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# Current Management of Fungal Infections

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## Abstract

The management of superficial fungal infections differs significantly from the management of systemic fungal infections. Most superficial infections are treated with topical antifungal agents, the choice of agent being determined by the site and extent of the infection and by the causative organism, which is usually readily identifiable. One exception is onychomycosis, which usually requires treatment with systemically available antifungals; the accumulation of terbinafine and itraconazole in keratinous tissues makes them ideal agents for the treatment of onychomycosis. Oral candidiasis in immunocompromised patients also requires systemic treatment; oral fluconazole and itraconazole oral solution are highly effective in this setting.

Systemic fungal infections are difficult to diagnose and are usually managed with prophylaxis or empirical therapy. Fluconazole and itraconazole are widely used in chemoprophylaxis because of their favourable oral bioavailability and safety profiles. In empirical therapy, lipid-associated formulations of amphotericin-B and intravenous itraconazole are safer than, and at least as effective as, conventional amphotericin-B (the former gold standard). The high acquisition costs of the lipid-associated formulations of amphotericin-B have limited their use.

In humans, fungal infections can be classified into three broad groups: superficial, subcutaneous and systemic (see Garber[1]). Superficial infections of keratinised tissues such as nails and hair are usually by dermatophytes, whereas mucous membranes are most frequently infected by *Candida* spp. A variety of organisms cause subcutaneous infections, which are usually acquired by traumatic inoculation. The most serious life-threatening fungal infections are systemic. In some geographical locations systemic fungal infections are endemic, such as histoplasmosis in the Mississippi valley. However, immunocompromised patients worldwide are at risk of systemic infection from commensal and ubiquitous species, primarily *Candida* spp. and *Aspergillus* spp.

The recent increase in the number of patients at risk of systemic fungal infections (patients with HIV, cancer patients receiving intensive chemotherapy)[2-4] has highlighted the need for effective therapy of fungal infections. Some superficial fungal infections can be treated or prevented with topical antifungal agents but others require systemic treatment with oral antifungals. Systemic infections are treated with orally and intravenously administered agents. Here we discuss the use and potential of the three classes of antifungal agents used most frequently – polyenes, azoles and allylamines (table I).

**Table I.** Selected properties of antifungal agents

| Drug | Spectrum of activity | Properties/formulations |
|---|---|---|
| **Polyene macrolides** | | |
| Amphotericin-B | *Candida* spp., *Aspergillus* spp. and other filamentous fungi, life-threatening infections with the endemic fungi *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis*<br>Reports of resistance in non-*albicans Candida* spp. | Delivered topically or systemically, most frequently used in IV form for treatment of systemic fungal infections; oral tablets used mainly to treat thrush and gastrointestinal candidiasis; conventional formulations are nephrotoxic; lipid-associated formulations have reduced nephrotoxicity |
| Nystatin | *Candida* spp. and *Aspergillus* spp. | Oral formulation used for topical treatment of oropharyngeal candidiasis |
| **Allylamines** | | |
| Terbinafine | *Candida* spp., *Aspergillus* spp., dermatophytes and dimorphic fungi | Topical and oral formulations used in treatment of cutaneous and nail dermatophyte infections; lipophilic and accumulates in skin, hair, sebum and nail plate |
| **Imidazoles** | | |
| Ketoconazole | *Candida* spp., all dermatophytes, *Malassezia furfur*, *B. dermatitidis*, *C. immitis*, *H. capsulatum*, *Paracoccidioides brasiliensis* and *Phialophora* spp.<br>NOT *Aspergillus* spp. | Oral formulations previously used in treatment of systemic infections; largely supplanted by other azole antifungals |
| Miconazole | *C. albicans*, *Pseudallescheria boydii*, *M. furfur* and all common dermatophytes<br>NOT *Aspergillus* spp. | Available as topical cream, oral gel and IV formulation; parenteral form rarely used, because of toxicity |
| **Triazoles** | | |
| Fluconazole | *Cryptococcus* spp., and many *Candida* spp., including *C. albicans*<br>NOT *Aspergillus* spp. or some non-*albicans Candida* spp., e.g. *C. glabrata* and *C. krusei*<br>Reports of resistance | Water-soluble oral capsules (or tablets), suspension or IV formulation used extensively in prophylaxis; treatment of choice for mucocutaneous candidiasis in neutropenic patients and one of the preferred treatments for oral candidiasis in patients with HIV infection |
| Itraconazole | *Candida* spp. *Aspergillus* spp., *B. dermatitidis*, *H. capsulatum*, *Cryptococcus* spp., *C. immitis*, *Trichophyton* spp., *Sporothrix schenckii*, *Penicillium marneffei* and *P. brasiliensis*<br>Reports of resistance in *Aspergillus fumigatus* | Oral capsules taken with food; oral (taken before food) and IV solution have improved bioavailability; drug of choice for some rare fungal infections; valuable for prophylaxis and treatment of systemic fungal infections; lipophilic and accumulates in keratinous tissue |

