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(Review Article)

Current and Emerging Trends in Antifungal Treatment: A Review

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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 clinical problem 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 are currently 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.

Keywords: Fungal infections, Candidiasis, Systemic mycoses, Immunocompromised patients, HIV/AIDS, Antifungal drugs, Drug resistance, Chemotherapy-induced infections, Aging population, Clinical challenges.

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. Of the 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 in humans, 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 fungi static 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

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.

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.

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.

Subcutaneous mycoses: 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.

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.

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

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.

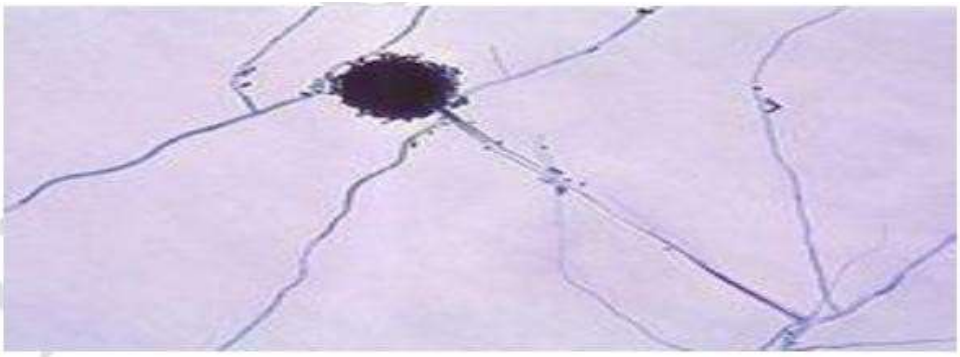

Figure 1: Candial head of Aspergillus niger.

