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An Overview of Fungal Infections

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Abstract

The incidence of fungal infections is increasing at an alarming rate, presenting an enormous challenge to healthcare professionals. This increase is directly related to the growing population of immunocompromised individuals, resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. HIV and other diseases which cause immunosuppression have also contributed to this problem.

Superficial and subcutaneous fungal infections affect the skin, keratinous tissues and mucous membranes. Included in this class are some of the most frequently occurring skin diseases, affecting millions of people worldwide. Although rarely life threatening, they can have debilitating effects on a person's quality of life and may in some circumstances spread to other individuals or become invasive. Most superficial and subcutaneous fungal infections are easily diagnosed and readily amenable to treatment.

Systemic fungal infections may be caused by either an opportunistic organism that infects an at-risk host, or may be associated with a more invasive organism that is endemic to a specific geographical area. Systemic infections can be life threatening and are associated with high morbidity and mortality. Because diagnosis is difficult and the causative agent is often confirmed only at autopsy, the exact incidence of systemic infections is difficult to determine. The most frequently encountered pathogens are *Candida albicans* and *Aspergillus* spp. but other fungi such as non-*albicans Candida* spp. are increasingly important.

Fungi exist in two basic forms: yeasts and moulds. Yeasts are typically single, small, oval cells, whereas mould colonies consist of filamentous strands called hyphae. Some fungi are dimorphic, existing as either yeasts or moulds depending on the external environment (e.g. temperature).

Most fungi are ubiquitous, propagating successfully in their natural environments with no need for human or animal substrates. Some species, however, are adventitious pathogens in humans, causing superficial, subcutaneous or systemic infection. Most fungi causing systemic (or deep seated) infection do so by direct inhalation into the lung or by invasion of a wound site. Others, such as *Candida albicans*, are commensal inhabitants of the gastrointestinal tract and skin, which under certain conditions may proliferate and migrate into the systemic circulation, for example, when introduced into the body via medical devices such as vascular catheters.

Some fungi cause disease in otherwise healthy individuals, but many species become pathogenic only when the host is debilitated in some way, for example, when the immune system is compromised. The number of individuals in this situation is increasing because of the complications of advanced HIV infection and developments in modern medicine, such as intensive chemotherapy and the use of immunosuppressive drugs.[1,2] Mortality among infected patients may be as high as 75 to

100%,[3] presenting a major challenge to healthcare professionals.

1. Superficial Fungal Infections

Superficial fungal infections occur in the outermost layers of the skin, nails, hair and mucous membranes. In recent years, the incidence of these infections has risen steadily, mainly because of the increasing number of immunocompromised patients and the growing popularity of health clubs and communal swimming pools, which facilitate the spread of infection.[4]

1.1 Infections of the Skin and Keratinised Tissues

Superficial fungal infections include some of the most frequently observed skin diseases, affecting millions of people worldwide.[5] Dermatophytes – specifically, *Trichophyton* spp., *Microsporum* spp. and *Epidermophyton* spp. – are responsible for most superficial fungal infections, although yeasts and some non-dermatophyte moulds can also be causative agents.

Dermatophytes infect the stratum corneum of the epidermis and keratinised tissues derived from it, such as hair or nail. Fungal transmission occurs through direct contact with infected people, animals, soil or fomites. Specific dermatophyte infections are named according to their location on the body (see table I). Tinea pedis is the most prevalent fungal infection in the developed world and is usually caused by *Trichophyton rubrum* or *T. mentagrophytes* var. *interdigitale*.[6] Individuals with tinea pedis may be susceptible to secondary bacterial infection with, for example, group A streptococcus.[7] Tinea capitis is another frequently occurring superficial disease, primarily affecting children over the age of 6 months (fig. 1a).[8] During the past 50 years, the predominant causative agent of this infection has changed from *Microsporum audouinii* to *T. tonsurans*,[9] which now accounts for as many as 96% of infections in the USA[10] and an increasing number of infections in the UK.[11] Tinea versicolor, an infection of the stratum corneum, is caused by *Malassezia furfur*, a commensal yeast of the skin.[12] Some patients with tinea versicolor are at risk of the infection becoming invasive.[13]

Nail infections, or onychomycoses, are thought to account for approximately 33% of all fungal skin infections and 50% of all nail disorders (see fig. 1b).[14] Studies suggest that they affect between 2% and 13% of the population worldwide and up to 30% of groups at high risk, such as the elderly.[15] The incidence of onychomycosis among people with diabetes is particularly high; this group is nearly 3 times as likely to be infected as healthy individuals[16] and is at risk of developing serious sequelae if the infection is neglected. The dermatophytes *T. rubrum* and *T. mentagrophytes* are the principal causes of onychomycosis, accounting for approximately 90% of toenail infections and 50% of fingernail infections, although non-dermatophyte yeasts (*C. albicans* and other non-*albicans Candida* spp.) and moulds (*Aspergillus* spp., *Fusarium* spp., *Acremonium* spp., *Scopulariopsis* spp. and *Scytalidium* spp.) appear to be causative pathogens in an increasing number of cases.[17-19]

Most fungal infections of the skin and keratinised tissues are treatable and are readily diagnosed through a combination of patient history, physical examination, and microscopy and culture of skin or nail specimens. However, the causative agent is not routinely identified.

