Chapter 29

The Antifungal Agents

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KEY TERMS AND DEFINITIONS

Aspergillus—a fungus that is widespread in nature and has the potential to cause infection in immunocompromised patients.

Candida—a yeast that can cause a variety of infections in both healthy and immunocompromised patients.

Dermatophytes—fungal pathogens that typically cause skin infections.

Eukaryotic—a cell type that is distinguished by the presence of an internal membrane-bound nucleus and structures (organelles), such as mitochondria and vacuoles.

Fungal—referring to a fungus.

Fungicidal—able to kill fungal cells.

Fungus—a class of spore-forming cellular organisms that obtain nourishment from other living organisms or the byproducts of their decay.

Immunocompromise—a state in which part of the immune system is absent or does not function properly; as a result, the body is unable to properly defend itself from infection.

Mold—a filamentous (threadlike) fungus with colonies that typically appear fuzzy and grow by branching.

Opportunistic pathogen—an organism that is not typically infectious but that is able to cause infection in an immunocompromised host.

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Postantifungal effect (PAFE)—continued antifungal activity seen even after the antifungal agent has been removed.

Yeast—although technically a yeast is a member of the family Saccharomycetaceae, the term yeast or yeast-like is used to describe fungi that are round or oval, form smooth colonies, and reproduce by budding.

LEARNING OBJECTIVES

After completing this chapter, you should be able to

1. Compare and contrast the mechanisms of action of various classes of antifungal agents.
2. Describe side effects commonly associated with each of the antifungal classes.
3. Describe the drug interaction potential for each class of antifungals.
4. List the formulations available for each antifungal agent.

A fungus is a cellular organism that requires organic compounds, obtained from other living organisms or their decay products, for energy. Fungi (the plural of fungus) can grow in long, branching filaments (threads) that contain multiple cells or as single, round cells. A variety of organisms are classified as fungi, from the familiar mushroom to microscopic **yeasts** and **molds**. The latter are the cause of **fungal** infections and will be the topic of this chapter. Fungi can reproduce sexually, asexually through a process called budding, and through the release of spores. In general, if a fungus is filamentous, it is described as a mold, and if it is a single, rounded cell that reproduces by budding, it is called a yeast. However, some fungi can switch between these two forms, making classification difficult.

CASE STUDY

Ms. Andrews is a 26-year-old female who was recently diagnosed with systemic lupus erythematosus, an autoimmune disorder, and prescribed a high dose (80 mg per day) of oral prednisone (a corticosteroid) to suppress her immune system. Over the past several days, Ms. Andrews has developed a sore throat and difficulty swallowing.

Fungal cells are defined as **eukaryotic** because, like human cells, they contain a membrane-bound nucleus and membrane-bound organelles (internal structures). This is different from other infectious agents such as bacteria. The fungal cell has a cell membrane, which contains distinctive compounds called sterols. Unlike human cells, but similar to bacterial cells, however, a fungal cell also has a cell wall. The cell wall serves to protect the shape and integrity of the cell and both the wall and the membrane serve as barriers to the entrance of fluids and other materials. Differences between fungal cells and bacterial cells account for some of the differences in treatment between fungal and bacterial infections.

BACKGROUND AND EPIDEMIOLOGY

Significant medical advances have been made over the past several decades in the management of a variety of disease states and conditions. Specifically, advances in the treatment of human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), oncology (cancer therapy), autoimmune diseases (such as rheumatoid arthritis and systemic lupus erythematosus, discussed in Chapter 13) and transplantation of bone marrow and solid organs mean that now patients suffering these conditions can experience a much longer life expectancy. Therapies utilized to treat these patients (chemotherapy for oncology patients and drugs that suppress the activity of the immune system for transplant patients and those with autoimmune disease) or the disease state itself (HIV/AIDS) often result, however, in a state of significant **immunocompromise**. In other words, because the immune systems of such patients cannot mount an appropriate protective response against infectious organisms, they are more susceptible not only to typical microbial pathogens, but also to a unique group of **opportunistic pathogens** (organisms that are not typically infectious but which are able to cause infection in an immunocompromised host). Although opportunistic pathogens seldom infect normal, healthy individuals, they can cause serious illness in patients who are in some state of immune compromise. Fungal infections are a commonly encountered type of opportunistic pathogen among immunocompromised patients.