**IV** = intravenous.

## 1. Antifungal Agents

### 1.1 Polyenes

The most frequently used polyene macrolides are amphotericin-B and nystatin. These drugs act by binding to ergosterol in cell membranes (fig. 1), increasing permeability, disrupting metabolism and causing cell death.[5] Both amphotericin-B and nystatin have a broad spectrum of activity against most species of *Candida* and *Aspergillus*.

Amphotericin-B has been available for more than 40 years and exists in a variety of formulations; however, because the oral bioavailability of amphotericin-B is less than 5%,[6] the oral formulations are essentially topical agents for the treatment or prevention of oral or intestinal colonisation. Intravenous formulations of amphotericin-B are used in the management of systemic fungal infections.

Nystatin also has low oral bioavailability and is generally used only as a topical treatment for thrush or in preventing colonisation with *Candida albicans* in the gut.[7]

### 1.2 Allylamines

The allylamine terbinafine inhibits squalene epoxidase (an enzyme involved in ergosterol synthesis; fig. 1), which results in ergosterol depletion,

membrane disruption and cell death.[8] Terbinafine has activity against dermatophytes, low activity against *Aspergillus* spp. and other filamentous fungi but limited activity against *Candida* spp. The drug is registered for topical and oral treatment of cutaneous and nail dermatophyte infections[9] and, because terbinafine is lipophilic and keratinophilic, it accumulates in sebum, hair and nails. Terbinafine has been used alone or in combination with amphotericin-B or azoles for the treatment of invasive fungal infections[10] but no controlled studies have been published.

### 1.3 Azoles

The azole antifungals are synthetic compounds that inhibit the fungal cytochrome P450 (CYP) 14α-demethylase (fig. 1);[11] this results in a depletion of ergosterol and a loss of membrane integrity and activity. The azoles are divided into imidazoles and triazoles on the basis of their chemical structure and clinical effectiveness.

#### *1.3.1 Imidazoles*

Miconazole has potent antifungal activity but is inactive against *Aspergillus* spp., and its insolubility restricts its use. Ketoconazole has a spectrum of activity similar to that of miconazole. When introduced 20 years ago, ketoconazole was the first orally absorbable antifungal azole (bioavailability approximately 75%);[12] it is now also available as a topical cream. Ketoconazole is primarily used for the topical treatment of superficial yeast and dermatophyte infections.

Miconazole and ketoconazole have been largely supplanted by the triazoles in the treatment of serious fungal infections.

#### *1.3.2 Triazoles*

Itraconazole and fluconazole are the only systemic triazole antifungal agents currently available. Itraconazole has a broad spectrum of antifungal activity against *Candida* spp., *Aspergillus* spp. and dermatophytes; it accumulates in keratinous tissue, such as hair and nails, and is widely used for the treatment of fungal nail infections. In addition, itraconazole is orally absorbed and accu-

