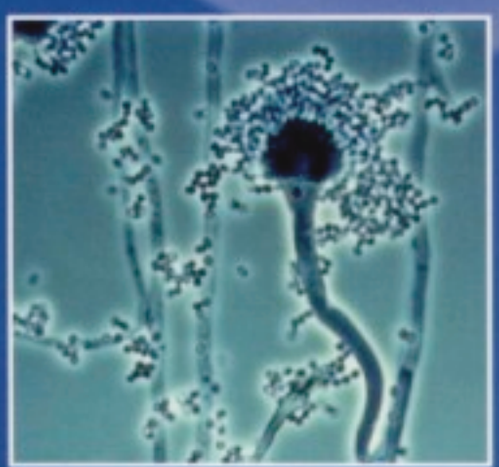
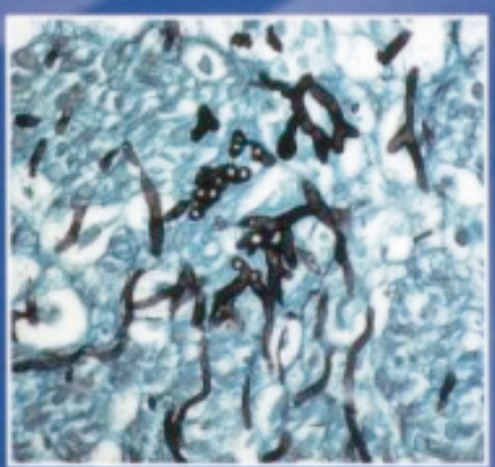
Fungal Infection

Diagnosis and Management

Malcolm D. Richardson
& David W. Warnock





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DIAGNOSIS
AND MANAGEMENT

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AND MANAGEMENT

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Preface to the third edition

In the six years that have elapsed since the second edition of this book was published, there have been a number of significant developments in the diagnosis and management of fungal infections. In developed countries, the introduction of combination antiretroviral treatment regimens has led to a marked reduction in the incidence of opportunistic fungal infections among persons with the acquired immunodeficiency syndrome (AIDS). In contrast, in countries where these drugs are unavailable, the burden of these diseases is large and increasing. Other developments in medical practice that have led to significant changes in the incidence of fungal infections include the increasing use of aggressive therapeutic technologies in intensive care units, novel immunosuppressive regimens among patients undergoing transplants or treatment for malignancies, the increasing use of azole antifungal agents for chemoprophylaxis, and the widespread use of amphotericin B for empirical treatment. In many instances, these developments have resulted in improved survival of individuals with life-threatening illnesses, but some have also contributed to the emergence of new populations at risk for fungal infections.

We have tried to include as many of these developments as possible without, we hope, confusing what is intended to be a concise introduction to the subject. For this edition, the general format of the book has been retained, but extensive revision has been undertaken, and separate sections on epidemiology and prevention have been added to most of the chapters. Another feature we have introduced is a short list of further reading at the end of each chapter. These lists are not by themselves all-embracing, but rather are intended to highlight some of the most important papers that we have drawn upon for the information provided in the text.

We have made every effort to ensure that our drug and dosage recommendations are accurate and in agreement with current guidelines. It should be noted that the

formulations and usages of the different drugs described do not necessarily have the specific approval of the regulatory authorities of all countries. Because dosage regimens can be modified in the light of new clinical research findings, readers are advised to check the manufacturers' prescribing information to see whether changes have been made in the recommended dosages, or whether additional contraindications for use have been introduced.

M.D.R., D.W.W.

Preface to the first edition

Fungal infections are assuming a greater importance, largely because of their increasing incidence among transplant patients and other immunocompromised individuals, including those with AIDS. As a result, clinicians and microbiologists alike need to be familiar with the clinical presentation and methods for the diagnosis of these infections, as well as the current treatment choices.

In this book we have attempted to provide a succinct account of the clinical manifestations, laboratory diagnosis and management of fungal infections found in European, American and Australasian practice. The book covers problems encountered both in hospitals and general practice, and is designed to permit clinicians to make the best use of the various laboratory investigations available. Emphasis is placed on clinical presentation, specimen collection, interpretation of laboratory findings, and choice of treatment regimen. In general, the length of the chapters reflects the frequency or the importance of the clinical problem, or both.

We have designed this book to facilitate rapid information retrieval. Our reading list of established literature has been carefully selected to permit efficient access to specific aspects of fungal infections and has been annotated to guide the reader.

We hope this book will be of interest to medical students, junior hospital medical staff, hospital specialists and general practitioners. In particular it should appeal to microbiologists, infectious disease specialists, dermatologists, haematologists, genitourinary medicine specialists, oncologists and intensive-care staff.

M.D.R., D.W.W.

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Fungal Infection: Diagnosis and Management, Third Edition
Malcolm D. Richardson, David W. Warnock

1 Introduction

The last two decades have seen unprecedented changes in the pattern of fungal infections in humans. These diseases have assumed a much greater importance because of their increasing incidence in persons with the acquired immunodeficiency syndrome (AIDS), in recipients of solid organ or haematopoietic stem cell transplants (HSCT), in persons with haematological malignancies and in other debilitated or immunocompromised individuals. Although gains have been made in the treatment and prevention of fungal infections, major changes in health care practices have resulted in the emergence of new at-risk populations.

1.1 The nature of fungi

The fungi form a separate group of higher organisms, distinct from both plants and animals in several major respects. First, fungal cells are encased within a rigid cell wall, mostly composed of chitin and glucan. This feature contrasts with animals, which have no cell walls, and plants, which have cellulose as the major cell wall component. Second, fungi are heterotrophic and cannot make their organic food as plants can, through photosynthesis. Fungi obtain their nourishment by secreting enzymes for external digestion and by absorbing the nutrients that are released. Third, fungi are simpler in structure than plants or animals. There is no division of cells into organs or tissues. The basic structural unit of fungi is either a chain of tubular, filament-like cells (termed a hypha) or an independent single cell. Many fungal pathogens of humans and animals change their growth form during the process of tissue invasion. These dimorphic pathogens usually change from a multicellular hyphal form in the natural environment to a budding, single-celled form in tissue.

In most multicellular fungi the vegetative stage consists of a mass of branching hyphae, termed mycelium. Each individual hypha has a rigid cell wall and increases

in length as a result of apical growth. In the more primitive fungi, the hyphae remain aseptate (without cross-walls). In the more advanced groups, however, the hyphae are septate, with more or less frequent cross-walls. Fungi that exist in the form of microscopic multicellular mycelium are often called moulds.

Many fungi that exist in the form of independent single cells propagate by budding out similar cells from their surface. The bud may become detached from the parent cell, or it may remain attached and itself produce another bud. In this way, a chain of cells may be produced. Fungi that do not produce hyphae, but simply consist of a loose arrangement of budding cells are called yeasts. Under certain conditions, continued elongation of the parent cell before it buds results in a chain of elongated cells, termed a pseudohypha.

Fungi reproduce by means of microscopic propagules called spores. Many fungi produce spores that result from an asexual process. Except for the occasional mutation, these spores are identical to the parent. Asexual spores are generally short-lived propagules that are produced in enormous numbers to ensure dispersion to new habitats. Many fungi are also capable of sexual reproduction. Some species are homothallic and able to form sexual structures within individual colonies. Most, however, are heterothallic and do not form their sexual structures unless two different mating strains come into contact. Meiosis then leads to the production of the sexual spores. In some species the sexual spores are borne singly on specialized generative cells and the whole structure is microscopic in size. In other cases, however, the spores are produced in millions in 'fruiting bodies' such as mushrooms. In current mycological parlance, the sexual stage of a fungus is known as the teleomorph, and the asexual stage the anamorph.

1.2 Classification and nomenclature of fungi and fungal diseases

The classification of fungi is largely based on the appearance, rather than on the nutritional and biochemical differences that are of much importance in bacterial classification. The sexual spores and structures in which they are produced form the main basis for fungal classi-

fication. In some fungi, however, the anamorphic stage has proved so successful as a means of rapid dispersal to new habitats that the teleomorphic stage has diminished or even disappeared. In these fungi the shape of the asexual spores and the arrangement of the spore-bearing structures are of major importance in classification and identification.

The scientific names of fungi are subject to the International Botanical Code of Nomenclature. In general the correct name for any organism is the first name published in line with the requirements of the Code. To avoid confusion, however, the Code allows for certain exceptions. The most significant of these is when an earlier generic name has been overlooked, a later name is in general use, and a reversion to the earlier name would cause much confusion. There are two main reasons for renaming a fungus. The first is reclassification in the light of more detailed investigation of its characteristics. The second is the discovery of the teleomorph of a previously anamorphic fungus. Many fungi bear two names, one designating their sexual stage and the other their asexual stage. Often this is because the anamorphic and teleomorphic stages were described and named at different times without the connection between them being recognized. Both these names are valid under the Code, but that of the teleomorph should take precedence. In practice, however, it is more common (and correct) to refer to a fungus by its asexual designation because this is the stage that is usually obtained in culture.

Unlike the names of fungi, the names of fungal diseases are not subject to strict international control. Their usage tends to reflect local practice. One popular method has been to derive disease names from the generic names of the causal organisms: for example, aspergillosis, cryptococcosis, histoplasmosis and so on. However, if the fungus changes its name, the disease name has to be changed as well. For example, moniliasis has become candidosis or candidiasis. In 1992, a subcommittee of the International Society for Human and Animal Mycology recommended that the practice of forming disease names from the names of their causes should be avoided, and that, whenever possible, individual diseases should

be named in the form 'pathology A due to (or caused by) fungus B'. This recommendation was not intended to apply to long-established disease names, such as aspergillosis, but rather to offer a more flexible approach to nomenclature.

There is also much to be said for the practice of grouping together mycotic diseases of similar origins under single headings. One of the broadest and most useful of these collective names is the term 'phaeohyphomycosis' which is used to refer to a range of superficial, subcutaneous and systemic infections caused by any brown-pigmented mould that adopts a septate hyphal form in host tissue (see Chapter 26). The number of organisms implicated as aetiological agents of phaeohyphomycosis has increased from 16 in 1975 to more than 100 at present. Often these fungi have been given different names at different times and the use of the collective disease name has helped to reduce the confusion in the literature. The term 'hyalohyphomycosis' is another collective name which is increasing in usage. This term is used to describe infections caused by colourless (hyaline) moulds that adopt a septate hyphal form in tissue (see Chapter 24). To date, more than 70 different organisms have been implicated, including a number of important emerging fungal pathogens.

1.3 Fungi as human pathogens

Among the 50 000 to 250 000 species of fungi that have been described, fewer than 500 have been associated with human disease, and no more than 100 are capable of causing infection in otherwise normal individuals. The remainder are only able to produce disease in hosts that are debilitated or immunocompromised in some way. In general these organisms are free living in nature and are in no way dependent on humans (or animals) for their survival. With few exceptions, fungal infections of humans originate from an exogenous source in the environment and are acquired through inhalation, ingestion or traumatic implantation.

Fungal infections can be classified into a number of broad groups according to the initial site of infection. This brings out clearly the degree of parasitic adaptation of the different groups of fungi and the way in which the

site affected is related to the route by which the fungus enters the host.

1.3.1 The superficial mycoses

These are infections limited to the outermost layers of the skin, the nails and hair, and the mucous membranes. The principal infections in this group are the dermatophytoses and superficial forms of candidosis. These diseases affect millions of individuals worldwide, but are readily diagnosed and usually respond well to treatment.

The dermatophytes are limited to the keratinized tissues of the epidermis, hair and nail. Most are unable to survive as free-living saprobes in competition with other keratinophilic organisms in the environment and thus are dependent on passage from host to host for their survival. These obligate pathogens seem to have evolved from unspecialized saprobic forms. In the process, most are now no longer capable of sexual, and some even asexual, reproduction. In general, these organisms have become well adapted to humans, evoking little or no inflammatory reaction from the host.

The aetiological agents of candidosis, like the dermatophytes, are largely dependent on the living host for their survival, but differ from them in the manner by which this is achieved. These organisms, of which *Candida albicans* is the most important, are normal commensal inhabitants of the human digestive tract or skin. Acquisition of these organisms from another host seldom results in overt disease, but rather in the setting-up of a commensal relationship with the new host. These organisms do not produce disease unless some change in the circumstances of the host lowers its natural defences. In this situation, endogenous infection from the host's own reservoir of the organism may result in mucosal, cutaneous or systemic infection.

1.3.2 The subcutaneous mycoses

These are infections involving the dermis, subcutaneous tissues and adjacent bone. These infections are usually acquired as a result of the traumatic implantation of organisms that grow as saprobes in the soil and on decomposing vegetation. These infections are most

frequently encountered among the rural populations of the tropical and subtropical regions of the world, where individuals go barefoot and wear the minimum of clothing. The disease may remain localized at the site of implantation or spread to adjacent tissue. More widespread dissemination of the infection, through the blood or lymphatics, is uncommon, and usually occurs only if the host is in some way debilitated or immunocompromised.

1.3.3 The systemic mycoses

These are infections that usually originate in the lungs, but may spread to many other organs. These infections are most commonly acquired as a result of inhaling spores of organisms that grow as saprobes in the soil or on decomposing organic matter, or as pathogens on plants.

The organisms that cause systemic fungal infection can be divided into two distinct groups: the true pathogens and the opportunists. The first of these groups consists of a handful of organisms, such as *Histoplasma capsulatum* and *Coccidioides immitis*, that are able to invade and develop in the tissues of a normal host with no recognizable predisposition. Often these organisms possess unique morphological features that appear to contribute to their survival within the host. The second group, the opportunists, consists of less virulent and less well-adapted organisms, such as *Aspergillus fumigatus*, that are only able to invade the tissues of an immunocompromised host.

In many instances, infections with true pathogenic fungi are asymptomatic or mild and of short duration. Most cases occur in geographical regions where the aetiological agents are found in nature and follow inhalation of spores that have been released into the environment. Individuals who recover from these infections enjoy marked and lasting resistance to reinfection, while the few patients with chronic or residual disease often have a serious underlying illness.

In addition to their well-recognized manifestations in otherwise normal persons, infections with true pathogenic fungi have emerged as important diseases in immunocompromised individuals. Histoplasmosis

and coccidioidomycosis, for instance, have been recognized as AIDS-defining illnesses. Both have been seen in significant numbers of human immunodeficiency virus (HIV)-infected persons throughout North and South America. In immunocompromised individuals, infections with true pathogenic fungi are often life-threatening and unresponsive to antifungal treatment, or may relapse following discontinuation of treatment.

Opportunistic fungal infections occur in individuals who are immunosuppressed as a result of an underlying illness or treatment. In most cases, infection results in significant disease. Resolution of the infection does not confer protection, and reinfection or reactivation may occur if host resistance is again lowered. In contrast to the restricted geographical distribution of most of the true pathogenic fungi, many opportunistic fungi are ubiquitous in the environment worldwide, being found in the soil, on decomposing organic matter and in the air. Although new species of fungi are regularly being identified as causes of disease in immunocompromised patients, four diseases still account for most reported infections: aspergillosis, candidosis, cryptococcosis and mucormycosis. These infections are associated with high mortality rates, but estimates of their incidence are thought to be quite conservative in comparison with their true magnitude because many cases go undiagnosed or unreported.

1.4 The changing pattern of fungal infection

Over the past few years, major advances in health care have led to an unwelcome increase in the number of life-threatening infections due to true pathogenic and opportunistic fungi. These infections are being seen in ever increasing numbers, largely because of the increasing size of the population at risk. This population includes persons with HIV infection, transplant recipients, cancer patients and other individuals receiving immunosuppressive treatment. Among patients undergoing transplants or treatment for malignancies, novel and more intensive regimens have resulted in more profound levels of immunosuppression that are sustained for longer periods. Likewise, the increasing use of invasive

monitoring and aggressive therapeutic technologies in intensive care units has resulted in improved survival of individuals with life-threatening illnesses, but has also contributed to an increase in the number of persons at risk for fungal infections. Other developments in medical practice that have led to significant changes in the incidence of fungal infections among the different groups of at-risk patients include the increasing use of azole antifungal agents for treatment and chemoprophylaxis, and the widespread use of amphotericin B for empirical treatment.

In addition to the rise in prevalence of opportunistic fungal infections due to such well-recognized organisms as *A. fumigatus* and *C. albicans*, an ever increasing number of fungi, hitherto regarded as harmless saprobes, are being reported as the cause of serious or lethal infection in immunocompromised individuals. For instance, *Fusarium* species, long recognized as a cause of nail and corneal infections, are now well documented as the aetiological agents of lethal disseminated infections in neutropenic cancer patients and HSCT recipients. The emergence of these organisms as significant pathogens has important implications for diagnosis and management, not only because the clinical presentation can mimic a more common disease, aspergillosis, but also because the organisms are usually resistant to amphotericin B, the drug of choice for empirical treatment of suspected fungal infections in febrile neutropenic patients.

There has also been a marked increase in the incidence of several of the fungal diseases that are endemic in North America, in particular histoplasmosis and coccidioidomycosis. Urban development and changing land use in the endemic regions have contributed to this trend, as has the seasonal migration of previously unexposed populations from non-endemic regions to the Desert South West. Many of these migrants are older, have underlying chronic illness and debilitation, and consequently are at greater risk of developing the more serious forms of coccidioidomycosis. In addition, there is evidence that the increase in reported cases of this disease could be linked to changing climatic conditions.

Increased international travel has also led to a rise in the number of reported outbreaks and sporadic cases of histoplasmosis and coccidioidomycosis among individuals who normally reside in places far from the endemic regions. The largest number of travel-related mycoses has been reported from US residents, many of whom have acquired an infection while visiting an endemic region within North or Central America or, less commonly, in South America, Africa or Asia. Travel-related fungal infections have also been reported among international visitors to North America, or to countries in Latin America, Africa and Asia. Most of these infections have occurred among persons returning to European countries, Australia or Japan. However, with increasing numbers of visitors and immigrants to the USA from Asia, travel- and migration-related infections are now being reported from countries such as India.

In many respects the current pattern of fungal infection in developing countries is quite different from that seen in developed countries. Throughout the developed world, the widespread use of combination antiretroviral treatment regimens has led to a marked reduction in the rates of AIDS-associated opportunistic infections. In contrast, in developing countries the burden of these diseases is large and increasing. In Thailand, cryptococcosis is the third most common opportunistic infection among HIV-infected persons, accounting for 18.5% of AIDS-defining illnesses reported between 1994 and 1998. Infections with *Penicillium marneffei*, a fungus endemic to South East Asia and South China, are the fourth most common opportunistic infections in the northern region of Thailand. In many parts of Africa, the prevalence of cryptococcosis has risen to more than 30% among persons with HIV infection. Reports from this continent have highlighted the high mortality rates (85–100%) associated with infection treated under local conditions, where adequate doses and constant supplies of antifungal drugs are often unavailable.

1.5 New directions in diagnosis

Early diagnosis and treatment of invasive fungal infections is essential to reduce the high mortality rates of these diseases in immunocompromised individuals.

There has been some progress in the field of diagnosis in recent years largely due to the increased use of computed tomographic (CT) scanning and other imaging procedures. Laboratory methods for the diagnosis of fungal infections continue to be updated, but still depend, for the most part, on isolation of the fungus in culture, on its microscopic detection in clinical material, and on the detection of a serological response to the pathogen (see Chapter 2). Nevertheless, the search for more rapid, sensitive and specific tests is continuing.

New approaches to the diagnosis of invasive fungal infections include the detection of fungal cell wall components or metabolites and the detection of fungal genomic sequences in clinical specimens. Despite recent progress, the goal of developing simple, rapid and cost-effective clinical tests for the diagnosis remains elusive. It is to be hoped that, in the future, the relevance of serial monitoring of fungal antigens and fungal-specific nucleic acid sequences in blood and other biological fluids will be demonstrated, and that reliable tests will be available in both developed and developing countries.

1.6 New directions in treatment and prevention

The rising prevalence of invasive fungal infections has brought about an increased use of existing antifungal agents and has stimulated research for new ones. The antifungal drugs in clinical development include several new azoles (posaconazole and ravuconazole) and new echinocandins (anidulafungin and micafungin). In addition, new classes of compounds aimed at novel targets in the fungal cell, such as the sordarins, are under development. The new drugs that have been introduced have improved the treatment of many forms of fungal infection, but problems remain (see Chapter 3). There are still important infections, such as mucormycosis, for which no reliable treatment has been developed. Then again, many strains of the unusual organisms that are now being isolated from immunocompromised patients are insensitive to current antifungal compounds.

Numerous studies have been conducted to assess risk factors for invasive fungal infections. However, few of the factors that have been identified are either prevent-

able or modifiable. Vascular catheters are unavoidable in patients receiving intensive care, as are immunosuppressive treatments for those with haematological malignancies. In addition, the ubiquitous nature of many moulds in the environment makes it difficult to prevent exposure. Housing high-risk patients, such as HSCT recipients, in laminar airflow (LAF) rooms supplied with filtered air has helped to prevent the acquisition of opportunistic fungal infections, such as aspergillosis, within the hospital. However, recent reports suggest that these infections are now more likely to develop some months after transplant, once engraftment has occurred and usually in the setting of chronic graft-versus-host disease (GVHD) and its treatment. Late infections are also becoming more common among recipients of lung or liver transplants. It is difficult to prevent environmental exposures long after transplant recipients have been discharged from hospital, and expensive to use LAF rooms to nurse patients for long periods, or during multiple admissions after transplantation. Now that high-risk individuals are spending more time outside the healthcare setting, the cost-effectiveness of other prevention strategies, such as antifungal chemoprophylaxis, requires careful evaluation.

Although opportunistic fungal infections in persons with AIDS are no longer a major problem in developed countries, this burden is continuing to increase in many developing countries with large HIV epidemics. Throughout the developed world, the use of combination antiretroviral treatment has proved to be the most effective method of preventing all opportunistic infections in persons with AIDS. Because these drugs are seldom available in developing countries, other measures will be needed to prevent diseases such as cryptococcosis and penicilliosis. In this respect, antifungal chemoprophylaxis is currently the most promising of the potential prevention strategies. A recent clinical trial from Thailand found that itraconazole was effective in preventing fungal infections in persons with AIDS, although no effect on survival was noted. However, itraconazole is expensive and beyond the reach of almost all HIV-infected persons in developing countries. Similar studies with fluconazole, a drug found to be

effective as primary prophylaxis in the USA, have not been conducted in developing countries. There is an urgent public health and humanitarian need to conduct such trials, and to evaluate the cost-effectiveness of antifungal prophylaxis in developing countries, as well as its effect on survival and quality of life.

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Fungal Infection: Diagnosis and Management, Third Edition
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2 Laboratory diagnosis of fungal infection

2.1 Introduction

As with other microbial infections, the diagnosis of fungal infections depends upon a combination of clinical observation and laboratory investigation. Superficial fungal infections often produce characteristic lesions which suggest a fungal diagnosis, but it is not unusual to find that the appearance of lesions has been modified and rendered atypical by previous treatment. In most situations where deep fungal infection is entertained as a diagnosis, the clinical presentation is nonspecific and can be caused by a wide range of infections, underlying illness or complications of treatment. Nor can radiological or other diagnostic imaging methods be relied upon to distinguish fungal infection from other causes of disease.

Laboratory tests can help in establishing or confirming the diagnosis of a fungal infection, in providing objective assessments of response to treatment, and in monitoring resolution of the infection. The successful laboratory diagnosis of fungal infection depends in major part on the collection of appropriate clinical specimens for investigation. It is also dependent on the selection of appropriate microbiological test procedures. These differ from mycosis to mycosis, and depend on the site of infection as well as the presenting symptoms and clinical signs. Interpretation of the results can sometimes be made with confidence, but at times the findings can be unhelpful or even misleading. It is in these situations that close liaison between the clinician and the laboratory is particularly important.

In neutropenic patients and transplant recipients, invasive fungal infection often presents as persistent fever that fails to respond to broad-spectrum antibacterial treatment. The successful management of these patients often depends on the prompt initiation of empirical antifungal treatment without waiting for formal confirmation of the diagnosis. It is essential that these

high-risk individuals be subjected to frequent microbiological surveillance for fungal infection.

2.2 Collection of specimens

To establish or confirm the diagnosis of suspected fungal infection, it is essential for the clinician to provide the laboratory with adequate specimens for investigation. Inappropriate collection, storage or processing of specimens can result in a missed diagnosis. Moreover, to ensure that the most appropriate laboratory tests are performed, it is essential for the clinician to indicate that a fungal infection is suspected and to provide sufficient background information.

In addition to specifying the source of the specimen and its time of collection, it is important to provide information on any underlying illness, recent travel or previous residence abroad, any animal contacts and the patient's occupation if considered relevant. This information will help the laboratory to anticipate which fungal pathogens are most liable to be involved and permit the selection of the most appropriate test procedures. In addition, the laboratory *must* be informed if there are particular risks associated with the handling of the specimen, for instance if the patient has hepatitis or human immunodeficiency virus (HIV) infection.

With the exception of skin, hair and nails, specimens for mycological examination should be collected into and transported to the laboratory in sterile containers appropriate to the type of material being investigated. All specimen containers should be clearly labelled.

2.2.1 Skin, nails and hair

Skin, nails and hair should be collected into folded squares of black paper (about 10 × 10 cm). The use of paper permits the specimen to dry out, which helps to reduce bacterial contamination, and also provides a convenient means of storing specimens for long periods (12 months or longer). It is often helpful to clean superficial lesions with 70% alcohol prior to sampling as this will improve the chances of detecting fungus on microscopic examination, as well as reducing the likelihood of bacterial contamination of cultures. Prior cleaning is

essential if ointments, creams or powders have been applied to the lesion.

Material should be collected from cutaneous lesions by scraping outwards from the margin of the lesion with a blunt scalpel. If there is minimal scaling, it is helpful to use clear adhesive tape, or adhesive skin sampling discs, to remove material for examination. The sellotape strip or disc should be pressed against the lesion, peeled off and placed, adhesive-side-down, on a clean glass microscope slide for transportation to the laboratory.

It is often helpful to use a Wood's light to select infected scalp hairs for laboratory investigation. If none of the hairs give the green fluorescence which is a feature of some forms of dermatophyte scalp infection, a search should be made for lustreless hairs or stumps, and for hairs broken off at follicle mouths. Hairs should be plucked from the scalp with forceps. Cut hairs without roots are unsuitable for mycological investigation because the infection is usually confined near or below the surface of the scalp.

Another method which is useful for collection of adequate material from patients with inconspicuous scalp lesions is to brush the scalp with a plastic massage pad that is then pressed into the surface of an agar plate. The pad should be sterilized in 1% chlorhexidine for 1 h and rinsed in sterile water before being reused.

Nail specimens should be taken from any discoloured, dystrophic or brittle parts of the nail. Specimens should be cut as far back as possible from the edge of the nail and should include the full thickness of the nail because some fungi are confined to the lower parts. If the nail is thickened, scrapings can also be taken from beneath it.

2.2.2 Mucous membranes

Although scrapings from oral lesions are better than swabs for diagnosis of oral infections, the latter are more frequently used, mainly because they are more convenient for transporting material to the laboratory. Swabs should either be moistened with sterile water or saline prior to taking the sample, or sent to the laboratory in transport medium.

For vaginal infections, swabs should be taken from discharge in the vagina and from the lateral vaginal wall. Swabs should be sent to the laboratory in transport medium.

2.2.3 Ear

Scrapings of material from the ear canal are to be preferred, although swabs can also be used.

2.2.4 Eye

Material from a corneal ulcer with a suspected fungal cause should be collected by scraping the ulcer with a sterile platinum spatula. The entire base of the ulcer as well as the edges should be sampled. Because the amount of material that can be obtained will be small, it is best transferred to an agar plate for culture and to a glass slide for microscopic examination at the bedside. The plate should be marked to indicate the point of inoculation before being sent to the laboratory. Swabs are not suitable for sampling corneal lesions.

In patients with suspected fungal endophthalmitis, vitreous humour should be collected whenever possible. Vitreous humour specimens that have been diluted by the irrigating solution should be concentrated by centrifugation before being examined in the laboratory.

2.2.5 Blood

Blood culture should be performed in all cases of suspected deep fungal infection. However, unless specialized techniques or media are used, clinicians should not expect blood cultures taken for isolation of bacteria to detect fungi other than *Candida* species, *Cryptococcus neoformans* or *Trichosporon* species. Isolation of fungi from blood depends on a number of factors, including the amount of blood sampled, the number of samples collected, and the method of processing. Culture of arterial blood should be considered if venous blood cultures are unsuccessful in a patient with suspected deep mycosis.

In general, *Candida* species are more readily recovered from blood than are dimorphic fungi and moulds. Isolation rates are higher when the medium is vented and aerated, and biphasic media incorporating

both agar and broth phases are more effective than broth alone. The chances of successful isolation are increased if multiple samples of blood are collected and larger volumes are cultured. The lysis-centrifugation method (Isolator, Wampole Laboratories) is currently the most reliable procedure for isolation of fungi from blood, but it is more expensive and labour-intensive than other methods. Recent improvements in the formulation of blood culture media, together with the development of improved automated blood culture systems, have made the recovery of *Candida* species from blood culture bottles almost as effective as that from lysis-centrifugation tubes. However, lysis centrifugation remains superior to other systems for recovery of *C. neoformans*, dimorphic fungi and moulds.

2.2.6 Cerebrospinal fluid

Cerebrospinal fluid (CSF) specimens of 3–5 ml are ideal, but are often smaller than this. Samples can be centrifuged and the supernatant fluid used for serological tests. The sediment can be cultured, but is also useful for microscopic examination.

2.2.7 Urine

In non-catheterized patients, fresh midstream specimens of urine are adequate for mycological investigation, provided care is taken to ensure that vaginal or perineal infection does not lead to contamination. In infants, suprapubic aspiration is the best method of urine collection. Urine samples should be processed for microscopic examination and culture, but can also be tested for fungal antigens.

Patients with blastomycosis or cryptococcosis may have prostatic infection, and it is therefore important to collect urine specimens following prostatic massage. The specimen should be centrifuged and the sediment cultured. Other disseminated infections that can be diagnosed on the basis of a positive urine culture include coccidioidomycosis and histoplasmosis.

2.2.8 Other fluids

Chest, abdominal and joint fluids, whether aspirated or drained, should be collected into sterile containers

which include a small amount of sterile heparin (diluted 1:1000) to prevent clotting. The specimens should be centrifuged and the sediment cultured. Drain fluid from patients on continuous peritoneal dialysis should be collected in a sterile container without heparin.

2.2.9 Lower respiratory tract specimens

Fresh, early morning samples of sputum are ideal. These should be collected in sterile containers and processed within 2 h of collection. If delay in processing is unavoidable, specimens must be stored at 4°C. If the patient does not have a productive cough, a sputum sample may be induced by introducing nebulized saline into the bronchial tree. It is recommended that at least three samples of sputum be submitted for microscopic examination and culture whenever a fungal infection is suspected: 24-h collections of sputum are not suitable for mycological investigation.

In immunocompromised patients, the most useful procedures for collection of lower respiratory tract specimens are bronchoalveolar lavage (BAL) or a bronchial wash. These procedures are carried out with a fibreoptic bronchoscope and provide good material for microscopic examination and culture. Specimens should be centrifuged and the sediment examined.

Percutaneous needle biopsies are useful in patients with focal lung disease, in particular those with peripheral lesions which are not accessible to a bronchoscope. Large needles are better than fine needles and the procedure should be carried out under radiological guidance. Specimens should be processed for microscopic examination and culture.

2.2.10 Pus

If possible, swabs should not be used to collect material from draining abscesses or ulcers. If a swab must be used, then material should be taken from as deep as possible within the lesion. Pus from undrained subcutaneous abscesses or sinus tracts should be aspirated with a sterile needle and syringe. If grains are visible in the pus (as in mycetoma), these should be collected. In mycetoma, if the crusts at the opening of sinus tracts are lifted, grains can often be found in the pus underneath.

2.2.11 Bone marrow

These specimens are useful for making the diagnosis in a number of deep fungal infections, including histoplasmosis, cryptococcosis and paracoccidioidomycosis. About 3–5 ml aspirated material should be collected into a sterile container which includes a small amount of sterile heparin (diluted 1:1000).

2.2.12 Tissue

Tissue specimens should be placed in sterile saline and *not* in formalin. If possible, material should be obtained from both the middle and the edge of lesions. Total excision of small cutaneous, subcutaneous or mucosal lesions is often possible.

2.3 Specimens for serological tests

Serological tests for dimorphic fungal pathogens are much more helpful if paired or sequential specimens are collected. Blood, CSF, urine and other biological fluids for serological testing should be collected into glass or plastic tubes without anticoagulants; 5–10 ml is usually sufficient.

2.4 Specimens for antifungal drug level determinations

The concentrations of antifungal drugs are measured for two principal reasons: to ensure that adequate drug concentrations are attained and to ensure that concentrations that could cause unpleasant or even harmful side-effects are avoided.

Blood and other biological fluids should be collected into glass or plastic tubes without anticoagulants; 5–10 ml is usually sufficient. Specimens should be taken at the most appropriate times; samples should be collected just before a dose is due and/or around the expected time of peak blood concentrations (see Chapter 3).

2.5 Transport of specimens

Unlike specimens from cases of suspected dermatophytosis which can often be stored for weeks or even months before processing, specimens for mycological investigation must be processed as soon as possible

after collection. Delay may result in the death of fastidious organisms, in overgrowth of contaminants, and/or multiplication in the number of organisms present.

Specimens mailed to laboratories must be packaged and labelled according to the guidelines laid down for the transport of biological material by the relevant postal authorities. Metal canisters are now recommended for packaging of certain hazardous materials such as specimens from HIV-infected persons. Plastic petri dishes are unsuitable for sending through mail. The specimen container or culture should be sealed within a plastic bag before packaging so that any breakage and subsequent spillage is contained. The sender's name should be clearly marked on the outside of the package so that they may be contacted for instructions should a problem arise.

2.6 Interpretation of laboratory test results

Interpretation of the results of laboratory tests can sometimes be made with confidence, but at times the findings may be unhelpful or even misleading. The investigations available include microscopic examination, culture and serological tests. The choice of appropriate tests differs from one disease to another and depends on the site of infection as well as the presenting symptoms and clinical signs. It must always be appreciated that every laboratory test has its limitations, and that negative results can be obtained which may lead to unjustified exclusion of a mycological diagnosis.

2.6.1 Direct microscopic examination

The direct microscopic examination of clinical material is one of the simpler and most helpful procedures for the laboratory diagnosis of fungal infection. Various methods can be used: unstained wet-mount preparations may be examined by light-field, dark-field or phase-contrast illumination; or dried smears can be stained and examined. Chemical brighteners, such as calcofluor white, can be helpful in revealing fungal elements in wet mounts of sputum, skin and other clinical materials when examined under a fluorescence microscope.

Direct microscopic examination is most useful in the diagnosis of superficial and subcutaneous fungal infections. Recognition of fungal elements in skin scrapings, hair or nail specimens can provide a reliable indication of the mycosis involved, whether it be dermatophytosis, candidosis or pityriasis versicolor. In certain situations, direct microscopic examination of fluids or other clinical material can establish the diagnosis of a deep mycosis. Instances include the detection of encapsulated *C. neoformans* cells in CSF, or *Histoplasma capsulatum* cells in peripheral blood smears. More often, however, only a tentative diagnosis of deep fungal infection can be made on the basis of microscopic examination. Nevertheless, microscopic examination can help to determine whether an organism recovered later in culture is a contaminant or a pathogen, and to assist the laboratory in selecting the most appropriate culture conditions to recover organisms visualized on direct smear.

2.6.2 Histopathological examination

Histopathological examination of tissue sections is one of the most reliable procedures for the diagnosis of subcutaneous and deep-seated fungal infections. However, the ease with which a fungal pathogen can be recognized in tissue is dependent not only on its abundance but also on the distinctiveness of its appearance. Many fungi stain poorly with hematoxylin and eosin and this method alone may be insufficient to reveal fungal elements in tissue. There are a number of special stains for detecting and highlighting fungi and the clinician should request these if a mycotic disease is suspected. Methenamine-silver (Grocott or Gomori) and periodic acid-Schiff staining are among the most widely used procedures for specific staining of the fungal cell wall.

It should be appreciated that these staining methods, although useful at revealing the presence of fungal elements in tissue, seldom permit the precise fungal genus involved to be identified. For example, the detection of non-pigmented branching, septate hyphae is typical of *Aspergillus* infection, but it is also characteristic of a large number of less common organisms, including species of *Fusarium* and *Scedosporium*. Likewise, the

detection of small, budding yeast cells seldom permits a specific diagnosis. Tissue-form cells of *H. capsulatum* and *Blastomyces dermatitidis*, for instance, can appear similar and may be confused with non-encapsulated cells of *C. neoformans*.

To overcome this problem, a number of methods have been developed for identifying various fungi in tissue. Immunoperoxidase and immunofluorescent staining reagents, both monoclonal and polyclonal, are available for some fungi. Immunochemical staining can facilitate the identification of atypical fungal elements and the detection of small numbers of organisms. It can also assist with the diagnosis of mixed infections. Currently under investigation are a number of techniques that involve specific binding of DNA probes to the nucleic acid of the fungal agent either directly on the slide (*in situ* hybridization) or in a test tube.

2.6.3 Culture

Isolation in culture will permit most pathogenic fungi to be identified. Most of these organisms are not fastidious in their nutritional requirements and will grow on the media used for bacterial isolation from clinical material. However, growth on these media can be slow and development of the spores and other structures used in fungal identification can be poor. For these reasons, most laboratories use several different culture media and incubation conditions for recovery of fungal agents. Most laboratories use a medium, such as glucose peptone (Sabouraud's) agar or malt agar, that will recover most common fungi. However, certain fastidious organisms such as yeast-phase *H. capsulatum* will not grow on these substrates, and require the use of richer media such as brain–heart infusion agar. The laboratory should be made aware of the particular fungal agent(s) that are suspected in a given sample so that the most appropriate media can be included.

Many clinical specimens submitted for fungal culture are contaminated with bacteria and it is essential to add antibacterial antibiotics to fungal culture media. Media containing chloramphenicol are commercially available. However, gentamicin, vancomycin and other antimicrobial agents are increasingly being used to suppress growth

of bacteria resistant to older agents. If dermatophytes or dimorphic fungi are being isolated, cycloheximide (actidione) should be added to the medium to prevent overgrowth by faster-growing fungi.

The optimum growth temperature for most pathogenic fungi is around 30°C. Material from patients with a suspected superficial infection should be incubated at 25–30°C, because most dermatophytes will not grow at higher temperatures. Material from subcutaneous or deep sites should be incubated at two temperatures, 25–30°C and 37°C. This is because a number of important pathogens, including *H. capsulatum*, *B. dermatitidis* and *Sporothrix schenckii*, are dimorphic and the change in their growth form, depending on the incubation conditions, is useful in identification. At 25–30°C these organisms develop as moulds on glucose peptone agar, but at higher temperatures on an enriched medium, such as brain–heart infusion agar, these organisms grow as budding yeasts. Some pathogenic fungi grow slowly in culture and require plates to be held for up to 2 weeks, and in some case up to 4 weeks, before being discarded as negative. However, many common pathogenic fungi, such as *Aspergillus fumigatus* and *Candida albicans*, will produce identifiable colonies within 1–3 days. Cultures should be examined at frequent intervals (at least three times weekly) and appropriate subcultures made, particularly from blood-enriched media on which fungi often fail to sporulate.

It is important to recognize that growth of an organism in culture does not necessarily establish its role as a pathogen. Only if the organism is identified as an unequivocal pathogen, such as *Trichophyton rubrum* or *H. capsulatum*, can the diagnosis be firmly established. If, however, an opportunistic organism such as *A. fumigatus* or *C. albicans* is recovered, its isolation may have no clinical relevance unless there is additional evidence of its involvement in a pathogenic process. In this situation, culture results should be compared with those of microscopic examination. Isolation of opportunistic fungal pathogens from sterile sites, such as blood or CSF, often provides reliable evidence of significant infection, but their isolation from material such as pus, sputum or urine must be interpreted with caution.

Attention should be given to the amount of fungus isolated and further investigations undertaken.

Many unfamiliar moulds have been reported as occasional causes of lethal systemic infection in immunocompromised patients. No isolate should be dismissed as a contaminant without careful consideration of the clinical condition of the patient, the site of isolation, the method of specimen collection, the amount of organisms recovered, and the likelihood of contamination.

Although culture often provides the definitive diagnosis of a fungal infection, it also has some limitations. Chief amongst these is failure to recover the organism. This may be due to inadequate specimen collection or delayed transport of specimens. Incorrect isolation procedures or inadequate periods of incubation are other important factors. It is essential for the clinician to inform the laboratory if a particular fungal infection is suspected and provide sufficient information to permit the most appropriate culture procedures to be followed.

The isolation and identification of moulds and yeasts can take several weeks. In such unavoidable instances, the result may become available too late either to help with the diagnosis or with the choice of treatment. Nevertheless, culture should always be attempted so that a definitive diagnosis can be obtained.

2.6.4 Serological tests

Serological testing often provides the most rapid means of diagnosing a fungal infection. The majority of tests are based on the detection of antibodies to specific fungal pathogens, although tests for fungal antigens are now becoming more widely available. At their best, individual serological tests can be diagnostic, for example, tests for antigenaemia in cryptococcosis and histoplasmosis. In general, however, the results of serological testing are seldom more than suggestive or supportive of a fungal diagnosis. These tests must be interpreted with caution and considered alongside the results of other clinical and laboratory investigations.

Tests for antibodies have proved useful in diagnosing endemic fungal diseases, such as histoplasmosis and

coccidioidomycosis, in immunocompetent persons. In these individuals, the interval between exposure and the development of symptoms (2–6 weeks) is usually sufficient for a humoral response to develop. Tests for fungal antibodies are most helpful when paired serum specimens (acute and convalescent) are obtained, so that it can be determined whether titres are rising or falling. Tests for detection of antibodies are much less useful in immunocompromised persons, many of whom are incapable of mounting a detectable humoral response to infection.

In this situation, serological tests for detecting fungal antigens can be helpful. Antigen detection is an established procedure for the diagnosis of cryptococcosis and histoplasmosis, and similar tests are currently being evaluated for aspergillosis and candidosis. Antigen detection methods are complicated by several important factors. First, antigen is often released in minute amounts from fungal cells necessitating the use of highly sensitive test procedures to detect low amounts circulating in serum. Second, antigen is often cleared very rapidly from the circulation necessitating frequent collection of samples. Third, antigen is often bound to circulating IgG, even in immunocompromised individuals, and therefore steps must be taken to dissociate these complexes before antigen can be detected.

Numerous tests are available for the detection of fungal antibodies. Immunodiffusion (ID) is a simple, specific and inexpensive method, but it is insensitive and this reduces its usefulness as a screening test. Complement fixation (CF) is more sensitive, but more difficult to perform and interpret than ID. However, CF remains an important test for a number of fungal diseases, including histoplasmosis and coccidioidomycosis. Latex agglutination is a simple but insensitive method that can be used for detection of antibodies or antigens. It has proved most useful for detection of the polysaccharide capsular antigens of *C. neoformans* that are released in large amounts in most patients with cryptococcosis. More sensitive procedures, such as radioimmunoassay and enzyme-linked immunosorbent assay (ELISA), have also been developed and evaluated for the diagnosis of a number of fungal diseases.

2.7 Molecular diagnosis of fungal infection

Numerous methods have been developed and evaluated for the detection of fungal nucleic acid sequences in blood, CSF, respiratory tract fluids and other clinical samples. Most of these molecular diagnostic tests are based on the use of the polymerase chain reaction (PCR) to take advantage of the enormous increase in sensitivity offered by the manifold amplification of PCR targets as well as the specificity offered by appropriate primer and probe design. Several regions within the fungal genome have been evaluated as potential targets for detection, but much effort has focused on the ribosomal DNA (rDNA) gene complex. This section of the genome includes the relatively conserved regions of the *18S*, *5.8S* and *28S* genes and the more variable intervening transcribed spacer (ITS) regions.

Most of the diagnostic methods devised have been based on the use of conventional PCR formats, but many modified approaches have also been evaluated. These include multiplex PCR, in which more than one target sequence is amplified by including multiple sets of primers in the reaction and nested PCR, in which a first round of amplification with generic fungal primers generates a DNA product that is then reacted with species-specific internal primers in a second round of PCR. In panfungal PCR, amplification with generic fungal primers generates a product that is then hybridized with various short species-specific DNA probes until a positive reaction is achieved. The latest developments in molecular diagnostics involve the use of real-time PCR methods in which thermocycling is combined with fluorescence monitoring of the amplified product during its generation. These techniques permit quantification of the amounts of fungal nucleic acid that are present in clinical samples, thus allowing the microbial load to be measured.

Despite recent progress, the goal of developing rapid and cost-effective tests for the molecular diagnosis of acute life-threatening fungal infections remains elusive. Although numerous research laboratories now offer 'in-house' procedures for molecular detection of fungal infection from tissue specimens or from body fluids, the sensitivity, specificity and predictive value of these

tests have not always been thoroughly investigated. It is to be hoped that, in the future, the relevance of these assays will be demonstrated and that they will become available to a much broader group of clinical laboratories.

Further reading

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Malcolm D. Richardson, David W. Warnock

3 Antifungal drugs

3.1 Introduction

In comparison with the number of antibacterial drugs available, there are far fewer antifungal compounds. Even so the number of antifungal drugs is increasing all the time. There are four major families of compounds: the polyenes, the azoles, the allylamines and the echinocandins. In addition there is a miscellaneous group of compounds, such as flucytosine and griseofulvin, which do not belong to one of the major families. This is not a static picture and there are new groups of compounds under development all the time.

This chapter reviews the principal antifungals in current use for superficial, subcutaneous and deep-seated fungal infections.

3.2 Amphotericin B

Amphotericin B is a macrocyclic polyene antibiotic derived from *Streptomyces nodosus*. It remains the drug of choice for many forms of deep fungal infection.

Parenteral administration of the conventional micellar suspension formulation of amphotericin B is often associated with unpleasant infusion-related reactions and treatment-limiting toxic effects, in particular renal impairment. This problem has led to the development of three lipid-based formulations of the drug: liposomal amphotericin B (AmBisome) in which the drug is encapsulated in phospholipid-containing liposomes, amphotericin B lipid complex (Abelcet, ABLC) in which it is complexed with phospholipids to form ribbon-like structures, and amphotericin B colloidal dispersion (Amphocil, Amphotec, ABCD) in which the drug is complexed with cholesterol sulphate to form small lipid discs. These formulations appear to be less toxic than the micellar suspension because of their altered pharmacological distribution.

3.2.1 Mechanism of action

Amphotericin B binds to ergosterol, the principal sterol in the membrane of susceptible fungal cells, causing impairment of membrane barrier function, loss of cell constituents, metabolic disruption and cell death. In addition to its membrane permeabilizing effects, the drug can cause oxidative damage to fungal cells. Mammalian cell membranes also contain sterols, and it has been suggested that amphotericin B-induced damage to human and fungal cells shares common mechanisms.

3.2.2 Spectrum of action

Amphotericin B has a broad spectrum of action including many *Aspergillus* species, *Blastomyces dermatitidis*, *Candida* species, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis* and *Penicillium marneffei*. *Aspergillus terreus*, *Fusarium* species, *Malassezia furfur*, *Scedosporium* species and *Trichosporon asahii* are often resistant.

3.2.3 Acquired resistance

Treatment failure attributable to the development of amphotericin B resistance is rare. Resistant strains of *Candida lusitaniae* and *C. tropicalis*, with qualitative and quantitative alterations in membrane sterol composition, including reduced amounts of ergosterol, have been isolated during treatment. There are a few reports of resistant strains of *C. neoformans* isolated from persons with the acquired immunodeficiency syndrome (AIDS) with relapsed infection.

3.2.4 Pharmacokinetics

Amphotericin B is not absorbed following mucosal or cutaneous application. Minimal absorption occurs from the gastrointestinal tract. Oral administration of a 3 g dose will produce serum concentrations in the region of 0.1–0.5 mg/L.

CONVENTIONAL FORMULATION

Parenteral administration of a 1 mg/kg dose of the conventional formulation of the drug will produce maximum serum concentrations of 1.0–2.0 mg/L. Less than 10% of the dose remains in the blood 12 h after

administration, and more than 90% of this is protein-bound. Most of the remainder can be found in the liver (up to 40% of the dose), lungs (up to 6%) and kidneys (up to 2%). Levels in cerebrospinal fluid (CSF) are less than 5% of the simultaneous blood concentration. Amphotericin B binds to tissues for prolonged periods of time, re-entering the circulation slowly from these storage sites. The conventional formulation has a second-phase half-life of about 24–48 h and a third-phase half-life of about 2 weeks.

No metabolites have been identified. More than 70% of a given dose is excreted as unchanged drug in the bile and urine within 1 week. Blood concentrations are unchanged in hepatic or renal failure. Likewise, haemodialysis does not influence blood levels unless the patient is hyperlipemic, in which case there is some drug loss due to adherence to the dialysis membrane.

LIPID-BASED FORMULATIONS

The pharmacokinetics of the different lipid-based formulations of amphotericin B are quite diverse. Large structures, such as ABLC, are rapidly removed from the blood, but smaller liposomes remain in the circulation for much longer periods.

The pharmacokinetics of amphotericin B after parenteral administration of AmBisome are non-linear and there is a disproportionate increase in serum concentrations when the dose is increased from 1 to 5 mg/kg per day. The maximum serum concentrations obtained have ranged from 10 to 35 mg/L for a 3 mg/kg dose and from 25 to 60 mg/L for a 5 mg/kg dose. Levels of 5–10 mg/L have been detected 24 h after a 5 mg/kg dose. Administration of AmBisome results in much higher drug concentrations in the liver and spleen than are achieved with conventional amphotericin B. Levels in renal tissue are much lower than those obtained with equivalent amounts of the conventional formulation. Less than 10% of a given dose of AmBisome appears as unchanged drug in the bile and urine within 1 week. This formulation has a terminal half-life of 100–150 h.

The maximum serum concentrations obtained after parenteral administration of ABLC are lower than after administration of equivalent amounts of conventional

amphotericin B due to more rapid distribution of the drug to tissue. Maximum levels have ranged from 1 to 2 mg/L after administration of a 5 mg/kg dose for 1 week. Administration of ABLC results in much higher drug concentrations in the liver, spleen and lungs than are achieved with conventional amphotericin B. Levels in renal tissue are much lower than those obtained with equivalent amounts of the conventional formulation. This formulation has a terminal half-life of about 170 h.

Maximum serum concentrations of about 2 mg/L have been obtained following a 1 mg/kg dose of ABCD, but levels in the blood decline soon after the end of the infusion due to rapid distribution of the drug to tissue. Administration of ABCD results in much higher drug concentrations in the liver and spleen than are achieved with conventional amphotericin B. Levels in renal tissue are much lower than those obtained with equivalent amounts of the conventional formulation.

The effect of renal or hepatic impairment on the disposition of amphotericin B after administration of the lipid-based formulations of the drug has not been studied.

3.2.5 Pharmaceutics

Amphotericin B is available in oral, topical and parenteral forms.

CONVENTIONAL FORMULATION

Amphotericin B is supplied for parenteral administration in lyophilized form in 50-mg amounts together with 41 mg sodium deoxycholate (which acts as a dispersing agent) and a sodium phosphate buffer. The addition of 10 ml sterile water gives a clear micellar suspension. This is further diluted with 490 ml 5% dextrose solution prior to injection to give a final drug concentration of 100 mg/L. The dextrose solution should have a pH of 4.2 or greater to prevent precipitation of the drug. The diluted drug should be used within 24 h, but does not need to be protected from light. Other preparations for injection should not be added to an amphotericin B infusion. If there are signs of precipitation, the infusion must be discarded.

LIPID-BASED FORMULATIONS

AmBisome is supplied for parenteral administration in lyophilized form in 50-mg amounts and is first reconstituted in 12 ml sterile water (for injection) to give a drug concentration of 4 mg/ml. The drug solution is further diluted with between 1 and 19 parts of 5% dextrose (for injection) to give a final drug concentration in the range of 0.2–2.0 mg/ml amphotericin B and filter sterilized. The reconstituted drug in water can be stored in a refrigerator for up to 24 h prior to dilution with 5% dextrose solution. Infusion of the drug should be commenced within 6 h of dilution with 5% dextrose solution.

ABLC is supplied for parenteral administration as a sterile suspension in 50- or 100-mg amounts which must be filter sterilized and diluted before use with 5% dextrose (for injection) to a final infusion concentration of 1 mg/ml. For paediatric patients, the drug may be diluted to a final infusion concentration of 2 mg/ml. The final infusion volume should be about 500 ml (250 ml in children). The diluted suspension can be stored in a refrigerator for up to 48 h prior to infusion.

ABCD is supplied for parenteral administration in lyophilized form in 50- or 100-mg amounts and is first reconstituted in 10 or 20 ml sterile water (for injection) to give a drug concentration of 5 mg/ml. The drug solution is then diluted eightfold with 5% dextrose (for injection) to give a final concentration of 0.625 mg/ml amphotericin B. The reconstituted drug in water can be stored in a refrigerator for up to 24 h prior to dilution with 5% dextrose solution. After further dilution with 5% dextrose solution, the drug should be stored in a refrigerator and used within 24 h.

To avoid precipitation, AmBisome, ABLC and ABCD must not be reconstituted or diluted with saline and should not be mixed with other drugs. Existing lines must be flushed with 5% dextrose solution prior to the infusion or, if this is not feasible, a separate line should be used.

3.2.6 Therapeutic use

Topical amphotericin B preparations can be used to treat mucosal and cutaneous forms of candidosis.

Parenteral amphotericin B is still the drug of choice for many forms of deep fungal infection, including aspergillosis, blastomycosis, candidosis, coccidioidomycosis, cryptococcosis, histoplasmosis and paracoccidioidomycosis. It is also effective in certain forms of mucormycosis, hyalohyphomycosis and phaeohyphomycosis. However, it is often ineffective in *Scedosporium* infection and trichosporonosis, as well as in aspergillosis and candidosis in immunocompromised patients. Administration of the conventional formulation of the drug is associated with harmful side-effects and unpleasant reactions which often limit the amount that can be given.

