Mycoses and anti-fungals – an update

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Abstract

Fungi normally originate from the environment that surrounds us, and appear to be harmless until inhaled or ingestion of spores occur. For many years fungal infections were thought of as superficial diseases or infections such as athlete's foot, or vulvovaginal candidiasis. Subsequently, when invasive fungal infections were first encountered, amphotericin B was the only treatment for systemic mycoses. However, with the advances in medical technology such as bone marrow transplants, cytotoxic chemotherapy, indwelling catheters as well as with the increased use of broad spectrum antimicrobials in antimicrobial resistance, there has been a marked increase of fungal infections worldwide.

Populations at risk of acquiring fungal infections are those living with human immunodeficiency virus (HIV), cancer, patients receiving immunosuppressant therapy, neonates and those of advanced age.

The management of superficial fungal infections is mainly topical, with agents including terbinafine, miconazole and ketoconazole. Oral treatment includes griseofulvin and fluconazole.

Historically the management of invasive fungal infections involved the use of amphotericin B, however newer agents include the azoles and the echinocandins.

This paper provides a general overview of the management of fungus infections.

Keywords: invasive fungal diseases, superficial fungal diseases, fungal skin infections

S Afr Pharm J 2020;87(1):18-25

Introduction

Fungi normally originate from the environment that surrounds us, and appear to be harmless until inhaled or ingestion of spores occur. Infection with fungi is also more likely when the body's immune system becomes weakened. A pathogenic fungus may lead to infection. The number of fungus species ranges in the millions and only a few species seem to be harmful to humans; the ones found mostly on the mucous membrane and the skin have been noted to cause fatal infections.[1] Fungal infections have now emerged as a major cause of mortality, especially in immunocompromised individuals such as cancer patients, HIV-positive patients, and transplant patients.[2] The rise in antimicrobial resistance has also brought about a rise in the use of broad spectrum antimicrobials, in turn increasing the incidence of fungal infections.[2] In low- and middle-income countries where there are crowded living conditions and low-income communities, the prevalence of fungal infections is much higher.[3]

Fungi are eukaryotic organisms with a very defined nucleus that is enclosed with a nuclear membrane, called the cytoplasmic membrane, which contains lipids, glycoproteins, and sterols, mitochondria, Golgi apparatus, and ribosomes bound to the endoplasmic reticulum.[2]

Furthermore, there is a cytoskeleton with microtubules, microfilaments, and intermediate filaments.[2] Fungi have rigid cell walls that are composed of chitin and cellulose – in some instances both – that stain with Gomori methenamine silver or periodic acid-Schiff reagent. Clinically it is important to remember that most fungi, except the Candida species, are weakly Gram-positive and are therefore not seen well with Gram-staining.[2]

Morphologically, fungi that are pathogenic can be grouped as either unicellular yeasts or filamentous moulds. Many of the pathogenic fungi exist as either a yeast or a mould, depending on the pathogen, site of growth (either host or laboratory setting), and temperature. Some can be a combination of both, which are called dimorphic. Some fungi are also seen as atypical.[4] Moulds are filamentous fungi that are multicellular in structure. They grow best in warm and damp conditions. They can reproduce and survive in extreme conditions by producing spores.[5] Yeasts are unicellular and mainly reproduce asexually by budding.[6] Dimorphic fungi appear to be in a mould form between 25°C to 30°C, however, at body temperature (37°C) they appear as a yeast or yeast-like structure.[5] An important clinical distinction for yeasts or moulds, is that yeasts are the parasitic form that invade human or animal host tissue, whereas moulds are the free-living form found in the environment.

Identification of the genus is made by examining the colony under a microscope, whereas the identification of the species requires more advanced biochemical or molecular testing.[4]

Important concepts
Topical agents are first-line treatment for fungal skin infections. Oral therapy is indicated for the treatment of extensive or severe infection or those of tinea capitis or onychomycosis.
Patients with human immunodeficiency virus (HIV) infection must be on concurrent optimal antiretroviral therapy. This is important to prevent new and recurrent candidiasis.
Primary or secondary prophylaxis of fungal infections is NOT recommended routinely for HIV-infected patients. Secondary prophylaxis should be individualised by a specialist.
Toe and fingernail onychomycosis, should be treated with oral agents such as terbinafine.
Systemic mycoses caused by pathogenic fungi may include histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis or opportunistic fungi such as *Candida albicans*, *Aspergillus* species, *Candida glabrata* and others.

