP450 enzyme inducers may require an increase in the daily dose administered. Caspofungin should not be co administered with cyclosporine due to the high incidence of elevation of hepatic transaminases with concurrent use. Caspofungin is a second-line antifungal for those who have failed or cannot tolerate amphotericin B or an azole.

**2. Micafungin and anidulafungin**: Micafungin (mi-ka-FUN-gin) and anidulafungin (ay-nid-yoo-la-FUN-jin) are the newer members of the echinocandins class of antifungal drugs. Micafungin and anidulafungin have similar efficacy against Candida species, but the effi- cacy for treatment of other fungal infections has not been established. The dose of micafungin and anidulafungin does not need to be adjusted in renal impairment or mild-to-moderate hepatic dys- function. No studies have been done with the use of micafungin in severe hepatic dysfunction, but andulafungin can be administered in this condition. Also, they are not substrates for CYP450 enzymes and do not have any associated drug interactions.

**III. DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS**

Mold-like fungi that cause cutaneous skin infections are called dermatophytes or tinea. These tinea infections are classified by the site of their infection, such as 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.” This is a mis- nomer, because fungi rather than worms cause the disease. The three differ- ent fungi that cause the majority of cutaneous infections are Trichophyton, Microsporum, and Epidermophyton. These pathogens have a high affinity for keratinized tissue such as skin, hair, and nails. The drugs used in the treatment of cutaneous mycoses are listed in Figure 35.1. A. Squalene epoxidase inhibitors These agents act by inhibiting squalene epoxidase, resulting in the blocking of the biosynthesis of ergosterol, an essential component of fungal cell membrane. 1. Terbinafine: Oral terbinafine [TER-bin-a-feen] is the drug of choice for treating dermatophytoses and, especially, onychomycoses (fun- gal infections of nails). It is better tolerated, requires shorter dura- tion of therapy, and is more effective than either itraconazole or griseofulvin.

**a. Mechanism of actio**n: Terbinafi ne inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol (Figure 35.14). This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell. [Note: Significantly higher concentrations of terbinafi ne are needed to inhibit human squalene epoxidase, an enzyme required for the cholesterol synthetic pathway.]

**b. Antifungal spectrum**: The drug is primarily fungicidal. Topical terbinafi ne is active against Trichophyton rubrum and Trichophyton mentagrophytes . It may also be effective against Candida albicans, Epidermophyton fl occosum, and Scopulariopsis brevicaulis, but the safety and effi cacy in treating clinical infections due to these pathogens has not been established. Topical terbinafi ne 1% cream and solution are used to treat tinea pedis, tinea corporis, and tinea cruris. Therapy is prolonged (usually about 3 months) but considerably shorter than that with griseofulvin.

**c. Pharmacokinetics**: Terbinafi ne is available for oral and topical administration, although its bioavailability is only 40 percent due to fi rst-pass metabolism. Absorption is not significantly enhanced by food. Terbinafine is greater than 99 percent bound to plasma proteins. It is deposited in the skin, nails, and fat. Terbinafine accumulates in breast milk and 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. Oral terbinafine is extensively metabolized prior to urinary excretion (Figure 35.15). Patients with either moderate renal impairment or hepatic cirrhosis have reduced clearance.

**d. Adverse effects**: The most common adverse effects from terbinafine 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. All adverse effects resolve upon drug discontinuation. Rarely, terbinafine may cause hepatotoxicity and neutropenia. 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.

**2. Naftifine**: Naftifine [NAF-ti-feen] is active against Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, and Epidermophyton fl occosum. Naftifi ne 1% cream and gel is used for topical treatment of tinea corporis, tinea cruris, and tinea pedis.

**3. Butenafine**: Butenafine [byoo-TEN-a-feen] is active against Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum, and Malassezia furfur. Butenafine 1% cream is used for topical treatment of tineacorporis, tinea cruris, interdigital tineapedis, and tinea versicolor.

**B. Griseofulvin**

 Griseofulvin [gris-e-oh-FUL-vin] has been largely replaced by oral terbinafine for the treatment of dermatophytic infections of the nails, although it is still used for ringworm and dermatophytosis of the skin and hair. Griseofulvin requires treatment of 6 to 12 months in duration. It is only fungistatic. Griseofulvin accumulates in newly synthesized, keratin-containing tissue, where it causes disruption of the mitotic spindle and inhibition of fungal mitosis (Figure 35.16). 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. Griseofulvin induces hepatic CYP450 activity (Figure 35.17). It also increases the rate of metabolism of a number of drugs, including anticoagulants. It may exacerbate intermittent porphyria.

**C.Nystatin**

Nystatin [nye-STAT-in] is a polyene antibiotic, and its structure, chemistry, mechanism of action, and resistance profile resemble those of amphotericin B. Its use is restricted to topical treatment of Candida infections because of its systemic toxicity. The drug is negligibly absorbed from the gastrointestinal tract, and it is never used parenterally. It is admin- istered as an oral agent (“swish and swallow” or “swish and spit”) for the topical treatment of oral candidiasis. Excretion in the feces is nearly quantitative. Adverse effects are rare because of its lack of absorption orally, but nausea and vomiting occasionally occur.

**D.Imidazoles**

Imidazoles are azole derivatives, which currently include butocon- azole [byoo-toe-KON-a-zole], clotrimazole [kloe-TRIM-a-zole], econazole [e-KONE-a-zole], ketoconazole, miconazole [my-KON-a-zole], oxicon- azole [oks-i-KON-a-zole], sertaconazole [ser-ta-KOE-na-zole], sulconazole [sul-KON-a-zole], terconazole [ter-KON-a-zole], and tioconazole [tye-oh- KONE-a-zole]. As a class of topical agents, they have a wide range of activity against Epidermophyton, Microsporum, Trichophyton, Candida albicans, and Malassezia furfur, depending on the agent. Topical use is associated with contact dermatitis, vulvar irritation, and edema. Miconazole is a potent inhibitor of warfarin metabolism and has pro- duced bleeding in warfarin-treated patients even when applied locally to the vaginal area. No significant difference in clinical outcomes is associated with any azole or nystatin in the treatment of vulvar candidiasis.

**E. Ciclopirox**

Ciclopirox [sye-kloe-PEER-oks] inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and protein. Ciclopirox is active against Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis, Candida albicans, and Malassezia furfur. Ciclopirox 1% shampoo is used for treatment of seborrheic dermatitis. Ciclopirox 0.77% gel is used for treatment of interdigital tinea pedis, tinea corporis, and seborrheic dermatitis. Ciclopirox 8% solution is used for treatment of onychomycosis of nails without lanula involvement. Ciclopirox 0.77% cream and sus- pension is used for treatment of dermatomycosis, candidiasis, and tinea versicolor.

**F. Tolnaftate**

Tolnaftate [tole-NAF-tate] 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, tineacruris, and tinea corporis. It is available as a 1% solution, cream, and powder.