have a cell membrane composed of lipids, glycoproteins, and sterols. One of the sterols is ergosterol, a lipid that is similar to the cholesterol component of human cell membranes. Within the cell membrane, structures are essentially the same as those in human cells (eg, a nucleus, mitochondria, Golgi apparatus, ribosomes attached to endoplasmic reticulum, and a cytoskeleton with microtubules and filaments).

FUNGAL INFECTIONS

Fungal infections (mycoses) may be mild and superficial or life-threatening and systemic. Dermatophytes cause superficial infections of the skin, hair, and nails. They obtain nourishment from keratin, a protein in skin, hair, and nails. Dermatophytic infections include tinea pedis (athlete's foot) and tinea capitis (ringworm of the scalp) (see Chap. 66).

Most fungal infections occur in healthy people but are more severe and invasive in immunocompromised hosts. For example, *C. albicans* organisms often cause superficial mucosal infections (eg, oral, intestinal, or vaginal candidiasis) with antibacterial drug therapy. In immunocompromised hosts, candidal infections are more likely to be deep, widespread, and caused by non-*albicans* species. Other fungi that cause serious infections are not part of the body's normal flora. Instead, they grow in soil and decaying organic matter. Most invasive fungal infections are acquired by inhalation of airborne spores from contaminated soil and severity of disease increases with intensity of exposure. Infections such as histoplasmosis, coccidioidomycosis, and blastomycosis usually occur as pulmonary disease but may be systemic. Other serious, systemic infections include aspergillosis, cryptococcosis, and sporotrichosis.

Serious, systemic fungal infections commonly occur and are increasing in incidence, largely because of human immunodeficiency virus (HIV) infections, the use of immunosuppressant drugs to treat clients with cancer or organ transplants, the use of indwelling intravenous (IV) catheters for prolonged drug therapy or parenteral nutrition, implantation of prosthetic devices, and widespread use of broad-spectrum antibacterial drugs. Characteristics of selected fungal infections are described in Box 40–1.

Antifungal Drugs

Development of drugs that are effective against fungal cells without being excessively toxic to human cells has been limited because fungal cells are very similar to human cells. Available antifungal drugs, which differ in their chemical structures and mechanisms of action, produce their therapeutic effects by disrupting the structure and function of various fungal cell components (Fig. 40–1).

Polyenes (eg, amphotericin B) and azoles (eg, fluconazole) act on ergosterol to disrupt fungal cell membranes. Amphotericin B (and nystatin) binds to ergosterol and forms holes in the membrane, causing leakage of the fungal cell contents and lysis of the cell. The azole drugs bind to a cytochrome P450 enzyme (14-alpha demethylase) that is required for synthesis of ergosterol from lanosterol, a precursor. This action causes production of a defective cell membrane, which also allows leakage of intracellular contents and destruction of the cell. Both types of drugs also affect cholesterol in human cell membranes, and this characteristic is considered primarily responsible for the drugs' toxicities.

Echinocandins or glucan synthesis inhibitors (eg, caspofungin) are a new class of antifungal drugs that disrupt fungal cell walls rather than fungal cell membranes. They act by inhibiting beta-(1,3)-D-glucan synthetase, an enzyme required for synthesis of glucan. Glucan is an essential polysaccharide in the fungal cell wall; its depletion leads to leakage of cellular contents and cell death. Because human cells do not contain cell walls, these drugs are less toxic than the polyene and azole antifungals.

Drugs for superficial fungal infections of skin and mucous membranes are usually applied topically. Numerous preparations are available, many without a prescription. Drugs for systemic infections are given IV or orally. Patients with HIV infection need aggressive treatment of primary fungal infections and prolonged or lifelong secondary prophylaxis. Patients with prolonged or severe neutropenia secondary to treatment with cytotoxic cancer drugs also require aggressive treatment of fungal infections, because they are at high risk for acute, life-threatening, systemic mycoses such as candidiasis and aspergillosis. Selected antifungal drugs are further described in the following sections. In addition, pharmacokinetic characteristics of selected drugs are listed in Table 40–1; clinical indications for use and dosage ranges are listed in Drugs at a Glance: Selected Antifungal Drugs.

Polyenes

Amphotericin B is active against most types of pathogenic fungi, including those that cause aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, and sporotrichosis. The drug is fungicidal or fungistatic depending on the concentration in body fluids and on the susceptibility of the causative fungus. Amphotericin B is highly toxic to humans and is therefore recommended only for serious, potentially fatal fungal infections, in which it is usually the initial drug of choice. The drug is usually given for 4 to 12 weeks but may be needed longer by some clients.

Lipid formulations were developed to decrease adverse effects, especially nephrotoxicity. Compared to the original deoxycholate formulation (Fungizone), these mixtures of amphotericin B with lipids penetrate and reach higher concentrations in diseased tissues (eg, those infected or inflamed). This increases therapeutic effects. At the same time, lipid formulations do not penetrate normal tissues well and therefore reach lower concentrations in normal tissues. This decreases adverse effects and also allows higher doses to be given. Although these products cause much less nephrotoxicity, chills, and fever, they are much more expensive than the deoxycholate formulation. As a result, they are usually recommended for use only in clients who cannot tolerate the