Aspergillosis can be caused by a variety of Aspergillus species that can cause superficial infections, pneumonia, allergic bronchopulmonary aspergillosis and other invasive infections.

The diagnosis of fungal infections includes evaluation of clinical symptoms, results of laboratory tests, histopathological examinations and the culture of clinical specimens.

Superficial fungal infections

Either yeasts or fungi can cause dermatomycosis, or superficial fungal infections.[7] Fungi that infect the hair, skin, nails and mucosa can cause a superficial fungal infection. Dermatophytes are found naturally in soil, human skin and keratin-containing structures, which provide them with a source of nutrition.[3]

Overview and management of superficial fungal infections

An overview of different fungi causing superficial fungal infections and the management thereof is set out in Table II.

Invasive fungal infections

Invasive fungal infections are usually uncommon, except when in immunocompromised and neutropenic patients.[5] Treating invasive fungal infections can be challenging due to limited antifungal agents available and considering factors such as toxicity, drug interactions and emerging resistance.[15] Variations in species occur due to different geographical areas, hospital-associated factors and the antifungal agents that are used to treat patients.[15]

Risk factors for invasive fungal infection include a history of prior exposure to antifungals or broad spectrum antibiotics, immunocompromised conditions such as in organ transplants or HIV-infected patients,[15] exposure to intravenous lines, catheters and dialysis,[6] poorly controlled diabetes, cancer chemotherapy[16] and neutropenic patients.[5]

Table I: Superficial fungal infections classification according to the site of infection[8]

	Classification	Common names
Scalp	*Tinea capitis*	Ringworm of the head
Beard	*Tinea barbae*	–
Face	*Tinea facie*	Ringworm of the face
Skin (body)	*Tinea corporis*	Ringworm
	Tinea vesicolor	–
Hands	*Tinea manuum*	–
Nails	*Tinea unguium*	–
Groin	*Tinea cruris*	Jock itch
Feet	*Tinea pedis*	Athletes foot

Overview and management of invasive fungal infections

An overview of fungi causing invasive infections and the management thereof is set out in Table III.

Conclusion

The increase in antimicrobial resistance and the subsequent use of broad spectrum antimicrobials and the limited number of antifungals available for treating fungal infections all require careful use of antifungals. The increase in the emergence of opportunistic fungus infections requires a thorough understanding about fungi and its related infections, the antifungals available, their mechanism of action and resistance profile. In this article we provided a brief overview of the topics at hand and their importance for the pharmacist.