CASE?

What type of infection is Ms. Andrews likely to have developed?

Healthy individuals can acquire a variety of fungal infections, such as ringworm, endemic fungal infections, and onychomycosis (each of which will be discussed further later in this chapter and at length in Chapter 33). Fungi such as ***Candida*** and ***Aspergillus*** species are more likely to infect patients who are immunocompromised. Many effective antifungal agents have been introduced to combat these pathogens. The aim of this chapter is to discuss some of the most commonly utilized antifungal agents and to review some of the fungal infections that are most likely to be clinically encountered.

FUNGAL CELL BIOLOGY

The treatment of fungal infections presents a unique challenge in the development of safe and effective agents. To be effective, an antifungal drug must be able to target and disrupt a critical area of fungal cell biology, which will result in cell damage or death. Additionally, because these agents also come in contact with human cells, the target for antifungal drugs must be a cell component that is unique to fungal cells and absent in human cells. The same principle is used to develop antibacterial agents; however, there are many more biological differences between human and bacterial cells. Because fungal cells, like human cells, are also eukaryotic, there are fewer unique targets for the antifungal agents. This means drugs that harm fungal cells are more likely to have human toxicity, making the development of antifungal agents particularly difficult. Despite this challenge, several successful antifungal agents are available. To understand how antifungal agents work, it is first important to understand a few of the key differences between fungal cell biology and human cell biology.

CASE?

Ms. Andrews's doctor has diagnosed her with oral/esophageal candidiasis, a yeast (fungal) infection. Why would antibiotics like penicillin not be effective for this infection?

A major element differentiating fungal cells is the cell wall, which is absent in human cells and composed of a different material than that of bacterial cells. The cell wall serves to protect the shape and integrity of the cell and serves as a barrier to the influx (entrance) of fluids and other materials. Interfering with components of the cell wall can result in a loss of cell structure, leading to cell damage or cell death. The cell wall is one example of a unique biological target for antifungal agents.

A second difference between human and fungal cells is the composition of the cell membrane. In both cell types, the function of the cell membrane is, among other things, to help regulate the flow of fluids and solutes into and out of the cell. However, although there are many similarities, the composition of the fungal cell membrane differs in some aspects (especially the inclusion of the steroid ergosterol) from human cells, providing another potential target area for antifungal agents. Finally, human and fungal cells contain different enzymes and proteins used to perform critical cell functions. For example, the enzymes used to synthesize the components of the cell membrane in fungal cells differ from those found in human cells, providing yet another potential antifungal target.

CASE?

Ms. Andrews was not sick enough to be admitted to the hospital, but her infection does warrant antifungal therapy. The doctor wants to treat Ms. Andrews at home with an oral antifungal preparation. What antifungals might be prescribed for Ms. Andrews?

THE ANTIFUNGAL AGENTS

Polyenes

The polyenes are a class of antifungal agents that are **fungicidal**—they have the ability to kill fungal cells. Polyenes bind to ergosterol, a substance that is not part of human cell membranes but is a critical component of fungal cell membranes, which helps to maintain their structure and integrity. The binding of the polyenes to ergosterol disrupts the ability of the fungal cell membrane to prevent the cell's contents from "leaking" out and ultimately results in cell death. Polyene effectiveness is concentration dependent (effectiveness increases with concentration); hence, these agents are more active at higher doses. The polyenes also exhibit a **postantifungal effect (PAFE)**, a continued antifungal activity seen even after they are no longer present, meaning that sustained inhibition of cell growth occurs for

a period of time after the drug has been eliminated from the body. Owing to these properties (concentration dependence and PAFE), the most effective dosing strategy would be to use large doses (to maximize the concentration-dependent activity) that are given less frequently (since the PAFE will result in prolonged antifungal activity). However, the toxicity of these agents is often a significant dose-limiting factor. The two polyene agents that are in use clinically are amphotericin B and nystatin.