Few large clinical trials have been performed comparing the lipid-based preparations to conventional amphotericin B, or to each other. Moreover, the randomized trials that have been conducted in patients with documented fungal infections have not provided clear evidence that the lipid-based formulations are superior to conventional amphotericin B for invasive aspergillosis, candidosis or cryptococcosis. The lipid-based formulations of amphotericin B are better tolerated than conventional amphotericin B and higher doses can be given over shorter periods with fewer toxic reactions. These formulations are licensed for the treatment of serious fungal infections in patients who have failed to respond or have developed severe side-effects to conventional amphotericin B, or in whom conventional amphotericin B is contraindicated because of renal impairment. In the USA, AmBisome is also licensed for the empirical treatment of presumed fungal infection in febrile neutropenic patients.

The conventional parenteral formulation of amphotericin B has been instilled into a number of sites, including the bladder, peritoneum and joints. However, intraperitoneal infusion of the drug is painful and has been associated with adhesion formation.

3.2.7 Mode of administration

The dose and duration of topical treatment will differ from patient to patient and depend on the nature and extent of infection. The usual adult dose of the oral suspension for oral forms of candidosis is 1–2 ml

(100–200 mg) at 6-h intervals. As the drug is not absorbed the success of treatment depends on maintaining an adequate concentration in the mouth for as long as possible. The recommended dosage of the oral suspension for infants and children is 1 ml (100 mg) at 6-h intervals.

CONVENTIONAL FORMULATION

Most patients with deep fungal infection are treated with 1–2 g of amphotericin B over 6–10 weeks, but this will differ from person to person, depending upon the nature and extent of the infection and the underlying illness. In adults with normal renal function the usual dose is between 0.6 and 1.0 mg/kg.

An initial test dose of 1 mg of amphotericin B in 50 ml dextrose solution should be given over 1–2 h (0.5 mg in children weighing less than 30 kg), with general clinical observation and monitoring of temperature, pulse and blood pressure at 30-min intervals. This is because occasional patients have an idiosyncratic reaction of severe hypotension or an anaphylaxis-like reaction. In the few patients with a reaction, the test infusion should be discontinued, supportive treatment including hydrocortisone given, and a repeat test dose administered over a longer period. If the test dose is well tolerated, there can be progression to larger doses. Several dosage regimens are available (see Tables 3.1 and 3.2).

In patients who are not immunocompromised or suffering a serious life-threatening infection, optimum dosage is best achieved through gradual augmentation of the dose. The dose can be increased up to 1.0 mg/kg, but individual infusions should not contain more than 50 mg of the drug.

In immunosuppressed patients and others with a serious infection, the dose of amphotericin B should be increased as rapidly as the patient's tolerance of the drug will allow. Rapid augmentation of the dose carries a greater risk of acute renal failure, but immunosuppressed patients often tolerate these regimens well.

Four-hour infusions appear to be as well tolerated as the more traditional 6-h infusion period in patients with normal renal function. However, it is not advisable to give the infusion over less than 4 h.

Table 3.1 Regimens for rapid escalation of amphotericin B dosage

Time infusion started (h)	Duration of infusion (h)	Dosage (mg)	Volume of solution 1 (ml)	Volume of solution 2 (ml)
0	2	1	10	40
4	6	24	240	760
16	6	25	250	750
40	6	50	500	500
(then at 24-h intervals, dose not to exceed 50 mg or 1.0 mg/kg per infusion, whichever is less)				
0	2	1	10	40
2	6	9	90	360
12	6	10	100	400
24	6	20	200	300
48	6	30	300	700
72	6	40	400	600
96	6	50	500	500
(then at 24-h intervals, dose not to exceed 50 mg or 1.0 mg/kg per infusion, whichever is less)				

Solution 1: amphotericin B at 100 mg/L in 5% dextrose solution.
Solution 2: 5% dextrose solution.

Table 3.2 Regimen for gradual escalation of amphotericin B dosage

Time infusion started (h)	Duration of infusion (h)	Dosage (mg)	Volume of solution 1 (ml)	Volume of solution 2 (ml)
0	2	1	10	40
2	6	9	90	360
24	6	10	100	400
48	6	20	200	300
72	6	30	300	700
96	6	40	400	600
120	6	50	500	500
(then at 24-h intervals, dose not to exceed 50 mg or 1.0 mg/kg per infusion, whichever is less)				

Solution 1: amphotericin B at 100 mg/L in 5% dextrose solution.
Solution 2: 5% dextrose solution.

After 2 weeks of treatment, blood concentrations become stable, tissue levels begin to accumulate and it becomes possible to administer the drug at 48- or 72-h intervals. The maximum dose can then be increased from 1.0 to 1.5 mg/kg.

Intrathecal administration of amphotericin B is often associated with side-effects and complications, and oral triazole treatment has largely replaced this form of management in patients with fungal meningitis. Intracisternal injection is to be preferred to lumbar intrathecal administration, because of the risk of chronic lumbar arachnoiditis, but even with this the meninges become damaged and a subcutaneous reservoir may be required to deliver the drug to the CSF. Injections should be given two or three times per week, with the dose increased from 0.025 mg as tolerated to 0.25–1.0 mg.

LIPID-BASED FORMULATIONS

It is not possible to define the total dosage requirements and duration of treatment needed to cure particular fungal infections. For this reason, the dosage of lipid-based formulations of amphotericin B should be adjusted to the individual requirements of each patient. It is prudent to give an initial test dose of 1 mg to all patients (0.5 mg in children weighing less than 30 kg) because of the risk of anaphylactoid reactions.

It is usual to begin treatment with AmBisome at a dose of 1.0 mg/kg, but this can be increased to 3.0–5.0 mg/kg, or even higher. This formulation should be infused over a 2-h period; if this is well tolerated, the infusion time can be reduced to 1 h. AmBisome has been administered to individuals for up to 3 months, to a cumulative dosage of 15 g without significant toxic side-effects. However, a cumulative dosage of 1–3 g given over 3–4 weeks has been more typical. The recommended dosage of AmBisome for empirical treatment of presumed fungal infection is 3 mg/kg per day.

The recommended dosage of ABLC is 5 mg/kg and this should be infused at a rate of 2.5 mg/kg per h. This formulation of amphotericin B has been administered to individuals for up to 11 months, to a cumulative dosage of 50 g without significant toxic side-effects.

It is usual to begin treatment with ABCD at a dose of 1.0 mg/kg, increasing to the recommended dose of 3.0–4.0 mg/kg as required. This formulation is infused at a rate of 1 mg/kg per h. ABCD has been administered to individuals to a cumulative dosage of 3 g without significant toxic side-effects.

3.2.8 Adverse reactions

CONVENTIONAL FORMULATION

The immediate side-effects of the intravenous infusion of amphotericin B include fever, chills and rigors. These unpleasant reactions differ from patient to patient, but usually begin 1–3 h after starting the infusion and last for about 1 h. They are most common during the first week of treatment and often diminish thereafter. These reactions can be prevented or lessened by slowing the rate of infusion, or giving 25 mg of parenteral hydrocortisone just before the infusion is started or 25–50 mg during it if a reaction occurs. Parenteral chlorpheniramine (12.5–25 mg) or oral ibuprofen (10 mg/kg) can also reduce chills if given prior to the infusion. Parenteral meperidine (25–50 mg) can help to control severe rigors.

Nausea and vomiting are less frequent side-effects and, just as with fever and rigors, often diminish as treatment proceeds. Premedication with antiemetics is helpful.

Local phlebitis from intravenous administration of the conventional formulation of amphotericin B is common. If the drug is given through a peripheral vein, the infusion site should be changed for each dose. Phlebitis can be prevented or ameliorated by slowing the rate of the infusion or by adding a small amount of heparin (500–1000 units/L) to the solution.

The most serious toxic effect of amphotericin B is renal tubular damage. Most patients receiving the conventional formulation of the drug suffer some impairment of renal function, but it occurs most often in individuals given more than 0.5 mg/kg per day. Infants and children are less susceptible to the nephrotoxic effects of amphotericin B. Renal function will return to almost normal levels in most patients several months after treatment has ceased, but irreversible renal failure can occur.

Renal damage can be reduced or prevented by careful monitoring during treatment. In the stable patient, renal

function should be measured twice weekly and the treatment interrupted or the dosage modified if the serum creatinine concentration exceeds 250 μmol/L. The risk of amphotericin B-induced renal impairment can be reduced by pre- and post-infusion hydration and sodium repletion with 500 ml saline, provided the clinical status of the patient will allow sodium loading.

Amphotericin B also causes renal wasting of potassium and magnesium due to renal tubular damage, which can reach symptomatic proportions. Serum concentrations of potassium and magnesium should be monitored at regular intervals. Their loss can be reduced by administering 10–20 mg of oral amiloride per day, but intravenous electrolyte supplements must be given if low levels are seen.

Patients treated for more than 2 weeks often develop a mild normochromic, normocytic anaemia. Blood transfusion may be of benefit, but is not usually required.

Pulmonary reactions, with acute dyspnoea, hypoxaemia and interstitial infiltrates, can occur when treatment with amphotericin B is combined with granulocyte transfusion. For this reason it is advisable to separate the infusion of the drug from the time of granulocyte transfusion.

LIPID-BASED FORMULATIONS

The prevalence of immediate side-effects after administration of ABLC or ABCD is lower than reported for conventional amphotericin B. Fever and chills tend to occur during the first two infusions and are less frequent with subsequent infusions. Infusion-related adverse events are more common with ABLC and ABCD treatment than with AmBisome treatment. Infusion-related hypoxia has been documented in up to 25% of ABLC and ABCD recipients, but is usually reversible. Infusion-related side-effects can be attenuated or prevented by premedication with acetaminophen, antihistamines, corticosteroids and meperidine. Patients intolerant of one lipid-based formulation of amphotericin B may tolerate another well.

Renal impairment is less common with all three lipid-based formulations of amphotericin B than with the conventional preparation. In comparative trials, the

respective rates of renal damage (defined as twice baseline serum creatinine concentrations) have been: ABLC, about 25%; ABCD, about 15%; AmBisome, about 20%; conventional amphotericin B, 30–50%. Administration of lipid-based formulations has been reported to stabilize, or even improve, renal function in patients with pre-existing renal impairment following conventional amphotericin B treatment, even when the dose is increased. Renal function should be monitored at regular intervals, particularly in patients receiving other nephrotoxic drugs.

Other adverse events associated with lipid-based formulations of amphotericin B have included elevations in liver transaminases, alkaline phosphatase, and serum bilirubin concentrations. Liver function test abnormalities have been noted in 25–50% of patients treated with AmBisome, but these findings are reversible without drug discontinuation in most patients.

3.2.9 Drug interactions

Amphotericin B can augment the nephrotoxic effects of other drugs such as aminoglycoside antibiotics, cyclosporin and certain antineoplastic agents. These drugs, when combined, should be administered with caution. Individuals receiving concurrent treatment with other nephrotoxic drugs are less likely to have renal dysfunction when receiving lipid-based formulations of amphotericin B. Concurrent use of amphotericin B and corticosteroids or digitalis glycosides can potentiate hypokalaemia.

Amphotericin B and flucytosine have an additive or synergistic effect when used in combination against *Candida* species or *C. neoformans*. However, the nephrotoxic effects of amphotericin B can impair the excretion of flucytosine when these drugs are given together.

3.3 Other polyene compounds for topical administration

3.3.1 Natamycin

Natamycin is used for the topical treatment of oral and vaginal candidosis. It has also been used to treat corneal infections.

3.3.2 Nystatin

Nystatin is used for the topical treatment of oral, oesophageal, gastrointestinal, genital and cutaneous forms of candidosis. It has been used to treat corneal infections and also as gastrointestinal prophylaxis. For oral candidosis, 500 000 units should be given every 6 h; the dose should be doubled in severe infections. For vaginal candidosis, one or two pessaries (100 000 units each) should be inserted high in the vagina for at least 14 days. For prophylaxis, adults should receive 1 million units daily, children 100 000 units four times daily, and infants 100 000 units daily as a single dose.

3.4 Fluconazole

Fluconazole is a synthetic bis-triazole compound.

3.4.1 Mechanism of action

Fluconazole is a potent inhibitor of ergosterol biosynthesis through its action on the cytochrome P-450-dependent enzyme, lanosterol 14 α-demethylase. Depletion of ergosterol, the principal sterol in the membrane of susceptible fungal cells, and accumulation of methylated sterols leads to alterations in membrane structure and function.

3.4.2 Spectrum of action

Fluconazole is most active against *Candida* species, *C. neoformans* and *C. immitis*. It has more limited activity against *B. dermatitidis*, *H. capsulatum* and *Sporothrix schenckii*, and is used as a second-line agent in infections with these fungi. Fluconazole is active against the dermatophytes (*Trichophyton*, *Microsporum* and *Epidermophyton* species), but appears to be ineffective against most other moulds, including *Aspergillus* species and Zygomycetes.

Although it is active against many *Candida* species, *C. krusei* is intrinsically resistant to fluconazole. Isolates of *C. glabrata* are also less susceptible, and as many as 10% of bloodstream isolates of this species are resistant.

3.4.3 Acquired resistance

There have been few reports of resistance developing in *C. albicans* or *C. tropicalis* during short-term

fluconazole treatment in patients with mucosal or deep-seated forms of candidosis. In AIDS patients, resistant strains of *C. albicans* have appeared following repeated courses of low-dose fluconazole treatment for oral or oesophageal infection. Many of these fluconazole-resistant *C. albicans* strains appear to be cross-resistant to other azoles. This is an uncommon problem at present (see Chapter 5). There are a few reports of resistant strains of *C. neoformans* from AIDS patients with relapsed infection following long-term maintenance treatment with fluconazole.

Several molecular mechanisms of azole drug resistance in *C. albicans* have now been elucidated. These include overexpression of a number of efflux pump genes, including the ABC transporter genes, *CDR1* and *CDR2*, and the major facilitator gene, *MDR1*. Overexpression of these pumps leads to reduced drug accumulation in the cells of resistant strains. The second resistance mechanism is point mutations in the *ERG11* gene that encodes the target enzyme, lanosterol 14 α-demethylase. These mutations result in structural alteration of the enzyme and this leads to reduced binding to azole antifungals. The third resistance mechanism is overexpression of the *ERG11* gene. This leads to overproduction of the target enzyme. In addition, evidence is accumulating that changes in other enzymes involved in ergosterol biosynthesis, such as C5(6) sterol desaturase, can also contribute to azole resistance.

3.4.4 Pharmacokinetics

Oral administration of fluconazole leads to rapid and almost complete absorption of the drug. Identical serum concentrations are attained after oral and parenteral administration indicating that first-pass metabolism of the drug does not occur. Blood concentrations increase in proportion to dosage over a wide range of dose levels. Two hours after a single 50-mg oral dose, serum concentrations in the region of 1.0 mg/L can be anticipated, but after repeated dosing this increases to about 2.0–3.0 mg/L. Administration of the drug with food does not affect absorption.

Oral or parenteral administration of fluconazole results in rapid and widespread distribution of the drug.

Unlike other azole antifungals, the protein binding of fluconazole is low (about 12%) resulting in high levels of circulating unbound drug. Levels of the drug in most tissues and fluids usually exceed 50% of the simultaneous blood concentration.

Unlike other azole antifungals, fluconazole is not extensively metabolized in man. More than 90% of a given dose is eliminated in the urine: about 80% as unchanged drug and 10% as inactive metabolites. The drug is cleared through glomerular filtration, but significant tubular reabsorption occurs. Fluconazole has a serum half-life of about 30 h (range 20–50 h), but this is prolonged in renal failure, necessitating adjustment of the dosage regimen in patients with glomerular filtration rates below 50 ml/min. In children the volume of distribution and clearance rates are increased, and the half-life is considerably shorter (15–25 h). In infants fluconazole has a prolonged half-life of 55–90 h.

Fluconazole is removed during haemodialysis and, to a lesser extent, during peritoneal dialysis. A 3-h haemodialysis session will reduce the blood concentration by about 50%.

3.4.5 Pharmaceutics

Fluconazole is available in oral and parenteral forms: as tablets, oral suspension and an intravenous infusion. The drug is supplied for parenteral administration at a concentration of 2.0 mg/ml in 0.9% sodium chloride solution. Dosing recommendations are identical for all dosage forms.

3.4.6 Therapeutic use

Fluconazole can be used to treat mucosal and cutaneous forms of candidosis. It is also effective in various forms of dermatophytosis and pityriasis versicolor.

It is an effective drug for treatment of deep forms of *C. albicans*, *C. tropicalis* and *C. parapsilosis* infection in patients who are stable (individuals who do not have an unexplained fever, are improving, and are not hypotensive). Opinion is divided as to whether fluconazole should be used in patients with *C. glabrata* infection, but it should not be used in those with *C. krusei* infection. Fluconazole has proved to be an effective

prophylactic treatment against candidosis in haematopoietic stem cell transplant (HSCT) recipients. However, it is ineffective in aspergillosis and mucormycosis.

Fluconazole is a useful drug in acute cryptococcal meningitis, but should not be used as first-line treatment in persons with AIDS unless there are particular reasons for witholding amphotericin B. However, it is more effective and better tolerated than amphotericin B as maintenance treatment to prevent relapse of cryptococcosis in patients with AIDS.

Fluconazole is the drug of choice for patients with coccidioidal meningitis. However, it must be continued for life to prevent relapse.

3.4.7 Mode of administration

As absorption following oral administration is good, this is the preferred method of administration. If the patient cannot take the drug by mouth, the intravenous solution can be used. This should be infused at a maximum rate of 200 mg/h.

Vaginal candidosis can be treated with a single 150-mg oral dose of fluconazole. Oropharyngeal candidosis should be treated with 200 mg on the first day followed by 100 mg/day for 2 weeks. Oesophageal candidosis should be treated with 200 mg on the first day followed by 100 mg/day for at least 3 weeks; treatment should be continued for at least 2 weeks following resolution of symptoms.

The recommended dose for adult patients with cryptococcosis or deep forms of candidosis is 6 mg/kg per day (400 mg/day in a 70-kg patient). However, some clinicians have used higher dosages in life-threatening infections. The duration of treatment will differ from patient to patient, depending upon the nature and extent of the infection and the underlying illness. At least 6-8 weeks is usually required for successful treatment of cryptococcosis in human immunodeficiency virus (HIV)-negative persons. The recommended dose for children is 3 mg/kg for oropharyngeal and oesophageal candidosis, and 6 mg/kg for cryptococcosis or deep forms of candidosis. Because of its more rapid clearance in children, fluconazole should be administered at 12-h intervals for the treatment of life-threatening infections.

Long-term maintenance treatment with fluconazole to prevent relapse in AIDS patients with cryptococcosis should be administered at a dosage of 200 mg/day. To reduce the risk of invasive candidosis in neutropenic HSCT recipients, prophylactic treatment with fluconazole should be given at a dosage of 400 mg/day.

Patients with renal impairment should be given the normal dose for the first 48 h of treatment. Thereafter, in persons with a creatinine clearance of 21–40 ml/min, the dosage interval should be doubled to 48 h or the dose halved. Persons with a clearance of 10–20 ml/min require a 72-h interval between doses.

Patients receiving regular haemodialysis require the usual dose after each dialysis session.

3.4.8 Adverse reactions

Fluconazole is well tolerated. The commonest side-effects are gastrointestinal in origin, such as nausea and abdominal discomfort, but these seldom necessitate discontinuation of treatment in patients receiving up to 400 mg/day. Transient asymptomatic elevations of serum transaminase levels are quite common in AIDS patients treated with the drug, and treatment should be discontinued in patients who have test findings indicative of progressive or persistent hepatic dysfunction. There have been rare cases of serious hepatic reactions during fluconazole treatment, including hepatitis, cholestasis, and fulminant hepatic failure. Occasional fatal hepatic reactions have occurred, particularly in patients with serious underlying medical conditions such as AIDS or malignancies.

Fatal exfoliative skin rashes (Stevens–Johnson syndrome) have been reported in patients with AIDS or cancer, but the causal relationship with fluconazole is unclear because of the concomitant administration of other drugs. It is advisable to discontinue fluconazole in a patient with a superficial fungal infection who develops a skin rash. Patients with deep-seated fungal infection who develop rashes should be monitored and the drug discontinued if the lesions progress.

Unlike ketoconazole, fluconazole, when given in recommended doses, does not inhibit human adrenal or testicular steroid metabolism.

3.4.9 Drug interactions

Unlike other azoles, absorption of fluconazole is not reduced if it is given together with drugs that reduce gastric acid secretion.

The concomitant use of fluconazole in patients taking other drugs that are metabolized by the human hepatic cytochrome P-450 enzyme system can lead to alterations in the metabolism and blood concentrations of these compounds. Fluconazole has been shown to increase the serum concentration of cisapride and should not be administered with this drug. It can also increase blood levels of terfenadine and the combined use of fluconazole at doses of 400 mg or greater with this drug is contraindicated.

Fluconazole has been shown to reduce the metabolism, thus augmenting the hypoglycaemic effects of drugs such as glipizide, glyburide and tolbutamide. Blood glucose concentrations should be monitored when these drugs are administered together. Fluconazole can increase the serum concentration of warfarin, augmenting its anticoagulant effects. Prothrombin time should be monitored in patients receiving both drugs. Fluconazole can prolong the half-life of cyclosporin in renal transplant recipients, leading to increased blood levels of that drug. Serum concentrations of cyclosporin should be monitored if these drugs are given together.

Concomitant administration of fluconazole with drugs, such as rifampicin and rifabutin, that are potent inducers of the human cytochrome P-450 enzyme system leads to a less marked reduction in the blood levels of the antifungal agent than is seen with other azoles. However, depending on clinical circumstances, consideration should be given to increasing the dose of fluconazole when it is administered with rifampicin. Like rifampicin, phenytoin is a human cytochrome P-450 inducer. If given together with fluconazole, serum concentrations of phenytoin should be monitored and the dose adjusted to maintain therapeutic levels.

3.5 Itraconazole

This is a synthetic dioxolane triazole compound.

3.5.1 Mechanism of action

Like other azoles, it interferes with the cytochrome P-450-dependent enzyme, lanosterol 14 α-demethylase. This leads to 14-methylsterol accumulation and ergosterol depletion in fungal cells, which results in alterations in membrane structure and function.

3.5.2 Spectrum of action

Itraconazole has a broad spectrum of action including *Aspergillus* species, *B. dermatitidis*, *Candida* species, *C. immitis*, *C. neoformans*, *H. capsulatum*, *M. furfur*, *P. brasiliensis*, *P. marneffei*, *Scedosporium apiospermum* and *S. schenckii*. It is less active against *Fusarium* species. It is effective against many dematiaceous moulds and dermatophytes, but ineffective against the Zygomycetes.

3.5.3 Acquired resistance

Acquired resistance is rare, but ketoconazole-resistant *C. albicans* strains from patients with chronic mucocutaneous candidosis have been cross-resistant to itraconazole, as have some fluconazole-resistant *C. albicans* strains from AIDS patients with chronic relapsing oropharyngeal candidosis. Itraconazole-resistant strains of *A. fumigatus* have been reported following treatment, but this is a rare problem.

3.5.4 Pharmacokinetics

Absorption of itraconazole from the gastrointestinal tract is incomplete (about 55%), but is improved if the drug is given with food. Oral administration of a single 100-mg capsule will produce peak serum concentrations of 0.1–0.2 mg/L about 2–4 h later. Higher concentrations are obtained after repeated dosing, but there is marked variation between individuals. As with ketoconazole, there is a disproportionate increase in blood levels with increasing dosage. Serum concentrations are markedly reduced when gastric acid production is impaired.

Much higher blood concentrations (up to 1.0–1.5 mg/L) have been attained in AIDS patients and neutropenic individuals following administration of a 5 mg/kg dose of the oral solution formulation of itraconazole for 1–2 weeks. This formulation is better absorbed if given without food.

Like most other azole antifungals, the protein binding of itraconazole is high, exceeding 99% in human serum. As a result, concentrations of the drug in body fluids such as CSF are minimal. In contrast, drug concentrations in tissues, such as lung, liver and bone, are two to three times higher than in serum. High concentrations of itraconazole are also found in the stratum corneum as a result of drug secretion in sebum. Itraconazole has been found to persist in the skin for 2–4 weeks after the end of a 4-week course of treatment. It persists in toenails for up to 6 months after the end of a 3-month course of treatment, but levels in the fingernails decline about 3 months after the end of treatment. Less than 0.03% of an administered dose of itraconazole is excreted unchanged in the urine, but up to 18% is eliminated in faeces as unchanged drug.

Itraconazole is extensively metabolized by the human hepatic cytochrome P-450 enzyme system. Most of the metabolites are inactive and are excreted with the bile and urine. However, the major metabolite, hydroxyitraconazole, is bioactive. The serum half-life of itraconazole is about 20–30 h, increasing to 40 h after prolonged dosing.

Itraconazole is not removed by dialysis.

3.5.5 Pharmaceutics

Itraconazole is available in oral and parenteral forms as oral capsules, oral solution and intravenous infusion.

The drug is supplied for parenteral administration as 25-ml solution containing 250 mg itraconazole and 400 mg hydroxypropyl-β-cyclodextrin. The drug solution is diluted with 50 ml 0.9% sodium chloride solution (for injection) prior to infusion. After reconstitution, the diluted drug solution can be stored in a refrigerator for up to 48 h, provided it is protected from direct light. Intravenous itraconazole must not be infused with other drugs.

3.5.6 Therapeutic use

Itraconazole can be used to treat various superficial fungal infections, including the dermatophytoses, pityriasis versicolor, and mucosal and cutaneous forms of candidosis. It is also effective in patients with subcutaneous infections such as chromoblastomycosis, sporotrichosis and certain forms of phaeohyphomycosis. It

has become the drug of choice for non-life-threatening forms of blastomycosis and histoplasmosis, and is a useful alternative to amphotericin B for invasive aspergillosis. Itraconazole is the drug of choice for maintenance treatment to prevent relapse in AIDS patients with histoplasmosis. However, it is less effective than fluconazole as maintenance treatment in AIDS patients with cryptococcosis. Itraconazole oral suspension has helped to prevent aspergillosis in neutropenic patients, and has proved an effective treatment for oropharyngeal candidosis in HIV-infected individuals. However, the drug has not been adequately evaluated as treatment for deep-seated forms of candidosis.

3.5.7 Mode of administration

Vaginal candidosis can be treated with two 200-mg oral doses of itraconazole taken 6–8 h apart. In non-compromised individuals, oropharyngeal candidosis can be treated with 100 mg/day for 2 weeks, but AIDS and neutropenic patients often require 200–400 mg/day because of impaired oral absorption. Administering the oral solution formulation (200–400 mg/day for 1–2 weeks) often results in improved absorption.

The recommended dosage for patients with cutaneous dermatophytoses is 100 mg/day, but the duration of treatment depends on the site of infection. Tinea corporis or tinea cruris should be treated for 2 weeks, but tinea pedis and tinea manuum require treatment for 4 weeks. Pulsed treatment (in which 1 week of treatment is alternated with 3 weeks without treatment) has given good results in nail infections. Two pulses of itraconazole (400 mg/day) are recommended for fingernail infections, but toenails require three or more pulses of treatment. Itraconazole is also available for continuous treatment of nail infection and a dosage of 200 mg/day for 3 months is recommended.

The recommended dosage for patients with pityriasis versicolor is 200 mg/day for 1 week.

The recommended oral dosage of itraconazole for patients with deep fungal infections, such as aspergillosis, blastomycosis and histoplasmosis, is 200–400 mg/day. Some clinicians have used loading doses of 600 mg/day at the start of treatment in patients with

life-threatening infections. Impaired absorption in AIDS and neutropenic patients will lead to low blood levels and higher dosages, or substitution of the intravenous formulation may be required to ensure adequate serum concentrations. Absorption of itraconazole is reduced if it is given together with compounds that reduce gastric acid secretion; these drugs should be administered at least 2 h after the intake of itraconazole. Oral dosages above 200 mg/day should be given as two divided doses.

The recommended intravenous dose of itraconazole for patients with aspergillosis, blastomycosis or histoplasmosis is 200 mg at 12-h intervals for four doses followed by 200 mg/day for up to 2 weeks. Each dose should be infused over a 1-h period.

Itraconazole is the drug of choice for long-term maintenance treatment to prevent relapse in AIDS patients with histoplasmosis. It should be administered at an oral dosage of 200 mg twice daily.

3.5.8 Adverse reactions

Oral itraconazole is well tolerated. The most frequently reported side-effects are gastrointestinal in origin, such as nausea, abdominal discomfort and constipation. Less common side-effects include headache, dizziness, pruritus and allergic rashes. Isolated cases of Stevens–Johnson syndrome have been reported. The most frequent adverse events among patients treated with intravenous itraconazole have been nausea, diarrhoea and hypokalemia.

There have been rare cases of liver failure and death among persons taking itraconazole, including some within the first week. The drug is best avoided in patients with liver disease and those with elevated liver function tests, unless the expected benefit outweighs the risk. If signs of liver disease develop during treatment, the drug should be discontinued and liver function tests performed. Itraconazole should not be used to treat nail infections in patients who have had heart failure, nor should it be used to treat more serious infections, unless the expected benefit exceeds the risk. If signs of congestive heart failure should appear during treatment, itraconazole should be discontinued.

3.5.9 Drug interactions

Absorption of itraconazole is reduced if it is given together with drugs that reduce gastric acid secretion, such as antacids, H2-antagonists, omeprazole and lansoprazole.

Both itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of the human hepatic cytochrome P-450-3A4 enzyme system. Concomitant administration of itraconazole with other drugs that are metabolized by this system can result in increased concentrations of the azole, the interacting drug, or both. Itraconazole has been shown to prolong the half-life of terfenadine, astemizole, midazolam, triazolam, lovastatin, simvastatin, cisapride, pimozide, quinidine and dofetilide. It should not be administered with these drugs.

Itraconazole has been shown to increase the serum concentrations of digoxin, cyclosporin and tacrolimus, and levels of these drugs should be monitored if they are given together. Itraconazole can also increase the serum concentration of warfarin, enhancing its anticoagulant effect. Careful monitoring of prothrombin time in patients receiving both drugs is recommended. Co-administration of itraconazole with anti-HIV protease inhibitors, such as ritonavir, indinavir and saquinavir, can result in increased blood concentrations of both the azole and the interacting drug.

Itraconazole can inhibit the metabolism of vincristine. Patients receiving both agents should be monitored for signs of toxic effects of the vinca alkaloid. Should these occur, the dose of vincristine should be adjusted, or itraconazole treatment discontinued.

Concomitant administration of itraconazole with drugs that are potent inducers of the human cytochrome P-450 enzyme system results in a marked reduction in blood levels of the azole agent. Interacting drugs include phenytoin, phenobarbital, carbamazepine, rifampicin and rifabutin.

3.6 Ketoconazole

This is a synthetic dioxolane imidazole compound.

3.6.1 Mechanism of action

Like other azoles, it interferes with the biosynthesis of ergosterol, leading to alterations in membrane structure and function.

3.6.2 Spectrum of action

Ketoconazole is active against *B. dermatitidis*, *Candida* species, *C. immitis*, *H. capsulatum*, *M. furfur* and *P. brasiliensis*. It is also active against the dermatophytes, but ineffective against *Aspergillus* species and Zygomycetes.

3.6.3 Acquired resistance

Acquired resistance is rare, but resistant *C. albicans* strains have been recovered from patients treated for chronic mucocutaneous candidosis and AIDS patients with chronic relapsing oropharyngeal candidosis. Some fluconazole-resistant *C. albicans* strains from persons with AIDS are cross-resistant to ketoconazole.

3.6.4 Pharmacokinetics

Ketoconazole is not absorbed after topical application, but is well absorbed after oral administration, peak serum concentrations being reached 2–4 h later. Food delays absorption but does not significantly reduce the peak concentration. Two hours after a 400-mg dose serum concentrations in the region of 5–6 mg/L can be anticipated, but there is much variation among individuals. Much higher concentrations can be obtained with doses of 600–1000 mg. Penetration into CSF is poor and unreliable, although effective concentrations have been recorded with high doses (1200 mg) in some cases of meningitis. Less than 1% of an oral dose is excreted unchanged in the urine.

The drug is metabolized in the liver and the metabolites are excreted in the bile. None of the metabolites are active. The half-life appears to be dose-dependent. There is an initial half-life of 1–4 h and an elimination half-life ranging from 6–10 h.

3.6.5 Pharmaceutics

Ketoconazole is available in a number of oral and topical forms.

3.6.6 Therapeutic use

Until the introduction of fluconazole and itraconazole, ketoconazole was regarded as the drug of choice for chronic mucocutaneous candidosis and an effective alternative treatment for certain forms of histoplasmosis, blastomycosis and paracoccidioidomycosis. However, prolonged administration of high dosage was often required and later relapse was a common problem. Ketoconazole has not been adequately evaluated in deep-seated candidosis or cryptococcosis and is ineffective in aspergillosis and mucormycosis. It should not be used for the oral treatment of dermatophytosis or cutaneous or vaginal candidosis, because of its possible effects on the liver and on steroid metabolism. However, it is a useful topical drug for dermatophytosis, cutaneous candidosis, pityriasis versicolor and seborrhoeic dermatitis.

3.6.7 Mode of administration

Topical ketoconazole cream should be applied morning and evening and treatment should be continued for 48 h after all symptoms and signs have cleared. Pityriasis versicolor and sebhorrhoeic dermatitis can be treated with ketoconazole shampoo.

The usual adult oral dose is 200–400 mg/day depending on the infection being treated. In children a dose of 3 mg/kg can be used. The duration of treatment will depend upon the nature of the infection.

3.6.8 Adverse reactions

Anorexia, nausea and vomiting are the commonest side-effects. These dose-related effects occur in up to 50% of patients receiving oral doses of >800 mg, but taking the drug with food or at bedtime may improve tolerance.

Mild hepatotoxic effects are common with oral ketoconazole, but serious liver damage is rare. Transient transaminase elevations occur in about 5–10% of patients on oral ketoconazole. Treatment must be discontinued if these persist, if the abnormalities increase or if symptoms associated with hepatic dysfunction appear. The serious hepatotoxic side-effects of ketoconazole are idiosyncratic and rare, occurring in between 1:10 000 and 1:15 000 patients treated for longer than 2 weeks. Most cases have been reported in patients

treated for onychomycosis or chronic recalcitrant dermatophytosis. In most cases, hepatic damage is reversible when the drug is discontinued. Liver function tests should be performed before starting treatment and at monthly intervals thereafter, particularly in patients on prolonged treatment or in those receiving other hepatotoxic drugs.

High doses of ketoconazole (over 800 mg/day) inhibit human adrenal and testicular steroid synthesis, with clinical consequences such as alopecia, gynaecomastia and impotence. High dose ketoconazole should be avoided in conditions associated with hypoadrenalism which include AIDS, histoplasmosis, paracoccidioidomycosis and tuberculosis.

3.6.9 Drug interactions

As with itraconazole, serum concentrations of ketoconazole are lower in patients taking drugs that reduce gastric acid secretion, such as antacids, anticholinergics and H2-antagonists. These drugs should be given at least 2 h after ketoconazole administration.

Oral ketoconazole has been shown to prolong the half-life of terfenadine, astemizole and cisapride. It should not be administered with these drugs. Ketoconazole can also prolong the half-life of midazolam and triazolam, thus augmenting their serum concentrations. It has been shown to increase the blood levels of cyclosporin and levels of this drug should be monitored if it is given together with this antifungal agent. Ketoconazole can increase the serum concentration of warfarin, enhancing its anticoagulant effect. Careful monitoring of prothrombin time in patients receiving both drugs is recommended.

Concurrent administration of ketoconazole with rifampicin can reduce the effectiveness of both drugs

3.7 Voriconazole

Voriconazole is a synthetic triazole compound derived from fluconazole.

3.7.1 Mechanism of action

Voriconazole is a potent inhibitor of ergosterol biosynthesis through its action on the cytochrome

P-450-dependent enzyme, lanosterol 14-α-demethylase. This leads to depletion of ergosterol and accumulation of methylated sterols, resulting in disruption of fungal membrane structure and function.

3.7.2 Spectrum of action

Voriconazole has a broad spectrum of action including *Aspergillus* species, *B. dermatitidis*, *Candida* species, *C. immitis*, *C. neoformans*, *Fusarium* species, *H. capsulatum*, *P. marneffei* and *Scedosporium apiospermum*. It is active against many dematiaceous moulds, but appears to be ineffective against Zygomycetes.

3.7.3 Acquired resistance

Acquired resistance has not been reported, but fluconazole-resistant *C. albicans* strains from AIDS patients with chronic relapsing oropharyngeal candidosis have been less susceptible to voriconazole.

3.7.4 Pharmacokinetics

Oral administration of voriconazole leads to rapid and almost complete absorption (about 96%) of the drug. Two hours after a single 400-mg dose, serum concentrations in the region of 2 mg/L can be anticipated. As with itraconazole, there is a disproportionate increase in blood levels with increasing oral and parenteral dosage due to saturable first-pass metabolism. Absorption of the drug is reduced with high-fat meals, but is not affected by changes in gastric pH.

Voriconazole has a large volume of distribution (4.6 L/kg) indicating extensive distribution in tissues. Its protein binding is estimated to be 58%. Less than 2% of a given dose is excreted as unchanged drug in the urine.

Voriconazole is extensively metabolized by the human hepatic cytochrome P-450 enzyme system. None of the metabolites is active. More than 80% of an administered dose is eliminated as metabolites in the urine. The elimination half-life is dose-dependent, and is about 6–9 h at a 3 mg/kg parenteral dose or 200-mg oral dose.

Three hepatic cytochrome P-450 enzyme systems, CYP-2C19, CYP-2C9 and CYP-3A4, have a major role in the metabolism of voriconazole. Of these,

CYP-2C19 demonstrates genetic polymorphism, dividing the population into poor and extensive metabolizers as a result of point mutations in the gene encoding the protein of CYP-2C19. About 3–5% of black and Caucasian populations, and 15–20% of Asian populations are poor metabolizers. Among normal individuals, poor metabolizers have, on average, fourfold higher voriconazole exposure (AUC) than extensive metabolizers.

3.7.5 Pharmaceutics

Voriconazole is available in oral and parenteral forms.

The drug is supplied for intravenous administration in lyophilized form in 200-mg amounts. It is reconstituted in 19 ml sterile water (for injection) to give an extractable volume of 20 ml concentrated solution containing 10 mg/ml voriconazole. The drug solution is further diluted with 5% dextrose (for injection) or 0.9% sodium chloride (for injection). The reconstituted drug can be stored in a refrigerator for up to 24 h.

3.7.6 Therapeutic use

Voriconazole has been approved for the treatment of immunocompromised patients with serious fungal infections, including acute invasive aspergillosis, invasive candidosis due to fluconazole-resistant *Candida* species (including *C. krusei*) and infections due to *Fusarium* and *Scedosporium* species.

In the USA, voriconazole has been approved as a first-line agent for the treatment of acute invasive aspergillosis. It has also been approved for salvage treatment of infections due to *Fusarium* species and *Scedosporium apiospermum*.

3.7.7 Mode of administration

Intravenous treatment with voriconazole should be initiated with two loading doses of 6 mg/kg 12-h apart, followed by 4 mg/kg at 12-h intervals. Each dose should be infused at a maximum rate of 3 mg/kg per hour over a 1–2-h period. The concentration of the infusion solution should not exceed 5 mg/ml.

Once the patient can tolerate oral medication, intravenous administration can be discontinued. Patients who weigh more than 40 kg should receive an oral

dose of 200 mg at 12-h intervals. Adult patients who weigh less than 40 kg should receive 100 mg at 12-h intervals. If treatment is initiated with oral voriconazole, patients who weigh more than 40 kg should receive two loading doses of 400 mg at 12-h intervals. Adult patients who weigh less than 40 kg should receive two loading doses of 200 mg at 12-h intervals. If the patient response is inadequate, the oral dose can be increased to 300 mg twice daily (or 150 mg twice daily for patients weighing less than 40 kg).The drug should be taken at least 1 h before, or 1 h following, a meal. The duration of treatment will differ from patient to patient and depend on the nature of the infection and the clinical response.

If a patient is unable to tolerate treatment with voriconazole, the intravenous maintenance dose can be reduced to 3 mg/kg at 12-h intervals. The oral dose can be reduced in 50-mg steps to a minimum of 200 mg twice daily (100 mg twice daily in patients weighing less than 40 kg).

No dosage adjustment is required in patients with abnormal liver function tests (up to fivefold the upper limit of normal), but continued monitoring is recommended. No adjustment of oral dose is required for patients with renal impairment. However, in individuals with moderate or severe renal impairment (creatinine clearance <50 ml/min) accumulation of the intravenous carrier, sulphobutyl ether-β-cyclodextrin, occurs. Oral voriconazole should be used in these patients.

A 4-h haemodialysis session does not remove a sufficient amount of voriconazole to necessitate dosage adjustment.

3.7.8 Adverse reactions

The most frequent adverse events noted in patients treated with voriconazole have been visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache and abdominal pain.

About 30% of patients experience altered or enhanced visual perception, blurred vision, colour vision change and/or photophobia. In general, these visual disturbances are transient and reversible, mostly resolving within 1 h. These disturbances seldom require

discontinuation of treatment. The mechanism of action is unclear, but there is some evidence that visual disturbances may be associated with higher serum concentrations or dosages of the drug. It is recommended that visual function be monitored if voriconazole treatment is continued for longer than 4 weeks.

There have been rare cases of severe exfoliative cutaneous reactions, such as Stevens–Johnson syndrome, among persons taking voriconazole. If patients develop a skin rash, they should be closely monitored and the drug discontinued if the lesions progress. It is recommended that patients avoid strong direct sunlight during voriconazole treatment.

About 13% of patients have developed elevations in liver function tests during voriconazole treatment. Liver function test abnormalities may be associated with higher serum concentrations or dosages of the drug. These abnormalities have usually been reversible on discontinuation of treatment. Isolated cases of hepatitis, cholestasis and fulminant hepatic failure (including fatalities) have also been reported and it is advisable to discontinue the drug if signs of liver disease appear. Voriconazole should only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. In such cases, monitoring of liver function is essential.

3.7.9 Drug interactions

Unlike other azoles, absorption of voriconazole is not reduced if it is given together with drugs such as cimetidine and ranitidine that reduce gastric acid secretion.

Voriconazole is a less potent inhibitor of the human hepatic cytochrome P-450-3A4 enzyme system than itraconazole or ketoconazole. However, it has been shown to increase the serum concentration of sirolimus, terfenadine, astemizole, cisapride, pimozide and quinidine. It should not be co-administered with these drugs.

Voriconazole has been shown to increase the serum concentrations of cyclosporin and tacrolimus, and levels of these drugs should be monitored and/or dosage adjusted if they are given together with the azole agent. Voriconazole can also increase the serum concentration of warfarin, enhancing its anticoagulant effect.

Careful monitoring of prothrombin time in patients receiving both drugs is recommended. Voriconazole has the potential to inhibit the metabolism of lovastatin and midazolam, and it is recommended that the dose of these drugs be adjusted. It also has the potential to increase the serum concentrations of tolbutamide and glipizide, augmenting their hypoglycaemic effects. Frequent monitoring of blood glucose levels is recommended. Voriconazole can inhibit the metabolism of anti-HIV protease inhibitors, such as saquinavir, amprenavir and nelfenavir, while ritonavir, amprenavir and saquinavir can inhibit the metabolism of the azole.

Concomitant administration of voriconazole with drugs that are potent inducers of the human cytochrome P-450 enzyme system results in a marked reduction in blood levels of the azole agent. Voriconazole should not be given together with carbamazepine, phenobarbital, rifabutin and rifampicin. If co-administered with phenytoin the intravenous dose of voriconazole should be increased from 4 to 5 mg/kg at 12-h intervals, and the oral dose from 200 to 400 mg at 12-h intervals. Serum concentrations of phenytoin should be monitored and the dose adjusted to maintain therapeutic levels.

3.8 Other imidazole compounds for topical administration

3.8.1 Bifonazole

Bifonazole is used for the treatment of dermatophytosis and pityriasis versicolor. The dosage and duration of treatment varies according to the condition being treated.

3.8.2 Butoconazole

Butoconazole is used for the treatment of vaginal candidosis. Pessaries (100 mg) should be inserted high in the vagina for 3 consecutive days.

3.8.3 Clotrimazole

Clotrimazole is used for the treatment of dermatophytosis and oral, cutaneous and genital candidosis. For oral candidosis, oral troches (10 mg) should be dissolved in the mouth five times daily for 2 weeks or longer. For vaginal candidosis, pessaries (500, 200 or 100 mg) should

be inserted high in the vagina for 1, 3 or 6 consecutive days, respectively. For fungal skin infections, dosage and duration of treatment varies according to the condition being treated.

3.8.4 Econazole nitrate

Econazole nitrate is used for the treatment of dermatophytosis and oral, cutaneous and genital candidosis. It has also been used to treat corneal infections. For vaginal candidosis, pessaries (150 mg) should be inserted high in the vagina for 3 consecutive days. For fungal skin infections, dosage and duration of treatment varies according to the condition being treated.

3.8.5 Fenticonazole nitrate

Fenticonazole nitrate is used for the treatment of vaginal candidosis. Pessaries (600 or 200 mg) should be inserted high in the vagina for 1 or 3 consecutive days, respectively.

3.8.6 Isoconazole nitrate

Isoconazole nitrate is used for the treatment of dermatophytosis and cutaneous and vaginal candidosis. For vaginal candidosis, a single-dose pessary (600 mg) should be inserted high in the vagina. For fungal skin infections, dosage and duration of treatment varies according to the condition being treated.

3.8.7 Miconazole nitrate

Miconazole nitrate is used for the topical treatment of dermatophytosis, pityriasis versicolor, and oral, cutaneous and genital candidosis. It is no longer available for intravenous use in deep-seated fungal infections. For vaginal candidosis, pessaries (200 or 100 mg) should be inserted high in the vagina for 7 or 14 consecutive days, respectively. For oral candidosis, oral gel (125 mg) should be placed in the mouth four times daily. For fungal skin infections, dosage and duration of treatment varies according to the condition being treated.

3.8.8 Oxiconazole

Oxiconazole is used for the treatment of dermatophytosis and cutaneous candidosis. The dosage and dur-

ation of treatment varies according to the condition being treated.

3.8.9 Sulconazole nitrate

Sulconazole nitrate is used for the treatment of dermatophytosis and cutaneous candidosis. The dosage and duration of treatment varies according to the condition being treated.

3.8.10 Terconazole

Terconazole is used for the treatment of dermatophytosis and cutaneous and genital candidosis. For vaginal candidosis, pessaries (80 mg) should be inserted high in the vagina for 3 consecutive days. For fungal skin infections, dosage and duration of treatment varies according to the condition being treated.

3.8.11 Tioconazole

Tioconazole is used for the treatment of the dermatophytoses (including nail infections) and cutaneous and genital candidosis. For vaginal candidosis, a single-dose pessary (300 mg) should be inserted high in the vagina. For fungal skin and nail infections, dosage and duration of treatment vary according to the condition being treated.

3.9 Terbinafine

Terbinafine is a synthetic allylamine compound.

3.9.1 Mechanism of action

Terbinafine inhibits the action of squalene epoxidase, a crucial enzyme in the formation of ergosterol, the principal sterol in the membrane of susceptible fungal cells. The consequent accumulation of squalene leads to membrane disruption and cell death.

3.9.2 Spectrum of action

Terbinafine is effective against the dermatophytes and *M. furfur*. It is fungistatic for *C. albicans* but fungicidal for some other *Candida* species including *C. parapsilosis*. It has also been shown to be active against *Aspergillus* species, *B. dermatitidis*, *H. capsulatum*, *S. schenckii* and some dematiaceous moulds.

3.9.3 Acquired resistance

Acquired resistance has not been reported.

3.9.4 Pharmacokinetics

About 5% of a given dose of terbinafine is absorbed following topical application. The drug is well absorbed (>70%) after oral administration, peak serum concentrations in the region of 0.8–1.5 mg/L being attained 2 h after a single 250-mg dose. Levels increase in proportion to dosage up to at least 750 mg. Administration of the drug with food does not affect absorption.

Terbinafine is a lipophilic drug which appears to concentrate in the dermis, epidermis and adipose tissue. It appears in the stratum corneum within a few hours of oral administration being commenced, as a result of diffusion through the dermis and epidermis and secretion in sebum. Diffusion from the nail bed is the major factor in its rapid penetration of nails. Terbinafine has been found to persist in nail for long periods after cessation of treatment.

Terbinafine is metabolized by the liver and the inactive metabolites are excreted in the urine. The drug has an elimination half-life of 17 h, but this is prolonged in patients with hepatic or renal impairment.

3.9.5 Pharmaceutics

Terbinafine (as hydrochloride) is available in oral and topical forms.

3.9.6 Therapeutic use

Topical terbinafine is effective against cutaneous dermatophytoses and candidosis, as well as pityriasis versicolor. Oral terbinafine can be used to treat dermatophytoses of the skin and nails where topical treatment is considered inappropriate or has failed. However, oral treatment is ineffective against pityriasis versicolor.

3.9.7 Mode of administration

Topical terbinafine should be applied morning and/or evening for 2–4 weeks depending on the site of infection. Tinea pedis should be treated for 2 weeks, and tinea corporis and cruris for 2–4 weeks. Cutaneous

candidosis and pityriasis versicolor should be treated for 2 weeks.

The usual adult dose of oral terbinafine is 250 mg/day, but this should be halved in patients with impaired hepatic or renal function (creatinine clearance less than 50 ml/min or serum creatinine concentration >300 μmol/ml). The duration of treatment will depend upon the site and extent of infection (see Chapter 4). Tinea pedis should be treated for 2–6 weeks, and tinea corporis and cruris for 2–4 weeks. Most nail infections require at least 6–12 weeks of oral terbinafine treatment. Fingernail infection can often be cured with treatment periods of less than 3 months, but some patients with toenail infection require treatment for 6 months or longer.

3.9.8 Adverse reactions

Terbinafine is well tolerated. The commonest side-effects are gastrointestinal in origin, such as diarrhoea, dyspepsia and abdominal pain. Allergic skin reactions have also been reported, and isolated cases of Stevens–Johnson syndrome have occurred. If a progressive skin rash develops which is considered to be attributable to terbinafine, the drug should be discontinued. Taste disturbance and taste loss have been reported, but these usually resolve within several weeks once the drug is stopped.

There have been rare cases of liver failure and death among persons taking terbinafine for nail infections. The drug is not recommended for patients with chronic or active liver disease. Liver function tests should be performed before treatment is started. Should signs of hepatic dysfunction appear during terbinafine treatment, the drug must be discontinued and liver function evaluated.

3.9.9 Drug interactions

Unlike the azole antifungals, terbinafine does not affect the clearance of other drugs that undergo cytochrome P-450-dependent hepatic metabolism. However, blood concentrations of terbinafine are reduced following its concomitant administration with drugs such as rifampicin which is a potent inducer of the hepatic cytochrome P-450 enzyme system. Blood levels of terbinafine are

increased if it is given together with cimetidine, a cytochrome P-450 inhibitor.

3.10 Other allylamine compounds for topical administration

3.10.1 Naftifine

Naftifine is used for the treatment of the dermatophytoses, including tinea corporis, tinea cruris and tinea pedis. The dosage and duration of treatment varies according to the condition being treated.

3.11 Caspofungin

Caspofungin is a semi-synthetic derivative of pneumocandin B_0, a lipopeptide fermentation product derived from the fungus *Glarea lozoyensis*.

3.11.1 Mechanism of action

Caspofungin inhibits the synthesis of β-(1,3)-D-glucan, an integral component of the cell wall of susceptible fungi.

3.11.2 Spectrum of action

Caspofungin has a limited spectrum of action. It is effective against *Aspergillus fumigatus*, *A. flavus* and *A. terreus*, but not against the dermatophytes. It has variable activity against *C. immitis*, *H. capsulatum* and dematiaceous moulds. It is active against most *Candida* species, with a rapid fungicidal effect, but *C. parapsilosis* and *C. krusei* are less susceptible, and *C. neoformans* is resistant. It is also effective against *Pneumocystis carinii*.

3.11.3 Acquired resistance

Acquired resistance has not been reported.

3.11.4 Pharmacokinetics

One hour after a single 70-mg parenteral dose, administered over a 1-h period, serum concentrations of caspofungin in the region of 10 mg/L can be anticipated. Blood concentrations increase in proportion to dosage. Less than 10% of the dose remains in the blood 36–48 h after administration and more than 96% of this is protein-bound. Most of the remainder is distributed to the tissues (about 92% of the dose), with the highest

concentrations being found in the liver. Levels in the CSF are negligible. About 1% of a dose is excreted unchanged in the urine.

There is little excretion or metabolism of caspofungin during the first 30 h after administration. The drug is metabolized by the liver and the inactive metabolites are excreted in the bile (35%) and urine (40%). There is an initial half-life of about 9–11 h and an elimination half-life of 40–50 h.

Caspofungin is not cleared by haemodialysis.

3.11.5 Pharmaceutics

Caspofungin (as acetate) is only available for parenteral administration. The drug is supplied in lyophilized form in 50- and 70-mg amounts and is reconstituted in 10.5 ml 0.9% sodium chloride (for injection). The reconstituted drug solution is further diluted by adding 10 ml to 250 ml 0.9% sodium chloride (for injection). The infusion solution must be used within 24 h, during which time it should be stored at a temperature of less than 25°C.

3.11.6 Therapeutic use

Caspofungin is approved for the treatment of invasive forms of candidosis. It is also licensed for the treatment of aspergillosis in patients who have failed to respond to, or are intolerant of, other antifungal agents.

3.11.7 Mode of administration

The recommended dosage for patients with aspergillosis is 70 mg on the first day followed by 50 mg daily thereafter. Each dose should be infused over a 1-h period. The duration of treatment will differ from patient to patient and depend on the extent of disease and the clinical response.

No dosage adjustment is required in patients with renal impairment. However, a dose reduction to 35 mg following the 70-mg loading dose is recommended for patients with moderate hepatic impairment. There is no clinical experience in patients with severe liver disease.

The safety and effectiveness of caspofungin in children has not been established.

3.11.8 Adverse reactions

Caspofungin is well tolerated. The most common side-effects are fever, rash, nausea and vomiting. Transient elevations of liver function tests have been reported in some patients.