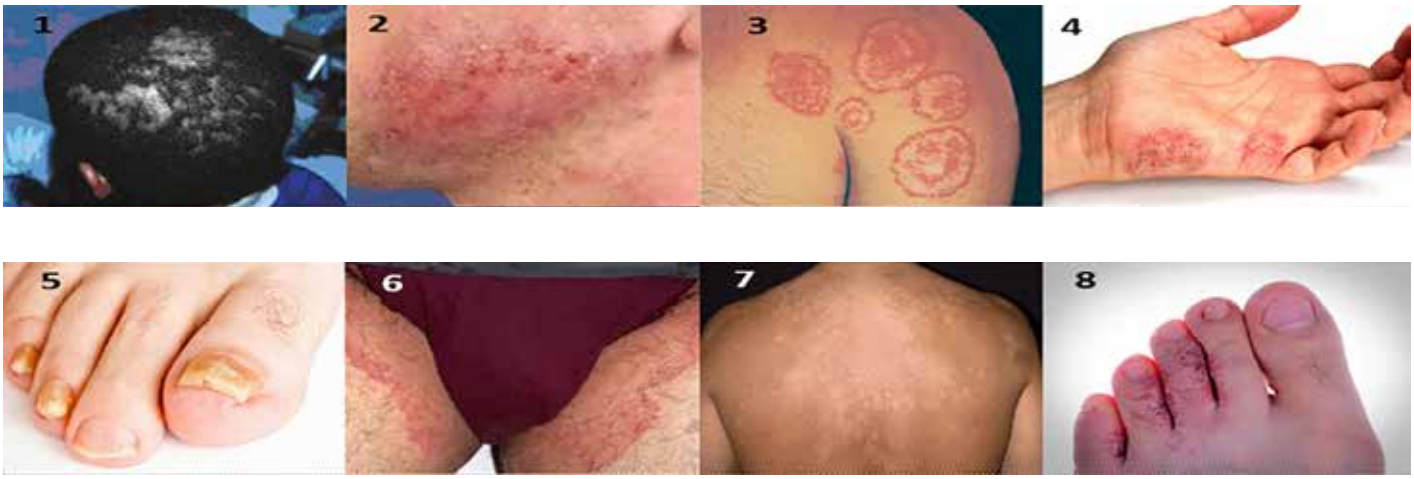

Figure 1: Prevalent superficial fungal infections:
1. Tinea capitis 2. Tinea barbae 3. Tinea corporis 4. Tinea manuum 5. Tinea unguium 6. Tinea cruris 7. Tinea versicolor and 8. Tinea pedis

Table II: Overview and management of superficial fungal infections

	Aetiology	Transmission	Causative agents	Diagnosis	Signs and symptions	Management
Tinea capitis	• Affects children between 3–9 years. • Adults are usually asymptomatic carriers. • Prevalent in crowded and poverty-stricken areas.	• Direct contact. • Sharing of combs, hairbrushes, and hats. • Cats and dogs.	• *Trichophyton tonsurans* • *Microsporum canis*	• Signs and symptoms • Microscopy • Cultures[9,10]	• Itching. • Scaly patches with no hair. • Black dots on area of hair loss. • Cervical and suboccipital lymphadenopathy.	• Griseofulvin, terbinafine, fluconazole, itraconazole.[3,11] Decreases viable spores on patients and asymptomatic carriers. • All patients and household contacts should be treated with ketoconazole, selenium sulphide, and povidone iodine.[3,11]
Tinea barbae	• Affects mostly males on the beard/moustache and neck areas.	• Farm and domestic animals can spread it to humans.	• *Trichophyton verrucosum* • *Trichophyton mentagrophytes*	• Appearance • Microscopy • Culture	• One or more flat circular erythematous patch with raised borders. • Scaly and itchy. • Sometimes causes hair loss.	• Terbenafine, itraconazole. • Topical creams are ineffective.[11,12]
Tinea unguium	• Also referred to as onychomycosis (fungal infection that affects the nail unit). • It affects children, adolescents and adults. • Infection of toenails is more prevalent than fingernails. • Onychomycosis takes about 3–6 months to treat.		• *Trichophyton rubrum* • *Trichophyton mentagrophytes*	• Microscopy • Cultures • Periodic acid–Schiff (PAS) stain	• Thickened nails. • Brittle nails. • Discoloured nails.	• Local treatment: amorolfine 5% nail lacquer. • Topical creams are ineffective in nail infections due to inadequate penetration in the nail. • Oral: terbinafine (first-line), itraconazole and fluconazole.[9,11]
Tinea pedis	• Commonly seen in young adolescent males. • Affects males more than females. • Fungal growth is promoted by moisture and warmth. • Risk of acquiring infection from locker room floors, swimming pools, athletic shoes and sports equipment.		• *Trichophyton rubrum* (common) • *Trichophyton mentagrophytes* • *Epidermophyton floccosum*	• Clinical examination • Microscopic examination • Cultures[10,13]	• Occurs within interdigital spaces and soles of the feet. • Maceration, soggy or dry. • Scaly and itching of the affected area, associated with burning. • Malodour.	• Topical: miconazole, clotrimazole and terbinafine. • Oral: terbinafine, griseofulvin, or itraconazole.[11]
Tinea versicolor	• Also known as *Pityriasis versicolor*, which is part of the normal skin flora. • Harmless unless the yeast assumes its mycelial form. • Causes emotional distress mainly due to effects on the skin. • The condition can return despite adequate treatment and the skin lesions take time (weeks to months) to clear. • Affects adolescents and young adults and appears on the neck, trunk, arms and abdomen. • Children can develop the macules on the face.	• It is part of normal flora, it becomes pathogenic once triggered by excessive sweating, immunosuppression, high temperatures and humidity.	• *Malassezia* species: • *M. furfur* • *M. globose* • *M. sympodialis*	• Microscopy[10,14]	• Small round to oval macules, lesions differ with skin colour where they appear lighter on darker skin and vice versa. • Itching and scaling of smaller macules.	• Topical: clotrimazole, and miconazole, ketoconazole, terbinafine. • Oral: fluconazole, itraconazole. • Others: zinc pyrithione, selenium sulphide.[10,11]
Tinea corporis	• Occurs at any age, and involves the face (occasionally), shoulders, trunk, legs and arms.	• Person-to-person contact	• *Trichophyton tonsurans* (common) • *Trichophyton rubrum* • *Microsporum canis* • *Epidermophyton floccosum*	• Patient history • Physical examination • Microscopy[9,10]	• Starts with one or more circular plaques with a raised border. • Itchy. • Erythematous scaly spots. Plague size ranges from 1–5 cm.	• Topical: miconazole, terbinafine and clotrimazole. • Oral: terbinafine, fluconazole and itraconazole.[11]

