Chapter 21

TREATMENT OF COMMON FUNGAL INFECTIONS

ASPERGILLOSIS

Aspergillus spp. have emerged as an important cause of life-threatening infections in immunocompromised patients, including those with prolonged neutropenia, advanced HIV infection, primary immunodeficiency and patients who have undergone haematopoietic stem cell transplantation or lung transplantation. Three forms of aspergillosis exist: invasive aspergillosis, chronic (saprophytic) aspergillosis, and allergic forms of aspergillosis.

INVASIVE ASPERGILLOSIS

Invasive aspergillosis includes invasive pulmonary aspergillosis, invasive sinonasal aspergillosis, disseminated aspergillosis, and single-organ invasive aspergillosis.

Primary treatment for invasive aspergillosis in most patients is voriconazole (IV or oral) which has been shown to be superior to amphotericin B. For seriously ill patients, the IV formulation is recommended.

Surgical resection of the infected focus should be considered in the following conditions: pulmonary lesions contiguous with the heart or great vessels, invasion of the chest wall, osteomyelitis, pericardial infection and endocarditis.

TREATMENT: INVASIVE ASPERGILLOSIS

TREATMENT OF CHOICE

Voriconazole 6 mg/kg IV 12 hourly on day 1, then 4 mg/kg IV 12 hourly

Switch to oral voriconazole when the patient can take oral medication. Voriconazole dose is 200–300 mg PO 12 hourly

SALVAGE OR POORLY RESPONSIVE

Lipid formulations of amphotericin B OR itraconazole OR posaconazole OR caspofungin

TREATMENT DURATION

The duration of antifungal therapy is dependent upon the location of the infection, the patient's underlying disease, the need for further immunosuppression and response to therapy. Antifungal therapy is generally continued until all signs and symptoms of the infection have resolved. The minimum duration of therapy is 6–12 weeks.

CHRONIC (SAPROPHYTIC) ASPERGILLOSIS

Chronic aspergillosis includes *Aspergillus* otomycosis and pulmonary aspergilloma.

- Single pulmonary aspergillomas may be best managed by surgical resection of the cavity and removal of the fungal ball, whereas chronic cavitatory and chronic necrotising pulmonary aspergillosis requires long-term antifungal therapy with voriconazole, itraconazole or posaconazole. When antifungal therapy is given, it should be continued for 3–6 months following resolution of all associated symptoms and normalisation of the x-rays or CT scans taken at the onset of therapy.
- Topical therapy with irrigating solutions of acetic acid or boric acid, with a topical antifungal agent may be effective in eradicating *Aspergillus* otomycosis.

ALLERGIC FORMS OF ASPERGILLOSIS

Allergic forms of aspergillosis includes allergic *Aspergillus* sinusitis and allergic bronchopulmonary aspergillosis.

TREATMENT: ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Adults: Itraconazole 200 mg PO 8 hourly for 3 days followed by 200 mg PO 12 hourly for 3–6 months

Children: Itraconazole 5 mg/kg PO once daily

AND

Oral corticosteroids

TREATMENT: ALLERGIC ASPERGILLUS SINUSITIS

Itraconazole **AND** nasal or systemic corticosteroids

Endoscopic drainage in patients who have obstructive symptoms

CANDIDIASIS

Although *Candida albicans* is the most common *Candida* spp. involved in all of the clinical syndromes, any of the *Candida* species can cause clinical infections. The major importance of identifying the infecting *Candida* spp., especially for invasive candidiasis, is that certain species e.g. *Candida glabrata*, *Candida krusei* and *Candida auris* are more resistant to the azole antifungal agents.

ORAL CANDIDIASIS (THRUSH)

Oral candidiasis is a common infection seen in infants, older adults who wear dentures, patients treated with antibiotics, patients receiving chemotherapy or radiation therapy to the head and neck and those with cellular immune deficiencies.