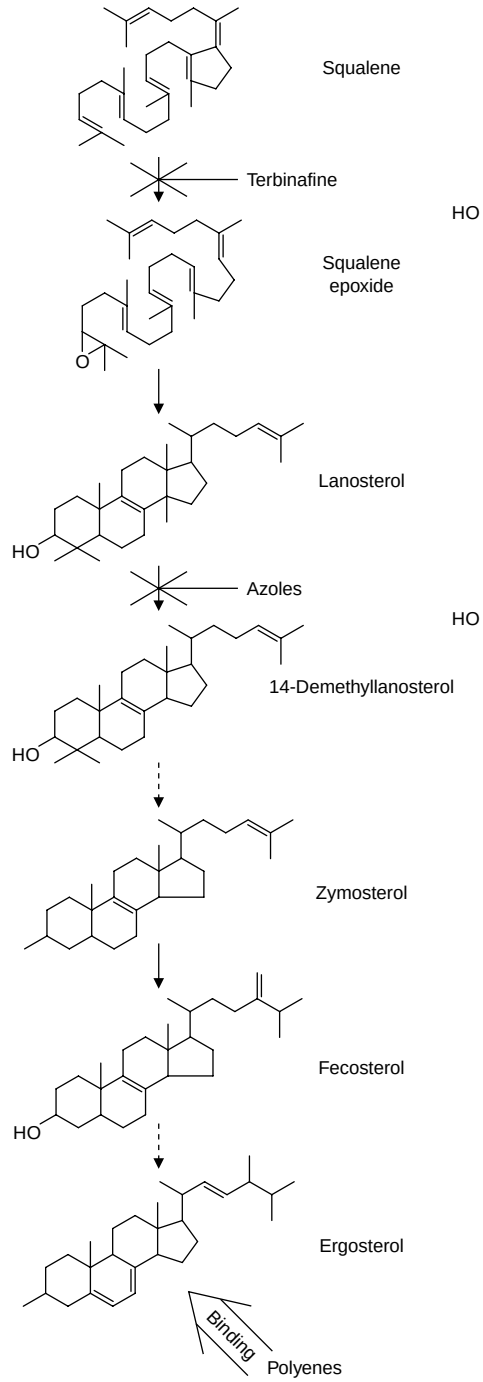


**Fig. 1.** Ergosterol synthesis pathway and points of inhibition by antifungal agents.

mulates in organs that are frequent sites for systemic fungal infections (such as the spleen and lungs),[13] and can therefore be used to treat and prevent a variety of systemic fungal infections (see Boogaerts and Maertens [14]). The bioavailability and clinical efficacy of itraconazole for systemic infections have recently been improved with the development of oral solution and intravenous (IV) formulations (see De Beule and Van Gestel[15]).[16]

Fluconazole has a narrower spectrum of antifungal activity than itraconazole; it is inactive against *Aspergillus* spp. and some species of *Candida*. Despite this, fluconazole is still used widely for the prophylaxis of systemic fungal infections and the treatment of confirmed systemic *Candida* infections in immunocompromised patients. Fluconazole is also an effective treatment for cryptococcal meningitis in patients with AIDS,[17] and is effective in preventing relapse when given as secondary prophylaxis.[18] Fluconazole has oral bioavailability of approximately 90% and can also be used to treat mucosal and cutaneous candidiasis. Because, like itraconazole, fluconazole accumulates in fingernails and toenails, it can also be used to treat onychomycosis.[19,20]

### 1.4 Other Agents

Griseofulvin acts by binding to microtubular proteins and inhibiting fungal cell mitosis. Griseofulvin is effective only against dermatophytes and is indicated for the treatment of dermatophytoses of the skin, hair or nails when other treatments are considered inappropriate.

Flucytosine is a synthetic fluorinated pyrimidine that disrupts DNA and RNA synthesis. It has a narrow spectrum of activity and is largely used in combination with amphotericin-B for the treatment of cryptococcal meningitis or deep candidiasis.[21]

## 2. Treatment of Superficial Fungal Infections

Superficial fungal infections often produce characteristic lesions, and a combination of clinical observation and laboratory investigation usually provides an accurate diagnosis.

### 2.1 Dermatophytosis

Fungal infections of the skin, nails and hair are usually caused by dermatophytes. Tinea corporis, tinea cruris, tinea pedis and tinea manuum are managed with administration of topical imidazoles or allylamines for 2 to 4 weeks; generally, more than 80% of patients are cured.[22-24] However, when the infections are extensive or when topical treatment fails, an oral antifungal agent is required. Treatment for 1 week with itraconazole capsules 200 to 400 mg/day or for 2 to 4 weeks with terbinafine 250 mg/day is usually effective.[25-30] The choice of first-line treatment for tinea capitis is less well defined; oral itraconazole capsules or terbinafine may be preferred to topical imidazoles. In a recent small trial, week-12 cure rates were 86% and 78% with itraconazole capsules and terbinafine, respectively.[31]