Table II: Overview and management of superficial fungal infections (*Continued*)

	Aetiology	Transmission	Causative agents	Diagnosis	Signs and symptions	Management
Tinea cruris	• Commonly affects men more than women. • Involves the groin area, portion of the upper thigh, usually doesn't affect the scrotum but can spread to the buttocks.	• Occurs in warm and moist climates, is prevalent in athletes, overweight people, excessive sweating	• *Trichophyton rubrum* • *Trichophyton mentagrophytes* • *Epidermophyton floccosum*	• Clinical presentation	• Well-demarcated borders, itching. • Erythema. • Scaling of patches.[10]	• Topical: miconazole, terbinafine or clotrimazole and clotrimazole 1% and hydrocortisone 1% 30g (if there is inflammation). • Oral: terbinafine, griseofulvin, or itraconazole.[11]
Tinea manuum	• Affects the palmar and interdigital areas of the hand/s, and can appear at the same time as tinea pedis. • It is commonly referred to as the 'one hand two feet syndrome'.	• Direct contact with infected person, animal or soil	• *Trichophyton rubrum* (common) • *Trichophyton mentagrophytes* • *Epidermophyton floccosum*	• See tinea pedis	• Dry, scaly, sometimes itchy diffuse hyperkeratosis.	• See tinea pedis