TREATMENT: ORAL CANDIDIASIS

MILD ORAL CANDIDIASIS

Clotrimazole troches at doses 10 mg 5 times daily

OR

Nystatin suspension at a concentration of 100 000 U/mL: 4–6 mL 4 times daily

MODERATE TO SEVERE ORAL CANDIDIASIS AND FOR HIV-INFECTED PATIENTS

Fluconazole 150 mg (3 mg/kg) PO daily

FLUCONAZOLE-REFRACTORY DISEASE

Itraconazole solution 200 mg PO daily OR

Posaconazole suspension 400 mg PO 12 hourly for 3 days, then 400 mg daily

Treat for 7–14 days

OESOPHAGEAL CANDIDIASIS

Oesophageal candidiasis is most common in HIV-infected patients as well as occurring in patients with haematological malignancies. Systemic antifungal therapy is always required.

TREATMENT: OESOPHAGEAL CANDIDIASIS

Fluconazole 200–400 mg (3–6 mg/kg) PO/IV daily

OR

An echinocandin: caspofungin 50 mg IV daily or micafungin 150 mg IV daily

OR

Amphotericin B deoxycholate 0.6–1 mg/kg IV daily

Treat for 14–21 days. For HIV-infected patients, antiretroviral therapy should be prescribed

TREATMENT: SUPPRESSIVE THERAPY POST OESOPHAGEAL CANDIDIASIS TREATMENT

Fluconazole 200 mg 3 times a week PO until the CD4 count is > 200 cells/μl in HIV-infected patients

VULVOVAGINAL CANDIDIASIS

TREATMENT: UNCOMPLICATED VULVOVAGINAL CANDIDIASIS IN NON-PREGNANT WOMEN

TOPICAL IMIDAZOLES

Several topical antifungal agents are effective with no agent clearly superior e.g.

Clotrimazole 1 single 500 mg vaginal pessary

OR

Clotrimazole 2 x 100 mg vaginal pessary nocte for 3 nights

OR

Clotrimazole 2% vaginal cream nocte for 6 nights

Alternative topical preparations: miconazole, econazole, miconazole, tioconazole and terconazole

ORAL TREATMENT

Fluconazole 150 mg PO as a single dose

OR

Itraconazole 200 mg PO 12 hourly x 2 doses

TREATMENT: VULVOVAGINAL CANDIDIASIS IN PREGNANT WOMEN

Only topical imidazole therapies (clotrimazole, miconazole, tioconazole or econazole) should be used to treat pregnant women.

Treat for 7 days

Oral azole antifungal agents should not be used during pregnancy

Recurrent infection

Four or more episodes of symptomatic vulvovaginal candidiasis within 1 year:

Clotrimazole 500 mg vaginal pessary intravaginally weekly for 6 months

OR

Fluconazole 150 mg PO daily for 10–14 days followed by fluconazole 150 mg given once per week for 6 months

A swab should be taken from symptomatic sexual partners (usually balanitis in the uncircumcised male) and treated if infection is present.

TREATMENT OF CANDIDA GLABRATA VULVOVAGINAL CANDIDIASIS

Candida glabrata is relatively resistant to the azoles, and the failure rate of treatment with these agents is high.

Intravaginal flucytosine cream 5 g nocte for 2 weeks is the agent of choice. 5-flucytosine is only available as a section 21 agent in South Africa and the vaginal cream has to be prepared by a pharmacist.

Intravaginal boric acid capsules 600 mg nocte for 2 weeks. This agent is not available commercially and has to be prepared by a pharmacist. The response rate to this treatment is reported as 70%.

CANDIDAEMIA IN NON-NEUTROPENIC AND NEUTROPENIC PATIENTS

Empiric antifungal therapy should be considered for critically ill patients with risk factors for invasive candidiasis and no other known cause of fever.

RISK FACTORS INCLUDE

- Use of broad-spectrum antibiotics
- Central venous catheters
- Parenteral nutrition
- Neutropenia
- Prosthetic devices
- Immunosuppressive therapy (e.g. chemotherapy, glucocorticosteroids)
- Tertiary peritonitis
- Chronic pancreatitis

An echinocandin is recommended for empiric therapy, particularly for neutropenic patients, those with recent azole exposure and those with severe illness. Subsequent antifungal therapy should be based on the *Candida* species isolated and its antifungal susceptibility. Fundoscopic examination of all patients with candidaemia is required to exclude ophthalmic involvement. Intravascular catheter removal is strongly recommended. Replace catheters at a new site. For patients with septic thrombophlebitis, catheter removal and incision and drainage or resection of the infected vein is recommended.