In most patients, the symptoms are mild and not life threatening, but the impact on the patient's quality of life can be severe.[20-23] In onychomycosis, for example, toenail dystrophy may interfere with walking, standing, exercise or proper shoe fit, and fingernail infection may limit daily activities such as dressing or typing. Patients with unsightly infected nails may also be embarrassed by the condition, which, in turn, can affect their personal relationships and social lives by causing loss of confidence and self-esteem.[23-25]

Superficial fungal infections, particularly of the toenails and feet, can also act as a reservoir of organisms, which could spread to other areas of the body or other individuals. Immunocompromised patients, in particular, should be examined for early

Table I. Clinical classification of some frequently observed fungal infections

Infection type	Disease	Typical causative pathogen	Clinical manifestation
Superficial (outermost layers of skin, nails, hair, mucous membranes)	Tinea pedis (feet)	*Trichophyton rubrum*, *T. mentagrophytes* var. *interdigitale*	Scaling and itching between the toes, which may spread to the sole
	Tinea capitis (scalp)	*T. tonsurans*, *Microsporum audouinii*	Scalp hair loss and scaling, sometimes with crusting, oozing and itchiness
	Tinea unguium or onychomycosis (nails)	*T. rubrum*, *T. mentagrophytes* var. *mentagrophytes*, *Candida* spp., and some moulds, e.g. *Aspergillus* spp., *Scopulariopsis* spp., *Scytalidium* spp.	Thickened, discoloured and broken nail, with separation of the nail plate from its bed
	Tinea versicolor (chest, back, neck and arms)	*Malassezia furfur*	Individual reddish, slightly scaly lesions on white skin; hypo- or hyperpigmentation on black or white skin
	Mucosal candidiasis: oral candidiasis genital candidiasis	*Candida* spp. (usually *C. albicans)*	White plaques (often on the soft palate and buccal mucosa) Itching, redness, thick white discharge and irritation when urinating
Subcutaneous (skin and subcutaneous tissues)	Sporotrichosis	*Sporothrix schenckii*	Localised cutaneous or subcutaneous lesion, which may spread via the lymphatic system and form further lesions
	Chromoblastomycosis	Dematiaceae family	Raised, crusted lesions of the skin
	Chronic mucocutaneous candidiasis	*Candida* spp. (predominantly *C. albicans*)	Various manifestations including: white fissured lesions; hyperkeratotic, granulomatous and vegetating lesions; autosomal recessive trait associated with endocrine disorders, e.g. hypoparathyroidism
Systemic (deep tissue invasion of one or more internal organs)	**Opportunistic:** Invasive candidiasis/candidaemia	*C. albicans* and other non-*albicans Candida* spp.	Prolonged antibiotic-resistant fever, often associated with weight loss, abdominal pain, and hepatic and/or spleen enlargement; CT scan may reveal small radiolucent lesions in liver or spleen in patients with chronic invasive candidiasis (hepatosplenic candidiasis)
	Invasive aspergillosis	*Aspergillus* spp.	Prolonged antibiotic-resistant fever; histopathological appearance of nonpigmented, septate hyphae with dichotomous branching; CT scan shows characteristic halo and/or air crescent signs; radiography may reveal single or multifocal lesions
	Cryptococcosis	*Cryptococcus neoformans*	Meningitis most common clinical manifestation; haematogenous spread may occur, giving rise to widespread cutaneous lesions
	Zygomycosis	*Rhizopus* spp. *Absidia* spp. *Mucor* spp.	May manifest as rhinocerebral, pulmonary, gastrointestinal or cutaneous mucormycosis; disseminated mucormycosis can follow, spreading most frequently to the brain, with possible metastatic lesions in the spleen, heart and other organs
	Other invasive infections	*Malassezia* spp.	Catheter-associated sepsis related to hyperalimentation with lipid emulsions; pneumonia may also be present
		Trichosporon spp.	Infrequent disseminated disease occurs in granulocytopenic patients, with fatal outcome; bloodstream infections manifest as skin and lung lesions and give false positives in cryptococcal antigen tests
		Fusarium spp.	Infection of mycetoma, endophthalmitis, facial granuloma, osteomyelitis and brain abscess; disseminated disease in neutropenic patients with positive blood cultures and skin lesions

Table I. Continued

Infection type	Disease	Typical causative pathogen	Clinical manifestation
	Endemic:		
	Blastomycosis	*Blastomyces dermatitidis*	Chronic progressive form may disseminate to skin, genitourinary tract, bone or central nervous system, involving ulcerative or verrucous cutaneous lesions
	Histoplasmosis	*Histoplasma capsulatum*	Pulmonary, extrapulmonary or disseminated infection, which includes hepatosplenomegaly, pancytopenia and oral ulcers; multiple cutaneous lesions may be evident in HIV-infected patients
	Coccidioidomycosis	*Coccidioides immitis*	Primary pulmonary infection, which may disseminate to extrapulmonary sites, resulting in cutaneous/soft tissue infection, osteomyelitis, arthritis and meningitis
	Paracoccidioidomycosis	*Paracoccidioides brasiliensis*	Pulmonary and/or disseminated disease, frequently involving skin, mucosa and lymph nodes
	Penicilliosis	*Penicillium marneffei*	Multiple organ involvement, manifesting as lymphadenitis, skin lesions, subcutaneous abscesses, bone lesions, arthritis, enlarged spleen, or lung, liver or bowel lesions

CT = computed tomography.

signs of superficial disease because they are at increased risk of these infections developing into an invasive form. Thus, there is a strong rationale for treating patients with non–life-threatening but disfiguring skin conditions.

1.2 Infections of the Mucous Membrane

Mucosal candidiasis affects the oesophagus, mouth, genitals or moist areas of the skin. Vaginal candidiasis is the most frequently occurring gynaecological infection in healthy women, with up to 95% of cases being caused by *C. albicans*.[26,27] The condition is readily diagnosed and can be treated effectively with topical or oral azoles.[28]

Mucosal candidiasis is a common complication of HIV infection, with more than 90% of individuals with progressive HIV disease developing oropharyngeal candidiasis at some time during the course of their disease (fig. 1c).[29] Although *C. albicans* is the predominant causative agent in this condition, a number of non-*albicans Candida* strains are currently emerging.[30] Oropharyngeal candidiasis usually responds well to topical and systemic azole therapy,[30] although treatment-resistant *Candida* strains have emerged in severely immunosuppressed HIV-infected patients with recurrent disease.[31] The frequency of oropharyngeal candidiasis is reduced in HIV-infected patients treated with, and responding to, protease inhibitor therapy.[32]