3.11.9 Drug interactions

Unlike the azole antifungals, caspofungin does not inhibit the human hepatic cytochrome P-450 enzyme system. Nor has it been shown to induce the cytochrome P-450-3A4 metabolism of other drugs. Co-administration of caspofungin with cyclosporin has resulted in transaminase elevations of two-to-threefold the upper limit of normal that resolved when both drugs were discontinued. In addition, caspofungin serum concentrations were increased, but there was no effect on cyclosporin pharmacokinetics. Concomitant administration of caspofungin with cyclosporin is not recommended unless the expected benefit outweighs the risk. No other drug interactions have been reported.

3.12 Flucytosine

Flucytosine (5-fluorocytosine) is a synthetic fluorinated pyrimidine.

3.12.1 Mechanism of action

Flucytosine is transported into susceptible fungal cells by the action of cytosine permease and there converted by cytosine deaminase to 5-fluorouracil which is incorporated into RNA in place of uracil, with resulting abnormalities of protein synthesis. In addition, it blocks thymidylate synthetase causing inhibition of DNA synthesis.

3.12.2 Spectrum of action

Flucytosine has a limited spectrum of action including *Candida* species, *C. neoformans*, *Cladophialophora carrionii*, *Fonsecaea* species and *Phialophora verrucosa*.

3.12.3 Acquired resistance

Induction of resistance during treatment is a common problem. Moreover, about 10% of *C. albicans* strains, 20% of *C. tropicalis* strains and 2% of *C. neoformans*

strains are resistant from the outset. The most common cause of resistance appears to be loss of the enzyme uridine monophosphate pyrophosphorylase.

3.12.4 Pharmacokinetics

Oral administration of flucytosine leads to rapid and almost complete absorption of the drug. Identical serum concentrations are obtained after oral and parenteral administration. In adults with normal renal function an oral dose of 25 mg/kg given at 6-h intervals will produce peak serum concentrations at 1–2 h of 70–80 mg/L and trough concentrations of 30–40 mg/L. Absorption is slower in persons with impaired renal function but peak serum concentrations are higher. There is slight accumulation of the drug during the first 4 days of treatment, but thereafter peak serum concentrations remain almost constant. Peak levels are reached in a shorter period of 1–2 h in persons who have received several previous doses of the drug. The protein binding of flucytosine is low (about 12%) resulting in high levels of circulating unbound drug.

Flucytosine is widely distributed, with levels in most tissues and fluids usually exceeding 50% of the simultaneous blood concentration. The main means of elimination is renal excretion of the unchanged drug. About 90% of an administered dose appears in the urine and concentrations of 1000 mg/L are not unusual in persons with normal renal function. The serum half-life is between 3 and 6 h, but is much longer in renal failure, necessitating modification of the dosage regimen.

Less than 1% of an administered dose of flucytosine is metabolized in man. The drug is deaminated to 5-fluorouracil or dihydrofluorouracil and this could account for the myelotoxic effects associated with high serum concentrations. The remainder of the compound is excreted unchanged in the urine.

3.12.5 Pharmaceutics

Flucytosine is available as oral tablets and as an infusion for parenteral administration. The latter is supplied in 250-ml amounts containing 10 mg/ml in aqueous saline solution.

3.12.6 Therapeutic use

Flucytosine is seldom used as a single drug, other than in patients with certain forms of chromoblastomycosis (see Chapter 18). Its principal use is in combination with amphotericin B in the treatment of cryptococcosis and deep forms of candidosis. Combination treatment with fluconazole has been shown to be effective in AIDS-associated cryptococcal meningitis. However, this regimen is associated with a high incidence of toxic side-effects.

3.12.7 Mode of administration

As absorption following oral administration is good, this is the preferred method of administration. If the patient cannot take the drug by mouth, the intravenous solution should be used. This can be administered through a venous catheter or as an intraperitoneal infusion. The drug should be infused over a 20–40-min period provided this is balanced with the fluid requirements of the patient. Twice-weekly blood counts (total white cells and platelets) should be performed.

In adults with normal renal function the usual starting dose of flucytosine is 50–150 mg/kg given as four divided doses at 6-h intervals. If renal function is impaired, an initial dose of 25 mg/kg should be given, but the subsequent dose and interval should be adjusted so as to produce peak serum concentrations of 70–80 mg/L and trough concentrations of 30–40 mg/L. The drug accumulates in renal failure necessitating modification of the dose regimen (see Table 3.3). The half-life of flucytosine is prolonged in small infants and the drug should be administered at 12- or 24-h intervals.

3.12.8 Adverse reactions

Nausea, vomiting and diarrhoea are the most common side-effects. Thrombocytopenia and leucopenia can occur if excessive blood concentrations are maintained (more than 100 mg/L). The effect is usually reversible if treatment is discontinued. Bone marrow suppression is a common problem in persons with AIDS and usage of flucytosine should be minimized or avoided in these individuals.

Table 3.3 Regimens for administration of flucytosine in renal impairment

Dosage clearance (ml/min)	Creatinine dosage (mg/kg)	Individual interval (h)
>40	25–37.5	6
40–20	25–37.5	12
20–10	25–37.5	24
<10	25–37.5	> 24*

Renal function is considered to be normal when creatinine clearance is greater than 40–50 ml/min or concentration of creatinine in serum is less than 180 μmol/L; concentration of creatinine in serum is not reliable unless renal function is stable.
*Dosage interval must be based on serum drug concentration measurement at frequent intervals.

Elevated transaminase levels develop in some patients, but usually return to normal after the drug is discontinued. Liver necrosis leading or contributing to death has been reported in occasional patients.

3.12.9 Drug interactions

The antifungal effect of flucytosine is competitively inhibited by cytarabine (cytosine arabinoside). For this reason, co-administration of the antifungal agent with cytarabine is contraindicated. Because the harmful myelosuppressive and hepatotoxic effect of flucytosine can be elicited by many other agents, it is important to be cautious when it is co-administered with drugs that could augment these side-effects, such as immunosuppressive or cytostatic agents. Drugs that are known to be myelosuppressive, such as zidovudine, should be used with caution in individuals receiving flucytosine.

Amphotericin B and flucytosine have an additive or synergistic effect when used in combination against *Candida* species and *C. neoformans*. However, the nephrotoxic effects of amphotericin B can impair the excretion of flucytosine. Blood levels of flucytosine should be monitored when these compounds are administered together.

There have been numerous reports of successful treatment of candidosis, cryptococcosis and chromoblastomycosis with combinations of flucytosine and fluconazole or itraconazole.

3.13 Griseofulvin

Griseofulvin is an antifungal antibiotic derived from a number of *Penicillium* species. It was the first oral drug for treatment of dermatophytosis.

3.13.1 Mechanism of action

Griseofulvin is a fungistatic drug which binds to microtubular proteins and inhibits fungal cell mitosis. It also acts as an inhibitor of nucleic acid synthesis.

3.13.2 Spectrum of action

Griseofulvin has a limited spectrum of action which is almost restricted to the dermatophytes (*Epidermophyton floccosum*, *Microsporum* species and *Trichophyton* species). Its clinical use is limited to these infections. It is ineffective in cutaneous candidosis and pityriasis versicolor.

3.13.3 Acquired resistance

Treatment failure attributable to the development of griseofulvin resistance is an uncommon problem in patients with dermatophytoses.

3.13.4 Pharmacokinetics

Absorption of griseofulvin from the gastrointestinal tract is dependent on drug formulation. Administration of the drug with a high-fat meal will increase the rate and extent of absorption, but individual patients tend to achieve consistently high or low serum concentrations. Four hours after a single 1000-mg dose, blood levels in the region of 0–3.75 mg/L can be anticipated.

Griseofulvin appears in the stratum corneum within 4–8 h of oral administration, as a result of drug secretion in perspiration. However, levels begin to fall soon after the drug is discontinued, and within 48–72 h it can no longer be detected. The mechanisms by which griseofulvin is delivered to the hair and nails is not well understood; deposition in newly formed cells is thought to be the major factor.

Griseofulvin is metabolized by the liver to 6-desmethyl griseofulvin which is excreted in the urine. The drug has an elimination half-life from 9 to 21 h.

Less than 1% of a given dose appears in the urine in unchanged form.

3.13.5 Pharmaceutics

Griseofulvin is available as oral tablets and oral suspension.

3.13.6 Therapeutic use

Griseofulvin is indicated in moderate to severe dermatophytoses of the skin, scalp hair or nails where topical treatment is considered inappropriate or has failed.

3.13.7 Mode of administration

It is important to adjust the dose of griseofulvin to the weight of the patient. The adult dose can range from 500 to 1000 mg either as a single or divided doses; not less than 10 mg/kg should be given. Children with tinea capitis should be given the drug at a dose of at least 10 mg/kg per day. This can be increased to 20 mg/kg per day in patients with *T. tonsurans* infection or where there is failure to respond after 6 weeks of treatment. The drug should be taken after meals.

The duration of treatment will differ from patient to patient and depend upon the nature and extent of the infection. Children with tinea capitis should be treated for a period of 6–8 weeks. Some patients with *M. canis* scalp infection require treatment for up to 12 weeks. Long courses (usually 6–12 months) and high doses may be needed for nail infections. Long-term relapse rates are high; between 40 and 70% for toenails, but somewhat lower for fingernails.

3.13.8 Adverse reactions

In most cases, prolonged courses and high doses are well tolerated. Patients have complained of headaches, nausea, vomiting and abdominal discomfort. Urticarial reactions and erythematous rashes occur in occasional patients.

The drug is contraindicated in patients with liver disease as hepatic function may deteriorate and the risk of other side-effects is increased.

3.13.9 Drug interactions

Griseofulvin has been shown to stimulate the metabolism of warfarin, thus reducing its anticoagulant effect. Absorption is reduced in patients receiving concomitant treatment with phenobarbitone, but the effect can be reduced by administration of griseofulvin with food. Failure of contraception has been reported in patients taking griseofulvin and oral contraceptive steroids.

3.14 Other miscellaneous compounds for topical administration

In addition to the antifungal compounds described so far, a number of other drugs are available for topical use. Not all the preparations listed in the following sections are available in all countries.

3.14.1 Amorolfine hydrochloride

Amorolfine hydrochloride is a morpholine compound which inhibits fungal ergosterol biosynthesis. It can be used to treat tinea corporis, tinea cruris and tinea pedis, as well as localized distal onychomycosis. For fungal skin infections, amorolfine should be applied once daily for at least 2–3 weeks (up to 6 weeks for tinea pedis). For fingernail infections, amorolfine nail solution should be applied once or twice weekly for at least 6 months. Toenail infections should be treated for 9–12 months.

3.14.2 Butenafine hydrochloride

Butenafine hydrochloride is a synthetic benzylamine compound which acts as an ergosterol biosynthesis inhibitor. It is used for the treatment of tinea corporis, tinea cruris and tinea pedis. The dosage and duration of treatment varies according to the condition being treated.

3.14.3 Ciclopirox

Ciclopirox is a synthetic pyridinone compound used in tinea corporis, tinea cruris, tinea pedis, onychomycosis, cutaneous candidosis and pityriasis versicolor. For fungal skin infections, it should be applied twice daily for at least 2–4 weeks. For nail infections, the solution should be applied once daily for at least 6 months.

3.14.4 Haloprogin

Haloprogin is a halogenated phenolic compound which is effective in tinea corporis, tinea cruris, tinea pedis and pityriasis versicolor. The dosage and duration of treatment varies according to the condition being treated.

3.14.5 Tolnaftate

Tolnaftate is a thiocarbamate compound used in the treatment of tinea cruris and tinea pedis. The dosage and duration of treatment varies according to the condition being treated.

3.15 Empirical treatment of suspected fungal infection in the neutropenic patient

Two clinical trials in the 1980s suggested that up to one-third of febrile neutropenic patients who do not respond to a 1-week course of antibacterial treatment have systemic fungal infections that, in most cases, are caused by *Aspergillus* or *Candida* species. Both trials suggested that there were fewer fungal infections in patients who received empirical treatment with amphotericin B. Although clinicians still disagree as to when, and even if, amphotericin B should be used, most believe that the patient who remains febrile and profoundly neutropenic for 5 days or longer, despite the administration of broad-spectrum antibacterial agents in adequate dosage, should receive empirical antifungal treatment. Individual cases may have clinical features that will dictate use of amphotericin B earlier, later or not at all. Such an exception might be an individual who has no detectable lesions, has neither *Aspergillus* nor *Candida* species isolated from any site, and is expected to have an increased neutrophil count in a few days. Every effort should be made to determine whether a systemic fungal infection exists before empirical amphotericin B treatment is started.

In the mid-1990s, several large clinical trials in which composite end-points (including defervescence, survival and prevention of infection) were used, indicated that lipid formulations of amphotericin B are as effective, but safer than the conventional preparation. Other trials have demonstrated that empirical treatment with fluconazole or itraconazole is as effective as amphotericin B in preventing infections with *Candida* species, with fewer

toxic side-effects. These drugs can be used in low-risk patients, but are best avoided in those who have received prophylactic triazoles, those in whom the duration of neutropenia portends a high risk of mould infections, and those who have signs of sinusitis or pulmonary infection.

Empirical treatment should be initiated with the usual test dose (1 mg) of amphotericin B. If possible, the full therapeutic dosage level (0.7–1.0 mg/kg per day of the conventional formulation) should be reached within the first 24 h of treatment. There is no need for gradual escalation of dosage, nor is there evidence to support the clinical prejudice that a lower dose can be used in suspected candidosis. Should the conventional formulation of amphotericin B be contraindicated, one of the lipid-based formulations should be used instead. The recommended dosage of AmBisome for empirical treatment of presumed fungal infection is 3 mg/kg per day.

The duration of empirical treatment will differ from individual to individual. If a diagnosis of systemic fungal infection is established, a full course of treatment should be given, and this will be determined by the causative agent and the extent of the disease. More often, however, the patient responds and/or the neutrophil count recovers, but a firm diagnosis is not obtained. In this situation it is not clear how long amphotericin B or other antifungal drugs should be administered. It is reasonable to discontinue amphotericin B when the neutrophil count exceeds 1×10^9/L, the fever resolves, other relevant symptoms and signs resolve, and computerized tomography (CT) scans of the chest and abdomen reveal no suspicious lesions. If a patient is clinically well, but has persistent neutropenia, it is reasonable to discontinue amphotericin B after 2 weeks, if no lesions can be found by clinical evaluation, or CT scans of the chest and abdomen. If the patient appears ill or is at high-risk, treatment with amphotericin B should be continued until the neutrophil count has recovered.

3.16 Prophylactic treatment for prevention of fungal infection

Because the diagnosis and treatment of fungal infections continues to be difficult, antifungal drug prophylaxis is

often appropriate among high-risk individuals such as neutropenic cancer patients, HSCT recipients, organ transplant recipients, critical-care patients and those with advanced HIV infection.

In several large clinical trials, fluconazole prophylaxis was found to reduce the incidence of superficial and deep forms of candidosis among HSCT recipients. As a result, its use (at a dosage of 400 mg/day during the period of neutropenia) has been endorsed in published guidelines for prevention of infection in allogeneic and high-risk autologous transplant recipients. However, fluconazole prophylaxis has been associated with an increase in colonization and infection with *C. glabrata* and *C. krusei*, and it offers no protection against infection with *Aspergillus* species or other moulds.

Several trials of prophylaxis suggest that itraconazole oral solution (at a dosage of 2.5 mg/kg twice daily) administered to neutropenic patients can reduce the risk for invasive fungal infections. It is unfortunate that the rate of mould infections in these trials was too low to establish whether itraconazole is effective in preventing the development of aspergillosis. Itraconazole should be considered as prophylaxis in units where high-risk patients are nursed without high efficiency particulate air (HEPA) filtration of incoming air, where there is a high incidence of mould infections or where building works are being undertaken. It should be substituted for fluconazole prophylaxis in such units in patients who have been neutropenic for longer than 3 weeks.

Fluconazole prophylaxis (at a dosage of 400 mg/day) also appears to be effective in preventing candidosis among some high-risk non-neutropenic patient populations. These include surgical patients with recurrent gastrointestinal perforations or anastomotic leakages, and liver and pancreatic transplant recipients. Unlike HSCT recipients, improved survival with fluconazole prophylaxis has never been documented in a randomized trial with liver transplant recipients. The need for prophylaxis in these patients should be assessed on the basis of institutional trends in the incidence of invasive candidosis in the immediate post-operative period, and should be targeted towards high-risk individuals.

Clinical trials have demonstrated that long-term prophylactic administration of fluconazole (200 mg/day) or itraconazole (200 mg/day) to persons with advanced HIV infection can prevent the development of cryptococcosis and histoplasmosis, respectively. However, because the use of combination antiretroviral treatments has greatly reduced the incidence of AIDS-associated opportunistic infections in developed countries, routine antifungal prophylaxis is not recommended at present. Additional concerns are the high cost of such treatment, the lack of survival benefits associated with prophylaxis, and the potential for the development of drug resistance.

A controlled trial demonstrated that long-term prophylactic administration of itraconazole (200 mg/day) to persons with advanced HIV infection residing in northern Thailand prevented the development of cryptococcosis and penicilliosis. Further trials are needed to determine whether antifungal prophylaxis has a role in preventing these and other opportunistic fungal infections among HIV-infected persons in developing countries with a high burden of these diseases.

3.17 Laboratory monitoring

3.17.1 Antifungal drug susceptibility testing

As with antibacterial drugs, tests designed to ascertain the minimum amount of an antifungal compound needed to inhibit the growth of fungal strains in culture (minimum inhibitory concentration or MIC) are often assumed to be the most dependable means of determining the relative effectiveness of different antifungal agents and detecting the development of drug-resistant strains. In addition, it is often assumed that the clinical outcome of treatment can be predicted from the results of *in vitro* testing of a patient's isolate against a panel of potentially useful agents. Such an approach has become more reasonable with the development of reliable and reproducible reference procedures for *in vitro* testing of *Candida* species against azole antifungal agents (particularly fluconazole), and the demonstration of correlations with clinical outcome for some forms of candidosis. However, the pitfalls of assuming a correlation between the results of susceptibility testing of

other antifungal drugs and organisms *in vitro* and outcome *in vivo* should not be underestimated.

Antifungal susceptibility testing is often helpful for isolates of *Candida* species (particularly other than *C. albicans*) from deep sites, but not for other fungi or settings. Testing of oropharyngeal isolates of *Candida* species in patients who have failed to respond to standard azole treatment can help to distinguish failures due to drug resistance from other causes. Testing of mould isolates should not at present be done on a routine basis. However, these isolates should be identified to species level as this can give useful therapeutic information.

3.17.2 Monitoring of blood concentrations of antifungal drugs

The optimum serum concentrations of amphotericin B for particular fungal infections have not been determined. For this reason, routine monitoring of blood levels during treatment is not indicated. Although amphotericin B is nephrotoxic, high blood concentrations do not lead to greater impairment of renal function nor does renal failure result in higher blood concentrations.

In general, serum concentrations of fluconazole are more predictable than those of other azole drugs and there is no need for their measurement. Excessive concentrations have not been associated with unwanted side-effects. Concentrations are unchanged in persons with AIDS and in HSCT recipients, and the reduction in concentration following concomitant administration with rifampicin is smaller than that seen with other azole antifungals.

Absorption of itraconazole after oral administration shows marked variation between individuals. Lower blood concentrations can be anticipated in persons with AIDS and HSCT recipients, as well as in patients receiving concomitant treatment with rifampicin. Low concentrations of itraconazole (less than 0.25 mg/L at 4 h) may predict failure of treatment. Levels should be measured in patients with life-threatening fungal infections, in patients in whom poor absorption or drug interactions are anticipated, and when there is treatment failure or relapse. High serum concentrations have not so far been associated with unwanted side-effects. Serum concentrations of itraconazole should be determined only after

the patient has reached the steady state, typically after 1–2 weeks. Blood should be taken just before, and 4 h after, an oral dose of itraconazole. High performance liquid chromatography (HPLC) is the preferred method for determining itraconazole concentrations because microbiological methods detect the active metabolite, hydroxyitraconazole, in addition to the drug itself.

Serum concentrations of flucytosine should be measured in all patients; this is essential when there is renal impairment or when the drug is given in combination with amphotericin B, to ensure adequate therapeutic concentrations and avoid excessive concentrations that can cause toxic effects. Levels should be determined twice weekly or more frequently if renal function is changing. Blood should be taken just before a dose of flucytosine is due, and 2 h after an oral dose or 30 min after an intravenous dose. In patients with renal impairment peak concentrations tend to occur later after oral dosing.

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4 Dermatophytosis

4.1 Introduction

The term dermatophytosis is used to describe infections of the skin, hair and nails due to a group of related filamentous fungi, the dermatophytes which are also known as the ringworm fungi. These infections are among the most common causes of skin disease. They can be difficult to diagnose, however, and are often mistaken for other disorders. With the exception of nail infections, dermatophytosis can be managed satisfactorily if treated correctly.

The clinical presentation of these infections depends on several factors including the site of infection, the immunological response of the host and the species of infecting fungus. In most forms of dermatophytosis, the fungus is confined to the superficial stratum corneum, nails and hair. However, deeper infection involving the dermis can occur, as in kerion, and this can result in the formation of suppurative lesions.

4.2 The causal organisms and their habitat

There are three genera of dermatophytes: *Trichophyton*, *Microsporum* and *Epidermophyton*. Of the 40 or so species that are recognized at present, some are worldwide in distribution, but others are restricted to particular continents or regions. About 10 species are common causes of human infection.

The dermatophytes are termed geophilic, zoophilic or anthropophilic depending upon whether their normal habitat is the soil, an animal or man. Members of all three groups can cause human infection, but their different natural reservoirs have important epidemiological implications in relation to the acquisition, site and spread of human infection.

Although the geophilic group of dermatophytes can cause infection in both animals and humans, their normal habitat is the soil. Members of the anthropophilic and zoophilic groups are thought to have evolved

from these and other keratinophilic soil-inhabiting fungi, different species having adapted to different natural hosts. Individual members of the zoophilic group are often associated with a particular animal host, for instance *M. canis* with cats and dogs and *T. verrucosum* with cattle. However, these organisms can also spread to humans.

Those dermatophytes for whom humans are the usual host are termed anthropophilic. These species can be divided into those which are common causes of scalp infections, for instance *M. audouinii* and *T. tonsurans*, and those which cause foot and nail infections, for instance *E. floccosum* and *T. rubrum*. The anthropophilic species are the most highly specialized group of dermatophytes. They rarely infect other animals and often show a strong preference for a particular body site, only occasionally being found in other regions. For instance, *M. audouinii* infects scalp hair, but is seldom found on the skin.

The dermatophytes are keratinophilic fungi that are normally found growing only in the dead keratinized tissue of the stratum corneum of the skin, within and around the scalp hair, and in the nails. In these tissues, dermatophyte growth is restricted to the production of hyphae, which branch and segment into chains of spores called arthrospores (or arthroconidia). Arthrospores are the main means of dissemination and propagation of the fungus, and can remain viable and infective on exfoliated skin and hair in the environment for months, or even years. Although arthrospores are common in skin and in nail, hyphae may be present without arthrospore formation, irrespective of the species involved. In hair, the type and extent of invasion varies according to the species of dermatophyte, and this affects the clinical presentation. The hyphae and arthrospores of some species of dermatophytes remain within the hair shaft (endothrix), while others form a sheath of arthrospores around the outside of the shaft (ectothrix). In endothrix infection, the hair shaft is almost completely destroyed and breaks off at, or below, the mouth of the follicle. In ectothrix infection, the hair remains sufficiently robust to stay intact to a length of 2–3 mm above the mouth of the follicle. The variations in the form of hair invasion

are not specific, however, and, as with infections of the skin and nail, culture is required to identify the species of fungus causing the infection.

4.3 Laboratory diagnosis of dermatophytosis

Superficial fungal infections, such as dermatophytosis, often present with characteristic lesions, but where this is not the case laboratory investigations are essential for correct diagnosis and management. It has been estimated that as much as 50% of suspicious material sampled from infected persons may not contain any fungus. It is important, therefore, to employ the correct procedures when taking specimens of skin, nails or hair for laboratory investigation (see Chapter 2). It is also essential to provide sufficient details about the patient. In addition to specifying the part of the body from which the specimen was taken, details on any underlying illness, drug treatment, contact with animals, recent travel, and previous residence abroad, should be given.

Direct microscopic examination of skin and nail material is often sufficient for the diagnosis of a dermatophyte infection but it gives no indication as to which species is involved. With hair specimens, the size and disposition of the arthrospores can give some indication as to which group of species is involved. Culture is a more specific method of diagnosis than microscopic examination. It permits the species of dermatophyte to be determined and this can aid in the selection of the most appropriate form of treatment. It can also provide information as to the source of the infection.

Microscopic examination and culture of clinical specimens should both be attempted on all occasions. If, however, there is insufficient material for both microscopic examination and culture of a specimen, the former should be performed. The results of culture can be positive even if microscopic examination is negative, but it is more common for microscopic examination to be positive while culture is negative.

Skin, nail and hair specimens can be cultured on glucose peptone (Sabouraud's) or malt agar supplemented with chloramphenicol to reduce bacterial growth and cycloheximide (actidione) to suppress moulds other

than dermatophytes. Most dermatophyte cultures can be identified after 1–2 weeks' incubation at 28–30°C.

It is not unusual to isolate moulds other than dermatophytes from abnormal skin and nails. In many cases, these are casual, transient contaminants and direct microscopic examination of clinical material is negative. However, certain moulds are capable of causing infection and when this is so, it is important that their significance is recognized. These infections are described in Chapters 6 and 7.

4.4 Tinea capitis

4.4.1 Definition

The term tinea capitis is used to refer to dermatophyte infections of the scalp hair and scalp skin. The main clinical signs are scaling and hair loss, but inflammation can also occur. Individuals who have neither symptoms nor signs, but from whose scalps dermatophytes can be isolated are described as 'carriers'.

4.4.2 Geographical distribution

The condition is worldwide in distribution, but is most prevalent in Africa, Asia and southern and eastern Europe, where it is the most common form of dermatophytosis. Favus used to be worldwide in distribution, but is now confined to North Africa, the Middle East and parts of southern and eastern Europe.

4.4.3 Epidemiology

Tinea capitis due to anthropophilic *Microsporum* and *Trichophyton* species is a contagious disease endemic in many countries. It is primarily a disease of pre-pubertal children, being more common in males than females, and most prevalent between 6 and 10 yr of age. The disease seldom persists beyond the age of 16. Large outbreaks can occur in schools or other places where children are congregated. Spread is thought to be mediated through direct contact, although indirect spread through contaminated fomites is sometimes a factor in the dissemination of infection.

The prevalence of tinea capitis has not been determined. In the USA, it has been estimated to occur in 3–8% of the paediatric population, with asymptomatic

carriage occurring in up to one-third of household contacts of infected persons.

The predominant aetiological agents of anthropophilic tinea capitis differ from one region to another, and can change within a particular region over time. For instance, *M. audouinii* was the predominant cause of scalp infection in Europe and North America until the 1950s, but *T. tonsurans* is now predominant in the USA and is becoming more frequent in the UK and Europe. At least two factors are thought to be responsible for this shift in species distribution. The first is the widespread use of griseofulvin to treat scalp infections. Because *M. audouinii* is susceptible to this antifungal agent, this species may have been eradicated, allowing *T. tonsurans*, which is less susceptible to griseofulvin, to become predominant. The second factor is changes in immigration patterns and the increase in international travel which might have facilitated the spread of *T. tonsurans* to new regions.

In addition to *T. tonsurans*, other anthropophilic species, such as *T. violaceum*, have appeared and increased in prevalence in urban populations in the UK and Europe. These infections are more common in black children in general, with *T. violaceum* being associated with children from the Indian subcontinent or Africa. However, children from all ethnic backgrounds are susceptible. In the USA, *T. tonsurans* is also more common in urban populations, particularly among African American children.

Little is known about the risk factors for anthropophilic tinea capitis. Among those that have been suggested are overcrowding within households or schools, use of shared brushes and combs, social and cultural factors, and ethnic group. Although the current spread of *T. tonsurans* in the USA and Europe is most often seen in black communities, this infection also occurs among children from other ethnic backgrounds.

Both adults and children living with cases of anthropophilic tinea capitis have been found to harbour organisms without showing symptoms. The prevalence of asymptomatic carriage shows marked variation, but tends to mirror the prevalence of tinea capitis in the local population. It has been reported to occur in 21%

of adults living with children with *T. violaceum* scalp infections, and in 12% of adults and 44% of siblings living with children with *T. tonsurans* infections. The risk factors appear to be similar to those for overt scalp infection.

Infection with a zoophilic *Microsporum* and *Trichophyton* species is often the result of direct contact with an infected animal. However, indirect spread can also occur as a result of environmental contamination due to an infected domestic pet, or when buildings, gates or implements are contaminated by farm animals.

The distribution of zoophilic infections in humans mirrors the geographic range of the animal host. The most common zoophilic cause of tinea capitis is *M. canis* which is spread from cats and dogs. Household pets are a common source of infection, but feral cats are another prolific source of *M. canis*. Sporadic cases of *M. canis* infection occur worldwide. *T. verrucosum*, which is acquired from cattle, is the second most frequent cause of zoophilic tinea capitis in the UK. However, it is uncommon and mostly seen in rural districts. The worldwide distribution of this infection is not well documented, although sporadic cases have been reported from many countries. It is more prevalent in countries where cattle are housed indoors during the winter. Among the other less common causes of zoophilic tinea capitis are *M. equinum* (acquired from horses) and *T. mentagrophytes* (acquired from rodents).

T. schoenleinii is considered to be the sole aetiological agent of favus, although infections with other dermatophytes, such as *M. gypseum*, *T. verrucosum* and *T. violaceum*, can sometimes produce somewhat similar lesions. Although *T. schoenleinii* is an anthropophilic dermatophyte, favus is less contagious than other forms of tinea capitis due to *Microsporum* or other *Trichophyton* species. It is usually contracted in childhood and may persist into adult life. Debilitated or malnourished children, or children suffering from a chronic disease such as tuberculosis, are more susceptible to this infection. Instances have been reported in which several generations of the same family were affected.

4.4.4 Clinical manifestations

The clinical manifestations of tinea capitis are varied and can range from mild scaling (similar to sebhorrhoeic dermatitis) and hair loss to widespread alopecia, or less commonly to a highly inflammatory suppurating lesion termed a kerion. The latter condition is usually caused by infection with a zoophilic dermatophyte.

In *M. audouinii* infection the lesions consist of one or more discrete, round or oval, erythematous patches of scaling and hair loss (2–6 cm in diameter). These may extend with time to involve the entire scalp. Inflammation is minimal, but fine scaling is characteristic. The hairs in these lesions are all parasitized and most of them are broken about 2–3 mm above the surface of the scalp. In *M. canis* infection the picture is similar, but there is usually more inflammation. In both these infections the hair surface is covered with a dense mass of small (2–3 μm in diameter) arthrospores (ectothrix infection). The infected hairs show green fluorescence under Wood's light.

In *T. tonsurans*, *T. violaceum* and *T. soudanense* infections, the lesions are often inconspicuous and inflammation may be minimal. The typical lesions are irregular patches of scaling (0.5–1.0 cm in diameter). The affected hairs often break off at the scalp surface, leading to alopecia and giving a black-dot appearance in dark-haired patients. Other hairs are broken off 1–2 mm from the scalp surface and are often obscured under a layer of scales. The infected hairs are filled with arthrospores (endothrix infection) and do not fluoresce under Wood's light.

The most florid form of tinea capitis is a kerion. This is a painful inflammatory mass in which the hairs that remain are loose. Thick crusting with matting of adjacent hairs is common. Pus may be discharged from one or more points. A kerion may be limited in extent, but a large confluent lesion can develop that involves most of the scalp. In most cases kerion formation results from infection with a zoophilic dermatophyte such as *T. verrucosum* or *T. mentagrophytes*. In *T. verrucosum* infections the hairs are covered with chains of large arthrospores but they do not fluoresce under Wood's light.

The main clinical manifestations of favus are the formation of crusted, inflamed patches on the scalp, with permanent hair loss due to follicular scarring. The scalp itches and gives off a foetid odour. The crusts (scutula) develop around the follicular openings and can fuse to cover large areas of the scalp. Long-standing favus can lead to permanent diffuse patches of alopecia. Although infected, the hairs tend not to break off and can grow to normal length. Infected hairs give off a dull green fluorescence under Wood's light.

4.4.5 Differential diagnosis

Tinea capitis is often difficult to distinguish from other causes of scaling (such as psoriasis and seborrhoeic dermatitis) or hair loss (such as alopecia areata and discoid lupus erythematosus). For this reason, Wood's light examination and laboratory tests should be performed in any patient with scaling scalp lesions or hair loss of undetermined origin. A kerion can be misdiagnosed as a bacterial abscess, and then incised, drained and treated with antibiotics. Such treatment has no effect on the fungus. The longer the infection remains undiagnosed, the greater the risk of scarring alopecia. It is important that any pustular eruption, particularly of the scalp, is recognized as a possible fungal infection and investigated accordingly.

4.4.6 Essential investigations and their interpretation

Specimens from the scalp should include hair roots, the contents of plugged follicles and skin scales. Except for favus, the distal portion of infected hair seldom contains any fungus. For this reason, cut hairs without roots are unsuitable for mycological investigation. One method which is useful for collecting material from the scalp is hair brush sampling.

Hairs infected with *T. tonsurans* do not fluoresce under Wood's light. Those infected with *M. audouinii* or *M. canis* produce a brilliant green fluorescence under Wood's light in a darkened room. However, in recent infections, or at the spreading margin of lesions, the fluorescent part of the hair may not yet have emerged from the follicle and fluorescence can only be detected after the hair is plucked. *T. schoenleinii* causes a pale

dull green fluorescence of infected hair. The fluorescent hairs tend to be long, in contrast to the short hair stumps characteristic of *Microsporum* infection.

It is important to remember that creams and ointments applied to scalp lesions, as well as host tissue and exudates, can produce a pale bluish or purplish fluorescence under Wood's light.

Direct microscopic examination of infected material should reveal arthrospores of the fungus located outside (ectothrix) or inside (endothrix) the affected hair. The arthrospores can be either small (2–4 μm in diameter) or large (up to 10 μm in diameter) in size. Skin scales will contain hyphae and arthrospores. In *T. schoenleinii* infection (favus), loose chains of arthrospores and air spaces are seen within the affected hairs. The scutulum (crust) consists of mycelium, neutrophils and epidermal cells.

Isolation of the aetiological agent in culture will permit the species of fungus involved to be determined. This will provide information as to the source of the infection and aid the selection of appropriate treatment.

4.4.7 Management

If possible, specimens for mycological examination should be taken before starting treatment. Tinea capitis must be treated with an oral antifungal agent. Topical treatment is not effective.

The recommended treatment for children with tinea capitis is griseofulvin. This should be given at a dose of at least 10 mg/kg per day for a period of 6–8 weeks. The dosage can be increased to 20 mg/kg per day in patients with *T. tonsurans* infection or where there is failure to respond after 6 weeks of treatment. Some patients with *M. canis* infection require treatment for up to 12 weeks and the general rule is to treat the individual until the hair starts regrowing and fungal culture is negative.

Three new antifungal agents (terbinafine, itraconazole and fluconazole) have entered into clinical trials for tinea capitis. However, none of these drugs has been approved for use in children with this indication.

Terbinafine is available in tablet form for treatment of tinea capitis. The recommended adult dose is 250 mg/day. The recommended paediatric dosage is 62.5 mg/day

for children of less than 20 kg, 125 mg/day for those of 20–40 kg, and 250 mg/day for those of more than 40 kg. Treatment should be continued for at least 4 weeks, but more prolonged treatment may be required for *M. canis* infections. If a patient fails to respond to griseofulvin, or if side-effects necessitate discontinuation of that drug, terbinafine is the best documented treatment for *T. tonsurans* infection. It appears to be less effective against *Microsporum* than *Trichophyton* infections.

The results of several clinical trials with itraconazole in paediatric tinea capitis have been reported, but inconsistent outcomes have been obtained. In one open-label trial that involved 120 children who had failed griseofulvin treatment, itraconazole treatment (at a dosage of 3–5 mg/kg per day for 4–6 weeks) produced a 100% clinical and mycological cure rate. Other trials have, however, produced much lower cure rates. Pulse-dosing with itraconazole (in which 1 week of treatment is alternated with 2 weeks without treatment) also appears to be effective. High cure rates have been achieved in children with *T. tonsurans* infections when 1–3 pulses were used.

The use of fluconazole in tinea capitis is still being evaluated. The doses used have ranged from 1.5 to 6.0 mg/kg per day. The results to date suggest that fluconazole is effective against both *Microsporum* and *Trichophyton* infections, but no comparative trials have been performed. Fluconazole is licensed for use in children (although not for dermatophytosis) and is a useful alternative treatment for patients with *Microsporum* infections that fail to respond to griseofulvin.

Although topical antifungal agents do not have a role in the treatment of tinea capitis, they can be used as an adjunct to oral agents during the initial stages of treatment. Both ketoconazole and selenium sulphide shampoos have been found to reduce scalp carriage of organisms. Topical antifungal treatment is also recommended for asymptomatic carriers.

Most specialists consider that children receiving treatment for tinea capitis can continue to attend school, despite the potential risk of infection spreading to those around them. In most cases, the child would have been at school for some time before the infection

was detected, and then exclusion will be too late to prevent its spread to other children.

4.4.8 Prevention

To prevent spread or recurrence of anthropophilic infections, it is important to screen all members of infected households for tinea capitis. Contacts with infected children who are asymptomatic carriers can be an ongoing source of infection. These individuals should use selenium sulphide or ketoconazole shampoo, but do not require oral antifungal treatment. It is also important to ensure that inanimate objects, such as combs, brushes and other hair accessories, are discarded or disinfected. The former is preferable.

Tinea capitis in schools presents a serious public health problem. It is important that children, parents and staff are informed about the infection and are reassured that the disease is treatable and not a sign of neglect. If more than two children in a class are infected, it is recommended that the remainder be screened after parental consent is obtained. Thereafter carriers and infected children should be treated as described. Contacts without scalp infection but with cutaneous lesions can be treated with topical antifungal agents.

To prevent spread or recurrence of zoophilic tinea capitis, it is important to identify potential sources of infection and, in the case of household pets, take the animal for treatment of suspected dermatophytosis. *M. canis* infection in cats and dogs can often be detected with Wood's light examination. It is more difficult to detect and eliminate *T. verrucosum* infection in cattle, because infected hairs are not fluorescent and because the fungus can survive for long periods on hairs and skin scales that have been deposited on the walls of buildings and gates. Fungicidal washes have sometimes been effective in controlling the spread of this infection.

4.5 Tinea corporis

4.5.1 Definition

The term tinea corporis is used to refer to dermatophyte infections of the trunk, legs and arms, but excluding the groin, hands and feet.

4.5.2 Geographical distribution

The condition is worldwide in distribution, but is most prevalent in tropical and subtropical regions.

4.5.3 Epidemiology

Tinea corporis is caused by *E. floccosum* and many species of *Trichophyton* and *Microsporum*. Infection with anthropophilic species, such as *E. floccosum* or *T. rubrum*, often follows spread from another infected body site, such as the feet. Tinea corporis caused by *T. tonsurans* is sometimes seen in children with tinea capitis and their close contacts.

Tinea corporis can also occur following contact with infected household pets or farm animals. Less commonly, it results from contact with wild animals or contaminated soil. *M. canis* is a frequent cause of human infection, and *T. verrucosum* infection is common in rural districts. Tinea corporis is more common among individuals in regular contact with animals or with the soil. Human-to-human spread of infection with geophilic or zoophilic species is unusual.

4.5.4 Clinical manifestations

Tinea corporis may affect any body site, but infections with zoophilic species are more likely to occur on exposed parts such as the face, neck and arms. Patients may complain of mild pruritus. The clinical manifestations are variable, depending on the species of fungus involved and the extent of progression, but in typical cases, round scaling lesions which are dry, erythematous and clearly circumscribed are seen. The fungus is more active at the margin of the lesions and hence this is more erythematous than the middle, which tends to heal earlier. As the first ring of advancing infection continues to spread outwards, it may become surrounded by one or more concentric rings or arcuate patterns. Adjacent lesions may fuse producing gyrate patterns. In some instances, particularly when a zoophilic dermatophyte is involved, the lesion can become indurated and pustular.

The lesions of tinea corporis are often more extensive but less obvious in immunosuppressed individuals.

4.5.5 Differential diagnosis

Tinea corporis can be difficult to distinguish from other causes of erythematous, scaling skin lesions such as discoid eczema, impetigo, psoriasis and discoid lupus erythematosus. For this reason, laboratory tests should be performed in any patient with skin lesions of undetermined origin.

4.5.6 Essential investigations and their interpretation

Material for mycological investigation should be collected from the raised border of the lesion by scraping outwards with a blunt scalpel held perpendicular to the skin. If vesicles are present, the entire top should be submitted for examination.

Direct microscopic examination of infected material should reveal the branching hyphae characteristic of a dermatophyte infection.

Isolation of the aetiological agent in culture will permit the species of fungus involved to be determined. This will provide information as to the source of the infection and aid the selection of appropriate treatment.

4.5.7 Management

Topical antifungal preparations are the treatment of choice for localized lesions. Numerous imidazole compounds (including bifonazole, clotrimazole, econazole, isoconazole, miconazole, oxiconazole, sulconazole, terconazole and tioconazole) and two allylamine compounds (naftifine and terbinafine) are available in different countries in a number of topical formulations. All give similar high cure rates (70–100%) and side-effects are uncommon. These drugs should be applied morning and evening for 2–4 weeks. Treatment should be continued for at least 1 week after the lesions have cleared and the medication should be applied at least 3 cm beyond the advancing margin of the lesion.

If the lesions are extensive or the patient fails to respond to topical preparations, oral treatment is usually indicated. Itraconazole (100 mg/day for 2 weeks) and terbinafine (250 mg/day for 2–4 weeks) have proved more effective than griseofulvin (10 mg/kg per day for 4–6 weeks).

4.5.8 Prevention

To prevent spread or recurrence of zoophilic tinea corporis, it is important to identify potential sources of infection and, in the case of household pets, take the animal for treatment of suspected dermatophytosis. Infection with anthropophilic species, such as *T. rubrum*, sometimes follows spread from another infected body site, such as the scalp, feet, hands or nails. To prevent reinfection, these sites should be examined and treated if dermatophytosis is present. Tinea corporis can also result from close body contact with other infected individuals, who should be identified and treated if possible.

4.6 Tinea cruris

4.6.1 Definition

The term tinea cruris is used to refer to dermatophyte infections of the groin, perianal and pubic region.

4.6.2 Geographical distribution

The condition is worldwide in distribution.

4.6.3 Epidemiology

The dermatophytes most often encountered in tinea cruris are the anthropophilic species, *T. rubrum* and *E. floccosum*. Maceration and occlusion of the skin in the groin give rise to warm moist conditions that favour the development of the infection. The disease is more prevalent in tropical climates.

Tinea cruris is mostly seen in men. The infection often follows spread from another infected site, such as the feet, in the same individual. It can also be transmitted from person to person through direct contact, or through indirect contact via contaminated fomites such as towels, clothing and bed linen. Tinea of the groin is a highly contagious condition and outbreaks of infection have sometimes occurred in schools and other closed groups such as sports teams.

4.6.4 Clinical manifestations

Tinea cruris usually presents as one or more rapidly spreading, erythematous lesions with central clearing on the inside of the thighs. The lesions, which tend to

coalesce, have a raised erythematous border which encloses a brown area of scaling. Patients often complain of intense pruritus. Scratching may result in small satellite lesions which sometimes fuse with the primary lesion altering its outline. The infection may spread from the inside of the thigh to the scrotum, penis, natal cleft and gluteal folds, as well as to the anterior and posterior aspects of the thighs. Localized scrotal infection is quite common: the clinical signs are often inconspicuous.

4.6.5 Differential diagnosis

Tinea cruris can be difficult to distinguish from other causes of erythematous groin lesions, such as bacterial and *Candida* intertrigo, erythrasma, psoriasis and seborrhoeic dermatitis. Women with a crural dermatosis are often infected with *Candida*, whereas men are more likely to have a dermatophyte infection. For these reasons, laboratory tests should be performed in any patient with groin lesions of undetermined origin.

4.6.6 Essential investigations and their interpretation

Direct microscopic examination of infected material should reveal the branching hyphae characteristic of a dermatophyte infection. Isolation of the aetiological agent in culture will permit the species of fungus involved to be determined.

4.6.7 Management

Most patients with tinea cruris will respond to local antifungal treatment within 2–4 weeks. Topical imidazoles, such as clotrimazole, econazole, miconazole or sulconazole, and allylamines, such as naftifine or terbinafine, should be applied morning and evening for at least 2 weeks. To prevent relapse, treatment should be continued for at least 1 week after the lesions have cleared.

If a patient has extensive lesions, or fails to respond to topical treatment, or has tinea pedis as well, oral treatment should be given. Itraconazole (100 mg/day for 2 weeks) and terbinafine (250 mg/day for 2–4 weeks) have proved more effective than griseofulvin (10 mg/kg per day for 2–6 weeks).

Tinea cruris recurs in about 20–25% of patients. If this happens, patients should be given further antifungal treatment and advice about non-pharmacological control measures should be repeated.

4.6.8 Prevention

To prevent reinfection following treatment, the patient should be advised to dry the groin thoroughly after bathing and to use separate towels to dry the groin and the rest of the body. The feet should be examined and treated if tinea pedis is present. Occlusive or synthetic garments should be avoided. If the patient is obese, weight loss may be of benefit by reducing chafing and sweating.

4.7 Tinea pedis

4.7.1 Definition

The term tinea pedis is used to refer to dermatophyte infections of the feet. These infections often involve the interdigital spaces, but chronic diffuse desquamation can affect the entire sole.

4.7.2 Geographical distribution

The condition is worldwide in distribution.

4.7.3 Epidemiology

The anthropophilic dermatophytes *T. rubrum*, *T. mentagrophytes* var. *interdigitale* and *E. floccosum* are the commonest causes of tinea pedis in Europe and North America. *T. rubrum* is the principal cause of chronic tinea pedis.

Tinea pedis is a contagious condition and is easily spread from person to person. Transfer within households has been reported, but the main spread occurs in communal bathing places and showers. The infection is usually acquired by walking barefoot on contaminated floors. Tinea pedis is a modern affliction, associated with the wearing of occlusive footwear. Heat and moisture are essential for the growth of the fungus and it is notable that infections in temperate climates tend to be more common during the summer months.

Tinea pedis is more commonly seen in men than women. It often begins in late childhood or adolescence

and is most frequent between the ages of 20 and 50. The disease is most prevalent among individuals frequenting swimming pools and fitness centres, involved in sporting activities, or living in closed communities, such as residential schools and prisons, where bathing facilities are shared. Tinea pedis has been found to affect about 15–20% of adult males. Among industrial workers such as coal miners, who are exposed on a daily basis to infection, the prevalence of infection is much higher. It has been estimated that about one-third of patients with tinea pedis also have a fungal nail infection.

4.7.4 Clinical manifestations

Tinea pedis may be unilateral, but bilateral involvement is more common. Three main clinical forms may be distinguished: acute or chronic interdigital infection; chronic hyperkeratotic (moccasin or dry type) infection of the soles and lateral borders of the feet; and vesicular (inflammatory) infection of the instep and sole. Occasional patients develop an acute ulcerative infection of the soles. It is not unusual for patients to develop a combined clinical presentation involving two or even three of these forms of tinea pedis.

Acute or chronic interdigital infection is the commonest form of tinea pedis and is characterized by itching, peeling, maceration and fissuring of the toe webs. The skin beneath the whitish build-up of debris may appear red and weeping. A foul odour is sometimes present. The cleft between the fourth and fifth toes is most often involved, but the infection may spread to adjacent areas of the feet, including the toenails. In a patient with supposed chronic tinea pedis, an absence of nail involvement makes the diagnosis of dermatophytosis questionable.

Chronic hyperkeratotic infection is characterized by areas of pink skin covered with fine white scaling. Vesicles and pustules are absent. Hyperkeratosis is usually limited to the heels, soles and lateral borders of the feet. The distribution of the infection may be patchy or involve the entire weight-bearing surface, in which case the disease is termed 'moccasin' or 'dry type' tinea pedis. The condition is usually bilateral and may be asymptomatic.

Vesicular or vesiculobullous tinea pedis is characterized by the development of vesicles, usually beginning on the sole, the instep and the interdigital clefts. The eruptions vary in size, may be isolated or coalesce into vesicles or bullae, and are initially filled with a clear fluid. After rupturing, the lesions dry, leaving a ragged ring-like border. The disease may resolve without treatment, but often recurs.

Ulcerative tinea pedis is characterized by maceration and ulceration of large areas of the soles. White hyperkeratosis and strong odour are common. Bacterial superinfection, usually with gram-negative organisms, is frequent and should be taken into account in treating this condition.

In certain parts of the world, concomitant mould, *Candida* and/or bacterial infection is relatively common in patients with tinea pedis. These conditions usually represent secondary infection following fissuring or maceration of a toe cleft. The secondary infection may induce inflammation and further maceration.

4.7.5 Differential diagnosis

The symptoms and clinical signs of tinea pedis can be difficult to distinguish from those of a number of other infectious causes of toe web intertrigo such as bacterial or *Candida* infection. Non-infectious conditions which resemble tinea pedis include contact dermatitis, eczema and psoriasis.

Candidosis most often presents as mild interdigital erosion and maceration. It sometimes occurs in patients with diabetes mellitus and is more common in hot climates. It often occurs in conjunction with a dermatophyte infection. Other moulds which produce lesions indistinguishable from tinea pedis include *Scytalidium dimidiatum* (*Hendersonula toruloidea*) and *S. hyalinum* (see Chapter 6).

Dermatophytosis of the feet is often associated with itching. In contrast, gram-negative bacterial infection tends to produce more painful inflammatory lesions, often with marked erosion of the skin. The clinical appearance of erythrasma (*Corynebacterium minutissimum* infection) is difficult to distinguish from interdigital tinea pedis.

Laboratory tests should be performed in any patient with foot lesions of undetermined origin.

4.7.6 Essential investigations and their interpretation

Direct microscopic examination of infected material should confirm a clinical diagnosis of dermatophyte infection. It is sometimes possible to distinguish a yeast infection from tinea pedis. Isolation of the aetiological agent in culture will permit the species of fungus involved to be determined. Media containing cycloheximide (actidione) should not be used if infection with a *Scytalidium* species is suspected.

Wood's light examination of the lesion should be performed to establish whether the patient has erythrasma. The coral red fluorescence characteristic of this condition does not, however, exclude coexistent tinea pedis.

4.7.7 Management

Interdigital tinea pedis will often respond to topical treatment with an imidazole compound, such as bifonazole, clotrimazole, econazole, isoconazole, miconazole, oxiconazole, sulconazole, terconazole or tioconazole, or an allylamine, such as naftifine or terbinafine. Terbinafine should be applied to the toe clefts and other affected sites morning and evening for at least 2 weeks. Imidazoles often need to be applied for up to 4 weeks. The patient may also benefit by applying the cream to the soles to help prevent the infection from spreading. The recurrence rate following topical treatment is quite high, and chronic infection with minor scaling that persists despite treatment is not uncommon. Exacerbations of previous infection may also occur.

Mixed fungal and bacterial infections of the feet are common. For this reason, topical antifungal preparations that are effective against dermatophytosis and candidosis, and which possess some antibacterial action (such as miconazole) are often recommended.

If the disease is extensive, involving the sole and dorsum of the foot, or if there is acute inflammation, oral treatment with terbinafine (250 mg/day for 2–6 weeks) or itraconazole (100 mg/day for 4 weeks) should be given in addition to topical treatment (which

should be continued for 8 weeks or longer). However, relapse is common.

Chronic tinea pedis is often associated with infection of the nails. Inadequate treatment of onychomycosis may result in reinfection of the feet.

Tinea pedis is a chronic condition which seldom resolves if left untreated. Exacerbations, which tend to occur in the summer, alternate with partial remissions. Nevertheless, the prognosis in general remains benign.

4.7.8 Prevention

It is important to inform the patient of measures that can help to control the infection or prevent reinfection. These include use of antibacterial soaps; daily bathing of the feet, followed by thorough drying of the toes and interdigital spaces; liberal application of antifungal powders to the feet after bathing; wearing of cotton socks to absorb sweat; frequent changing of socks; application of antifungal powders to footwear; avoidance of occlusive footwear that increases sweating; and wearing of protective footwear in hotels, changing rooms, gymnasiums and other public facilities.

Educating infected individuals not to expose others to their infection by not walking barefoot on the floors of communal changing rooms and by avoiding public baths and showers can help to reduce the spread of tinea pedis. Frequent hosing of the floors of public baths and the discouraging of antifungal foot dips near communal baths are helpful preventive measures.

4.8 Tinea manuum

4.8.1 Definition

The term tinea manuum is used to refer to dermatophyte infections of one or both hands.

4.8.2 Geographical distribution

The condition is worldwide in distribution.

4.8.3 Epidemiology

The anthropophilic dermatophytes *T. rubrum* and *T. mentagrophytes* var. *interdigitale* are the commonest causes of tinea manuum. Less commonly, the condition is caused by zoophilic dermatophytes, such as *M. canis*

and *T. verrucosum*, or geophilic dermatophytes, such as *M. gypseum*.

Dermatophytosis of the hands can be acquired as a result of contact with another person, an animal or soil, either through direct contact, or via a contaminated object such as a towel or gardening tool. Autoinoculation from another site of infection can also occur. Manual work, profuse sweating and existing inflammatory conditions, such as contact eczema, are predisposing factors.

4.8.4 Clinical manifestations

Tinea manuum is usually unilateral, the right hand being more commonly affected, and should be suspected where a dry scaling eruption of one palm is seen.

Lesions on the dorsum of the hand or in the interdigital spaces appear similar to those of tinea corporis. They have a distinct margin and central clearing may occur.

Two clinical forms of palmar infection may be distinguished: the dyshidrotic or eczematoid form; and the hyperkeratotic form. In the former condition, periods of partial remission intervene between successive exacerbations. In contrast, the hyperkeratotic form is chronic and spontaneous healing does not occur. It is not unusual for one form to turn into the other.

