

## AN OVERVIEW OF THE AZOLES OF INTEREST

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### ABSTRACT

In the last years, the risk of human fungal infections has been extensively increased with the increasing immune suppressed patients. Fortunately, the therapy of fungal infections has been undergone an explosive period of development. It was found that the use of currently available azoles in combination with other antifungals is likely to provide enhanced efficacy. But, several factors lead to therapeutic failure or relapse after the antifungal therapy. These factors are concerned with the different characteristics of the antifungal (s) used. Thus, specialists should be carefully investigated the different characteristics of antifungals to avoid these factors and further to use the antifungals optimally.

The present review discussed the different characteristics of the azoles of interest, to recognize the differences in pharmacology, pharmacokinetics, spectrum of activity, safety, toxicity and potential drug interactions of these antifungal agents.

However, the present review explore that the azoles of interest are sufficiently diverse in pharmacology, pharmacokinetics, spectrum of activity, safety, toxicity and potential drug interactions allowing specialists to differentiate among these agents based upon their characteristics when tailoring therapy to meet the needs of a particular patient. Moreover, further advances in antifungal chemotherapy will be necessary to improve management of invasive mycoses in the future.

**Keywords:** Human fungal infections, Azoles of interest, Different characteristics and development in the antifungal chemotherapy.

### INTRODUCTION

Human fungal infections have been increased dramatically in incidence and severity in the recent years, due mainly to advances in surgery, cancer treatment and critical care accompanied by increase in the use of broad-spectrum antimicrobials and the human immunodeficiency virus (HIV) epidemic [1-3]. These changes have been resulted in a progressive increase in the number of patients at the risk of mycotic infections [4].

There are more than 100.000 different species of fungi; many of which are beneficial, but few hundreds are pathogens [2]. Fewer than 20 species of fungi causes greater than 90% of all human mycotic infections [2]. Pathogenic fungi affecting human is eukaryotes, generally existing as filamentous molds or intracellular yeasts [1-3]. Fungal organisms are characterized by a low invasiveness and virulence [2]. Factors that contribute to fungal infections include necrotic tissue, a moist environment, and immunosuppression [2]. Fungal infections can be primarily superficial and irritating (e. g., dermatophytosis) or systemic and life threatening (e. g., blastomycosis, cryptococcosis, histoplasmosis, coccidioidomycosis) [1-3]. Dimorphic fungi, which grow in the host as a yeast-like form but as molds in vitro at room temperature, include *Coccidioides immitis*, *Histoplasma* and *Rhinosporidium*, which grow inside host cells [1-3].

Topical infections caused by fungi may become established on the skin and adnexa or mucous membranes (buccal, ruminal, vaginal) [4-6]. The external auditory canal and cornea may also be invaded by yeasts and fungi that are opportunistic pathogens [4-6]. Systemic mycoses are infections with fungal organisms that exist in the environment, enter the host from a single portal of entry, and disseminate within the host usually to multiple organ systems [4-6]. The soil reservoir is the primary source of most infections, which can be acquired by inhalation, ingestion, or traumatic introduction of fungal elements [4-6].

The antifungal drugs are drugs which used in the treatment and prophylaxis of human fungal infections [1-6]. The antifungals are grouped into five groups on the basis of their site of action: azoles, which inhibit the synthesis of ergosterol (the main fungal sterol); polyenes, which bind to fungal membrane sterol, resulting in the formation of aqueous pores through which essential cytoplasmic materials leak out; allylamines, which block ergosterol biosynthesis,

leading to accumulation of squalene (which is toxic to the cells); candins (inhibitors of the fungal cell wall), which function by inhibiting the synthesis of beta 1,3-glucan (the major structural polymer of the cell wall); and flucytosine, which inhibits macromolecular synthesis [1-6].

Most antifungal agents are fungistatic in action, with clearance of infection largely dependent on host response [1]. Several factors can lead to therapeutic failure or relapse after antifungal therapy [1]. In some instances, therapeutic failure reflects poor penetration of drug into infected tissues (particularly the CNS and bone) or into those organisms that are encapsulated. Toxicity of antifungals is a common cause of therapeutic failure. Because both the antifungal target organism and the host cells are eukaryotic, the cellular targets of fungal organisms are often similar to the host structures. Discontinuing therapy after resolution of clinical signs but before eradication of infection also leads to therapeutic failure [1]. Therapy should extend well beyond clinical cure.

