

Fungal infections – An overview

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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 occurs. A pathogenic fungus may lead to infection. People who are at risk of acquiring fungal infection are those living with human immunodeficiency virus (HIV), cancer, 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.

Invasive fungal infections are difficult to treat, and are managed with agents including the azoles, echinocandins and amphotericin B. This paper provides a general overview of the management of fungus infections.

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Introduction

Fungi normally originate from the environment that surrounds us, and appear to be harmless until inhaled or ingestion of spores occurs. 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

People who are at risk of acquiring fungal infection are those living with human immunodeficiency virus (HIV), cancer, receiving immunosuppressant therapy, neonates and those of advanced age.² In crowded living conditions and low income communities the prevalence of fungal infections is much higher.³

Fungi are divided into yeasts and moulds, and 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

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

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

Table I. The classification of superficial fungal infections according to the site of infection⁸

	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 versicolor	–
Hands	Tinea manuum	–
Nails	Tinea unguium	–
Groin	Tinea cruris	Jock itch
Feet	Tinea pedis	Athletes foot

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.

Table II. Overview and management of superficial fungal infections

	Aetiology	Transmission	Causative agents	Diagnosis	Signs and symptoms	Management
Tinea capitis	<ul style="list-style-type: none"> Affects children between 3–9 years. Adults are usually asymptomatic carriers. Prevalent in crowded and poverty-stricken areas. 	<ul style="list-style-type: none"> Direct contact Sharing of combs, hairbrushes, and hats. Cats and dogs 	<ul style="list-style-type: none"> <i>Trichophyton tonsurans</i> <i>Microsporum canis</i> 	<ul style="list-style-type: none"> Signs and symptoms Microscopy Cultures^{9,10} 	<ul style="list-style-type: none"> Itching Scaly patches with no hair Black dots on area of hair loss Cervical and suboccipital lymphadenopathy 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Affects mostly males on the beard/moustache and neck areas. 	<ul style="list-style-type: none"> Farm and domestic animals can spread it to humans 	<ul style="list-style-type: none"> <i>Trichophyton verrucosum</i> <i>Trichophyton mentagrophytes</i> 	<ul style="list-style-type: none"> Appearance Microscopy Culture 	<ul style="list-style-type: none"> One or more flat circular erythematous patch with raised borders Scaly and itchy Sometimes causes hair loss 	<ul style="list-style-type: none"> Terbinafine, itraconazole. Topical creams are ineffective.^{11,12}
Tinea unguium	<ul style="list-style-type: none"> 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. 		<ul style="list-style-type: none"> <i>Trichophyton rubrum</i> <i>Trichophyton mentagrophytes</i> 	<ul style="list-style-type: none"> Microscopy Cultures Periodic acid–Schiff (PAS) stain 	<ul style="list-style-type: none"> Thickened Brittle Discoloured nails 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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. 		<ul style="list-style-type: none"> <i>Trichophyton rubrum</i> (common) <i>Trichophyton mentagrophytes</i> <i>Epidermophyton floccosum</i> 	<ul style="list-style-type: none"> Clinical examination Microscopic examination Cultures^{10,13} 	<ul style="list-style-type: none"> Occurs within interdigital spaces and soles of the feet Maceration, soggy or dry Scaly and itching of the affected area, associated with burning Malodour 	<ul style="list-style-type: none"> Topical: miconazole, clotrimazole and terbinafine. Oral: terbinafine, griseofulvin, or itraconazole.¹¹
Tinea cruris	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Occurs in warm and moist climates, is prevalent in athletes, overweight people, excessive sweating 	<ul style="list-style-type: none"> <i>Trichophyton rubrum</i> <i>Trichophyton mentagrophytes</i> <i>Epidermophyton floccosum</i> 	<ul style="list-style-type: none"> Clinical presentation 	<ul style="list-style-type: none"> Well-demarcated borders, itching Erythema Scaling of patches¹⁰ (Kaushik et al, 2015) 	<ul style="list-style-type: none"> Topical: miconazole, terbinafine or clotrimazole and clotrimazole 1% and hydrocortisone 1% 30 g (if there is inflammation). Oral: terbinafine, griseofulvin, or itraconazole.¹¹
Tinea corporis	<ul style="list-style-type: none"> Occurs at any age, and involves the face (occasionally), shoulders, trunk, legs and arms. 	<ul style="list-style-type: none"> Person-to-person contact 	<ul style="list-style-type: none"> <i>Trichophyton tonsurans</i> (common) <i>Trichophyton rubrum</i> <i>Microsporum canis</i> <i>Epidermophyton floccosum</i> 	<ul style="list-style-type: none"> Patient history Physical examination Microscopy^{9,10} 	<ul style="list-style-type: none"> Starts with one or more circular plaques with a raised border Itchy Erythematous scaly spots; plaque size Ranges from 1–5 cm 	<ul style="list-style-type: none"> Topical: miconazole, terbinafine and clotrimazole. Oral: terbinafine, fluconazole and itraconazole.¹¹

Table II. Overview and management of superficial fungal infections (Cont.)

