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Review Article

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REVIEW AND STUDY ON ANTIFUNGAL AGENTS

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ABSTRACT

Nowadays, most of fungal infections such as candidiass can range from superficial mucous membrane infection to life threatening systemic mycoses. Candida infections give significant clinicalproblem globally due to most rapid rise in compromised host populations including HIV/AIDS, organ transplant recipients, and patients those are on chemotherapy. In addition to this, a sharp increase in the aging populations which are susceptible to fungal infections is expected in next few decades. Antifungal drugs for these problems are relatively difficult to develop compared to the antibacterial drugs owing to the eukaryotic nature of the cells. Therefore, only a handful of antifungal agents arecurrently available to treat the myriad of fungal infections. Moreover, the rising antifungal resistance and host-related adverse reactions have limited the antifungal arsenal against fungal pathogens.

INTRODUCTION

The fungal kingdom encompasses a massive diversity of taxa with varied ecological niches, life-cyclemethods, and morphologies. However, a little-known fact is true biodiversity of Kingdom Fungi. Ofthe 1.5 million species estimated to belong to this present kingdom solely 5% are formally classified. Several fungi are parasites for plants, animals, human, and other different fungi. Plant infective fungi are able to cause harm and losses to agriculture and forestry together with the rice blast fungus, Dutch elm disease, and chestnut blight. Some different fungi may cause serious diseases inhumans, many of which can be fatal if left untreated. Currently, four antifungal drug classes are used by clinicians and veterinarians for systemic treatment. These classes target different parts of the fungal cell. First, the polyene class includes the heptaene amphotericin B (AMB), which interacts with ergosterol, the major part of the fungal cell membrane. AMB is highly fungicidal against Candida genera and Aspergillus fumigatus and A. flavus. Second, first- and second- generation of triazoles disrupt the ergosterol biosynthesis in the lanosterol demethylation step. Generally, triazoles exhibit the fungistatic effect against yeasts but are fungicidal for Aspergillus spp. Echinocandins block the synthesis of β- D- glucans located in the fungal cell wall. Echinocandins are fungicidal and fungistatic against Candida and Aspergillus spp., respectively. Finally, the pyrimidine analogue flucytosine (5- FC) interacts at the nucleus level of the fungus, affecting protein and deoxyribonucleic acid (DNA) biosynthesis. The overuse of antifungal agents increases the opportunistic pathogen resistance. The World Health Metabolites 2020, 10, 106 2 of 16 Organization has identified this type of antimicrobial resistance as one of the dominant threats of 2019.

The antifungal agents are fungistatic in nature and are used to prevent and treat fungal infections such as candidiasis, ringworm, etc. Antifungal is basically the drugs which help in detecting and eliminating fungal pathogens from the foreign body with less toxic side effects to the body.

In this review, I attempt to assess the various fungal organisms, fungal infections, various types of antifungal agents, their pharmacokinetics and pharmacodynamics, toxicity of antifungal agents and antifungal drug resistance.

Types of Fungal Organisms

Fungi can be divided into four classes

1. **Yeasts:** Crypyococcus neoformans
2. **Yeast like fungi:** It Partly grows like yeast and partly as filaments (hyphae) and these type offungi caused of Oral thrush Vaginal thrush Systemic Candidiasis. Example of these types of fungi is Candida albicans
3. **Dimorphic fungi:** This type of fungi Grow as filaments or as yeast and they caused Histoplasmosis Coccidiomycosis Blastomycoses Sporotrichosis. Fungi SPECIES INVOVLVED of this category is Histoplasma capsulatum Coccidiodes immitis Blastomyces deramtides
4. **Moulds:** Filamentous fungi reproduce by forming spores. These type of fungal organism caused Skin/ nail infections. Example Trichophyton sp., Microsporum sp., Epidermophyton sp.

Classification of Fungal Infections

Mycoses is a fungal infection of animals, including human. Mycoses are classified according to the tissue levels initially colonized. The clinical nomenclatures used for the mycoses are based on the –

1. Classification Based on Site
2. Classification Based on Route of Acquisition
3. Classification Based on Virulence

1. Classification Based on Site

Mycoses are classified as superficial, cutaneous, subcutaneous, or systemic (deep) infections depending on the type and degree of tissue involvement and the host response to the pathogen.

I. Superficial mycoses

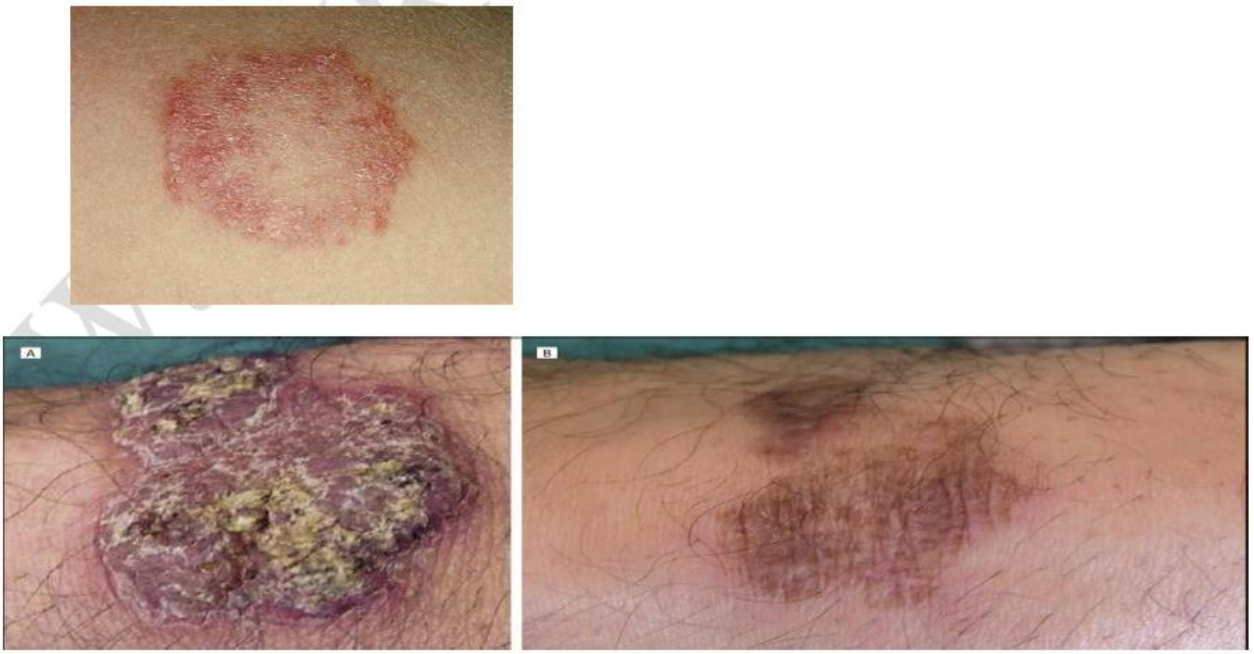
Superficial mycoses are limited to the outermost layers of the skin and hair. An example of such a fungal infection is Tinea versicolor, a fungus infection that commonly affects the skin of young people, especially the chest, back, and upper arms and legs. Tinea versicolor is caused by a fungus that lives in the skin of some adults. It does not usually affect the face. This fungus produces spots that are either lighter than the skin or a reddish brown. This fungus exists in two forms, one of themcausing visible spots. Factors that can cause the fungus to become more visible include high humidity, as well as immune or hormone abnormalities. However, almost all people with this very common condition are healthy.