2. Subcutaneous Fungal Infections

Although subcutaneous mycoses can disseminate, they are usually limited to the dermis and subcutaneous tissues. Disease is caused by a variety of pathogens, which are often restricted to tropical and subtropical regions of the world. Sporotrichosis, for example, is caused by the dimorphic fungus *Sporothrix schenckii* and is the most prevalent subcutaneous infection in parts of Latin America.[33] The fungus is found in soil and vegetation and usually causes disease in farmers or gardeners, especially those who tend roses. Infection manifests as a lesion, which may spread to other subcutaneous sites via the lymphatic channels. Lymphocutaneous sporotrichosis is a non–life-threatening disease and normally responds well to treatment with itraconazole.[34] However, diagnosis can be delayed because the clinical presentation may mimic diseases caused by mycobacteria and other infectious agents.

Chromoblastomycosis is a chronic cutaneous or subcutaneous fungal infection caused by members of the Dematiaceae family found in wood, vegetable

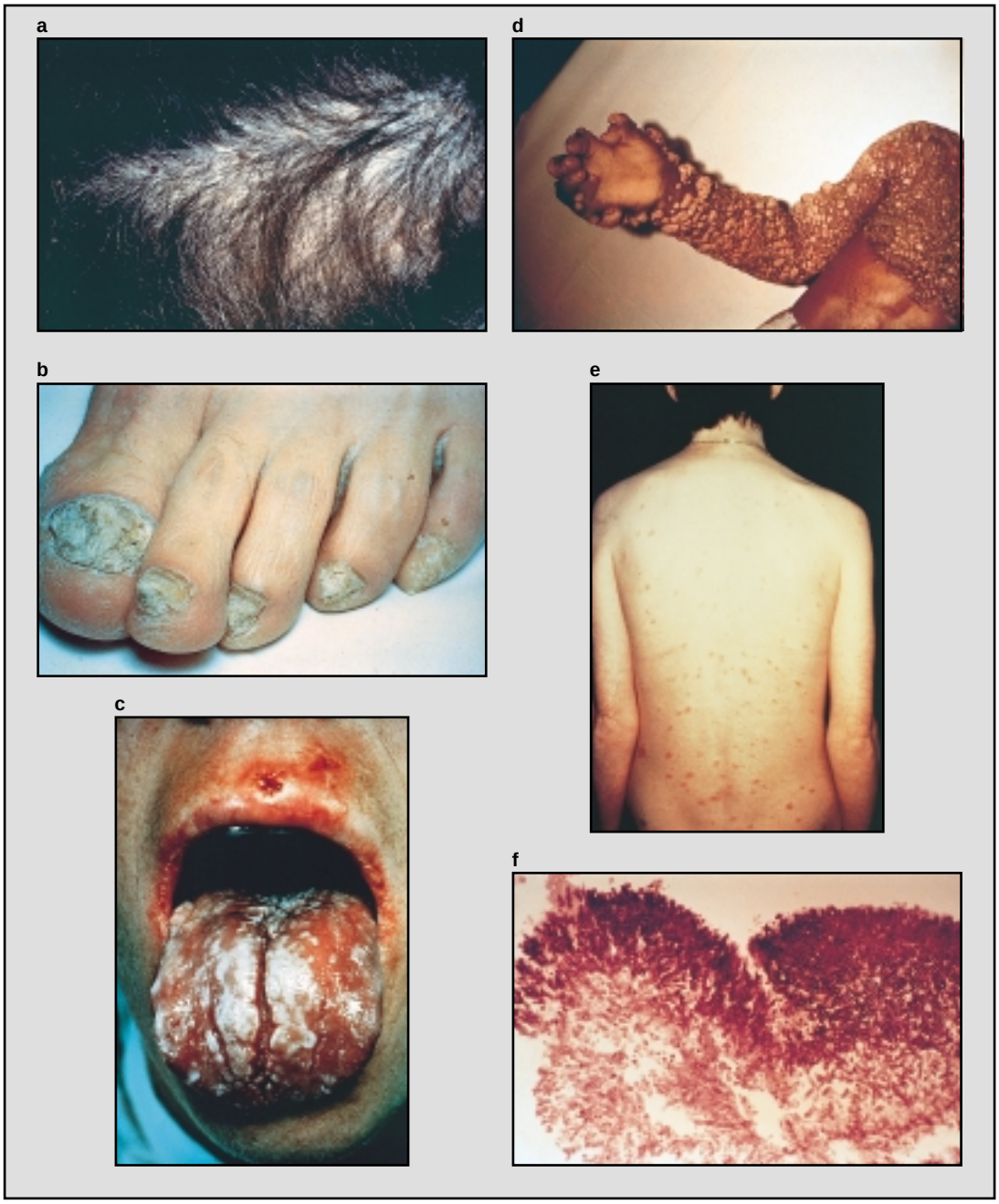

Fig. 1. Clinical presentations of some frequently observed fungal infections: (**a**) tinea capitis due to *Trichophyton tonsurans*; (**b**) onychomycosis due to *Trichophyton rubrum*; (**c**) chronic oral candidiasis; (**d**) chromoblastomycosis; (**e**) cutaneous lesions in a patient with disseminated candidiasis; (**f**) histopathological appearance of an aspergilloma. (Reproduced with permission from Richardson et al.[8])

debris and soil; these include *Fonsecaea pedrosoi*, *Cladosporium carrionii*, *F. compacta*, *Phialophora verrucosa* and *Rhinocladiella aquaspersa* (fig. 1d).[35] The disease has a worldwide distribution, with most cases occurring in tropical and subtropical regions, such as the Amazon.[36] Diagnosis is made by the histological examination of scrapings or biopsy material, where the presence of sclerotic bodies confirms the disease. The characteristic primary lesion may acquire a secondary infection, leading to lymph stasis and elephantiasis and, in rare cases, haematogenous spread to the brain, lymph nodes, liver, lungs and other organs. There is no standard treatment for this disease, but combinations of therapies have proved to be effective.[37]

