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The Pharmacology and Efficacy of Antifungals: A Literature Review

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ABSTRACT

Antifungal medications, also known as antimycotic medication are pharmaceutical fungicide or fungistatic agents used to treat and prevent mycosis either topically or systematically. A fungal infection may be superficial, systemic, subcutaneous, or allergic in nature. Polyenes, echinocandins, antimetabolites, and azoles have a major role in the antifungal classification. Many topical antifungals have been available since the antiseptic era. Two important antibiotics, amphotericin B, to deal with systemic mycosis, and griseofulvin to supplement attack on dermatophytes were introduced around 1960. Antifungal property or flucytosine was noted in 1970, but it could serve only as a companion drug to amphotericin. The development of imidazoles in the mid-1970s and triazoles in the 1980s provided safer and more convenient alternatives to amphotericin B and griseofulvin. Terbinafine is a novel antifungal. A group of potent semisynthetic antifungal antibiotics, the echinocandins are the latest addition. The selection of an appropriate antifungal agent depends upon the susceptibility of the organism, and the adverse effects of the drug. Antifungal pharmacokinetic properties are often the most important consideration in drug selection because impaired GI tract function or reduced renal/hepatic drug clearance can profoundly influence the safety and efficacy of antifungal therapy. Despite the advances, serious fungal infections remain problematic to treat with emerging clinical resistance to the available drugs.

INTRODUCTION

Fungi are eukaryotic organisms; i.e., their cells contain membrane-bound organelles and clearly defined nuclei. Historically, fungi were included in the plant kingdom; however, because fungi lack chlorophyll and are distinguished by unique structural and physiological features (i.e., components of the cell wall and cell membrane), they have been separated from plants. Also, fungi are clearly distinguished from all other living organisms, including animals, by their principal modes of vegetative growth and nutrient intake. Fungi grow from the tips of filaments (hyphae) that make up the bodies of the organisms (mycelia), and they digest organic matter externally before absorbing it into their mycelia. Fungus, plural fungi, any of about 1,44,000 known species of organisms of the kingdom Fungi, which includes the yeasts, rusts, smuts, mildews, molds, and mushrooms. There are also many fungus-like organisms, including slime molds and oomycetes (water molds), which do not belong to the kingdom Fungi but are often called fungi. Many of these fungus-like organisms are included in the kingdom Chromista.

Types of fungal organisms

Fungi are among the most widely distributed organisms on Earth and are of great environmental and medical importance. Many fungi are free-living in soil or water; others form parasitic or symbiotic relationships with plants or animals. Mycota is an alternative taxonomic name for the kingdom Fungi. While mushrooms and toadstools (poisonous mushrooms) are by no means the most numerous or economically significant fungi, they are the most easily recognized. The Latin word for mushroom, fungus (plural fungi), has come to stand for the whole group. Similarly, the study of fungi is known as mycology—a broad application of the Greek word for mushroom, mykēs. Fungi other than mushrooms are sometimes collectively called molds, although this term is better restricted to fungi of the sort represented by bread mold.[1] Classification of fungal organisms based upon the reproductive method is illustrated in Table 1. Classification of fungi by Alexopolous is explained in Table 2.

Kingdom mycota				
Sexual reproduction not identified	**Sexual reproduction identified**			
Funga limperfectii or DUETEROMYCETES e.g. *Corcospora fusarium*	Primitive fungi OOMYCOTA (*Mycelium aseptato*)		Advanced fungi EUMYCOTA (*Mycelium septate*)	
	Phycomycetes [algal fungi]	Zygomycetes [comjugation fungi]	Ascomycetes [sac fumgi]	Basidiomycetes [club fungi]
	e.g. *Phytophthora albugo*	e.g. *Mucor rhizopus*	e.g. *Yeast candida*	e.g. *Puccinia agaricus*

Table No. 1: Classification based upon reproduction[1].

Division MYCOTA		
Subdivision MYXOMYCOTINA [slimemolds]	**Subdivision EUMYCOTINA**	
Class MYXOMYCETES	**LOWER FUNGI[aseptate fungi]**	**HIGHER FUNGI**
	Class1 CHYTRIDIOMYCETES	**Class 7** ASCOMYCETES **Sub class:** HEMIASCOMYCETIDAE EUASCOMYCETIDAE LOCULOASCOMYCETIDAE
	Class 2 HYPOCHYRIDIOMYCETES	
	Class 3 OOMYCETES	**Class 8** BASIDIOMYCETES **Subclass:** HETEROBASIDIOMYCETIDAE HOMOBASIDIOMYCETIDAE
	Class 4 PLASMODIOPHOROMYCETES	
	Class 5 ZYGOMYCETES	**Class 9** DEUTEROMYCETES
	Class 6 TRICHOMYCETES	

Table No. 2: Classification of fungi by Alexopolous[1].