Amphotericin B

Historically, amphotericin B was considered the "gold standard" for treating serious fungal infections, particularly because of its activity against some difficult-to-treat fungal species. For many clinicians, it is the drug of choice for difficult-to-treat invasive fungal infections. However, dosing problems and significant systemic toxicities have provided clinical challenges for the use of amphotericin B. The development of newer antifungal agents with spectra and activity similar to those of amphotericin B, but without the same issues with administration and toxicity, has caused the use of this agent to fall out of favor.

Although some patients experience no side effects, many patients receiving amphotericin B suffer from severe infusion reactions, such as itching, flushing, fever, shaking chills, and low blood pressure. Other serious systemic effects, such as nephrotoxicity (kidney damage) and electrolyte abnormalities (especially changes in levels of sodium, potassium, and magnesium) can also occur with amphotericin B and warrant frequent laboratory monitoring. Despite its long history of treatment success, many healthcare providers avoid amphotericin B due to its extensive side effect profile (about 80% of patients will develop infusion-related reactions or nephrotoxicity). Today, amphotericin B is only considered in emergencies or when treating pathogens without other effective antifungal options.

Amphotericin B deoxycholate was the first polyene developed and was administered as an intravenous (IV) solution. The potential for infusion-related reactions required that amphotericin B deoxycholate be administered as a slow infusion over at least 2 to 6 hours, often accompanied by premedications such as corticosteroids, acetaminophen, meperidine, and antihistamines to aid in preventing some of its side effects. In an effort to eliminate some of the toxicities associated with amphotericin B deoxycholate (especially nephrotoxicity), several new formulations of amphotericin B were developed: amphotericin B lipid complex (Abelcet®) and amphotericin B liposomal (AmBisome®). Because of their comparable efficacy and lower incidence of serious side effects and adverse reactions, the lipid-based formulations have replaced amphotericin B deoxycholate in most clinical situations. Lipid-based amphotericin B formulations are among the few suspensions currently indicated for IV administration. This is because they are suspensions of liquid globules and contain no solid particulate matter.

ALERT!

The lipid-based amphotericin B formulations are not interchangeable with one another. Confusion between these products could lead to significant dosing errors and potential patient toxicity. (See Medication Table 29-1 for additional information; Medication Tables are located at the end of the chapter).

PRACTICE POINT

In addition to differences in dosing, differences in product reconstitution, preparation, and stability exist among the amphotericin B products. It is important to read the package insert for each product carefully to ensure that the proper preparation technique and diluent are being utilized.

Nystatin

Nystatin is the other polyene antifungal agent in current use. It is available in several different formulations and is generally utilized for the treatment of mild or topical *Candida* infections (candidiasis). The oral suspension (500,000 units/5 mL) is commonly used for the treatment of oral or gastrointestinal candidiasis (also referred to as thrush). Patients are instructed to "swish" the suspension in their mouth for as long as possible, and then swallow the dose (usually three to four times daily). Nystatin is not well absorbed into the body following oral administration so most of the dose included in the oral suspension remains in the mouth, throat, and gastrointestinal tract. Thus, the most common side effects from this preparation are stomach upset or diarrhea.

ALERT!

Containers of nystatin oral suspension must be shaken well before each administration.

Nystatin is also available as a topical cream, topical ointment, and a topical powder (each 100,000 units/g) for the treatment of *Candida* skin infections. The powder is generally utilized for areas of the body that are known to be moist. Additionally, the nystatin topical cream is also available in combination with the topical corticosteroid triamcinolone. The addition of the corticosteroid is useful for patients with fungal skin infections who are also suffering from bothersome itching. Finally, nystatin is also available as a vaginal tablet for the treatment of vaginal *Candida* infections.

The Azole Antifungals

The azole antifungals work by blocking the fungal enzyme used to produce ergosterol, a critical component of the fungal cell membrane. Without ergosterol, the fungal cell membrane loses its ability to function as a semipermeable barrier between the fungal cell and its external environment—one that allows some fluids and solutes to pass through while stopping others from moving in or out. Without ergosterol, some materials can freely enter and exit the fungal cell, disrupting its functions and equilibrium. Additionally, the enzyme inhibition leads to an accumulation of unused ergosterol precursors, which can become toxic to the fungal cell and impair its functions. In general, the azole antifungals exhibit fungistatic activity against most of the common fungal pathogens (although some agents are fungicidal against some molds). Unlike the polyenes, they do not cause immediate fungal cell death; rather these agents impair the ability of the fungal cell to grow and function normally. Unlike the polyenes, the azole antifungals do not become more effective once doses are increased above a certain threshold so increasing overall time of exposure to these agents is more important than achieving high peak concentrations.