Chronic mucocutaneous candidiasis is a rare syndrome consisting of chronic infection of mucous membranes (usually by *C. albicans*), which may extend to the skin and nails. The condition is associated with impaired cell-mediated responses to *Candida*, although the underlying defect remains poorly understood.[38,39]

3. Systemic Fungal Infections

3.1 Opportunistic Systemic Fungal Infections

Opportunistic systemic fungal infections occur primarily when some aspect of the normal host defence is compromised. Such infections are life threatening and are associated with high rates of death. Because of the growing population of immunocompromised individuals, the frequency of systemic fungal infections is increasing significantly.[1,2] Between 1980 and 1990, the number of nosocomial fungal infections rose from 2.0 to 3.8 infections per 1000 discharges from US hospitals.[40] A smaller study in one Taiwanese hospital recorded an increase from 0.9 to 6.6 nosocomial fungal infections per 1000 discharges between 1981 and 1993.[41]

3.1.1 High-Risk Patient Groups

Patients with haematological malignancies, such as myeloid and lymphocytic leukaemias, are at particularly high risk of infectious complications. Infections can occur when the patient develops neutropenia of long duration caused by the haematological malignancy itself or the treatment administered. For example, patients receiving bone marrow transplants are given immunosuppressive drugs (e.g. corticosteroids or cyclosporin) to prevent or treat rejection. Intensive myelosuppressive chemotherapy also causes neutropenia in patients. Approximately 20 to 50% of patients who die from haematological malignancies have evidence of invasive fungal infections at autopsy.[42,43] In one retrospective study, mortality was 73% for bone marrow recipients with *Candida* infections and 84% for those with *Aspergillus* or other mould infections. The death rate was even higher in patients with mixed *Aspergillus* and *Candida* tissue infections.[3]

Solid organ transplant recipients who receive immunosuppressive medications to limit the risk of rejection also have an increased susceptibility to systemic fungal infections. Fungal infections occur in 5 to 45% of all solid organ transplant patients[44,45] and are a primary cause of morbidity and mortality in this population. Burns patients are another population at high risk; the wound site is susceptible to colonisation by opportunistic fungi such as *Candida*,[46] but nowadays this is generally well managed and candidiasis in burns patients may originate in the gastrointestinal tract or from intravenous catheters.

Changes in medical procedures have contributed to the increased incidence of systemic fungal infections. The skin and mucosal surfaces normally prevent micro-organisms entering the body, but, if these barriers are compromised, for example, during surgery or when indwelling catheters are used, fungal cells are able to invade. Myelosuppressive chemotherapy may also cause mucosal lesions, allowing the invasion of fungi. Allogeneic bone marrow transplant recipients face the additional risk of developing graft-versus-host disease, which can damage the mucosal surfaces and normally requires an increase in immunosuppressive therapy. In lung transplant recipients, the donor organ can also be a reservoir for pathogenic fungi, which

may have been dormant or harmless in the donor but can be a source of post-transplantation infection in the immunosuppressed recipient.

Previous fungal infection may predispose high-risk patients to subsequent systemic infections because fungi can remain dormant for some time and become reactivated when the patient is immunosuppressed.[47,48] High-risk patients with damaged mucosal surfaces caused by bacterial or viral infections may be at a higher risk of infection by *Candida* spp. A high level of colonisation by *Candida* in the gastrointestinal tract and oral cavity may also increase the threat of systemic candidal infection in patients at high risk.[47,48] An additional contributory factor is the use of antibiotics, which disrupt the microbial flora, allowing colonisation by fungi. Antibiotic therapy also leads to increased survival of patients who are predisposed to fungal infection.

Immunocompromised patients readily acquire fungal infections from their environment if standard safety procedures are not followed. For example, *Aspergillus* spp. are airborne fungi and may be propagated through ventilation systems. The risk of infection can be greatly reduced by the use of high-efficiency particulate air (HEPA) filtration.[49] Transmission of *Candida* from the hands of medical professionals is also an important cause of nosocomial infections. Handwashing is therefore vital, but unfortunately the rigorous compliance necessary to reduce infection is not always present.[50]

Other patients at risk include those with medical conditions that compromise the immune system, the most notable being advanced HIV immune dysfunction or AIDS. Because of the extreme degree of immunosuppression in this patient group, fungal infections can be unusually virulent and persistent. Between 60% and 90% of individuals with progressive HIV disease develop at least one fungal infection during the course of the disease.[29,51] Among the most frequently occurring fungal infections in this group are candidiasis, cryptococcosis, and less frequently aspergillosis,[52] although, in specific geographical regions, endemic mycoses are important (for example, coccidioidomycosis, penicilliosis with *Penicillium marneffei*, and histoplasmosis).[53,54]

Individuals with chronic granulomatous disease (CGD), an inherited abnormality of the neutrophils that serve as an important defence against fungi, are also predisposed to infection. In one study of 245 patients with CGD, fungi – including *Aspergillus* and *Candida* – were isolated in 20% of cases.[55]

3.1.2 Diagnosis

Diagnosis of systemic fungal infections is problematical and many infections are confirmed only at autopsy.[43] The clinical symptoms are nonspecific and similar to those of bacterial and viral infections. In addition, the isolation of fungi from clinical samples is unreliable and may be complicated by the presence of a colonising commensal organism, or ubiquitous fungi in the environment, causing false-positive results.[56] Furthermore, the collection of clinical samples often requires an invasive procedure, which may not be advisable in critically ill patients. Direct microscopic examination of clinical samples may provide a tentative diagnosis, but this is often difficult to confirm by culture because of the presence of atypical fungal elements or sparse fungal populations. Serological tests that detect antibodies are low in sensitivity and specificity because many patients with systemic fungal infections are immunocompromised and therefore have an impaired antibody response. However, even in immunocompetent individuals, the delay between the onset of infection and the development of the antibody response reduces the practical value of these tests.