TREATMENT: CANDIDAEMIA

EMPIRIC ANTIFUNGAL THERAPY FOR NON-NEUTROPENIC PATIENTS

Caspofungin – loading dose of 70 mg IV, then 50 mg IV daily

OR

Micafungin 100 mg IV daily

OR

Anidulafungin: loading dose of 200 mg IV, then 100 mg IV daily

Alternative agents include:

Amphotericin B deoxycholate 0.5–1 mg/kg/day IV

OR

Liposomal amphotericin B 3–5 mg/kg/day IV

OR

Fluconazole – loading dose of 800 mg IV (12 mg/kg), then 400 mg IV (6 mg/kg) daily (for mild to moderate illness and no prior azole exposure)

OR

Voriconazole 400 mg (6 mg/kg) 12 hourly for 2 doses and then 200 mg (3 mg/kg) 12 hourly (for mild to moderate illness and no prior azole exposure)

EMPIRIC ANTIFUNGAL THERAPY FOR NEUTROPENIC PATIENTS

Caspofungin – loading dose of 70 mg IV, then 50 mg IV daily

OR

Micafungin 100 mg IV daily

OR

Anidulafungin – loading dose of 200 mg IV, then 100 mg IV daily

Alternative agents include:

Amphotericin B deoxycholate 0.5–1 mg/kg/day IV

OR

Liposomal amphotericin B 3–5 mg/kg/day

The recommended duration of therapy for candidaemia is 2 weeks after documented clearance of *Candida* from the bloodstream (i.e. 2 weeks from the first negative blood culture).

Duration should be extended for 4–6 weeks for eye involvement.

CENTRAL NERVOUS SYSTEM CANDIDIASIS

CNS *Candida* infections in adults can occur as a manifestation of disseminated candidiasis, or as a complication of a neurosurgical procedure, e.g. CSF shunt placement. Although there are no reports of the use of voriconazole which achieves excellent levels in CSF, its use currently is limited to *Candida glabrata* or *Candida krusei* meningitis following initial treatment with liposomal amphotericin B. Removal of infected intraventricular devices is recommended.

TREATMENT: CNS CANDIDIASIS

Amphotericin B deoxycholate 0.5–1 mg/kg/day IV or liposomal amphotericin B 3–5 mg/kg/day

AND

Flucytosine 25 mg/kg PO 6 hourly is recommended for the initial several weeks of treatment

FOLLOWED BY (after the patient has responded to initial treatment)

Fluconazole 400–800 mg (6–12 mg/kg) PO or IV daily (given until signs and symptoms, CSF abnormalities and radiological abnormalities have resolved)

CANDIDA ENDOPHTHALMITIS

Candida endophthalmitis can develop exogenously following trauma or surgery to the eye or endogenously through haematogenous seeding of the retina and choroid as a complication of candidaemia. *Candida* endophthalmitis/chorioretinitis occurs in approximately 10% of patients with candidaemia thus ophthalmological assessment is required in all patients with candidaemia. Refer to the chapter, 'Infections of the eye' for treatment recommendations.

CANDIDA NATIVE OR PROSTHETIC VALVE ENDOCARDITIS

Candida endocarditis results from candidaemia and is usually seen in patients with prosthetic heart valves, in intravenous drug users and in patients who have indwelling central venous catheters. Valve replacement is recommended, particularly with prosthetic valves.