Most cases of tinea unguium and other fungal infections of the nails (onychomycosis) can be treated effectively only with the oral administration of itraconazole, terbinafine or to a lesser extent fluconazole.[32] Terbinafine 250 mg/day is usually administered for 6 or 12 weeks for the treatment of fingernail or toenail onychomycosis, respectively. These regimens provide mycological cure rates of 88% in fingernails and 82% in toenails.[33-35]

Therapeutic concentrations of itraconazole can be detected in the nail 6 to 9 months after therapy is stopped.[36] This has led to the development of pulse therapy, in which itraconazole capsules 400 mg/day are administered for only 1 week each month, repeated twice for fingernail onychomycosis and 3 times for toenail onychomycosis. The advantages of a pulse therapy regimen include reduced costs and improved compliance.[37] Comparative trials of continuous terbinafine therapy and itraconazole pulse therapy have given contradictory results.[38-40]

### 2.2 Superficial Candidiasis

*Candida* nail infections require oral treatment:[41] a 6-week course of itraconazole capsules 200 to 400 mg/day or 3 cycles of pulse therapy (each cycle consists of 1 week of drug therapy followed by 3 weeks with no therapy) with itraconazole capsules 400 mg/day are effective (mycological and clinical cure rates of more than 90%).[41-43] Other superficial *Candida* infections, such as vaginal, penile and cutaneous candidiasis respond well to topical treatment with nystatin or an imidazole, or oral treatment with itraconazole or fluconazole.

Oral candidiasis in immunocompetent patients can be controlled with topical imidazoles or a 2- to 3-week course of amphotericin-B oral suspension or nystatin oral suspension. However, in neutropenic cancer patients and patients with HIV infection, treatment with topical agents is associated with a high relapse rate and oral antifungals are preferred.[44] Oral fluconazole (100 to 200 mg/day for 2 weeks) has proven efficacy in treating oral candidiasis (48% of patients mycologically cured; 84% of patients clinically cured),[45] but fluconazole-resistant candidiasis is frequently reported during prolonged exposure in patients with HIV infection or chronic mucocutaneous candidiasis,[46-48] and fluconazole is ineffective against some species of *Candida*. Itraconazole capsules (200 mg/day for 2 to 4 weeks) are effective against oral and oesophageal candidiasis (40% of patients mycologically cured; 74% of patients clinically cured),[49] but absorption of the capsule formulation can be variable in patients with HIV and hypochlorhydria. Itraconazole oral solution has reliable absorption and greater bioavailability than the capsule,[50,51] and is at least as effective as fluconazole in immunocompromised patients with oral candidiasis (mycological cure rates of 88% and 77% for itraconazole oral solution and fluconazole, respectively; clinical response rate of 97% and 87% for itraconazole oral solution and fluconazole, respectively).[52] In addition, most patients with fluconazole-refractory oral candidiasis respond to treatment with itraconazole oral solution (200 mg/day for 2 weeks).[53-55]

## 3. Management of Systemic Fungal Infections

Systemic fungal infections are life threatening and affect immunocompromised people, such as patients with HIV, bone marrow transplant recipients, patients with haematological malignancies and solid organ transplant recipients. Diagnosis of systemic fungal infections is difficult because symptoms are not specific and can be confused with those of bacterial infections, viral infections or the underlying condition, or with complications of treatment (see Garber[1]).

Although diagnostic techniques for systemic fungal infections are improving, prophylaxis and empirical treatment continue to play a key role in the management of systemic fungal infections. The poor prognosis associated with systemic fungal infections means that chemoprophylaxis is frequently administered to patients at high risk and empirical therapy is initiated without proof of infection – usually when the patient has persistent fever of unknown origin that is unresponsive to broad spectrum antibiotics. Both approaches can result in the prolonged administration of antifungal agents to high-risk patient groups.

### 3.1 Endemic Infections

Most endemic mycoses are treated with amphotericin-B or itraconazole (table II). Ketoconazole may also be effective for treating immunocompetent patients with non–life-threatening histoplasmosis, blastomycosis or paracoccidioidomycosis,[56] but fluconazole has relatively poor efficacy against endemic mycoses.