General classification: MYCOTA
Kingdom: PLANTAE
Division: MYCOTA
Sub-division: MYCOTINA
Class: MYCETES
Sub-class: MYCETIDAE
Order: ALES
Family: ACEA

What are antifungal agents?

An antifungal medication, also known as an antimycotic medication, is a pharmaceutical fungicide or fungistatic agent used to treat and prevent mycosis such as athletes foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others.[2] An antifungal agent is a drug that selectively eliminates fungal pathogens from a host with minimal toxicity to the host.

Antifungal agents:

Polyene Antifungal Drugs: Amphotericin, nystatin, and pimaricin interact with sterols in the cell membrane (ergosterol in fungi, cholesterol in humans) to form channels through which small molecules leak from the inside of the fungal cell to the outside.

Azole Antifungal Drugs: Fluconazole, itraconazole, and ketoconazole inhibit cytochrome P_{450}-dependent enzymes (particularly C14-demethylase) involved in the biosynthesis of ergosterol, which is required for fungal cell membrane structure and function.

Allylamine and Morpholine Antifungal Drugs: Allylamines (naftifine, terbinafine) inhibit ergosterol biosynthesis at the level of squalene epoxidase. The morpholine drug, amorolfine, inhibits the same pathway at a later step.

Antimetabolite Antifungal Drugs: 5-Fluorocytosine acts as an inhibitor of both DNA and RNA synthesis via the intracytoplasmic conversion of 5-fluorocytosine to 5-fluorouracil.[3]

Symptoms of Fungal Infection:

A fungal skin infection might cause[4]:

- Irritation
- Scaly skin
- Redness
- Itching
- Swelling
- Blisters

Who is prone to fungal infection?

Those who are prone to fungal infections include:

- People with weakened immune systems such as children, elderly people, people suffering AIDS, HIV infection, cancer, diabetes.
- People with a genetic predisposition toward fungal infections.
- People who sweat a lot since sweaty clothes and shoes can enhance fungus growth on the skin.
- People who come in contact with a person suffering from a fungal infection.
- People who frequent communal areas with moisture, such as locker rooms and showers, since fungi require moisture to grow and reproduce.
- People who are obese as they have excessive skin folds.
- People with weak immune systems are very prone to fungal infections.

Examples of common fungal infections include[5]:

- Tinea pedis (athlete's foot)

- Tinea corporis (ringworms)
- Yeast infection
- Onychomycosis (fungal infection of the toenails)
- Tinea versicolor (fungal infection of the skin)
- Tinea cruris (jock itch)

Table No. 3: Signs and symptoms associated with common fungal infections[5]

Tinea Pedis	Tinea Corporis	Yeast infection	Onychomycosis	Tinea versicolor	Tinea cruris
Peeling, craking and scalinf of feet	Itchy red ring shaped patch that can be scaly	Itching, swelling around vagina	Nail discolouration	Affected area is lighter or darker than surrounding area	Redness in gron or buttocks
Redness, blistering/softening, breaking down of skin		Burning sensation/pain during urination or sexual intercourse	Nail flaking	Dry, itchy, scaly skin	Chafing, irritation or burning in infected area
Itching, burning or both		Redness, soreness in and around vagina	Nail thickening		Red rash with circular shape and rough edges
		Unusual vaginal discharge			

Types of fungal infections – Mycoses

1. *Superficial mycoses:* Affect the skin, hair, and nails. These types of infections do not penetrate the body and have few symptoms. Most people are concerned about the cosmetic

effects of the infection. Examples include athlete's foot, cradle cap, ringworm (not a worm at all), and thrush.

2. *Subcutaneous mycoses (tropical):* Affect the muscle and connective tissue, immediately below the skin. The fungi that cause subcutaneous mycoses normally live in soil and on decaying vegetation. They cause infection by entering the skin through an injury. Feet are most often affected. Characterized by hard lumps (abscesses) beneath the skin at the original point of injury. These abscesses can be present for a long time and, if left untreated, can become disfiguring. If these types of infections spread to the internal organs through blood or lymphatics they can be life-threatening. However, this is a rare occurrence and usually occurs if the host is immunocompromised. Superficial mycoses occur primarily in tropical areas.