TREATMENT: CANDIDA NATIVE OR PROSTHETIC VALVE ENDOCARDITIS

Amphotericin B deoxycholate 0.6–1 mg/kg IV daily

OR

Liposomal amphotericin B 3–5 mg/kg IV daily **AND** flucytosine 25 mg/kg PO 6 hourly

OR

Caspofungin 50–150 mg/day IV

OR

Micafungin 100-150 mg/day IV

OR

Anidulafungin 100–200 mg/day IV

OR

If the *Candida* is susceptible to fluconazole (provided the patient is stable and blood cultures are negative):

Fluconazole 400–800 mg (6–12 mg/kg) PO daily

Treat for at least 6 weeks after valve replacement

LONG TERM SUPPRESSION: PATIENTS WHO DO NOT HAVE THE AFFECTED VALVE(S) REPLACED

Fluconazole 400–800 mg PO daily

OSTEOARTICULAR CANDIDA INFECTIONS

Candida spp. infect bones and joints as a result of either haematogenous seeding or exogenous inoculation during trauma, intra-articular injection, a surgical procedure, or injection drug use. Treat osteomyelitis for a total of six to 12 months, septic arthritis for a minimum of six weeks.

Surgical debridement is essential with septic arthritis and removal of hardware where possible is recommended. If hardware is retained then indefinite treatment is recommended.

TREATMENT: CANDIDA OSTEOMYELITIS, SEPTIC ARTHRITIS AND PROSTHETIC JOINT INFECTIONS

Fluconazole 400 mg (6 mg/kg) IV or PO daily

OR

Amphotericin B deoxycholate 0.5–1 mg/kg/day IV

OR

Liposomal amphotericin B 3–5 mg/kg/day IV

OR

Caspofungin 50 mg IV daily or micafungin 100 mg IV daily or anidulafungin 100 mg IV daily

Use above for several weeks and switch to fluconazole 400 mg PO daily

URINARY CANDIDA INFECTIONS

ASYMPTOMATIC CANDIDURIA

Treatment is not recommended unless the patient belongs to a group at high risk of dissemination.

TREATMENT: ASYMPTOMATIC CANDIDURIA (HIGH RISK GROUPS)

- Neutropenic patients: manage as for candidaemia
- Infants of low birth weight: manage as for candidaemia
- Patients undergoing urological procedures: fluconazole 150–300 mg (3–6 mg/kg) PO daily for several days before and after the procedure

SYMPTOMATIC CANDIDURIA

Amphotericin B bladder irrigation is generally not recommended since there is a high relapse rate, but may be useful for treating fluconazole-resistant *Candida* spp.

TREATMENT: CANDIDA CYSTITIS

- Fluconazole susceptible *Candida*: Fluconazole 150 mg (3 mg/kg) PO daily for 2 weeks
- Fluconazole resistant *Candida*: Amphotericin B deoxycholate 0.3–0.6 mg/kg IV daily for 1–7 days

TREATMENT: PYELONEPHRITIS

- Fluconazole susceptible *Candida*: Fluconazole 150–300 mg (3–6 mg/kg) PO daily for 2 weeks
- Fluconazole-resistant *Candida*: Amphotericin B deoxycholate 0.5–0.7 mg/kg IV daily for 1–7 days
- For fungus balls: surgical removal is strongly recommended

PULMONARY CANDIDIASIS

Candida pneumonia and lung abscesses are extremely uncommon. Rarely after aspiration of oropharyngeal material does a primary *Candida* pneumonia or abscess develop. More commonly, haematogenously disseminated candidiasis produces lesions in the lung. A diagnosis of *Candida* pneumonia required histopathological confirmation. In contrast to pneumonia, colonisation of the airways with *Candida* spp. and/or contamination of the respiratory secretions are extremely common, especially in critically ill patients who receive mechanical ventilation. Due to the rarity of *Candida* pneumonia and the extremely common finding of *Candida* in respiratory secretions and the lack of specificity of this finding, a decision to initiate antifungal therapy should not be made on the basis of respiratory culture results alone and in the majority of patients antifungal therapy is not warranted.

NEONATAL CANDIDIASIS

The primary risk factor is prematurity.