To avoid these factors, specialists should recognize the different characteristics of the antifungal agents to differentiate among these agents in pharmacology, pharmacokinetics, spectrum of activity, safety, toxicity and potential drug interactions of the antifungal agents to use these agents optimally.

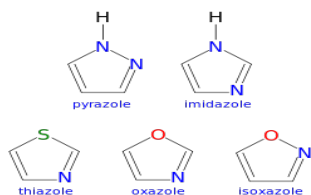
Fortunately, the fungi that cause most of serious infections are susceptible to clinically achievable concentrations of the azoles [7-9]. The azoles are therapeutically useful antifungal agents with wide spectra against yeasts and filamentous fungi responsible for either superficial or systemic infections. Clotrimazole, miconazole, ketoconazole, econazole, itraconazole, fluconazole and voriconazole are the most clinically important members of this group [10].

The present review focuses on the pharmacology, pharmacokinetics, spectrum of activity, safety, toxicity and potential drug interactions of the azoles of interest.

### Classifications of azoles

The azoles are classes of five-membered nitrogen heterocyclic ring compounds that contain at least one other non-carbon atom of nitrogen, sulfur, or oxygen [11], as showed in fig. (1). The parent compounds are aromatic and have two double bonds with fewer one and only one ion pair of electron from each heteroatom in the ring

[11]. The numbering of ring atoms in azoles starts with the heteroatom that is not part of a double bond, and then proceeds towards the other heteroatom [11].



**Fig. 1: The different basic structural rings of azoles**

Azoles are groups of fungistatic agents with broad-spectrum activity. They are classified into two groups: imidazoles and triazoles. The members of each group are structurally related and alterations in side-chain structure determine the antifungal activity as well as the degree of toxicity [10].

Clotrimazole, miconazole (base or nitrate salt), ketoconazole, econazole (base or nitrate salt), butaconazole, teraconazole, voriconazole, itraconazole, and fluconazole are the most clinically important members of this group [10]. Table 1 showed the interest members of these groups and their available formulations.

**Table 1: The interest members of azoles and their available formulations**

Agents class	Examples	Available formulations
Imidazole group	Clotrimazole[12],	Topical lotion, cream and powder, buccal troche and lozenge, vaginal cream and suppository
	Econazole[13],	Topical cream, spray foam and powder, vaginal cream and suppository
	Miconazole[14],	IV injection, oral suspension, gel and tablet, topical cream, vaginal cream and suppository
	Butaconazole[15],	Topical cream and ointment, vaginal cream and suppository
	Ketoconazole[16]	Oral tablet, topical cream and shampoo vaginal cream and suppository
Triazole group	Teraconazole[17],	Topical cream, ointment and gel, vaginal cream and suppository
	Itraconazole[18],	IV injection, oral suspension and capsule
	Fluconazole[19],	IV injection, oral suspension and capsule
	Voriconazole[20]	IV injection, oral tablet

### Spectrum of activity [1-10]

Azoles possess the broad spectrum of activity against yeasts and moulds. However, as this therapeutic class expands, differences in spectrum of activity among the individual agents emerge. The difference in the spectrum of activity may be attributed to variation in the inhibition of 14 $\alpha$ -demethylase and secondary targets among species. The azoles also have some antibacterial action but are rarely used for this purpose. Miconazole has a wide antifungal spectrum against most fungi and yeasts of interest [14, 24].

Sensitive organisms include *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum*, *Candida* species, including (*C. Krusei*, *C. Inconspicua*, *C. Albicans*, *C. Lusitaniae*, *C. Glabrata*, *C. Guilliermondii*, *C. Tropicalis*, *C. and C. Parapsilosis*), *Cryptococcus neoformans*, and *Aspergillus fumigatus* [14, 24]. Ketoconazole has an antifungal spectrum similar to that of miconazole, but it is more effective against *C immitis* and some other yeasts and fungi [15, 25]. It is active against *Candida* species including *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. lusitaniae* and much less active against other *Candida* species. Like as *C. glabrata* and *C. guilliermondii* [15, 25]. Fluconazole has activity against *C. neoformans* and *Coccidioides immitis*, but no activity against *Aspergillus* species. *Fusarium* species. and the agents of zygomycosis [18, 22, 23]. Itraconazole has fungicidal activity against filamentous fungi and some strains of *C. Neoformans* and is generally fungistatic against many yeasts. It has moderately to very active against most medically important fluconazole-susceptible and-resistant *Candida* species (except *C. Glabrata*) [19, 22, 23]. Itraconazole has excellent in vitro activity against common dimorphic or endemic fungi including *C. Immitis*, *H. capsulatum*, *B. Dermatitidis*, and *S. Schenckii* [19, 22, 23, 26]. Itraconazole has good activity against many *Aspergillus* species. but it has variable activity