Because the azole antifungals work by inhibiting a critical fungal enzyme, they also have the potential to inhibit human enzymes. In particular, many of the azole antifungals have the ability to inhibit the human liver enzymes that are responsible for the metabolism of many different drugs. As such, there is high potential for drug interactions with the azole antifungals when they are given systemically. Additionally, because of their effects on the liver, one of the most common side effects of the azole antifungals is an elevation in various liver enzymes.

ALERT!

Azole antifungals interact with many drugs, including widely prescribed drugs such as warfarin, and also some drugs such as rifampin and cyclosporine that may be prescribed for a patient with a compromised immune system.

Although all of the azole antifungals share the same mechanism of action, there is a variety of products in this class that differ both in their indications and how they are administered. There are two broad categories of azole antifungals: the imidazoles and triazoles (named for the number of nitrogen atoms found in the azole ring). The triazole agents have proven to be the superior choice for systemic treatment, but the imidazoles are still in common use for topical treatment and are available in a variety of different preparations (creams, ointments, vaginal applications, etc.). Some of the topical azole products (covered in more detail in Chapter 33) are available over the counter (OTC), while others require a prescription for dispensing. Additionally, some of the topical products are available in combination with topical corticosteroids for patients who have significant itching associated with their infection.

PRACTICE POINT

When dispensing a topical azole prescription, it is important not only to verify the drug name, but also to verify the dosage form (cream, ointment, powder, vaginal application, etc.) to ensure that patients receive the appropriate product.

While the topical azole agents are used widely, the five most clinically important azole antifungals that are administered systemically are itraconazole (Sporanox®), fluconazole (Diflucan®), voriconazole (VFEND®) posaconazole (Noxafil®), and isavuconazonium sulfate (Cresemba®).

Itraconazole

Itraconazole is currently available for oral use as a tablet and an oral solution. It has antifungal activity against a variety of *Candida* and *Aspergillus* species. Additionally, it is active against several of the endemic (regional) fungal species and is the first-line treatment in a number of these infections. One of its major drawbacks is inconsistent bioavailability, meaning that when it is administered orally, it is difficult to predict the amount of medication that will be absorbed from the gastrointestinal tract and reach the systemic circulation. For this reason, patients receiving itraconazole may need blood testing to monitor drug concentrations. Itraconazole also has many drug interactions, making its use difficult in patients on interacting agents.

Fluconazole

Fluconazole is available as an oral tablet, oral liquid (suspension), and a solution for intravenous (IV) administration. Compared with itraconazole, the oral bioavailability of fluconazole is much more reliable. For these reasons it is commonly utilized as oral therapy for a variety of uncomplicated *Candida* infections. It has become a mainstay in the treatment of vaginal candidiasis, and because of its long half-life it can be administered for this indication as a one-time oral dose of 150 mg. The IV formulation is also commonly utilized for the treatment of more severe *Candida* infections, such as bloodstream infections or infections of the central nervous system. In addition to its activity against a variety of *Candida* species, fluconazole is also active against a number of the endemic fungi and is sometimes used as an alternative agent in the treatment of these infections. However, fluconazole possesses no antifungal activity against *Aspergillus* species, and some species of *Candida* have developed resistance to fluconazole. Additionally, there are some isolates of *Candida* that have reduced susceptibility to fluconazole.

