Chapter

20

ANTIFUNGAL THERAPY

POLYENES

AMPHOTERICIN B

- Amphotericin B is a polyene antifungal drug that is both fungistatic and fungicidal depending on the concentration at the infection site and the susceptibility of the pathogen. It acts by binding to sterols, primarily ergosterol in the fungal cell membrane of susceptible fungi with a resultant change in membrane permeability which allows leakage of intracellular components.
- It has a broad spectrum of activity which includes the following: *Candida* species, including *C. albicans, C. parapsilosis, C. tropicalis, C. krusei, C. glabrata, Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces*, *Aspergillus fumigatus*, *Sporothrix schenckii*, and zygomycetes. In vitro resistance has been reported in *Candida lusitaniae*, *Pseudoallescheria boydii* (*Scedosporium* spp.) and *Fusarium* spp. The IV form is registered for the treatment of life-threatening infections such as albicans and non-albicans candidaemia, cryptococcosis and mucormycosis.
- Side effects with amphotericin B are common and include chills, fever, vomiting, pain, nephrotoxicity and anaemia. It is worth noting that the ESCMID guideline for the diagnosis and management of *Candida* diseases does not recommend amphotericin B deoxycholate for any indication due to severe side effects.

AMPHOTERICIN B IS AVAILABLE AS:

IV AMPHOTERICIN B DEOXYCHOLATE (FUNGIZONE®)

Intravenous infusions are prepared by combining amphotericin B with five percent dextrose in water at a final concentration of 0.1 mg/mL. Although the incidence of acute hypersensitivity reactions from amphotericin B is extremely rare, a test dose of 1 mg is administered and this is followed by the remainder of the dose if no apparent reaction occurs within 30 minutes. Infusion times are traditionally over four to six hours, but may be given over 24 hours. The dose is 0.5–1.0 mg/kg/day.

IV LIPOSOMAL AMPHOTHERICIN B (AMBISOME®)

The liposomal technology utilised in AmBisome® has been associated with improved response rates and decreased mortality in the treatment of invasive fungal infections in neutropaenic patients over amphotericin B deoxycholate. Liposomal amphothericin B is well established therapy for a number of proven or suspected invasive fungal infections. Its safety is supported by data in a range of patient populations, including children and neonates. AmBisome® is registered for the treatment of symptomatic and/or deep mycoses in adults and children in whom toxicity (particularly nephrotoxicity) precludes the use of conventional deoxycholate amphotericin B, and for the empirical treatment of presumed fungal infection in febrile neutropaenic adults and children unresponsive to antibacterial treatment. The dose of AmBisome® is 3–5 mg/kg per day.

AMPHOTERICIN B LOZENGES (FUNGIZONE®)

These are registered for the treatment of thrush in oral and perioral areas, non-specific oral infections, complicated candida-denture stomatitis, angular cheilitis and antibiotic stomatitis. The lozenges are not systemically absorbed.

NYSTATIN (CANDACIDE®, CANSTAT®)

This is a topical polyene antifungal used for the treatment of oral candidiasis and vaginal yeast infection during pregnancy. It is only available for topical application.

NATAMYCIN (NATACYN®)

It is the therapy of choice for keratitis due to filamentous fungi. It is only available for topical application.

AZOLES

There are two subclasses of azoles – the imidazoles and the triazoles.

IMIDAZOLES

Imidazole antifungals are active against a variety of different fungi, including yeasts, especially *C. albicans*, and dermatophytes, including *Trichophyton* spp., *Epidermophyton* spp., and *Microsporum* spp. Most of the imidazoles available in South Africa are topical agents (creams, lotions, shampoos, powders, vaginal tablets) and have few side effects. These are still widely used for superficial mycoses, including tinea corporis, tinea pedis, tinea crusis, and vaginal candidiasis. Those available in South Africa include:

- Clotrimazole (Canesten®)
- Miconazole (Daktarin®)
- Econazole (Pervaryl®)
- Tioconazole (Trosyd®)
- Ketoconazole – oral ketoconazole (Ketazol®) is an imidazole that has potential hepatotoxicity and endocrine effects and is poorly absorbed in the absence of gastric acidity. The newer triazole antifungals have proven to be more effective than oral ketoconazole, and hence its use is limited to the treatment of tinea versicolor.
- Ketoconazole is also available in topical formulations (Nizshampoo®, Nizcreme®).
- Miconazole is the only imidazole available in an intravenous form – its use is obsolete except for the treatment of *Pseudoallescheria boydii* (also known as *Scedosporium* spp.) infection.

TRIAZOLES

FLUCONAZOLE (DIFLUCAN®)

Fluconazole, a triazole antifungal, is well absorbed after oral administration with more than 90% bioavailability. The long plasma elimination half-life (approximately 30 hours) provides the basis for once daily dosing in the treatment of systemic infections and a single dose therapy for vaginal candidiasis. Fluconazole is indicated in systemic and oropharyngeal candidiasis, and the prevention of fungal infections in patients with malignancy who are at risk as a result of chemotherapy and radiotherapy.

Fluconazole has no activity against *Aspergillus* spp., and resistance particularly in *Candida kruseii* and *Candida glabrata*, is common. Fluconazole is available in capsules, IV infusion and as a dry powder for reconstitution to produce an oral suspension.