II. Cutaneous mycoses

Cutaneous mycoses extend deeper into the epidermis, and also include invasive hair and nail diseases. These diseases are restricted to the keratinized layers of the skin, hair, and nails. The organisms that cause these diseases are called dermatophytes, the resulting diseases are often called ringworm, dermatophytosis or tinea.

III. Subcutaneous mycoses

Subcutaneous mycoses involve the dermis, subcutaneous tissues, muscle and fascia. These infections are chronic and can be initiated by piercing trauma to the skin which allows the fungi to enter. These infections are difficult to treat and may require surgical interventions such as debridement.



2. Classification Based on Route of Acquisition

Infecting fungi may be either exogenous or endogenous.Routes of entry for exogenous fungi include airborne, cutaneous or percutaneous. Endogenous infection. involves colonization by a member of the normal flora or reactivation of a previous infection.

3. Classification Based on Virulence

Primary pathogens can establish infections in normal hosts. Opportunistic pathogens cause disease in individuals with compromised host defence mechanisms.

I. Systemic mycoses due to primary pathogens Systemic mycoses due to primary pathogens originate primarily in the lungs and may spread to many organ systems. Organisms that cause systemic mycoses are inherently virulent. In general, primary pathogens that cause systemic mycoses are dimorphic.

II. Systemic mycoses due to opportunistic pathogens Systemic mycoses due to opportunistic pathogens are infections of patients with immune deficiencies who would otherwise not be infected. Examples of no compromised conditions include AIDS, alteration of normal flora by antibiotics, immunosuppressive therapy, and metastatic cancer. Examples of opportunistic mycoses include Candidiasis, Cryptococcosis and Aspergillosis.

Opportunistic Mycosal disease Candidiasis

Candidiasis (due to C albicans and other Candida spp.) is the most common opportunistic fungal infection. Candida albicans is the most common cause of candidiasis. Candidiasis may be classified as superficial or deep. Superficial candidiasis may involve the epidermal and mucosal surfaces, including those of the oral cavity, pharynx, esophagus, intestines, urinary bladder, and vagina. The alimentary tract and intravascular catheters are the major portals of entry for deep (or visceral) candidiasis. The kidneys, liver, spleen, brain, eyes, heart, and other tissues are the major organ sites involved in deep or visceral candidiasis. The principal risk factors predisposing to deeply invasive candidiasis are protracted courses of broad spectrum antibiotics, cytotoxic chemotherapy, corticosteroids, and vascularcatheters.

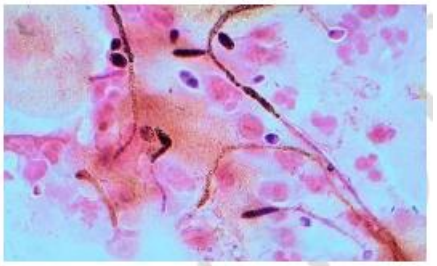


Figure 1: Candida albicans visualized by Gram stain and microscopy.

Aspergillosis

Invasive aspergillosis most frequently involves the lungs and paranasal sinuses. This fungus may disseminate from the lungs to involve the brain, kidneys, liver, heart, and bones. The main portal of entry for aspergillosis is the respiratory tract, however, injuries to the skin may also introduce the organism into susceptible hosts. Quantitative and functional defects in circulating neutrophils are key risk factors for development of invasive aspergillosis. For example, neutropenia due to cytotoxic chemotherapy and systemic corticosteroids are common predisposing factors for invasive aspergillosis.

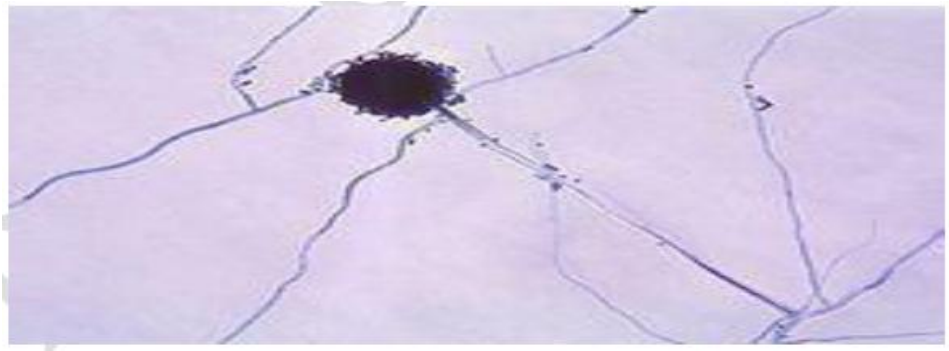


Figure 2: Candial head of Aspergillus niger.

Zygomycosis

Zygomycosis is the broadest term to refer to infections caused by bread mold fungi of the zygomycota phylum. However, because zygomycota has been identified as polyphyletic, and is not included in modern fungal classification systems, the diseases that zygomycosis can refer to are better called by their specific names: mucormycosis (after Mucorales), phycomycosis (after Phycomycetes) and basidiobolomycosis (after Basidiobolus). Zygomycosis due to Rhizopus, Rhizomucor, Absidia, Mucor species, or other members of the class of Zygomycetes, also causes invasive sinopulmonary infections. An especially lifethreatening form of zygomycosis (also known as mucormycosis), is known as the rhinocerebral syndrome, which occurs in diabetics with ketoacidosis. In addition to diabetic ketoacidosis, neutropenia and corticosteroids are other major risk factors for zygomycosis. Aspergillus sp. and the Zygomycetes have a strong propensity for invading blood vessels.

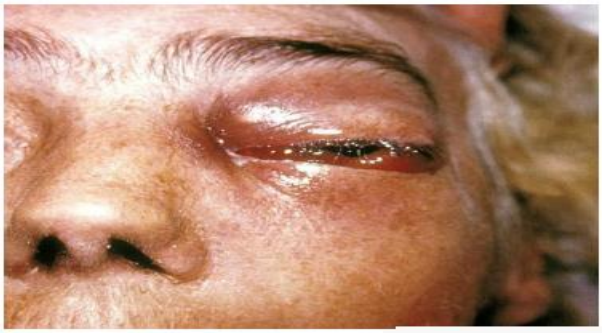


Figure 3: Periorbital fungal infection known asmucormycosis, or phycomycosis.