Voriconazole

Voriconazole is supplied for oral administration (as a tablet and as an oral suspension) as well as for IV administration. While its bioavailability is relatively reliable compared to that of itraconazole, it has a considerable number of clinically significant drug interactions, which present a challenge to its use in some settings. Voriconazole has demonstrated good efficacy against a wide variety of fungal pathogens, including *Candida* species, the endemic fungi, and *Aspergillus* species, as well as several other mold species. While the azoles are generally fungistatic, voriconazole actually possesses fungicidal activity against *Aspergillus* species, making it particularly useful and efficacious for infections by this organism. Side effects associated with voriconazole are more significant than other azole agents and include temporary vision changes and hallucinations. Because of the side-effect profile and variable absorption, patients treated with voriconazole need to have blood drawn to assess drug concentrations as well as periodic liver function tests.

Posaconazole

Posaconazole is available as an oral delayed-release tablet, oral suspension, or IV solution. The oral tablet has better absorption than the oral suspension, and it is recommended that the oral dosage forms be taken with a meal to enhance bioavailability. Like the other azoles, posaconazole possesses antifungal activity against *Candida* species (including some species that are resistant to fluconazole), as well as activity against a variety of mold species, including *Aspergillus*. Of particular interest is posaconazole's activity against the Mucormycetes, a group of fungal organisms that cause devastating infection in immunocompromised patients and are especially difficult to treat. Patients receiving extended courses (>7 days) of posaconazole need to have blood drawn to assess drug concentrations.

Isavuconazole (Isavuconazonium Sulfate)

Isavuconazole is the newest medication in the azole antifungal family and is available as an oral capsule or IV solution. It is administered as isavuconazonium sulfate, which is metabolized in the body into the active molecule, isavuconazole. Isavuconazole exhibits activity against *Candida* species and *Aspergillus*, and, most notably, *Mucormycetes*. The most common side effect seen is gastrointestinal upset, which is markedly more severe than with other azole antifungals.

The Echinocandins

The echinocandins are the newest class of antifungal agents. They work by inhibiting the fungal enzyme responsible for synthesis of glucan, an essential element of the fungal cell wall. Without glucan, the cell wall loses its ability to regulate water flowing in and out of the cell; this results in cell death. Echinocandins are only available for IV administration and have similar antifungal spectrums of activity. They all have broad activity against *Candida* species, as well as some mold species such as *Aspergillus*. Although they do not have as many significant drug interactions as the azole agents, the echinocandins can cause elevations in human liver enzymes and patients must be monitored regularly for this side effect.

The three echinocandin agents currently available are caspofungin, anidulafungin, and micafungin. All three agents are currently approved for the treatment of *Candida* infections;

however, caspofungin is currently the only agent with an FDA-approved indication for invasive *Aspergillus* infections. Because they have few toxicities, the echinocandins have become the preferred agents for treatment of suspected fungal infections in immunocompromised patients.

ALERT!

Caspofungin and anidulafungin are usually ordered with a double (loading) dose for the first administration, followed by a smaller dose on subsequent days of therapy.

Miscellaneous Antifungals

Terbinafine

Terbinafine is an allylamine antifungal, which works by blocking an enzyme involved in ergosterol synthesis, different from the one affected by the azoles. It is available in a variety of formulations (creams, powders, sprays, etc.) that are applied topically for the treatment of fungal infections of the skin. It is also available as an oral tablet under the trade name Lamisil. Owing to its chemical structure, when terbinafine is administered systemically it accumulates in the fatty tissues, skin, and nails. As a result, it has become a mainstay in the treatment of fungal infections of the nail (onychomycosis), which is difficult to treat with topical antifungals due to their poor penetration into the nail bed.

ALERT!

LOOK-ALIKE/SOUND-ALIKE—The name brand for terbinafine, Lamisil, may look similar to the trade name Lamictal, which is a medication used to treat seizures. Confusing these medications could have serious adverse effects.

PRACTICE POINT

While most (though not all) topical terbinafine products are available OTC, the oral tablet is prescription only.