The dyshidrotic form of tinea manuum is characterized in the acute stage by vesicles which tend to appear in an annular or segmental pattern. These are localized to the edges of the hand, to the lateral and palmar aspects of the fingers, or to the palm itself where the vesicles are rather larger, tense, often single, and contain a clear viscous fluid. Removal of the top of the vesicles exposes a pinkish-red weeping surface with fine scaling margins. Pruritus, formication and burning are common symptoms.

The hyperkeratotic form of tinea manuum is a subacute or chronic condition. It begins as a succession of adjacent vesicles which desquamate. This results in a reddened scaling lesion which is round or irregular in outline and enclosed by a thick white squamous margin from which extensions run straight towards the centre. Once the chronic stage is reached, the disease involves

most or all of the palm and fingers. The dry hyperkeratosis, with underlying erythema, readily causes fissuring in the palmar creases. The hand has a mealy appearance because of the furfuraceous scales that remain adherent to the horny layer. This is thickened and black in the creases.

4.8.5 Differential diagnosis

Tinea manuum must be distinguished from other forms of dyshidrosis. This condition, whatever its origin, is usually bilateral or even symmetrical. In its typical form, clear vesicles are grouped on the lateral and volar aspects of the fingers as well as on the palm. There is little or no inflammation of the base. Dyshidrotic eczema is usually bilateral, but mycological examination is often required to distinguish it and other conditions (such as psoriasis, whether pustular or not) from tinea manuum.

4.8.6 Essential investigations and their interpretation

Direct microscopic examination of infected material, such as vesicle tops and contents and skin scales, should reveal the branching hyphae characteristic of a dermatophyte infection. Isolation of the aetiological agent in culture will permit the species of fungus involved to be determined.

4.8.7 Management

Tinea manuum often coexists with tinea pedis. Local treatment with a topical imidazole, such as clotrimazole, econazole, miconazole or sulconazole, or an allylamine, such as naftifine or terbinafine, will often suffice.

In cases that fail to respond to topical treatment, oral terbinafine (250 mg/day for 2–6 weeks), or itraconazole (100 mg/day for 4 weeks) should be prescribed.

4.8.8 Prevention

To prevent spread or recurrence of zoophilic tinea manuum, it is important to identify potential sources of infection and, in the case of household pets, take the animal for treatment of suspected dermatophytosis. Infection with anthropophilic species, such as *T. rubrum*,

sometimes follows spread from another infected body site, such as the feet, groin or nails. To prevent reinfection, these sites should be examined and treated if dermatophytosis is present.

4.9 Tinea unguium

4.9.1 Definition

The term tinea unguium is used to describe dermatophyte infections of the fingernails or toenails. Onychomycosis is a less specific term used to describe fungal disease of the nails. In addition to dermatophytes, it can be caused by a number of other moulds (see Chapter 7) and by *Candida* species (see Chapter 5).

4.9.2 Geographical distribution

The condition is worldwide in distribution.

4.9.3 Epidemiology

Onychomycosis is the most common nail disorder in adults, accounting for up to 50% of all nail diseases. There is wide geographical variation in the causative agents, but in the UK it has been estimated that 85–90% of nail infections are due to dermatophytes and about 5% are due to non-dermatophyte moulds. In North America, dermatophytes account for about 60% of nail infections, with non-dermatophyte moulds and *Candida* species representing about 20% each. The most commonly implicated dermatophyte is the anthropophilic species, *T. rubrum*, followed by *T. mentagrophytes* var. *interdigitale*.

Onychomycosis is most prevalent in older adults but, because of the limited number of large-scale studies, the actual incidence of the condition is difficult to assess. Moreover, many reports do not distinguish between dermatophytosis and other forms of onychomycosis, or between infections of the fingernails and toenails. It has been estimated that onychomycosis occurs in about 3% of the adult population in the UK and Spain, but a recent report revealed that 14% of North American adults had onychomycosis. However, the participants in this investigation were not selected at random.

Many risk factors for onychomycosis have been identified. They include male gender, increasing age,

peripheral vascular disease, hyperhidrosis, tinea pedis and dystrophic nails. The difference between the incidence of onychomycosis in men and women might be a reflection of the degree to which individuals are concerned about the appearance of their nails. Likewise the higher incidence of onychomycosis in older individuals could be due to the greater likelihood of younger patients seeking treatment at an earlier stage.

4.9.4 Clinical manifestations

There are four recognized clinical patterns of dermatophyte onychomycosis: distal and lateral subungual onychomycosis; superficial white onychomycosis; proximal subungual onychomycosis; and total dystrophic onychomycosis. It is very rare to see a patient with fingernail infection without toenail involvement.

Distal and lateral subungual disease is the most common presentation. The affected nail becomes thickened and discoloured, with a varying degree of onycholysis (separation of the nail plate from the nail bed). Toenails are more commonly affected than fingernails. Tinea unguium of the toenails is usually secondary to tinea pedis, while fingernail infection often follows tinea manuum, tinea capitis or tinea corporis. Tinea unguium may involve a single nail, more than one nail, both fingernails and toenails, or in exceptional circumstances, all of them. The first and fifth toenails are more frequently affected, probably because footwear causes more damage to these nails. Fingernail infections are usually unilateral.

In superficial white onychomycosis, the infection begins at the superficial layer of the nail plate and spreads to the deeper layers. Crumbling white lesions appear on the nail surface, particularly the toenails. These gradually spread until the entire nail plate is involved. This condition is usually due to *T. mentagrophytes* var. *interdigitale* infection.

Most cases of proximal subungual onychomycosis involve the toenails. This infection originates in the proximal nail fold, with subsequent penetration into the newly forming nail plate. The distal portion of the nail remains normal until late in the course of the disease. *T. rubrum* is the usual cause. Although proximal

subungual onychomycosis is the least common presentation of dermatophyte nail infection in the general population, it is common in persons with the acquired immunodeficiency syndrome (AIDS) and has sometimes been considered a useful marker of human immunodeficiency virus (HIV) infection. In AIDS patients, the infection often spreads rapidly from the proximal margin and upper surface of the nail to produce gross white discoloration of the plate without obvious thickening.

These different clinical forms of nail disease may eventually lead to total dystrophic onychomycosis, in which the whole of the nail bed and nail plate is involved. The pattern of infection is variable. In occasional cases, pockets of tightly packed hyphae develop in the subungual space leading to a dense white lesion visible beneath the nail. The type of infection can be resistant to antifungal treatment without prior removal of the lesion. This appearance is most often seen in the great toenail. In total dystrophic onychomycosis, the infected nail generally begins to lift up from the nail bed due to an accumulation of debris (hyperkeratosis) under the nail. The nail becomes thickened and yellow or brown in colour. The nail plate may crumble, beginning at the free end. The infection may be confined to only one nail, but more commonly several nails on one or both feet are affected. Most patients have concurrent interdigital or moccasin tinea pedis, and some may also have tinea cruris. Most patients complain about nail discomfort, particularly when cutting, and many may experience pain during activities such as running and jogging.

4.9.5 Differential diagnosis

The clinical signs of tinea unguium are often difficult to distinguish from those of a number of other infectious causes of nail damage, such as *Candida*, mould or bacterial infection. Unlike dermatophytosis, candidosis of the nails (see Chapter 5) usually begins in the proximal nail plate, and nail fold infection (paronychia) is also present. Mould infections of nails are described in Chapter 7. Bacterial infection, particularly when due to *Pseudomonas aeruginosa*, tends to result in green or black discoloration of nails. Sometimes bacterial infec-

tion can coexist with fungal infection and may require treatment in its own right.

Many other non-infectious conditions can produce nail changes that mimic onychomycosis, but the nail surface does not usually become soft and friable as in a fungal infection. Non-fungal causes of nail dystrophies include onychogryphosis, psoriasis, chronic eczema and lichen planus.

4.9.6 Essential investigations and their interpretation

Laboratory confirmation of a clinical diagnosis of tinea unguium should be obtained before starting treatment. This is important for several reasons: to eliminate non-fungal dermatological conditions; to detect mixed infections; and to diagnose patients with less responsive forms of onychomycosis, such as toenail infections due to *T. rubrum*. It is also helpful to repeat cultures after treatment has started to ensure that the infection is responding to treatment.

It is not uncommon to obtain negative results from culture of nail specimens from patients with dermatophytosis. One reason for this is that good specimens are often difficult to obtain. Because dermatophyte infection is a disease of the nail bed, subungual material will often give helpful positive culture results. The following methods are recommended. If distal subungual lesions are present, take scrapings or clippings from under the distal edge of the nail. If there is superficial white onychomycosis, take scrapings from the diseased nail surface. If there is proximal subungual involvement, a nail drill or scalpel may be used to obtain material.

Direct microscopic examination of infected nail material should confirm a clinical diagnosis of fungal infection. It is sometimes possible to distinguish *Candida* infection, or infection due to moulds such as *Scopulariopsis brevicaulis* from tinea unguium.

Isolation of the aetiological agent in culture will permit the species of dermatophyte involved to be determined. It is essential to inform the laboratory if nail material is suspected of being infected with non-dermatophyte moulds, so that duplicate plates with and without cycloheximide (actidione) can be inoculated. The results of culture can be positive even if

microscopic examination is negative, but it is more common for microscopic examination to be positive while culture is negative.

4.9.7 Management

Tinea unguium is a difficult condition to treat. In general, onychomycosis should be treated with an oral antifungal agent. However, localized distal nail disease can sometimes be treated with topical antifungals such as amorolfine, ciclopirox, or tioconazole solutions. Amorolfine should be applied once or twice weekly, while tioconazole should be applied twice daily. Amorolfine treatment must be continued for at least 6 months for success with fingernails and 9–12 months for toenails. Ciclopirox solution must be applied once daily for at least 6 months. Response rates are low compared with oral agents used in nail infections, and topical agents are usually reserved for infections of limited extent or where they can be combined with nail removal.

Two new oral antifungal agents, terbinafine and itraconazole, are effective in onychomycosis and have been approved for use in adults with this indication. Cure rates with these agents approach 80% in most trials. Both agents have been found to persist in the nail tissue for prolonged periods after cessation of treatment.

The allylamine terbinafine is now the treatment of choice for patients with dermatophytosis of the fingernails or toenails. Oral treatment with 250 mg/day for 6–12 weeks is often sufficient to cure a fingernail infection, but toenails may require treatment for 12 weeks or longer. Treatment with oral terbinafine will also clear associated cutaneous lesions without additional topical treatment. Terbinafine has proved to be effective in HIV-infected individuals and no interactions or significant adverse effects related to the drug have been reported.

Itraconazole is another effective treatment for dermatophyte nail infection. This drug persists in nail for at least 6 months and pulsed treatment (in which 1 week of treatment is alternated with 3 weeks without treatment) has given encouraging results. Two pulses of treatment with 200 mg twice daily are recommended for success

with fingernails and three pulses of treatment (or more) for toenail infections. Itraconazole is also available for continuous treatment and a dosage of 200 mg/day for 3 months is the most appropriate for severe nail disease.

Fluconazole has proven to be less effective than terbinafine or itraconazole for onychomycosis. The recommended regimen is 150–450 mg once weekly for 6–9 months in toenail infection or 3 months in fingernail infection.

With griseofulvin, up to 90% of fingernail infections can be cured in 4–8 months, but its low cure rate of 20–40% in toenail infections means that it is now less appropriate than terbinafine or itraconazole.

Although whole or partial nail plate removal is useful in some dermatophyte nail infections, this painful and disfiguring procedure is best reserved for isolated cases where there are either contraindications to the use of oral antifungals or a drug-resistant organism is present. An alternative approach is through the application of 40% urea ointment to the nail under occlusion for 4–7 days. The nail can be excised after this treatment.

4.9.8 Prevention

Many individuals with onychomycosis are unaware of their fungal infection and some believe that dystrophic nails are simply part of the ageing process. Patients should be made aware that the disease is contagious, and can be spread to those around them. Individuals with untreated or partially treated plantar or interdigital tinea pedis should be informed of the risk of developing onychomycosis.

Measures that can help to control nail infection or prevent reinfection include application of antifungal powders to the feet after bathing; wearing of absorbent cotton socks; frequent changing of socks; application of antifungal powders to footwear; avoidance of occlusive footwear that increases sweating; and wearing of protective footwear in hotels, changing rooms, gymnasiums and other public facilities. It is also important to keep the nails as short as possible and to avoid sharing nail clippers with other household members.

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Fungal Infection: Diagnosis and Management, Third Edition
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5 Superficial candidosis

5.1 Definition

The term candidosis (candidiasis) is used to refer to infections due to organisms belonging to the genus *Candida*. These opportunist pathogens can cause acute or chronic invasive infection in immunocompromised or debilitated individuals (see Chapter 11), but are more often seen causing mucosal, cutaneous or nail infection.

5.2 Geographical distribution

These conditions are worldwide in distribution.

5.3 The causal organisms and their habitat

Although *Candida albicans* is the most important cause of superficial forms of candidosis, many other members of the genus are recognized as human pathogens. Most of these organisms are dimorphic, growing as budding yeast cells, pseudohyphae and/or true hyphae. Typically, *C. glabrata* (which used to be classified as *Torulopsis glabrata*) produces only yeast cells and only *C. albicans* forms true hyphae in tissues.

Candida species can be recovered from the mouth and gastrointestinal tract of a substantial proportion (30–50%) of the normal adult population and from the genital tract of about 20% of normal women. *C. albicans* accounts for 60–80% of isolations from the mouth, and 80–90% from the genital tract. It is seldom recovered from normal skin, being much less prevalent than *C. parapsilosis* and *C. guilliermondii*, but is a frequent colonizer of moist or damaged skin and nails. Unlike *C. albicans*, *C. tropicalis*, *C. parapsilosis* and a number of other pathogenic members of this large genus can sometimes be recovered from the environment.

5.4 Epidemiology

In most cases, superficial *Candida* infection is derived from the individual's own endogenous reservoir in the mouth, gastrointestinal tract, lower genital tract or skin.

In some cases, however, transmission of organisms from person to person can occur. For instance, neonatal oral candidosis is more common in infants born of mothers with vaginal candidosis which suggests that infection occurs when the infant takes in some of the vaginal contents during parturition. The hands of mothers and healthcare workers are another potential source of neonatal infection.

Individuals colonized with *Candida* species possess numerous complicated and often interdependent mechanisms to prevent the organism from establishing an infection. Efficient protection is believed to involve both humoral and cell-mediated immunological mechanisms. Non-specific mechanisms are also important, but it is well recognized that the contribution of particular elements to protection against mucosal, cutaneous and deep-seated forms of candidosis is different. Even trivial impairments of these mechanisms are often sufficient to allow *C. albicans*, the most pathogenic member of the genus, to establish a cutaneous or mucosal infection. More serious impairment of the host can lead to life-threatening invasive infection, often with less pathogenic organisms, such as *C. parapsilosis*.

Most cases of oropharyngeal candidosis are caused by *C. albicans*. However, several other members of the genus, including *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*, have sometimes been associated with oropharyngeal disease. Both general and local predisposing factors are important in the development of oropharyngeal candidosis. Debilitated and immunosuppressed individuals, such as persons with diabetes mellitus, persons receiving corticosteroids, recipients of haematopoietic stem cell transplants (HSCT) and persons with human immunodeficiency virus (HIV) infection, are more susceptible to oropharyngeal candidosis. Local factors, such as xerostomia and trauma from unhygienic or ill-fitting dentures, are also important. Local tissue damage is also a critical factor in the development of cutaneous forms of candidosis. Most infections occur in moist, occluded sites and follow maceration of tissue.

Prior to the introduction of combination antiretroviral treatment, oropharyngeal candidosis was the

most common opportunistic infection seen in persons with HIV infection. Over 80% of untreated HIV-infected individuals developed candidosis at some time during their illness. Furthermore, oropharyngeal candidosis occurred in about 60% of those with a CD4 T-lymphocyte count of less than 100–200 cells/μl, more than half of whom experienced recurrent infection. Recent data indicate that the incidence of oropharyngeal (and oesophageal) candidosis has fallen since the widespread introduction of new antiretroviral therapies, including protease inhibitors, perhaps by as much as 50–60%. The development of this condition is often one of the earlier clinical manifestations of HIV infection in asymptomatic individuals, and is a reliable marker of disease progression.

About 20% of women of childbearing age harbour *Candida* species in the lower genital tract without symptoms or clinical signs of vulval or vaginal infection. Several host, behavioural and genetic factors have been associated with increased rates of asymptomatic colonization, including uncontrolled diabetes mellitus, recent antibiotic use, use of high-oestrogen-content oral contraceptives, and orogenital sex. Vaginal colonization with *Candida* species is more common among women who are genetic and phenotypic nonsecretors of blood group antigens. Colonization is also more prevalent among HIV-infected women than among HIV-negative high-risk behaviour women, but does not appear to increase with progressive decline in CD4 cell counts.

Up to 85% of cases of symptomatic vaginitis are due to *C. albicans*. Most of the remainder are due to *C. glabrata* (5–10% of cases) or *C. tropicalis* (less than 5% of cases). It is seldom possible for a precipitating factor to be identified to account for the transformation from asymptomatic colonization to infection. However, symptomatic vaginitis is much more common in pregnant women. Moreover, a significant proportion of women with chronic or recurrent candidosis first present with this infection while pregnant. Symptomatic vaginitis is also more common among women with uncontrolled diabetes mellitus, a disorder which has been implicated as a predisposing factor in other superficial forms of candidosis. The lower prevalence of vaginal candidosis after

menopause emphasizes the hormonal dependence of the infection. Most cases of the infection in older women are associated with uncontrolled diabetes mellitus or the use of exogenous oestrogen replacement treatment. Vaginal candidosis is often seen during or after use of broad-spectrum antibiotics. However, aberrations of iron metabolism and low-oestrogen oral contraception are no longer regarded as significant risk factors. Precipitating factors for *C. glabrata* infection include diabetes mellitus, older age, and previous use of azole antifungal agents.

Chronic mucocutaneous candidosis is a rare condition that occurs in individuals with underlying endocrinological disorders or inherited defects in the cell-mediated immunological response. The infection is seen in individuals with disorders in which T-lymphocyte activation is impaired or production of T-cell factors needed for macrophage activation is subnormal. These defects are often specific to *C. albicans*, but some patients have more profound defects that involve the T-cell-mediated response to other organisms as well. Patients with chronic mucocutaneous candidosis seldom develop deep-seated infection, despite their widespread or generalized cutaneous or mucosal lesions.

5.5 Clinical manifestations

5.5.1 Oropharyngeal candidosis

Oropharyngeal candidosis can be classified into three distinct clinical forms: pseudomembranous candidosis; erythematous (or atrophic) candidosis; and hyperplastic (or hypertrophic) candidosis.

Pseudomembranous candidosis (thrush) is an acute infection, but it can recur in patients using steroid inhalers and in immunocompromised individuals. It is the most common form of candidosis in persons with the acquired immunodeficiency syndrome (AIDS). It is also seen in neonates and among terminally-ill patients, in particular those with serious underlying disorders such as leukaemia and other malignancies.

Acute pseudomembranous candidosis presents as white raised lesions that appear on the surfaces of the buccal mucosa, tongue, hard and soft palate, and tonsils. If left untreated, these can develop to form confluent

plaques. The lesions are often painless, although mucosal erosion and ulceration may occur. The infection may spread to the throat, giving rise to severe dysphagia. In HIV-infected individuals, the lesions of the pseudomembranous form are persistent and often spread to affect all parts of the mouth.

It is important to distinguish this condition from hyperplastic candidosis (oral leukoplakia). The simplest test is to determine whether the white pseudomembrane can be dislodged. If it can be wiped off to reveal an eroded, erythematous and sometimes bleeding base, the condition is diagnostic for pseudomembranous candidosis.

Erythematous (atrophic) candidosis is often associated with broad-spectrum antibiotic treatment, chronic corticosteroid use and HIV infection. It can arise as a consequence of persistent pseudomembranous candidosis when pseudomembranes are shed or, in HIV infection, may precede pseudomembranous candidosis. It can affect any part of the oral mucosa and manifests as a flat red lesion, usually on the palate or dorsum of the tongue. If the tongue is affected, the dorsum is depapillated, shining and smooth. Tongue movement is restricted and swelling results in trauma to the lateral borders if a natural dentition is present. The mouth is often so tender that the patient finds it difficult to tolerate solid food and consumption of hot or cold liquids causes severe pain.

Hyperplastic candidosis (or *Candida* leukoplakia) is an important condition because the lesions can undergo malignant transformation. About 5% of all oral leukoplakias become malignant, but for *Candida* leukoplakias the figure is 15–20%. It remains unclear whether this condition is a hyperplastic lesion superinfected with *C. albicans* or the converse. The lesions of hyperplastic candidosis usually occur on the inside surface of one or both cheeks or, less commonly, on the tongue. The lesions are usually asymptomatic and the condition is often associated with smoking or local trauma due to dental neglect. The lesions range from small translucent white areas to large dense opaque plaques. Lesions which contain both red erythroplakic and white leukoplakic areas must be regarded with great suspicion as malignant

change is often present. In contrast to the pseudomembranous form of oral candidosis, the lesions cannot be rubbed from the surface of the buccal mucosa.

In addition to the three major forms of oropharyngeal candidosis, there are several other lesions associated with oral *Candida* infection. Chronic atrophic candidosis (or denture stomatitis) is usually associated with oral prostheses, occurring in up to 60% of denture wearers. It is most prevalent in individuals who do not remove and sterilize their dentures overnight. Apart from soreness, the condition is usually asymptomatic, often being discovered only when a new prosthesis is required. The only presenting complaint may be associated angular cheilitis. Lower dentures are seldom involved. The characteristic presenting signs are chronic mucosal erythema and oedema of the portion of the hard palate that comes into contact with the fitting surface of the upper denture. The condition is mainly due to the overgrowth of *C. albicans* beneath the dentures. The mucosa beneath the dentures is rarely involved.

Angular cheilitis often develops in association with other forms of oropharyngeal candidosis, in particular denture stomatitis, but it may occur without signs of other oral disease. The condition has been reported in up to 20% of HIV-infected persons. Angular cheilitis is most common in patients with moist, deep folds at the corners of their mouth. These angular folds are often due to overclosure of the mouth in individuals who do not wear their dentures on a regular basis or who have old worn dentures. The characteristic presenting signs are soreness, erythema and fissuring at the corners of the mouth.

5.5.2 Vaginal candidosis

Vaginal candidosis is a common condition, and while most patients respond well to treatment, in some the infection is recurrent and others have persistent symptoms that fail to respond to treatment. Up to 75% of all women will suffer at least one episode of this condition during their lifetime, with 40–50% suffering a further episode. *C. albicans* is the most important cause of vaginal candidosis, accounting for up to 85% of cases. *C. glabrata* accounts for about 5–10% of cases.

Infections with this species are apt to be milder, but they should not be ignored as *C. glabrata* is often resistant to azole antifungal treatment.

Most women with vaginal candidosis complain of intense vulval and vaginal pruritus and burning with or without vaginal discharge. The condition is often abrupt in onset and, in women who are not pregnant, it tends to begin during the week before menstruation. Some women complain of recurrent or increasing symptoms preceding each menstrual period. Pruritus is often more intense when the patient is warm in bed, or after a bath. Dysuria and dyspareunia are common.

Vulval erythema with fissuring is the most common clinical finding. This is often localized to the mucocutaneous margins of the vaginal introitus, but it can spread to affect the labia majora. Perineal intertrigo with vesicular or pustular lesions may be present. Vaginitis with discharge is another common clinical finding. The classical sign of florid vaginal candidosis in the pregnant woman is the presence of thick white adherent plaques on the vulval, vaginal or cervical epithelium. This is a useful sign in the non-pregnant patient as well. Often the discharge is thick and white and contains curds, but it can be thin or even purulent. Vulvitis may be present without a concomitant vaginal infection.

Vaginal candidosis is but one of a number of causes of vaginal discharge and must be distinguished from other conditions such as bacterial vaginosis, trichomoniasis, and chlamydial and gonococcal infections. Other causes of mucosal pruritus include herpes infections, contact dermatitis, psoriasis and allergies (including reactions to topical antifungals).

It is important to remember that some patients will have more than one genital infection. Simultaneous infection with *C. albicans* and *Trichomonas vaginalis* is, however, unusual. Candidosis is also less common among women with non-specific genital infection, contacts of men with non-specific urethritis and women with bacterial vaginosis.

5.5.3 Penile candidosis

In men, genital candidosis usually presents as a balanitis or balanoposthitis. Patients often complain of soreness

or irritation of the glans penis; less commonly there is a subpreputial discharge. Maculopapular lesions with diffuse erythema of the glans penis are often present; on occasion there is oedema and fissuring of the prepuce. Itching, scaling cutaneous lesions are sometimes found on the penis or in the groins.

Men with insulin-dependent diabetes may present with an acute fulminating oedematous form of balanoposthitis with ulceration of the penis and fissuring of the prepuce. White plaques can be found on gentle retraction of the prepuce.

About 20% of male contacts of women with vaginal candidosis complain of soreness and itching of the glans penis soon after intercourse, lasting for 24–48 h. Men who have a penile catheter inserted long-term or those using Paul's tubing often develop chronic or recurrent penile candidosis.

The diagnosis should not be made on clinical grounds alone as there are other causes of balanitis and balanoposthitis. Specimens for mycological investigation should be taken from the coronal sulcus and subpreputial sac. Patients should be investigated for diabetes mellitus.

5.5.4 Cutaneous candidosis

C. albicans is the most important cause of cutaneous candidosis. The lesions tend to occur in the folds of the skin, such as the groin and the intergluteal folds, where maceration and occlusion give rise to warm moist conditions. Lesions can also arise in small folds such as the interdigital spaces between the fingers. The infection is more common in overweight or diabetic individuals.

The initial lesions of superficial cutaneous candidosis (intertrigo) are papules or vesicopustules that later enlarge and become confluent. The larger lesions are erythematous and have an irregular margin. The main lesion is often surrounded by numerous small papulopustules, termed satellite lesions. Soreness and itching are common symptoms. Application of topical steroids will alter the appearance of the lesions, making them difficult to distinguish from those of dermatophytosis.

Candida infection of the toe webs is difficult to distinguish from a dermatophyte infection; indeed most

cases occur in association with dermatophytosis. Candidosis of the finger webs (sometimes termed erosio interdigitalis blastomycetica) presents as white fissures in the interdigital folds, with surrounding erythema and maceration. It is often uncomfortable and may be painful. This condition is not common and is usually seen in individuals whose occupations necessitate frequent immersion of the hands in water and who are also subject to interdigital trauma. Interdigital candidosis is often associated with onychia and paronychia of the same hand.

In infants with the uncommon condition, congenital cutaneous candidosis, discrete vesicopustules, often on an erythematous base, are present at birth or appear soon thereafter. The lesions are most often seen on the face and trunk and may spread rapidly to involve the whole surface in about 24 h. This condition is thought to result from intrauterine or interpartum infection; maternal vaginal candidosis is found in over 50% of cases. The pustules do not persist for very long and desquamate prior to spontaneous resolution of the lesions. In premature or low-birth-weight infants, or infants with prolonged rupture of membranes, congenital cutaneous candidosis can become invasive leading to acute disseminated candidosis (see Chapter 11).

The precise role of *C. albicans* in the evolution of rashes on the buttocks and in the perianal region of infants, associated with wearing napkins (diapers) remains unclear. This condition should not be considered a primary *Candida* infection as it is preceded by an irritant dermatitis.

Other cutaneous forms of candidosis include the erythematous, macronodular lesions seen in about 10% of neutropenic individuals with disseminated candidosis, and the purulent follicular and nodular cutaneous lesions seen in drug abusers (see Chapter 11).

5.5.5 *Candida* nail infection

Candida infection accounts for 5–10% of all cases of onychomycosis. Three forms of infection are recognized: infection of the nail folds (or *Candida* paronychia), distal nail infection, and total dystrophic onychomycosis. The last is a manifestation of chronic mucocutaneous

candidosis. Nail and nail fold infections with *Candida* are more common in women than men. Fingernails are more commonly affected than toenails. These infections often occur in individuals whose occupations necessitate repeated immersion of the hands in water and the nails affected tend to be those of the dominant hand. The fourth and fifth fingers are involved less frequently than thumbs and middle fingers. Among the various species implicated, *C. albicans* and *C. parapsilosis* are the most common.

Candida paronychia usually starts in the proximal nail fold, but the lateral margins are sometimes the first site to be affected. The periungual skin becomes swollen, erythematous and painful, and a prominent gap often develops between the fold and the nail plate. Nail plate involvement often follows, infection usually commencing in the proximal section. White, green or black marks appear in the proximal and lateral portions of the nail and then in the distal parts. The nail becomes more opaque, and transverse or longitudinal furrowing or pitting occurs. The nail becomes friable and may become detached from its bed. Unlike dermatophyte infections, pressure on, and movement of, the nail is painful. Bacterial superinfection is common and it is often difficult, if not impossible, to determine which organism is the cause of the nail damage.

Distal *Candida* nail infection presents as onycholysis and subungual hyperkeratosis. It is often difficult to distinguish from dermatophytosis, but the degree of nail damage tends to be less than in dermatophyte infections. Moreover, fingernails are nearly always involved, while 80% of dermatophyte infections affect the toenails. Many patients with distal *Candida* nail infection suffer from Raynaud's phenomenon.

In patients with chronic mucocutaneous candidosis, the organism invades the nail plate from the outset causing gross thickening and hyperkeratosis. This condition is often referred to as total dystrophic onychomycosis.

5.5.6 Chronic mucocutaneous candidosis

The term chronic mucocutaneous candidosis is used to describe a group of uncommon conditions in which

individuals with congenital immunological or endocrinological disorders develop persistent or recurrent mucosal, cutaneous or nail infections with *C. albicans*. The disease often appears within the first 3 yr of life. The mouth is the first site to be involved, but lesions then appear on the scalp, trunk, hands and feet. The nails and sometimes the whole of the fingertips are affected.

Four childhood forms of chronic mucocutaneous candidosis are recognized. Two forms are inherited, one as an autosomal dominant trait and the other as an autosomal recessive trait. The third form is associated with a range of endocrine disorders. The most common is hypoparathyroidism, but hypoadrenalism and hypothyroidism also occur. The fourth form has no recognized inheritance pattern and is not associated with endocrinopathies. In some forms of chronic mucocutaneous candidosis there is an enormous proliferation of epidermal cells which results in disfiguring hyperkeratotic lesions on the mucous membranes, skin and nails.

Adult forms of chronic mucocutaneous candidosis usually occur in association with thymoma or systemic lupus erythematosus. Like the childhood forms, this disease is characterized by recalcitrant infections of mucous membranes, nails and skin.

5.6 Essential investigations and their interpretation

The clinical manifestations of oropharyngeal candidosis are often characteristic, but can be confused with other disorders. For this reason, the diagnosis should be confirmed by demonstration of the various morphological forms of the fungus in smears prepared from swabs or scrapings of lesions and its isolation in culture. As *Candida* species are normal commensals in the mouth, their isolation alone cannot be considered diagnostic of infection. Swabs should be moistened with sterile water or saline prior to taking the specimen, or sent to the laboratory in transport medium.

The diagnosis of vaginal candidosis depends on a combination of typical symptoms and signs and the demonstration of the fungus in smears or its isolation in culture. The latter is much more sensitive and reliable (about

90%) than the former (about 40%). Swabs should be taken from discharge in the vagina and from the lateral vaginal wall, and sent to the laboratory in transport medium.

Intertriginous candidosis is often difficult to diagnose if the lesions are other than typical in appearance. Isolation of *Candida* species from swabs or scrapings is of dubious significance, because the organisms are frequent colonizers of a range of cutaneous lesions. Microscopic demonstration of the organism in scrapings of lesions is much more significant.

The diagnosis of nail fold infections rests in part on the characteristic clinical appearance. However, microscopic examination and culture is needed to confirm the diagnosis. Material can be taken from the swollen periungual nail wall, or from under the nail fold using a disposable microbiological loop or moistened swab. Pus can be obtained from under the nail fold by applying light pressure. Microscopic demonstration or isolation of the fungus from nail can be difficult with proximal lesions, but material from a distal or lateral lesion together with subungual debris will often reveal the diagnosis. Isolation of *C. albicans* from nails is seldom significant unless the organism is seen on microscopic examination.

5.7 Management

5.7.1 Oropharyngeal candidosis

Immunocompetent patients with uncomplicated oropharyngeal candidosis respond to topical treatment with nystatin, amphotericin B or an imidazole. In infants, pseudomembranous candidosis can be treated with nystatin oral suspension (100 000 units/ml) or amphotericin B oral suspension (100 mg/ml). This should be dropped into the mouth after each feed or at 4–6 h intervals. In most cases the lesions will clear within 2 weeks. Older children and adults with the pseudomembranous form of oral candidosis can be treated with clotrimazole troches (one 10 mg troche five times daily), or nystatin or amphotericin B oral suspension (1 ml at 6-h intervals for about 2–3 weeks), or miconazole oral gel (250 mg at 6-h intervals). It is essential that any medication should be retained in the

mouth for as long as possible. Treatment should be continued for at least 48 h after all lesions have cleared and symptoms have disappeared.

In HIV-infected persons and other immunocompromised individuals with oropharyngeal candidosis the relapse rate with topical antifungal treatment is high and now that safe oral agents are available, these are to be preferred. In addition to antifungal treatment, patients must be given careful instruction in oral hygiene. Oral fluconazole (100–200 mg/day for 7–14 days) has been found to be more effective than itraconazole (200–400 mg/day for 14 days) or ketoconazole (200–400 mg/day for 14 days) in controlling oropharyngeal candidosis in HIV-infected individuals. Unlike itraconazole and ketoconazole, absorption of fluconazole is not affected if it is given together with agents that reduce gastric acid secretion. Nor is the reduction in blood levels as marked as seen when other azole agents are administered with rifampicin. The oral solution formulation of itraconazole (200–400 mg/day for 7–14 days) is better absorbed than the capsules and has proved as effective as fluconazole. This may reflect the improved absorption of the solution or an additional topical effect.

Most immunocompromised patients with oropharyngeal candidosis will respond initially to oral antifungal treatment. Prior to the introduction of highly active antiretroviral therapy (HAART), up to 60% of patients with AIDS relapsed within 3 months of the successful completion of azole treatment for oropharyngeal candidosis. However, recent data indicate that the use of HAART has been associated with declining rates of oral colonization and symptomatic infection; the relapse rate has also decreased. In HIV-infected individuals, it is important to recognize that recurrence does not necessarily denote the development of azole-drug-resistant strains of *C. albicans*, nor does it imply that the recurrent episode will be unresponsive to standard treatment. Antifungal drug susceptibility testing has been shown to be predictive of clinical response to fluconazole and itraconazole.

Management of oropharyngeal candidosis in AIDS patients from whom fluconazole-resistant strains of

C. albicans have been isolated is difficult. In the first instance, higher dosages of fluconazole (400–800 mg/day) should be tried, but the benefit is usually transient. If this is unsuccessful, itraconazole solution (400 mg/day) can be prescribed, as this has been found to be effective in up to 65% of patients who had earlier failed to respond to fluconazole. Amphotericin B oral suspension (1 ml at 6-h intervals) is sometimes effective in patients who do not respond to itraconazole. As a last resort, patients with unresponsive oropharyngeal candidosis can usually be managed with parenteral amphotericin B (0.3–0.5 mg/kg per day for 1 week). In persons with AIDS, treatment of the underlying HIV infection with HAART is critical for the prevention and management of oropharyngeal candidosis.

Chronic atrophic candidosis should be treated with topical antifungal agents such as nystatin, amphotericin B or an imidazole. Patients should be instructed to remove and place their dentures in a sterilizing solution overnight. When the condition is resolved, a new prosthesis is usually required. Angular cheilitis should be treated with a topical antifungal preparation containing a steroid and perhaps an antibacterial agent as well. It is also important to correct the reason for overclosure of the mouth; a replacement denture may be required.

5.7.2 Vaginal candidosis

Most patients with vaginal candidosis respond to topical treatment with nystatin or an imidazole, such as clotrimazole or miconazole. Nystatin requires a longer treatment period and has a lower cure rate (75–80%) than the topical azoles (85–90%). However, it is often useful in women whose condition has failed to respond to azole treatment. Treatment of vaginal candidosis in HIV-infected women is identical to that recommended for HIV-negative women.

If a patient is to be treated with nystatin, one or two vaginal pessaries (100 000 units each) should be inserted high in the vagina at bedtime for 14 consecutive nights, regardless of an intervening menstrual period. If vulvitis is a problem, nystatin cream should also be applied for 2 weeks.

Numerous imidazole compounds (including butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, terconazole and tioconazole) are available in different countries in a number of topical formulations for the treatment of vaginal candidosis (see Chapter 3). These drugs give higher cure rates than nystatin with shorter courses of treatment and all of them have a similar low relapse rate. These drugs are safe and side-effects after topical application are uncommon. Treatment times range in duration from 1 to 7 days. Shorter regimens (with higher antifungal dosages) achieve better patient compliance, but treatment courses of less than 6 nights should be reserved for first episodes. The management of vaginal candidosis in pregnant women is more difficult, because the clinical response tends to be slower and recurrence is more frequent. Most topical agents are effective, especially when prescribed for longer periods of 1–2 weeks.

Itraconazole and fluconazole have been licensed for short-term oral treatment of vaginal candidosis. These drugs are more expensive than topical preparations, but patient compliance is improved. Fluconazole is given as a single 150-mg dose and itraconazole is given as two doses of 200 mg, 8 h apart with food. Oral treatment appears to be at least as effective, if not superior to topical treatment.

Women with recurrent vaginal candidosis (more than three episodes within 12 months) present a difficult management problem. These patients often suffer from depression and many develop psychosexual problems as a result of their illness. It is essential to make a correct diagnosis and to ensure that the patient avoids potential precipitating factors, though these may not be obvious. Other diagnoses include herpes infection, allergic reactions and bacterial vaginosis. Physical examination, investigations to exclude diabetes mellitus, and mycological investigation are essential and, if possible, should be performed when the patient has symptoms but has had no treatment.

There is no need to investigate oral or intestinal colonization with *C. albicans* in women with recurrent vaginal candidosis. Trials have demonstrated that oral nystatin treatment, given to reduce intestinal colonization with

C. albicans, fails to prevent recurrence of symptoms of vaginal infection. The role of sexual transmission in vaginal infection is unknown, and topical or oral treatment of the male partner does not seem to prevent recurrence in the woman. In most cases, symptomatic recurrence is thought to result from vaginal relapse after inadequate treatment of a previous episode.

Many patients with recurrent candidosis can be managed with intermittent prophylactic treatment with a single dose or multiple doses of topical or oral antifungals given to prevent symptomatic episodes. Local treatment with clotrimazole (500 mg as a single dose) at 2- or 4-week intervals has been shown to suppress symptoms even if mycological cure is not achieved. Intermittent single doses of oral fluconazole (150 mg at 1-week intervals) are also effective. After symptoms have been suppressed for 3–6 months, regular treatment can be discontinued to allow the patient to be reassessed. Many women do not revert to the previous pattern of frequent recurrence.

Although antifungal drug resistance does sometimes have a role in treatment failure, other factors such as allergic reactions or poor compliance are much more common reasons for a poor response. Nevertheless, drug resistance should be considered if organisms other than *C. albicans* are isolated from women with recurrent candidosis. By comparison with *C. albicans*, isolates of *C. glabrata* are much less susceptible to fluconazole and other azoles. Women with recurrent *C. glabrata* infection can sometimes be managed with nystatin or topical boric acid treatment (600 mg/day for 14 days).

5.7.3 Penile candidosis

Genital candidosis in men should be treated with saline washes or local applications of an antifungal cream. Nystatin should be applied morning and evening for at least 2 weeks. Clotrimazole, miconazole or econazole creams should be applied morning and evening for at least 1 week. The female contacts should also be investigated. Men who fail to respond to treatment should be investigated for other infectious or non-infectious causes of their condition.

5.7.4 Cutaneous candidosis

Most patients with cutaneous candidosis respond to topical treatment with nystatin, an imidazole, or an allylamine. If the infection is associated with an underlying condition, such as diabetes mellitus, control of the underlying problem is essential. Treatment with combination preparations containing a topical steroid, and perhaps an antibacterial agent as well, is often helpful.

The prognosis for congenital cutaneous candidosis in healthy normal-birth-weight term infants is good and spontaneous cure often occurs after several weeks. The use of topical antifungal agents, such as nystatin or an imidazole, will hasten the cure. Premature or low-birth-weight infants, or infants with prolonged rupture of membranes, may require systemic antifungal treatment. Amphotericin B is well tolerated in infants, and has been used successfully at a dose of 0.5–1.0 mg/kg per day (see Chapter 11).

In infants, napkin dermatitis with associated *Candida* infection can be treated with combination topical preparations. It is advisable to use preparations containing hydrocortisone, rather than more potent steroids, because of the risk of absorption. Mothers of affected infants should be advised of the basic irritant cause of the problem.

5.7.5 *Candida* nail infection

Topical treatment with an imidazole or terbinafine will often cure *Candida* paronychia when this is confined to the nail folds. The antifungal cream or lotion should be applied morning and evening for up to 6 months. Measures to reduce maceration of the nail folds should be incorporated into the management of such cases. If patients have developed proximal nail damage, oral antifungal treatment is usually required.

Localized distal nail infection can sometimes be treated with topical amorolfine (applied twice weekly) or tioconazole solution (applied twice daily).

Severe nail infection seldom responds to topical treatment. In this situation itraconazole is the most appropriate oral treatment: a dose of 200–400 mg/day for 6 weeks or three pulses of 400 mg/day for one week per month should be sufficient for most fingernail

infections. Terbinafine (250 mg/day) is less effective in *Candida* nail infection than in dermatophytosis and treatment periods of 6–12 months are often required.

5.7.6 Chronic mucocutaneous candidosis

In most patients, oral and cutaneous lesions will respond to short courses of antifungal treatment. Much longer courses of treatment are needed to clear nail infections. However, the improvement is often transient and the infection will recur unless the underlying immunological defect is corrected.

Oral treatment with ketoconazole led to a marked improvement in the condition of a substantial number of patients with chronic mucocutaneous candidosis, but protracted treatment was required to sustain remission and this led to the development of drug resistance in some cases. Itraconazole and fluconazole have now superseded ketoconazole. These drugs are no more effective than the older imidazole, but they are probably safer for long-term use. The required dosages are similar to those used for other forms of mucocutaneous candidosis.

5.8 Prevention

Among the prevention measures that have been shown to be effective in oropharyngeal candidosis are improved oral hygiene, smoking cessation, and the avoidance of non-essential antibiotic and steroid use. Avoidance of broad-spectrum antibiotics has also proved effective in some women with vaginal candidosis, but many of those affected have no obvious predisposing factors. Most cases of cutaneous candidosis affect moist occluded sites and follow maceration of the tissue. Prevention can sometimes be achieved by careful drying.

There have been numerous attempts to develop chemoprophylaxis regimens that will reduce oral colonization with *Candida* species and help prevent the development of oropharyngeal candidosis in neutropenic individuals. There have, however, been no convincing demonstrations that either nystatin or amphotericin B oral suspensions or tablets prevent mucosal forms of candidosis in this setting. In large randomized trials among neutropenic cancer patients and transplant

recipients, chemoprophylaxis with fluconazole (50–200 mg/day) has been shown to reduce the incidence of oral colonization and infection with all *Candida* species, apart from *C. glabrata* and *C. krusei*. The use of fluconazole prophylaxis (at a higher dosage of 400 mg/day) has been endorsed in published guidelines for prevention of invasive candidosis in allogeneic and high-risk autologous HSCT recipients (see Chapter 11). Its use is not, however, recommended in other neutropenic individuals in whom the incidence of invasive candidosis is low.

There have also been a few trials of azole chemoprophylaxis for prevention of superficial forms of candidosis in persons with HIV infection. Oral fluconazole (50–200 mg/day, or 150–200 mg once weekly) has been shown to reduce the incidence of oropharyngeal and vaginal candidosis, but colonization is not eliminated, and infection still recurs. The most effective method of preventing mucocutaneous candidosis in HIV-infected individuals is the reversal of the underlying immunosuppression with HAART.

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6 Other cutaneous fungal infections

6.1 Pityriasis versicolor

6.1.1 Definition

Pityriasis versicolor (tinea versicolor) is a common, mild, but often recurrent infection of the stratum corneum due to lipophilic yeasts of the genus *Malassezia*. Less frequently, these organisms cause serious systemic infection in low-birth-weight infants and other immunocompromised and debilitated individuals (see Chapter 27).

6.1.2 Geographical distribution

The disease is worldwide in distribution, but is much more prevalent in tropical and subtropical regions.

6.1.3 The causal organisms and their habitat

Until recently, only three *Malassezia* species were recognized: two lipid-dependent species, *M. furfur* and *M. sympodialis,* and one non-obligate lipophile, *M. pachydermatis*. Following genomic and ribosomal sequence comparisons of a large number of human and animal isolates, the genus has now been enlarged into seven species comprising the three former taxa, *M. furfur, M. pachydermatis* and *M. sympodialis*, and four new taxa, *M. globosa, M. obtusa, M. restricta* and *M. slooffiae*. With the exception of *M. pachydermatis*, six of the seven *Malassezia* species are lipid-dependent. Methods have been developed to separate the seven species of *Malassezia* on the basis of morphological and physiological differences, but these are time-consuming and difficult to perform, and several of the species are difficult to distinguish. Molecular methods have been found to be a rapid and reliable method for the differentiation of *Malassezia* species.

6.1.4 Epidemiology

Malassezia species form part of the normal microbial flora of the skin of humans and other warm-blooded animals and most infections are endogenous in origin.

The prevalence of skin colonization with these organisms is dependent upon age, anatomical site, and, to a lesser degree, race. The incidence of skin colonization rises from around 25% in children to almost 100% in adolescents and adults. The density of colonization in post-pubertal individuals is greater in anatomical sites that contain pilosebaceous glands; *Malassezia* species have been isolated from 100% of samples from the backs of adults, but from only 75% taken from the face and scalp. It is thought that colonization with *Malassezia* species primarily occurs at the time of puberty when the sebaceous glands become active and the concentration of lipids on the skin increases.

The precise conditions which lead to the development of pityriasis versicolor and other forms of superficial *Malassezia* infection (see Section 6.2) have not been defined, but host and environmental factors both appear to be important. The lesions of pityriasis versicolor and seborrhoeic dermatitis have a predilection for sites well supplied with sebaceous glands, such as the chest, back and upper arms, and it has been shown that patients with the latter condition have higher concentrations of lipids on their skin than do other individuals. Instances where non-cohabiting members of the same family have developed pityriasis versicolor suggest a genetic predisposition. The increased incidence of *Malassezia* folliculitis and seborrhoeic dermatitis in persons with the acquired immunodeficiency syndrome (AIDS) and those receiving corticosteroid or other immunosuppressive treatment, suggests that the relationship between *Malassezia* species and the immune system is important.

Pityriasis versicolor is worldwide in distribution, but is most prevalent in hot, humid tropical and subtropical climates, where 30–40% of the adult population may be affected. In temperate climates, the disease affects 1–4% of the adult population, but is most common during the hot summer months. *Malassezia* folliculitis is also more prevalent in tropical countries and, in temperate regions, it is more common during the summer months.

Human-to-human transmission of *Malassezia* species is possible, either through direct contact or via contaminated clothing or bedding. In practice, however,

infection is endogenous in most cases and spread between persons is uncommon.

6.1.5 Clinical manifestations

Pityriasis versicolor is a disfiguring but otherwise harmless condition. The characteristic lesions consist of patches of fine brown scaling, particularly on the trunk, neck and upper portions of the arms. The lesions may become confluent and progress to cover large areas of the trunk and limbs. In the tropics the lesions are more commonly localized on the face.

In light-skinned subjects, the affected skin may appear darker than normal. The lesions are light pink in colour but grow darker, turning a pale brown shade. In dark-skinned or tanned individuals, the affected skin loses colour and becomes depigmented. The same patient may have lesions of different shades, the colours depending on the thickness of the scales, the severity of the infection and the inflammatory reaction of the dermis, and in particular the amount of exposure to sunlight, which may vary from one lesion to another. The disease is exacerbated by sunlight and sweating.

The clinical manifestations of pityriasis versicolor in immunocompromised persons are similar to those seen in normal individuals. However, the lesions are usually more erythematous and may appear raised.

In most cases the lesions show a pale yellow fluorescence under Wood's light, permitting the extent of the disease to be judged.

6.1.6 Differential diagnosis

Hyperpigmented lesions must be distinguished from a number of conditions, including erythrasma, naevi, seborrhoeic dermatitis, pityriasis rosea and tinea corporis. Hypopigmented lesions can be confused with pityriasis alba and vitiligo.

6.1.7 Essential investigations and their interpretation

Material for direct microscopic examination should be obtained by taking scrapings from the affected skin. Pityriasis versicolor lesions contain a mixture of budding yeast cells, typical of the organism observed in normal skin sites, and numerous short, broad

unbranched hyphae. These hyphae, which are thought to be the same organism in its pathogenic phase, are not seen at unaffected skin sites or in culture. Direct microscopic examination of scrapings from lesions is sufficient to permit the diagnosis of pityriasis versicolor if clusters of round or oval budding cells and short hyphae are seen.

Because *Malassezia* species are part of the normal cutaneous flora, their isolation in culture does not contribute to diagnosis. Besides, with the exception of *M. pachydermatis*, these organisms cannot be isolated on routine mycological media unless lipid is added.

6.1.8 Management

If left untreated pityriasis versicolor will persist for long periods. Most patients respond to topical treatment, but more than 50% relapse within 12 months. Oral treatment is indicated in patients with extensive or recalcitrant lesions.

There are numerous topical agents which can be used to treat pityriasis versicolor. Selenium sulphide (2%) shampoo should be applied at night and washed off the following morning. The treatment should be repeated 1 and 6 weeks later. Ketoconazole shampoo should be applied once daily for 5 days. It should be left in contact with the lesions for 3–5 min before being rinsed off.

Other topical imidazoles, such as bifonazole, clotrimazole, econazole, miconazole and sulconazole, should be applied morning and evening for 4–6 weeks. Topical terbinafine should be applied to the lesions each morning and evening for 2 weeks. Pityriasis versicolor is often a difficult disease to clear and topical preparations may need to be reused at intervals to ensure that the infection is eradicated.

Oral antifungal treatment should be reserved for patients with extensive lesions or recalcitrant infection that is unresponsive to topical treatment. Both itraconazole (200 mg/day for 1 week) and ketoconazole (200 mg/day for 1 week) are effective treatments. Oral griseofulvin and terbinafine are inactive in patients with pityriasis versicolor.

6.2 Other *Malassezia* infections

In addition to pityriasis versicolor, two other cutaneous diseases are associated with *Malassezia* species. These are *Malassezia* folliculitis and seborrhoeic dermatitis.

6.2.1 *Malassezia* folliculitis

There are three main forms of this chronic disorder, in which a cutaneous folliculitis is associated with *Malassezia* species. The first, which is most common in young adults, is a folliculitis on the back, chest or upper arms that consists of small, scattered, itching, erythematous follicular papules that slowly enlarge and become pustular. These often appear after sun exposure, or antibiotic or immunosuppressive treatment. These patients do not usually have seborrhoeic dermatitis.

In the second form, which is seen in some patients with seborrhoeic dermatitis, there are numerous small follicular papules over the upper and lower chest and back. The rash is more florid and particularly marked on the back. The third form, which is seen in persons with AIDS, consists of multiple pustules on the trunk and face. This form is very similar to the second form, and the patients usually have severe seborrhoeic dermatitis.

Treatment with a topical imidazole or selenium sulphide is often effective, but oral treatment with ketoconazole (200 mg/day for 1–2 weeks) may be required in patients with extensive or recalcitrant lesions. To prevent recurrence, maintenance treatment should be given once or twice per week.

6.2.2 Seborrhoeic dermatitis

Seborrhoeic dermatitis is a chronic relapsing scaling dermatosis of the face, scalp and trunk. It affects 2–5% of the human population, although it is more frequent in men than women. Dandruff (scalp scaling) is the mildest clinical manifestation.

The role of *Malassezia* species in the pathogenesis of seborrhoeic dermatitis remains controversial and is based on the fact that most cases respond to topical or oral treatment with an azole antifungal. Improvement is associated with disappearance of the organisms, and relapse with recolonization. While it is improbable

that invasion of the epidermis is responsible for the development of seborrhoeic dermatitis, an indirect disease mechanism such as sensitization is possible.

Seborrhoeic dermatitis is a common and troublesome problem in persons with human immunodeficiency virus (HIV) infection. The lesions take the form of an erythematous scaling rash on the scalp, face, ears, chest and the upper part of the back. Scaling of the eyelid margins and around the nasolabial folds is a common presentation. Itching is common on the scalp. In HIV-infected persons, the onset of seborrhoeic dermatitis is often an early sign of CD4 T-lymphocyte cell suppression. Onset may be sudden and the rash is often more extensive than in other individuals.

The clinical signs and distribution of the lesions are typical and mycological investigation is not required.

Topical imidazoles and mild corticosteroid creams are effective in the treatment of seborrhoeic dermatitis. Relapse is common, but re-treatment as required is the simplest method of management. Ketoconazole shampoo, used twice per week for 2–4 weeks, is an effective treatment for seborrhoeic dermatitis and dandruff of the scalp. Thereafter it should be used at 1- or 2-week intervals to prevent recurrence.

Oral treatment with ketoconazole (200 mg/day for 1–2 weeks) should be reserved for patients not responding to topical treatment.

6.3 Piedra

The term piedra refers to two uncommon fungal infections in which firm, irregular nodules, composed of fungal elements, are formed on and along the hair shafts. These two disorders are distinguished according to the colour of the nodules and the aetiological agent. White piedra is less common than black piedra.

6.4 White piedra

6.4.1 Definition

The term white piedra is used to refer to an uncommon, asymptomatic fungal infection of scalp, facial or pubic hair in which soft greyish-white nodules are formed along the hair shafts.

6.4.2 Geographical distribution

The condition is worldwide in distribution, but is more common in tropical and subtropical regions.