### Antifungal activity

#### Mode of action

Imidazole drugs exert their antifungal effects through alteration of the cell membrane permeability of susceptible yeasts and fungi by blocking the synthesis of ergosterol (demethylation of lanosterol is inhibited), the primary cell sterol of fungi [1-7, 21]. In addition, other enzyme systems are also impaired, such as those required for fatty acid synthesis. Further, imidazole drugs induce changes of oxidative and peroxidative enzyme activities, toxic concentrations of hydrogen peroxide develop intracellularly. The overall effect is cell membrane and internal organelle disruption and cell death.

Triazole drugs like as imidazole ones, exert its antifungal effect by dose-dependent inhibition of CYP-dependent 14 $\alpha$ -demethylase, which is necessary for the conversion of lanosterol to ergosterol which ergosterol is important for the stability of the fungal cell membrane and inhibition of its biosynthesis compromises cell membrane integrity [1-7, 21]. Triazole drugs also secondarily target other steps in the ergosterol biosynthesis pathway. For example, in fluconazole-susceptible *C. albicans* fluconazole only partially inhibits ergosterol and completely blocks obtusifoliol synthesis, whereas voriconazole completely inhibits both ergosterol and obtusifoliol synthesis [22, 23]. Itraconazole and fluconazole may also inhibit 3-ketoreductase, which catalyzes the reduction of the 3-ketosteroid obtusifolione to obtusifolium in *C. neoformans* [22, 23].

against *Fusarium* species. and very limited activity against the agents of zygomycosis [19, 22, 23]. Clotrimazole and econazole are used for superficial mycoses (dermatophytosis and candidiasis); econazole also has been used for oculomycosis. They have fungicidal activity against most yeast and certain opportunistic fungi, and fungicidal activity against some non-albicans *Candida* species. and *C. neoformans* [12, 13]. Voriconazole has very broad spectrum of activity against dermatophytes, yeasts, and moulds [20, 27]. It is active against all *Candida* species. including fluconazole-resistant *C. Albicans*, *C. Glabrata*, and *C. Krusei*, and more active than fluconazole against medically important *Candida* species. (except *C. Tropicalis*.) [20, 27, 28]. It is very active against other yeasts, including *C. Neoformans* and most *Trichosporon* species., including *T. Asahii*, but it is not very active against *T. Beigelii*/ and *T. Cutaneum* [20]. It has excellent in vitro activity against *Aspergillus* species. many amphotericin-resistant moulds, including certain strains of *Scedosporium apiospermum* and is highly active against *A. Fumigatus*, *A. Flavus*, and *A. Terreus* [20]. Similar to fluconazole, voriconazole has poor or no activity against the agents of zygomycosis [28].

#### Clinical characteristics

The clinical characteristics including the route of administration and therapeutics indications of the azoles of interest are shown in table (2)

#### Pharmacokinetics of azoles

##### Absorption, distribution, biotransformation and excretion [29, 30]

Chemically, the azoles are lipophilic weak bases. They have good relative or absolute bioavailability after oral administration (except the capsule form of itraconazole). Except for fluconazole, an acidic environment is required for the dissolution of the azoles, and a

decrease in gastric acidity can reduce the bioavailability after administration PO. The rate of absorption appears to be increased when the drug is given with meals, but reports are conflicting. Dissolution of ketoconazole and itraconazole in the stomach, administered as solid oral dosage forms are significantly influenced by elevations in gastric pH [31].