Flucytosine

Flucytosine is an antimetabolite, meaning that its antifungal activity is the result of interference with fungal deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis. Flucytosine was one of the earliest antifungal agents developed; however, owing to some rare but serious side effects, such as bone marrow suppression, central nervous system effects, and liver and kidney toxicity, as well as the emergence of fungal resistance to flucytosine monotherapy (used alone, without other antifungals), its use has now become relatively rare in clinical practice. Although it was once available as an IV formulation, it is now only available for oral administration. Flucytosine possesses antifungal activity against *Candida, Aspergillus*, and *Cryptococcus* species as well as the **dermatophytes**, fungal pathogens, which cause skin infections. The nonpolyene agents for systemic fungal infections are listed in **Medication Table 29-2.**

Griseofulvin

Griseofulvin is an oral antifungal agent used primarily for the treatment of fungal infections of the skin, hair, and nails caused by dermatophytes. In particular, it is used commonly for fungal infections of the scalp since it distributes well to the skin and hair follicles. The antifungal activity of griseofulvin is a result of its ability to inhibit fungal mitosis (cell division). There are few side effects associated with griseofulvin, although it can affect the metabolism of other medications, resulting in drug interactions. Because it is available as both a tablet and a pediatric oral suspension, it is commonly prescribed for children with fungal infections of the scalp. Its use and preparations are covered in more detail in Chapter 33 and Medication Table 33-7.

Topical Antifungals

A large variety of antifungal agents are available as topical formulations, including both OTC and prescription products. Many of the azole agents are available as topical formulations, such as creams and powders, as well as products for the treatment of vaginal yeast infections, such as creams, vaginal suppositories, and vaginal tablets. In addition, terbinafine and several other allylamines are available in a variety of topical formulations, such as creams, gels, powders, and spray forms. Nystatin is also available as a cream and an ointment for topical application. As mentioned previously, several topical antifungal agents are also supplied in combination with a corticosteroid to help with itching and inflammation. It is important for clinicians to be aware of the various agents and formulations of topical antifungals when recommending and dispensing a product. Topical antifungals will be discussed in detail in Chapter 33.

FUNGAL INFECTIONS

Candida Infections

Candidiasis describes any variety of opportunistic fungal infections caused by species of the genus *Candida*. The most common *Candida* pathogen in humans is *Candida albicans*. Candidiasis can vary greatly in its severity, presentation, and location. *Candida* infections commonly occur on mucous membranes, including the oral cavity (called thrush), the gastrointestinal tract, and the vagina. *Candida* can also cause skin infections (such as diaper rash). In severe cases, generally in patients with profound immunosuppression or other risk factors, infections of the deep organ systems, such as the liver, heart, bone, lung, and central nervous system, can occur. *Candida* infections can also occur in the bloodstream.

The treatment of *Candida* infections varies based on the clinical presentation, severity of infection, and patient-specific considerations. For infections of the skin and mucous membranes, nystatin or the azoles are generally utilized as first-line therapy. For more severe infections, systemic azole therapy may be used, although resistance to fluconazole among *Candida* species is becoming more common. The echinocandins as well as amphotericin B may also be considered in the treatment of severe *Candida* infections.

Aspergillus Infections

Aspergillosis is the term used to describe infections that may result from inhalation of the spores of *Aspergillus* species (most commonly one of three species: *A. fumigatus, A. niger*, or *A. flavus*). Frequently, inhalation exposure to *Aspergillus* can result in an allergic-type reaction, but *Aspergillus* can also result in severe disease if it spreads from the lungs to other parts of the body. Such infections occur in immunocompromised patients and generally either present as a pulmonary (lung) infection or as a disseminated (widely spread) infection. Invasive aspergillosis is associated with an overall mortality rate of nearly 60%, and treatment is difficult. Early diagnosis and treatment are imperative in the management of such infections. While amphotericin B was the historical treatment of choice for invasive aspergillosis, newer agents such as voriconazole, posaconazole, and isavuconazole are now recommended over amphotericin B owing to their equal efficacy and fewer side effects.

CASE?

Several months later, Ms. Andrews is admitted to the hospital with persistent cough, shortness of breath, and a widespread rash. She states that she has recently returned from a trip to Phoenix to visit her nephew. What type of infection might be suspected?

Endemic Fungal Infections

The term endemic infections refers to infections that are usually diagnosed only among certain populations or in certain regions. The three most important endemic fungal infections in the United States are *Histoplasma capsulatum* (generally found in the eastern United States, especially in the Ohio River Valley), *Coccidioides immitis* (occurring in the southwestern United States and northern Mexico), and *Blastomyces dermatitidis* (found in the eastern United States and Canada). These infections are transmitted through the inhalation of fungal spores. They typically cause pulmonary infections, including pneumonia and pulmonary cavitations (abnormal spaces in the lungs), but the infection can spread to other parts of the body, especially in immunocompromised patients. Treatment of these infections generally involves treatment with antifungal agents but may also include surgical intervention.