6.4.3 The causal organisms and their habitat

The disease is caused by members of the genus *Trichosporon*. Until recently, this genus encompassed a heterogeneous group of species that were the anamorph (asexual) stages of both ascomycetous and basidiomycetous fungi. Following genomic and ribosomal sequence comparisons of a large number of human, animal and environmental isolates, the genus is now considered to be a basidiomycetous yeast genus, consisting of 19 species. Four of these newly delineated taxa (*T. asteroides*, *T. beigelii*, *T. inkin* and *T. ovoides*) have been associated with superficial infection, most commonly white piedra. Two taxa (*T. asahii* and *T. mucoides*) are associated with systemic infections in immunocompromised individuals (see Chapter 27).

These organisms have a widespread natural distribution, being found in soil and water and on plants. They are also common commensal inhabitants of the skin and gastrointestinal tract in humans.

6.4.4 Epidemiology

Trichosporon species form part of the normal cutaneous flora of humans, and most cases of white piedra are endogenous in origin. Shared cosmetics or lotions may serve to spread the infection from person to person. The disease affects both men and women of all ages, but is most common in young adults.

6.4.5 Clinical manifestations

The presence of irregular, soft, white or light brown nodules, about 1.0–1.5 mm in diameter, along the hairs is characteristic of white piedra. The nodules, which are mainly located on the distal half of the hair shaft, are adherent to the hairs but can usually be detached. The uncovered part of the hair shafts and the underlying skin appear unaffected. No broken hairs are seen. The infection is more commonly found on the hairs of the beard and moustache. Less frequently it affects the scalp and genital region. Usually, only

localized parts of the scalp are involved. In other sites, however, there is a more widespread distribution of nodules.

6.4.6 Differential diagnosis

White piedra of the genital hair can be confused with pediculosis and trichomycosis axillaris.

6.4.7 Essential investigations and their interpretation

MICROSCOPY

Direct microscopic examination of epilated hairs mounted in potassium hydroxide will reveal that the nodules consist of septate hyphae, arthrospores and blastospores.

CULTURE

Hairs should be inoculated on to the surface of glucose peptone (Sabouraud's) agar plates and incubated at 25–30°C. Identifiable white to cream heaped colonies will appear within 2–3 days. These consist of hyaline mycelium, which is septate and fragmented into rectangular, oval, or round arthrospores. Numerous budding blastospores are also present.

6.4.8 Management

Treatment is difficult. Shaving or clipping the hairs of the affected region is usually sufficient to clear the infection, but relapse is common. Oral itraconazole (100 mg/day for 8 weeks) has been reported to be an effective treatment for white piedra affecting scalp hair.

6.5 Black piedra

6.5.1 Definition

The term black piedra is used to refer to an uncommon hair disease in which small, dark brown to black, hard, adherent nodules are formed on the distal portion of the scalp hair shafts.

6.5.2 Geographical distribution

The disease occurs in humid tropical regions of South and Central America, South East Asia and Africa.

6.5.3 The causal organism and its habitat

The disease is caused by *Piedraia hortae*, a mould which penetrates the cuticle, but does not invade the hair shaft itself. The natural habitat of *P. hortae* other than mammalian hair is not known.

6.5.4 Epidemiology

Black piedra affects young adults of both sexes with a slight predominance among men. There are reports of epidemics in families and communities. The infection is spread by the common use of combs, hairbrushes or utensils used for washing the hair. Certain hygienic habits, such as the application of plant oils to the scalp hair, seem to predispose to the condition.

6.5.5 Clinical manifestations

The disease is most commonly found on the scalp, but it can also occur at other sites. Affected hairs show from 4 to 8 (or more) firmly attached nodules, 1–2 mm in diameter. These are oval or elongated, hard, dark brown to black in colour, and may surround the hair. The uncovered part of the hair shafts and the underlying skin appear unaffected. Broken hairs are sometimes seen.

6.5.6 Differential diagnosis

Black piedra can be confused with trichorrhexis nodosa and trichonodosis, but mycological examination will always confirm the diagnosis.

6.5.7 Essential investigations and their interpretation

MICROSCOPY

Direct microscopic examination of the nodules will reveal a packed mass of brown pigmented branching hyphae surrounding asci, each of which holds eight ascospores.

CULTURE

Hair fragments should be implanted in the usual media and incubated at room temperature. Identifiable dark brown to black colonies will appear after 2–3 weeks. They have a folded surface with a flat margin. Microscopy of a direct mount reveals thick-walled, septate, branched, pigmented hyphae.

6.5.8 Management

Treatment with a topical salicylic acid preparation or an imidazole cream is often effective. However, relapse is common.

6.6 Tinea nigra

6.6.1 Definition

The term tinea nigra is used to refer to a rare, chronic infection of the stratum corneum due to *Phaeoannellomyces werneckii*, a dematiaceous (brown-pigmented) mould. This condition often affects the palms. Less commonly it involves the soles.

6.6.2 Geographical distribution

The disease has a worldwide distribution, but is more common in tropical and subtropical regions.

6.6.3 The causal organism and its habitat

P. werneckii (which used to be named *Exophiala werneckii*) is a saprobic mould found in the soil and on decomposing vegetation.

6.6.4 Epidemiology

Human infection is thought to follow traumatic inoculation. Tinea nigra is most common in children and young adults: it has a predilection for individuals who are hyperhidrotic. Although familial infections have been reported, the condition does not appear to be contagious.

6.6.5 Clinical manifestations

Tinea nigra occurs most commonly on the palm of the hand. Less frequently, it involves the sole of the foot, or other sites.

The lesion consists of one or several, flat, dark brown to black, non-scaling patches with a well-defined rim. Inflammation is absent. The patches are very small at first, then later expand and become confluent forming polycyclic or irregularly contoured lesions. The pigmentation is irregularly distributed over larger lesions. The disease is asymptomatic and may remain undiagnosed for a long time.

6.6.6 Differential diagnosis

Tinea nigra must be differentiated from naevi, malignant melanoma and chemical stains (such as silver nitrate).

6.6.7 Essential investigations and their interpretation

MICROSCOPY

Direct microscopic examination of scrapings from the margin of a lesion will reveal rather irregular, branched, septate, brown hyphae.

CULTURE

Scrapings should be inoculated on to glucose peptone (Sabouraud's) agar plates and incubated at 25–28°C. Identifiable olive-black colonies of *Phaeoannellomyces werneckii* should appear within 1 week.

6.6.8 Management

Many methods of treatment have proved effective. Benzoic acid compound ointment or 10% thiabendazole solution should be applied morning and evening for several weeks. Most lesions will disappear within 2–4 weeks, but treatment should be continued for at least 3 weeks to avoid recurrence. Topical imidazoles are also effective.

6.7 *Scytalidium* infection

The brown-pigmented (dematiaceous) mould *Scytalidium dimidiatum* (which used to be named *Hendersonula toruloidea*) is a tropical plant pathogen which can also cause human infection of the palms, soles and nails. More recently, similar infections have been attributed to the related, non-pigmented mould *Scytalidium hyalinum*. Although most of these infections have been described in immigrants from the tropics and subtropics, cases have also been seen in West Africa and South East Asia. The geographic range as defined by immigrants with the infection is large: it includes most of the Caribbean islands, parts of South America, Africa, the Indian subcontinent, South East Asia and West Pacific islands. Unlike dermatophytosis, these mould infections are not contagious.

The clinical signs of *Scytalidium* infection are identical to those of *Trichophyton rubrum* infection. There is scaling of the interdigital spaces, over the soles, and on one or both palms. Itching is minimal. Nail infection may also develop (see Chapter 7).

Direct microscopic examination of scrapings shows fungal hyphae and arthrospores which may be difficult to distinguish from those of a dermatophyte. Both organisms will grow on glucose peptone agar, but are inhibited if cycloheximide (actidione) is incorporated in the medium. Therefore, it is essential to inform the laboratory if skin material is suspected of being infected with *S. dimidiatum* or *S. hyalinum*, so that duplicate plates with and without cycloheximide can be inoculated.

Both moulds are resistant to the modern treatments for cutaneous fungal infection. However, benzoic acid compound ointment can sometimes be used to treat these infections.

6.8 *Alternaria* infection

Members of the genus *Alternaria* are common soil organisms and important plant pathogens. These dematiaceous moulds have been implicated as occasional causes of subcutaneous and paranasal sinus phaeohyphomycosis (see Chapter 26), but they are more commonly reported as the aetiological agents of cutaneous infections in immunocompromised individuals. About 60% of published cases have occurred in persons receiving corticosteroid treatment.

The clinical manifestations of cutaneous *Alternaria* infection are varied. The lesions can appear as shallow-based non-healing ulcers that evolve from nodules, or as crusted lesions, or erythematous scaling lesions. The arms and legs are the most common sites of infection.

Because *Alternaria* species are common culture contaminants, detection of fungal elements during direct microscopic examination of specimens or in tissue sections is important to establish the clinical significance of a positive culture. The organisms appear as distorted brown-pigmented, branching hyphae.

Anecdotal case reports suggest that itraconazole (100–400 mg/day for 2–6 months) is the treatment of

choice for this infection. However, amphotericin B has also been used in parenteral or intralesional form.

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7 Mould infections of nails

7.1 Definition

The term onychomycosis is used to describe infection of the nails due to fungi. Nail infections due to dermatophyte fungi (tinea unguium) and *Candida* species have been described in Chapters 4 and 5. This chapter deals with infections caused by other, less common moulds.

7.2 Geographical distribution

The disease is worldwide in distribution.

7.3 The causal organisms and their habitat

Various filamentous fungi other than dermatophytes have been isolated from abnormal nails. Often, these are casual, transient contaminants and direct microscopic examination of nail clippings and scrapings is negative. However, certain environmental moulds are capable of causing nail infection and when this is so it is important that their significance is recognized.

There is wide geographical variation in the causative organisms, but *Scopulariopsis brevicaulis*, a ubiquitous soil fungus, is the most common cause of non-dermatophyte nail infection. *Scytalidium dimidiatum* (*Hendersonula toruloidea*) and *S. hyalinum* have been isolated from diseased nails as well as from skin infections of the hand and foot (see Chapter 6) in patients from the tropics. Other causes of nail infection include *Acremonium* species, *Aspergillus* species, *Fusarium* species and *Onychocola canadensis*.

7.4 Epidemiology

Mould infections of nails have been reported in all age groups, but are most prevalent in older individuals. Men are more commonly affected than women, and toenails are more frequently involved than fingernails. The incidence of mould infection of the nails is difficult to assess from published work because many reports do not distinguish between dermatophytosis and other forms of

onychomycosis. However, it has been estimated that non-dermatophyte moulds account for about 5% of cases of onychomycosis diagnosed in the UK, and around 20% in North America. Unlike dermatophytosis, these mould infections are not contagious, but many of them will not respond to the standard treatments for dermatophyte or *Candida* onychomycosis.

7.5 Clinical manifestations

With the exception of *Scytalidium* species, non-dermatophyte moulds usually occur as secondary invaders in nails that have previously been diseased or traumatized. This may account for the fact that these infections often affect only one nail. The toenails, especially the big toenail, are more frequently affected than the fingernails.

Non-dermatophyte moulds have been implicated as occasional causes of several forms of fungal nail infection, particularly proximal subungual onychomycosis and superficial white onychomycosis. In proximal subungual onychomycosis, the infection originates in the proximal nail fold, with subsequent penetration into the newly forming nail plate. The distal portion of the nail remains normal until late in the course of the disease. In superficial white onychomycosis, the infection begins at the superficial layer of the nail plate and spreads to the deeper layers. Crumbling white lesions appear on the nail surface, and gradually spread until the entire nail plate is involved.

7.6 Differential diagnosis

Mould infections of nails have no specific clinical features. For this reason mycological and histopathological examinations should be performed on any patient with nail lesions of undetermined origin.

7.7 Essential investigations and their interpretation

Laboratory confirmation of a clinical diagnosis of onychomycosis must be obtained before treatment is commenced. Methods for collecting nail specimens are as detailed in Chapter 4. It is essential to inform the laboratory if nail material is suspected of being infected

with a non-dermatophyte mould, so that duplicate plates with and without cycloheximide (actidione) can be inoculated.

Isolation of a mould is not a sufficient reason for ascribing a pathogenic role to it without further investigation. Moulds are ubiquitous and their aetiological role must be assessed whenever they are isolated from nail material. The fungus must be seen on direct microscopic examination and the mould must be isolated in pure culture without the simultaneous appearance of a dermatophyte. It is sometimes possible to distinguish infections with *S. brevicaulis* from tinea unguium on microscopic examination: the characteristic, roughened thick-walled oval spores of this mould are often present in infected nails.

If an environmental mould has been found on mycological investigation, the relationship between it and the nail plate can be determined with the aid of histopathological sections.

7.8 Management

Mould infections of nails are difficult to treat and even if the mould can be eradicated, this seldom leads to normal nail growth. Localized distal nail disease can sometimes be treated with topical amorolfine or tioconazole solutions. Amorolfine should be applied once or twice weekly, while tioconazole should be applied twice daily. Amorolfine treatment must be continued for at least 6 months for success with fingernails and 9–12 months for toenails.

Proximal nail disease or severe nail bed involvement may respond to treatment with topical terbinafine and ciclopirox solution if this is preceded by chemical dissolution of the diseased nail with 40% urea ointment, or mechanical avulsion. Nail avulsion can result in permanent damage, but it often leads to some improvement in the appearance of the nail.

There are anecdotal reports that oral treatment with terbinafine (250 mg/day for 12 weeks or longer) or itraconazole (200 mg/day for 12 weeks or longer) has been effective in some patients with mould infections of nails. Pulsed treatment with itraconazole (in which 1 week of treatment is alternated with 3 weeks without treatment)

has also given good results. Three pulses of treatment with 200 mg twice daily are recommended.

Patients who fail to respond to oral terbinafine or itraconazole after 6 months should be given additional treatment. This usually consists of one pulse of itraconazole in those individuals initially treated with itraconazole and 4 weeks of terbinafine in patients who were started with this drug.

Most patients with *Aspergillus* onychomycosis can now be cured with topical or oral antifungal treatment. It is also possible to cure about 70% of patients with *Scopulariopsis* or *Acremonium* nail infection. However, the cure rate for *Fusarium* onychomycosis is significantly lower (about 40%).

7.9 Prevention

In recent years, several non-dermatophyte moulds (including *Fusarium* species and *S. brevicaulis*) that cause nail infection have emerged as causes of the invasive fungal disease, hyalohyphomycosis, in neutropenic cancer patients and transplant recipients (see Chapter 24). Many of these infections have followed inhalation. In some cases, however, the source of the invasive infection has been identified as a pre-existing toenail infection. Because of the risk of life-threatening invasive fungal disease, it is essential that patients who require immunosuppressive or cytotoxic treatment be evaluated by a dermatologist before commencing immunosuppression. All sites of tissue breakdown should be identified and suspicious skin and nail lesions cultured.

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8 Keratomycosis

8.1 Definition

The term keratomycosis (mycotic keratitis) is used to describe fungal infection of the cornea. This infection is difficult to treat and can cause severe visual impairment or blindness.

8.2 Geographical distribution

The condition is worldwide in distribution, but is more common in the tropics and subtropical regions.

8.3 The causal organisms and their habitat

More than 70 different fungi have been reported to cause mycotic keratitis. Moulds are the principal aetiological agents of this infection worldwide, but especially in tropical and subtropical regions. Members of the genera *Fusarium* (in particular *F. solani*) and *Aspergillus* (in particular *A. fumigatus* and *A. flavus*) are the most common causes of keratomycosis in the tropics and subtropics, accounting for 36 and 30% of isolates, respectively, in a recent report from India. Other hyaline moulds that have been reported include *Acremonium* species, *Paecilomyces* species, *Penicillium* species and *Scedosporium* species. Dematiaceous moulds (in particular the genera *Curvularia*, *Bipolaris* and *Exserohilum*) are the third most common group of aetiological agents of mycotic keratitis, accounting for 16% of cases in India.

Members of the genus *Candida*, particularly *C. albicans*, *C. guilliermondii and C. parapsilosis*, have also been reported to cause corneal infection. These human commensal organisms are an infrequent cause of corneal disease in the tropics. However, in the USA and other countries where traumatic keratitis is uncommon, but where other predisposing factors are important, *Candida* species are the most frequent cause of keratomycosis.

8.4 Epidemiology

The aetiological agents of keratomycosis are widespread in the environment, being commonly found in indoor and outdoor air, in the soil and dust, and on decomposing plant matter. Human infection usually follows the traumatic implantation of spores into the corneal epithelium. Less commonly, it results from their inadvertent introduction during surgical procedures such as corneal transplantation.

Keratomycosis is most common in men, particularly those with an outdoor occupation. The principal, and sometimes only, predisposing factor is minor trauma. Often this trauma is so slight as not to attract the patient's attention. The traumatizing agent may be of plant or animal origin (such as leaves, wood chips or an animal's tail). Other materials such as dust, stone chips or metal splinters may be involved. The traumatizing agent itself may harbour fungal spores which are thus implanted into the cornea, or the injuring agent may cause a superfical abrasion that exposes the cornea to exogenous infection. Seasonal variations in the incidence of the disease have been noted, with infections being more common during the harvesting season in India.

Information on the incidence and prevalence of mycotic keratitis is limited, but published reports suggest that it accounts for up to 50% of all cases of ulcerative keratitis seen at specialist hospitals in the Indian subcontinent. In south Florida, fungal infections account for up to 35% of cases of microbial keratitis, compared with 1% in New York.

Individuals who use extended-wear soft contact lenses are also at risk for fungal keratitis. Although these patients are otherwise normal, the hypoxia and surface abrasive effect from contact lens wear can compromise the corneal epithelium and thus increase the risk of keratitis. Many patients with keratomycosis have received topical antibiotic or steroid treatment for ocular disease, which is an important predisposing factor.

8.5 Clinical manifestations

The clinical manifestations of keratomycosis are similar regardless of the organism involved. The infection is often insidious in onset, with mild symptoms having

been present for some time. Often the patient has been treated with antibiotics and the correct diagnosis is not suspected until the condition fails to respond. The most common symptoms include increasing ocular pain, ocular redness, photophobia, diminished vision, tearing and discharge. On examination, the eye appears injected, and the cornea may have a noticeable haze or an area of opacification. A mucopurulent discharge may be present.

Examination of the affected eye should be carried out using a slit lamp. The usual clinical finding is a raised corneal ulcer with a white, ragged border. Around and beneath the ulcer is a dense infiltrate extending deep into the corneal stroma. Although the lesion has a radiating margin, it is well defined. Discrete satellite lesions often develop. In the more severe cases, involvement of the anterior chamber occurs, leading to formation of a sterile hypopyon. If left untreated, the infection will spread into the anterior chamber and result in corneal perforation and loss of the eye. Enucleation is usually required because of pain.

Although the clinical manifestations of mycotic keratitis are similar, regardless of the mould involved, the rate of progression of the infection shows marked differences. In cases due to *Fusarium* species, the infection is usually severe, tends to progress rapidly and may end in deep lesions, perforation or malignant glaucoma. In keratitis due to *Aspergillus* species, the infection is usually less severe, does not progress as rapidly, and is more amenable to treatment than *Fusarium* infection. In keratitis due to *Curvularia* species, a low-grade keratitis lasting for several weeks with minimal inflammation or structural alteration, is usually observed. Macroscopic pigmentation is seen only in about 30% of cases.

In contrast to mould infections, mycotic keratitis due to *Candida* species presents as a small, well-demarcated area of epithelial ulceration and expanding, but discrete, stromal infiltration. The infection may be indistinguishable from gram-positive bacterial keratitis.

8.6 Essential investigations and their interpretation

Although the clinical picture is distinctive, the diagnosis of keratomycosis requires the demonstration of fungal

elements on microscopic examination of smears prepared from corneal scrapings, together with the isolation and identification of the aetiological agent and the elimination of other causes for the disease.

Because the aetiological agents of keratomycosis are common contaminants of the corneal surface, isolation alone is inadequate for making a diagnosis. Neither is a superficial corneal surface specimen adequate. The organisms are often difficult to find, being located deep inside the corneal stroma, rather than on the surface.

Specimens should be taken using a sterile platinum spatula to scrape corneal fragments from the margins and base of the ulcer. Swabs are not appropriate. Because the amount of material that can be obtained will be small, it is best transferred to a clean glass slide for microscopic examination and to an agar plate for culture at the bedside. The scrapings should be examined with a potassium hydroxide wet mount, Calcofluor white staining, or a Gram stain. Some material should also be inoculated on to plates or slopes of glucose peptone (Sabouraud's) agar, blood agar, or chocolate agar supplemented with an antibacterial antibiotic, such as chloramphenicol. These should be incubated at 25–30°C (rather than 37°C) for at least 2 weeks before being discarded as negative. The colonies of most aetiological agents of keratomycosis appear within 3–5 days. Isolation of a fungus is more convincing if multiple colonies are obtained on a plate, or if the same organism is recovered on more than one occasion.

If corneal scrapings are negative, but a diagnosis of keratomycosis is still suspected because the patient is not responding to antibacterial treatment, it is essential for the lesion to be biopsied. This should involve partial thickness trephination, with half the specimen being sent for culture and the remainder for histopathological examination.

Anterior chamber paracentesis is not recommended because it is not without risk and the hypopyon, if present, is usually sterile.

8.7 Management

The management of keratomycosis entails removal of infected tissue, discontinuation of topical corticosteroids

and topical or oral treatment with an antifungal drug. Prolonged treatment with careful follow-up is essential.

Topical treatment with natamycin 5% solution is often recommended for the initial management of corneal mould infection. Topical amphotericin B remains the preferred treatment for *Candida* infection. This drug can be toxic, but a 0.15% solution is well tolerated and shows reasonable ocular penetration. The imidazole compounds, clotrimazole, econazole and miconazole, are active against many moulds and topical treatment with a 1% solution is well tolerated. Miconazole achieves good concentrations in damaged corneal tissue and the aqueous humour following topical or subconjunctival administration. Although topical amphotericin B has sometimes proved unsuccessful against the dematiaceous moulds, topical miconazole has proved effective against these organisms.

Topical treatment should be applied at hourly intervals for the first week. Thereafter it should be applied at similar intervals when the patient is awake. Treatment should be continued for at least 6 weeks for a *Candida* infection and for up to 12 weeks for a mould infection. Signs of improvement include lessening of pain, disappearance of satellite lesions, decreasing size of the infiltrate and rounding out of the ulcer margin. Negative scrapings during treatment are not significant and should not be regarded as an indication of response to treatment.

Oral treatment should be considered in patients with severe or worsening lesions. Fluconazole is not effective in mould infections, but shows good corneal penetration. It can be used to treat *Candida* infection at a dose of 200–800 mg/day. Ketoconazole (400 mg/day) has benefited some patients with mould infection, but itraconazole (200 mg twice daily) has proved more successful.

Surgical intervention is indicated in cases of medical treatment failure. Superficial debridement will improve the penetration of topical antifungal drugs. Superficial or lamellar keratectomy may be effective if the lesion is small and localized, and particularly if it is located in the peripheral cornea. If, despite appropriate antifungal treatment, the inflammatory reaction or infection leads to corneal necrosis with actual or impending perforation, a

penetrating keratoplasty (corneal transplant) may be required. However, about 95% of grafts will fail, usually within 4 weeks. Nonetheless, repeat corneal transplant can be successfully peformed several months after resolution of infection.

Fusarium infections often result in rapid corneal sloughing and marked visual loss, and are difficult to treat. *Aspergillus* infections are less difficult to manage with antifungal agents, but the larger the ulcer and the deeper the hypopyon, the greater the likelihood of loss of vision. Even with intensive antifungal treatment, progression to corneal perforation, scleral suppuration or anterior chamber infection can occur. Corneal scarring with consequent reduction in vision is a frequent complication, even with successful treatment.

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9 Otomycosis

9.1 Definition

The term otomycosis is used to describe a superficial fungal infection of the ear canal.

9.2 Geographical distribution

The condition is worldwide in distribution, but is more common in tropical and subtropical regions.

9.3 The causal organisms and their habitat

Otomycosis is most commonly caused by *Aspergillus* species, particularly *A. fumigatus*, *A. niger*, *A. nidulans* and *A. flavus*, and *Candida* species, particularly *C. albicans* and *C. tropicalis*. In temperate regions, there is a slight preponderance of infections with *Candida* species while in tropical and subtropical regions, *A. niger* is the most common cause of infection. Other moulds that have been implicated include *Penicillium* species, and *Rhizopus* species. Mixed bacterial and fungal cultures are common and account for more than 50% of all cultures in otomycosis.

9.4 Epidemiology

The aetiological agents of otomycosis are commonly found in indoor and outdoor air, in the soil and dust, and on decomposing plant matter. Their prevalence varies with climatic conditions, but warm humid environments support their growth and the human ear canal is ideal for their proliferation. In the tropics, otomycosis accounts for up to 6% of patients with symptomatic ear disease, but the condition is less prevalent in temperate climates. In temperate regions it is most frequently seen during the summer months. Otomycosis occurs in men and women of all ages; children are less commonly affected. It is not a contagious condition.

Otomycosis often develops in individuals with pre-existing dermatological conditions of the ear, such as seborrhoeic dermatitis or psoriasis. Bacterial infection is

common in such cases, and prolonged use of topical antibiotics and steroids will often result in fungal superinfection.

9.5 Clinical manifestations

The initial symptoms of fungal and bacterial otitis externa are often indistinguishable. However, while pain is the dominant symptom in bacterial infection, the most common complaint in otomycosis is aural fullness and pruritus deep inside the ear canal. Sometimes discharge is present, but it is not mucoid, which would suggest that there is a tympanic perforation. Obstruction of the meatus can lead to partial hearing loss and tinnitus.

In most cases otoscopic examination reveals the presence of debris and an oedematous and erythematous ear canal. If *A. niger* is the causative agent, a mat of fungus, often covered with black sporing heads, can be seen. This mass lining the meatus, which it can obstruct, is often described as resembling greyish blotting paper. In chronic infections, eczematoid changes and lichenification of the canal can become marked.

In immunosuppressed patients with haematological malignancies or persons with the end stage of the acquired immunodeficiency syndrome (AIDS), fungal infection of the external ear can progress to a necrotizing otitis externa. There is erythema and superficial ulceration, together with bleeding and discharge. Pain is common. The infection can spread to the middle ear and mastoid. This is most commonly caused by *A. fumigatus*, but *Scedosporium apiospermum* has also been implicated.

9.6 Differential diagnosis

The clinical diagnosis of otomycosis is difficult, although a lack of response to topical antibiotics and steroids, and the onset of hearing loss are suggestive of fungal infection. The diagnosis can be established with confidence only by mycological investigation.

9.7 Essential investigations and their interpretation

Material for mycological investigation should be obtained from the deposits blocking the ear canal.

Microscopic examination will reveal branching hyphae, or budding yeast cells or both. In cases of *Aspergillus* infection, the typical sporing heads can sometimes be seen.

Isolation of the aetiological agent in culture will enable the species of the fungus involved to be identified.

9.8 Management

The treatment of otomycosis consists of removal of debris from the ear canal and thorough cleaning, together with the local application of an antifungal agent. Topical nystatin can be applied three times daily for 2–3 weeks. The local application of an imidazole cream, such as clotrimazole or econazole nitrate, also gives good results. Another method is to insert gauze packs, soaked in amphotericin B or an imidazole preparation, for 1 week. These should be replaced at frequent intervals. In developing countries, or when these agents are not readily available, mercurochrome solution and boric acid have been used with success.

Most patients with otomycosis will respond to treatment. Complications are rare, but include recurrence or perforation of the tympanic membrane. Most perforations will heal spontaneously usually within 1 month.

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10 Aspergillosis

10.1 Definition

The term aspergillosis is used to refer to infections due to moulds belonging to the genus *Aspergillus*. In immunocompromised individuals, inhalation of spores can give rise to life-threatening invasive infection of the lungs or sinuses and dissemination to other organs often follows. This condition is termed invasive aspergillosis. In non-immunocompromised persons, these moulds can cause localized infection of the lungs, sinuses and other sites. Human disease can also result from non-infectious mechanisms: inhalation of spores of these ubiquitous organisms can cause allergic symptoms in both atopic and non-atopic individuals.

10.2 Geographical distribution

These conditions are worldwide in distribution.

10.3 The causal organisms and their habitat

Moulds of the genus *Aspergillus* are widespread in the environment, growing in the soil, on plants and on decomposing organic matter. These moulds are often found in the outdoor and indoor air, in water, on food items and in dust. Although there are more than 200 species of *Aspergillus*, fewer than 20 cause disease in humans. Most cases are caused by *A. fumigatus*, with *A. flavus* the second most frequent pathogen. Less common species include *A. nidulans*, *A. niger* and *A. terreus*.

10.4 Epidemiology

Inhalation of *Aspergillus* spores is the usual mode of infection in humans. The incubation period is unknown. Less frequently, infection follows the traumatic implantation of spores as in corneal infection (see Chapter 8), or inadvertent inoculation as in endocarditis.

The aetiological agents of aspergillosis are ubiquitous in the environment and the likelihood that infection will

occur following inhalation or implantation of spores largely depends on host factors. Invasive aspergillosis has emerged as a major problem in several groups of immunocompromised patients. Those at greatest risk include persons with haematological and lymphoreticular cancer, in particular acute leukaemia, haematopoietic stem cell transplant (HSCT) recipients, solid organ transplant recipients, individuals receiving high-dose corticosteroid treatment, and persons with neutrophil deficiencies or dysfunction, such as children with chronic granulomatous disease (CGD). The likelihood of aspergillosis developing in these individuals depends on a number of host factors, the most important of which is the level of immunosuppression, whether this manifests as profound or prolonged neutropenia, as graft-versus-host disease (GVHD) in HSCT recipients, or as rejection in organ transplant recipients. With new developments in the management of the underlying disorders, the patient groups who are at highest risk of developing invasive aspergillosis are changing, and there is an ongoing need to reassess the factors that can affect different groups of susceptible hosts.

The occurrence rate of invasive aspergillosis in neutropenic cancer patients is variable and is dependent on the underlying disorder, the treatment regimen, and other supportive measures used. Most at risk are those patients who remain neutropenic for 2 weeks or longer. The use of corticosteroids in an antineoplastic regimen increases the risk for aspergillosis.

Allogeneic HSCT recipients, particularly unrelated donor recipients, are at high risk for invasive aspergillosis for a prolonged period of time because of disruption of mucosal barriers, delayed engraftment, GVHD, and the use of steroids and broad-spectrum antibacterial agents. Active acute GVHD has been identified as a major risk factor for the early development of *Aspergillus* infection, while extensive chronic GVHD is a major risk factor for late infection.

Among solid organ transplant recipients, those with renal allografts are least at risk. In contrast, lung transplantation carries a high risk of invasive aspergillosis. Among the risk factors that have been identified are graft rejection, obliterative bronchiolitis,

cytomegalovirus infection and increased immunosuppression. Liver transplant recipients are another high-risk group. Many of those who develop aspergillosis have signs of poor allograft function and/or renal dysfunction that requires dialysis.

It has long been recognized that few patients with haematological malignancies and invasive aspergillosis will survive unless their neutrophil count recovers. Earlier diagnosis and treatment have also been associated with a better prognosis. Among the factors that have been associated with a poor outcome in allogeneic HSCT recipients with aspergillosis are active acute GVHD of grade II or more, or extensive chronic GVHD at the time of diagnosis, and a high cumulative dose of prednisolone.

The incidence of invasive aspergillosis in high-risk patient groups is difficult to determine for a number of reasons. These include the lack of a consistent case definition which makes it difficult to compare the incidence rates reported in different studies. This situation should improve with the recent development of an agreed set of definitions for invasive fungal infections. In the USA, active population-based surveillance, conducted in San Francisco between 1992 and 1993, showed that aspergillosis developed in 12.4 persons per million population. Given the limitations of current diagnostic methods for this infection and the conservative case definition used, it is almost certain that this figure is a significant underestimate of disease incidence. Other data indicate that the incidence of aspergillosis as a hospital discharge diagnosis in the USA increased about eightfold from 4.8 to 38 cases per million population between 1976 and 1996.

The incidence of invasive aspergillosis differs from one high-risk patient group to another. In recent reports, the disease has been estimated to occur in 5–25% of patients with acute leukaemia, 0.5–5% of autologous HSCT recipients, 5–10% of sibling allogeneic transplant recipients, and 10–15% of recipients of grafts from unrelated donors. It has been estimated to occur in 2–8% of liver transplant recipients, 3–16% of lung transplant recipients, 5% of heart transplant recipients, and 1% of renal transplant recipients. However, it is

difficult to determine the true incidence of the disease in these different groups because the rates are dependent on the length of follow-up after transplantation.

The mortality rate from invasive aspergillosis is high, ranging from 50 to 100% in almost all groups of immunocompromised patients. With a 3-month length of follow-up, the case–fatality ratios associated with invasive pulmonary disease have ranged from 50% for heart transplant recipients to 90% for HSCT recipients, and 95% for liver transplant recipients. In a large review of cases reported up to 1995, case–fatality ratios for cerebral, pulmonary and sinus infections were 99%, 86% and 66%, respectively. Little improvement has been achieved since 1995: disseminated or central nervous system (CNS) disease still carries a case–fatality ratio of 88% while diffuse pulmonary infection has a case–fatality ratio of 60%.

Hospital outbreaks of invasive aspergillosis have become a well-recognized complication of construction or renovation work in or near units in which high-risk patients are housed. These reports have served to highlight the fact that the hospital environment is often contaminated with *Aspergillus* spores, and have contributed to the widespread perception that most cases of aspergillosis in immunocompromised persons are hospital acquired. However, despite the fact that most hospital outbreaks of aspergillosis go unpublished, it is clear that these events in general are uncommon.

Most cases of invasive aspergillosis are sporadic in nature, and it is much more difficult to determine whether these infections are acquired inside or outside the hospital setting. It seems probable that some individuals are colonized before their admission to hospital and develop invasive disease when rendered neutropenic. Indeed, it has been estimated that up to 70% of cases of invasive aspergillosis diagnosed over a 2-yr period of surveillance during construction in one North American hospital were acquired outside the hospital setting.

There is other evidence that a significant number of sporadic cases of invasive aspergillosis are now being acquired outside the hospital environment. In the 1970s

and 1980s, most cases of *Aspergillus* infection among leukaemic patients occurred during the first few weeks after transplantation, before engraftment occurred, or while individuals were undergoing intensive remission induction treatment. However, recent reports have indicated that many HSCT recipients now develop aspergillosis some months after transplantation, usually in association with GVHD and its treatment.

10.5 Clinical manifestations

Inhalation of *Aspergillus* spores can give rise to a number of different clinical forms of aspergillosis, depending on the immunological status of the host. In immunocompromised patients, there is widespread growth of the fungus in the lungs or sinuses and dissemination to other organs often follows. It must, however, be emphasized that with early diagnosis and treatment, a significant number of patients can now be cured. In non-compromised individuals, *Aspergillus* can cause localized infection of the lungs, sinuses and other sites, or act as a potent allergen.

10.5.1 Acute invasive pulmonary aspergillosis

Acute invasive pulmonary aspergillosis occurs in immunocompromised individuals. It can be classified as focal or diffuse, the former having the better prognosis. Haematogenous dissemination to distant organs is a frequent complication in neutropenic cancer patients and transplant recipients. The CNS is the most common secondary site of invasive disease, being involved in 10–20% of cases. In patients with CGD or the acquired immunodeficiency syndrome (AIDS), a more indolent course is typical, but local spread of infection into the ribs or spine can occur.

The hallmark of invasive *Aspergillus* infection is angioinvasion. Once this occurs, thrombosis, infarction and necrosis of the surrounding lung tissue follows. Erosion of the vessel wall can occur, leading to catastrophic haemorrhage.

The clinical presentation of invasive pulmonary aspergillosis is varied and diagnosis is difficult. The commonest initial presentation in the neutropenic patient is an unremitting fever (greater than 38°C), without any

respiratory tract symptoms, that fails to respond to broad-spectrum antibacterial treatment. Corticosteroid-treated patients often present without fever, and low-grade chest pain, which can be pleuritic, is a common finding. Non-productive cough is another common presenting symptom, but haemoptysis is unusual.

Initial investigations should include a chest radiograph and blood cultures, although the latter are usually negative in patients with invasive *Aspergillus* infection. Wedge-shaped, pleural-based densities and cavities (both late findings) are highly suggestive of invasive pulmonary aspergillosis. However, the disease can also present as diffuse infiltrates.

Computed tomographic (CT) scans will often reveal lesions in the lungs of patients with normal plain chest radiographs. In neutropenic patients the most distinctive signs of focal *Aspergillus* infection are small nodules and/or small pleural-based lesions. Often there is a characteristic region of lower attenuation (termed a halo sign) around the nodules. Over time, the nodules may cavitate (often as the neutrophil count recovers), resulting in the characteristic crescent sign, a thin air crescent near the edge of a lung nodule, caused by contraction of infarcted tissue. The signs of diffuse *Aspergillus* infection of the lungs are much less distinctive than those of focal infection and other investigations are required to confirm the diagnosis.

If focal disease is identified on a CT scan or radiograph, percutaneous lung biopsies should be obtained for microbiological and histopathological investigation. Bronchoscopic examination is seldom helpful. However, if diffuse disease is seen on a CT scan or radiograph, bronchoscopic examination is essential. In neutropenic cancer patients and HSCT recipients, microscopic examination and culture of bronchoalveolar lavage (BAL) specimens is the most useful method for confirming the diagnosis of invasive pulmonary aspergillosis.

10.5.2 Tracheobronchitis and obstructing bronchial aspergillosis

Aspergillus tracheobronchitis is most often seen in persons with AIDS and lung transplant recipients. The most frequent symptoms are dyspnoea and wheezing, but

some patients develop a cough and fever. The symptoms become more pronounced as the infection develops. Some patients die as a result of occlusion of the trachea or a bronchus, while others develop disseminated *Aspergillus* infection.

CT scans often fail to detect *Aspergillus* tracheobronchitis. Bronchoscopic examination will reveal ulcerative lesions or necrotic pseudomembranes and will permit the diagnosis to be established.

Obstructing bronchial aspergillosis is a non-invasive condition that has been described in persons with AIDS. The presenting symptoms include cough, fever and wheezing. Large mucus plugs full of *Aspergillus* mycelium are expectorated or are encountered during bronchoscopic examination. These plugs form in the bronchi, leading to segmental or lobar atelectasis. Chest radiographs reveal bilateral lower lobe or generalized infiltrates. If left untreated, the disease can become invasive and spread upwards to produce tracheobronchitis. The diagnosis is established at bronchoscopic examination.

10.5.3 Acute invasive sinusitis

Acute invasive *Aspergillus* sinusitis is a rapidly progressive disease that is most commonly seen in neutropenic cancer patients, HSCT recipients and other immunocompromised individuals. *A. fumigatus* and *A. flavus* are the commonest aetiological agents. The clinical presentation is similar to that of rhinocerebral mucormycosis (see Chapter 13). The presenting symptoms include fever, unilateral facial swelling, unilateral headache, nasal or sinus congestion or pain, and a serosanguinous nasal discharge. Necrotic black lesions on the hard palate or nasal turbinate are a characteristic diagnostic sign. As the infection spreads into the orbit, periorbital or perinasal swelling occurs, and progresses to disfiguring destruction of facial tissue. Ptosis, proptosis, ophthalmoplegia and loss of vision can occur. In 25% of cases, the infection spreads into the brain and causes death.

CT scans can be used to determine the extent of bone destruction and pattern of sinus and orbital involvement. The commonest findings include involvement of several sinuses (in particular ethmoid and sphenoid), but with a clear unilateral predilection; no

air-fluid levels; thickening of sinus linings; and destruction of surrounding bone. Magnetic resonance imaging (MRI) scans are not clearly superior to CT, but are more accurate in providing information about cavernous sinus and cerebral involvement. Local biopsies with histopathological examination and culture of nasal tissue or sinus contents will confirm the diagnosis.

10.5.4 Cerebral aspergillosis

It is much more common for cerebral aspergillosis to occur following haematogenous dissemination of infection from the lungs than for it to result from direct spread from the nasal sinuses. The CNS is involved in 10–20% of cases of disseminated aspergillosis, but cerebral infection is seldom diagnosed during life. In HSCT recipients *Aspergillus* infection is a common cause of brain abscess. In contrast, in persons with AIDS it is an unusual cause of cerebral infection.

The clinical presentation and rate of progression of cerebral aspergillosis differs from patient to patient. Those who are less immunosuppressed often present with focal neurological deficits and headache. Immunocompromised individuals often present with non-specific findings such as alterations in mental status and seizures. Multiple brain lesions with infarction due to cerebral arterial thrombosis can result in focal neurological signs, fits and raised cerebrospinal fluid (CSF) pressure. Meningeal signs are rare.

CT scans are helpful in locating the well-demarcated, hypodense lesions, but the findings are non-specific. MRI will often reveal additional lesions in the brain. Biopsy or aspiration of material from a suspicious lesion is seldom possible but, if feasible, will often permit the aetiological agent to be detected on microscopic examination or isolated in culture. Examination of CSF is seldom helpful.

10.5.5 Cutaneous aspergillosis

Two forms of cutaneous *Aspergillus* infection have been described in immunocompromised patients. In primary cutaneous aspergillosis, the lesion arises at or near an intravenous catheter insertion site in patients who have had contaminated dressings or splints applied to their

skin. The lesion, which may act as the source of a subsequent disseminated infection, begins as an erythematous to violaceous, indurated plaque and evolves into a necrotic ulcer covered with a black eschar.

In secondary cutaneous aspergillosis, the lesions result either from haematogenous spread of infection from the lungs, or from extension to the skin from underlying infected tissue. This form of aspergillosis is seen in about 5% of patients with invasive disease. The lesions may be single or multiple, erythematous macules or papules. They evolve into necrotic ulcers with distinct borders covered with a black eschar. The lesions enlarge and may become confluent.

10.5.6 Pulmonary aspergilloma

An aspergilloma (or fungus ball) is a dense amorphous mass of fungal mycelium that is sometimes found in residual lung cavities formed following tuberculosis, sarcoidosis, bronchiectasis, pneumoconiosis or ankylosing spondylitis. Haemoptysis is the only serious complication. Fungus balls are usually located in the upper lobes. Less frequently they occur in the apical segments of the lower lobes. Spontaneous lysis has been reported to occur in up to 10% of cases.

Patients are often asymptomatic, but may present with chronic cough, malaise and weight loss. Haemoptysis is the most common symptom, occurring in 50–80% of cases. Most patients have intermittent episodes of small amounts of bleeding, but up to 25% suffer massive life-threatening haemoptysis.

Chest radiographs will reveal a characteristic solid oval or round mass, with a radiolucent halo or crescent of air over the superior aspect. If peripheral, pleural thickening is characteristic. The mass can often be shown to move as the patient changes position. CT scans will help to delineate the lesion.

10.5.7 Chronic necrotizing pulmonary aspergillosis

Chronic necrotizing pulmonary aspergillosis is an indolent condition seen in middle-aged or older persons with an underlying lung disease, such as inactive tuberculosis, bronchiectasis, sarcoidosis or pneumoconiosis. More men than women are affected. Many of these

individuals have other illnesses, such as alcoholism or diabetes mellitus, which can cause mild immunological impairment, or have received long-term, low-dose steroid treatment. Patients with *Aspergillus* fungus balls in their lungs have a similar clinical profile and it is sometimes difficult to distinguish between the two disorders because chronic necrotizing aspergillosis is often complicated by fungus ball formation.

The most frequent symptoms include chronic productive cough, haemoptysis, malaise and weight loss. Chest pain is uncommon. The earliest radiological changes are ill-defined infiltrates, usually in one or both upper lobes, that progress to form multiple, well-defined cavities with thickened walls. About 50% of patients develop single or multiple fungus balls inside the necrotic lung cavities. Some patients develop pleural thickening and this can progress to form a bronchopleural fistula.

If this form of aspergillosis is left untreated, the cavities will expand and local pulmonary fibrosis will occur until the patient is left with little functional lung. Occasional patients suffer fatal haemoptysis.

10.5.8 Chronic invasive sinusitis

Aspergillus species are a frequent cause of chronic invasive sinusitis (see also Chapter 26). This is a slowly progressive condition, analogous to chronic necrotizing pulmonary aspergillosis. It has a worldwide distribution, but the largest number of cases has been reported from North America. It can occur in normal individuals, but is more often seen in patients who have received steroids for some other condition or have diabetes mellitus. Affected individuals often complain of long-standing allergic rhinitis, or chronic bacterial sinusitis. Thick nasal polyposis and thick purulent mucus are common. If left untreated, the infection can spread from the ethmoid sinuses into the orbit, leading to impaired vision and restricted ocular movement. Proptosis can also occur. Posterior erosion from the ethmoid sinus can result in cavernous venous thrombosis.

A second form of chronic sinus aspergillosis, termed chronic granulomatous invasive sinusitis or paranasal granuloma, has been reported from North Africa, the Middle East and the Indian subcontinent. This is

another slowly progressive disease that occurs in immunocompetent individuals who often have had chronic sinusitis. Affected individuals present with long-standing symptoms of nasal obstruction and unilateral facial discomfort, or with a silent proptosis, but are otherwise normal. There is profuse fungal growth with localized tissue invasion. The granulomatous response is often intense enough to cause pressure necrosis of sinus walls and proptosis if the orbit is breached. Unless removed, the fungal mass can spread into the orbit and brain. *A. flavus* is the predominant cause of this condition.

Imaging studies can assist in determining the presence and the anatomical extent of sinus disease, however, plain radiographs are insensitive and do not distinguish fungal from bacterial infection. CT scanning is more discriminating. In patients with chronic invasive sinusitis, non-contrast CT scans will reveal a hyperdense mass within the involved sinus with erosion of the sinus walls. The most common radiographic findings in patients with paranasal granuloma are opacifications of the ethmoid, maxillary or all sinuses (pansinusitis), together with bone erosions.

10.5.9 Paranasal sinus fungus ball

A paranasal sinus fungus ball (sometimes termed a sinus mycetoma) is a dense mass of fungal mycelium that is sometimes found in sinus cavities of patients undergoing investigation for chronic sinusitis, nasal obstruction, facial pain or other conditions. There is no fungal invasion of the mucosa, associated blood vessels, or bone. Older individuals appear to be more susceptible. The symptoms are often similar to those of chronic bacterial rhinosinusitis, but some patients are asymptomatic. Affected persons often present with long-standing nasal obstruction, purulent nasal discharge, cacosmia (foetid smell) or facial pain. The symptoms are often unilateral. *A. fumigatus* is the predominant cause.

CT scans will reveal partial or total opacification of the involved sinus, often associated with calcification. The maxillary sinus is the most common site affected. Air-fluid levels, which are characteristic of acute bacterial sinusitis, are uncommon.

10.5.10 Endocarditis

Aspergillus endocarditis is most often seen in patients undergoing open heart surgery, although it has also been described as a complication of parenteral drug abuse. The aortic and mitral valves are the most frequent sites of infection. It often gives rise to large friable vegetations and large emboli are common.

The symptoms and clinical signs are similar to those of bacterial endocarditis. The illness may be abrupt in onset or insidious. Fever, weight loss, fatigue and loss of appetite are common but non-specific symptoms. Heart murmurs can be detected in 50–90% of patients, and an enlarged spleen in 30%. More specific diagnostic signs include large friable vegetations. Emboli that obstruct major arteries, particularly those of the brain, occur in about 80% of cases.

10.5.11 Osteomyelitis

Aspergillus osteomyelitis is an uncommon condition, but children with CGD seem to be at particular risk. In these individuals, spread from an adjacent pulmonary lesion is usual and the ribs and spine are the most common sites of *Aspergillus* infection. In immunocompromised adult patients, the spine is also the commonest site of infection, but haematogenous dissemination of the organism may be more common. *Aspergillus* osteomyelitis can also result from the inadvertent inoculation of organisms during surgical procedures.

The clinical and radiological findings in vertebral aspergillosis are similar to those of tuberculosis. Most patients complain of fever and of pain and tenderness at the affected site. Many patients with *Aspergillus* osteomyelitis also have surrounding soft tissue involvement, with pleural disease and paraspinal abscesses. Joint involvement is rare.

10.5.12 Endophthalmitis

Aspergillus endophthalmitis is an uncommon condition, but it has been described in drug abusers, patients with endocarditis and organ transplant recipients. It can arise following ocular trauma or haematogenous spread of the fungus. The latter is more usual in immunocompromised patients. The symptoms include ocular pain

and impaired vision. On examination most patients have an iridocyclitis or vitritis in association with yellow-white retinal lesions. Retinal haemorrhage or abscess can occur and hypopyon has also been described. *A. fumigatus* is the usual aetiological agent, but *A. flavus*, *A. niger* and *A. terreus* have also been implicated.

10.5.13 Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis is a hypersensitivity disease of the lungs, most often seen in atopic individuals who develop episodic bronchial obstruction (asthma) and peripheral blood eosinophilia following inhalation of *Aspergillus* spores. Antigens released from the fungus colonizing the bronchi cause a vigorous humoral response that leads to eosinophilia and the release of immune mediators. Mucus secretion becomes pronounced and results in the formation of plugs that obstruct the bronchi; chronic obstruction leads to bronchiectasis. The illness can be mild, but it often progresses from acute corticosteroid-responsive asthma to corticosteroid-dependent asthma and then to fibrotic end-stage lung disease.

The most frequent symptoms include fever, intractable asthma, productive cough, malaise and weight loss. The diagnostic criteria include episodic bronchial obstruction (asthma), peripheral blood eosinophilia, an immediate prick test reaction to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated serum IgE concentration, and history of pulmonary infiltrates (transient or fixed) and central bronchiectasis. Other findings include repeated detection of *Aspergillus* in sputum, expectoration of brown eosinophilic mucus plugs, elevated specific IgE against *Aspergillus* antigen, Arthus reaction to prick test with *Aspergillus* antigen, and characteristic defects on intrabronchial challenge with *Aspergillus*.

The radiographic findings range from small, fleeting, unilateral or bilateral infiltrates with ill-defined margins (often in the upper lobes) and hilar or paratracheal lymph node enlargement, to chronic consolidation and lobar contractions. The typical transient opacifications are usually due to bronchial obstruction with mucus plugs and disappear when these are expectorated.

10.5.14 Allergic sinusitis

Aspergillus species are a frequent cause of allergic fungal sinusitis (see also Chapter 26). This condition occurs in young immunocompetent adults with chronic relapsing rhinosinusitis, unresponsive to antibiotics, antihistamines or corticosteroids.

Patients often present with unilateral nasal polyposis and thick yellow-green nasal or sinus mucus. The nasal polyposis may form an expansive mass that causes bone necrosis of the thin walls of the sinus. Should the ethmoid bone be traversed, allergic mucin can enter the orbit and cause proptosis. Polypoid material can also cause nasal septal deviation. Sinus radiographs show mucosal thickening. CT scans often reveal a characteristic serpiginous sinus opacification of more than one sinus, mucosal thickening, and erosion of bone, but this does not represent tissue invasion.

The diagnosis of allergic sinusitis requires the microscopic examination of the characteristic allergic mucin (either at the time of surgical debridement for chronic sinusitis or endoscopic examination for drainage) to determine the presence of eosinophils and fungal elements, and of sinus tissue to rule out invasion. The laboratory findings are identical to those seen in allergic bronchopulmonary aspergillosis, including eosinophilia, elevated serum IgE concentration, elevated specific IgE against *Aspergillus* antigen, and an immediate prick test reaction to *Aspergillus* antigen.

10.6 Essential investigations and their interpretation

Establishing the diagnosis of invasive aspergillosis in patients with cancer and transplant recipients is often difficult to accomplish. In most cases, the diagnosis is based on a combination of clinical, radiological, microbiological and histopathological findings. These might include a positive culture result for a specimen obtained from a normally sterile and clinically or radiologically abnormal site, or histopathological or cytopathological examination showing hyphae consistent with *Aspergillus* in a biopsy specimen or aspirate. The use of antigen detection and polymerase chain reaction (PCR)-based tests to detect invasive aspergillosis has been reported,

but the methods are still undergoing evaluation and their routine use cannot be recommended at present.

10.6.1 Microscopy

Among the most reliable methods for the diagnosis of invasive aspergillosis is the histopathological examination of stained tissue sections. The detection of non-pigmented, septate hyphae which show repeated dichotomous branching is characteristic of *Aspergillus* infection. However, other less common hyaline moulds, such as *Fusarium* species and *Scedosporium apiospermum*, can appear similar (see Chapter 24), and isolation of the aetiological agent in culture is essential to confirm the diagnosis. More precise identification can sometimes be achieved with immunohistochemical staining methods.

Direct microscopic examination of sputum preparations is seldom helpful in patients with suspected invasive aspergillosis, but examination of BAL-fluid specimens is often rewarding. Typical branching, septate hyphae may also be detected in potassium hydroxide preparations of necrotic material from cutaneous or sinus lesions.

Microscopic examination of sputum is often helpful in the diagnosis of allergic bronchopulmonary aspergillosis because abundant branching, septate hyphae with characteristic dichotomous branching are usually seen.

10.6.2 Culture

In general, culture is not a sensitive method for the diagnosis of invasive forms of aspergillosis. Moreover, because *Aspergillus* species are commonly found in the air, their isolation must be interpreted with caution. These moulds are seldom recovered from blood or CSF specimens, although cultures of the former have been positive in occasional patients with endocarditis. More often, however, their isolation is due to contamination. It has not been established whether lysis centrifugation is any more useful than traditional blood culture methods in the diagnosis of aspergillosis.

Isolation of an *Aspergillus* species from a BAL or sputum specimen obtained from an immunocompromised patient with a pulmonary infiltrate is usually

indicative of infection, but the success rate does depend on the patient group and the pattern of disease. In neutropenic cancer patients and HSCT recipients with diffuse infection, culture of BAL fluid is positive in up to 60% of cases. The success rate is lower in organ transplant patients, with the exception of lung transplant recipients. Culture of BAL fluid is seldom helpful in patients with focal lung disease.

A. fumigatus can often be recovered from sputum specimens from patients with allergic bronchopulmonary aspergillosis.

10.6.3 Skin tests

Skin tests with *Aspergillus* antigens are only useful in the diagnosis of allergic aspergillosis. Patients with uncomplicated asthma due to *Aspergillus* give an immediate type I reaction. Those with allergic bronchopulmonary aspergillosis give an immediate type I reaction and 70% also give a delayed type III reaction.