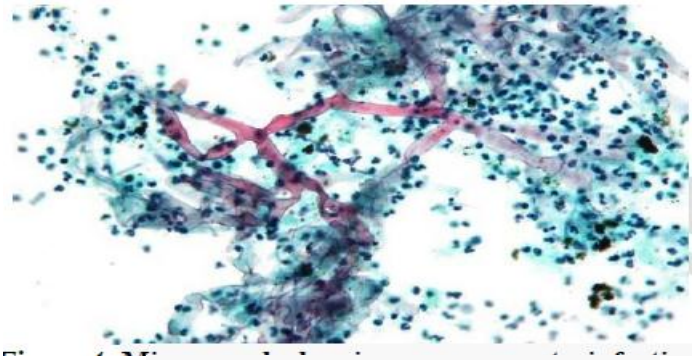


Figure 4: **Micrograph showing a zygomycetesinfection.**

Mucormycosis: The 'black fungus'

Mucormycosis is a very rare infection. It is caused by exposure to mucor mould which is commonly found in soil, plants, manure, and decaying fruits and vegetables. It is ubiquitous and found in soil and air and even in the nose and mucus of healthy people. It affects the sinuses, the brain and the lungs and can be life-threatening in diabetic or severely immunocompromised individuals, such as cancer patients or people with HIV/AIDS.

Doctors believe mucormycosis, which has an overall mortality rate of 50%, may be being triggered by the use of steroids, a life-saving treatment for severe and critically ill Covid-19patients.

Steroids reduce inflammation in the lungs for Covid-19 and appear to help stop some of the damage that can happen when the body's immune system goes into overdrive to fight off coronavirus. But they also reduce immunity and push up blood sugar levels in both diabetics and non-diabetic Covid-19 patients.

It's thought that this drop in immunity could be triggering these cases of mucormycosis.

Cryptococcosis

Cryptococcosis is most typically an opportunistic fungal infection that most frequently causes pneumonia and/or meningitis. Defective cellular immunity, especially which associated with the acquired immune deficiency syndrome, is the most common risk factor for developing Cryptococcosis.

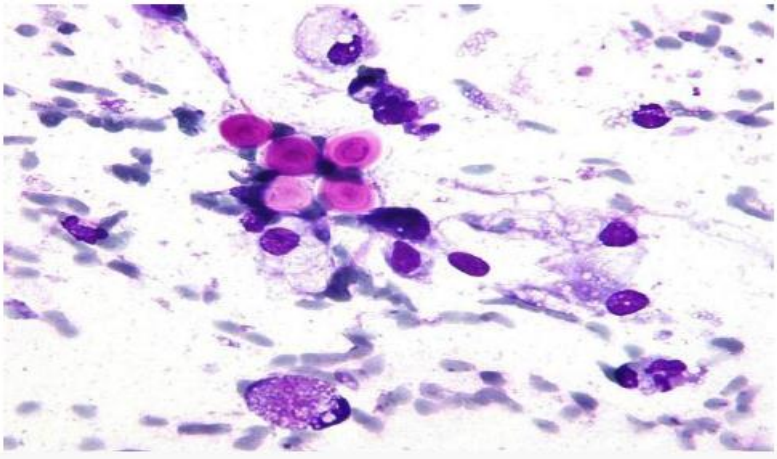


Figure 5: Micrograph of cryptococcosis showing thecharacteristically thick capsule of Cryptococcus.

Hyalohyphomycosis

Hyalohyphomycosis is an opportunistic fungal infection caused by any of a variety of normally saprophytic fungi with hyaline hyphal elements. For example, Fusarium spp. infect neutropenic patients to cause pneumonia, fungemia, and disseminated infection with cutaneous lesions.

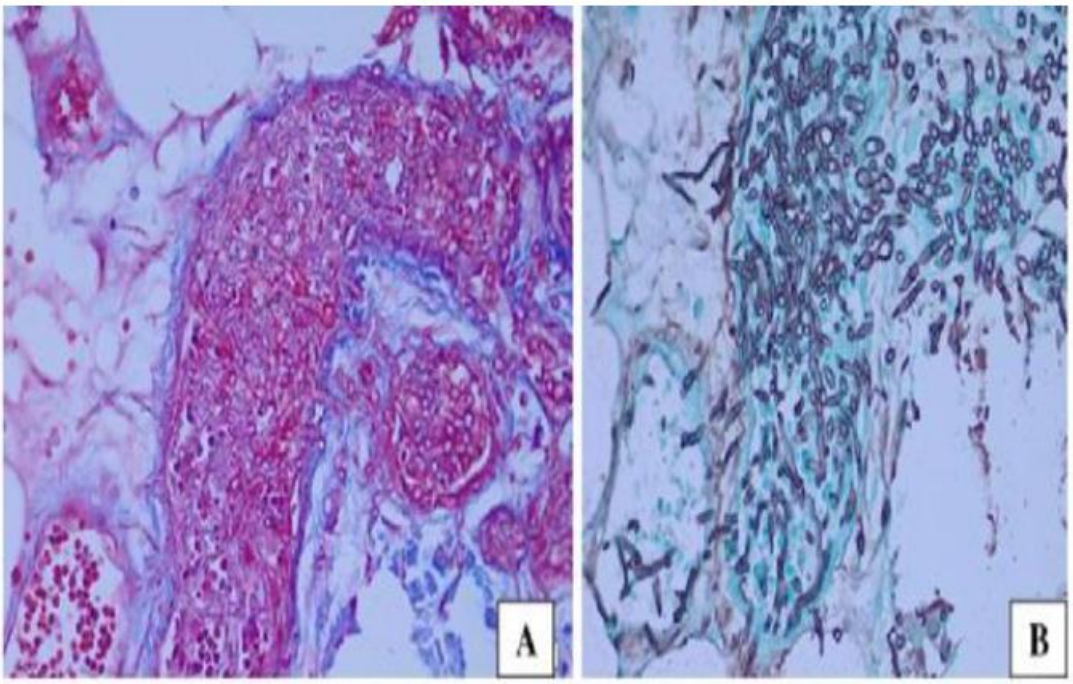


Figure 6: Hyalohyphomycosis (Fusarium sp.). Septate hyphaebranching in acute or right angles infiltrate the blood vessels.