CASE?

What treatment might the doctor prescribe for Ms. Andrews's lung condition?

Histoplasmosis

Infection with *Histoplasma capsulatum* (histoplasmosis) occurs following inhalation of the fungal spores and is generally self-limiting and may resolve without treatment. However, in rare cases it may go on to cause acute infections of the lungs and/or disseminated infections (usually in immunocompromised individuals). Mild to moderate pulmonary infections may be treated with itraconazole monotherapy, but in severe cases of acute histoplasmosis, an initial course of IV amphotericin B followed by a prolonged course of itraconazole is warranted. The duration of therapy can range from 6 weeks to 24 months depending on the severity of infection and patient-specific risk factors.

Blastomycosis

Like histoplasmosis, blastomycosis is primarily a pulmonary disease caused by inhalation of *Blastomyces dermatitidis* spores present in the soil but may go on to cause severe disseminated infection in some patients. Although it may resolve without treatment, the clinical manifestations of this infection are more difficult to predict, so it is generally treated, even in otherwise healthy patients. Mild or moderate blastomycosis can be effectively treated with itraconazole (6 months), but for severe infections, IV amphotericin B is the drug of choice, generally in high doses, followed by itraconazole for an additional 6 to 12 months once the patient has stabilized. Fluconazole, voriconazole, or itraconazole may be utilized in the setting of central nervous system involvement or in patients who cannot tolerate amphotericin B therapy.

Coccidioidomycosis

Like the other endemic fungi, coccidioidomycosis results from inhalation of *Coccidioides immitis* spores. Most of these infections will resolve without therapy; therefore, treatment is only recommended for patients who are immunocompromised and at risk for the more severe, disseminated forms of the disease. For patients with severe disease, treatment with fluconazole or itraconazole is recommended. For patients with severe disease and respiratory failure, amphotericin B is utilized as initial therapy followed by itraconazole or fluconazole once the patient is stable. Fluconazole is preferred when the central nervous system is involved. It is recommended that therapy with the azole agent be continued for at least 1 year to try to minimize the risk of relapse.

Cryptococcal Infection

Like the endemic fungi, *Cryptococcus* infection results from the inhalation of the spores of the yeast *Cryptococcus neoformans* or other *Cryptococcus* species. It is of particular concern among immunocompromised patients, such as those with HIV/AIDS or cancer, or those on immunosuppressants following a transplant because of its potential to disseminate and cause central nervous system infection in these populations. The historic treatment of choice for central nervous system involvement is amphotericin B in combination with flucytosine. This combination may be continued for the entire treatment course or may be changed to fluconazole alone after 2 weeks of treatment.

SUMMARY

Owing to an increasing population of immunocompromised patients, the treatment of opportunistic infections caused by fungal pathogens has become an area of much interest over the past several decades. Many antifungal agents are available, diversifying the treatment options for serious systemic fungal infections. Additionally, a number of topical antifungal preparations are available both over the counter (OTC) and with prescription for the management of fungal skin infections. It is essential that the differences among these agents be recognized as they relate to dosing, side effects, drug interactions, compounding, storage, and administration.

CHAPTER RESOURCES

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REVIEW QUESTIONS

1. Describe the similarities and differences between fungal and human cells. How do antifungal agents harm the fungus and not the patient?
2. Describe the difference between fungal and bacterial infections. Why are different drugs used to treat them?
3. Patients at risk for fungal infections typically share what characteristic? Why is this important for the acquisition of fungal infections?
4. What are the major toxicities associated with polyene antifungals such as amphotericin B?
5. Which class of antifungal agents has the greatest potential for causing drug-drug interactions? Why?