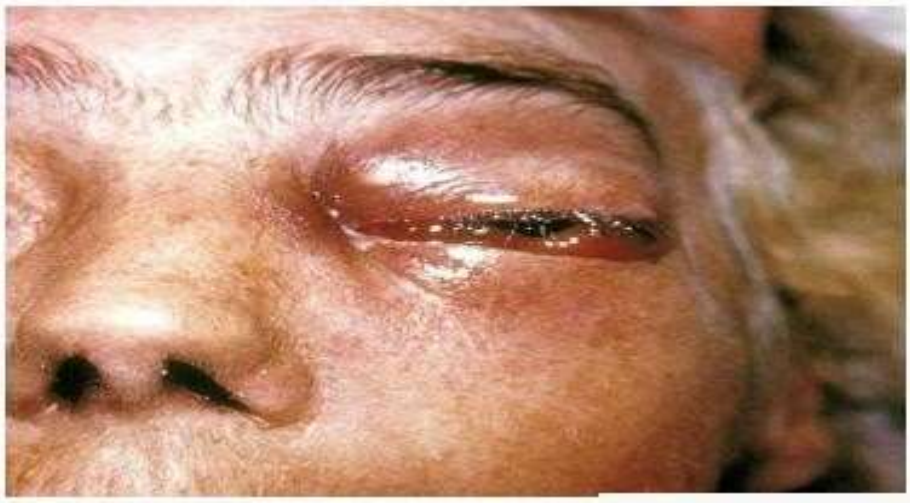

Figure 2: Periorbital fungal infection known asmucormycosis, or phycomycosis

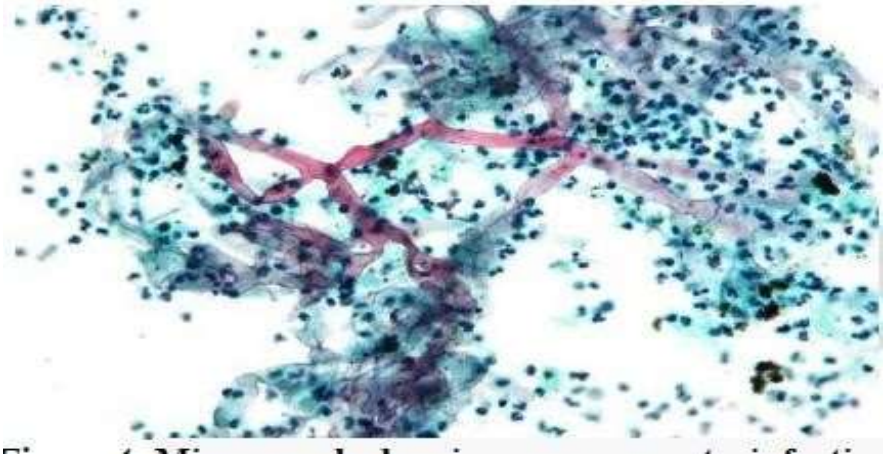

Figure 3: **Micrograph showing a zygomycetesinfection.**

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.

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

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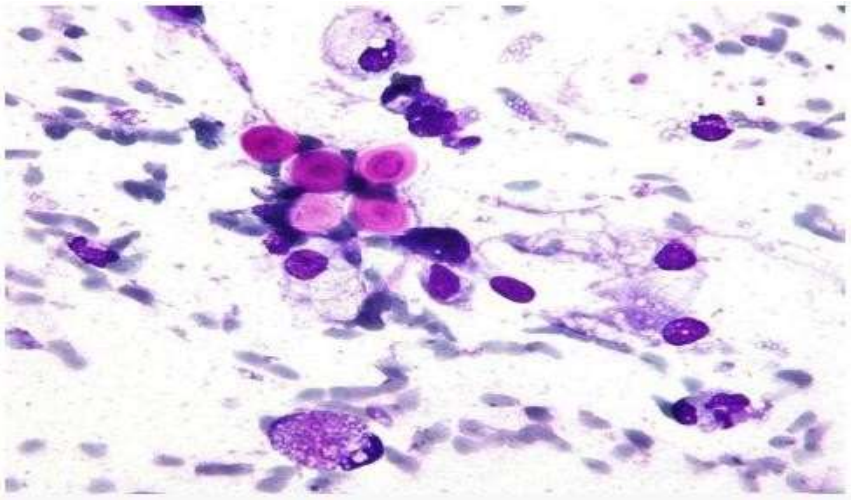

Figure 4: Micrograph of cryptococcosis showing thecharacteristically thick capsule of Cryptococcus

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.

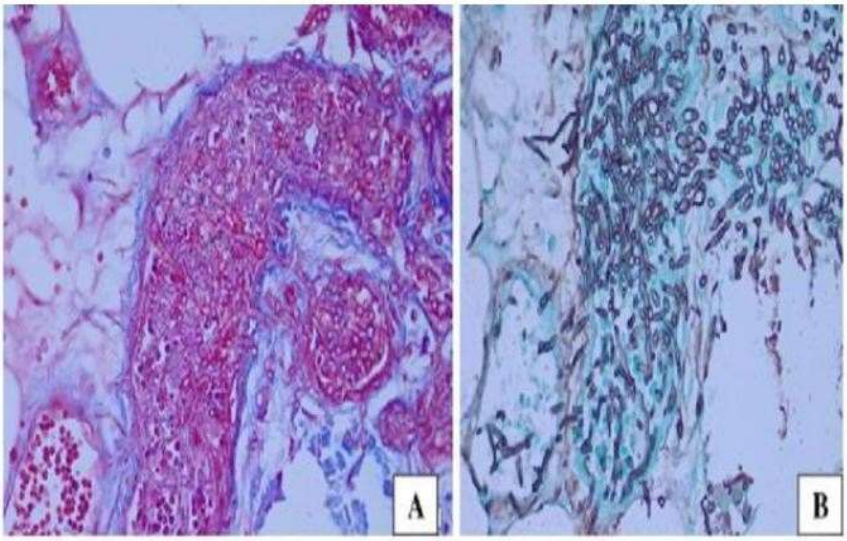

Figure 5: Hyalohyphomycosis (Fusarium sp.). Septate hyphaebranching in acute or right angles infiltrate the bloodvessels

Classification of Antifungal Agents

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.

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

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.

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 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).

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.

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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