Classification of Antifungal Agents

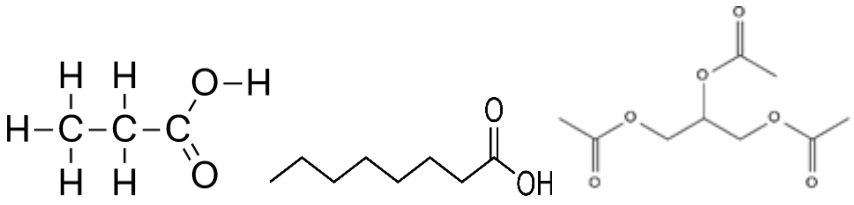
Antifungal agents are mainly classified into following types

1. Synthetic agents
- Acids and derivatives
- Phenolic derivatives
- Halogen containing compounds
- Thiocarbamate derivatives
- Pyrimidine derivatives
- Acridine derivatives
- Azole derivatives (imidazole derivatives and triazole derivatives)
- Allylamine derivatives

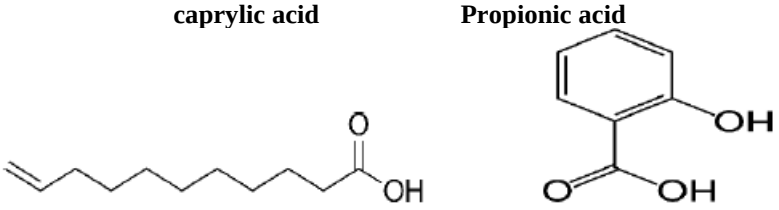
2. Antibiotics
- Polyenes
- Nonpolyenes

1. Synthetic agents

Acids and derivatives: Fatty acids, benzoic acid, salicylic acid and triacetin (glyceryl triacetate). Fatty acids like propionic acid, caprylic acid, and undecylenic acid are this type of antifungal agents.



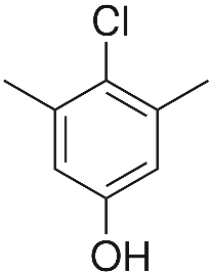
caprylic acid **Propionic acid**



Salicylic acid **Undecylenic acid**

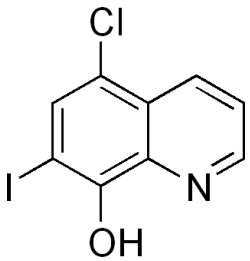
Phenolic derivatives
Parachlorometaxylenol is an example of phenol derivative antifungal agent Mode of action: Denaturation of protein via the reaction of the acidic phenolic group with basic centers in the protein molecule located on cell wall of fungal cell.

Uses: It is used topically in the treatment of tinea infection such as athlete's Foot 4-Chloro-3,5-dimethylphenol.



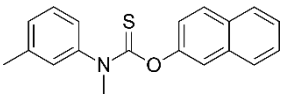
Halogen containing compounds
Clioquinol is an example of this kind of antifungal agents. It is neurotoxic in large doses. It is a member ofa family of drugs called hydroxyquinolines which inhibit certain enzymes related to DNA replication. The drugs have been found to have activity against both viral and protozoal infections.

Mode of action: Competes with co-enzymes for metal binding sites on enzymes.



Thiocarbamate derivatives clioquinol
The thiocarbamate group of fungicides structurally resembles the rubber accelerator disulfiram (Antabuse, tetraethylthiuram disulfide, a common sensitizer present in both the European and the North American standard patch test series (Adams and Fischer, 1990).
E.g. Tolnaftate

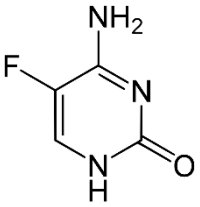
Uses: Treatment of superficial tinea infections of the skin in the formof 1% cream, powder, aerosol, gel, and solution.



O-2-Naphthyl-N-methyl-m-tolylthiocarbamate.

Pyrimidine derivatives
Pyrimidines also known to exhibit antifungal properties. Flucytosine, a pyrimidine derivative is useful in the case of infection due to *candida albicans* and *Cryptococcus neoformans.* Another pyrimidine analogue hexitidine is also used for aphthous ulceration. E.g.: Flucytosine (Ancbon)5- Fluorocytosine or 5-FC : Flucytosine, also known as 5-fluorocytosine, is an antifungal medication. It is specifically used, together with amphotericin B, for serious Candida infections and cryptococcosis. It may be used by itself or with other antifungals for chromomycosis. Flucytosine is used by mouth and by injection into a vein.

Uses: 5-FC has narrow spectrum. It is used orally for treatment of serious systemic infections caused by pathogenic yeasts such as Candida albicans.

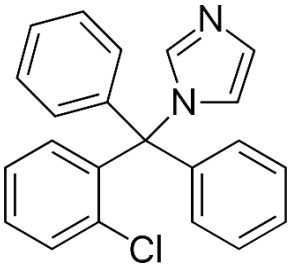


5-fluorocytosine (5-FC)

Azole derivatives
The azole antifungal agents have five-membered organic rings that contain either two or three nitrogen molecules (the imidazoles and the triazoles respectively).

Clotrimazole
Uses: Clotrimazole is used for the treatment of topical infections like tinea, mucocutaneous candidiasis, and vaginal candidiasis. It is not used orally for treatment of systemic infections as it causes severe GIT disturbances.

Side effects: Side effects of the oral formulation include itching, nausea, and vomiting. Less than 10% of patients using the oral formulation may have abnormal liver function tests. Side effects include rash, hives, blisters, burning, itching, peeling, redness, swelling, pain or other signs of skin irritation.



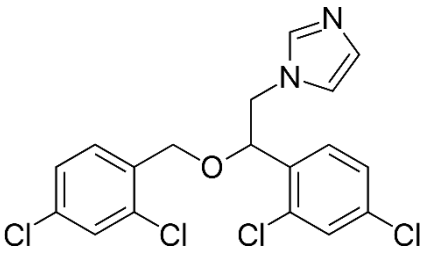
1-[(o-Chloro-α,α-diphenyl)benzyl]- 1H- imidazole.

Miconazole
Uses: Miconazole base can be used intravenously in the treatment of systemic fungal infections.

Topically miconazole nitrate can be used in the treatment of tinea versicolor, mucocutaneous candidiasis, and of corneal infection caused by candida and aspergillus.

Side effects : Miconazole is generally well tolerated. The oral gel can cause dry mouth, nausea and an unpleasant taste in about 1–10% of people. Anaphylactic reactions are rare. Thedrug prolongs the QT interval.

Mechanism of action: Miconazole inhibits the fungal enzyme



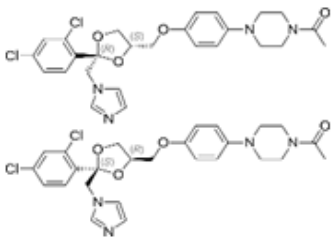
14α-sterol demethylase, resulting in a reduced production of ergosterol. In addition to its antifungal actions, miconazole, Miconazole similarly to ketoconazole, is known to act as an antagonist of the glucocorticoid receptor.