3. *Systemic (invasive) mycoses:* Involve the internal organs, Primary vs. Opportunistic. Most often acquired via inhalation of airborne spores and is initiated in the lungs. The initial pulmonary infection is often subclinical or mild and resolves on its own. However, some patients may develop progressive disease involving spread to other parts of the body. Many of the fungi that cause mycoses live in association with humans as commensals or are present in the environment; but until recently, serious superficial infections were relatively uncommon, and systemic infections were very uncommon indeed-at least in cool and temperate climatic zones. In these zones, a fungal infection usually meant an athlete's foot or vaginal thrush, which caused discomfort but were not life-threatening. But in the last 30 years, there has been a steady increase in the incidence of serious secondary systemic fungal infections. One factor has been the widespread use of broad-spectrum antibiotics, which eliminate or decrease the non-pathogenic bacterial populations that normally compete with fungi. Another has been the increase in the number of individuals with reduced immune responses due to AIDS or the action of immunosuppressant drugs or cancer chemotherapy agents; this has led to an increased prevalence of opportunistic infections i.e. infections with fungi which are either innocuous or readily overcome in immunocompetent individuals. In the UK, the commonest systemic fungal disease is systemic candidiasis. Others include cryptococcal meningitis, pulmonary aspergillosis (invasive pulmonary aspergillosis is now a leading cause of death in recipients of bone marrow transplants). However, in other parts of the world, blastomycosis, histoplasmosis, coccidioidomycosis, and paracoccidioidal mycosis are the commonest; these are often primary infections i.e. they are not secondary to reduced immunological function or altered commensal microorganisms.

4. *Allergic mycoses:* Affect lungs or sinuses, Patients may have chronic asthma, cystic fibrosis, or sinusitis.Allergic broncho-pulmonary aspergillosis (ABPA). This is a condition produced by an allergy to the spores of the Aspergillus molds. It is quite common in asthmatics; up to 20% of asthmatics might get this at some time during their lives. ABPA is also common in cystic fibrosis patients, as they reach adolescence and adulthood. The symptoms are similar to those of asthma: intermittent episodes of feeling unwell, coughing, and wheezing. Some patients cough up brown-colored plugs of mucus.[6]

DISCUSSION

Classification of antifungal agents

Many topical antifungals have been available since the antiseptic era. Two important antibiotics, amphotericin B, to deal with systemic mycosis, and griseofulvin to supplement attack on dermatophytes were introduced around 1960. Antifungal property or flucytosine was noted in 1970, but it could serve only as a companion drug to amphotericin. The development of imidazoles in the mid-1970s and triazoles in the 1980s provided safer and more convenient alternatives to amphotericin B and griseofulvin. Terbinafine is a novel antifungal. A group of potent semisynthetic antifungal antibiotics, the echinocandins are the latest addition.