10.6.4 Serological tests

Tests for *Aspergillus* antibodies are often helpful in the diagnosis of the different forms of aspergillosis that occur in the non-compromised patient. The available tests include immunodiffusion (ID), indirect haemagglutination and enzyme-linked immunosorbent assay (ELISA). The ID test is simple to perform and precipitins can be detected in up to 70% of patients with allergic bronchopulmonary aspergillosis and over 90% of those with pulmonary aspergilloma or chronic necrotizing pulmonary aspergillosis. The ID test is also useful for diagnosing other invasive forms of *Aspergillus* infection, such as endocarditis, provided the patient is not immunosuppressed.

Tests for *Aspergillus* antibodies have been extensively evaluated for the rapid diagnosis of invasive aspergillosis, but their role remains uncertain. The detection of precipitins in a neutropenic patient with unresponsive fever or a pulmonary infiltrate is often sufficient to prompt the initiation of antifungal treatment, but it must be stressed that a positive ID test result is not proof of infection. Nor does a negative test result preclude the diagnosis of aspergillosis in an immunosuppressed patient, because such

individuals are often incapable of mounting a detectable antibody response.

Tests for the detection of *Aspergillus* antigen in blood and other biological fluids offer a rapid means of diagnosing aspergillosis in the immunocompromised patient. Low concentrations of galactomannan, a major cell wall component of *Aspergillus*, have been detected in serum, urine and BAL specimens from neutropenic cancer patients and HSCT recipients with invasive aspergillosis. However, galactomannan levels fluctuate during the course of the infection, and it has been suggested that testing is only helpful in management if performed on a regular basis (i.e. at least twice per week). A negative antigen test result does not exclude the diagnosis of aspergillosis, particularly if only a single specimen has been tested and the patient has clinical signs consistent with the infection.

Two tests to detect circulating *Aspergillus* galactomannan are commercially available in a number of countries. A latex particle agglutination (LPA) test was the first to be developed (Pastorex Aspergillus, Sanofi Diagnostics Pasteur, Paris, France) but, despite its ease of use, it is relatively insensitive. More recently, a sandwich ELISA (Platelia Aspergillus, Sanofi Diagnostics Pasteur) has been marketed for the detection of *Aspergillus* galactomannan. In several large prospective evaluations in haematological patients, this test has been reported to have a sensitivity of 90–93% and specificity of 94–98%. In some studies, positive results were only obtained during the later stages of infection, although early detection of galactomannan in serum has been noted in other reports. Platelia Aspergillus is now approved for diagnostic use in the USA.

10.6.5 Molecular diagnostics

Numerous PCR-based methods have been developed for the detection of *Aspergillus* DNA in blood, serum, BAL fluid and other clinical specimens. Several regions within the *Aspergillus* genome have been evaluated as potential targets for detection, but most effort has focused on the ribosomal DNA gene complex. Both nested and panfungal PCR formats have been employed. More recently, quantitative PCR methods have been

used to monitor the fungal burden during antifungal treatment. Nucleic acid sequence-based amplification (NASBA) assays have also been developed for the detection and identification of *Aspergillus* genus-specific RNA sequences in blood specimens. Molecular diagnostics appear promising for the rapid detection of *Aspergillus* infection directly from tissue or body-fluid specimens, but false-positive results can occur and standardized commercial methods are not available. At present, the routine use of PCR in the diagnosis of invasive aspergillosis cannot be recommended.

10.7 Management

10.7.1 Acute invasive pulmonary aspergillosis

The successful management of acute invasive pulmonary aspergillosis in the immunocompromised patient depends on the prompt initiation of effective antifungal treatment, correction of the underlying immunological defect that precipitated the infection, and surgical intervention as appropriate. The response rate differs from one host group to another and depends on the length of time over which treatment is administered. Patients who survived have all received at least 2 weeks of amphotericin B treatment. In HSCT recipients the response rate is about 30% and in neutropenic cancer patients it is around 50%. Heart and renal transplant patients have a response rate of about 80%, but liver transplant recipients have a rate of 20%. In neutropenic patients the prognosis is poor if the neutrophil count does not recover. Use of adjunct modalities, such as granulocyte transfusions, colony-stimulating factors and interferon, has not been shown to lead to increased survival. These modalities are not recommended for routine clinical use in neutropenic or immunocompromised patients.

Amphotericin B is the historical standard for treatment of invasive pulmonary aspergillosis, particularly for life-threatening and severe infections, despite the fact that its use is limited by a range of serious side-effects, notably renal damage. There are numerous regimens for administration of this drug, but widespread agreement that in immunocompromised patients it is important to give the maximum tolerated dose of amphotericin B (1.0–1.5 mg/kg per day) from the outset

(see Chapter 3). Treatment should be continued despite modest increases in serum creatinine concentrations.

If the disease fails to respond to the conventional formulation of amphotericin B, treatment should be changed to one of the lipid-based formulations of the drug at the highest approved dosages (3–5 mg/kg or higher) (see Chapter 3). This should be continued until the patient recovers, or for at least 2 weeks before reverting to conventional amphotericin B. Lipid-based amphotericin B is also recommended for patients in whom the conventional formulation is contraindicated because of renal impairment, or who develop side-effects that would otherwise necessitate discontinuation of the drug. The results of open-label clinical trials have demonstrated that these new formulations are at least as effective as conventional amphotericin B in patients with aspergillosis, and that they can be of benefit when the conventional preparation is not.

Voriconazole proved superior to amphotericin B for induction treatment of invasive aspergillosis in a large open randomized trial, and has been approved as a first-line agent for the treatment of this disease. Treatment should be started with an intravenous loading dose of 6 mg/kg at 12-h intervals for two doses followed by 4 mg/kg at 12-h intervals. Each dose should be infused over a 1–2-h period. Once the patient can tolerate oral medication, the usual adult dose is 200 mg at 12-h intervals (see Chapter 3).

Itraconazole is also an effective agent for the treatment of invasive aspergillosis, although its use is limited by a number of important drug interactions (see Chapter 3). In addition, poor absorption has been a serious problem with the original oral capsule formulation of this agent, particularly in neutropenic patients and HSCT recipients, and blood concentrations should be measured at regular intervals. Higher dosages or substitution of the oral solution formulation should ensure adequate blood levels (see Chapter 3).

The recommended oral dose of itraconazole is 200 mg at 12-h intervals, but some clinicians have used loading doses of 600 mg/day at the start of treatment. Capsules should be taken with meals, but the oral solution should be taken without food. The recommended intravenous

dose is 200 mg at 12-h intervals for four doses followed by 200 mg/day for up to 2 weeks. Each dose should be infused over a 1-h period.

The echinocandin agent, caspofungin, has been approved for the treatment of invasive aspergillosis in patients who have failed to respond to, or are intolerant of, other antifungal agents. Treatment should be started with an intravenous loading dose of 70 mg followed by 50 mg/day thereafter. Each dose should be infused over a 1-h period (see Chapter 3).

The optimum duration of antifungal treatment has not been established, but it is dependent on the extent of the infection, the response to treatment, and the patient's underlying disease. Treatment should be continued for as long as the patient is immunocompromised and until there has been complete or near complete resolution of disease. In neutropenic patients this means continuing treatment until the neutrophil count is greater than 1×10^9/L and until relevant clinical and radiological abnormalities are resolved. This can take weeks or months. AIDS patients and organ transplant recipients also require long-term treatment. Clinicians often prefer to change from parenteral amphotericin B treatment to an oral triazole after the first 2–3 weeks. This is reasonable provided that the patient has no problems with itraconazole absorption.

Because it has become clear that the earlier the treatment is started the better the prognosis, it has become common practice to begin empirical amphotericin B treatment without waiting for formal proof that a patient who remains febrile and profoundly neutropenic for 5 days or longer, despite the administration of broad-spectrum antibacterial agents in adequate dosage, has aspergillosis. Empirical treatment should be initiated with the usual test dose (1.0 mg) of amphotericin B. If possible, the full therapeutic dosage level (1.0 mg/kg of the conventional formulation) should be reached within the first 24 h of treatment. There is no need for gradual escalation of dosage. The duration of empirical treatment will differ from individual to individual (see Chapter 3).

Neutropenic patients with apparently resolved aspergillosis may suffer from reactivation of the infection during subsequent periods of immunosuppression. One

solution to this problem is to begin empirical treatment with amphotericin B (1.0 mg/kg per day of the conventional formulation) not less than 48 h before immunosuppressive treatment is recommenced. The drug should then be continued until the neutrophil count has recovered.

Some clinicians recommend immediate surgical resection of one or more localized *Aspergillus* lesions in the lungs during neutropenia. Most, however, reserve lung resection for patients with persistent *Aspergillus* infection who require further induction treatment or HSCT, for those with significant haemoptysis, or for those with focal lesions in a central location (near the mediastinum). The latter group is at higher risk of death from perforation of a bronchus, the trachea or one of the great vessels, and rapid surgical intervention is essential.

10.7.2 Tracheobronchitis and obstructing bronchial aspergillosis

In AIDS patients, *Aspergillus* tracheobronchitis can sometimes be controlled with amphotericin B (1.0 mg/kg per day) or itraconazole (400 mg/day). The absorption of itraconazole in late-stage AIDS is often poor, and interactions with other drugs (such as rifampicin) can be a problem. Blood concentrations of itraconazole should be measured at regular intervals.

Patients with obstructing bronchial aspergillosis often respond to oral treatment with itraconazole (400 mg/day).

10.7.3 Acute invasive sinusitis

Immunocompromised patients with acute invasive sinusitis should be treated with amphotericin B (1.0–1.5 mg/kg per day). If the disease fails to respond to the conventional formulation, treatment should be changed to one of the lipid-based formulations of the drug at dosages of 3–5 mg/kg or higher (see Chapter 3). This should be continued until the patient recovers, or for at least 2 weeks before reverting to conventional amphotericin B. Lipid-based amphotericin B is also recommended for patients in whom the conventional formulation is contraindicated because of renal

impairment, or who develop side-effects that would otherwise necessitate discontinuation of the drug.

Treatment should be continued at least until progression of disease ceases and the underlying disorder is well controlled. Surgical debridement of infected sinus material is useful, but carries the risk of haemorrhage in thrombocytopenic patients.

10.7.4 Cerebral aspergillosis

Cerebral aspergillosis is an infection that has a dismal prognosis and even with aggressive treatment, most patients will die. The lesions are often located deep in the brain and are difficult to remove without causing serious damage. A few patients have survived following surgical resection and treatment with high doses of the liposomal formulation of amphotericin B. There are also anecdotal reports of patients who have recovered following treatment with high doses of voriconazole or itraconazole.

10.7.5 Cutaneous aspergillosis

The management of this disease depends on the extent of the infection and the underlying status of the patient. Systemic antifungal treatment is recommended for neutropenic individuals and most other immunocompromised patients. Amphotericin B (1.0 mg/kg per day) is the historical treatment of choice. In catheter-site infections, removal of the catheter is required in addition to amphotericin B treatment. Surgical debridement is also essential for successful management of lesions that arise at catheter insertion sites. This should not be done until the neutrophil count has recovered.

10.7.6 Pulmonary aspergilloma

There is no consensus concerning the optimal treatment of this disease. Because of potential complications, surgical removal of the lesion should be reserved for high-risk individuals, such as those with life-threatening haemoptysis. On occasion, segmental or wedge resection will suffice, but lobectomy is usually required to ensure complete eradication of the disease. Pulmonary resection is hazardous, owing to the presence of dense vascular adhesions and the risk of *Aspergillus* infection

of the post-surgical space. Serious post-operative complications, such as haemorrhage and bronchopleural fistulae, are common.

If surgical intervention is contraindicated, endobronchial instillation or percutaneous injection of amphotericin B may be helpful. The optimum dosage has not been determined, but 10–20 mg amphotericin B in 10–20 ml distilled water instilled two or three times per week for about 6 weeks has proved successful. Larger doses (40–50 mg) have been instilled into lung cavities using percutaneous catheters.

The treatment of mild to moderate bleeding and asymptomatic patients remains controversial, but observation without intervention may be the best form of management.

10.7.7 Chronic necrotizing pulmonary aspergillosis

Treatment with an antifungal drug, such as itraconazole (200–400 mg/day), will often relieve the symptoms of this condition, but surgical resection of necrotic lung and surrounding infiltrated tissue is usually required to eradicate this form of aspergillosis. Medical treatment is often the best option for older patients with a poor prognosis because of other underlying lung disease. In healthier patients consideration should be given to both parenteral and local administration of amphotericin B, as well as surgical resection.

10.7.8 Chronic invasive sinusitis

Treatment of chronic invasive *Aspergillus* sinusitis consists of extensive surgical debridement, with removal of all necrotic material, combined with amphotericin B at a dose of 1.0 mg/kg per day. The optimum duration and total dose of amphotericin B that should be given have not been defined, and it is not uncommon for this condition to recur, necessitating further surgical intervention. There is limited evidence that long-term suppressive treatment with itraconazole can reduce the rate of recurrence following surgical resection and amphotericin B treatment.

In patients with chronic granulomatous invasive sinusitis, surgical removal of the paranasal granuloma

is recommended. Often, however, complete removal is difficult and the condition will recur, necessitating further surgical intervention. There is some evidence that post-operative treatment with itraconazole (200–400 mg/day for at least 6 weeks) reduces the rate of recurrence.

10.7.9 Paranasal sinus fungus ball

Surgical removal of paranasal sinus fungus balls is recommended. Endoscopic techniques are also adequate, although there have been recurrences with this form of treatment. Antifungal treatment is not indicated. Patients with sphenoid sinus fungus balls are at risk for intracerebral bleed or infarct as a complication of their surgical treatment.

10.7.10 Endocarditis

Aspergillus endocarditis requires aggressive medical and surgical treatment. Treatment with amphotericin B (1.0 mg/kg per day) should be commenced as soon as the diagnosis is made. Because of the poor penetration of the drug into the vegetations and the risk of embolic complications, infected valves should be replaced 1–2 weeks after treatment has started, but earlier surgical intervention is indicated if there are large vegetations, signs of heart failure or dysfunction of a prosthesis. The optimum length of amphotericin B treatment is uncertain, but 2–3 months have been recommended to reduce the likelihood of relapse.

Treatment with a lipid-based formulation of amphotericin B should be considered in patients who fail to respond to the conventional formulation, or who develop side-effects that necessitate discontinuation of the drug.

10.7.11 Osteomyelitis

Amphotericin B (1.0 mg/kg per day) remains the treatment of choice for patients with *Aspergillus* osteomyelitis, but successful management usually requires aggressive surgical debridement of necrotic tissue. Itraconazole penetrates bone well, and long-term treatment with this drug (400 mg/day) has sometimes proved successful.

10.7.12 Endophthalmitis

Aspergillus endophthalmitis requires both medical and surgical treatment. Penetration of amphotericin B and itraconazole into the vitreous and aqueous humours following parenteral administration is inadequate to treat this infection. Intravitreal administration of amphotericin B results in inflammation and retinal damage, but doses up to 10 μg can be tolerated. Vitrectomy is an essential part of the management of this infection.

10.7.13 Allergic bronchopulmonary aspergillosis

Management of this disease is directed at treating the acute asthmatic exacerbations and avoiding end-stage fibrosis. Mild disease may not require treatment. Increasing serum IgE concentrations and new or worsening infiltrates on chest radiographs are among the findings that suggest that corticosteroids should be used. Prednisone is the drug of choice because it is effective in reducing symptoms, improving chest radiographs, and abolishing positive sputum cultures. The usual dosage regimen is 1.0 mg/kg per day until radiographs are clear, then 0.5 mg/kg per day for 2 weeks. The same dose is again given at 48-h intervals for another 3–6 months, and then the dose is tapered off over another 3 months. The initial regimen should be resumed if the condition recurs. Bronchodilators and postural drainage may help to prevent mucus plugging.

The role of antifungal drug treatment is unclear, but itraconazole appears useful as a corticosteroid-sparing agent in several non-comparative trials. More recently, a randomized trial showed that itraconazole, at a dose of 200 mg/day for 16 weeks, had a beneficial effect.

10.7.14 Allergic sinusitis

Treatment of allergic *Aspergillus* sinusitis consists of surgical debridement to remove polyps and the allergic mucin containing fungal debris which is thought to be the cause of the immune reaction in the sinus mucosa. More than one surgical procedure may be required to accomplish this goal. Adjunctive medical management is also required because it is unlikely that all fungal debris can be removed. Despite surgical debridement

and post-operative systemic corticosteroid treatment, the condition recurs in up to two-thirds of patients.

There is no evidence that oral or topical antifungal treatment is of benefit in allergic fungal sinusitis.

10.8 Prevention

Because the diagnosis and treatment of invasive aspergillosis is difficult, and because the mortality rate from this disease exceeds 90% in some high-risk patient groups, preventive measures have become an issue of major importance in the management of all high-risk groups. These measures can be divided into two main approaches: environmental precautions and antifungal drug prophylaxis.

10.8.1 Environmental strategies

Aspergillus infection can be acquired following a wide range of exposures inside or outside the hospital environment. Because most cases of invasive aspergillosis either start in, or are confined to, the lungs, and because *Aspergillus* spores are commonly found in the indoor and outdoor air, inhalation is thought to be the usual mode of infection in humans. Therefore the first steps in the prevention of infection in high-risk patients should consist of measures to reduce or eliminate obvious sources of environmental exposure, such as removing plants and flower arrangements from rooms where these individuals are being treated. Food items, such as spices, that are often contaminated with moulds should not be offered to immunocompromised patients. Thorough and regular cleaning of all surfaces should be undertaken to prevent dust accumulation.

It has been shown that high efficiency particulate air (HEPA) filtration can reduce or even eliminate *Aspergillus* spores from the air. Caring for high-risk patients in hospital rooms supplied with HEPA filtration has led to reduced rates of nosocomial *Aspergillus* infection. Components of a protected hospital environment should include a well-sealed room, HEPA filtration of incoming air, direct (or laminar) airflow within the room, positive room air pressure relative to the corridor, and high rates of room air exchange. This approach is expensive, and

while it is feasible for the highest-risk groups for limited periods, housing patients in rooms supplied with sterile air has never been cost-effective for all groups at risk. Moreover, *Aspergillus* infection can develop if patients are colonized before their admission to hospital, or are moved from the protected environment to other parts of the hospital for essential procedures to be performed. Improper operation or poor maintenance of even the most elaborate ventilation systems can lead to nosocomial outbreaks of infection.

Hospital water has been suggested as another possible source of *Aspergillus* infection in hospitals. Although *Aspergillus* has been recovered from hospital showerheads and hot water taps, further work is needed to confirm transmission from water and the proportion of cases it accounts for. In addition to hospital-based investigations, it will be essential to conduct epidemiological studies to look for potential sources of waterborne infection in the home environment.

Immunocompromised individuals should not be treated in units with ongoing, adjacent construction work, but if this cannot be avoided, measures should be instituted to minimize the entry of dust and contaminated air. Patient care areas should be sealed off from areas of hospital construction by plastic sheeting or other suitable barriers.

Strict environmental control measures do not appear to be a practical option for patients who are being managed on an outpatient basis. Nevertheless, individuals should be advised to avoid high-risk activities, such as house cleaning and gardening, that might result in increased exposure to *Aspergillus* spores.

10.8.2 Therapeutic strategies

Environmental control measures, designed to protect high-risk individuals from exposure to *Aspergillus* spores in the hospital or at home, are difficult. For this reason, novel approaches to prevention are needed. These include the use of antifungal prophylaxis, although there is currently only limited evidence that the available agents are effective in reducing the incidence of aspergillosis.

Itraconazole prophylaxis has been widely employed to prevent invasive aspergillosis, but few large comparative trials have been conducted and its usefulness remains controversial. It is unfortunate that the rate of mould infections in these trials was too low to establish whether itraconazole, at dosages of 200–400 mg/day, is effective in preventing the development of aspergillosis. Numerous anecdotal reports of breakthrough infection occurring while patients were receiving low-dose parenteral amphotericin B (up to 0.25 mg/kg per day) indicate that this approach is unreliable as prophylaxis against aspergillosis in neutropenic cancer patients and transplant recipients. Lipid-based formulations of amphotericin B are less nephrotoxic, but more expensive, and have not been clearly shown to provide effective prophylaxis. The efficacy of nebulized amphotericin B, administered by inhalation, as prophylaxis is also unproven.

Because the efficacy of prophylaxis against invasive aspergillosis has not been clearly established, azole prophylaxis of all immunocompromised patients does not appear to be justified. However, now that high-risk patients are spending more time outside the hospital setting, the cost-benefit of prophylaxis with itraconazole, as well as with the newer oral agents such as voriconazole, requires careful evaluation. The high incidence of infection, coupled with a high mortality rate, supports the use of azole prophylaxis in those individuals at highest risk of developing aspergillosis. These include high-risk patients nursed in units without HEPA filtration of incoming air or where building work is being undertaken, as well as allogeneic HSCT recipients receiving corticosteroids for GVHD, HSCT recipients with delayed engraftment, other patients with prolonged neutropenia, and liver and lung transplant recipients.

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11 Invasive candidosis

11.1 Definition

The term candidosis (candidiasis) is used to refer to infections due to organisms belonging to the genus *Candida*. In addition to causing mucosal and cutaneous infection (see Chapter 5), these opportunist pathogens can cause acute or chronic invasive infection in immunocompromised or debilitated individuals. This may be confined to one organ or become widespread (disseminated candidosis).

11.2 Geographical distribution

These conditions are worldwide in distribution.

11.3 The causal organisms and their habitat

Candida albicans is the predominant cause of both superficial and invasive forms of candidosis, although the proportion of serious infections attributed to other members of the genus is rising. There is, however, considerable variation in the range of organisms isolated in different hospitals and different patient groups. *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis* have become significant causes of human infection. Other species, such as *C. dubliniensis*, *C. guilliermondii*, *C. inconspicua*, *C. lusitaniae*, *C. norvegensis* and *C. rugosa*, have been isolated from occasional patients. It has been suggested that the intrinsic resistance of some of these species, particularly *C. glabrata* and *C. krusei*, to fluconazole might be a factor in their emergence as pathogens. It should, however, be noted that many hospitals have reported no increase in the incidence of infections with azole-resistant *Candida* species, despite the widespread use of fluconazole.

C. albicans is found in the mouth and gastrointestinal tract of around 30–50% of normal individuals, but much higher isolation rates have been recorded among patients receiving medical attention. Although *C. albicans* is still the most prevalent species recovered from

both normal and sick individuals, it appears to be less common in the environment than many other *Candida* species. *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis* have also been recovered from the digestive tract of normal individuals. In addition, *C. parapsilosis* is a frequent colonizer of the skin.

11.4 Epidemiology

In most cases, invasive *Candida* infection is endogenous in origin, but transmission of organisms from person to person can also occur. In the healthcare setting, the main mechanisms of cross-infection include direct patient-to-patient transmission; transmission from a colonized or infected person to a recipient via a third person, often a healthcare worker; transmission from a colonized or infected person to another individual via a medical device; and more or less simultaneous transmission to two or more patients from a common source, such as contaminated intravenous infusions. In most reports of outbreaks or cross-infections due to *C. albicans* in intensive care unit (ICU) patients, the suspected or proven source has been the hands of healthcare workers. In contrast, most outbreaks of *C. parapsilosis* infection among ICU patients have been linked to nosocomial acquisition via medical devices such as vascular catheters, and/or parenteral nutrition. There are also a few reports of *C. parapsilosis* cross-infection related to hand carriage by healthcare workers.

Invasive forms of candidosis are a significant problem in several distinct groups of hospitalized patients. These groups include neutropenic cancer patients and recipients of haematopoietic stem cell transplants (HSCT); recipients of liver transplants; and patients who have been hospitalized in an ICU, particularly adult surgical and neonatal units. More cases of invasive candidosis now occur among ICU patients than are diagnosed among neutropenic individuals. The reduction in incidence of the disease among high-risk cancer patients and HSCT recipients has been attributed to the widespread use of fluconazole in these groups. The predominant pathogen is still *C. albicans*, but the number of serious infections due to less susceptible species, such as *C. glabrata*, has increased.

Invasive candidosis is not a notifiable disease. As a result, most of the published data on the incidence of this infection have been derived from individual institutions. These studies sometimes have similar designs, but different denominators have been used, making it difficult to compare rates of infection. Although still few in number, sentinel and population-based surveillance programs have helped to define changing trends in species distribution, and have served to highlight the growing importance of *Candida* species as compared with other groups of hospital-associated pathogens.

Between 1980 and 1989, the incidence of candidosis as a hospital discharge diagnosis in the USA increased almost threefold, from 1.4 to 3.8 cases per 1000 admissions; cases of disseminated candidosis increased elevenfold to 0.15 per 1000 admissions over this period. Longitudinal data from the Centers for Disease Control and Prevention (CDC) National Nosocomial Infections Surveillance (NNIS) program showed that the rate of nosocomial fungal infections almost doubled between 1980 and 1989, and that *Candida* species accounted for almost 80% of these infections. In the mid-1990s, data from the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) sentinel surveillance program showed that *Candida* species remained the fourth most common cause of nosocomial bloodstream infection, and were responsible for 8% of all bloodstream infections in US hospitals.

More recently, data from more than 300 North American hospitals participating in the NNIS sentinel program showed that the incidence rate of *Candida* bloodstream infections among patients in ICUs decreased during the 1990s. This decline was largely due to a reduction in the rate of *C. albicans* infections, from over 8 cases per 10 000 catheter days in 1989 to only 2 cases per 10 000 catheter days in 1999. However, the rate of *C. glabrata* infections increased significantly over the same period. The incidence of infections caused by other *Candida* species remained unchanged. Population-based surveillance programs conducted in the USA during 1992–1993, and again during 1998–2000, showed that the overall incidence of *Candida* bloodstream infections increased from 8 to 10 cases per 100 000 population

between the two periods. Incidence rates were highest among black neonates (158 per 100 000).

Sentinel and population-based surveillance programs have enabled trends in the rank order of species distribution to be studied. In one of the earliest efforts, the CDC population-based surveillance program conducted during 1992–1993, *C. albicans* was found to be the most common cause of *Candida* bloodstream infections (52% of cases) followed in order by *C. parapsilosis*, *C. tropicalis* and *C. glabrata*. Subsequent surveillance programs in the USA have noted an increase in the proportion of bloodstream infections caused by species other than *C. albicans,* and especially an increase in the rate of infections caused by *C. glabrata*. In contrast, surveillance data from other countries continue to reflect the importance of *C. parapsilosis* over *C. glabrata*. Several programs have demonstrated a significant trend towards an increased proportion of bloodstream infections due to *C. glabrata* with increasing patient age. In neonates, *C. albicans* has long been the leading cause of *Candida* bloodstream infection, followed by *C. parapsilosis* and *C. tropicalis*. However, several recent reports have documented a decrease in the proportion of infections due to *C. albicans* and an increase in the proportion of *C. parapsilosis* infections.

Many risk factors for invasive candidosis have been described. These can be divided into host-related factors, such as underlying immunosuppression and low birth weight, and healthcare-related factors, such as intravascular catheterization, broad-spectrum antibiotic use, total parenteral nutrition, haemodialysis and surgical procedures. Among adult patients cared for in surgical ICUs, *Candida* bloodstream infection has a case–fatality ratio of about 40%. The major risk factors independently associated with candidosis in this setting include previous surgical procedures, acute renal failure, and receipt of parenteral nutrition. In addition, triple-lumen catheters have been associated with an increased risk of infection among surgical patients. However, not all patients in the surgical ICU are at equal risk of invasive candidosis. Those who undergo neurosurgical or ear, nose and throat procedures appear to be at lowest risk, while those who undergo abdominal pro-

cedures are at the highest risk. Invasive *Candida* infections are infrequent if adequate closure and resolution of the underlying problem is achieved. However, complications, such as anastomotic breakdown and recurrent abdominal leakage, are important predisposing factors that identify a high-risk subgroup who might benefit from antifungal prophylaxis.

The incidence of *Candida* bloodstream infection among pre-term infants in neonatal ICUs has increased since the 1980s. The condition has been reported in 1% of infants in neonatal ICUs and in 2–5% of very low-birth-weight infants. When birth weight is adjusted for, other risk actors include gestational age of <32 weeks; 5 min activity, pulse, grimace, appearance, respiration (APGAR) score of <5; receipt of parenteral nutrition, H2 blocker treatment and intubation. Differences in the incidence of *Candida* bloodstream infection between white and black infants have been reported from the USA, with rates among black infants being 2–3 times higher than among white infants. These differences have been attributed to the higher prevalence of low birth weight among black infants.

Without chemoprophylaxis, invasive candidiasis develops in about 15–20% of allogeneic HSCT recipients. In this setting, the condition has a case–fatality ratio of 40–50%. With fluconazole chemoprophylaxis, the case–fatality ratio has fallen to around 20%, largely due to the virtual elimination of *C. albicans* and *C. tropicalis* infections. Recent reports suggest that risk factors such as prolonged neutropenia, patient age, receipt of corticosteroids, and presence of acute graft-versus-host disease (GVHD) are less significant predictors of *Candida* bloodstream infections in patients receiving fluconazole. Other factors, including prior colonization, bacteraemia and cytomegalovirus infection now appear to be significant risk factors for the development of *Candida* infections in HSCT recipients.

Among recipients of solid organ transplants, invasive candidosis is most prevalent in liver and pancreatic transplant recipients. In earlier reports, the disease was documented in 16–30% of liver transplant recipients. More recently, many transplant units have reported an

incidence of less than 10%, even without fluconazole prophylaxis. Improved methods of immunosuppression and surgical technological improvements are among the factors that are thought to have led to this reduction in incidence of candidosis. The major risk factors independently associated with invasive *Candida* infection in this setting include renal failure; high transfusion requirement during operation; retransplantation; choledochojejunostomy; and fungal colonization detected within the first 3 days after transplantation. The risk for candidosis following pancreatic transplantation is similar to that following liver transplantion. Up to 10% of pancreatic transplant recipients have developed intra-abdominal infection after transplantation.

In all risk groups, previous colonization is an independent risk factor for bloodstream infection with all *Candida* species except *C. parapsilosis* (perhaps because this species is usually acquired through an indwelling catheter). The risk of infection increases with the number of sites colonized, but depends on the colonizing species (*C. tropicalis* colonization is more predictive of infection than *C. albicans* colonization). The extent of colonization, expressed in terms of the number of sites colonized, has sometimes been helpful in predicting invasive *Candida* infections in surgical patients receiving intensive care.

11.5 Clinical manifestations

11.5.1 Acute disseminated candidosis and candidaemia

Candidaemia is defined as the isolation of *Candida* species from one or more blood cultures. It can lead to the development of deep-organ candidosis, or follow the development of such an infection. It is a critical diagnostic sign of acute disseminated candidosis, which is defined as infection of two or more non-contiguous organs following haematogenous spread. Acute disseminated candidosis is most commonly seen in seriously ill individuals who usually have one or more indwelling vascular catheters, although these are not necessarily the source of the infection. Many cases are thought to arise from translocation of organisms across the wall of the intestinal tract. In this situation, haematogenous spread can then lead to catheter colonization.

Adults with candidaemia usually present with a persistent fever that fails to respond to broad-spectrum antibacterial treatment, but with few other symptoms or clinical signs. Macronodular cutaneous lesions (seen in about 10% of neutropenic individuals, but rare in ICU patients) and endophthalmitis (found in up to 45% of ICU patients, but seldom seen in neutropenic individuals) are useful clinical signs of acute disseminated candidosis. Other manifestations include meningitis, brain abscess, renal abscess, myositis, myocarditis and endocarditis. Late complications include osteomyelitis and septic arthritis. Occasional patients present with septic shock which has a poor prognosis. Others present with minimal symptoms and the isolation of *Candida* species from blood cultures may be the only evidence of invasive candidiasis. It was this group of patients who gave rise to the term 'benign transient candidaemia', a condition which was thought not to require antifungal treatment. This has now been shown to be a hazardous interpretation, given the high incidence of metastatic complications.

In neonates, invasive candidosis can present as candidaemia, as single organ candidosis, or as disseminated candidosis. The disease is most common in low-birth-weight infants (<1500 g) requiring prolonged neonatal intensive care. It usually presents at between 2 and 5 weeks of life with non-specific signs, such as deteriorating respiratory function, apnoea, bradycardia, acidosis, fever and abdominal distension. Septic shock has also been reported. Prolonged vascular catheterization, tracheal intubation, parenteral nutrition and broad-spectrum antibacterial treatment are among the important risk factors for disseminated candidosis in low-birth-weight infants. Meningitis occurs more frequently than in older patients and is sometimes associated with arthritis and osteomyelitis. Renal involvement is another common manifestation. Endophthalmitis is rare.

C. albicans is the leading cause of *Candida* bloodstream infection in pre-term infants. However, several recent reports have documented an increase in the proportion of *C. parapsilosis* infections in this group. Comparisons of neonatal bloodstream infections due to

C. albicans and *C. parapsilosis* have demonstrated no significant differences in the overall mortality rate.

11.5.2 Chronic disseminated candidosis

This is an indolent illness which occurs in leukaemic patients who have regained an adequate neutrophil count after remission induction treatment. It has sometimes been called hepatosplenic candidosis, but lesions are found in other organs as well.

In most cases, the infection begins while the patient is neutropenic and presents as a persistent fever that fails to respond to broad-spectrum antibacterial treatment. There are no discernible lesions in any organ, nor are there signs of infection in any particular organ. The neutrophil count then returns to normal, but the fever persists and is often associated with continuing weight loss. The patient may complain of abdominal pain, and hepatic and/or splenic enlargement may be detected. Many patients have highly elevated blood levels of alkaline phosphatase, but other liver function abnormalities may be mild or absent. The diagnosis should be suspected if computed tomographic (CT) scans reveal numerous, small radiolucent lesions in the liver or spleen.

Microscopic examination of stained sections of biopsied tissue will often confirm the diagnosis, but the organism is isolated from no more than 30% of specimens. In most cases blood cultures are negative. *C. albicans* is the principal aetiological agent, but *C. tropicalis* has sometimes been implicated.

11.5.3 Lower urinary tract candidosis

The presence of *Candida* species in the urine is sometimes indicative of renal candidosis, but more commonly it represents lower urinary tract colonization or infection due to the presence of an indwelling urinary catheter. The clinical presentation is varied, but unlike those with bacterial infections, most patients with candiduria have no symptoms. Candiduria tends to persist while the catheter is *in situ*, whether or not antifungal treatment is given. In most cases, however, the problem resolves with the removal of the catheter.

Although *C. albicans* is the commonest organism, *C. glabrata* accounts for up to 30% of isolations from

the urine. *C. glabrata* is often recovered from patients with urethral catheters and individuals with diabetes mellitus. It is often resistant to antifungal treatment (see Chapter 3).

11.5.4 Renal candidosis

It is much more common for renal candidosis to result from the haematogenous spread of organisms than for it to occur as a result of ascending infection. At least 80% of patients with disseminated candidosis develop renal infection. For this reason, invasive infection should be suspected in a septic patient with persistent candiduria. Renal infection often results in abscess formation. Less commonly, it results in the formation of clumps of mycelium (fungus balls) which can obstruct the pelvis or ureters leading to hydronephrosis or anuria.

In adults, the symptoms of renal candidosis include fever, rigors, lumbar pain and abdominal pain. There are no specific radiological signs, apart from fungus balls in the renal pelvis or ureters, which appear as radiolucent, irregular filling defects. Pyuria is not a consistent indicator of infection. In neonates, renal candidosis can be asymptomatic or present with oliguria, anuria, haematuria and hypertension. Up to 35% of infants with candiduria have fungus balls that obstruct the pelvis or ureters leading to hydronephrosis.

11.5.5 Pulmonary candidosis

This condition is most common among neutropenic patients, but it has also been described in those receiving intensive care. It is seldom diagnosed during life due to difficulties in distinguishing lower respiratory tract colonization from infection. It can arise following haematogenous dissemination of organisms or as a result of aspiration of colonized oropharyngeal or gastric contents.

The clinical and radiological presentation is nonspecific. Patients present with fever, tachypnoea and diffuse nodular infiltrates on chest radiographs, indistinguishable from other causes of nosocomial pneumonia. Microscopic examination and culture of bronchoalveolar lavage (BAL) specimens cannot distinguish colonization from infection. The definitive diagnosis of this form

of candidosis depends on the histopathological demonstration of organisms in lung tissue with associated inflammation.

11.5.6 Osteomyelitis and arthritis

Osteomyelitis is an uncommon form of candidosis. It usually occurs as a late complication of the haematogenous dissemination of organisms in neutropenic patients and low-birth-weight infants. It can also result from direct inoculation following surgical or accidental trauma. In adult patients the lumbar spine is often involved. The commonest symptom is local pain, but fever is often absent. The infection gives rise to characteristic osteolytic lesions.

Arthritis is usually the result of haematogenous dissemination, but it can also result from the inadvertent inoculation of organisms into the joint during aspiration, or injection of corticosteroids, or during insertion of a prosthetic joint replacement. The symptoms include indolent joint pain and effusion. The large joints are most commonly involved.

11.5.7 Peritonitis

Candida peritonitis is one of the most common forms of candidosis among patients in intensive care. *Candida* species form part of the normal flora of the human digestive tract, and can often be isolated from abdominal drain fluid specimens from patients with perforation of the gastrointestinal tract or a leaking intestinal anastomosis. The clinical significance of *Candida* isolation from these specimens is often unclear, but it appears that intra-abdominal candidosis is primarily associated with acute pancreatitis or persistent gastrointestinal leakage. The symptoms and signs of *Candida* peritonitis are similar to those of bacterial peritonitis. The commonest symptoms are fever, abdominal pain and tenderness, abdominal distension, and paralytic ileus. *C. albicans* is the commonest pathogen, but *C. tropicalis* and *C. parapsilosis* are sometimes involved.

Candida peritonitis is an uncommon complication of peritoneal dialysis. The isolation of *Candida* species from polymicrobial peritoneal fluid cultures suggests

traumatic perforation of the bowel by the Tenchoff catheter.

11.5.8 Endocarditis, myocarditis, pericarditis and other vascular infections

Candida infection is the commonest form of fungal endocarditis, accounting for 30–45% of cases of this disease. Three groups of individuals develop this condition: patients with underlying native valve disease; patients with prosthetic heart valves; and intravenous drug abusers. The aortic and mitral valves are the most frequent sites of infection, but the tricuspid valve is often involved in drug abusers.

In surgical patients, endocarditis tends to occur within the first 2 months after the operation. The prognosis has been poor and more than 80% of patients given antifungal treatment alone have died. Earlier and improved surgical intervention has led to more patients surviving.

The symptoms and clinical signs are similar to those of bacterial endocarditis. The illness may be abrupt in onset or insidious. Fever, weight loss, fatigue and loss of appetite are common, but non-specific, symptoms. Heart murmurs can be detected in 50–90% of patients, and an enlarged spleen in 30–50%. More specific diagnostic signs include large vegetations, large vessel embolization and endophthalmitis. Blood cultures are positive in up to 80% of cases, although the disease is often diagnosed post-mortem following histopathological examination and culture of vegetations.

Myocardial infection with abscess formation is a complication of endocarditis, but it may also occur as a result of haematogenous spread of organisms. It has been found in 50% of patients dying with disseminated candidosis. The diagnosis is difficult. Non-specific echocardiogram abnormalities are common.

Purulent pericarditis is an unusual complication of haematogenous dissemination of *Candida* infection. It can arise also from extension of a superficial myocardial abscess. The diagnostic signs are non-specific and include chest pain, pericardial friction rub and pericardial effusion.

Other vascular infections include septic thrombophlebitis of peripheral or central veins and prosthetic graft infections.

11.5.9 Meningitis

Candida meningitis has been reported in up to 60% of low-birth-weight infants with disseminated candidosis. It has a high mortality rate and survivors have a significant incidence of neurological deficits. The presenting signs are non-specific, and cerebrospinal fluid (CSF) findings may be normal. CSF cultures are positive in about 50% of cases.

In adults, *Candida* meningitis is often a post-neurosurgical complication. Prolonged broad-spectrum antibacterial treatment, multiple neurosurgical procedures, prior bacterial meningitis and persistent CSF leakage are significant risk factors. Infection can occur as a result of haematogenous dissemination, direct inoculation of organisms into the subdural space, or retrograde spread along the distal portion of a ventriculoperitoneal shunt (if the distal tip has caused bowel perforation). *Candida* meningitis often follows an indolent course with minimal fever.

The diagnosis is difficult, but *Candida* meningitis should be suspected in a neurosurgical patient with bacterial meningitis who fails to respond to, or deteriorates despite, appropriate antibacterial treatment. It should also be suspected in a patient with other signs of disseminated candidosis who develops neurological signs.

The CSF findings are indistinguishable from those of bacterial meningitis. The protein concentration may be increased, the glucose concentration may be low or normal, and a neutrophilic or lymphocytic pleocytosis may be present. Isolation of a *Candida* species from the CSF confirms the diagnosis; *C. albicans* is the principal aetiological agent.

In adults, many cases are diagnosed by isolation of *Candida* species from CSF obtained through indwelling neurosurgical devices. Multiple isolations from these specimens in patients with clinical sepsis confirms the diagnosis. However, even a single positive CSF culture in a patient with symptoms consistent with

meningitis should prompt the initiation of antifungal treatment.

Other forms of central nervous system candidosis include brain abscess and diffuse metastatic encephalitis. These manifestations are seldom diagnosed during life. Large brain abscesses may give rise to focal neurological signs. The lesions can be detected with CT or magnetic resonance imaging (MRI) scans. More often, however, haematogenous spread of organisms results in multiple small lesions that produce no obvious neurological deficits.

11.5.10 Endophthalmitis and chorioretinitis

Haematogenous dissemination of *Candida* species to the eye can lead to chorioretinitis that can then spread to the vitreous humour to cause endophthalmitis. This condition has been reported to occur in up to 45% of non-neutropenic patients with disseminated candidosis. If left untreated, the infection can progress to retinal necrosis and visual loss and thus early diagnosis and treatment is essential.

The symptoms include blurred vision, ocular pain and floaters. Fundoscopic examination will reveal the typical yellow-white retinal, chorioretinal or vitreoretinal lesions with indistinct borders. The lesions may be unilateral or bilateral and can develop into a vitreous abscess. Extension into the anterior chamber may occur. The definitive diagnosis is made by histopathological demonstration or isolation of a *Candida* species from an intravitreal biopsy specimen. *C. albicans* is the most common cause, but up to 40% of cases are due to other *Candida* species.

11.5.11 Oesophagitis

This condition often develops in persons with the acquired immunodeficiency syndrome (AIDS) or patients undergoing treatment for cancer. It tends to occur in individuals with oral candidosis (see Chapter 5), but, although unusual, can also occur without oropharyngeal involvement. It must be distinguished from cytomegalovirus and herpes simplex virus oesophagitis, which can give rise to similar symptoms and clinical and radiological findings. Up to 30% of AIDS patients

with oesophageal candidosis have concurrent viral oesophagitis. Prior to the introduction of highly active antiretroviral therapy (HAART), *Candida* oesophagitis was the AIDS-defining illness in 10–15% of human immunodeficiency virus (HIV)-infected individuals in the USA.

The principal symptoms are oesophadynia and dysphagia. In patients with more advanced infection, barium contrast radiographs will often reveal irregular ragged mucosal margins, ulcers, large filling defects or oedematous mucosal folds. However, endoscopic examination is required to confirm the cause of the ulceration. The characteristic finding is white plaques with intense inflammation. This method has permitted a diagnosis of oesophageal candidosis to be established in up to 25% of patients with normal oesophagrams.

11.5.12 Gastrointestinal candidosis

Although gastric candidosis is common in debilitated cancer patients, this condition is often asymptomatic and is seldom diagnosed during life. Mucosal ulcerations are the most common lesions, but it is unclear to what extent these are chronic gastric ulcers superinfected with *Candida* species. Perforation can lead to disseminated infection.

Intestinal candidosis is a controversial condition. It is clear that intestinal infection does result in mucosal ulceration in some debilitated individuals with AIDS or cancer. It is much more difficult to be certain whether intestinal colonization leads to illness in less sick individuals. It has been claimed that *Candida* colonization can produce an alarming range of symptoms, including weight loss, headaches, diarrhoea and general malaise. However, these claims have not been subjected to rigorous clinical investigation.

11.5.13 Intrauterine candidosis

Although symptomatic candidosis of the lower genital tract is one of the most common infections encountered in pregnant women (see Chapter 5), foetal infection is unusual. Intrauterine candidosis is believed to result from ascending infection of the maternal genital tract. In most cases, foetal infection follows contamination of

the amniotic fluid. Spontaneous abortion associated with foetal candidosis has been reported in women fitted with an intrauterine contraceptive device.

Intrauterine candidosis presents as multiple small yellow-white lesions scattered over the surface of the umbilical cord. In some cases the fungus affects the foetus and in live births such infections manifest as the characteristic lesions of congenital cutaneous candidosis (see Chapter 5). Umbilical cord lesions are often associated with other lesions which are less characteristic and take the form of diffuse, generalized chorioamnionitis.

11.6 Candidosis in special hosts

11.6.1 Drug abusers

Addicts who inject heroin solutions contaminated with *C. albicans* often develop an unusual form of disseminated candidosis. This consists of a purulent follicular and nodular cutaneous infection associated with ocular and osteoarticular lesions. The symptoms include sudden onset of fever, rigors, headache and myalgia several hours after the injection of heroin. The fever lasts between 24 and 72 h and cutaneous lesions then appear in more than 90% of patients. Endophthalmitis develops in 40–60% of patients, occurring 1–2 weeks after the onset of fever. Osteoarticular lesions develop in 20–30% of patients, appearing 2 weeks to several months after the cutaneous lesions. Costochondral involvement is a frequent and characteristic finding.

11.7 Essential investigations and their interpretation

Establishing the diagnosis of invasive candidosis is difficult because the clinical presentation is varied and non-specific, and because the results of laboratory tests are often difficult to interpret. In most cases, the diagnosis is based on a combination of clinical, radiological, microbiological and histopathological findings. These might include a positive blood culture result, or a positive culture result for a specimen obtained from a normally sterile and clinically or radiologically abnormal site, or histopathological or cytopathological examination showing budding yeast cells or pseudohyphae

consistent with *Candida* in a biopsy specimen or aspirate. The use of antigen detection and polymerase chain reaction (PCR)-based tests has been reported, but the methods are still undergoing evaluation, and their routine use cannot be recommended at present.

11.7.1 Microscopy

The microscopic detection of typical budding yeast cells, pseudohyphae and/or true hyphae of *Candida* species in tissue sections or normally sterile body fluids is indicative of invasive candidosis. Typically, *C. glabrata* produces only yeast cells and only *C. albicans* produces true hyphae in tissues.

11.7.2 Culture

Many *Candida* species are normal commensal inhabitants of the mouth and gastrointestinal tract and their isolation from sputum or faecal specimens cannot be considered diagnostic of infection. Prior colonization has, however, been identified as an independent risk factor for invasive candidosis in adult patients receiving intensive care. Although it is difficult to distinguish between colonization and infection, isolation of *Candida* species from blood or other normally sterile body fluids, or from tissue or aspirates from other closed sites, is usually indicative of deep-seated infection. It is important that specimens are processed as soon as possible after collection to avoid problems of interpretation because of multiplication of organisms. It is recommended that all isolates from blood or other significant sites are speciated before commencing treatment, because of the differing susceptibilities of the various *Candida* species to certain antifungal agents (see Chapter 3).

Blood cultures should be performed in all cases of suspected invasive candidosis. However, it is not unusual for several attempts to be required before the organism is recovered. *Candida* species can be recovered from the blood via a peripheral venous puncture, through an indwelling catheter, from an arterial puncture, or from the tip of a vascular catheter that has been removed and cultured. It is reasonable to attribute the same significance to all these methods. Lysis centrifugation is a more sensitive technique than culture in vented

biphasic media or broth. Blood cultures are positive in no more than 50% of neutropenic patients with disseminated candidosis or 80% of patients with endocarditis.

Isolation of *Candida* from urine is often indicative of serious infection, provided the patient does not have an indwelling urinary catheter. In non-catheterized patients, care must be taken to ensure that vaginal or perineal infection does not lead to contamination of urine specimens. In infants, suprapubic aspiration is the best method of urine collection. A negative urine culture does not exclude invasive candidosis. Isolation of *C. tropicalis* from urine is more often indicative of invasive candidosis than isolation of *C. albicans*. It has been suggested that counts of $>1 \times 10^4$ cfu/ml in a non-catheterized patient should be regarded as significant, but this has never been validated. High counts in a patient with an indwelling urinary catheter are seldom significant.

Isolation of *Candida* from the CSF provides reliable evidence for the diagnosis of meningitis, but often requires repeated culture of large amounts of fluid. All specimens obtained from ventricular shunts or reservoirs should be cultured for *Candida* species.

Particular care must be taken in interpreting the results of sputum culture as this material is often contaminated with organisms from the mouth. Isolation of *Candida* species from BAL in a patient with pulmonary infiltrates is not sufficient to establish a diagnosis of candidosis. Lung biopsies provide more reliable evidence of infection.

11.7.3 Serological tests

Tests for *Candida* antibodies have been extensively evaluated but remain of limited usefulness in the diagnosis of invasive forms of candidosis. These tests are complicated by false-positive results in patients with mucosal colonization or superficial infection, and by false-negative results in immunocompromised individuals. In an attempt to reduce the number of false-positive results, efforts have been made to identify antigens of *Candida* species which are associated with invasive infection rather than colonization. However, despite the numerous methods and reagents which

have been developed for antibody detection, none of them has achieved widespread clinical use.

Antigen detection tests have also been extensively evaluated for the rapid diagnosis of invasive forms of candidosis. Several circulating antigens have been studied as potential targets, including mannan (a heat-stable cell wall component), enolase, proteinase and other immunodominant cytoplasmic antigens. Test formats that have been evaluated include latex particle agglutination (LPA), enzyme-linked immunosorbent assay (ELISA) and dot immunoassay. Several LPA tests for detection of mannan are commercially available in a number of countries. However, these tests have been found to be relatively insensitive.

11.7.4 D-arabinitol detection

Another approach to the diagnosis of invasive candidosis involves the detection in serum or urine of a metabolite, D-arabinitol, which is produced by most of the medically important *Candida* species with the exception of *C. krusei* and perhaps *C. glabrata*. Various methods have been developed to measure D-arabinitol concentrations in human serum and urine, including enzymatic-fluorometric and enzymatic-colorimetric procedures. Because increased levels of arabinitol are also found in human body fluids when renal function is impaired, the results are reported as the D-arabinitol–creatinine ratio. Although several large studies have demonstrated that patients with candidaemia have elevated serum D-arabinitol–creatinine ratios, this approach has still to achieve widespread clinical use.

11.7.5 Molecular diagnostics

Numerous polymerase chain reaction (PCR) based methods have been developed for the detection of *Candida* DNA in blood, serum, CSF and other clinical specimens. Several regions within the *Candida* genome have been evaluated as potential targets for detection, but most effort has focused on the ribosomal DNA gene complex. Both nested and panfungal PCR formats have been employed. More recently, quantitative real-time PCR methods have been developed. Molecular diagnostics appear promising for the rapid diagnosis of *Candida*

infection directly from tissue or body-fluid specimens, but false-positive results can occur and standardized commercial methods are not available. At present, the routine use of PCR in the diagnosis of invasive candidosis cannot be recommended.

11.8 Management

11.8.1 Acute disseminated candidosis and candidaemia

All patients with candidaemia require treatment, regardless of whether or not this is associated with an intravascular catheter. Treatment should be started at once, without waiting for confirmation from further blood cultures. If feasible, all existing central vascular catheters should be removed. The evidence for this recommendation is strongest for non-neutropenic patients. In neutropenic individuals, the gastrointestinal tract is a frequent source for disseminated infection, and routine catheter removal is not justified. An exception is *C. parapsilosis* bloodstream infection, which is often catheter-related and not asssociated with previous colonization.

The choice of antifungal treatment depends on both the clinical status of the patient and the species of infecting organism. In general, bloodstream isolates of *C. albicans*, *C. parapsilosis* and *C. tropicalis* are susceptible to both amphotericin B and fluconazole, and bloodstream infections with these organisms can be treated with either drug. Many isolates of *C. glabrata* are less susceptible to fluconazole, and *C. krusei* (an infrequent cause of bloodstream infection) is resistant to this drug. Many, but not all, isolates of *C. lusitaniae* are resistant to amphotericin B, as are some isolates of *C. glabrata* and *C. krusei*. If amphotericin B is used to treat infections due to *C. glabrata* or *C. krusei*, doses approaching or exceeding 1.0 mg/kg per day may be needed, particularly in immunocompromised patients.

In non-neutropenic patients who are stable (i.e. those who do not have an unexplained fever, are improving, and are not hypotensive), treatment can be initiated with fluconazole (6 mg/kg per day, or 400 mg/day in a 70-kg adult). In those patients who are not stable (i.e. those who have an unexplained fever despite antibacterial antibiotics, are deteriorating or are hypotensive) and

in whom the species of infecting organism has not been determined, amphotericin B (0.7–1.0 mg/kg per day) is often preferred, because of its broader spectrum. In patients with more severe infections, the full dose of amphotericin B (50 mg/day) can be given from the outset (see Chapter 3). Combination treatment with flucytosine (100 mg/kg per day in four divided doses) is another option.

It is still unclear whether fluconazole is as effective as amphotericin B in treating neutropenic patients, or whether it is safe to start treatment with amphotericin B and then change to fluconazole. It is reasonable to use fluconazole (400 mg/day) in neutropenic patients who are stable, provided the infecting organism is susceptible, and provided the patient has not been receiving prophylactic treatment with an azole. Amphotericin B (0.7–1.0 mg/kg per day), with or without flucytosine (100 mg/kg per day), should be used in all other situations.

Caspofungin proved at least as effective as amphotericin B for the treatment of invasive candidosis and candidaemia in a large double-blind randomized trial. There were significantly fewer drug-related adverse events in the group of patients treated with the echinocandin agent. Treatment with caspofungin should be started with an intravenous loading dose of 70 mg followed by 50 mg/day thereafter. Each dose should be infused over a 1-h period (see Chapter 3).