TREATMENT: DISSEMINATED NEONATAL CANDIDIASIS

Amphotericin B deoxycholate 1 mg/kg IV daily

OR

Liposomal amphotericin B 5 mg/kg IV daily

OR

Fluconazole (loading dose of 25 mg/kg IV then 12 mg/kg IV daily) provided no prior azole exposure

The recommended length of therapy is 3 weeks

SALVAGE THERAPY OR RESISTANCE OR TOXICITY TO THE RECOMMENDED AGENTS

Caspofungin: loading dose of 1 mg/kg IV daily x 2 days, followed by maintenance dose of 2 mg/kg IV daily (use with caution)

OR

Voriconazole*: loading dose of 6 mg/kg/dose IV12 hourly x 2 doses followed by maintenance doses of 4 mg/kg/dose IV 12 hourly

* Paediatric dosing has not been well established and the potential for neurotoxicity in neonates should be considered.

CRYPTOCOCCAL INFECTIONS

CRYPTOCOCCOSIS IN HIV-INFECTED INDIVIDUALS (CRYPTOCOCCAEMIA AND/OR MENINGITIS)

Induction therapy should be used for a minimum of two weeks or until the CSF is sterilised before changing to oral fluconazole. Monitoring of CSF pressures and therapeutic taps is an essential component of the treatment of meningitis. Antiretroviral therapy should be delayed for four to six weeks after initiation of cryptococcal meningitis treatment as early treatment significantly increases patient mortality.

TREATMENT: HIV-INFECTED PATIENTS WITH CRYPTOCOCCAEMIA AND/OR MENINGITIS

INDUCTION TREATMENT

Amphotericin B deoxycholate 1 mg/kg IV daily

AND

5-flucytosine 25 mg/kg PO 6 hourly for 2 weeks (available as a section 21 agent in South Africa)

OR

Liposomal amphotericin B IV 3–4 mg/kg IV daily

AND

5-flucytosine 25 mg/kg PO 6 hourly for 2 weeks (available as a section 21 agent in South Africa)

INDUCTION TREATMENT (IF 5-FLUCYTOSINE IS NOT AVAILABLE)

Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily

AND

Fluconazole 800 mg PO daily for 2 weeks

OR

Liposomal amphotericin B 3–4 mg/kg IV daily

AND

Fluconazole 800 mg PO daily for 2 weeks

FOLLOWING INDUCTION TREATMENT

Fluconazole 800 mg PO daily for a minimum of 8 weeks

SUPPRESSION (CHRONIC MAINTENANCE)

Fluconazole 200 mg PO daily until CD4 count > 100–200 cells/μl for at least 6 months

CRYPTOCOCCOSIS IN ORGAN-TRANSPLANT RECIPIENTS

TREATMENT: CNS INFECTION, SEVERE NON-CNS OR DISSEMINATED DISEASE WITHOUT CNS INVOLVEMENT IN ORGAN TRANSPLANT RECIPIENTS

Liposomal amphotericin B 3–4 mg/kg IV daily

AND

5-flucytosine 25 mg/kg PO 6 hourly for 2 weeks

FOLLOWED BY

Fluconazole 400–800 mg (6–12 mg/kg) PO for 8 weeks

FOLLOWED BY

Fluconazole 200–400 mg PO daily for 6–12 months

TREATMENT: MILD-TO-MODERATE NON-CNS DISEASE IN ORGAN TRANSPLANT RECIPIENTS

Fluconazole 400 mg PO daily (6 mg/kg) for 6–12 months

CRYPTOCOCCAL MENINGITIS IN NON-HIV AND NON-TRANSPLANT PATIENTS

TREATMENT: CRYPTOCOCCAL MENINGITIS IN NON-HIV, NON-TRANSPLANT PATIENTS

INDUCTION TREATMENT (UNTIL PATIENT AFEBRILE AND CULTURE NEGATIVE (TYPICALLY ~ 6 WEEKS)

Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily

AND

5-flucytosine 25 mg/kg PO 6 hourly

OR

Liposomal amphotericin B 3–4 mg/kg IV daily (for patients with or predisposed to renal dysfunction)

AND

5-flucytosine 25 mg/kg PO 6 hourly

Following induction treatment

Fluconazole 400 mg PO daily for 8 weeks

PULMONARY CRYPTOCOCCOSIS

TREATMENT: PULMONARY CRYPTOCOCCOSIS

IMMUNOSUPPRESSED PATIENTS (HIV-UNINFECTED)

Rule out CNS disease by lumbar puncture; if meningitis is present then treat as for cryptococcal meningitis.