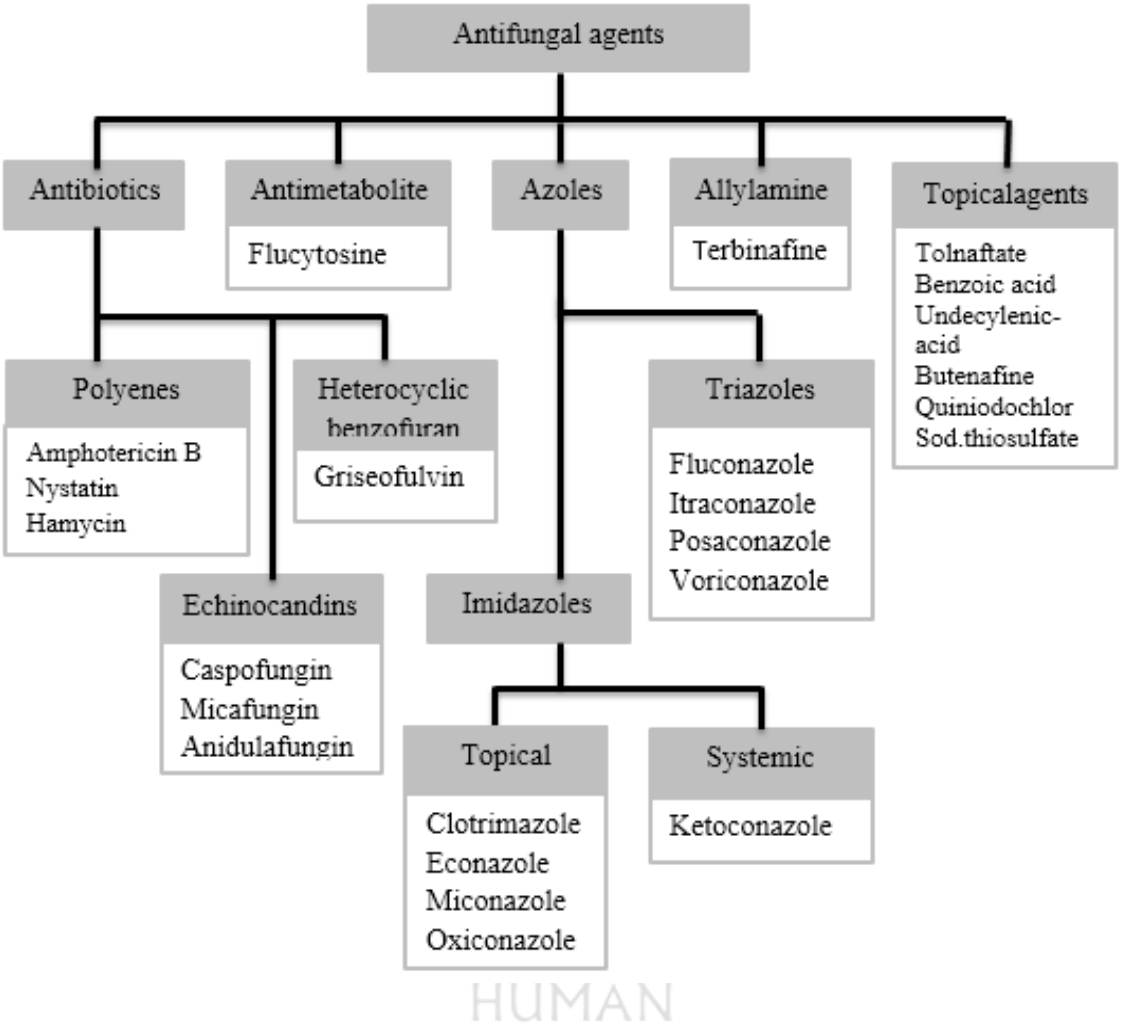

Figure No. 1: Classification of antifungal agents

Overview of antifungal pharmacology

Despite differences in the composition of the cell membrane and the presence of the cell wall, fungi are metabolically similar to mammalian cells and offer few pathogen-specific targets. Systemic antifungal agents can be generally grouped based on their site of action in pathogenic fungi (Fig. 2)[7]. Azole and polyene antifungal agents exert their antifungal effects by targeting ergosterol—the principal cell membrane sterol of many pathogenic fungi. By inhibiting 14α-demethylase (lanosterol demethylase), a fungal cytochrome P450 (CYP)–dependent enzyme, azole antifungal agents deplete cell membrane ergosterol, impair membrane fluidity, and lead to accumulation of toxic 14α-methylated sterols, resulting in growth arrest and eventual fungal cell death.[8] However, this inhibition is not entirely selective to fungi; indeed, collateral inhibition of human CYP enzymes by azoles is often responsible for pharmacokinetic drug-drug interactions. The fungal target for azole binding is

a heme-containing pocket on the 14α-demethylase enzyme.[9] For molecules derived from ketoconazole (i.e, itraconazole, posaconazole), the extension of the nonpolar side chains enhances azole binding to the 14α-demethylase apoprotein, resulting in an enhanced spectrum of activity against molds. Voriconazole, a derivative of fluconazole, possesses an α-o-methyl group that confers activity against Aspergillus species and other filamentous fungi.[10] Resistance to triazole antifungal agents is most commonly the result of mutations in the azole binding pocket of 14α-demethylase [10,11]and/or the overexpression of MDR1 efflux pumps that expel fluconazole or the multidrug adenosine triphosphate–dependent efflux pumps CDR1 and CDR2, which expel all triazoles, thereby leading to cross-resistance.[12]