Itraconazole is recommended for the treatment of many endemic mycoses and as maintenance therapy in immunocompromised patients. Life-threatening histoplasmosis and blastomycosis may require intravenous treatment, such as with amphotericin-B.[57,58] However, oral itraconazole 100 to 400 mg/day for at least 6 months is the usual

**Table II.** First-choice therapies for endemic and other mycoses

| Fungal infection | First-choice therapy |
|---|---|
| Blastomycosis | |
| Life-threatening and CNS | Amphotericin-B (1 mg/kg/day) |
| Mild or moderate | Itraconazole (≥200 mg/day) |
| Histoplasmosis | |
| Life-threatening and CNS | Amphotericin-B (1 mg/kg/day) |
| Mild or moderate | Itraconazole (≥200 mg/day) |
| Maintenance therapy in immunocompromised | Itraconazole (400 mg/day) |
| *Histoplasma duboisii* infection | Itraconazole (100-400 mg/day) |
| Paracoccidioidomycosis | Itraconazole (≥ 100 mg/day) |
| Coccidioidomycosis | |
| Life-threatening | Amphotericin-B (1-1.25 mg/kg/day) |
| Mild or moderate | Azoles (400 mg/day) |
| Maintenance therapy in immunocompromised | Azoles at recommended dose |
| Immunocompetent and non-meningeal | Itraconazole (400 mg/day; >1 year) |
| Immunocompetent and meningeal | Fluconazole (≥400 mg/day; life) or itraconazole (400 mg/day; life) |
| *Penicillium marneffei* | Amphotericin-B (≥0.6 mg/kg/day) then itraconazole (≥200 mg/day) |
| Sporotrichosis | |
| Lymphocutaneous | Itraconazole (200 mg/day) |
| Visceral | Itraconazole (400 mg/day) |
| Severe disseminated | Amphotericin-B (1 mg/kg/day) |
| Chromoblastomycosis | Itraconazole (100-200 mg/day) |

**CNS** = central nervous system.

first-line treatment for infections caused by *Histoplasma duboisii*.[56]

Itraconazole capsules (≥200 mg/day for up to 6 months) are the treatment of choice for paracoccidioidomycosis and ketoconazole or amphotericin-B are the best alternatives.[56] The most effective therapeutic strategy for coccidioidomycosis in immunocompetent hosts is unclear: amphotericin-B, itraconazole capsules, ketoconazole and fluconazole have all been tested in clinical trials, with similar results.[56,59-61] However, a recent comparison of itraconazole capsules 400 mg/day with fluconazole 400 mg/day suggested that itraconazole may be more effective in the treatment of progressive nonmeningeal coccidioidomycosis, particularly skeletal infections.[62] In immunocompromised patients, amphotericin-B may be the first choice for treatment of coccidioidomycosis, although the potential benefit of itraconazole has not been tested.[56] In diffuse interstitial pneumonia, amphotericin-B is the most effective treatment, and in coccidioidal meningitis high dose fluconazole (400 to 1000 mg/day) has been recommended,[63] although itraconazole 400 mg/day may be as effective.[64]

In general, initial treatment with itraconazole capsules or amphotericin-B followed by itraconazole capsules are the recommended treatments for other rare endemic mycoses (table II).

### 3.2 Aspergillosis and Deep Candidiasis

The most frequently encountered systemic fungal infections of immunocompromised patients are those caused by species of *Candida* or *Aspergillus*. The various formulations of amphotericin-B and itraconazole are the most effective antifungal agents for the treatment and prevention of these systemic infections (table III). Fluconazole is effective only for the management of infections by susceptible species of *Candida*, such as *C. albicans*, and *C. parapsilosis*.

#### *3.2.1 Chemoprophylaxis*

Prophylaxis of systemic fungal infections is usually given when patients are considered to be at a particular risk of infection – for example, bone marrow transplant recipients. In addition, preemptive therapy is frequently given; this is antifungal prophylaxis in patients who have some evidence of infection but who do not meet the usual criteria for definitive diagnosis or for initiating empirical therapy.

Because of its poor oral absorption, amphotericin-B is an ineffective prophylactic agent for systemic fungal infection. The use of low dose IV amphotericin-B (<1 mg/kg/day) is associated with breakthrough infections,[65,66] and infusion-related adverse events and renal toxicity restrict the use of higher doses of amphotericin-B.