The drug of choice for neonatal candidosis is amphotericin B (1.0 mg/kg per day), with or without flucytosine (100 mg/kg per day) (provided the infecting organism is susceptible). The latter drug is useful because of the high incidence of meningitis in this age group. The half life of flucytosine is prolonged in small infants and the drug should be administered at 12- or 24-h intervals. Fluconazole (5 mg/kg per day) is another option.

Lipid-based formulation of amphotericin B have been approved for the treatment of candidosis in patients who have failed to respond to the conventional parenteral formulation, or who have developed severe side-effects to conventional amphotericin B, or in whom conventional amphotericin B is contraindicated because

of renal impairment. The results of a large randomized trial demonstrated that amphotericin B lipid complex (5 mg/kg per day) was less toxic, but as effective as conventional amphotericin B (0.6–1.0 mg/kg per day) in treating candidaemia.

In patients with candidaemia, treatment should be continued for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection. If the response to amphotericin B is rapid or if the patient was less seriously ill at the outset, it is reasonable to change to fluconazole (400 mg/day) after 1–2 weeks.

The shortcomings of current methods of diagnosis often require clinicians to proceed to amphotericin B treatment without waiting for formal proof that a patient who remains febrile and profoundly neutropenic for 5 days or longer, despite the administration of broad-spectrum antibacterial agents in adequate dosage, has a fungal infection. Empirical treatment should be initiated with the usual test dose (1 mg) of amphotericin B. If possible, the full therapeutic dosage level (0.7–1.0 mg/kg per day of the conventional formulation) should be reached within the first 24 h of treatment. There is no need for gradual escalation of dosage. The duration of empirical treatment will differ from individual to individual (see Chapter 3). Several large clinical trials have demonstrated that lipid formulations of amphotericin B are less toxic, but as effective as the conventional formulation in preventing *Candida* infections.

The role of empirical treatment in the management of suspected disseminated candidosis in febrile non-neutropenic patients has not been defined. If such treatment is given, it is recommended that its use be limited to patients with multiple sites of *Candida* colonization, multiple other risk factors and no other uncorrected causes of fever.

11.8.2 Chronic disseminated candidosis

Administration of oral fluconazole (400 mg/day) has proved successful in cancer patients with chronic disseminated candidosis (hepatosplenic candidosis). This is now the preferred treatment option for individuals who are stable. Amphotericin B (0.7–1.0 mg/kg per day) is

recommended for acutely ill patients and those who are not responding to fluconazole treatment. Another option is to give all patients an initial 1–2-week course of amphotericin B, followed by a prolonged course of fluconazole.

Treatment should be continued until clinical signs have resolved and calcification or resolution of the lesions has occurred. Premature discontinuation of treatment can lead to recurrent infection.

11.8.3 Lower urinary tract candidosis

Asymptomatic individuals with persistent candiduria and an indwelling urinary catheter should have the catheter changed, but do not require antifungal drug treatment. Candiduria should be treated in symptomatic patients, neutropenic patients, low-birth-weight infants, renal transplant recipients and patients undergoing multiple manipulations. Removal of stents and catheters is often helpful, but if complete removal is not possible, placement of new materials can be beneficial. Oral treatment with fluconazole (200 mg/day) for 1–2 weeks is the simplest and best option for candiduria. However, it should not be used to treat *C. glabrata* or *C. krusei* infections. Amphotericin B (0.3–1.0 mg/kg) for 1–7 days has also been used.

Local instillation of an antifungal drug is reasonable in individuals with persistent candiduria related to an indwelling urinary catheter, provided there are no signs of pyelonephritis, or of renal or ureteric obstruction. These patients often respond following catheter change and intermittent instillation (200–300 ml of a 50 mg/L solution in sterile water at 6–8-h intervals) or continuous irrigation with amphotericin B (50 mg/L in sterile water) for 5–7 days.

11.8.4 Renal candidosis

There are three basic approaches to the management of renal candidosis: local irrigation of the renal pelvis with antifungal drugs, oral or parenteral treatment with antifungals, and surgical removal of obstructions or resection. In practice, a combined approach is often required.

Amphotericin B (1.0 mg/kg per day), with or without flucytosine (100 mg/kg per day), remains the treatment

of choice for renal candidosis. Fluconazole is excreted unchanged and in high concentrations in the urine. Its use is still under evaluation, but it is a useful alternative to amphotericin B, provided the infecting organism is susceptible. It should not be used to treat *C. glabrata* or *C. krusei* infections. The recommended dose of fluconazole is 400 mg/day, but this may need to be modified in patients with impaired renal function (see Chapter 3).

11.8.5 Pulmonary candidosis

Candida pneumonia is often a lethal infection. In most cases, however, isolation of *Candida* species from sputum or BAL fluid is indicative of tracheobronchial or oropharyngeal colonization. If a patient is to be treated for presumptive *Candida* pneumonia without histopathological confirmation, only those with a persistent infiltrate despite treatment with broad-spectrum antibacterial agents, and with multiple positive sputum cultures for *Candida* species, should be selected. Anecdotal reports suggest that amphotericin B (0.7–1.0 mg/kg per day) is effective.

11.8.6 Osteomyelitis and arthritis

Amphotericin B (0.7–1.0 mg/kg per day for 6–10 weeks), with or without flucytosine (100 mg/kg per day), remains the treatment of choice for *Candida* osteomyelitis. Debridement of necrotic bone (with bone grafting at the same procedure) is recommended if extensive vertebral destruction is present. Fluconazole (400 mg/day for 6–12 months) has proved effective in a few patients.

In patients with infected non-prosthetic joints, parenteral amphotericin B (1.0 mg/kg per day for 6–10 weeks) is the most appropriate treatment. If there is no improvement within a week, flucytosine (100 mg/kg per day) can be added (provided the organism is susceptible). Fluconazole (400 mg/day for 6–12 months) has proved effective in a few patients. Adequate and/or repeated drainage is often essential for treatment to be successful. In particular, management of *Candida* arthritis of the hip requires open drainage. Intra-articular injection of amphotericin B is seldom required, and its use is now discouraged.

In patients with infected prosthetic joints, treatment involves removal of all foreign material and necrotic bone tissue. Subsequent medical treatment is the same as that for native joint disease, and a new prosthesis can be inserted after successful eradication of the infection. This is defined by lack of return of symptoms following cessation of antifungal treatment. Eradication of infection is often difficult to achieve, and long-term maintenance treatment with an azole may be an alternative, particularly in older patients.

11.8.7 Peritonitis

It is not unusual for *Candida* species to be recovered from abdominal drains in a post-operative patient receiving intensive care. If the individual is stable, is asymptomatic with respect to a possible peritoneal infection or an intra-abdominal abscess, and is not growing *Candida* species from other sites, antifungal treatment may not be needed. If, however, the patient is febrile despite appropriate antibacterial treatment and is at high risk for disseminated candidosis, antifungal treatment should be administered. *Candida* peritonitis due to intra-abdominal leakage of faecal material first requires surgical repair and drainage. It should then be treated with either amphotericin B (0.7–1.0 mg/kg per day) or fluconazole (400 mg/day). Intraperitoneal amphotericin B has been used, but most patients develop a painful chemical peritonitis. Local instillation of the drug should be avoided if possible.

In cases where *Candida* peritonitis has developed during peritoneal dialysis, the catheter should be removed as soon as possible and the patient should be started on parenteral amphotericin B treatment (1.0 mg/kg per day for at least 2 weeks), with or without flucytosine (100 mg/kg per day), and haemodialysis (if required). If the dialysate is grossly turbid, peritoneal lavage (until the returning fluid is clear) should be performed before the catheter is removed. It can be replaced once antifungal treatment has been discontinued.

Patients who are diagnosed as having *Candida* peritonitis within 2 weeks of starting dialysis can sometimes be managed without catheter removal, provided their symptoms and clinical signs are mild. Patients who

cannot have their catheter removed should be treated with amphotericin B or fluconazole, depending on the organism. Intraperitoneal administration of amphotericin B is painful, but may need to be considered. The peritoneal catheter should be removed as soon as the patient can be managed with haemodialysis.

The optimum duration of treatment for all forms of *Candida* peritonitis has not been well defined and should be guided by the patient's response. In general, 2–3 weeks of treatment is required.

11.8.8 Endocarditis and vascular infection

The management of *Candida* endocarditis is difficult. Treatment with amphotericin B at the maximum tolerated dose (1.0 mg/kg per day) and flucytosine (100 mg/kg per day) (provided the organism is susceptible) should be commenced as soon as the diagnosis is made. Both native and prosthetic valves should be replaced 1–2 weeks after treatment has started, but earlier surgical intervention is indicated if there are large vegetations, signs of heart failure or dysfunction of a prosthesis. The optimum length of treatment remains uncertain, but 2–3 months have been recommended to reduce the likelihood of relapse. Patients require careful follow-up for at least 12 months. If valve replacement is not possible, lifelong suppressive treatment with fluconazole is recommended.

Treatment with a lipid-based formulation of amphotericin B should be considered in patients who fail to respond to the conventional formulation, or who develop side-effects that necessitate discontinuation of the drug, or in whom conventional amphotericin B is contraindicated because of renal impairment. A few patients have been treated with fluconazole but this drug is more commonly employed as part of a long-term suppressive regimen.

Unlike endocarditis, septic central vein thrombosis is often curable with antifungal treatment alone. The catheter should be removed and amphotericin B given for 1–2 months; flucytosine can be added during the initial phase of treatment. Anticoagulation is desirable but not essential for a successful outcome. Septic *Candida* thrombophlebitis of a peripheral vein requires resection

of the vein followed by amphotericin B treatment for 2 weeks.

11.8.9 Meningitis

Meningitis in neurosurgical patients and low-birth-weight infants is best treated with amphotericin B (0.7–1.0 mg/kg per day) and flucytosine (100 mg/kg per day) (provided the infecting organism is susceptible). The half-life of flucytosine is prolonged in small infants and the drug should be administered at 12- or 24-h intervals. Treatment should be continued for a minimum of 4 weeks after resolution of all signs and symptoms related to the infection. Infected shunts should be removed or replaced.

11.8.10 Endophthalmitis

This is best treated with amphotericin B (0.7–1.0 mg/kg per day) and flucytosine (100 mg/kg per day) (provided the organism is susceptible). Treatment should be continued for 6–12 weeks until complete resolution of visible disease or convincing stabilization. Fluconazole (400 mg/day) reaches high concentrations in the vitreous humour, but until there is more experience with this agent, it is difficult to recommend it as first-line treatment.

Large progressive lesions usually require surgical intervention and intravitreal dosing with amphotericin B. The drug is toxic, but two or three intravitreal doses (of 5 μg each) can be tolerated. Subconjunctival treatment with amphotericin B is not required.

11.8.11 Oesophagitis

Oesophageal candidosis can be treated with fluconazole (100 mg/day) or itraconazole oral solution (200 mg/day) for 2–3 weeks. Treatment should be continued for at least 2 weeks following resolution of symptoms. Itraconazole capsules and ketoconazole are less effective because of variable absorption. Patients who remain symptomatic after 2 weeks require further investigation for drug resistance, drug interactions and other causes of oesophagitis.

Management of oesophagitis in AIDS patients from whom fluconazole-resistant strains of *C. albicans* have

been isolated is difficult. Higher doses of fluconazole (400–800 mg/day) should be tried, but the benefit is often transient. Itraconazole solution (400 mg/day) can be prescribed as this has sometimes proved successful in patients who had failed to respond to fluconazole. However, it is not unreasonable to expect these patients to need higher than usual doses of itraconazole.

As a last resort, patients with azole-resistant oesophagitis can be managed with parenteral amphotericin B (0.3–0.7 mg/kg per day for 1 week). However, relapse is common and intermittent maintenance treatment (1 mg/kg twice or three times per week) may be required. In persons with AIDS, treatment of the underlying HIV infection with HAART is critical for prevention and management of *Candida* oesophagitis.

11.9 Prevention

Although many risk factors have been identified for invasive candidiasis, few of these factors are preventable or modifiable. The only prevention measures shown to be effective have been in the setting of outbreaks, and have usually consisted of improved hygiene and hand washing procedures among healthcare workers, or removal of a contaminated source of infection. Hand washing should be encouraged between patient contacts and after contact with infectious materials. Hand antisepsis is recommended before the insertion of invasive devices. Gloves should be used in addition to hand washing to provide an additional physical barrier to cross-transmission. Gloves should be changed before and after contact with patients or with infectious materials.

Good barrier precautions during the insertion of vascular catheters should provide adequate protection against *Candida* infection, and the risk of subsequent catheter contamination and catheter-related bloodstream infection will be minimized. The longer the duration of catheterization, the greater the risk of infection. However, routine replacement of central venous catheters at specified intervals is not currently recommended.

In several large randomized trials, chemoprophylaxis with fluconazole (400 mg/day) was found to reduce the

incidence of superficial and deep forms of candidosis among HSCT recipients. Long-term follow-up (8 yr) of one of these trials showed a significant survival benefit among the fluconazole recipients. Moreover, fewer patients who received fluconazole developed acute GVHD involving the gastrointestinal tract. The use of fluconazole prophylaxis has been endorsed in published guidelines for prevention of infection in allogeneic and high-risk autologous HSCT recipients. Its use is not, however, recommended in low-risk neutropenic individuals, such as autologous peripheral blood stem cell transplant recipients, in whom the incidence of invasive candidosis is low.

Fluconazole prophylaxis (400 mg/day) also appears to be effective in preventing candidosis among some high-risk non-neutropenic patient populations. These include surgical patients with recurrent gastrointestinal perforations or anastomotic leakages, and liver and pancreatic transplant recipients. Unlike HSCT recipients, improved survival with fluconazole prophylaxis has never been documented in a randomized trial with liver transplant recipients. The need for prophylaxis in these patients should be assessed on the basis of institutional trends in the incidence of invasive candidosis in the immediate post-operative period, and should be targeted towards high-risk individuals. The risk of invasive candidiasis following transplantation of other solid organs appears to be too low to warrant prophylaxis.

One potential problem associated with the injudicious use of prophylaxis with antifungal triazoles in low-risk populations is the selection of less susceptible *Candida* species. The emergence of fluconazole-resistant *C. glabrata* and *C. krusei* infections has been reported from some hospitals, but not from others, despite the widespread use of fluconazole. Nonetheless, the selection and nosocomial spread of azole-resistant strains remains a matter of continued concern.

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Fungal Infection: Diagnosis and Management, Third Edition
Malcolm D. Richardson, David W. Warnock

12 Cryptococcosis

12.1 Definition

The term cryptococcosis is used to refer to infections due to the encapsulated yeast *Cryptococcus neoformans*. This ubiquitous organism can cause disease in normal individuals, but a large proportion of human infections occur in immunocompromised persons. Infection follows inhalation, but meningitis is the most common clinical presentation, and widespread disseminated infection can also occur.

12.2 Geographical distribution

The disease is worldwide in distribution.

12.3 The causal organism and its habitat

C. neoformans is an encapsulated, environmental yeast. Isolates of *C. neoformans* can be divided into two varieties, *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii*, on the basis of differences in a number of mycological, biochemical, ecological and epidemiological characteristics. Isolates of *C. neoformans* can also be divided into five serotypes, termed A, B, C, D and AD (both A and D determinants present) on the basis of antigenic differences between their capsular polysaccharides. The two varieties, var. *neoformans* and var. *gattii*, are comprised of serotypes A, D and AD, and serotypes B and C, respectively. It has recently been proposed that serotypes A and D should be given separate varietal status, as *C. neoformans* var. *neoformans* (serotype D) and *C. neoformans* var. *grubii* (serotype A), based on significant genetic differences between them. However, this proposal ignores the varietal status of serotype AD strains.

The two varieties of *C. neoformans* differ in their natural habitat and geographical distribution. In nature, *C. neoformans* var. *gattii* (serotypes B and C) has been isolated from decaying wood in the red gum group of eucalyptus trees. These trees are indigenous to

Australia, but have been planted in numerous countries, including the USA, parts of Central and South America, Africa, India, China and the Mediterranean region. The distribution of human infections with *C. neoformans* var. *gattii* in general corresponds to the distribution of the host gum trees.

C. neoformans var. *neoformans* (serotypes A and D) has been isolated most frequently from soil contaminated with pigeon or other bird droppings. It has also been recovered from old dried accumulations of bird droppings in buildings, but has not been found in fresh wet droppings. The two serotypes differ in their geographical distribution: human infections with serotype A have a global distribution while infections with serotype D are more prevalent in certain geographical areas such as northern Europe.

12.4 Epidemiology

Inhalation of *C. neoformans* is the usual mode of infection in humans. The incubation period is unknown and could be weeks, months or even longer. It is also unclear whether the infectious particles are small dessicated acapsular yeast cells or basidiospores of the sexual state of the fungus (which is named *Filobasidiella neoformans*). It is thought that the encapsulated yeast cells are too large to penetrate the upper respiratory tract.

Outbreaks, investigations of which have helped to elucidate the sources and risk factors for other fungal infections, such as histoplasmosis, have not been described for cryptococcosis. Thus, while bird roosting sites have been clearly implicated in outbreaks of histoplasmosis, the association of *C. neoformans* var. *neoformans* infection with exposure to pigeon droppings, the best recognized of the putative environmental risk factors for this disease, is mostly derived from information on isolation of var. *neoformans* from the environment, not from studies that attribute disease to this exposure. There are, however, a few anecdotal reports of cases associated with pigeon or bird exposures.

The likelihood that an infection with *C. neoformans* var. *neoformans* will develop after inhalation depends, in major part, on host factors. Even before the advent of the acquired immunodeficiency syndrome (AIDS), infec-

tions with var. *neoformans* tended to occur in individuals with T-cell-mediated immunological defects, such as are found in persons with lymphoproliferative disorders and those receiving corticosteroid treatment. Human immunodeficiency virus (HIV) infection is now the single most common immunocompromising illness among patients with *C. neoformans* var. *neoformans* infection. In HIV-infected persons, cryptococcosis is associated with severe immunological impairment, as reflected by CD4 T-lymphocyte counts of less than 100 cells/μl.

The major risk factor for development of infection with *C. neoformans* var. *gattii* appears to be environmental exposure, although there is indirect evidence that unidentified host factors contribute to the higher incidence of disease in Australian Aboriginals. In contrast to infections with *C. neoformans* var. *neoformans*, infections with var. *gattii* are uncommon in immunocompromised persons. The reasons for this remain unclear.

Until the 1980s, cryptococcosis was a rare disease. With the advent of the AIDS epidemic, it became the most common cause of meningitis in hospitals where persons with HIV infection are treated. In the USA, active population-based surveillance, conducted between 1992 and 1994, showed that cryptococcosis developed in 2–5% of HIV-infected persons per annum. The annual incidence of the disease has declined following the introduction of more effective combination antiretroviral treatments, including highly active antiretroviral therapy (HAART), and improvements in HIV health-care in general. Nonetheless, 85% of cryptococcosis cases diagnosed in the USA in the late 1990s still occurred in persons with AIDS. Among HIV-negative persons in the USA, the average annual incidence of cryptococcosis has remained almost constant at about 1 case per 100 000 population; about 25% of these individuals have no obvious predisposing factors. Although the incidence of cryptococcosis has also declined in other developed countries where routine HIV care is available, the incidence of the disease is rising in developing countries afflicted with large epidemics of HIV infection. Reports from Africa have

highlighted the high mortality rate (85–100%) associated with infection treated under local conditions, where adequate dosages and constant supplies of antifungal drugs are not consistently available.

12.5 Clinical manifestations

Most cases of cryptococcosis are not diagnosed until signs of central nervous system (CNS) disease have appeared. However, it is well established that the lungs are the usual initial site of involvement. In most patients, infection of the lungs occurs and resolves weeks to months before disseminated infection is detected.

The clinical manifestations of cryptococcosis in persons with HIV infection are similar to those in other groups of immunocompromised individuals. However, infected sites often contain a much higher burden of organisms. More than 80% of persons with AIDS have meningitis or meningoencephalitis at the time of diagnosis, but the disease is often more widespread. Because the clinical presentation can be so non-specific it is important to consider the diagnosis in all HIV-infected patients who present with a fever and to re-evaluate them at regular intervals for cryptococcal infection, even if the initial investigations are negative.

The clinical manifestations of *C. neoformans* var. *gattii* infection can be distinguished from those of var. *neoformans* by an increased incidence of mass lesions in the lungs and brain, increased neurological deficits and a slower response to treatment. These differences in clinical presentation are largely due to the effect of underlying immunocompromise in persons infected with var. *neoformans*.

12.5.1 Pulmonary cryptococcosis

Up to 30% of immunocompetent individuals develop no symptoms following inhalation of *C. neoformans* and their infection remains unrecognized until it has spread to other organs. However, the remainder present with symptoms, such as cough, fever, sputum production, chest pain and weight loss. The most frequent radiological findings are well-defined, non-calcified, single or multiple nodular lesions. Less common findings include indistinct to mass-like infiltrates, hilar and mediastinal

lymph node enlargement, pleural effusions and cavitation.

In immunocompromised individuals, cryptococcosis of the lungs follows a much more rapid course and patients often present with disseminated infection. Unlike normal individuals, most immunocompromised patients present with symptoms. The commonest are fever, malaise, chest pain, weight loss, dyspnoea, night sweats and cough. Chest radiographs will reveal diffuse interstitial or alveolar infiltrates. Nodular lesions, pleural effusions, and cavitation are sometimes found.

Pulmonary involvement has been reported in 30–40% of AIDS patients who present with *C. neoformans* meningitis. The clinical manifestations differ somewhat from those found in other groups of immunocompromised patients. Most present with symptoms, including fever, cough, dyspnoea, weight loss and headache. Some present with pleuritic chest pain and haemoptysis. The most frequent radiological findings are focal or diffuse interstitial infiltrates and hilar lymph node enlargement. Unlike other patients, nodular and alveolar infiltrates are rare, as are large mass lesions and pleural effusions.

Up to 14% of AIDS patients with cryptococcosis have presented with acute respiratory failure. The mortality rate in these cases is high (90–100%). The clinical presentation is identical to that of *Pneumocystis carinii* pneumonia, but serum antigen detection is a rapid and sensitive diagnostic test. Non-specific constitutional symptoms, such as fever, fatigue and weight loss, are common. The most frequent radiological findings are diffuse interstitial infiltrates.

Most HIV-infected persons in whom cryptococcosis of the lungs is diagnosed have disseminated infection: 60–70% have concurrent meningeal involvement. The organism can be isolated from sputum, bronchoalveolar lavage (BAL) fluid and tissue biopsies, as well as blood and other specimens. Antigen can often be detected in BAL fluid as well as serum, urine and cerebrospinal fluid (CSF) specimens.

12.5.2 CNS cryptococcosis

Infection of the brain and meninges is the commonest clinical form of cryptococcosis and the most frequent

cause of death. It follows dissemination of the organism from the lungs.

In HIV-negative patients the symptoms and signs are often indolent in onset. Headache is the most common presenting symptom: the pain is dull, bilateral and diffuse. Fever is often minimal or absent until late in the course of the infection. Mental changes, such as drowsiness and confusion, also occur. Hydrocephalus is a serious complication, but focal neurological lesions are uncommon. These lesions are insidious in onset and present with focal signs. Computed tomographic (CT) scans will reveal single or multiple, enhancing or non-enhancing nodular lesions. In some HIV-negative patients, CNS disease is associated with concurrent infection of other sites. In most, however, it presents without other manifestations of disease.

About 90% of HIV-negative patients have abnormal CSF findings including increased pressure, raised protein concentration, lowered glucose concentration and a lymphocytic pleocytosis. In persons with HIV infection, the CSF may appear normal: the protein and glucose concentrations may be unchanged and there is often only a very mild pleocytosis.

In HIV-infected persons, CNS infection with *C. neoformans* is often insidious in onset. Headache and fever are common, but overt meningeal symptoms and signs are unusual: fewer than 20% of patients are somnolent, confused or obtunded. Focal neurological signs are uncommon on initial presentation, occurring in about 10% of patients.

Both HIV-positive and negative patients with cryptococcal meningitis often develop symptoms and signs of increased intracranial presssure, such as severe headache, lowered consciousness, visual disturbance and hearing loss, soon after starting antifungal treatment. This can result in a rapid deterioration in their condition and death. The underlying mechanism is unclear, but it is thought to be due, at least in part, to interference with CSF reabsorption in the arachnoid villi caused by accumulation of fungal polysaccharide. Aggressive management of elevated intracranial pressure, by means of repeated lumbar drainage, is perhaps the most important factor in reducing mortality and minimizing

morbidity in acute cryptococcal meningitis. Because of the potential for mass lesions within the brain of persons with AIDS, imaging of the CNS is recommended before the initial lumbar puncture is performed. In obtunded or somnolent patients a repeat lumbar puncture should be done within 1 week of starting treatment to check the CSF pressure.

12.5.3 Cutaneous cryptococcosis

Haematogenous spread of *C. neoformans* gives rise to skin lesions in 10–15% of patients with disseminated cryptococcosis. Direct extension from a bone lesion can also occur. In some cases these lesions are the earliest clinical sign of infection. They are often located on the face and scalp, but may occur on the trunk or limbs. The lesions may present as single or multiple nodules, which sometimes progress to ulcers or abscesses.

Cutaneous lesions are common in HIV-infected persons with cryptococcosis. Multiple small maculopapular lesions, some of which show central necrotic umbilication resembling molluscum contagiosum, are frequently reported. Microscopic examination and culture of biopsied material from a suspicious lesion should permit the diagnosis to be established.

12.5.4 Osteomyelitis

Osteomyelitis occurs in 5–10% of patients with disseminated cryptococcosis. Most patients present with a single isolated lesion, the commonest site of involvement being the spine. Patients may complain of local pain and soft tissue tenderness at the affected site. Radiographs will reveal well-defined osteolytic lesions without marginal sclerosis or periosteal change. Joint involvement is rare. CT scans can be used to define the extent of bone involvement. Microscopic examination and culture of aspirated or biopsied material from a suspicious lesion should permit the diagnosis to be established.

12.5.5 Other forms of cryptococcosis

Ocular infection with *C. neoformans* is not uncommon, occurring in up to 40% of patients with meningitis. In some cases endophthalmitis is present before the

diagnosis of meningitis is made. Prompt diagnosis and rapid treatment are essential to prevent visual loss. Catastrophic visual loss has also been reported in HIV-infected persons without endophthalmitis. In some cases visual loss has occurred over a period as short as 12 h. Others have presented with slower visual loss related to raised intracranial pressure following CNS infection.

Asymptomatic infection of the prostate is common in HIV-infected persons with cryptococcosis. Moreover, cultures of urine and prostatic secretions often remain positive following apparently successful antifungal treatment of meningitis and other disseminated forms of cryptococcosis. It is possible that the prostate is an important reservoir for relapse of infection in HIV-infected men.

Other unusual sites of infection include the adrenal gland, heart, liver and spleen.

12.6 Essential investigations and their interpretation

Establishing the diagnosis of cryptococcosis is less difficult than diagnosis of many other fungal infections. It requires the isolation of *C. neoformans* in culture from body fluids or tissue, or the detection of cryptococcal capsular antigen in blood, CSF or urine.

12.6.1 Microscopy

Encapsulated *C. neoformans* cells can often be detected in specimens of CSF, other host fluids or secretions mounted in Indian ink or nigrosin. However, lymphocytes in particular can be confused with the organism. In persons with AIDS, *C. neoformans* cells are usually plentiful in the CSF, although the capsules are often small making recognition difficult. Persistently positive CSF findings in patients undergoing treatment should be considered evidence of failure or relapse only if they are confirmed by a deterioration in the patient's clinical condition or by positive cultures.

12.6.2 Culture

C. neoformans can be isolated from the CSF in 75–90% of cases of cryptococcal meningitis. The likelihood of success is increased if multiple specimens are taken and

the centrifuged sediment of large amounts (4–8 ml) of fluid are plated out. The organism grows well on standard microbiological media. It grows best at 30–35°C and it is advisable to prolong incubation of plates in suspected cases for up to 2 weeks.

C. neoformans can also be recovered from blood, sputum, urine, prostatic fluid and other specimens. Positive blood cultures have been obtained in 35–70% of HIV-infected persons with cryptococcosis. Lysis centrifugation has been the most sensitive method. Because of the greater load of organisms, microscopic examination and culture of other specimens is more often positive in untreated patients with HIV infection than in other individuals. Isolation of the organism from sputum, BAL or lung tissue should be attempted if pulmonary cryptococcosis is suspected, especially in persons with AIDS in whom the recovery rate is high.

12.6.3 Serological tests

Antibodies to *C. neoformans* can often be detected in patients with localized or past infection, but are seldom found in patients with untreated meningeal or disseminated infection in whom tests for antigen are much more helpful.

Testing for *C. neoformans* capsular antigen is one of the most reliable methods for the diagnosis of cryptococcosis. Several latex particle agglutination (LPA) and enzyme-linked immunosorbent assay (ELISA) tests have been marketed for the detection of antigen in serum, CSF, urine and BAL fluid specimens. These tests are specific, provided that rheumatoid and other interfering factors are removed. False-negative results can occur if the organism load is low or if the organisms are not well encapsulated. It is also important to remember that different manufacturers' products can give different titres with the same clinical specimen.

A serum antigen titre of 1:8 or greater is considered strong presumptive evidence of *C. neoformans* infection. A negative serum antigen test result does not exclude the diagnosis of cryptococcosis, particularly if only a single specimen has been tested and the patient has symptoms consistent with the infection. Repeated negative test results for serum antigen in HIV-infected

persons without neurological symptoms or signs makes the diagnosis improbable, but should not preclude the clinician who still suspects cryptococcal meningitis from performing a lumbar puncture.

The CSF antigen test is positive in over 90% of patients with untreated meningeal cryptococcosis. Levels of antigen in the CSF often decline with treatment, but the test can remain positive for several weeks. This is more common in patients whose initial load of organisms is high. Positive CSF antigen test results may be obtained despite failure to recover *C. neoformans* from the CSF. This may represent the persistent release of antigen from dead cells or slow elimination of capsular antigen from the CSF, rather than ongoing infection.

In HIV-negative individuals, high levels of serum and CSF antigen prior to treatment are often predictive of death during treatment. In persons with AIDS abnormal mental status prior to treatment is the most important factor, but a high CSF antigen titre (greater than 1:1000) is also a sign of a poor prognosis.

In HIV-negative patients, high antigen levels at the end of treatment are often predictive of later relapse. In contrast, in persons with AIDS changes in serum antigen levels do not correlate with response, and although an unchanged or increased titre of antigen in CSF is often associated with clinical and mycological failure to respond to treatment, its usefulness in management is uncertain.

12.7 Management

All patients with cryptococcosis, apart from a few immunocompetent individuals with infection of the lungs, require treatment. The choice of treatment depends on both the anatomic sites of involvement and the immunological status of the host.

12.7.1 Pulmonary and non-CNS cryptococcosis

HIV-NEGATIVE PATIENTS

Individuals presenting with pulmonary or other forms of non-CNS cryptococcosis should have a lumbar puncture performed to rule out concomitant CNS infection. Immunocompetent individuals with asymptomatic pulmonary infection have done well without treatment.

However, careful observation is essential. If treatment is given, fluconazole (200–400 mg/day for 3–6 months) is recommended.

Immunocompetent patients who present with mild or moderate symptoms should be treated with fluconazole (200–400 mg/day for 6–12 months). Itraconazole (200–400 mg/day for 6–12 months) is an acceptable alternative. If oral treatment cannot be given, or if the disease is severe or progressive, amphotericin B (0.4–0.7 mg/kg per day) is recommended. A total dose of 1000–2000 mg should be administered.

Immunocompromised individuals with non-CNS disease should be treated in the same manner as patients with CNS disease.

HIV-INFECTED PATIENTS

All HIV-infected persons with non-CNS cryptococcosis require treatment because of the high rate of dissemination of the disease to the CNS. Patients who present with mild or moderate symptoms, or who present with asymptomatic pulmonary infection, should be treated with fluconazole (200–400 mg/day) for life. Itraconazole (200 mg twice daily) is an acceptable alternative. It is unclear whether azole maintenance treatment can be discontinued in patients who have responded well to HAART (see later).

In patients with more severe disease, amphotericin B (0.7–1.0 mg/kg per day) should be used until the symptoms are controlled. Oral treatment with fluconazole can then be substituted.

12.7.2 CNS cryptococcosis

HIV-NEGATIVE PATIENTS

The historical standard for treatment of immunocompetent patients with CNS infection is the combination of amphotericin B (0.7–1.0 mg/kg per day) and flucytosine (100 mg/kg per day in four divided doses) for 6–10 weeks. An alternative to this regimen is an induction course of amphotericin B (0.7–1.0 mg/kg per day) and flucytosine (100 mg/kg per day) for 2 weeks followed by consolidation treatment with fluconazole (400 mg/day) for an additional 8–10 weeks. Lumbar puncture should be performed after 2 weeks of treatment; patients with a

positive CSF culture require a longer course of induction treatment. It is optional to continue fluconazole (200 mg/day) for 6–12 months.

Immunocompromised patients, such as solid organ transplant recipients, require more prolonged treatment. Amphotericin B (0.7–1.0 mg/kg per day) should be given for 2 weeks, followed by 8–10 weeks of fluconazole (400–800 mg/day) and 6–12 months of maintenance treatment with a lower dose of fluconazole (200 mg/day). If the patient is receiving corticosteroids, reduction of the prednisone dosage (or its equivalent) to 10 mg/day may improve the outcome.

For both immunocompetent and immunocompromised patients, lipid formulations of amphotericin B can be substituted for the conventional formulation during the induction phase of treatment. For patients who cannot tolerate fluconazole, itraconazole (200 mg twice daily) is an acceptable alternative. All patients should be monitored for signs of elevated intracranial pressure and managed in a manner similar to HIV-positive patients (see below).

Intrathecal or intraventricular amphotericin B can be used in cases where other forms of treatment have failed.

HIV-INFECTED PATIENTS

HIV-infected persons with CNS cryptococcosis should be treated with amphotericin B (0.7–1.0 mg/kg per day) and flucytosine (100 mg/kg per day in four divided doses) for at least 2 weeks. In cases where flucytosine cannot be used, amphotericin B alone (0.7–1.0 mg/kg per day) is an acceptable alternative. If the initial 2-week period of induction treatment is successful, consolidation treatment can then be commenced with fluconazole (400 mg/day) for a further 8 weeks, or until CSF cultures are sterile. In cases where fluconazole cannot be used, itraconazole (200 mg twice daily) is an acceptable alternative.

Administration of one of the lipid-based forms of amphotericin B should be considered in patients who develop side-effects that necessitate discontinuation of the conventional formulation, or in whom conventional amphotericin B is contraindicated because of renal

impairment. There are different dosage recommendations for the various lipid-based preparations (see Chapter 3), but liposomal amphotericin B (AmBisome) has proved effective at doses of 4 mg/kg per day.

Combination treatment with fluconazole (400–800 mg/day) and flucytosine (100 mg/kg per day) has been shown to be effective in the treatment of AIDS-associated cryptococcal meningitis. However, this regimen is associated with a high incidence of toxic side-effects.

Intrathecal or intraventricular amphotericin B can be used in cases where other forms of treatment have failed.

Because of the high rate of recurrence of cryptococcal disease among persons with AIDS, it has long been recommended that all patients who survive beyond the initial induction treatment should receive lifelong maintenance treatment to prevent relapse. The drug of choice is fluconazole (200 mg/day) as this has proven superior to itraconazole (200 mg/day). The latter drug can be used in cases where the patient is intolerant of fluconazole, or has failed fluconazole treatment. However, it may be prudent to use itraconazole at a dosage of 200 mg twice daily.

It appears that adult and adolescent patients with AIDS are at low risk for relapse of cryptococcosis if they have remained asymptomatic and have had a sustained increase (for 6 months or longer) in their CD4 T-lymphocyte count to greater than 100–200 cells/μl after HAART. The number of individuals who have been evaluated remains limited, but CDC guidelines now suggest that it is reasonable to discontinue maintenance treatment among such patients. Maintenance treatment should be restarted if the CD4 T-lymphocyte count falls to 100–200 cells/μl.

12.7.3 Management of increased intracranial pressure

In all cases of cryptococcal meningitis, careful attention must be paid to the management of intracranial pressure to assure optimal clinical outcome. The principal intervention for reducing elevated intracranial pressure is percutaneous lumbar drainage. In cases where repeated lumbar punctures or use of a lumbar drain

fail to control symptoms of elevated pressure, or when persistent or progressive neurological deficits are present, a ventriculoperitoneal shunt is indicated. Adjunctive treatment with corticosteroids is not recommended in HIV-infected persons. Oral acetozolamide and mannitol have not been shown to provide any clear benefit in the management of elevated pressure resulting from cryptococcal meningitis.

12.8 Prevention

In the USA, several clinical trials have demonstrated that prophylactic administration of fluconazole to persons with HIV infection at high risk for cryptococcosis can significantly reduce the risk of developing the disease. However, routine antifungal prophylaxis is not recommended to prevent cryptococcosis because of the relatively low prevalence of the disease, the high cost of fluconazole, the lack of survival benefits associated with prophylaxis, and the potential for development of drug resistance.

A recent clinical trial from Thailand found that itraconazole was effective in preventing fungal infections in persons with AIDS, although no effect on survival was noted. However, itraconazole is expensive and beyond the reach of almost all HIV-infected persons in developing countries. Similar clinical trials with fluconazole have not been performed. There is an urgent public health and humanitarian need to conduct such trials, and to determine whether antifungal prophylaxis has a role in preventing cryptococcosis and improving survival among HIV-infected persons in developing countries with a high burden of the disease.

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13 Mucormycosis

13.1 Definition

The term mucormycosis (zygomycosis) is used to refer to infections due to moulds belonging to the Order Mucorales. These organisms can cause rhinocerebral, pulmonary, gastrointestinal, cutaneous or disseminated infection in predisposed individuals, the different clinical forms often being associated with particular underlying disorders.

13.2 Geographical distribution

These infections are worldwide in distribution.

13.3 The causal organisms and their habitat

Mucormycosis is caused by moulds belonging to the Order Mucorales of the Class Zygomycetes. The Mucorales are divided into six families of significance in human or animal disease, but most cases of human infection are caused by members of the Mucoraceae. These include the genera *Absidia*, *Mucor*, *Rhizomucor* and *Rhizopus*. Two additional pathogenic families are the Cunninghamellaceae and the Saksenaceae. Many different organisms have been implicated, but the commonest cause of human infection is *Rhizopus arrhizus*. Other less frequent aetiological agents include *Absidia corymbifera*, *Apophysomyces elegans*, *Cunninghamella bertholletiae*, *Rhizomucor pusillus* and *Saksenaea vasiformis*. All these moulds cause similar diseases in humans, and the diagnostic and therapeutic approaches are similar.

The species isolated from cases of human infection are thermotolerant, and many are ubiquitous in the soil and on decomposing organic matter. These moulds are found in the indoor and outdoor air, on food items and in dust.

13.4 Epidemiology

Most human infections follow inhalation of spores that have been released into the air, and the lungs and nasal sinuses are the commonest initial sites of infection. Less frequently, infection follows ingestion of contaminated food or traumatic inoculation of organisms into the skin and soft tissue.

The aetiological agents of mucormycosis are ubiquitous in the environment and the likelihood that infection will occur following inhalation, ingestion or implantation of spores largely depends on host factors. The major risk factors predisposing individuals to mucormycosis include prolonged or profound neutropenia, uncontrolled diabetes mellitus, other forms of metabolic acidosis and burns. Other contributing factors include the use of corticosteroids and treatment with the iron chelating agent, desferrioxamine (deferoxamine). Certain predisposing conditions seem to be more commonly associated with particular clinical forms of disease. For instance, persons with diabetic ketoacidosis often develop fulminant rhinocerebral mucormycosis, while neutropenic individuals often develop pulmonary or disseminated disease.

Uncontrolled diabetes mellitus is the principal cause of acidosis in most patients with rhinocerebral mucormycosis, but the disease has also been seen in acidotic patients with renal disease. Impairment of macrophage and neutrophil function has been identified as the principal factor responsible for the increased risk of developing mucormycosis in diabetic individuals. Correction of the underlying ketoacidosis is essential for the successful treatment of mucormycosis in these persons.

Mucormycosis is an uncommon, but often lethal infection, among several groups of immunocompromised patients. Those at greatest risk include persons with acute leukaemia in relapse, and allogeneic haematopoietic stem cell transplant (HSCT) recipients with severe graft-versus-host disease (GVHD). In neutropenic patients, the prognosis is poor unless neutrophil regeneration occurs.

Mucormycosis is an uncommon infection, being found in about 2.5% of HSCT recipients and 2% of

patients with haematological malignancies. In the USA, active population-based surveillance, conducted in 1992 and 1993, showed that mucormycosis developed in 1.7 persons per million population per annum (in the same report the incidence of aspergillosis was 12.4 per million population).

The mortality rate from mucormycosis among immunocompromised patients remains high, ranging from 80 to 100% in recent reports. This contrasts with a much better prognosis for individuals with non-malignant underlying disorders. The higher survival rate among diabetics (about 75%) has been attributed to the relative ease with which the underlying ketoacidosis can be reversed.

Nosocomial outbreaks of mucormycosis are not as common as hospital-related *Aspergillus* infections, but have sometimes been linked to construction or renovation work, as well as to contaminated ventilation systems. Nosocomial clusters of cutaneous infections with *Rhizopus rhizopodiformis* and *R. microsporus* have been traced to contaminated biomedical devices, or associated with the use of non-sterile surgical dressings and splints. However, most cases of mucormycosis in hospitalized patients are sporadic in nature and it is much more difficult to determine whether these infections are acquired inside or outside the hospital setting.

13.5 Clinical manifestations

There are five major clinical forms of mucormycosis, of which rhinocerebral and pulmonary infections are by far the most common. Other manifestations include gastrointestinal, cutaneous and disseminated disease. Like the aetiological agents of aspergillosis, the causal organisms of mucormycosis have a predilection for vascular invasion causing thrombosis, infarction and necrosis of the surrounding tissue. The clinical hallmark of mucormycosis is the rapid onset of necrosis and fever. In most cases, progress is rapid and death follows unless aggressive treatment is initiated.

13.5.1 Rhinocerebral mucormycosis

The terms rhinocerebral and craniofacial mucormycosis are used to describe an infection that begins in the

paranasal sinuses and then spreads to involve the orbit, face, palate and/or brain. The clinical presentation is similar to that of acute invasive *Aspergillus* sinusitis (see Chapter 10). This is a rapidly progressive disease that is most commonly seen in neutropenic cancer patients, HSCT recipients and diabetics with uncontrolled ketoacidosis. Immunocompetent individuals are seldom affected. It is the commonest clinical form of mucormycosis, accounting for 30–50% of all cases of the disease, and is often fatal within a week of onset if left untreated.

The presenting symptoms include fever, unilateral facial swelling, unilateral headache, nasal or sinus congestion or pain, and a serosanguinous nasal discharge. Necrotic black lesions on the hard palate or nasal turbinate are a characteristic diagnostic sign. As the infection spreads into the orbit, periorbital or perinasal swelling occurs and progresses to disfiguring destruction of facial tissue. Ptosis, proptosis, ophthalmoplegia and loss of vision can occur. Drainage of black pus from the eye is a useful diagnostic sign. From the orbit infection may spread into the brain leading to frontal lobe necrosis and abscess formation.

Imaging studies are helpful in defining the extent of bone and soft-tissue destruction, and the pattern of sinus and orbital involvement, but are more useful in planning surgical intervention than in establishing a diagnosis. Computed tomographic (CT) scans often reveal involvement of several sinuses (in particular ethmoid and sphenoid), but with a clear unilateral predilection, no air-fluid levels, thickening of sinus linings, and destruction of sinus bone. Magnetic resonance imaging (MRI) is not clearly superior to CT scanning, but is deemed more accurate in providing information about cavernous sinus and cerebral involvement, and may be preferred for the diabetic patient in whom CT contrast agents may be contraindicated.

Examination of the cerebrospinal fluid (CSF) is seldom helpful. The protein concentration may be slightly raised, but the glucose concentration is usually normal. There may be a modest mononuclear pleocytosis. CSF cultures are sterile.

13.5.2 Pulmonary mucormycosis

This form of mucormycosis is most commonly seen in neutropenic cancer patients undergoing remission induction treatment. It has also been reported in allogeneic HSCT recipients with GVHD. Mucormycosis may develop in the lungs as a result of aspiration of infectious material, or following inhalation, or from haematogenous or lymphatic spread during dissemination. If untreated, haematogenous dissemination to other organs, particularly the brain, will often occur. The infection is fatal within 2–3 weeks.

The clinical presentation is non-specific. Patients often present with an unremitting fever (greater than 38°C) that fails to respond to broad-spectrum antibacterial treatment. Cough is a common presenting symptom. Haemoptysis and pleuritic chest pain are uncommon, but when present are helpful in suggesting a fungal infection. However, there are no characteristic symptoms or clinical signs to distinguish mucormycosis from aspergillosis (see Chapter 10).

The radiological signs are also non-specific, but infiltrates and nodules are more frequent than consolidation or cavitation. Pleural effusion is uncommon.

13.5.3 Gastrointestinal mucormycosis

This is a rare condition that has usually been encountered in malnourished infants or children. All segments of the gastrointestinal tract can be involved, but lesions are most common in the stomach, colon and ileum. The disease is seldom diagnosed during life.

The symptoms are varied and depend on the site affected. Non-specific abdominal pain and haematemesis are typical. Complications include gastric or intestinal perforation, perirenal abscesses and renal infarction. Intestinal mucormycosis is a fulminant illness ending in death within several weeks due to bowel infarction, sepsis or haemorrhagic shock.

13.5.4 Cutaneous mucormycosis

Although inhalation is the usual route of infection in patients with mucormycosis, traumatic inoculation of spores can lead to extensive necrotic cutaneous infections. This form of disease is most often seen in

patients with burns or other forms of local trauma. Necrotizing cutaneous mucormycosis has also been reported in patients who have had contaminated surgical dressings or splints applied to their skin. In diabetic or immunosuppressed patients, cutaneous lesions may arise at an insulin injection site or a catheter insertion site. Cutaneous mucormycosis is an aggressive disease, even in the face of surgical debridement and antifungal treatment. It can lead to necrotizing fasciitis or to widespread disseminated infection.

The initial signs include cutaneous erythema and subcutaneous swelling. The margins of the lesion become raised and indurated, and the central region becomes necrotic and evolves into an ulcer covered with a black eschar. The lesions are indistinguishable from those caused by *Aspergillus* species (see Chapter 10), and can resemble ecthyma gangrenosum. The lesions are painful and the patient can be febrile. The development of severe underlying necrosis and infarction in a burn should suggest the diagnosis.

Less commonly, cutaneous mucormycosis develops following haematogenous dissemination of the fungus in immunosuppressed patients. The lesions begin as an erythematous, indurated painful cellulitis, then evolve into ulcers covered with a black eschar.

13.5.5 Disseminated mucormycosis

This may follow any of the four forms of mucormycosis described so far, but is usually seen in neutropenic patients with a pulmonary infection. Less commonly, dissemination occurs from the gastrointestinal tract, burns or other cutaneous lesions. The commonest site of spread is the brain, but metastatic necrotic lesions have also been found in the spleen, heart and other organs. Disseminated mucormycosis is seldom diagnosed during life, but occasional patients develop metastatic cutaneous lesions which permit an earlier diagnosis.

Cerebral infection following haematogenous dissemination is distinct from the rhinocerebral form of mucormycosis. The lesions often lead to focal neurological signs. The diagnosis is difficult but should be considered in a neutropenic patient who becomes lethargic, confused or obtunded. CT and MRI scans are useful in

locating the lesions, but the findings are non-specific. Investigation of the CSF is unhelpful; protein, glucose and cell abnormalities are non-specific and cultures are sterile.

13.5.6 Other forms of mucormycosis

Isolated mucormycotic brain lesions have been reported in parenteral drug abusers. Other unusual focal forms of mucormycosis include endocarditis, osteomyelitis and pyelonephritis.

13.6 Differential diagnosis

Rhinocerebral mucormycosis is a dramatic and distinctive condition, but it can be confused with cavernous sinus thrombosis, bacterial orbital cellulitis, and other forms of acute invasive fungal sinusitis, such as aspergillosis.

The clinical manifestations of pulmonary mucormycosis cannot be distinguished from gram-negative bacterial pneumonia, or aspergillosis or hyalohyphomycosis.

13.7 Essential investigations and their interpretation

Because mucormycosis is such an aggressive infection, an early diagnosis is essential for successful treatment.

13.7.1 Microscopy

The microscopic demonstration of Mucorales in clinical material taken from necrotic lesions, or in sputum or bronchoalveolar lavage (BAL) fluid is more significant than their isolation in culture. These organisms can be distinguished from other moulds, such as *Aspergillus* species, by their characteristic broad, non-septate hyphae with right-angled branching.

13.7.2 Culture

Isolation in culture is required for specific identification of the Mucorales. Despite their predilection for angioinvasion and haematogenous dissemination, blood cultures in all forms of mucormycosis are always negative. Nasal, palatal and sputum cultures are seldom helpful. Because the Mucorales are common

contaminants, isolation of these organisms from material obtained from a necrotic lesion, or from sputum or BAL fluid must be interpreted with caution. However, if the patient is diabetic or immunosuppressed, the isolation should not be ignored.

13.7.3 Serological tests

There are no routine serological tests for mucormycosis available at present.

13.8 Management

If the treatment of mucormycosis is to be successful, the underlying metabolic or immunological disorders that precipitated the infection must be corrected, infected necrotic tissue removed, and high doses of amphotericin B administered. Other antifungal drugs have no role in the management of this infection.

Immunosuppressive and cytotoxic drugs should be reduced in dose or discontinued, provided this will not harm the patient. Iron chelation treatment should also be discontinued. Shortening the duration of neutropenia with colony stimulating factors might be beneficial, but it remains unclear whether this improves outcome.

Amphotericin B remains the drug of choice for mucormycosis. It should be given at the maximum tolerated dosage of 1.0–1.5 mg/kg per day (see Chapter 3). If the disease fails to respond to the conventional formulation, treatment should be changed to one of the lipid-based formulations of the drug at dosages of 3–5 mg/kg or higher. This should be continued until the patient recovers, or for at least 2 weeks before reverting to conventional amphotericin B. Administration of lipid-based amphotericin B is also recommended for patients in whom the conventional formulation is contraindicated because of renal impairment, or who develop side-effects that would otherwise necessitate discontinuation of the drug. It remains unclear as to whether these new formulations differ from each other in terms of clinical benefit in mucormycosis.

In individuals with sino-orbital infection, aggressive surgical debridement of the necrotic lesions and surrounding infected tissue is the single most important component of treatment. Delay of just a few hours

may permit the organism to spread along blood vessels into the cavernous sinus or into the brain. Debridement may need to be repeated several times until a patient is stabilized.

If a patient with mucormycosis confined to one region of the lung does not respond to amphotericin B treatment within 48–72 h, surgical resection should be considered. Although a wedge resection is sometimes sufficient, complete lobar or segmental resection is often required. The more widespread the infection, the less beneficial is surgical intervention.

In individuals with cutaneous mucormycosis, aggressive surgical debridement of the necrotic lesions and surrounding infected tissue is an essential component of treatment. Administration of amphotericin B is also advised. Treatment is more successful in cutaneous than other forms of mucormycosis. However, it is not without complications: curative surgical intervention is often disfiguring, and amputation of affected limbs is sometimes required.

The optimum duration and total dose of amphotericin B that should be given to patients with mucormycosis has not been determined. Treatment must be individualized according to the patient's clinical response and the rate of clearing of the infection. Treatment should be continued until clinical and radiological abnormalities are resolving, and reversible underlying predispositions have abated. The duration of antifungal treatment should be guided by clinical response rather than the total drug dose administered. The ultimate response of patients to treatment is largely related to host factors, such as resolution of neutropenia and the return of neutrophil function, and the correction of diabetic ketoacidosis.

13.9 Prevention

Measures to reduce the incidence of mucormycosis are of major importance in the management of this difficult-to-diagnose infection. In the non-immunocompromised individual, preventive measures should focus on the underlying risk factors that lead to the development of mucormycosis. Adequate control of diabetes mellitus, the use of iron chelators other than desferrioxamine,

and limiting the use of aluminium-containing buffers in dialysis are among the best preventive measures that can be taken.

The Mucorales are among the most common moulds found in the environment. Therefore, the first steps in the prevention of infection in the immunocompromised patient should consist of measures to reduce or eliminate obvious sources of environmental exposure, such as removing plants and flower arrangements from rooms where these individuals are being treated. Food items, such as old bread and fruit, that are often contaminated with mucoraceous moulds should not be offered to immunocompromised patients. Clusters of cutaneous mucormycosis have sometimes been traced to contaminated biomedical devices or linked to the use of non-sterile surgical dressings.

Inhalation of spores is thought to be the commonest mode of infection in immunocompromised patients with mucormycosis. The most effective, and expensive, method of protecting these individuals from nosocomial infection is to confine them to hospital rooms provided with high efficiency particulate air (HEPA) filtration (see Chapter 10). Although this reduces the risk of disease to an insignificant level, infection can still occur if patients are colonized before their admission to hospital, or are moved from the protected environment to other parts of the hospital for essential procedures to be performed. Immunocompromised patients should not be nursed in units with ongoing, adjacent construction work, but if this cannot be avoided, measures should be instituted to minimize the entry of dust and contaminated air.

There is currently no effective antifungal prophylaxis available for prevention of mucormycosis.

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14 Blastomycosis

14.1 Definition

The term blastomycosis is used to refer to infections due to the dimorphic fungus *Blastomyces dermatitidis*. Following inhalation, this organism causes a wide spectrum of clinical manifestations ranging from asymptomatic pulmonary infection in normal persons to widespread disseminated infection in immunocompromised individuals.

14.2 Geographical distribution

Most cases of blastomycosis have been reported from North America: from the south-central, south-eastern and mid-western states of the USA, and the Canadian provinces that border the Great Lakes. The disease is also endemic in Africa and parts of Central and South America.

14.3 The causal organism and its habitat

B. dermatitidis is a thermally dimorphic fungus. It exists in nature as a mould. In human and animal tissue it forms large, round budding yeast cells.

The natural habitat of *B. dermatitidis* is the soil, although attempts to recover it have seldom proved successful. The fungus appears to survive best in moist acidic soil that contains a high nitrogen and organic content. Higher soil temperatures and recent rainfall facilitate growth of the fungus.