Table III: Overview and management of invasive fungal infections

Infection	Aetiology	Causative agents	Signs and symptions	Diagnosis	Management
Yeasts:					
Invasive candidiasis	• Candida species are part of the normal flora, thus any breach in the superficial surface can lead to invasive candidiasis.	• *Candida albicans* • *Candida krusei* • *Candidia glabrata* • *Candida parapsilosis* • *Candida tropicalis* • *Candida auris*[17]	• Asymptomatic • Fever, chills and reduced oxygenation • Symptoms of sepsis may be present such as hypotension and tachycardia.[4] The infection can disseminate causing endocarditis, meningitis and osteomyelitis.[19]	• Culture from sterile site such as spinal fluid or bone marrow. • Cultures taken from respiratory, digestive and urogenital tracts are difficult to interpret as they are part of the normal flora.[15]	• Fluconazole is first-line treatment of invasive candidiasis infections for those who are not critically ill, and have not had previous exposure to azoles.[15] • *C. krusei* displays intrinsic resistance towards fluconazole.[5] • Voriconazole is choice of drug for fluconazole-resistant species such as *C. krusei*.[17] Itraconazole is second-line treatment for invasive candidiasis.[15] • *C. krusei* is reported resistant.[5] • Posaconazole is used if treatment failure occurs with voriconazole. • *C. glabrata* is reported to be resistant to imidazoles.[5] • Treatment with echinocandins is preferred for patients infected with *C. glabrata*. • First-line for non-neutropenic patients with candidemia are echinocandins. • Treatment for neutropenic patients are echinocandins or amphotericin B. Continue treating for two weeks after negative culture.[17] • Caspofungin is used for treatment of *C. glabrata* and *C. krusei* infections, previously treated with azoles or for patients unable to tolerate amphotericin B and azoles.[15] • Micafungin is used for treatment *of C. albicans*, *C. krusei* and *C. glabrata* infections.[15] • Anidulafungin is used for treatment of any Candida species.[15] • Amphotericin B can be used for systemic fungal infections.[15] *C. glabrata*-resistance has been reported to amphotericin B.[5] • Endocarditis caused by candida: amphotericin B with or without flucytosine. Evidence suggests high doses of echinocandins are also effective. A valve replacement is recommended in those patients that are stable enough to undergo surgery. Treatment continued for at least six weeks after valve replacement surgery.[17] Lifelong azole-therapy considered in patients with or without prosthetic valve-replacements.[17]

Table III: Overview and management of invasive fungal infections *(Continue)*

Infection	Aetiology	Causative agents	Signs and symptions	Diagnosis	Management
Cryptococcus	• Cryptococcus species are encapsulated[6] which plays a role in protecting the organism in extreme conditions. • *C. neoformans* is a common cause of hospital-acquired meningitis in HIV-infected patients. • *C. gattii* can cause infections in immunocompetent and immunocompromised patients and is mostly found in tropical and subtropical areas. • High mortality rates are documented in areas such as sub-Saharan Africa, due to the high burden of HIV-infected patients.[5]	• *C. neoformans* (found worldwide) • *Cryptococcus gattii*[6]	• Infection starts in the lungs and spreads through the blood, normally to the central nervous system causing meningitis.[5]	• Diagnosis is made on culture taken of the tissue or fluids such as blood, cerebrospinal fluids or sputum. • Cryptococcal antigen test is a rapid test performed on blood or cerebrospinal fluid.[18]	• Cryptococcus species are intrinsically resistant to echinocandins. • Most azoles are susceptible, except for ketoconazole and miconazole. • When using fluconazole as a prophylactic agent there is a big chance of resistance developing. • Amphotericin B is effective, however if used over a long period, resistance is likely to occur.[4] • For more severe infections such as meningitis in HIV-infected patients, amphotericin B in combination with fluconazole (800–1 200 mg) should be used for two weeks, thereafter fluconazole 400 mg alone for eight weeks and then fluconazole 200 mg to be used for up to one year.[20]
Moulds:					
Aspergillus	• Most Aspergillus species are found globally. • It is a life-threatening opportunistic infection in immunocompromised patients. • Species *A. fumigatus* is commonly found in grasslands. • *A. niger* is commonly found in soil.	• *Aspergillus fumigatus* • *Aspergillus flatus* • *Aspergillus terreus* • *Aspergillus niger*[21]	• Aspergillus can cause a wide range of diseases. • Respiratory symptoms: fever, cough and haemoptysis, pleuritic chest pain, shortness of breath. • CNS: seizures.[21]	• Glucose in the cerebrospinal fluid is usually normal and cultures are negative. • Blood culture can be performed. • X-rays and CT scans also aid in diagnosis. • A tissue biopsy of the lungs can be done to establish the specific organism.[21]	• *A. fumigatus* has resistant strains to itraconazole and cross-resistance to voriconazole and posaconazole is emerging. • In rare cases resistance to echinocandins occurs.[4] • *A. niger* has been reported to have resistance against itraconazole. • *A. terreus* has been reported to have inherent resistance against amphotericin B.[4] • Voriconazole is preferred in most cases of invasive aspergillosis. Suspectiblity must be tested. However, patients with significantly elevated hepatic enzymes, hepatic dysfunction and a history of intolerance to voriconazole should not use voriconazole as first-line treatment. • Amphotericin B is an alternative, if voriconazole cannot be used. • Second-line drugs include caspofungin, posaconazole and itraconazole, however susceptibility must be tested.[21] • Duration of treatment depends on clinical response, immunocompromised condition and type of aspergillus species. Treatment for invasive pulmonary aspergillus is about 6–12 weeks.[21]
Dimorphic:					
Histoplasma	• It is classified as dimorphic as it grows as a mould at 25°C and as a yeast at 37°C. • *H. capsulatum* is found worldwide and can be referred to as the cave disease as it is found in bird and bat droppings, soil and dust. • It is an important cause of chronic pneumonia.[4] • Prevalence of histoplasma is increasing in HIV-infected patients in Africa.[5]	• *Histoplasma capsulatum* var. *capsulatum* • *Histoplasma capsulatum* var. *duboisii* [5]	• It is mostly acquired through the lungs and symptoms include fever, chills, cough, headache, chest pains and body aches.[22]	• Biopsy specimen is essential for pathological diagnosis. • Blood and bone marrow culture are positive in disseminated histoplasmosis. • Fluid from the respiratory tract, and CT or X-rays can assist in diagnosis.[5]	• *H. capsulatum* is susceptible to all antifungals except echinocandins. • HIV-infected patients co-infected *with H. capsulatum* reported acquired resistance against fluconazole. • Oral itraconazole is the choice of treatment; for more severe disease such as in the CNS, amphotericin B is required.[22]