The superior safety profiles of the triazole antifungals have made them the most widely used drugs in the prophylaxis of systemic fungal infec-

**Table III.** Management options for systemic fungal infections

| Approach | Options |
|---|---|
| Prophylaxis[a] | Itraconazole oral solution (5 mg/kg/day) |
| | Fluconazole capsules (50-400 mg/day) |
| Empirical treatment | Conventional amphotericin-B (0.6-1 mg/kg/day for 14 days or until resolution of symptoms) |
| | Amphotericin-B-liposomal (3 mg/kg/day for 14 days or until resolution of symptoms) |
| | ABLC (5 mg/kg/day for 14 days or until resolution of symptoms) |
| | ABCD (4 mg/kg/day for 14 days or until resolution of symptoms) |
| | IV itraconazole (400 mg/day for 2 days followed by 200 mg/day for 14 days or until resolution of symptoms) |
| Confirmed candidiasis | IV fluconazole (400 mg/day) for 3-7 days followed by capsules (400 mg/day until resolution of symptoms)[c] |
| | Conventional amphotericin-B (0.6-1 mg/kg/day until resolution of symptoms) |
| | ABLC (5 mg/kg/day until resolution of symptoms) |
| | IV itraconazole (400 mg/day until resolution of symptoms)[b] |
| Confirmed aspergillosis | Oral itraconazole (400 mg/day for 14 days or more) |
| | Conventional amphotericin-B (1-1.5 mg/kg/day for at least 14 days or until recovery of granulocytes and resolution of symptoms) |
| | Amphotericin-B-liposomal (3 mg/kg/day for at least 14 days or until recovery of granulocytes and resolution of symptoms) |
| | ABLC (5 mg/kg/day for at least 14 days or until recovery of granulocytes and resolution of symptoms) |
| | ABCD (4 mg/kg/day for at least 14 days or until recovery of granulocytes and resolution of symptoms) |
| | IV itraconazole (400 mg/day for 2 days followed by 200 mg/day for at least 14 days or until recovery of granulocytes and resolution of symptoms) |

a Value only established in selected patient groups (bone marrow transplant patients, high risk liver transplant patients, selected high risk neutropenic patients with haematological malignancy, and those with previously documented invasive *Aspergillus* or other mould infection who are undergoing further courses of chemotherapy).

b No clinical data.

c Only for infections by *Candida* spp. shown to be susceptible to fluconazole.

**ABLC** = amphotericin-B-lipid-complex; **ABCD** = amphotericin-B-colloidal dispersion; **IV** = intravenous.

tions. Prophylaxis often requires long term antifungal administration and the ease of use of oral formulations makes them a preferred option. However, some patients at high risk have severely impaired swallowing or are unconscious or intubated and can only be given intravenous agents.

The high oral bioavailability of fluconazole and its availability in intravenous and oral formulations have led to the widespread use of this agent. Fluconazole has been shown to reduce the incidence of systemic *C. albicans* infections,[67,68] but it may be less effective in some high-risk patient groups, such as patients with acute leukaemia undergoing remission-induction therapy or intensive rescue therapy.[69,70] The most important weakness of fluconazole as a prophylactic agent is its narrow spectrum of activity; in some trials the predominance of *Aspergillus* infections in fluconazole-treated patients has highlighted this weakness.[71] Similarly, fluconazole does not offer protection against non-*albicans Candida* infections; a concern surrounding the prophylactic use of fluconazole is the potential increase in fluconazole-resistant *Candida* spp. and increased colonisation by *C. krusei* and *C. glabrata*.[72-75]

The broad spectrum of activity and good safety profile of itraconazole make it an attractive choice for chemoprophylaxis. The capsule formulation is successful in preventing systemic fungal infections[76-78] and at a dosage of 200 mg/day is as effective as fluconazole (100 mg/day).[79] The absorption of the itraconazole capsule formulation may be variable in patients with damage to the intestinal epithelium or with reduced gastric acid-

ity.[80,81] An itraconazole oral solution, with its enhanced bioavailability, has overcome the limitations of the capsule formulation and is effective in the prophylaxis of systemic fungal infections in neutropenic patients.[82-85] In a placebo-controlled trial, itraconazole oral solution reduced the number of cases of invasive candidiasis but had no effect on the incidence of invasive aspergillosis.[86] However, in a comparative trial with oral fluconazole, itraconazole oral solution reduced the number of cases of aspergillosis.[87]