Ketoconazole

Uses – It is topically in treatment of many fungal infections and orally it is effective in many mucocutaneous and systemic mycoses, or to treat severe cutaneous dermatophytic infections, which do not respond to topical therapy or oral griseofulvin.

Adverse effects:

Gastrointestinal: Vomiting, diarrhoea, nausea, constipation, abdominal pain, upper abdominal pain, dry mouth, dysgeusia, dyspepsia, flatulence, tongue discoloration may occur.



Endocrine: The drug may cause adrenal insufficiency so the level of the adrenocortical hormones should be monitored while taking it. Oral ketoconazole at a dosage range of 400 to 2,000 mg/day has been found toresult in a rate of gynecomastia of 21% *(2*R,*4*S*)-(+)-ketoconazole (TOP)and (2*S,*4*R*)-(−)-ketoconazole (BOTTOM)*

Ketoconazole is categorized as pregnancy category C in the US. Research in animals has shown it to cause teratogenesis when administered in high doses. A subsequent trial in Europe failed to show a risk to infants of mothers receiving ketoconazole.

Bifonazole

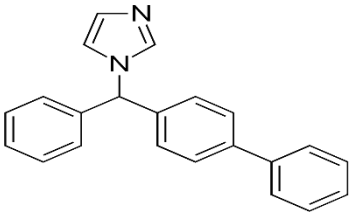
Bifonazole is an imidazole antifungal drug used in form of ointments. The most common side effect is a burning sensation at the application site. Other reactions, such as itching, eczema or skin dryness, are rare.

Mechanism of action

Bifonazole has a dual mode of action. It inhibits fungal ergosterol biosynthesis at two points, via transformation of 24-methylendihydrolanosterol to desmethyl-sterol, together with inhibition of HMG-CoA. This enables fungicidal properties against dermatophytes and distinguishes bifonazole from other antifungal drugs.

Pharmacokinetics

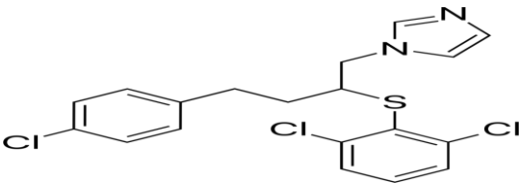
Six hours after application, bifonazole concentrations range from 1000 µg/cm³ in the stratum corneum to 5 µg/cm³ in the papillary dermis.



Bifonazole

Butoconazole

Butoconazole is an imidazole antifungal used in gynecology. It is administered as a vaginal cream.



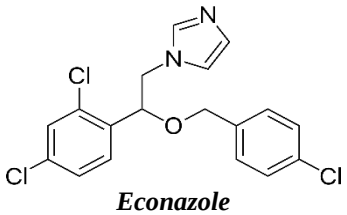
Butoconazole

Econazole

Econazole is used as a cream to treat skin infections such as athlete's foot, tinea, pityriasis versicolor, ringworm, and jock itch. It is also sold in Canada under the brand name Ecostatin as vaginal ovules to treat vaginal thrush.

Econazole nitrate exhibits strong anti-feeding properties against the keratin-digesting common clothes moth *Tineola bisselliella.*

About 3% of patients treated with econazole nitrate cream reported side effects. The most common symptoms were burning, itching, redness (erythema), and one outbreak of a pruritic rash.

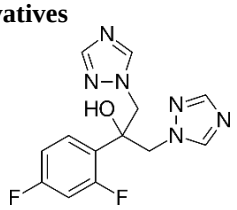


Econazole

Triazole derivatives
E.g.: Fluconazole
Uses: Fluconazole is taken orally for the treatment of mucocutaneous andsystemic mycoses.

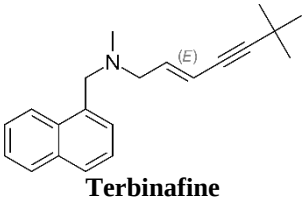
Side effects: rash, headache, dizziness, nausea, vomiting, abdominal pain,diarrhea, and/or elevated liver enzymes

Allylamine derivatives



Fluconazole

Derivatives of allylamine are utilized as both veterinary and human pharmaceuticals, including the antifungal agent terbinafine**.** Terbinafine hydrochloride (Lamisil)® is a synthetic allylamine antifungal. It is highly lipophilic in nature and tendsto accumulate in skin, nails, and fatty tissues.



Terbinafine

Mode of action: Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that is part of the fungal cell membrane synthesis pathway. Because terbinafine prevents conversion of squalene to lanosterol, ergosterol cannot be synthesized. This is thought to change cell membrane permeability.

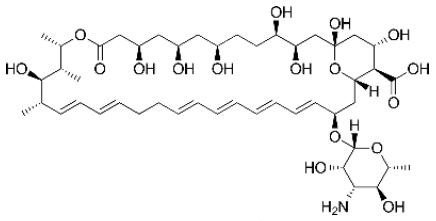
2. Antibiotics

Polyenes

They are structurally complex antifungal antibiotics isolated from soil bacteria containing a conjugated system of double bonds in large lactone ring. They fall into two groupings either 26- membered ring polyenes such as natamycin, or 38-membered ring polyenes such as nystatin, amphotericin B, and candicidin.

Nystatin

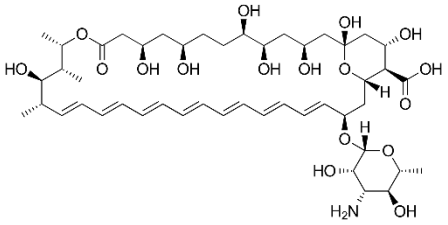
It is a valuable agent for the treatment of local and GIT monilial infections, for the management of cutaneous and mucocutaneous candidiasis. It is considered safe, as the systemic absorption of nystatin following oral administration is practically nil.



Natamycin

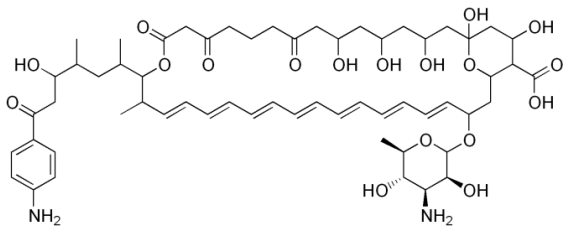
Amphotericin B

As the name implies, amphotericin is an amphoteric substance containing a primary amino group in the sugar moiety and a carboxyl group attached to the macrolide group. Intravenously, it is indicated for the treatment of serious potentially life threatening fungal infections & leishmaniasis, also it is used topically for treatment candida albicans. A high prevalence of adverse reactions limits the usefulness of amphotericin B. some formsof nephrotoxicity in nearly 80 % of the patients is the most important adverse reaction.