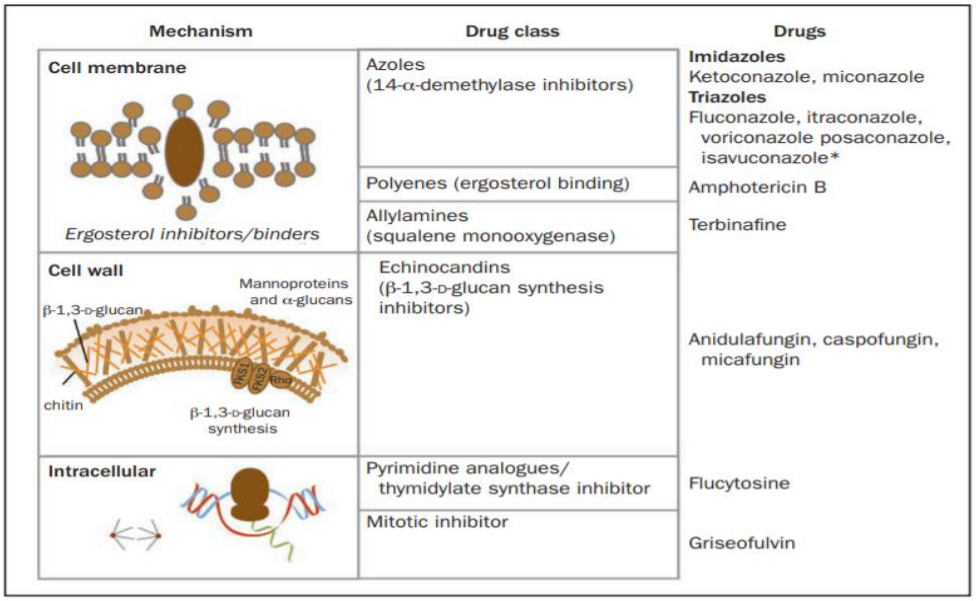

Figure No. 2: Sites of action and mechanisms of systemic antifungal agents
FKS1, FKS2 catalytic subunits of the glucan synthase complex are the putative target binding site of echinocandins. Rho is a cell wall–regulating protein. *Isavuconazole is still in phase 3 trials.[7]

Similar to azole antifungal agents, the allylamine terbinafine inhibits ergosterol biosynthesis by inhibiting squalene monooxygenase—an enzyme in fungi responsible for the conversion of squalene to squalene epoxide, which is a precursor to lanosterol in the ergosterol synthesis pathway.[9] Although allylamines do not seem to have the same collateral effects on human CYP enzymes as azole antifungal agents, drugs such as rifampin that strongly induce CYP metabolism in mammals will increase the metabolism of terbinafine.[13] Once taken orally, terbinafine concentrates in the skin and nail beds and has relatively low bloodstream

concentrations.[14] Consequently, its use as a systemic antifungal agent is primarily restricted to the treatment of onychomycosis and cutaneous fungal infections.[14] The broad-spectrum polyene amphotericin B is the only other antifungal agent that targets the fungal cell membrane (Fig.2).[7]

Amphotericin B directly binds to ergosterol, forming complexes that intercalate the cell membrane, thereby resulting in pore formation and leakage of intracellular contents.[15] Amphotericin B has a greater affinity for ergosterol-rich fungal cell membranes vs cholesterol-rich mammalian cell membranes. However, this specificity may be lost when the drug accumulates to high concentrations in organs such as the kidney, where the drug causes direct damage to distal tubular membranes.[16] Consequently, nephrotoxicity is a common dose-limiting adverse effect of amphotericin B therapy. Amphotericin B also directly stimulates the release of proinflammatory cytokines by mononuclear phagocytic cells, often resulting in fever, rigors, and chills during drug infusion.[17] Two formulations of amphotericin B—a liposomal formulation and a lipid complex—are now commonly used to treat a wide range of invasive fungal infections. Although the development of amphotericin B resistance during therapy is a rare clinical phenomenon, substitution of alternative cell wall sterols[12,18]and increased resistance to oxidative damage in the cell membrane through increased production of neutralizing enzymes[19] are 2 mechanisms that have been identified in clinical isolates exhibiting innate or acquired resistance to amphotericin B.

Of the antifungal agents currently in clinical use, echinocandins are the only ones that target the fungal cell wall by competitively inhibiting the synthesis of β-1,3-d-glucan polymers—key cross-linking structural components of the cell wall in some pathogenic fungi (Fig.2).[20] Echinocandins bind to the β-1,3-d-glucan synthase enzyme complex in susceptible fungi, resulting in a glucan-depleted cell wall that is susceptible to osmotic lysis, especially in rapidly growing cells.[21] The degree of β-1,3-d-glucan polymerization in the fungal cell wall and the expression of the glucan synthase enzyme target largely define the spectrum of this antifungal class, which is generally considered to have fungicidal activity against candida species and fungistatic activity against Aspergillus species.[22] Although bona fide echinocandin resistance remains a relatively rare clinical phenomenon, mutations in defined "hot spot" regions of the FKS1 and FKS2 catalytic subunits of the glucan synthase are associated with reduced echinocandin inhibitory activity against the enzyme, higher minimum inhibitory concentrations (MICs), and an increased risk of treatment failure.[23]