	Aetiology	Transmission	Causative agents	Diagnosis	Signs and symptoms	Management
Tinea cruris	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Occurs in warm and moist climates, is prevalent in athletes, overweight people, excessive sweating 	<ul style="list-style-type: none"> <i>Trichophyton rubrum</i> <i>Trichophyton mentagrophytes</i> <i>Epidermophyton floccosum</i> 	<ul style="list-style-type: none"> Clinical presentation 	<ul style="list-style-type: none"> Well-demarcated borders, itching Erythema Scaling of patches¹⁰ (Kaushik et al, 2015) 	<ul style="list-style-type: none"> Topical: miconazole, terbinafine or clotrimazole and clotrimazole 1% and hydrocortisone 1% 30 g (if there is inflammation). Oral: terbinafine, griseofulvin, or itraconazole.¹¹
Tinea manuum	<ul style="list-style-type: none"> 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'. 	<ul style="list-style-type: none"> Direct contact with infected person, animal or soil 	<ul style="list-style-type: none"> <i>Trichophyton rubrum</i> (common) <i>Trichophyton mentagrophytes</i> <i>Epidermophyton floccosum</i> 	<ul style="list-style-type: none"> See tinea pedis 	<ul style="list-style-type: none"> Dry, scaly, sometimes itchy diffuse hyperkeratosis 	<ul style="list-style-type: none"> See tinea pedis.

Table III. Overview and management of invasive fungal infections

Infection	Aetiology	Causative agents	Signs and symptoms	Diagnosis	Management
Yeasts:					
Invasive candidiasis	<ul style="list-style-type: none"> Candida species are part of the normal flora, thus any breach in the superficial surface can lead to invasive candidiasis. 	<ul style="list-style-type: none"> <i>Candida albicans</i> <i>Candida krusei</i> <i>Candida glabrata</i> <i>Candida parapsilosis</i> <i>Candida tropicalis</i> <i>Candida auris</i>¹⁷ 	<ul style="list-style-type: none"> 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 osteomyelitis¹⁹ 	<ul style="list-style-type: none"> 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 flora¹⁵ 	<ul style="list-style-type: none"> 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 <i>C. krusei</i> displays intrinsic resistance towards fluconazole.⁵ Voriconazole is choice of drug for fluconazole-resistant species such as <i>C. krusei</i>.¹⁷ Itraconazole is second-line treatment for invasive candidiasis.¹⁵ <i>C. krusei</i> is reported resistant.⁵ Posaconazole is used if treatment failure occurs with voriconazole. <i>C. glabrata</i> is reported to be resistant to imidazoles.⁵ Treatment with echinocandins is preferred for patients infected with <i>C. glabrata</i>. 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 <i>C. glabrata</i> and <i>C. krusei</i> infections, previously treated with azoles or for patients unable to tolerate amphotericin B and azoles.¹⁵ Micafungin is used for treatment of <i>C. albicans</i>, <i>C. krusei</i> and <i>C. glabrata</i> infections.¹⁵ Anidulafungin is used for treatment of any Candida species.¹⁵ Amphotericin B can be used for systemic fungal infections.¹⁵ <i>C. glabrata</i>-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 (Cont.)