Mild-to-moderate symptoms without CNS involvement: fluconazole 400 mg (6 mg/kg daily) PO for 6–12 months

NON IMMUNOSUPPRESSED PATIENTS

Fluconazole 400 mg (6 mg/kg) PO daily

OR

Voriconazole 200 mg PO 12 hourly

OR

Posaconazole 400 mg PO 12 hourly

OR

Itraconazole 200 mg PO 12 hourly

Treat for 6–12 months

DERMATOPHYTE INFECTIONS (RINGWORM OR TINEA)

These superficial fungal infections are common infectious conditions. They are caused by the dermatophytes, which are moulds that can invade the stratum corneum of the skin or other keratinised tissues derived from epidermis, such as hair and nails. The three genera of dermatophyte fungi are *Trichophyton, Microsporum* and *Epidermophyton*. *Malassezia* causes the superficial skin infection, tinea versicolor.

DERMATOPHYTE INFECTIONS INCLUDE:

Tinea pedis: (athlete's foot): infection of the feet

Tinea capitis: infection of the scalp

Tinea corporis: infection of the body

Tinea cruris: (jock itch): infection of the crural fold

Onychomycosis: infection of the nail

Tinea versicolor: infection of the skin

Dermatophyte infections can be treated with topical antifungal therapy where possible. These include topical terbinafine and the imidazoles (e.g. miconazole, econazole, clotrimazole, tioconazole). In general, topical agents are applied twice a day for one to three weeks until the infection has cleared. Most nail and scalp infections and widespread infections are best treated with oral antifungal agents such as terbinafine, itraconazole or fluconazole. The topical agents are generally ineffective for scalp and nail infections. Oral terbinafine should not be used in patients with chronic or active liver disease due to serious, but rare, cases of hepatic failure reported following its use.

TREATMENT: TINEA PEDIS, CORPORIS AND CRURIS

Topical terbinafine (Lamasil®) OR an imidazole for 1–3 weeks:

Terbinafine 250 mg PO daily for 2 weeks (children 5 mg/kg/day)

OR

Fluconazole 150 mg PO once a week for 4 weeks (children 6 mg/kg/day)

TREATMENT: TINEA CAPITIS

Terbinafine 250 mg PO daily for 2–4 weeks (children 5 mg/kg/day)

OR

Itraconazole 5 mg/kg PO daily for 4 weeks

TREATMENT: ONYCHOMYCOSIS

Terbinafine 250 mg PO daily for 6 weeks (fingernails) and 12 weeks (toenails)
[Children 10–20 kg: 62.5 mg PO daily, 20–40 kg: 125 mg PO daily, > 40 kg: 250 mg PO daily]

OR

Itraconazole 200 mg PO 12 hourly for 1 week each month – repeat for 2–3 months

OR

Fluconazole 150–300 mg PO once a week for 8–16 weeks (fingernails) and 12–24 weeks (toenails)

TREATMENT: TINEA VERSICOLOR

Two weeks of a topical antifungal

OR

A single dose of oral ketoconazole 400 mg OR itraconazole 400 mg OR fluconazole 400 mg

SPOROTRICHOSIS

TREATMENT: LYMPHOCUTANEOUS SPOROTRICHOSIS

Itraconazole 200 mg (4–6 mg/kg) PO daily

Treatment duration: 4 weeks after all lesions have resolved (usually 3–6 months)

TREATMENT: LIFE THREATENING VISCERAL OR DISSEMINATED SPOROTRICHOSIS (RARE)

Amphotericin B IV initially

FOLLOWED BY (once the patient has shown a favourable response)

Itraconazole 200 mg (4–6 mg/kg) PO 12 hourly