Flucytosine (5-FC) is selectively taken up by 2 fungus specific enzymes, cytosine permease, and cytosine deaminase, and is converted to cytostatic 5-fluorouracil in fungal cells, where the active drug inhibits thymidylate synthase and causes RNA miscoding.[24] However, resident intestinal bacterial flora in the human gut can convert 5-FC to 5-fluorouracil, resulting in nausea, vomiting, diarrhea, and bone marrow suppression.[25] Flucytosine is primarily active against yeasts but must be given in combination with other drugs to avoid resistance that arises with mutations in cytosine permease and cytosine deaminase, resulting in decreased importation and conversion of the drug to its active form.[25] Griseofulvin is a systemic antifungal agent that binds to tubulin, interfering with microtubule formation. Because the drug concentrates in keratinocytes, it is only used for noninvasive dermatophyte infections. Interestingly, griseofulvin inhibits the proliferation of many types of cancer cells *in vitro*, which has led to renewed interest in this agent as a potential adjunctive treatment for breast cancer.[7]

Pharmacokinetics of antifungals

Besides their spectrum of activity, antifungal pharmacokinetic properties are often the most important consideration in drug selection because impaired GI tract function or reduced renal/hepatic drug clearance can profoundly influence the safety and efficacy of antifungal therapy. Several classes of antifungal agents must be administered intravenously, including amphotericin B and the echinocandins, because these agents are not sufficiently absorbed from the GI tract. This problem has been solved with the introduction of triazole antifungal agents; however, the degree of absorption varies considerably from one drug to the next.[7] Fluconazole and voriconazole both have oral bioavailability exceeding 90% and can be administered without regard to food (fluconazole) or preferably on an empty stomach (voriconazole).[26] Itraconazole capsules and posaconazole suspension require food to prolong gastric residence time to enhance drug dissolution. Absorption of posaconazole is dose limited at 800 mg/d but can be maximized when the drug is administered with a high-fat (>50% of the calories from fat) food or nutritional supplement[27]. Therefore, posaconazole is usually initiated at doses of 200 mg 3 to 4 times daily with food in patients with suspected or documented infections until infection stabilizes or adequate serum levels can be verified.

Posaconazole, a new triazole antifungal, exerts principally the same mechanism of action as the other azole derivatives, i.e. it inhibits the ergosterol production by binding and inhibiting the lanosterol-14α-demethylase which is present in almost all fungi

except Pneumocystis and Pythium. Posaconazole has an exquisitely high affinity to this target. Since posaconazole has a chemical structure different from fluconazole and voriconazole, it can interact with an additional domain of the target so that it may inhibit even mutated strains resistant to fluconazole and voriconazole. In addition, posaconazole is a bad substrate for efflux pumps in fungi, so it can stay active when other azoles are already inactive. Furthermore, the spectrum of posaconazole is rather large including also some zygomycetes resistant to other azoles.[28]

Unlike posaconazole, genetic variability in metabolism plays a more important role in the patient-to-patient pharmacokinetic variability of voriconazole.[29] Polymorphisms in the CYP2C19-encoding gene result in 3 populations of patients with markedly different rates of nonlinear voriconazole clearance despite the administration of the same fixed daily dose: (1) homozygous patients who extensively metabolize voriconazole, (2) heterozygous patients with moderate clearance rates of voriconazole, and (3) homozygous patients who metabolize drug poorly through this pathway and have slow rates of voriconazole clearance.[30]

Griseofulvin is used orally only for dermatophytosis. On getting deposited in the skin through circulation, it prevents fungal invasion of keratin. Because it is fungistatic and not cidal, the newly formed keratin is not invaded by the fungus, but the fungus persists in already infected keratin, till it is shed off. Thus, the duration of treatment is dependent upon the site of infection, the thickness of infected keratin, and its turnover rate. It is ineffective topically. Systemic azoles and terbinafine are more efficacious and are preferred now.

Drug interactions are another important cause of pharmacokinetic variability because coadministration of any triazole or caspofungin with potent inducers of phase 1 (CYP) and phase 2 metabolism (i.e, rifampin, phenytoin) can potentially result in low (fluconazole, caspofungin, posaconazole) or undetectable (itraconazole, voriconazole) bloodstream concentrations of the antifungal agent and an increased risk of treatment failure.[31] In the case of itraconazole, voriconazole, and posaconazole, interactions with potent inducers of CYP3A4 cannot always be overcome with higher antifungal drug doses.[32-35] Pharmacokinetic drug-drug interactions are further compounded by the fact that some antifungal agents inhibit the clearance or metabolism of other drugs. Nephrotoxicity associated with amphotericin B therapy (often accelerated by calcineurin inhibitors, aminoglycosides, intravenous radiocontrast agents, foscarnet, or aggressive diuresis) will reduce the clearance of other renally eliminated drugs.[36] Pharmacokinetic drug-drug interactions are most problematic,

