Antifungal Medications

Available treatments[1]

- Triazole antifungals: fluconazole, itraconazole, posaconazole, voriconazole.
- Imidazole antifungals: clotrimazole, econazole, miconazole, ketoconazole and tioconazole.
- Polyene antifungals: amphotericin, nystatin.
- Echinocandin antifungals: anidulafungin, caspofungin and micafungin.
- Other antifungals: these include flucytosine, griseofulvin and terbinafine and amorolfin.

NB: griseofulvin tablets are still available but have been largely superseded by other antifungal agents. It is, however, still the drug of choice in trichophyton infections in children.

Antifungals may be used topically or systemically. Most localised fungal infections are treated with topical preparations, but systemic treatment may be required for scalp disease, widespread infection, systemic spread, intractable infection and immunocompromised individuals.

Indications for use

Candidal vulvovaginitis[2]
See the separate article on Vaginal and Vulval Candidiasis.

- Imidazole drugs (clotrimazole, econazole, fenticonazole, and miconazole) are effective in the treatment of vulvovaginal candidiasis.
- Oral treatment with fluconazole or itraconazole is also effective.
- Oral antifungal treatment should be avoided during pregnancy.
- Treatment against candidal infection may need to be extended for six months in recurrent vulvovaginal candidiasis.
- In pregnant women, intravaginal clotrimazole or miconazole is the treatment of choice.
- In immunocompromised individuals, oral antifungals for seven days, or intravaginal preparations for 6-14 days are advised.

Oral candidiasis[3]
See the separate article on Candidiasis.

- First-line therapy is with topical treatment with miconazole gel.
- Nystatin suspension is second-line treatment.
- For extensive or severe candidiasis, prescribe oral fluconazole 50 mg a day for one week. If the infection has not resolved after seven days, offer treatment for a further week.
- Children should only receive topical anticandidal treatment. Offer miconazole oral gel first-line (off-label use in children less than 4 months of age). Offer nystatin suspension (off-label use in neonates) if miconazole oral gel is unsuitable.

Nail infections[4]
See the separate article on Fungal Nail Infections.

- For mild infections use topical amorolfin nail lacquer first-line. Use for six months for fingernails and 6-12 months for toenails.
- Oral terbinafine is the first-line oral treatment. Treat for between six weeks and three months for fingernails and for between three and six months for toenails.
Oral itraconazole is an alternative. (Terbinafine is most effective against dermatophyte nail infections. It has fungistatic activity against *Candida albicans*. Itraconazole is highly active against *Candida* spp. but much less so against dermatophytes.) Prescribe itraconazole as pulsed therapy, 200 mg twice a day for a week, repeating the course after 21 days.

**Skin infections**[5]
See the separate articles on Candidiasis, Tinea Capitis, Pityriasis Versicolor and Dermatophytosis (Tinea Infections).

- Topical antifungals should be prescribed in most cases. The imidazoles ( clotrimazole, econazole, and miconazole) are all effective.
- Systemic treatment is only indicated in severe, extensive skin infection, or if there is associated systemic infection (e.g., in immunosuppressed people), or in the rare person unresponsive to topical treatment. Referral to specialist care is indicated.
- Oral treatment is recommended first-line for tinea capitis.[6] This would be griseofulvin or terbinafine (off-label.) A topical shampoo should be used alongside this, for the first two weeks of oral treatment. Specialist advice should be sought for children.

**Fungal ear infections**
See the separate article on Fungal Ear Infection (Otomycosis).

**Fungal eye infections**
Most fungi causing orbital infections are ubiquitous aerobic organisms that are normal commensals of the respiratory, gastrointestinal and female genital tracts, as well as sometimes being present on normal conjunctiva.

Fungal eye infections are rare in Western countries; they are more frequently seen in tropical and subtropical regions.