Candicidin amphotericin B

Candicidin is used in the treatment of vaginal candidiasis in the form of vaginal tablets.



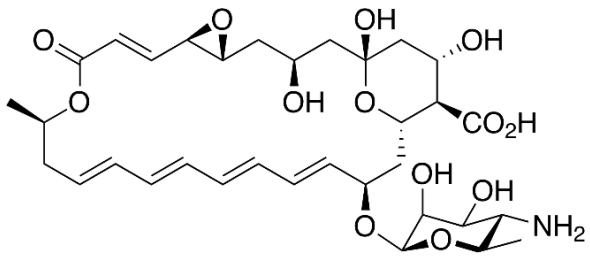
Natamycin

Natamycin is supplied as 5 % ophthalmic suspension, intended for the treatment of fungal conjunctivitis, blepharitis, and keratitis.

Mode of action of polyene antibiotics

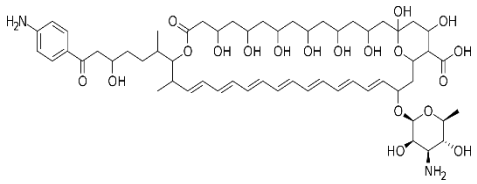
They interact with the lipids of fungal cell membranes to build 'tunnels' through the membrane. Once in place, the contents of the cell are drained away and the cell is killed. As shown from their structure one half of the structure is made up of double bonds and is hydrophobic, while the otherhalf contains a series of hydroxyl groups and is hydrophilic. It is a molecule of extremes and as suchis ideally suited to act on the cell membrane in the way that it does. Several polyenes molecules cluster together such that the alkene chains are to the exterior and interact favorably with the hydrophobic centre of the cell membrane. The tunnel resulting from this cluster is lined with the hydroxyl groups and so is hydrophilic,

allowing the polar contents of the cell to escape.In other words, they cause disorganization of the cell membrane resulting in the loss of cell constituents, especially K+.



Hamycin

Hamycin is a pair polyene antimycotic organic compounds described in India. It is aheptaene antifungal compound rather similar in chemical structure to amphotericin B except that it has an additional aromatic group bonded to the molecule. Whenpure, hamycin is a yellow, powdered solid. There are two versions of hamycin with very similar chemical structures hamycin A and hamycin B.



Hamycin

Use: It is useful as an antifungal antibiotic drug for topical as well as systemic mycoses.

Filipin

Filipin is a mixture of chemical compounds first isolated by chemists at the Upjohn company in 1955 from the mycelium and culture filtrates of a previously unknown actinomycete, *Streptomyces filipinensis*. The isolate possessed potent antifungal activity. It was identified as a polyene macrolide based on its characteristic UV-Vis and IR spectra.

Filipin is a mixture of four components - filipin I (4%), II (25%), III (53%), and IV (18%) - and should be referred to as the filipin complex.

- The major component, filipin III, has the structure which was proposed by Ceder and Ryhage for the filipin complex.
- Filipin I, which has been difficult to characterize, is probably a mixture of several components each having two hydroxyl groups fewer than filipin III.
- Mass spectrometry and NMR data indicate that Filipin II is 1'-deoxy-filipin III.
- Filipin IV is isomeric to filipin III. Their NMR spectra are nearly identical with the major difference being the splitting pattern of the proton at C2. This indicates that filipin IV is probably epimeric to filipin III at either C1' or C3.

The relative and absolute stereochemistry of filipin III was determined by 13C NMR acetonide analysis.

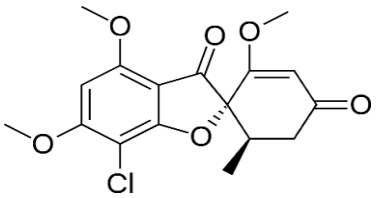
Non polyenes

E.g: Griseofulvin

Obtention: Griseofulvin is isolated from certain strains of Penicillium griseofulvum or obtained byother means.

Uses: Griseofulvin is recommended for the systemic treatment of refractory ringworm infections of the body, nails, hair, and feet i.e. tinea caused by variousspecies of dermatophytic fungi but not effective against tinea neither versicolor nor pathogenic yeasts.

Mode of action: Griseofulvin arrests cell division in metaphase in vitro. The drug causes a rapid, reversible dissolution of mitotic spindle apparatus, apparently by binding with tubulin dimer required for microtubule assembly.



Pharmacokinetics and Pharmacodynamics

The selection of an appropriate antifungal agent depends on multiple factors in addition to the spectrum of activity. As with antibacterial therapy, the routes of administration and elimination are often important considerations in selecting a drug. This is particularly true when the optimal therapy for a patient with a fungal infection is being determined. Alterations in gastrointestinal tract integrity, impaired renal or hepatic function, and limited intravenous access are frequent issues forpatients who are at high risk of acquiring fungal disease. Further complicating the clinical picture is the variability in available formulations among different antifungal agents. Many drugs are available only as intravenous preparations (e.g., amphotericin B preparations and echinocandin agents) or only as oral preparations (e.g., posaconazole and flucytosine) because of differences in solubility and oral bioavailability. For the agents that can be administered by multiple routes (e.g., fluconazole, itraconazole, and voriconazole), there are often difficulties in administration of these preparations because of toxicities, drug interactions, and variability with different product formulations. Therefore, it is important to have an appreciation of the differences among these drugs with regard to their pharmacokinetic properties, including absorption, distribution, metabolism, and excretion.

Absorption Several of the antifungal agents, including the polyene and echinocandin classes, do not have appreciable oral bioavailability. Until the early 1990s, the lack of oral treatment options left intravenous therapy

as the only alternative for the treatment of invasive fungal infections. Today, each member of the azole class can be administered orally; however, the degree of absorption and optimal administration conditions vary for each of these drugs. Differences can even exist between various formulations of the same agent. Fluconazole is readily absorbed, with oral bioavailability easily achieving concentrations equal to 90% of those achieved by intravenous administration. Absorption is not affected by food consumption, gastric pH, or disease state. Variable gastrointestinal absorption does occur with the other members of this class, however, and, for one compound (itraconazole), it varies according to the specific formulation. Oral bioavailability of these agents can be also be affected by food consumption and changes in gastric pH. Itraconazole capsules demonstrate optimal absorption in the presence of gastric acid and, therefore, cannot be coadministered with agents known to raise gastric pH, such as H2 receptor antagonists or proton pump inhibitors. Furthermore, itraconazole capsules should be administered after a full meal to optimize absorption. In general, the cyclodextrin solution is more efficiently absorbed (i.e., the areaunder the concentration curve [AUC] is increased by 30%) than is the capsule formulation. In addition, antacid therapy does not have a negative effect on absorption. Food can decrease serum concentrations of itraconazole solution; therefore, this preparation should be administered on an empty stomach. The oral bioavailability of voriconazole is 190% when the stomach is empty, but it decreases when food is present. Thus, this agent should be administered on an empty stomach. In contrast, posaconazole absorption is optimized when administered with a high-fat meal or a similarcomposition nutritional supplement, such as Boost Plus (Novartis Nutrition).