Improvements in the diagnosis of invasive pulmonary aspergillosis include the greater use of routine high-resolution computed tomography (CT) scanning,[57] polymerase chain reaction (PCR) for the detection of RNA or DNA[58] and enzyme-linked immunosorbent assay (ELISA) testing for circulating galactomannan, a component of the fungal cell wall in *Aspergillus*.[59] None of these tests has been proven to determine definitive

invasive disease but positive results are generally highly predictive of invasive disease.

Sequential positive results from laboratory diagnostic tests may be the best means of predicting systemic fungal infection; however, because of the life-threatening nature of the condition, there is usually not sufficient time to obtain a definitive diagnosis of the causative agent before treatment is required. Another complicating factor when considering appropriate antifungal therapy is that some patients are infected by more than one pathogen simultaneously.[3]

3.1.3 Epidemiology

Surveillance of bloodstream fungal pathogens is important in the identification of changing epidemiological trends. In the USA, for example, monitoring is performed on a national scale by groups such as the National Nosocomial Infections Surveillance System (NNISS), the National Epidemiology of Mycoses Survey (NEMIS) and the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE). Most nosocomial fungal infections are reported to be caused by *Candida* spp.,[40,43,60] although *Aspergillus* infections are becoming more frequent.[61,62]

Candida

In one international autopsy survey of cancer patients, *Candida* spp. were responsible for 58% of all fungal infections (fig. 1e).[43] *Candida* spp. currently rank as the fourth most frequent cause of nosocomial bloodstream infections, accounting for 8% of all cases.[63,64] Nosocomial candidiasis may be either endogenous (acquired through previous colonisation of the mouth, gastrointestinal tract, vagina or skin) or, less frequently, exogenous (acquired by cross-infection from another patient or healthcare worker).

C. albicans is the most frequently isolated species, causing between 48% and 60% of bloodstream fungal infections.[40,60,63] However, a change in the pattern of *Candida*-related disease has been seen in recent years, resulting in the emergence of a number of important non-*albicans Candida* spp., such as *C. krusei*, *C. parapsilosis*, *C. tropicalis* and *C. glabrata* (table II).[60,63-67] In one study of four hospitals over 3.5 years, the proportion of non-*albicans* spp. rose from 40% to 53% of all candidaemias during the study period.[66]

This epidemiological change has major clinical implications because infections by some non-*albicans Candida* spp. have higher complication and death rates than *C. albicans* infections and some species are resistant to antifungal agents. There is some evidence that the use of fluconazole prophylaxis has contributed to this shift in *Candida* epidemiology among cancer patients,[68,69] although the establishment of a causal relationship remains controversial.[70]

Aspergillus

Aspergillus spp. are ubiquitous, occurring most frequently in soil, water and decaying vegetation. Most *Aspergillus* infections are acquired through

Table II. Distribution of *Candida* bloodstream isolates from a range of epidemiology surveys between 1952 and 1996

Patient group	Candidaemia episodes (n)	Study period	*Candida* isolates from bloodstream infections (%)						Ref.
			C. albicans	*C. tropicalis*	*C. glabrata*	*C. parapsilosis*	*C. krusei*	Other *Candida* spp.	
Cancer pts	1591	1952-92	54	25	8	7	4	2	65
Nonspecified pts with confirmed candidaemia	446	1990-94	52	16	6	11	4	2	66[a]
Pts in surgical ICU	42	1993-95	48	19	24	7	NS	2	60
Pts in neonatal ICU	35	1993-95	63		6	29	NS	3	60
Nonspecified pts with nosocomial candidaemia	379	1995-96	52	11	20	8	5	4	63,64

a Figures in original paper did not add up to 100%.

ICU = intensive care unit; **NS** = not specified; **pts** = patients; **Ref**. = reference no.

the respiratory tract and are associated with hospital construction work or contaminated ventilation systems.[71] Infections may also be acquired from plants or from certain foods such as pepper.[72] *Aspergillus* infections have increased significantly in recent years, accounting for 30% of fungal infections in one postmortem survey of cancer patients (fig. 1f).[43]

The incidence of *Aspergillus* infections in neutropenic patients varies from centre to centre. In one survey of nonallografted patients with multiple myeloma who were treated at haematology or oncology centres in Europe between 1984 and 1996, 45% of patients with definite or probable invasive aspergillosis were considered to have died as a result of the infection.[73] In another study, *Aspergillus* spp. were isolated in 36% of patients with nosocomial pneumonia in a bone marrow transplant unit; the estimated crude mortality was 95%.[61] *Aspergillus* is the leading cause of fungal infection in bone marrow transplant patients who have received prophylaxis with fluconazole.[74]

Invasive aspergillosis is usually caused by *Aspergillus fumigatus* and to a lesser extent by *A. flavus*, *A. niger* and *A. terreus*. However, little information is available on the relative proportions of infections caused by the various *Aspergillus* spp.

Cryptococcus

Cryptococcal infection usually results from the inhalation of *Cryptococcus neoformans*, which is found primarily in soil contaminated by pigeon or chicken excreta. *Cryptococcus* has a particular affinity for the central nervous system, resulting in cryptococcal meningitis, and is one of the most significant life-threatening fungal infections associated with HIV.[75] Cryptococcal infection may also be seen in non-immunocompromised individuals[76] and in patients with impaired cell-mediated immunity, for example, those undergoing solid organ transplantation.[77]

Emerging Opportunistic Fungi

Rarer pathogens that have emerged during recent years include *P. marneffei*, *Fusarium* spp., *Malassezia* spp., *Trichosporon* spp., *Saccharomyces cerevisiae* and *Blastoschizomyces capitatus*.[54,78-80] Penicilliosis, for example, is now the third most frequently occurring opportunistic infection in HIV-infected patients in Southeast Asia, and isolated cases have also been reported in western countries.[54] Invasive infection by *M. furfur*, a commensal yeast of the skin normally associated with the superficial fungal infection tinea versicolor, has also increased in frequency in recent years, and is associated with parenteral nutrition.[13]

Fungal infections from the class Mucorales (e.g. *Mucor*, *Absidia* and *Rhizopus*) are seen increasingly in immunocompromised hosts[81] and may sometimes be associated with diabetic patients.[82,83] Typically an airborne disease, Mucorales infections are initiated in the upper or lower airways and have clinical symptoms similar to those of aspergillosis.