Infection	Aetiology	Causative agents	Signs and symptoms	Diagnosis	Management
Yeasts:					
Cryptococcus	<ul style="list-style-type: none"> Cryptococcus species are encapsulated⁶ which plays a role in protecting the organism in extreme conditions. <i>C. neoformans</i> is a common cause of hospital-acquired meningitis in HIV-infected patients. <i>C. gattii</i> 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 	<ul style="list-style-type: none"> <i>C. neoformans</i> (found worldwide) <i>Cryptococcus gattii</i> 	<ul style="list-style-type: none"> Infection starts in the lungs and spreads through the blood, normally to the central nervous system causing meningitis.⁵ 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Cryptococcus species are intrinsically resistant to echinocandins. Most azoles are effective, except for ketoconazole and miconazole. When using fluconazole as a prophylactic agent there is a significant potential 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 mg – 1200 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	<ul style="list-style-type: none"> Most Aspergillus species are found globally. It is a life-threatening opportunistic infection in immunocompromised patients. Species <i>A. fumigatus</i> is commonly found in grasslands. <i>A. niger</i> is commonly found in soil. 	<ul style="list-style-type: none"> <i>Aspergillus fumigatus</i> <i>Aspergillus flatus</i> <i>Aspergillus terreus</i> <i>Aspergillus niger</i>²¹ 	<ul style="list-style-type: none"> Aspergillus can cause a wide range of diseases. Respiratory symptoms: fever, cough, and haemoptysis; pleuritic chest pain, shortness of breath. CNS: seizures.²¹ 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> <i>A. fumigatus</i> has resistant strains to itraconazole and cross-resistance to voriconazole and posaconazole is emerging. In rare cases resistance to echinocandins occurs.⁴ <i>A. niger</i> resistance against itraconazole has been reported. <i>A. terreus</i> has been reported to have inherent resistance against amphotericin B.⁴ Voriconazole is preferred in most cases of invasive aspergillosis. Susceptibility 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

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

Infection	Aetiology	Causative agents	Signs and symptoms	Diagnosis	Management
Dimorphic					
Histoplasma	<ul style="list-style-type: none"> It is classified as dimorphic as it grows as a mould at 25 °C and as a yeast at 37 °C. <i>H. capsulatum</i> 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 	<ul style="list-style-type: none"> <i>Histoplasma capsulatum</i> var. <i>capsulatum</i> <i>Histoplasma capsulatum</i> var. <i>duboisii</i>⁵ 	<ul style="list-style-type: none"> It is mostly acquired through the lungs and symptoms include fever, chills, cough, headache, chest pains and body aches.²² 	<ul style="list-style-type: none"> Biopsy specimen is essential for pathologic 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 	<ul style="list-style-type: none"> <i>H. capsulatum</i> is susceptible to all antifungals except echinocandins. HIV-infected patients co-infected with <i>H. capsulatum</i> 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
Atypical					
Pneumocystis	<ul style="list-style-type: none"> <i>Pneumocystis jirovecii</i> (formerly called <i>Pneumocystis carinii</i>) 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 	<ul style="list-style-type: none"> <i>Pneumocystis jirovecii</i> 	<ul style="list-style-type: none"> Dyspnoea, fever, chills, hypoxaemia, cough and wheezing²³ 	<ul style="list-style-type: none"> Sputum sample or lung biopsy can be investigated under a microscope. Polymerase chain reaction can also be used to detect pneumocystis.²³ 	<ul style="list-style-type: none"> The cell walls of <i>P. jirovecii</i> 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



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 IV. Drugs used for the treatment of invasive fungal infections

Drug class	Drugs	Mechanism of action	Side-effects	Monitoring parameters
Imidazoles	<ul style="list-style-type: none"> Fluconazole Voriconazole Itraconazole Pasiconazole Isavuconazole 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> General side-effects: <ul style="list-style-type: none"> headaches diarrhoea dyspepsia abdominal pain nausea photosensitivity dermatological symptoms such as rash QT-elevation²⁴ 	<ul style="list-style-type: none"> Liver function QT-interval²⁴
Echinocandins	<ul style="list-style-type: none"> Caspofungin Micafungin Anidulafungin 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Hepatic dysfunction Rash Photosensitivity Bronchospasm Pruritus²⁴ 	<ul style="list-style-type: none"> Liver function²⁴
Polyenes	<ul style="list-style-type: none"> Amphotericin B 	<ul style="list-style-type: none"> Polyenes form aggregates in the cell membrane with ergosterol, leading to pores that cause leakage of cellular contents. This leads to cell lysis.²⁷ 	<ul style="list-style-type: none"> Chills and fever Liver toxicity Bronchospasm Renal toxicity Hypokalaemia Infusion-related reactions²⁴ 	<ul style="list-style-type: none"> Monitor magnesium levels twice a week Monitor creatinine, complete blood count and metabolic panel¹⁹

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 chemotherapy¹⁶ and neutropenic patients.⁵

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

Yeast, moulds or atypical fungi may cause fungal infections. The infection may be superficial or invasive. Superficial infections will mostly infect the skin, nails and hair of the patient, while invasive infections may cause blood stream infection, or infect organ systems like the central nervous system, lungs or heart. Management of superficial infections can be topical with agents like miconazole and ketoconazole, or systemic with agents like fluconazole or griseofulvin. Invasive infections need susceptibility testing and close monitoring and must be treated systemically with agents like the azoles, echinocandins or amphotericin B.

Treatment duration is usually longer than for superficial infections, and some invasive fungal infections require several months of treatment.

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