Distribution The distribution of antifungal agents in the body is another important factor to consider in the treatment of invasive fungal infections, because these infections may occur at physiologicallysequestered sites. As demonstrated by relatively large volumes of distribution, the available antifungal agents are widely distributed throughout the body, with a few significant exceptions discussed below. The main factors affecting drug distribution are molecular size, charge, degree of protein binding, and route of elimination. Fungal infections of the CNS are associated with high morbidity and mortality and are difficult to treat. Many antifungal agents have large molecular weights that preclude their ability to penetrate the blood-brain barrier and achieve therapeutic CSF concentrations. Currently, flucytosine, fluconazole, and voriconazole have the best CSF penetration, with each resulting in concentrations of at least 50% of those seen in serum. The concept of CSF concentrations predicting the efficacy of antifungal agents for CNS infections is a bit misleading. For example, amphotericin B, a drug that is essentially undetectable in CSF, has been the mainstay of treatment for cryptococcal meningitis, despite the lack of detectable drug concentrations in the CSF. In these instances, it is

Metabolism and elimination Many systemic antifungal agents undergo some degree of hepatic metabolism before elimination. One notable exception is flucytosine, which is not known to be metabolized hepatically, because urine excretion of unchanged drug accounts for 190% of its elimination. For the amphotericin B products, the exact routes of metabolism and elimination are largely unknown. All azole antifungals undergo some degree of hepatic metabolism. For fluconazole, the role of metabolism in drug elimination is minimal, but this is not the case with itraconazole, voriconazole, and posaconazole, which are highly dependent on metabolism for drugelimination. Given that there are few active antifungal metabolites, this results in production of inactive compounds that provide no clinically meaningful activity, with the notable exception of hydroxyitraconazole (a metabolite of itraconazole). Although oxidative metabolism is the primary process involved in azole metabolism, glucuronide conjugation does occur with some of these drugs, especially posaconazole. Each of the 2 available echinocandins (caspofungin and micafungin) undergoes metabolism to produce 2 distinct inactive metabolites. For caspofungin, these processesare hepatic hydrolysis and N-acetylation. Micafungin undergoes nonoxidative metabolism to produce 2 distinct compounds. Although it is a weak substrate for cytochrome P450 (CYP450), the metabolism of micafungin does not appear to be affected by inhibitors or substrates of this enzymesystem. Unlike caspofungin and micafungin, anidulafungin is not hepatically metabolized but undergoes nonenzymatic degradation.

Effect of organ dysfunction on drug dosing Although the various formulations of amphotericin B are knownfor their ability to cause nephrotoxicity, they do not require dose adjustment for patients with decreased renal function. In fact, of all the available systemic antifungal agents, only fluconazole and flucytosine require dosing modification when given to patients with decreased levels of creatinine clearance. In some instances, such as with amphotericin B, dosing regimens may be altered in attempts to ameliorate toxicity, but this is not done as a result of altered drug clearance. Another example is the cyclodextrins, which are present in the intravenous preparations of itraconazole and voriconazole and can accumulate in renal disease. Therefore, the use of these formulations in patients with creatinine clearance <50 mL/min, in the case of voriconazole, and 30 mL/min, in the case of itraconazole, is cautioned for these formulations. Hepatic disease can also affect the elimination of several antifungal agents. For the majority of these agents, however, no dose alteration is recommended. Of the azoles, only voriconazole requires dose reduction for patients with mild-tomoderate cirrhosis. Similarly, caspofungin is the only echinocandin with recommendations for dose modification in severe hepatic disease . The metric used to determine appropriate dosing in hepatic disease is the Child-Pugh scoring system, which is appropriate for

patients with chronic liver dysfunction but not for patients who have acute hepatic injury. Currently, information is not available to guide drug dosing in this clinical scenario.

Pharmacodynamics Another important consideration in the optimization of antifungal treatment regimens is the interaction between the fungal pathogen, the antifungal agent, and host factors. These pharmacodynamic principles have not been described for antifungal agents with the same level of detail as for the antibacterial agents. However, fairly extensive in vitro and animal model investigations have been undertaken with agents from the triazole, polyene, and echinocandin antifungal classes. A series of reports has defined the pharmacokinetic exposure of these compounds relative to the MIC of the infecting pathogen as a means of optimizing treatment efficacy. In animal models of disseminated candidiasis, killing of fungal organisms with echinocandins and polyenes is optimized by achieving peak drug concentrations 2–10-fold in excessof the MIC. Treatment outcome with the triazole antifungals has been shown to correlate with the drug exposure over time, which is similar to the concentration needed to inhibit the organism in vitro, or the MIC.

Antifungal Resistance

The term resistance includes both intrinsic resistance, as discussed in the spectrum of activity, and extrinsic resistance, which is acquired. The rate of extrinsic triazole resistance has been increasing, particularly for C glabrata. During the past decade, the frequency of fluconazole-resistant C glabratahas increased from 9% to 14%.Azole cross-resistance is common, with most fluconazole-resistant isolates exhibiting resistance to voriconazole as well. In recent years, the rate of azole-resistant A fumigatus has also been rising significantly, particularly in Europe, where rates are reported as highas 20%, although they vary by geographic region. The higher resistance rates in certain areas have been linked to antifungal use in agriculture. Azole-resistant invasive aspergillosis has a very poor prognosis, with mortality rates above 80%. The main mechanism of azole resistance for Aspergillus,Candida, and Cryptococcus sp. involves the mutation of the azole drug target, lanosterol 14a- demethylase. For Aspergillus sp., this commonly leads to resistance to all azole drugs. However, for Candida spp, the modification of this drug target may lead to resistance to fluconazole alone, azole pan-resistance, or resistance to a subset of azoles. A second mechanism of resistance, the upregulation of efflux pumps, has also been shown to promote drug resistance via a decrease in intracellular drug levels.

Mechanisms of Antifungal Drug Resistance

Azole resistance Azole antifungals such as fluconazole are often preferred treatment for many *Candida* infections as they are inexpensive, exhibit limited toxicity, and are available for oral administration. There is, however, extensive documentation of intrinsic and developed resistance to azole antifungals among several *Candida* species. As the frequency of azole resistant *Candida* isolates in the clinical setting increases, it is essential to elucidate the mechanisms of such resistancein order to both preserve and improve upon the azole class of antifungals for the treatment of *Candida* infections. This review examines azole resistance in infections caused by *C. albicans* as wellas the emerging non- *albicans Candida* species *C. parapsilosis, C. tropicalis, C. krusei*, and *C. glabrata* and in particular, describes the current understanding of molecular basis of azole resistance in thesefungal species.