Clearly, many patients at risk of systemic fungal infections are receiving co-medications. Because the azole antifungals are metabolised by CYP3A, they can interact with other drugs metabolised by this enzyme. In solid organ transplant or bone marrow transplant recipients, the interaction between azoles and cyclosporin is the most significant,[88,89] but elevated plasma concentrations of cyclosporin can be managed by routine monitoring and reducing the dosage as necessary. In patients with HIV infection, itraconazole may interact with protease inhibitors (by inhibiting CYP3A)[90] and fluconazole may interact with the HIV reverse transcriptase inhibitor zidovudine (by inhibiting glucuronidation).[89,91,92] As with the co-administration of cyclosporin, blood concentration monitoring and dosage reduction may be advisable when azoles and some anti-HIV drugs are used concurrently. In patients with HIV, the HIV protease inhibitor saquinavir has low bioavailability, and it has been suggested that the addition of itraconazole may increase saquinavir plasma concentrations and ultimately improve anti-HIV efficacy.[93]

#### 3.2.2 Empirical Treatment

Empirical treatment is usually initiated in immunocompromised patients with persistent fever of unknown origin (4 to 7 days) that is unresponsive to broad spectrum antibiotics or when pulmonary infiltrates or cavities are detected by computed tomography (CT) scan.

Amphotericin-B has been the first-choice treatment for systemic fungal infections for several years. A significant benefit (reduced death rate from fungal infection and a decrease in clinically documented infection) is seen in patients receiving IV amphotericin-B.[94] The broad spectrum of activity of amphotericin-B has been the key to its success in empirical therapy, but the use of higher doses – which could be more effective – is prevented by infusion-related adverse events (nausea, fever and chills) and renal toxicity.

The triazole antifungal agents are the best alternative to amphotericin-B for empirical therapy. However, there have been no large-scale clinical trials comparing triazoles with amphotericin-B for empirical therapy. Both fluconazole and itraconazole capsules have shown equivalence to amphotericin-B in small-scale clinical trials,[95,96] although fluconazole is useful only in the treatment of confirmed deep candidiasis, and even then only when the isolate is shown to be susceptible to fluconazole. Confirmed aspergillosis has been treated with success with high doses of IV amphotericin-B[97,98] or oral itraconazole.[99,100] A combination of amphotericin-B and itraconazole capsules may improve outcomes and has been suggested as an alternative treatment strategy for aspergillosis,[101] despite some previous evidence of antagonism between these agents in animal studies.[102]

Many patients who require empirical therapy have already received antifungal prophylaxis. Until recently, empirical therapy with amphotericin-B was usually initiated if prophylaxis with azole antifungals failed; however, after failure of prophylaxis with an azole, empirical therapy with another azole or even a different formulation of the same azole may be at least as effective as using amphotericin-B. This has not been confirmed in clinical trials, but a recent report indicated that patients receiving previous prophylaxis (primarily fluconazole) benefited more from empirical therapy with itraconazole than with amphotericin-B.[103]

#### 3.2.3 Advances in the Management of Systemic Fungal Infections

Despite the wide choice of antifungal agents available, death rates from systemic fungal infections are unacceptably high and improvements in management are still sought.

Several improvements in the diagnosis of systemic fungal infections have been made. Antigen detection methods for endemic fungal infections, such as histoplasmosis, have been developed; more recently, a double-sandwich enzyme-linked immunosorbent assay (ELISA) has been developed for detecting invasive *Aspergillus* infections. The sensitivity and specificity of the test were 92.6% and 95.4%, respectively, based on 71 autopsy-controlled patients.[104] The early use of CT scanning of the chest is also useful for the diagnosis of aspergillosis. The appearance of the distinctive 'halo' sign and later the 'air-crescent' sign on CT images can be highly suggestive of aspergillosis (or other fungal infections).[105] Other new diagnostic tools include biochemical methods and molecular biological techniques, such as polymerase chain reaction (PCR).[106] These tools may help to improve the diagnosis of fungal infections and thus the outcome of treatment; one group has reported reduced mortality among patients with aspergillosis when early CT scanning and antigen detection were used.[107]

Recent developments in antifungal therapy have produced useful re-formulations of the existing antifungal agents, including the lipid-associated formulations of amphotericin-B and cyclodextrin-associated formulations of itraconazole. In general, these formulations have been tested for the treatment of deep candidiasis and aspergillosis but not for the treatment of endemic mycoses.