Fluconazole is hydrophilic and is highly soluble in water and therefore, compared to the other azoles, it requires much less biotransformation to be eliminated from the body. Itraconazole and voriconazole are highly lipophilic and have limited aqueous solubility [32]. The azoles are inhibitors of CYP3A4, the primary

oxidative drug-metabolizing enzyme in humans [33]. The azoles differ in their affinity for this enzyme. Fluconazole and voriconazole also inhibit CYP2C9/19, and fluconazole inhibits a UGT pathway (UGT2B7) [34]. Hepatic metabolism is the primary route of elimination [32].

The azoles require extensive oxidative (CYP) metabolism to be eliminated from the body [32]. Only 2–4% of a dose administered PO appears unchanged in the urine. Itraconazole is metabolized to an active metabolite that may contribute significantly to antimicrobial activity. The biliary route is the major excretory pathway (>80%); 20% of the metabolites are eliminated in the urine [34].

**Table 2: The route of administration and therapeutics indications of the azoles of interest**

Azoles agent	Route of administration	Indications
Clotrimazole [1-7, 12]	Topical	For vulvovaginal candidiasis or skin yeast infections, for oropharyngeal candidiasis or prophylaxis against oral thrush in neutro- penicpatients, for tinea corporis (jock itch) or tinea pedis (athletes' foot). It may used in conjunction with betamethasone
Econazole [1-7, 13]	Topical	For tinea corporis (ring worm), corpus (jock itch), tinea pedis (athletes' foot), pityriasis vesicular, and vaginal thrush. It may used in conjunction with Triamcinolone acetomid.
Miconazole [1-7, 14]	Topical, systemic	For vaginal, oropharyngeal, esophageal and mucocutaneous candidiasis, oral thrush, candiduria, histoplasmosis, blastomycosis, coccidioidomycosis, chromoblastomycosis, paracoccidioidomycosis, and the skin yeast infections.
Butaconazole [1-7, 15]	Topical	For vaginal yeast infections (vaginal burning, itching, and discharge).
Ketoconazole [1-7, 16]	Topical, systemic	For candidiasis, coccidioidomycosis, chronic mucocutaneous candidiasis, coccidioidomycosis, chromoblastomycosis, candiduria, blastomycosis, histoplasmosis, paracoccidioidomycosis, severe recalcitrant cutaneous dermatophyte infections and that have not responded to topical therapy.
Teraconazole [1-7, 17]	Topical	For uncomplicated vulvovaginal candidiasis (mild to moderate, sporadic or infrequent, most likely caused by <i>Candida albicans</i> , occurring in immunocompetent women).
Fluconazole [1-7, 18]	Topical, Systemic	For cryptococcal meningitis, esophageal vaginal, and oropharyngeal candidiasis; prophylaxis to decrease the incidence of candidiasis in patients receiving cytotoxic chemotherapy and/or radiation, severe cutaneous dermatophyte infection and that have not responded to topical therapy.
Itraconazole [1-7, 19]	Topical, Systemic	For Pulmonary and extrapulmonary blastomycosis; histoplasmosis, including chronic cavitary pulmonary disease, nonmeningeal histoplasmosis; aspergillosis in patients refractory to or intolerant of amphotericin B therapy, onychomycosis of the toenail, with or without fingernail involvement, or of the fingernail alone, due to dermatophytes ( <i>tinea unguium</i> ), empiric therapy of febrile neutropenic patients with suspected fungal infections, oropharyngeal and esophageal candidiasis.
Voriconazole [1-7, 20]	Systemic	For invasive aspergillosis, candidemia in immunocompromised patients and the following <i>Candida</i> infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds, CNS fungal infections transmitted by epidural injection of contaminated steroids, esophageal candidiasis, serious infections by transmitted <i>Fusarium</i> species and <i>Scedosporium apiospermum</i> (asexual form of <i>Pseudallescheria boydii</i> ), and severe fungal corneal infection.

Drug disposition is facilitated by a variety of transport proteins which are expressed in tissues throughout the body in humans. The azoles vary in their interactions with transport proteins [35, 36]. The azoles appear to be widely distributed in the body with detectable concentrations in saliva, milk, and cerumen. Cerebrospinal fluid penetration is poor except for fluconazole, which reaches 50–90% of plasma concentrations.