ITRACONAZOLE (SPORANOX®)

Itraconazole, which is only available orally, has good activity against yeasts and moulds such as *Aspergillus, Sporothrix* and the dermatophytes.

VORICONAZOLE (VFEND®)

Voriconazole is a broad spectrum, triazole antifungal agent indicated for the treatment of invasive aspergillosis, treatment of infections caused by *Candida* spp. (including *Candida krusei* and *Candida glabrata*) refractory to fluconazole therapy, *Scedosporium* spp. and *Fusarium* spp. Voriconazole also has in vitro susceptibility against *Cryptococcus neoformas*, *Histoplasma capsulation* and *Blastomyces dermatitidis*. Voriconazole is also indicated for the prevention of breakthrough fungal infections in febrile high-risk patients. Voriconazole is available as a powder for infusion (requires reconstitution and dilution) and as oral film-coated tablets. Due to its complex pharmacokinetic properties, therapeutic drug monitoring is recommended to optimise antifungal therapy, where available.

POSACONAZOLE (NOXAFIL®)

Posaconazole is a new triazole which is currently only available as an oral suspension. An IV formulation will be available soon. It has a similar spectrum of activity as voriconazole, but in addition also has activity against the zygomycetes. Posaconazole is currently registered as prophylaxis in patients with acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS), for the treatment of oral *Candida* infections, and as salvage therapy for aspergillosis, mucormycosis and cryptococcal infections.

ECHINOCANDINS

The echinocandins inhibit the synthesis of ß (1,3)–D-glucan, an essential component of the cell wall of many filamentous fungi and yeasts. ß (1,3)–D-glucan is not present in mammalian cells. The echinocandins have in vitro activity against *Aspergillus* and *Candida* species, including those that are azole-resistant. *Candida lusitaniae*, usually resistant to amphotericin B, is susceptible to the echinocandins. In vitro MICs of the echinocandins for *Candida parapsilosis* and *Candida guilliermondii* appear to be significantly higher than for the other *Candida* spp. and thus these agents are probably not indicated for the treatment of these two *Candida* species. Other fungi, such as zygomycetes, *Cryptococcus neoformans* and *Fusarium* are poorly inhibited by the echinocandins in vitro.

The echinocandins are available only in intravenous formulations, and owing to their long half-lives, can be administered once daily.

CASPOFUNGIN (CANCIDAS®)

Caspofungin is indicated for the treatment of:

- Invasive candidiasis including candidaemia.
- Oesophageal candidiasis where IV antifungal therapy is appropriate.
- Oropharyngeal candidiasis where IV antifungal therapy is appropriate.
- Invasive aspergillosis, particularly in patients who are refractory to, or intolerant of other therapies, including amphothericin B, lipid formulations of amphothericin B and itraconazole. A single 70 mg loading dose is administered on day one, followed by 50 mg once daily thereafter.

MICAFUNGIN (MYCAMINE®)

Micafungin is registered for the following indications:

- Treatment of invasive candidiasis.
- Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate.
- Prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients expected to have neutropenia (absolute neutrophil count of < 500 cells/μl) for 10 days or more.
- The dose of micafungin is 100 mg daily, with no loading dose needed, for the treatment of candidiasis. The dose for treating oesophageal candidiasis is 150 mg daily, and for prophylaxis is 50 mg daily.

ANIDULAFUNGIN (ERAXIS®)

Anidulafungin is registered for the following indications:

- Treatment of invasive candidiasis including candidemia.
- Treatment of oesophageal candidiasis where IV therapy is appropriate.
- For candidiasis, the dose of anidulafungin is 200 mg on day one as a loading dose, followed by 100 mg daily. A loading dose of 100 mg on day one, followed by 50 mg daily thereafter is appropriate for treatment of oesophageal candidiasis.

OTHER ANTIFUNGAL AGENTS

TERBINAFINE (LAMISIL®)

This antifungal can be given orally for the treatment of tinea (ringworm) involving the hands, feet and nails (preferred to griseofulvin). Side effects are uncommon (gastrointestinal and skin reactions). The optimal clinical effect may only be observed some weeks after completion of therapy. A topical preparation is also available for cutaneous infections. Topical terbinafine is effective against tinea versicolor whereas the oral formulation is not.

AMOROLFINE (LOCERYL®)

This topical compound has been used with reasonable success in the treatment of onychomycosis. Although it is not as effective as terbinafine, it has excellent patient compliance, tolerability and safety.

GRISEOFULVIN (MICROCIDAL®)

Griseofulvin at 10 mg/kg/day with food to a maximum of one gram daily in three divided doses continued for 12 to 18 months, has in the past been used for difficult dermatophyte infections involving the hair shaft, feet and nails.

Potential teratogenicity and other adverse effects (e.g. reduction in effectiveness of oral contraceptives, photosensitivity, neurological problems) and the availability of other effective drugs now limit its use.

FLUCYTOSINE

Flucytosine is seldom used alone because of the risk of emergence of resistance during monotherapy. It is usually combined with amphotericin B to treat invasive *Candida* and *Cryptococcus* infections. It is not readily available in South Africa. The usual dose is 100–150 mg/kg/day in four divided doses.