Three lipid-associated formulations of amphotericin-B have been developed: amphotericin-B-liposomal, amphotericin-B-lipid-complex (ABLC) and amphotericin-B-colloidal dispersion (ABCD). These formulations are available for IV use and reduce the toxicity associated with amphotericin-B.

Amphotericin-B-liposomal (3 mg/kg/day) has efficacy equivalent to that of conventional amphotericin-B (1 mg/kg/day) and reduced toxicity.[108,109] Nephrotoxicity was significantly lower with amphotericin-B-liposomal (19%) than with conventional amphotericin-B (34%), but discontinuations because of toxic effects or lack of efficacy were similar between formulations.[109]

ABLC may also be effective for the treatment of confirmed or suspected systemic fungal infections and is generally well tolerated, except for infusion-related adverse events;[110,111] however, a high incidence of renal toxicity has been reported with ABLC.[112] This formulation has not been compared with conventional amphotericin-B in a randomised, double-blind trial, but, in a retrospective analysis, amphotericin-B-liposomal 1.9 mg/kg/day and ABLC 4.8 mg/kg/day were equally effective in treating systemic fungal infections and had similar safety profiles.[113]

Empirical therapy with ABCD 4 mg/kg/day and empirical therapy with conventional amphotericin-B 0.8 mg/kg/day were compared in a double-blind trial.[114] The results indicated that ABCD was as effective as conventional amphotericin-B, and was associated with less severe nephrotoxicity but more frequent infusion-related adverse events.

The use of the lipid-associated formulations of amphotericin-B is restricted by their high acquisition costs.[115-117] Although the costs of treating adverse events are lower with these formulations than with conventional amphotericin-B, it is not clear how significant these savings are.

Two new formulations of itraconazole have been developed using the solubilising excipient hydroxypropyl-β-cyclodextrin. The itraconazole oral solution has reliable oral bioavailability in healthy individuals and in a variety of patient groups at risk of systemic fungal infections (see De Beule and Van Gestel[15]). In clinical trials comparing itraconazole oral solution with oral amphotericin-B or fluconazole suspension as prophylaxis in neutropenic patients, fewer superficial fungal infections, proven deep fungal infections, cases of aspergillosis and deaths with proven deep fungal infection were observed in the itraconazole oral solution groups.[87,118]

A new IV itraconazole formulation has also been developed, which provides an alternative formulation for those patients who cannot take oral medications. In addition, this IV itraconazole formulation achieves therapeutic plasma concentrations less than 48 hours after starting treatment,[119]

a feature that is of particular importance in the treatment of systemic fungal infections (suspected or confirmed). In a recent clinical trial, the IV itraconazole formulation (with subsequent therapy with itraconazole oral solution) was at least as effective as conventional amphotericin-B in the empirical treatment of systemic fungal infections and caused significantly fewer adverse events.[103] The IV itraconazole formulation may also be effective for first- or second-line treatment of invasive aspergillosis in a variety of patients, such as patients with AIDS, haematological malignancy or chronic granulomatous disease.[120] Unlike the lipid-associated formulations of amphotericin-B, the use of the new itraconazole formulations is cost effective.[121]

## 4. Conclusion

The increasing number of antifungal agents, reformulations of existing agents and novel treatment strategies have all improved the management of fungal infections in recent years. Although high cure rates can be achieved in the treatment of many superficial infections, systemic fungal infections are still associated with high mortality. For several years, amphotericin-B was the most effective agent for the treatment and prevention of systemic fungal infections. However, the introduction of the triazoles – fluconazole and itraconazole – has challenged amphotericin-B as the gold standard. In particular, the triazoles have become the agents of choice in chemoprophylaxis; fluconazole has been widely used but the introduction of an itraconazole oral solution offers an agent with high bioavailability and a broader spectrum of activity than that of fluconazole. In the empirical treatment of systemic fungal infections, the lipid-associated formulations of amphotericin-B and the itraconazole IV formulation are at least as effective as conventional amphotericin-B and are less toxic. The high cost of lipid-associated formulations of amphotericin-B may make their use prohibitively expensive.

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