Fungal infections of the eye may cause orbital cellulitis, dacryocystitis, conjunctivitis, keratitis and endophthalmitis.[7] Thus, they can work at a superficial level or penetrate deeply into the eye.[8]

Treatment is initiated and monitored by a specialist ophthalmology team. Samples such as corneal scrapes will have been obtained prior to initiation of therapy. Any steroid treatment needs to be discontinued. Antifungal preparations for the eye are not generally available and have to be specifically made up under specialist management for each patient.[1]

**Systemic fungal infections**
See also the separate articles on Aspergillosis, Candidiasis, Cryptococcosis, Fungal Lung Infections and Systemic Mycoses.

Specialist treatment is required in most forms of systemic or disseminated fungal infections.

**Immunocompromised patients**[1]
Immunocompromised patients are at increased risk of fungal infections and may need prophylactic antifungal drugs. Management is a challenge, and a specialist field, and guidelines differ.[9]

Oral triazole antifungals are the drugs of choice for prophylaxis. Fluconazole is more reliably absorbed than itraconazole but is not effective against *Aspergillus* spp. Therefore, itraconazole is preferred in patients at risk of invasive aspergillosis. (Voriconazole is the treatment of choice for established aspergillosis.)

Posaconazole can be used for prophylaxis in patients who are undergoing haematopoietic stem cell transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome, if they are intolerant of fluconazole or itraconazole. Micafungin can be used when fluconazole, itraconazole or posaconazole cannot be used.

Amphotericin by intravenous infusion or caspofungin is used for the empirical treatment of serious fungal infections. Caspofungin is not effective against fungal infections of the central nervous system.
Cautions and contra-indications

- Amphotericin has a risk of toxicity when given parenterally. It should only be used parenterally in hospitalised patients, or for those under close clinical observation. It should be avoided if possible in those with renal impairment, and in pregnant women. A test dose is required. After this, the patient is observed closely for 30 minutes. Rapid infusion carries a risk of arrhythmias. Close monitoring is required of renal function, hepatic function, blood count, as well as potassium and magnesium levels.
- Fluconazole carries a risk of hepatic impairment. Use with caution in pregnancy, breast-feeding and impaired liver function. It is CONTRA-INDICATED in acute porphyria.
- Oral ketoconazole (for any indication) is not recommended, as the risks outweigh the benefits.
- Griseofulvin may impair the ability to perform skilled tasks - eg, driving. The toxic effects of alcohol are increased. It is CONTRA-INDICATED in severe liver disease, acute porphyria and systemic lupus erythematosus (SLE). Avoid in pregnancy and hepatic impairment.
- Miconazole gel is CONTRA-INDICATED in infants with an impaired swallowing reflex, and in the first six months of life for preterm infants. Avoid in liver disease, pregnancy, breast-feeding and acute porphyria.
- Terbinafine should be used with caution in liver or kidney disease, psoriasis (may exacerbate), autoimmune disease, pregnancy or breast-feeding. Liver function should be checked before starting treatment, and monitored every four to six weeks.

NB: many nystatin preparations are now withdrawn. This includes vaginal cream, pessaries, pastilles and Tri-Adcortyl Otic®.

Adverse effects

Many antifungals have similar adverse effects. They all may cause gastrointestinal upset, rashes, headaches, etc. In addition:

- Amphotericin may cause muscle and joint pain, hypokalaemia/hypomagnesaemia, hearing loss, diplopia, convulsions or peripheral neuropathy.
- Fluconazole may cause LFT abnormalities, and rash - toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported.
- Griseofulvin may aggravate or precipitate systemic lupus erythematosus (SLE).
- Flucytosine may cause marrow aplasia
- Application of topical imidazoles can be painful in some instances where there is particularly bad inflammation.
- Terbinafine is associated with loss of taste.

Further reading & references

1. British National Formulary; NICE Evidence Services (UK access only)
2. Candida - female genital; NICE CKS, December 2013 (UK access only)
3. Candida - oral; NICE CKS, July 2013 (UK access only)
4. Fungal nail infection; NICE CKS, September 2014 (UK access only)
5. Fungal skin infection - body and groin; NICE CKS, September 2014 (UK access only)
6. Fungal skin infection - scalp; NICE CKS, September 2014 (UK access only)
10. Press release: oral ketoconazole - containing medicines should no longer be used for fungal infections; Medicines and Healthcare products Regulatory Agency, July 2013