Table III. Overview and management of invasive fungal infections *(Continued)*

Infection	Aetiology	Causative agents	Signs and symptions	Diagnosis	Management
Atypical:					
Pneumocystis	• *Pneumocystis jirovecii* (formerly called *Pneumocystis carinii*) is commonly isolated from the human lung and can be spread via coughing. • Pneumocystis pneumonia, also known as PCP, is commonly seen in HIV patients or other immunocompromised patients.[4]	• *Pneumocystis jirovecii*	• Dyspnoea, fever, chills, hypoxaemia, cough and wheezing.[23]	• Sputum sample or lung biopsy can be investigated under a microscope. Polymerase chain reaction can also be used to detect pneumocystis.[23]	• The cell walls of *P. jirovecii* consist of cholesterol, therefore most antifungal drugs are not effective, as antifungals work on the ergosterol in the cell wall. • High doses of co-trimoxazole (trimethoprim/sulphamethoxazole).[4]

Table IV: Drugs used for the treatment of invasive fungal infections

Drug class	Drugs	Mechanism of action	Side-effects	Monitoring parameters
Imidazoles	• Fluconazole • Voriconazole • Itraconazole • Pasoconazole • Isavuconazole	• Imidazoles have a fungistatic effect with dose-dependent inhibition of CYP 14α-demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol, which plays an important role in the stability of the fungal cell membrane. This can lead to compromised membrane integrity.[25]	• Headaches • Diarrhoea • Dyspepsia • Abdominal pain • Nausea • Photosensitivity • Dermatological symptoms such as rash • QT-elevation[24]	• Liver function • QT-interval[24]
Echinocandins	• Caspufungin • Micafungin • Anidulafungin	• Mechanism of action of echinocandins includes the inhibition of glucan synthase, the enzyme responsible for the synthesis of β1–3 linked glucan, which is a major component of the polysaccharide, better known as the cell wall.[26]	• Hepatic dysfunction • Rash • Photosensitivity • Bronchospasm • Pruritus[24]	• Liver function[24]
Polyenes	• Amphotericin B	• Polyenes form aggregates in the cell membrane with ergosterol, leading to pores that cause leakage of cellular contents. This leads to cell lysis.[27]	• Chills and fever • Liver toxicity • Bronchospasm • Renal toxicity • Hypokalaemia • Infusion-related reactions[24]	• Monitor magnesium levels twice a week • Monitor creatinine, complete blood count and metabolic panel[19]

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