Most of the azoles (except fluconazole) are highly protein bound in the circulation (>95%), most to albumin [35, 36]. The highest concentrations of the azoles are found in the liver, adrenal glands, lungs, and kidneys. Itraconazole and ketoconazole interact with P-glycoprotein, the best-known efflux transport protein [35, 37]. Ketoconazole and itraconazole interact with another transporter,

known as breast cancer resistance protein (BCRP) [35, 36]. The significance of these interactions with BCRP has not been fully elucidated, but they may, in part, explain certain interactions that previously could not be adequately described by interactions with CYP [35, 36].

The rate of elimination of the azoles appears to be dose dependent: the greater the dose, the longer the elimination half-life [35, 36]. There is also a biphasic elimination pattern with rapid elimination in the first 1–2 hr, then, a slower decline over the next 6–9 hr. Because of the long half-life and mechanism of action (impaired synthesis of the fungal cell membrane), time to efficacy may take longer than drugs that have more rapid actions as amphotericin B [29].

### Adverse effects and toxicity [1-10]

The azoles given PO result in numerous adverse effects. The adverse effects include cardiopulmonary (hypotension, peripheral/pulmonary edema), CNS (dizziness, headache, seizure), dermatologic/hypersensitivity (anaphylaxis, eosinophilia, pruritus, rash), electrolyte disturbances (hypokalemia), gastrointestinal (abdominal pain/dyspepsia, diarrhea, disguise, nausea/vomiting), hematological (anemia, myelosuppression, thrombocytopenia), Hepatic (hepatic necrosis/hepatitis/cholestasis), and miscellaneous (alopecia, fever). But nausea, vomiting, and hepatic dysfunction can develop, particularly with ketoconazole [38]. Altered testosterone and cortisol metabolism have been reported, particularly with ketoconazole [38]. Reproductive disorders related to ketoconazole administration may be seen in dogs. Voriconazole is associated with a number of adverse effects in humans including vision disturbances [39].

The primary toxicities associated with the azoles involve the common transient elevations in serum transaminases to the less common fulminant hepatotoxicity and liver failure is rare [39]. Ketoconazole produce endocrine abnormalities that lead to gynecomastia and adrenocortical insufficiency. Voriconazole produces clinically significant transaminase abnormalities in approximately 13% of patients and visual disturbances in approximately 20% to 30% of subjects in clinical trials [39]. Itraconazole has been associated with the development of congestive heart failure [40]. In such case risk and benefits of using itraconazole for non-life-threatening infections (e. g., onychomycosis) must be seriously considered.

### Interactions [1-10]

Many of the azoles are lipophilic and thus they are subjected to interactions involving their biotransformation and disposition. Drug interactions associated with the azoles result from several different mechanisms. These agents can interact with drugs through different mechanisms (e. g. pharmacodynamic, pH, complexation and electrostatic interactions, CYP and P-glycoprotein) [41-44]. Interactions involving the azoles are pharmacokinetic and result as a consequence of their physicochemical properties. Ketoconazole and itraconazole are subject to pH-based and metabolic interactions. Drugs that will likely interact with these azoles include agents that are cationic or increase gastric pH or are lipophilic CYP3A4 substrates with poor oral bioavailability [41-44]. All azoles are weak bases and at elevated pH values, weakly basic compounds dissolve more slowly. Therefore, the absorption of azoles such as the capsule form of itraconazole is influenced by alterations in gastric pH. The absorption of the azoles, except for that of fluconazole, is inhibited by concurrent administration of cimetidine, ranitidine, anticholinergic agents, or gastric antacids [43]. Rifampin decreases the serum levels of active ketoconazole because of microsomal enzyme induction [41-44]. The azoles may be used concurrently with amphotericin B or 5-flucytosine to potentiate its antifungal activity [36, 41].

The azoles are substrates for p-glycoprotein transport protein and may compete with other substrates, causing higher concentrations [44]. Azoles in general and ketoconazole in particular, inhibit the metabolism of some drugs and, if administered concurrently, their concentrations may be higher than anticipated [41-44].

### Resistance of Azoles [21, 45]

In the 1990s, many human immunodeficiency virus (HIV)-infected patients received long-term, low-level azole antifungal therapy, which resulted in azole-resistant isolates of *C. albicans* [46]. One study documented azole resistance in up to one-third of the oral *C. albicans* isolates from HIV-positive patients.

Since the advances in development of the azole group of antifungal compound for the treatment of fungal infections, it has got widespread use. Consequently, with extensive use resistance to these agents has been reported, particularly fluconazole [46, 47]. Resistance to the azoles is attributed to quantitative or qualitative modifications of target enzymes, reduced access of the drug to the target enzyme or by a combination of these mechanisms [48].