3.2 Endemic Mycoses

Endemic mycoses occur in specific geographical locations and are a major public health problem in certain countries. They are becoming increasingly widespread because of land development in endemic areas and the proliferation of HIV infection. In addition, with travel becoming increasingly available, an endemic disease may be identified in a patient thousands of miles from the point of exposure. Examples in the USA include infections with *Blastomyces dermatitidis* in the central and southeastern states, *Histoplasma capsulatum* in the Mississippi river valley and *Coccidioides immitis* in the southwestern states (table I).[84-86] In Central and South America, endemic mycoses frequently encountered include *Paracoccidioides brasiliensis* infections and chromoblastomycosis. In Southeast Asia, infections with *P. marneffei* are a significant problem.[54] Life-threatening endemic mycoses occur in both immunocompetent and immunocompromised hosts, and the efficacy of antifungal agents for the treatment of these conditions is constantly being evaluated.[87] However, the clinical picture is not always specific; the symptoms of coccidioidomycosis, for example, are

similar to those of *Mycobacterium tuberculosis* infection.[88,89]

4. Conclusion

The incidence of local and systemic fungal infections is increasing at an alarming rate. This is primarily due to advances in medical practice, which have resulted in the proliferation of severely ill, immunocompromised, hospitalised patients. The HIV epidemic and other diseases of the immune system have added to this growing at-risk population.

Superficial fungal infections are mild but may spread to other areas of the body or, occasionally, to other individuals. More seriously, but less frequently, they may develop into invasive forms. Although not life threatening, conditions such as onychomycosis can have a severe impact on a patient's quality of life and self-image. It is therefore desirable to treat local fungal infections to prevent the risk of spread.

Systemic fungal infections in immunocompromised patients, such as bone marrow and solid organ transplant recipients, are associated with high rates of mortality. *C. albicans* and *Aspergillus* spp. are the most prevalent pathogens in systemic infections, but a recent shift in the burden of disease has seen the emergence of a number of important non-*albicans Candida* spp. in addition to rare infectious agents such as *M. furfur*. Although the incidence of fungal infections can be reduced by minimising risk factors in hospitals, such as poor hygiene practice, our inability to reliably prevent such infections highlights the need for effective treatments.

References

1. Groll AH, Shah PM, Mentzel C, et al. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect 1996; 33: 23-32
2. Denning DW, Evans EGV, Kibbler CC, et al. Guidelines for the investigation of invasive fungal infections in haematological malignancy and solid organ transplantation. Eur J Clin Microbiol Infect Dis 1997; 16: 424-36
3. Meyers JD. Fungal infections in bone marrow transplant patients. Semin Oncol 1990; 17 Suppl. 6: 10-3
4. Detandt M, Nolard N. Fungal contamination of the floors of swimming pools, particularly subtropical swimming paradises. Mycoses 1995; 38: 509-13
5. Piérard GE, Arrese JE, Piérard-Franchimont C. Treatment and prophylaxis of tinea infections. Drugs 1996; 52: 209-24
6. Evans EG. Tinea pedis: clinical experience and efficacy of short treatment. Dermatology 1997; 194 Suppl. 1: 3-6
7. Semel JD, Goldin H. Association of athlete's foot with cellulitis of the lower extremities: diagnostic value of bacterial cultures of ipsilateral interdigital space samples. Clin Infect Dis 1996; 23: 1162-4
8. Richardson MD, Warnock DW, Campbell CK. Slide Atlas of Fungal Infection. Oxford, UK: Blackwell Science Limited, 1995
9. Elewski BE. Tinea capitis: a current perspective. J Am Acad Dermatol 2000; 42 (1 Pt 1): 1-20; quiz 21-4
10. Bronson DM, Desai DR, Barsky S, et al. An epidemic of infection with *Trichophyton tonsurans* revealed in a 20-year survey of fungal infections in Chicago. J Am Acad Dermatol 1983; 8: 322-30
11. Hay RJ, Clayton YM, De Silva N, et al. Tinea capitis in south-east London - a new pattern of infection with public health implications. Br J Dermatol 1996; 135: 955-8
12. Savin R. Diagnosis and treatment of tinea versicolor. J Fam Pract 1996; 43: 127-32
13. Marcon MJ, Powell DA. Epidemiology, diagnosis, and management of *Malassezia furfur* systemic infection. Diagn Microbiol Infect Dis 1987; 7: 161-75
14. Chiritescu MM, Chiritescu ME, Scher RK. Newer systemic antifungal drugs for the treatment of onychomycosis. Clin Podiatr Med Surg 1996; 13: 741-58
15. Levy LA. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc 1997; 87: 546-50
16. Gupta AK, Konnikov N, MacDonald P, et al. Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. Br J Dermatol 1998; 139: 665-71
17. Tosti A, Piraccini BM, Lorenzi S. Onychomycosis caused by nondermatophytic molds: clinical features and response to treatment of 59 cases. J Am Acad Dermatol 2000; 42 (2 Pt 1): 217-24
18. Ellis DH, Watson AB, Marley JE, et al. Non-dermatophytes in onychomycosis of the toenails. Br J Dermatol 1997; 136: 490-3
19. Greer DL. Evolving role of nondermatophytes in onychomycosis [review]. Int J Dermatol 1995; 34: 521-4
20. Finlay AY. Quality of life measurement in dermatology: a practical guide. Br J Dermatol 1997; 136: 305-14
21. Morgan M, McCreedy R, Simpson J, et al. Dermatology quality of life scales - a measure of the impact of skin diseases. Br J Dermatol 1997; 136: 202-6
22. Drake LA, Scher RK. Onychomycosis: a significant and important disease. Second International Symposium on Onychomycosis; 1995 Sep 28-29; Florence, Italy
23. Drake LA, Scher RK, Smith EB, et al. Effect of onychomycosis on quality of life. J Am Acad Dermatol 1998; 38: 702-4
24. Scher RK. Onychomycosis is more than a cosmetic problem. Br J Dermatol 1994; 130 Suppl. 43.: 15-6
25. Lubeck DP, Patrick DL, McNulty P, et al. Quality of life of persons with onychomycosis. Qual Life Res 1993; 2: 341-8
26. Mendling W, Gutschmidt J, Gantenberg R, et al. Comparison of strain specificity of yeasts from various organs of women with vaginal candidiasis [in German]. Mycoses 1998; 41 Suppl. 2: 23-5
27. Regulez P, Garcia-Fernandez JF, Moragues MD, et al. Detection of anti-*Candida albicans* IgE antibodies in vaginal washes from patients with acute vulvovaginal candidiasis. Gynecol Obstet Invest 1994; 37: 110-4