however, with triazole antifungal agents because all of these agents inhibit human CYP enzymes to varying degrees.[37,38] These interactions can be dangerous if not anticipated in patients receiving drugs with a narrow therapeutic index, such as chemotherapeutic agents, immunosuppressants, and some cardiovascular medications. Although a detailed discussion of drug interactions is beyond the scope of this review, several recent reviews have been published on this topic.[31,38-40] Finally, the site of infection is an important consideration in the selection of antifungal therapy because some antifungal agents have limited distribution to anatomically privileged sites, such as the central nervous system and vitreous fluid, or, in the case of oral itraconazole and posaconazole, may not achieve sufficient concentrations in the bloodstream to treat a hematogenous infection. Fungal infections involving the central nervous system are notoriously difficult to treat, and many antifungal agents have high molecular weights and a large degree of protein binding that limits their ability to penetrate the blood-brain barrier.[41,42] Of the currently available antifungal agents, 5-FC, fluconazole, and voriconazole have the best penetration in the cerebrospinal fluid and vitreous chamber of the eye.[43] However, liposomal amphotericin B and perhaps other triazoles and echinocandins may still achieve concentrations in the brain parenchyma sufficient to be clinically effective.[44] Lipid formulations of amphotericin B, newer triazole antifungal agents, and echinocandins have no role in the treatment of candiduria because only small amounts of the microbiologically active drug are excreted in the urine.[39]

Isavuconazole is a new extended-spectrum triazole with activity against yeasts, molds, and dimorphic fungi. It is approved for the treatment of invasive aspergillosis and mucormycosis. The advantages of this triazole include the availability of a water-soluble intravenous formulation, excellent bioavailability of the oral formulation and predictable pharmacokinetics in adults. A randomized, double-blind comparison clinical trial for the treatment of invasive aspergillosis found that the efficacy of isavuconazole was non-inferior to that of voriconazole. An open-label trial that studied primary, as well as salvage therapy of invasive mucormycosis, showed efficacy with isavuconazole that was similar to that reported for amphotericin B and posaconazole. In patients in these studies, as well as in normal volunteers, isavuconazole was well tolerated, appeared to have few serious adverse effects, and had fewer drug–drug interactions than those noted with voriconazole.[45] Figure 3. depicts the spectrum of activity of systemic antifungals. Voriconazole, a recently introduced broad-spectrum azole, has excellent activity against Aspergillus and is generally well tolerated.

Voriconazole currently offers the best prospect for success and tolerance as a first-line treatment for aspergillosis.[46]

Table 1
Spectrum of activity for systemic antifungal agents

	AMB	5FC	FLU	ITR	VOR	POS	ISA	CAS	MICA	ANI
Candida albicans	++	++	++	++	++	++	++	++	++	++
Candida glabrata	++	++	+	+	++	++	++	+	+	+
Candida parapsilosis	++	++	++	++	++	++	++	++	++	++
Candida tropicalis	++	++	++	++	++	++	++	++	++	++
Candida krusei	++	+	–	+	++	++	++	++	++	++
Candida lusitaniae	–	++	++	++	++	++	++	++	++	++
Aspergillus fumigatus	++	–	–	+	++	++	++	+	+	+
Cryptococcus neoformans	++	++	++	++	++	++	++	–	–	–
Mucorales	++	–	–	–	–	++	++	–	–	–
Fusarium spp	+	–	–	+	++	++	++	–	–	–
Scedosporium spp	+	–	–	+	+	+	+	–	–	–
Blastomyces dermatitidis	++	–	+	++	++	++	++	–	–	–
Coccidioides immitis	++	–	++	++	++	++	++	–	–	–
Histoplasma capsulatum	++	–	+	++	++	++	++	–	–	–

Abbreviations: 5FC, flucytosine; AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; MICA, micafungin; POS, posaconazole; VOR, voriconazole.

Figure No. 3: The spectrum of activity of systemic antifungals[47]

Toxicities associated with antifungal agents

Although the safety and tolerability of systemic antifungal therapy have 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 (i.e, infusion-related toxicities and nephrotoxicity with amphotericin B, hepatotoxicity with triazole antifungal agents) but also longer-term risks, including recurrent drug interactions, organ dysfunction, and cutaneous reactions and malignancies[31](Fig.4). Oral itraconazole can cause nausea and GI disturbances associated with the cyclodextrin excipient, making it difficult to tolerate prolonged treatment courses. Itraconazole has also been described as causing (mostly in older adults) a unique triad of hypertension, hypokalemia, and edema that may be related to a negative inotropic effect of the drug or adrenal suppression.[48] Therefore, prolonged administration of itraconazole is not recommended in patients with a history of heart failure.