Polyene resistance Mechanisms of polyene resistance are less well studied than is the case for azoles. This is because amB resistance in clinical isolates is uncommon. One explanation for polyene resistance may be reduced ergosterol content in the fungal cell membrane. The ergosterol is replaced by other sterols that have reduced affinity for the polyene. The genetic mechanisms involved have not been comprehensively investigated.

- **Flucytosine resistance** Flucytosine resistance in Candida albicans or Cryptococcus neoformans is most commonly due to mutational changes in cytosine deaminase or uracilphosphoribosyltransferase, which are involved in the pyrimidine salvage pathway.
- **Allylamine resistance** Although resistance to terbinafine appears to be rare in clinical yeast isolates, it has been shown that some azoleresistant strains which over-express either CDRl or MDRl are cross- resistant to terbinafine.
- **Echinocandin resistance** Echinocandin resistance has not been investigated in any detail, because of insufficient clinical experience. The reduced activity of caspofungin against Cryptocoecus neoformans may be the result of lower affinity for the target glucan synthase enzyme. There is no evidence that strains of Candida spp. that are resistant to several azoles are cross-resistant to caspofungin, and this would suggest that efflux pumps do not impair the activity of this new drug.

Prevention and Control of Antifungal resistance

New strategies and techniques to avoid and to suppress the emergence of antifungal resistance have no longer been defined. However, approaches analogous to the ones recommended for antibacterial may be suggested. These measures consists (i) prudent use of antifungal, (ii) appropriate dosing with unique emphasis on avoiding treatment with low antifungal dosage, (iii) therapy with combinations of present agents, (iv) treatment with the appropriate antifungal (in cases where the etiological agent is known), and (v) use of surveillance studies to determine the true frequency of antifungal resistance. It has to further emphasize that data supporting the use of the suggested measures is largely lacking, and ongoing studies may provide some additional specificguidelinesin the near future. Additionally, advances in the rapid diagnosis of fungi can be beneficialin lowering the use of

inappropriate anti- fungals to treat organisms, which are resistant to a particular agent. Unfortunately, developing the diagnostic methods specific to fungi has been slow. The recent approval of a reference technique for the antifungal susceptibility testing of is encouraging and gives a possible way for performing surveillance studies.

Toxicities of Antifungal Agents

Although the safety and tolerability of systemic antifungal therapy has improved considerably, a growing proportion of heavily immunocompromised patients are receiving systemic antifungal agents for progressively longer treatment courses. As a result, clinicians need to be aware of not only the more familiar dose-limiting toxicities associated with systemic antifungal agents (ie, infusion-related toxicities and nephrotoxicity with amphotericin B, hepatotoxicity with triazole antifungal agents) but also longer-terms risks, including recurrent drug interactions, organ dysfunction, and cutaneous reactions and malignancies.

Amphotericin B preparations The toxicity of amphotericin B is well known. In addition to the nephrotoxicity and acute infusion-related reactions associated with the drug, a unique pulmonary reaction can be seen, particularly with certain lipid preparations. With the liposomal preparation ofamphotericin B, a triad of infusional toxicity has been characterized. This toxicity can manifest as a combination of the following clinical scenarios: pulmonary toxicity (i.e., chest pain, dyspnea, and hypoxia); abdominal, flank, or leg pain; or flushing and urticaria. Similarly, with amphotericin B colloidal dispersion, severe hypoxia has been reported in patients; in one study, hypoxia occurred more commonly in association with the use of amphotericin B colloidal dispersion than with amphotericin B deoxycholate. Hypoxia has also been reported in association with use of the lipid complex of amphotericin B. In one study, up to 20% of patients experienced this toxicity. Unique characteristics in this case included onset of symptoms beyond the second day of therapy for 170%of patients.

Azole antifungal agents Fluconazole is an extremely well tolerated agent that lacks significant toxicity, despite having been used for treatment and prophylaxis in many patient populations for more than a decade. However, reversible alopecia is not uncommon with this agent. Oral itraconazole solution is also relatively safe but can be associated with nausea and diarrhea severe enough to force discontinuation. This reaction is caused by the excipient hydroxypropyl-b- cyclodextrin, which is used to increase solubility of the parent drug. Itraconazole has been described as causing a unique triad of hypertension, hypokalemia, and edema, mostly in older adults. A negative inotropic effect resulting in congestive heart failure has also been described and has prompted changes to the package labeling to avoid administration of itraconazole to patients witha history of heart failure. Two unique adverse events have been associated with the use of voriconazole: visual disturbances and cutaneous phototoxicity. The mechanism for visual disturbances is not known but manifests itself as photopsia (i.e., the appearance of bright lights, color changes, or wavy lines) or abnormal vision in up to 45% of patients receiving the treatment.

Posaconazole has been well tolerated in clinical trials to date. The most frequently reported adverse events attributed to the drug have been associated with hepatic toxicities. These toxicities seem to occur less frequently than with other members of the triazole class. Fatal hepatotoxicity has been reported with itraconazole, voriconazole, and posaconazole. Therefore, close monitoring of hepatic function is warranted with all members of the azole class.

Echinocandins The echinocandins are associated with few toxicities, making them safe agents to administer. The most notable, yet uncommon, event reported is a histamine-mediated infusion- related reaction. As with vancomycin, this reaction can be relieved by slowing the rate of infusion or premedicating with an antihistamine, such as diphenhydramine.

Adequate antifungal dosing strategies are necessary for ensuring successful treatment. The optimal antifungal dosages vary by given patient populations and include both patient physical condition and type of treatment.

CONCLUSION

Now a days, antifungal drug resistance is becoming a most common problem in patients and is unavoidable due to wide availability and use of these agents. There is considerable knowledge concerning the biochemical, genetic and clinical aspects of antifungal agent resistance. New agents and classes are a welcome addition to the antifungal armamentarium and results of ongoing clinical trials are eagerly awaited. Newer broad-spectrum triazoles, in particular voriconazole and Posaconazole, display significant variability in bloodstream concentrations from one patient to the next that may necessitate TDM (Therapeutic Drug Monitoring) in select situations to guide drug therapy and dosing. Long-term toxicities have become more of a concern because ambulatory patients with long-term immunosuppression are taking antifungal therapies for prolonged periods. However, the currently available antifungals have many limitations, including poor oral bioavailability, narrow therapeutic indices, and emerging drug resistance resulting from their use, thus making it essential to investigate the development of novel drugs which can overcome these limitations and add to the antifungal armamentarium.

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