28. Woolley PD, Higgins SP. Comparison of clotrimazole, fluconazole and itraconazole in vaginal candidiasis. Br J Clin Pract 1995; 49: 65-6
29. Vazquez JA. Options for the management of mucosal candidiasis in patients with AIDS and HIV infection. Pharmacotherapy 1999; 19: 76-87
30. Powderly WG, Mayer KH, Perfect JR. Diagnosis and treatment of oropharyngeal candidiasis in patients infected with HIV: a critical reassessment. AIDS Res Hum Retroviruses 1999; 15: 1405-12
31. Hoepelman IM, Dupont B. Oral candidiasis: the clinical challenge of resistance and management. Int J Antimicrob Agents 1996; 6: 155-9
32. Diz-Dios P, Ocampo A, Miralles C, et al. Frequency of oropharyngeal candidiasis in HIV-infected patients on protease inhibitor therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87: 437-41
33. Rios-Fabra A, Moreno AR, Isturiz RE. Fungal infection in Latin American countries. Infect Dis Clin North Am 1994; 8: 129-54
34. Sharkey-Mathis PK, Kauffman CA, Graybill JR, et al. Treatment of sporotrichosis with itraconazole. NIAID Mycoses Study Group. Am J Med 1993; 95: 279-85
35. Chapman SW, Daniel CR 3rd. Cutaneous manifestations of fungal infection. Infect Dis Clin North Am 1994; 8: 879-910
36. Silva JP, de Souza W, Rozental S. Chromoblastomycosis: a retrospective study of 325 cases on Amazonic Region (Brazil). Mycopathologia 1998-99; 143: 171-5
37. Bonifaz A, Martinez-Soto E, Carrasco-Gerard E, et al. Treatment of chromoblastomycosis with itraconazole, cryosurgery, and a combination of both. Int J Dermatol 1997; 36: 542-7
38. Lilic D, Cant AJ, Abinun M, et al. Chronic mucocutaneous candidiasis. I. Altered antigen-stimulated IL-2, IL-4, IL-6 and interferon-gamma (IFN-gamma) production. Clin Exp Immunol 1996; 105: 205-12
39. Lilic D, Calvert JE, Cant AJ, et al. Chronic mucocutaneous candidiasis. II. Class and subclass of specific antibody responses in vivo and in vitro. Clin Exp Immunol 1996; 105: 213-9
40. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. National Nosocomial Infections Surveillance System. J Infect Dis 1993; 167: 1247-51
41. Chen YC, Chang SC, Sun CC, et al. Secular trends in the epidemiology of nosocomial fungal infections at a teaching hospital in Taiwan, 1981 to 1993. Infect Control Hosp Epidemiol 1997; 18: 369-75
42. Meunier-Carpentier F. Symposium on infectious complications of neoplastic disease (Part II). Chemoprophylaxis of fungal infections. Am J Med 1984; 76: 652-6
43. Bodey G, Bueltmann B, Duguid W, et al. Fungal infections in cancer patients: an international autopsy survey. Eur J Clin Microbiol Infect Dis 1992; 11: 99-109
44. Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. Infect Dis Clin North Am 1995; 9: 1045-74
45. Kanj SS, Welty-Wolf K, Madden J, et al. Fungal infections in lung and heart-lung transplant recipients. Report of 9 cases and review of the literature. Medicine 1996; 75: 142-56
46. Still Jr JM, Belcher K, Law EJ. Management of candida septicaemia in a regional burn unit. Burns 1995; 21: 594-6
47. Guiot HFL, Fibbe WE, van't Wout JW. Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. Clin Infect Dis 1994; 18: 525-32
48. Martino R, Lopez R, Sureda A, et al. Risk of reactivation of a recent invasive fungal infection in patients with hematological malignancies undergoing further intensive chemo-radiotherapy. A single-center experience and review of the literature. Haematologica 1997; 82: 297-304
49. Sherertz RJ, Belani A, Kramer BS, et al. Impact of air filtration on nosocomial *Aspergillus* infections. Unique risk of bone marrow transplant recipients. Am J Med 1987; 83: 709-18
50. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. Infection Control Program. Ann Intern Med 1999; 130: 126-30
51. Benedict S, Colagreco J. Fungal infections associated with malignancies, treatments and AIDS. Cancer Nursing 1994; 17: 411-7
52. Kappe R, Levitz S, Harrison TS, et al. Recent advances in cryptococcosis, candidiasis and coccidioidomycosis complicating HIV infection. Med Mycol 1998; 36 Suppl. 1: 207-15
53. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. Medicine 1990; 69: 361-74
54. Duong TA. Infection due to *Penicillium marneffei*, an emerging pathogen: review of 155 reported cases. Clin Infect Dis 1996; 23: 125-30
55. Cohen MS, Isturiz RE, Malech HL, et al. Fungal infection in chronic granulomatous disease. The importance of the phagocyte in defense against fungi. Am J Med 1981; 71: 59-66
56. Jensen HE, Salonen J, Ekfors TO. The use of immunohistochemistry to improve sensitivity and specificity in the diagnosis of systemic mycoses in patients with haematological malignancies. J Pathol 1997; 181: 100-5
57. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 1997; 15: 139-47
58. Einsele H, Hebart H, Roller G, et al. Detection and identification of fungal pathogens in blood by using molecular probes. J Clin Microbiol 1997; 35: 1353-60
59. Maertens J, Verhaegen J, Demuynck H, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive aspergillosis. J Clin Microbiol 1999; 37: 3223-8
60. Rangel-Frausto MS, Wiblin T, Blumberg HM, et al. National epidemiology of mycoses survey (NEMIS): variations in rates of bloodstream infections due to Candida species in seven surgical intensive care units and six neonatal intensive care units. Clin Infect Dis 1999; 29: 253-8
61. Pannuti CS, Gingrich RD, Pfaller MA, et al. Nosocomial pneumonia in adult patients undergoing bone marrow transplantation: a 9-year study. J Clin Oncol 1991; 9: 77-84
62. Wald A, Leisenring W, van Burik JA, et al. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 1997; 175: 1459-66
63. Pfaller MA, Jones RN, Messer SA, et al. National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 1998; 31: 327-32
64. Pfaller MA, Jones RN, Messer SA, et al. National surveillance of nosocomial blood stream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence