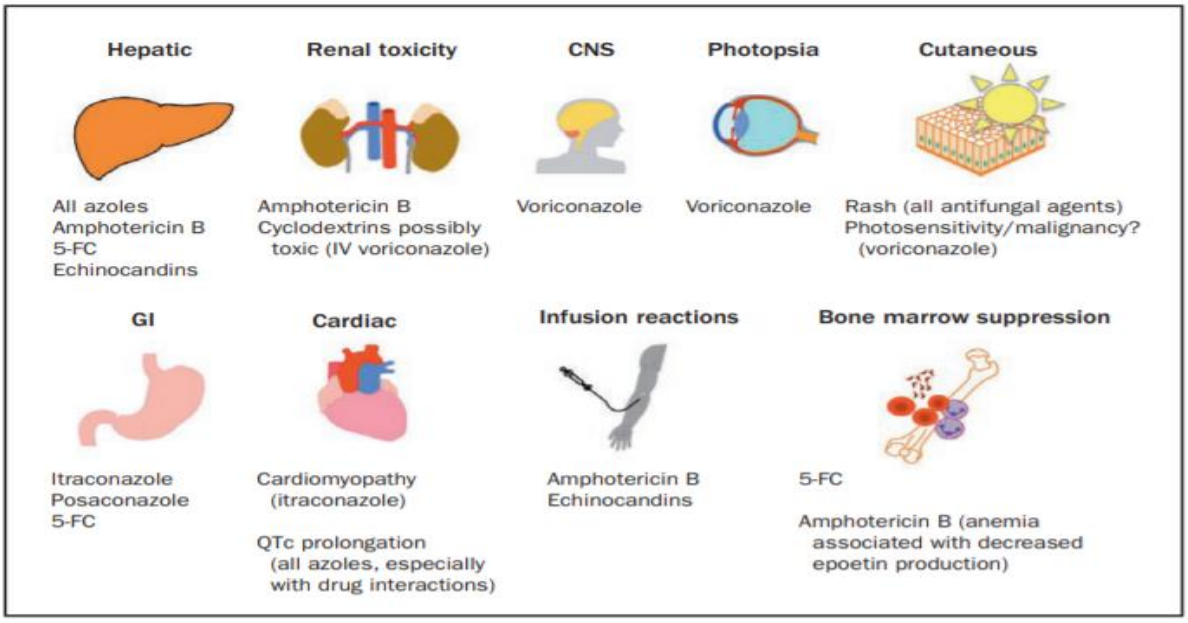

Figure No. 4: Common toxicities of antifungal agents. CNS = central nervous system; 5-FC = flucytosine; GI = gastrointestinal; IV = intravenous; QTc = corrected QT interval.

Although rash is reported with all antifungal classes in 5% to 15% of patients, voriconazole treatment in ambulatory patients has been associated with unique retinoid-like phototoxic reactions that present with cheilitis, erythema, and occasional blistering.[49] This phototoxic reaction is not prevented through the use of sunscreens but is generally reversible after discontinuation of therapy. However, recent reports have linked this phototoxic reaction to the subsequent development of squamous cell car cinoma[50] and melanoma,[40] suggesting that all patients who receive long-term voriconazole treatment should undergo careful screening for skin cancer, especially if they manifest evidence of photosensitivity or cutaneous photodamage.

New and evolving antifungal agents

- Rezafungin (CD101), a new echinocandin with a very long half-life, allowing a once a week dosing. *In vitro* activity against Candida and Aspergillus is similar to that of other echinocandins.[51]

- Ibrexafungerp (SCY-078) is an orally bioavailable β-D-glucan synthesis inhibitor that is not an echinocandin but a triterpenoid.[52] Ibrexafungerp is active against Candida (including multidrug-resistant C. auris and C. glabrata), Aspergillus, and Pneumocystis.

- Manogepix (APX001A and formerly E1210) is an oral and IV broad-spectrum antifungal targeting the highly conserved fungal enzyme Gwt1.[53] Inhibition of Gwt1 blocks the inositol acylation of glycosylphosphatidylinositol-anchored proteins and compromises fungal wall integrity. Manogepix is active against most pathogenic fungi such as Candida spp. (including caspofungin-resistant strains but not *C. krusei*), *C. neoformans*, *Aspergillus spp*., *Scedosporium spp*., and other rare molds.[53,54]

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