Qualitative modifications in target enzymes result from point mutations in ERG11, the gene responsible for producing 14 $\alpha$ -demethylase, which is the principal target of the azoles. Alternatively, the different chemical structures of the azoles may also contribute to this differential activity. Quantitative modifications in target enzymes also result from mutations in ERG11. Over expression of the gene results in over-production of the target enzymes, this then necessitates higher intracellular azole concentrations to inhibit the entire target enzyme.

In the last few years, several molecular mechanisms by which *C. albicans* develops resistance to antifungal drugs has been elucidated [49]. The azoles including fluconazole target lanosterol 14 $\alpha$ -demethylase, the product of the *ERG11* gene. Erg11p is one of the enzymes in the biosynthesis of ergosterol, the major sterol of fungal membranes and an analogue of cholesterol in mammalian systems. Antifungal drug resistance has been associated with point mutations and increased levels of expression of the *ERG11* gene [49]. Evidence is accumulating that changes in other enzymes in the ergosterol biosynthetic pathway can also contribute to resistance. Drug efflux from the cells is another component of resistance in *C. albicans*, as over expression of two types of efflux pump has been correlated with antifungal resistance. The ABC transporter genes *CDR1* and *CDR2* encode ATP-dependent efflux pumps that are over expressed in many azole-resistant isolates [46-49]. Deletion of these genes results in hypersensitivity to azoles. The major facilitator gene *MDR1* encodes a pump that uses the proton motive force at the membrane to transport drugs and other compounds across the plasma membrane. Over expression of this pump is also associated with resistance, and deletion results in hypersensitivity to the azoles. Moreover, another major facilitator gene, *FLU1*, was identified in *C. albicans* [46-49]. This gene increases the level of azole resistance when it is expressed in *Saccharomyces cerevisiae* and increases the level of susceptibility when it is deleted from *C. albicans*, but over expression of the gene has not yet been correlated with azole resistance in clinical isolates of *C. albicans* [46-49]. The changes in the level of susceptibility are associated with each of these molecular alterations. The level of susceptibility for fungal cells is usually measured as the MIC, and the MIC determination method has recently been standardized for reproducibility and inter laboratory consistency.

In recent years, resistance to antifungal drugs has been documented in other patient populations such as bone marrow transplant recipients [49]. In a clinical setting, there are many reasons why a fungal infection does not respond to antifungal drugs, including the immune status of the patient, the characteristics of the drug, and the susceptibility of the fungus to the drug [49]. The known molecular mechanisms of resistance are best illustrated by a series of 17 isolates from an HIV-infected patient [48]. Resistance developed over time in this series of isolates.

Up to date, mechanisms of resistance have been determined in clinical isolates in which matched sets of resistant and susceptible isolates of the same strain were analyzed [50]. In the most recently published work, the molecular mechanisms of resistance in matched sets of susceptible and resistant isolates of the same strain from an HIV-infected patient population were investigated [50]. The study found that 85% of isolates over expressed efflux pumps, 65% of isolates had mutations in *ERG11* and 35% of isolates over expressed *ERG11*. Most of the point mutations identified in that study were previously described in a survey of point mutations in *ERG11*.

In conclusion, different mechanisms contribute to the resistance of antifungal agents. These mechanisms include modification of ERG11 gene at the molecular level (gene mutation, conversion and over expression), over expression of specific drug efflux pumps, alteration in sterol biosynthesis, and reduction in the intracellular concentration of target enzymes

### CONCLUSION

The present review explore that fungal infections in critically ill or immuno-suppressed patients were increasing in incidence in the human population over the last ten years. In addition, some serious fungal infections remain difficult to treat and resistance to the

available antifungal drugs is emerging. Several developments in the area of the antifungal therapy have been conducted. The azoles in combination with other antifungal agents provided excellent therapy in the treatment of most clinically important mycoses. The azoles of interest are sufficiently diverse in activity, toxicity and drug interaction potential allowing clinicians to differentiate among these agents based upon their characteristics when tailoring therapy to meet the needs of a particular patient. Interestingly, further advances in the antifungal chemotherapy will be necessary to improve management of invasive mycoses in the future.

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