and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 1998; 30: 121-9
65. Wingard JR. Importance of *Candida* species other than *C. albicans* as pathogens in oncology patients [review]. Clin Infect Dis 1995; 20: 115-25
66. Nguyen MH, Peacock Jr JE,, Morris AJ, et al. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am J Med 1996; 100: 617-23
67. Odds FC. Epidemiological shifts in opportunistic and nosocomial *Candida* infections: mycological aspects. Int J Antimicrob Agents 1996; 6: 141-4
68. Abi-Said D, Anaissie E, Uzun O, et al. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis 1997; 24: 1122-8 [published erratum appears in Clin Infect Dis 997; 25: 352]
69. Wingard JR, Merz WG, Rinaldi MG, et al. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 1991; 325: 1274-7
70. White MH. The contribution of fluconazole to the changing epidemiology of invasive candidal infections [editorial]. Clin Infect Dis 1997; 24: 1129-30
71. Walsh TJ, Dixon DM. Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. Eur J Epidemiol 1989; 5: 131-42
72. Eccles NK, Scott GM. Aspergillus in pepper. Lancet 1992; 339: 618
73. Lortholary O, Ascioglu S, Moreau P, et al. Invasive aspergillosis as an opportunistic infection in nonallografted patients with multiple myeloma: a European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the Intergroupe Francais du Myelome. Clin Infect Dis 2000; 30: 41-6
74. van Burik JH, Leisenring W, Myerson D, et al. The effect of prophylactic fluconazole on the clinical spectrum of fungal diseases in bone marrow transplant recipients with special attention to hepatic candidiasis. An autopsy study of 355 patients. Medicine 1998; 77: 246-54
75. Dromer F, Mathoulin S, Dupont B, et al. Epidemiology of cryptococcosis in France: a 9-year survey (1985-1993). French Cryptococcosis Study Group. Clin Infect Dis 1996; 23: 82-90
76. Ruggieri M, Polizzi A, Vitaliti MC, et al. Fatal biphasic brainstem and spinal leptomeningitis with *Cryptococcus neoformans* in a non-immunocompromised child. Acta Paediatr 1999; 88: 671-4
77. Mitchell DH, Sorrell TC, Allworth AM, et al. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. Clin Infect Dis 1995; 20: 611-6
78. Fridkin SK, Jarvis WR. Epidemiology of nosocomial fungal infections. Clin Microbiol Rev 1996; 9: 499-511
79. Krcmery V, Krupova I, Denning DW. Invasive yeast infections other than Candida spp. in acute leukaemia. J Hosp Infect 1999; 41: 181-94
80. Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood 1997; 90: 999-1008
81. Sugar AM. Mucormycosis. Clin Infect Dis 1992; 14 Suppl. 1: S126-9
82. Parfrey NA. Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. Medicine 1986; 65: 113-23
83. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 38-1982. A 66-year-old diabetic woman with sinusitis and cranial-nerve abnormalities. N Engl J Med 1982; 307: 806-14
84. Reingold AL, Lu XD, Plikaytis BD, et al. Systemic mycoses in the United States, 1980-1982. J Med Vet Mycol 1986; 24: 433-6
85. Klein BS, Vergeront JM, Davis JP. Epidemiologic aspects of blastomycosis, the enigmatic systemic mycosis. Semin Respir Infect 1986; 1: 29-39
86. Kirkland TN, Fierer J. Coccidioidomycosis: a reemerging infectious disease. Emerg Infect Dis 1996; 2: 192-9
87. Lortholary O, Denning DW, Dupont B. Endemic mycoses: a treatment update. J Antimicrob Chemother 1999; 43: 321-31
88. Yozwiak ML, Lundergan LL, Kerrick SS, et al. Symptoms and routine laboratory abnormalities associated with coccidioidomycosis. West J Med 1988; 149: 419-21
89. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 21-1994. A 20-year-old Mexican immigrant with recurrent hemoptysis and a pulmonary cavitary lesion [clinical conference]. N Engl J Med 1994; 330: 1516-22

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