MEDICATION TABLES

MEDICATION TABLE 29-1. Polyene Antifungal Agents*

Generic Name (pronunciation)	Brand Name	Dosage Form	Route	Usual Dose	Notes
Amphotericin B deoxycholate (am foe TER i sin bee de ok se KO late)	Various generic products	Powder for reconstitution	IV	0.3–1.5 mg/kg daily	1 mg test dose should be given prior to full dose
Amphotericin B lipid complex (am foe TER i sin bee LIP id KOM pleks)	Abelcet	Suspension	IV	3–5 mg/kg daily for most diagnoses	Inline filters are contraindicated; premedication with acetaminophen, diphenhydramine, and/or hydrocortisone is recommended
Amphotericin B liposomal (am foe TER i sin bee lye po SO mal)	AmBisome	Suspension	IV	3–6 mg/kg daily (usual dosage range)	An inline membrane filter (not less than 1 micron) may be used
Nystatin (nye STAT in)	Bio-Statin	Capsule, 1,000,000 units	Oral	1,000,000 units 3–4 times daily	Suspension dosage form is swished in mouth and retained as long as possible before swallowing
	Generics	Tablet, 500,000 units	Oral	500,000 units 3–4 times daily	
	Generics	Suspension, 100,000 units/mL	Oral	400,000 to 600,000 units 4 times daily	
	Nyamic, Nystop,	Cream, ointment, powder, 100,000 units/g	Topical	Apply to affected area as directed	

IV = intravenous.
* Information and pronunciations from Lexicomp. Lexi-Drugs [database]. Hudson, OH: Wolters Kluwer.

MEDICATION TABLE 29-2. Nonpolyene Agents for Systemic Fungal Infections*

Generic Name (pronunciation)	Brand Name	Dosage Form	Route	Usual Dose
Echinocandins				
Anidulafungin (ay nid yoo la FUN jin)	Eraxis	Powder for reconstitution	IV	200 mg on day 1, then 100 mg daily thereafter
Caspofungin (kas poe FUN jin)	Cancidas	Powder for reconstitution	IV	70 mg on day 1, then 50 mg daily thereafter
Micafungin (mi ka FUN gin)	Mycamine	Powder for reconstitution	IV	50–150 mg daily
Imidazoles				
Ketoconazole (kee toe KOE na zole)	Generics	Tablet	Oral	200–400 mg daily
Miconazole (mi KON a zole)	Various	Cream, 2%–4%, suppository, 100 mg, 200 mg	Vaginal	Applicatorful or suppository inserted at bedtime × 3 or 7 days
	Oravig	Dissolving tablet	Buccal	50 mg (1 tablet) to the upper gum region (canine fossa) once daily × 14 days
Triazoles				
Fluconazole (floo KON na zole)	Diflucan	Premixed IV solution, powder for oral suspension, tablet	IV, oral	50–400 mg daily
Isavuconazonium sulfate (eye sa vue koe na ZOE nee um sul FATE)	Cresemba	Powder for reconstitution, capsule	IV, oral	372 mg (200 mg of isavuconazole) every 8 hours for 6 doses followed by 372 mg (200 mg of isavuconazole) daily
Itraconazole (i tra KOE na zole)	Sporanox	Capsule, 100 mg, solution, 10 mg/mL	Oral	200 mg daily, twice daily, or three times a day
	Tolsura	Capsule, 65 mg		130 mg once or twice daily
Posaconazole (poe sa KON a zole)	Noxafil	Premixed IV solution (requires dilution), oral tablet, oral suspension	IV, oral	600–800 mg daily in 3 or 4 divided doses
Voriconazole (vor i KOE na zole)	VFEND	Powder for reconstitution, powder for suspension, tablet	IV, oral	IV: 6 mg/kg every 12 hours × 2 doses, then 4 mg/kg every 12 hours; Oral: 200-300 mg every 12 hours
Antimetabolite				
Flucytosine (floo SYE toe seen)	Ancobon	Capsule	Oral	50–150 mg/kg daily divided every 6 hours
Allylamine Antifungal				
Terbinafine (TER bin a feen)	Generics	Granules, tablet	Oral	250 mg daily or 500 mg twice daily

IV = intravenous.
* Information and pronunciations from Lexicomp. Lexi-Drugs [database]. Hudson, OH: Wolters Kluwer.