14.4 Epidemiology

Inhalation of *B. dermatitidis* spores is the usual mode of infection in humans. The incubation period, which has been estimated from outbreaks in which exposure occurred over a limited time period, is 4–6 weeks. Occasional cases have followed traumatic cutaneous inoculation.

Outbreaks of blastomycosis are uncommon, but have provided us with important information on risk factors

for development of the disease. Most reported point-source outbreaks have been associated with occupational and recreational activities, often along streams or rivers, and have resulted from exposures to moist soil enriched with decaying vegetation. Apart from outbreaks, blastomycosis is more commonly seen in adults than children. More men than women are affected. The disease often occurs in individuals with an outdoor occupation, such as construction or farming, or recreational interest, such as hunting, fishing or boating.

B. dermatitidis is uncommon as an opportunistic pathogen, but it causes more aggressive disease in persons with underlying cell-mediated immunological defects, such as those with human immunodeficiency virus (HIV) infection, transplant recipients, and those receiving steroids or other immunosuppressive treatments. Immunocompromised persons with blastomycosis have a higher mortality rate (30–40%) than those who are not immunosuppressed.

Although blastomycosis is reportable in some states in the USA where it is endemic, information on the incidence of the disease is limited. In Wisconsin, as in several other endemic states, the average statewide annual incidence rate is about 1 case per 100 000 population. However, rates of 5–42 cases per 100 000 population have been reported from certain parts of Wisconsin, consistent with the hypothesis that *B. dermatitidis* exists in nature in reservoirs with a restricted geographic distribution.

14.5 Clinical manifestations

Inhalation of *B. dermatitidis* spores leads to a wide spectrum of clinical manifestations, ranging from a transient pulmonary infection which subsides without treatment to chronic pulmonary infection or to more widespread disseminated disease. The skin, bones and genitourinary system are the most frequent sites of extra-pulmonary disease.

14.5.1 Pulmonary blastomycosis

About 50% of individuals exposed to *B. dermatitidis* spores during outbreaks develop an acute symptomatic pulmonary infection, similar to that seen with histoplas-

mosis or coccidioidomycosis, about 4–6 weeks after exposure.

Acute pulmonary blastomycosis usually presents as a non-specific flu-like illness characterized by fever, chills, productive cough, myalgia, arthralgia, pleuritic chest pain and weight loss. The radiological findings are non-specific and include lobar or segmental consolidation, often in the lower lobes. Most otherwise healthy persons recover after 2–12 weeks of symptoms, but some return months later with infection of other sites. Other patients with acute blastomycosis fail to recover and develop a chronic pulmonary infection or disseminated infection.

The symptoms of chronic pulmonary blastomycosis are similar to those of tuberculosis and include productive cough, haemoptysis, weight loss, night sweats, malaise and fever that is often low grade. Spontaneous resolution of the infection is unusual. The radiological findings are more dramatic than those seen in patients with acute infection and include consolidation, fibronodular interstitial infiltrates, mass lesions, pleural thickening and pleural effusions. Cavitation is uncommon.

In immunocompromised individuals, pulmonary disease more commonly presents with fever, diffuse infiltrates and progressive respiratory failure. The mortality rate is high.

14.5.2 Cutaneous blastomycosis

The skin is the most frequent site of disseminated blastomycosis, being involved in more than 70% of cases. The lesions tend to be painless and present either as raised verrucous lesions with irregular borders or as ulcers. The former, which are more common, begin as small maculopustular lesions that slowly spread to form large nodular or papulonodular lesions with heaped-up borders. These lesions appear on exposed sites, such as the face, neck and scalp, and can be mistaken for squamous cell carcinoma. Besides the skin, ulcerative lesions can appear on the mucosa of the nose, mouth and throat. These lesions begin as a pustule that spreads to form a superficial ulcer or slightly raised lesion with a bed of red granulation tissue.

14.5.3 Osteoarticular blastomycosis

Osteomyelitis occurs in about 30% of patients with disseminated blastomycosis. The spine, ribs and long bones are the commonest sites of infection. The lesions often remain asymptomatic until the infection spreads into contiguous joints, or into adjacent soft tissue causing abscess formation and sinus tract development. Infection of the spine can involve adjacent vertebral bodies with destruction of the intervening disc space.

The radiological findings are not specific and the well-defined osteolytic or osteoblastic lesions cannot be distinguished from those of other fungal or bacterial infections. Periosteal proliferation is unusual.

Arthritis is less common than osteomyelitis, occurring in up to 10% of patients with blastomycosis either as a result of haematogenous dissemination from the lung or spread from a contiguous bone lesion. The commonest sites of infection are the knee, ankle, elbow and wrist. The symptoms include swelling, pain and limited movement in the affected joint.

14.5.4 Genitourinary blastomycosis

The prostate, epididymis or testis are involved in 15–35% of men with disseminated blastomycosis. The prostate may be tender and enlarged, resulting in obstruction. Epididymitis presents as scrotal swelling with or without a draining sinus. Infection often spreads to the adjacent testis.

On occasion, venereal transmission of *B. dermatitidis* infection has resulted in self-limited genital ulceration or endometrial infection in women.

14.5.5 Other forms of disseminated blastomycosis

Haematogenous spread of infection to the central nervous system (CNS) is rare, except in immunocompromised individuals. Manifestations of CNS infection include meningitis and spinal or brain abscess. Meningitis is indolent in onset and tends to occur late in the course of *B. dermatitidis* infection. It is often lethal and is indistinguishable from other forms of chronic meningitis such as tuberculosis or cryptococcosis.

Other organs such as the adrenal glands, thyroid, liver, spleen and gastrointestinal tract are sometimes

involved. Choroiditis and endophthalmitis have been reported.

Although blastomycosis has been reported in patients with impaired T-cell-mediated immunological function, it is much less common than histoplasmosis or coccidioidomycosis. However, immunocompromised individuals are predisposed to develop severe manifestations of the disease, which can relapse, and is often associated with a high mortality rate during the first few weeks after onset of symptoms. In persons with the acquired immunodeficiency syndrome (AIDS), disseminated blastomycosis is usually associated with CD4 T-lymphocyte counts of less than 200 cells/μl. Cutaneous lesions are less common in HIV-infected individuals than in non-immunocompromised persons. Up to 40% of AIDS patients with blastomycosis have CNS disease, which manifests as either meningitis or brain lesions. Others have presented with a septic shock-like syndrome, similar to that seen with histoplasmosis (see Chapter 16).

14.6 Differential diagnosis

Tuberculosis of the lung, skin, bone or genital tract, coccidioidomycosis of the lung, bone or meninges, and mucocutaneous paracoccidioidomycosis are other infections that can be confused with blastomycosis. However, the endemic regions for blastomycosis have almost no overlap with those of the other two fungal infections.

14.7 Essential investigations and their interpretation

14.7.1 Microscopy

Microscopic examination of wet preparations of pus, sputum, bronchial washings, urine or other clinical material can permit the diagnosis of blastomycosis if the characteristic large round cells with thick refractile walls and broad-based single buds are seen. Atypical *B. dermatitidis* cells can, however, be confused with other pathogens, such as single or non-budding cells of *Paracoccidioides brasiliensis*, *Histoplasma capsulatum* var. *duboisii* and non-encapsulated cells of *Cryptococcus neoformans*.

14.7.2 Culture

The definitive diagnosis of blastomycosis depends on isolation of the fungus in culture. Identifiable mould colonies can be obtained after incubation at 25–30°C for 1–3 weeks, but cultures should be retained for 4 weeks before being discarded. Unequivocal identification of an isolate as *B. dermatitidis* requires conversion to the yeast form which can take several weeks, or molecular testing with the Gen-Probe system which permits specific identification within 4 h.

14.7.3 Serological tests

Serological methods are of limited usefulness in the diagnosis of blastomycosis because of the high incidence of false-positive and false-negative reactions. The complement fixation (CF) test with unpurified antigen has been the least sensitive and least specific method. The immunodiffusion (ID) test is more specific, but negative reactions have been obtained in 10% of patients with disseminated infection and over 60% with localized infection. However, a positive reaction in the ID test can be considered diagnostic for blastomycosis.

14.8 Management

14.8.1 Pulmonary blastomycosis

All immunocompromised patients and patients with progressive pulmonary infection require treatment. Although spontaneous resolution has been reported in some immunocompetent individuals with acute pulmonary infection, patients who are left untreated must be followed up for long periods to detect signs of reactivation or progression of the disease.

Patients with mild to moderate pulmonary disease should be treated with oral itraconazole at a dosage of 200–400 mg/day for a minimum of 6 months. Oral ketoconazole (400–800 mg/day) is almost as effective, but less well tolerated than itraconazole. Fluconazole (400–800 mg/day) is less effective than itraconazole or ketoconazole, but it is sometimes useful in patients who do not tolerate or cannot absorb itraconazole or ketoconazole. If disease progression occurs during azole treatment, or if patients are unable to tolerate an azole, amphotericin B (0.5–0.7 mg/kg per day to a total dose of

1.5–2.5 g) is recommended. Pregnant women should be treated with amphotericin B.

Amphotericin B remains the drug of choice for patients with life-threatening infection such as acute respiratory distress syndrome. The recommended dose is 0.7–1.0 mg/kg per day. Patients who respond to initial treatment with amphotericin B can often be changed to itraconazole (200–400 mg/day) for the remainder of their treatment. Lipid-based formulations of amphotericin B have not been extensively evaluated in patients with blastomycosis, and their use should be restricted to patients who cannot tolerate the conventional formulation.

14.8.2 Disseminated blastomycosis

All patients with disseminated blastomycosis require treatment. Those with CNS infection should be given amphotericin B (0.7–1.0 mg/kg per day to a total dose of at least 2 g). Azoles should not be used for the initial treatment of CNS blastomycosis.

Patients with mild to moderate disseminated blastomycosis that does not involve the CNS should be treated with itraconazole (200–400 mg/day) for at least 6 months. Ketoconazole (400–800 mg/day) and fluconazole (400–800 mg/day) can be used in patients who do not tolerate or cannot absorb itraconazole.

Patients with life-threatening disseminated blastomycosis should be treated with amphotericin B (0.7–1.0 mg/kg per day to a total dose of 1.5–2.5 g). Patients who respond to initial treatment with amphotericin B can sometimes be changed to itraconazole (200–400 mg/day) for the remainder of their treatment.

Bone disease is more difficult to treat and more likely to relapse. For this reason, patients with osteomyelitis should be treated with an azole for at least 12 months. For patients whose disease progresses during treatment or who are unable to tolerate an azole, amphotericin B (0.5–0.7 mg/kg per day) is recommended.

Because of the high rate of relapse following amphotericin B treatment in patients with AIDS and other immunosuppressed individuals, long-term maintenance treatment with itraconazole is recommended. Maintenance treatment with ketoconazole is not recommended

because relapse rates are higher. Fluconazole is an option for patients who have had CNS disease and those who are unable to tolerate itraconazole.

14.9 Prevention

It is unusual for sites that are contaminated with *B. dermatitidis* to be identified. For this reason, such sites can neither be avoided nor decontaminated. Avoidance of outdoor activities in endemic regions might decrease the risk of infection, but it is neither practical nor justified.

The prevalence of blastomycosis in immunocompromised patients is too low to justify routine antifungal prophylaxis. The endemic regions of blastomycosis overlap those of histoplasmosis. Therefore, the recommendation that itraconazole prophylaxis be considered in HIV-infected persons who live, or have lived, in areas endemic for histoplasmosis if their CD4 T-lymphocyte counts are less than 100 cells/μl, should also provide protection against blastomycosis.

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15 Coccidioidomycosis

15.1 Definition

The term coccidioidomycosis is used to refer to infections due to the dimorphic fungus *Coccidioides immitis*. Following inhalation, this organism causes a wide spectrum of clinical manifestations ranging from asymptomatic illness in normal persons to widespread disseminated infection in immunocompromised and other high-risk individuals.

15.2 Geographical distribution

Most cases of coccidioidomycosis have been acquired in the south-western USA, but the disease is also endemic in parts of Mexico and in Central and South America. Outbreaks and sporadic cases of the disease have occurred among visitors to the endemic regions.

15.3 The causal organism and its habitat

C. immitis is a thermally dimorphic fungus. It exists in nature as a mould which fragments into single cells, termed arthrospores. In human and animal tissue, it forms characteristic large, round, thick-walled spherules which contain large numbers of endospores. Hyphae are seldom produced in tissue, but are sometimes found in chronic lung lesions.

C. immitis is a soil-inhabiting fungus with a restricted geographical distribution. It is confined to regions of the Western Hemisphere that correspond to the lower Sonoran desert life zone. In North America, the endemic region includes central and southern California, southern Arizona, southern New Mexico, and western Texas. The endemic region extends southwards into the desert regions of northern Mexico, and parts of Central and South America. An arid climate, alkaline soil, hot summers, and annual rainfall of 5–20 inches are characteristic of these regions.

Molecular analysis has demonstrated that isolates of *C. immitis* from California are distinct from isolates

of other geographical locations. As a result, it has been proposed that the organism should be separated into two species, *C. immitis* and *C. posadasii*, the former taxon being restricted to isolates from California. Isolates of both species cause identical forms of human disease.

15.4 Epidemiology

Inhalation of *C. immitis* arthrospores is the usual mode of infection in humans. The incubation period, which has been estimated from point source outbreaks (in which exposure occurred over a limited time period), is 1–3 weeks. In contrast to histoplasmosis, once individuals have recovered from *C. immitis* infection, they are usually immune to reinfection.

The major risk factor for development of infection with *C. immitis* is environmental exposure. The risk of infection depends on a number of factors including the nature of the environmental site, the activities performed, and the duration and degree of dust or soil exposure. Human infection has been associated with ground-disturbing activities, such as building construction, landscaping, farming, archaeological excavation and numerous recreational pursuits. Natural events that result in the generation of dust clouds, such as earthquakes and windstorms, have been associated with an increased risk of infection and have resulted in large outbreaks.

Certain persons are at increased risk for some forms of coccidioidomycosis. Risk factors for severe pulmonary disease include older age and diabetes mellitus, both of which are associated with alterations in host immunological response. Smoking is another risk factor for this form of coccidioidomycosis. Disseminated infection is more common among those of black, Asian or Filipino race, and among pregnant women in the third trimester. Individuals with underlying cell-mediated immunological defects, such as those with AIDS and those receiving immunosuppressive medications, are also at increased risk of disease dissemination.

It has long been recognized that coccidioidomycosis in California is a seasonal disease, with infection rates

peaking in October and November, the dustiest months of the year. It has also been observed that the number of cases is greatest when a wet winter follows a prolonged drought. Between 1991 and 1994, a major epidemic of coccidioidomycosis occurred in central California, during which the incidence of the disease increased from an average of 400 cases per annum to more than 4500 cases per annum. It has since been demonstrated that the principal factors governing the size of this epidemic were environmental. Most significantly, the drought that preceded the epidemic was the most sustained since the 1950s, ending in March 1991 with a period of heavy rainfall.

In Arizona, the incidence of coccidioidomycosis increased from 7 cases per 100 000 population in 1990, to 14.9 per 100 000 in 1995. This increase occurred in all age groups and in both men and women, but was greatest among persons aged 65 yr or older. In this age group the incidence of the disease increased from 14.6 to 34 cases per 100 000 between 1990 and 1995. This rise has been attributed to a recent surge in migration into the state of older non-immune individuals who were susceptible to *C. immitis* infection and more likely to manifest symptomatic illness.

In the 1980s coccidioidomycosis was recognized as an important opportunistic infection among human immunodeficiency virus (HIV)-infected persons living in the endemic regions. In southern Arizona, up to 27% of HIV-infected persons developed symptomatic coccidioidomycosis per annum, and 5–10% developed disseminated infection. The annual incidence of the disease has declined following the introduction of more effective combination antiretroviral treatments, including highly active antiretroviral therapy (HAART), and improvements in HIV healthcare in general. In southern Arizona, a review of surveillance data collected between 1995 and 1997 showed that symptomatic coccidioidomycosis developed in about 4% of persons living with the acquired immunodeficiency syndrome (AIDS) each year. This rate was much higher than the incidence among Arizona's general population in 1995 (15 cases per 100 000 population).

15.5 Clinical manifestations

Inhalation of *C. immitis* arthrospores leads to a wide spectrum of clinical manifestations, ranging from a transient pulmonary infection which resolves without treatment to chronic pulmonary infection or to more widespread disseminated disease.

15.5.1 Acute pulmonary coccidioidomycosis

Among immunocompetent persons, about 40% of those newly infected with *C. immitis* develop an acute symptomatic respiratory infection about 1–3 weeks after exposure. Higher rates of symptomatic infection (50–100%) have sometimes been reported during outbreaks.

Acute pulmonary coccidioidomycosis usually presents as a non-specific flu-like illness, characterized by fever, headache, chest pain, non-productive cough, myalgia, arthralgia, weight loss and malaise. Up to 50% of patients develop a mild, diffuse erythematous or maculopapular rash, covering the trunk and limbs, within the first few days of the onset of symptoms. More dramatic and persistent is the rash of erythema nodosum or erythema multiforme which occur in about 5% of infected persons, but are more common in women. These signs occur up to 3 weeks after symptoms first appear and resolve over several weeks. Both are often accompanied by non-infectious arthralgia in one or more joints. Most otherwise healthy persons will recover without treatment, their symptoms disappearing in a few weeks.

HIV-infected persons with *C. immitis* infection present with non-specific symptoms such as fever, chills, cough and weight loss. Chest radiographs will often reveal diffuse reticulonodular infiltrates. These are seldom seen in immunocompetent persons, and HIV-infected individuals who present with this form of disease usually have lower CD4 T-lymphocyte counts (mean of 50 cells/μl) than those with focal pneumonia due to *C. immitis*. The mortality rate in HIV-infected persons with diffuse pneumonia is high (about 70%).

15.5.2 Chronic pulmonary coccidioidomycosis

About 5–10% of infected individuals are left with residual signs of pulmonary coccidioidomycosis. In some

cases, solid nodules are formed in the infiltrate. These are benign. More commonly, peripheral thin-walled cavities develop. These often disappear within 2 yr. Most patients are asymptomatic, but haemoptysis occurs in up to 25% of cases. Immunocompromised individuals are more susceptible to the development of chronic pulmonary coccidioidomycosis. This is characterized by the presence of extensive thin-walled cavities that sometimes rupture into the pleural space causing bronchopleural fistulas and empyema.

Chronic progressive fibrocavitary pneumonia can occur in patients who are not debilitated or immunosuppressed. This illness mimics tuberculosis. The symptoms include fever, cough, chest pain and weight loss. These patients have apical fibronodular lesions with small cavities.

15.5.3 Disseminated coccidioidomycosis

Fewer than 1% of infected individuals develop disseminated coccidioidomycosis. This is a progressive disease that usually develops within 3–12 months of the initial infection, although it can occur much later following reactivation of a quiescent infection in an immunosuppressed individual.

The clinical manifestations of disseminated coccidioidomycosis range from a fulminant illness that is fatal within a few weeks if left untreated to an indolent chronic disease that persists for months or years. One or more sites may be involved, but the skin, soft tissue, bones, joints and meninges are most commonly affected.

Cutaneous and subcutaneous lesions are among the most common manifestations of disseminated coccidioidomycosis. Cutaneous lesions may be single or multiple and can persist for long periods. Their appearance is varied: verrucous papules, erythematous plaques and nodules have been described. Underlying bone or joint lesions may be found.

Osteomyelitis occurs in about 40% of patients with disseminated coccidioidomycosis. The spine, ribs, cranial bones and ends of the long bones are the most common sites of infection. Patients often remain asymptomatic, but persistent dull pain may occur. Irregular lytic or sclerotic lesions are seen on radiographs.

Computed tomographic (CT) scans are useful in detecting asymptomatic lesions and should be performed in all patients with serious or disseminated infection. The infection may spread into contiguous joints causing arthritis, or into adjacent soft tissue causing subcutaneous abscess formation. Draining sinuses often appear. The ankles and knees are the most common sites of joint infection.

Meningitis is the most serious complication of coccidioidomycosis. It occurs in 30–50% of patients with disseminated disease, and has a mortality rate of greater than 90% at 12 months if left untreated. It often gives rise to hydrocephalus. The symptoms are non-specific and insidious in onset. Persistent headache is often the earliest symptom. Mental changes, such as drowsiness and confusion, also occur. Other symptoms include loss of appetite, nausea and weight loss. Fever is minimal or absent in indolent cases. CT scans of the head are abnormal in most patients, the commonest finding being ventricular enlargement.

Most patients with symptomatic meningitis have abnormal cerebrospinal fluid (CSF) findings, including an elevated protein concentration, a lowered glucose concentration and a lymphocytic pleocytosis.

Disseminated disease is more common among HIV-infected individuals than among non-immunosuppressed persons with coccidioidomycosis. Meningitis is the most common presentation. The symptoms and signs are similar to those seen in HIV-negative individuals, except that concomitant diffuse pneumonia is often present. Other manifestations include skin, bone and joint disease, and some patients have hepatosplenic involvement. Disseminated disease is also common among solid organ transplant recipients with coccidioidomycosis; meningitis is a frequent clinical presentation.

15.6 Differential diagnosis

The clinical presentation of acute pulmonary coccidioidomycosis is similar to that of blastomycosis and histoplasmosis. The symptoms and clinical signs of chronic meningeal coccidioidomycosis are similar to those of cryptococcosis.

The large, cold abscesses that develop in soft tissue adjacent to *C. immitis* bone lesions can be mistaken for tuberculosis.

The radiological presentation in patients with residual lung cavities due to *C. immitis* infection is similar to that of a number of other infectious and non-infectious conditions, including cryptococcosis, tuberculosis and bacterial lung abscess. In most of these other conditions the cavities have a thicker wall, or more extensive surrounding infiltrate. The diffuse lung infiltrates that are found in AIDS patients with coccidioidomycosis can be confused with *Pneumocystis carinii* infection.

15.7 Essential investigations and their interpretation

It is essential to inform the laboratory if a diagnosis of coccidioidomycosis is suspected to ensure that proper precautions in handling of specimens and cultures are observed.

15.7.1 Microscopy

Direct microscopic examination of wet preparations of clinical material, such as sputum, joint fluid, pus or sediment of centrifuged CSF specimens, can permit the diagnosis of coccidioidomycosis if the characteristic large, thick-walled endospore-containing spherules are seen. Immature spherules and liberated endospores can, however, be confused with other pathogens, such as non-budding cells of *Blastomyces dermatitidis* or *Cryptococcus neoformans*. In general, spherules are easier to detect in pus, sputum or joint fluid than in blood or CSF.

15.7.2 Culture

The organism can be isolated from sputum, joint fluid, CSF sediment, pus and other specimens. Cultures must be set up in secure containers (slopes rather than plates) and handled with great care because of the danger of infection from the large concentrations of easily dispersed and highly infectious arthrospores. *C. immitis* is fast growing and identifiable colonies can be obtained after incubation at 25–30°C for 2–7 days.

In culture, *C. immitis* must be distinguished from other moulds that produce arthrospores. Molecular testing with the Gen-Probe system permits specific identification within 4 h. It is also useful for identifying atypical *C. immitis* isolates that fail to form arthrospores.

15.7.3 Skin tests

A positive coccidioidin (or spherulin) skin test result does not distinguish present from past infection. However, conversion from a negative to a positive result is a sign of recent infection because it occurs within 4 weeks of the onset of symptoms in 90–95% of patients. False-negative results are common in anergic patients with disseminated coccidioidomycosis. Unlike the histoplasmin skin test, coccidioidin does not interfere with the results of subsequent serological tests. The coccidioidin skin testing reagent is not currently available in the USA.

15.7.4 Serological tests

Serological tests are important in the diagnosis and management of coccidioidomycosis, although occasional cross-reactions occur in patients with histoplasmosis or blastomycosis.

The immunodiffusion tube precipitin (IDTP) test, which uses heated coccidioidin as antigen, detects IgM antibodies against *C. immitis* and is most useful for diagnosing recent infections. These antibodies can be found in most patients within 1–3 weeks after the onset of symptoms, but disappear within a few months in persons with acute pulmonary disease. The sensitivity of the IDTP test can be improved by first concentrating the serum. A latex particle agglutination (LPA) test is also available for the detection of IgM antibodies. This test is faster to perform than the IDTP test, but it has a >5% false-positive rate. For this reason a positive LPA test result must be confirmed by other methods.

The complement fixation (CF) test measures IgG antibodies against *C. immitis*. These antibodies do not appear until 4–12 weeks after infection, but may persist for long periods in patients with chronic pulmonary or disseminated disease. Low CF titres of 1:2 to 1:8 are commonly found in individuals without coccidioidomy-

cosis, but high or rising titres of CF antibodies are consistent with spread of *C. immitis* infection beyond the respiratory tract. More than 60% of patients with disseminated coccidioidomycosis have CF titres of 1:32 or greater. However, CF titres alone should not be used as the basis for diagnosis of dissemination, but should be considered along with the results of other clinical and laboratory investigations.

The detection of IgG antibodies in CSF is useful for the diagnosis of meningitis and, as with serum, CF titres diminish with successful treatment.

Between 70 and 80% of HIV-infected persons with coccidioidomycosis have at least one positive serological test result at the time of diagnosis. Most of those with negative results have diffuse pulmonary infection.

15.8 Management

Although disease will resolve without specific antifungal treatment in most individuals who present with acute pulmonary coccidioidomycosis, patients should be followed up for 1–2 yr, either to document resolution or to detect signs of pulmonary or extra-pulmonary complications. Patients who develop progressive pulmonary disease or disseminated disease require antifungal treatment, often for long periods of time. Treatment is indicated for all forms of coccidioidomycosis in persons with HIV infection and, as is the case for cryptococcosis and histoplasmosis, should be continued for life.

15.8.1 Acute pulmonary coccidioidomycosis

Up to 95% of newly infected individuals have an uncomplicated, self-limited illness and recover without antifungal treatment. No clinical trials have been completed to determine whether antifungal treatment shortens the course of the illness or reduces the likelihood of later complications. Therefore it is reasonable to refrain from treatment if the illness appears to be following a benign course.

Fewer than 5% of all newly infected patients require treatment. Those who should be treated to prevent progression or dissemination of infection include infants, pregnant women in the third trimester, individuals with HIV infection, organ transplant recipients, individuals

receiving high doses of corticosteroids and members of high-risk racial groups. Antifungal treatment is also indicated in non-immunocompromised patients with one or more of the following findings: persistent symptoms lasting for more than 2 months; weight loss of greater than 10%; intense night sweats persisting for more than 3 weeks; rising or elevated CF titres (>1:16) of IgG antibodies; failure to develop a skin test reaction; extensive or progressive infiltrates involving more than one half of one lung or portions of both lungs; prominent or persistent hilar or mediastinal lymph node enlargement; persistent debilitation.

The historical standard of treatment for patients who require active management is amphotericin B, despite the fact that its use is limited by a range of side-effects, particularly renal damage. The usual regimen is 0.5–0.7 mg/kg per day. It is usually recommended that treatment is continued until a total dose of 0.5–1.5 g has been given. With the advent of non-toxic oral antifungal agents, such as fluconazole and itraconazole, most clinicians are now using these drugs to treat patients with milder infections. The usual dose of fluconazole is 400 mg/day and this should be continued for 3–6 months. Pregnant women should be treated with amphotericin B.

Patients with diffuse pneumonia should receive amphotericin B (1.0 mg/kg per day). Once the patient has improved, usually within a few weeks, treatment can be changed to oral fluconazole (400 mg/day) or itraconazole (200 mg twice daily). The length of treatment depends on the underlying condition, but should be at least 12 months. In immunocompromised individuals, long-term azole maintenance treatment should be continued.

It is recommended that all HIV-infected persons who survive beyond the initial induction treatment should receive lifelong maintenance treatment to prevent relapse. The drug of choice is oral fluconazole (400 mg/day) or itraconazole (200 mg twice daily). Although patients with AIDS appear to be at low risk for relapse of coccidioidomycosis when their CD4 T-lymphocyte count rises to greater than 100 cells/μl in response to HAART, the number of individuals who have been

evaluated is insufficient to warrant a recommendation to discontinue maintenance treatment.

15.8.2 Chronic pulmonary coccidioidomycosis

Individuals with asymptomatic nodules do not require surgical resection or antifungal treatment. Those with small, asymptomatic cavities do not require intervention, but should be observed until spontaneous resolution occurs. Those with cavities that are still detectable after 2 yr, and those with enlarging cavities, often require surgical resection. This is recommended if the cavities are near the pleural surface, or if serious and persistent haemoptysis or bacterial superinfection is a problem. If surgical resection is not possible, oral treatment with fluconazole or itraconazole will often lead to improvement, although symptoms can recur after the antifungal is discontinued. In otherwise healthy individuals, rupture of a cavity into the pleural space requires surgical intervention, with closure by lobectomy and decortication along with pre- and post-operative antifungal treatment. In patients with coexisting disease, management includes amphotericin B or azole treatment before surgery, or chest tube drainage without surgery.

Patients with chronic fibrocavitary pneumonia should receive treatment with oral fluconazole (400 mg/day) or itraconazole (200 mg twice daily). If the patient's condition improves, treatment should be continued for at least 12 months. If the patient does not respond, the dose of fluconazole can be increased, or the treatment changed to amphotericin B (0.5–0.7 mg/kg per day). Surgical resection is an option if the lesions are well localized, or where significant haemoptysis has occurred.

15.8.3 Disseminated coccidioidomycosis

The historical standard of treatment for patients with non-meningeal disseminated coccidioidomycosis is amphotericin B. The adult dose is 1.0–1.5 mg/kg per day. It is usually recommended that treatment should be continued until a total dose of 2.5–3.0 g has been given. The results of treatment are often disappointing and relapse is a common problem.

Most clinicians are now using oral fluconazole (400 mg/day or higher) to treat patients with skin, soft

tissue, bone or joint infections. Itraconazole (200 mg twice daily) is also effective, but less well tolerated. Amphotericin B should be substituted if the lesions worsen and are in critical locations such as the spinal column.

Surgical debridement or stabilization of infected tissue is important in the management of osteomyelitis and in the diagnosis and drainage of soft tissue lesions.

HIV-infected persons with mild or moderate, non-meningeal forms of disseminated coccidioidomycosis, such as cutaneous or osteoarticular infection, can be treated with fluconazole (400 mg/day) from the outset. These patients should be evaluated, and have serological testing repeated at 3–4 month intervals. A rising CF titre is suggestive of relapse and should prompt more extensive evaluation. Treatment options include a higher dose of fluconazole or substitution of amphotericin B.

In HIV-infected persons with no clinical signs of coccidioidomycosis and negative CF test results, the dose of fluconazole can be reduced to 200 mg/day. This should be continued for life. Although patients with AIDS appear to be at low risk for relapse of coccidioidomycosis when their CD4 T-lymphocyte count rises to greater than 100 cells/μl in response to HAART, the number of individuals who have been evaluated is insufficient to warrant a recommendation to discontinue maintenance treatment.

15.8.4 Meningitis

Until the advent of oral treatment with fluconazole or itraconazole, the management of this most serious form of coccidioidomycosis consisted of prolonged courses of intrathecal treatment with amphotericin B. This was associated with a high incidence of side-effects and complications, including chemical arachnoiditis, but an estimated 50–75% of patients achieved a sustained remission. The intrathecal dose of amphotericin B ranges from 0.01 to 1.5 mg. It is administered at intervals ranging from daily to weekly, beginning at a low dose and increasing until patient intolerance develops.

Because oral fluconazole is so much more benign than intrathecal amphotericin B, it is now the drug of choice for coccidioidal meningitis. The dosage of fluconazole

used in clinical trials was 400 mg/day, and this led to clinical improvement in up to 80% of patients. However, some clinicians prefer to begin treatment with higher doses of oral fluconazole (800 or 1000 mg/day). Oral itraconazole, at dosages of 400–600 mg/day, has also been reported to be effective. Neither fluconazole nor itraconazole eradicate meningeal infection with *C. immitis* and patients who respond to these azoles should continue this treatment for life to prevent relapse. Individuals who do not respond to fluconazole or itraconazole should be considered for intrathecal amphotericin B, with or without continuation of azole treatment.

In most cases, hydrocephalus requires a shunt to reduce elevated intracranial pressure. This complication can develop regardless of the antifungal treatment being used, and changing to another drug is not required.

Oral fluconazole, at a dosage of 800 mg/day, is now the treatment of choice for HIV-infected persons with coccidioidal meningitis. Intrathecal amphotericin B is indicated for those who fail to respond to fluconazole treatment. The combination of an azole and parenteral amphotericin B appears to be useful for HIV-infected individuals with both meningitis and diffuse pneumonia due to *C. immitis*. In patients who no longer have clinical signs of meningitis, the dose of fluconazole can be reduced to 400 mg/day for lifelong suppression.

15.9 Prevention

With an ageing population and an increase in the number of immunosuppressed persons, serious forms of coccidioidomycosis are becoming an important public health problem in the south-western USA. Prevention of sporadic exposure to environmental sources of *C. immitis* arthrospores in this and other endemic regions is difficult. Nevertheless, individuals should be advised to avoid activities associated with increased risk, such as extensive exposure to disturbed soil at construction sites or exposure to dust storms. If a contaminated site must be disturbed, workers should be provided with personal protective equipment such as masks and respirators. Dust-control measures, such as wetting soils before disturbing the earth, should be used to decrease the amount of dust generated. Individuals should be warned to avoid

transporting soil and other potential contaminated fomites (e.g. geologic specimens) from endemic regions.

Although several clinical trials have documented the effectiveness of prophylaxis with fluconazole (200 mg/day) and itraconazole (200 mg/day) in preventing histoplasmosis and cryptococcosis in HIV-infected persons, low enrolment rates led to the discontinuation of a similar trial for coccidioidomycosis. However, a case-control study, conducted to evaluate risk factors for coccidioidomycosis in persons living with AIDS, showed that having received an azole drug was associated with a reduced risk of *C. immitis* infection. Routine prophylaxis with fluconazole is not recommended because of concerns about the high costs of such treatment, the lack of data on survival benefits, and the potential for drug interactions and resistance. Nonetheless, given the substantial risk of disseminated coccidioidomycosis in HIV-infected black persons, fluconazole chemoprophylaxis should be considered for individuals who live, or have lived, in endemic disease areas if their CD4 T-lymphocyte counts are less than 200 cells/μl, especially those who are at high risk because of occupational exposure.

In most cases, natural infection with *C. immitis* confers lifelong immunity to reinfection. Because of this, a formalin-killed spherule vaccine was developed and tested in a human trial in the 1980s. However, the results were disappointing. New vaccines are currently being developed, and they may offer the best way to prevent coccidioidomycosis in high-risk groups. Among those who might benefit from vaccination are persons at increased risk for severe pulmonary and disseminated infection.

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Fungal Infection: Diagnosis and Management, Third Edition
Malcolm D. Richardson, David W. Warnock

16 Histoplasmosis

16.1 Definition

The term histoplasmosis is used to refer to infections due to the dimorphic fungus *Histoplasma capsulatum*. Following inhalation, this organism causes a wide spectrum of clinical manifestations ranging from asymptomatic illness in normal persons to widespread disseminated infection in immunocompromised individuals.

16.2 Geographical distribution

Histoplasmosis is the most common endemic mycosis in North America, but it is also found throughout Central and South America. In the USA, the disease is most prevalent in the mid-western and central states. Other endemic regions include parts of Africa, Australia and eastern Asia, in particular India and Malaysia.

16.3 The causal organism and its habitat

H. capsulatum is a thermally dimorphic fungus. It exists in nature as a mould. In human and animal tissue it forms small round budding yeast cells. Two varieties of *H. capsulatum* are recognized: var. *capsulatum* and var. *duboisii*. The latter is the cause of African histoplasmosis. The two varieties are indistinguishable in their mould forms, but differ in their parasitic forms. The cells of the tissue form of var. *duboisii* are much larger and have thicker walls than those of var. *capsulatum*.

The natural habitat of *H. capsulatum* is the soil. The fungus has been recovered most frequently from soil enriched with bird or bat droppings. Unlike bats, birds do not become infected with *H. capsulatum* and their droppings are primarily a nutrient source for *H. capsulatum* already present in the soil. Soil samples from sites where birds have roosted have been found to remain contaminated for at least 10 yr after the roost has been cleared. Bats are capable of depositing *H. capsulatum*

with their droppings and can distribute the fungus far from an existing natural focus.

16.4 Epidemiology

Inhalation of *H. capsulatum* spores is the usual mode of infection in humans. The incubation period, which has been estimated from point-source outbreaks (in which exposure occurred over a limited time period), is 1–3 weeks. In cases of reinfection, the incubation period appears to be shorter (4–7 days after exposure).

The major risk factor for development of infection with *H. capsulatum* is environmental exposure. The risk of infection depends on a number of factors including the nature of the environmental site, the activities performed, and the duration and degree of dust or soil exposure. Longer and more intense exposures usually result in more severe pulmonary disease. Most reported outbreaks have been associated with exposures to sites contaminated with *H. capsulatum,* or have followed activities that disturbed accumulations of bird or bat droppings. These include building construction, renovation and demolition, soil excavation, spelunking, and clearing sites harbouring the fungus.

Persons with underlying illnesses are at increased risk for some forms of histoplasmosis. Chronic pulmonary histoplasmosis is common among persons with underlying lung disease such as emphysema. Disseminated histoplasmosis is more common among individuals with underlying cell-mediated immunological defects, such as persons with human immunodeficiency virus (HIV) infection, transplant recipients, persons with haematological malignancies, and those receiving steroids or other immunosuppressive treatments. Immunocompromised persons with histoplasmosis have a higher mortality rate than those who are not immunosuppressed.

Histoplasmosis is reportable in 13 states in the USA, but the extent of reporting of cases of the disease has been limited. As a result, the incidence of histoplasmosis in the USA is unknown. Information on the prevalence of the disease has mostly come from skin test surveys performed in the 1960s which defined the areas within each state where reactors to histoplasmin resided.

However, these studies were limited to young male adults and, therefore, were not representative of the whole population. Since then, no large prevalence studies have been conducted.

With the advent of the acquired immunodeficiency syndrome (AIDS), histoplasmosis emerged as an important opportunistic infection among HIV-infected persons living in endemic disease areas. Early in the AIDS epidemic, histoplasmosis occurred in about 5% of persons with AIDS living in areas of endemic disease in the USA. Many cases of histoplasmosis have also been reported from cities outside the endemic disease areas, such as New York. In most cases, these patients were Hispanic men who had previously lived in countries in Central or South America with endemic disease, suggesting reactivation of an old latent infection. In contrast, the marked increase in the incidence of disseminated histoplasmosis among AIDS patients in Indianapolis during a large outbreak of the disease in the late 1980s suggests that the infection was acquired during the outbreak rather than by reactivation. The incidence of histoplasmosis has declined following the introduction of more effective combination antiretroviral treatments, including highly active antiretroviral therapy (HAART) and improvements in HIV healthcare in general.

16.5 Clinical manifestations

Inhalation of *H. capsulatum* spores leads to wide spectrum of clinical manifestations, ranging from a transient pulmonary infection which subsides without treatment to chronic pulmonary infection or to more widespread disseminated disease.

16.5.1 Acute pulmonary histoplasmosis

Fewer than 5% of individuals exposed to *H. capsulatum* spores develop symptomatic disease in an endemic setting. However, during outbreaks, when higher levels of exposure occur, 50–100% of patients develop acute symptomatic and often severe infection after an incubation period of 1–3 weeks.

Acute pulmonary histoplasmosis usually presents as a non-specific flu-like illness characterized by high-grade fever, chills, headache, non-productive cough, myalgia,

pleuritic chest pain, loss of appetite and fatigue. A few patients present with an aseptic arthritis or arthralgia associated with erythema multiforme or nodosum. Most otherwise healthy persons will recover without treatment, their symptoms disappearing within 3 weeks. However, fatigue and weakness can persist for several months.

Chest radiographs will often reveal small, scattered, nodular infiltrates. Hilar lymph node enlargement is often evident and pleural effusion may be found. The infiltrates tend to heal over several months leaving scattered calcifications throughout both lung fields. Healing of a localized infiltrate may result in the development of a residual round nodule, often termed a histoplasmoma, that enlarges as fibrous material is deposited around the lesion. If calcification is absent, these benign lesions cannot be distinguished from a neoplasm on chest radiographs.

Individuals reinfected with *H. capsulatum* develop a similar illness, but this occurs after a much shorter incubation period (less than 1 week). These patients present with abrupt onset of malaise, headache, chills, fever and cough, but the symptoms may be less severe and of shorter duration. The radiological signs are different from those seen in newly infected individuals. Multiple, small, interstitial miliary nodules are present, but there is no mediastinal lymph node enlargement and pleural effusions are not seen. Late calcification does not occur. The illness tends to resolve without treatment.

Following inhalation of *H. capsulatum*, the organism gains access to the alveolar and interstitial lung tissue and then spreads through the lymphatics to the lymph nodes. In some patients this process results in mediastinal lymph node enlargement which in turn can lead to tracheal, bronchial or oesophageal obstruction. Symptoms that include cough, chest pain, shortness of breath and haemoptysis can be indicative of granulomatous mediastinitis. This is due to active inflammation of the lymph nodes, rather than fibrotic reactions to past infection. Although symptoms are often mild and usually resolve spontaneously over a few months, they may be more severe and protracted.

Fibrosing mediastinitis is a late complication of histoplasmosis arising from nodal regions and leading to invasion and occlusion of blood vessels. Patients often report symptoms of several years duration at the time of diagnosis. The course is progressive and often fatal.

Pericarditis occurs in 5–10% of individuals with acute histoplasmosis and appears to be caused by the inflammatory response to the infection. Patients respond to non-steroidal anti-inflammatory agents and do not require antifungal treatment.

16.5.2 Chronic pulmonary histoplasmosis

Chronic pulmonary histoplasmosis is a slowly progressive illness that usually occurs in middle-aged individuals with underlying chronic obstructive lung disease. It first manifests itself as a transient, segmental pneumonia that sometimes heals without treatment, but often progresses to fibrosis and cavitation with destruction of significant amounts of lung tissue. If left untreated, death can result from progressive lung failure.

In patients with pneumonia, the symptoms often include productive cough, fever, chills, weight loss, malaise, night sweats and pleuritic chest pain. The typical radiological findings in these patients are interstitial infiltrates in the apical segments of the upper lobes of the lung.

The most prominent symptoms in patients with chronic fibrosis and cavitation are cough and sputum production. Other symptoms include fever, chest pain, fatigue and weight loss. Haemoptysis develops in more than 30% of these individuals. Chest radiographs will reveal progressive cavitation and fibrosis. Cavities with walls thicker than 3 mm in diameter are associated with established and continuing infection. Lesions are more common in the right upper lobe than in the left, but bilateral lesions develop in about 25% of patients and, in time, the infection will spread to the lower lobes. Pleural effusion is uncommon, but pleural thickening adjacent to lesions is found in 50% of patients.

16.5.3 Disseminated histoplasmosis

Haematogenous dissemination from the lungs to other tissues occurs in most, if not all, infected individuals

during the first 2 weeks after infection before a specific immunological response has developed. In most cases, however, the infection is non-progressive and leads only to the development of calcified granulomata in the liver and spleen. Disseminated histoplasmosis has been estimated to occur in 1 in 2000 exposed individuals, in particular those with underlying T-cell-mediated immunological defects, or those at the extremes of age.

The clinical manifestations of disseminated histoplasmosis range from an acute illness that is fatal within a few weeks if left untreated (often seen in infants and immunosuppressed patients) to an indolent, chronic illness that can affect a wide range of sites. Treatment is essential for all patients with disseminated histoplasmosis.

In non-immunosuppressed individuals, disseminated histoplasmosis follows an indolent, chronic course. Often chest radiographs are normal. Hepatic infection is common, but enlargement of the liver and spleen is not as pronounced as in patients with fulminant infection. Adrenal gland destruction is a common problem. Mucosal ulcers are found in over 60% of patients with indolent infection. The mouth and throat are often affected, but lesions also occur on the lip, nose, glans penis and other sites. Most patients have a single lesion, painless at first, with a characteristic, distinct heaped-up margin. Cutaneous lesions are uncommon, occurring in less than 10% of patients.

Central nervous system (CNS) disease occurs in 5–20% of patients with indolent disseminated histoplasmosis, presenting as chronic meningitis or focal brain lesions. Headache is the most common presenting symptom in individuals with meningitis. Other symptoms include fever, headache, confusion and focal neurological deficits. Computed tomographic (CT) scans or magnetic resonance imaging (MRI) will reveal single or multiple enhancing lesions. Most patients have abnormal cerebrospinal fluid (CSF) findings, including an elevated protein concentration, a lowered glucose concentration and a mild lymphocytic pleocytosis. *H. capsulatum* has been isolated from the CSF in 25–50% of cases.

Other manifestations of chronic disseminated histoplasmosis include endocarditis (often with large

vegetations) and mucosal ulcerations in the gastrointestinal tract. Occasional cases of bone and joint infection have occurred in infants and children.

In infants and immunosuppressed patients, acute disseminated histoplasmosis often presents as high fever, chills, prostration, malaise, loss of appetite and weight loss. The liver and spleen are enlarged and liver function tests are abnormal. Anaemia is common. Chest radiographs are often normal, but if abnormal, diffuse interstitial infiltrates are more common than focal infiltrates. Pleural effusions are uncommon. Mucosal lesions can occur, but are much less common than in patients with indolent progression of the illness.

In AIDS patients, disseminated histoplasmosis is usually associated with advanced immunosuppression. Most patients have CD4 T-lymphocyte counts of less than 75 cells/μl, and present with non-specific symptoms, such as fever and weight loss, that are often gradual in onset. Up to 25% of patients have an enlarged liver and spleen and a similar proportion have anaemia, leucopenia and thrombocytopenia. Mucosal lesions are uncommon, but 15–20% of patients have an erythematous, maculopapular non-pruritic skin rash. About 30% of AIDS patients with histoplasmosis have normal chest radiographs on admission, but 50% have diffuse interstitial infiltrates. CNS involvement occurs in 10–20% of cases: the manifestations include meningitis and focal brain lesions.

From 10 to 20% of AIDS patients with disseminated histoplasmosis have presented with a septic shock-like syndrome, consisting of high fever, hypotension, hepatic and renal failure, respiratory distress and disseminated intravascular coagulation. This acute septic presentation appears to be a late manifestation of histoplasmosis in patients in whom the diagnosis has been missed. The mortality rate in these cases is high.

16.5.4 African histoplasmosis

The clinical manifestations of *H. capsulatum* var. *duboisii* infection differ in a number of respects from those of var. *capsulatum* infection described in the preceding sections. The illness is indolent in onset and the predominant sites affected are the skin and bones. Those with

more widespread infection involving the liver, spleen and other organs have a febrile wasting illness that is fatal within weeks or months if left untreated.

Cutaneous lesions are common in patients with African histoplasmosis. Multiple papular lesions often develop on the face and trunk. Nodular lesions are less common. Both nodules and papules often enlarge and ulcerate. Osteomyelitis occurs in about 30% of patients with African histoplasmosis. The spine, ribs, cranial bones, sternum and long bones are the most common sites of infection and multiple lesions are often found. The lesions are often painless. The infection may spread into contiguous joints causing arthritis, or into adjacent soft tissue, causing a purulent subcutaneous abscess. Draining sinuses often appear.

16.6 Differential diagnosis

The clinical presentation of acute pulmonary histoplasmosis is similar to that of many other illnesses. The clinical and radiological presentation of chronic pulmonary histoplasmosis is similar to that of tuberculosis and coccidioidomycosis. The mucocutaneous lesions of chronic disseminated histoplasmosis can be confused with a number of other infectious and non-infectious conditions, including tuberculosis, syphilis, paracoccidioidomycosis and lichen planus.

16.7 Essential investigations and their interpretation

16.7.1 Microscopy

Microscopic examination of wet preparations of clinical material, such as sputum or pus, is not a suitable method for the diagnosis of histoplasmosis. All material should be examined as stained smears.

If microscopic examination of Wright-stained peripheral blood smears, stained tissue sections or other specimens from individuals who have resided in or visited endemic areas reveals small oval budding cells (often clustered within macrophages), the diagnosis of histoplasmosis should be suspected. *H. capsulatum* var. *capsulatum* cells can, however, be confused with other pathogens, such as *Penicillium marneffei*, as well as with atypical small cells of *Blastomyces dermatitidis*

and small, non-encapsulated cells of *Cryptococcus neoformans*.

If clinical specimens contain large, thick-walled cells and the patient has resided in or visited the African continent, *H. capsulatum* var. *duboisii* should be suspected as the pathogen.

Organisms tend to be much more abundant in peripheral blood smears and bronchial washings from persons with AIDS.

16.7.2 Culture

The definitive diagnosis of histoplasmosis depends on isolation of the fungus in culture. Incubation of cultures should be at 25–30 °C for 4–6 weeks. It is often difficult to distinguish the mycelial colonies of *H. capsulatum* from those of *B. dermatitidis* and species of *Chrysosporium* and *Sepedonium*. Unequivocal identification of a mycelial isolate as *H. capsulatum* requires conversion to the yeast form which can take 3–6 weeks, or molecular testing with the Gen-Probe system which permits specific identification within 4 h.

H. capsulatum has been isolated from blood, sputum, bone marrow, pus, tissue and other specimens. Lysis centrifugation has been the most useful method for recovering it from blood.

16.7.3 Skin tests

The histoplasmin skin test is not recommended for diagnosis of histoplasmosis because a positive result does not distinguish present from past infection. Nor does a negative result rule out recent infection. Moreover, it can induce the formation of antibodies making the results of subsequent serological tests difficult to interpret. The histoplasmin skin testing reagent is not currently available in the USA.

16.7.4 Serological tests

Serological tests are often helpful in the diagnosis of the different forms of histoplasmosis. The immunodiffusion (ID) and complement fixation (CF) tests, with histoplasmin as antigen, remain the most useful methods. False-negative reactions can occur in immunosuppressed patients with disseminated histoplasmosis.

The CF test is more sensitive, but less specific than the ID test in histoplasmosis. It becomes positive 2–6 weeks following infection; a CF titre of at least 1:32 or a fourfold rise in titres between paired specimens is considered strong presumptive evidence of active infection. The CF test for histoplasmosis is not altogether specific and cross-reactions can occur in patients with blastomycosis or coccidioidomycosis. Non-specific CF tests tend to give titres of 1:8–1:32. However, similar titres are often obtained in tests with serum from patients with proven histoplasmosis.

The ID test is more specific, but less sensitive than CF for histoplasmosis. Using histoplasmin as antigen, two major precipitin bands can be detected. The H band is specific for acute pulmonary histoplasmosis, but only occurs in 10–20% of cases. The M band can be detected in up to 75% of cases of acute infection, but can persist for many months after the initial infection. It may also be found in those who have had a recent histoplasmin skin test. Because the H and M bands are specific for histoplasmosis, the ID test provides a more specific diagnosis with serum specimens that have low CF titres or that cross-react in CF tests.

Antigen detection in the urine is sometimes useful for the diagnosis of acute pulmonary histoplasmosis, provided samples are obtained within 2 weeks after exposure. Antigen testing is most useful for diagnosis of disseminated histoplasmosis in persons with AIDS. *H. capsulatum* antigen has been detected in the blood of 85% and in the urine of 95% of these individuals. Antigen has also been detected in CSF and bronchoalveolar lavage (BAL) fluid. Antigen levels in the urine decrease in AIDS patients receiving antifungal treatment and rise in those who have relapsed. If treatment is stopped before antigen concentrations in the urine and serum revert to negative, patients should be monitored for relapse and retested at 3–6-month intervals until antigen tests become negative.

16.8 Management

16.8.1 Acute pulmonary histoplasmosis

Antifungal treatment is not usually indicated for persons with acute, localized pulmonary infection, as this form

of the disease is self-limited, often resolving within a few weeks. In most cases spontaneous improvement has begun before the condition is diagnosed. If fever persists for more than 3 weeks, this may be a sign that the patient is developing progressive disseminated disease. Treatment with itraconazole (200 mg/day for 6–12 weeks) should be considered for patients who have shown no clinical improvement after 1 month of observation. However, it is unclear whether treatment hastens recovery or prevents complications.

Individuals with diffuse radiological involvement following more intense exposure often develop more severe disease. They may become hypoxemic and may even require ventilatory support. Without treatment, recovery is usually slow and the outcome may be fatal. Amphotericin B (0.7 mg/kg per day) is the initial treatment of choice in patients who require ventilatory support. As an alternative, one of the lipid-based formulations of amphotericin B (3 mg/kg per day) can be used. Once the patient has been discharged from hospital, itraconazole (200–400 mg/day) should be used to complete a 12-week course of treatment. Individuals who do not require hospitalization can be treated with itraconazole (200–400 mg/day) from the outset. This should be given for 6–12 weeks. The role of corticosteroids in treatment of extensive pulmonary histoplasmosis is unclear, but prednisolone (60 mg/day for 2 weeks) may be helpful.

Although symptoms are often mild and resolve over a few months, patients with enlarged mediastinal lymph nodes sometimes require treatment to relieve symptoms of obstruction. The initial treatment of choice in individuals with severe obstructive complications of mediastinal histoplasmosis is amphotericin B (0.7–1.0 mg/kg per day). Treatment can be changed to oral itraconazole (200–400 mg/day) once the patient is well enough to be discharged from hospital. Itraconazole (200–400 mg/day for 6–12 months) is recommended for patients with milder symptoms that persist for more than 1 month. Prednisone (40–80 mg/day for 2 weeks) can be helpful in individuals with major airways obstruction. Surgical resection of obstructive mediastinal masses

can be difficult and should be reserved for patients who remain symptomatic and continue to demonstrate obstruction, despite antifungal treatment.

There is insufficient information at present on which to make firm recommendations for the treatment of fibrosing mediastinitis. The progressive course of this condition makes it difficult to withhold antifungal treatment, however, patients who have fibrosing mediastinitis do not respond to this form of management. Nor has corticosteroid treatment been helpful. Surgery should be approached with great caution and should only be considered in those who are expected to die without intervention.

16.8.2 Chronic pulmonary histoplasmosis

Treatment is indicated in all individuals with chronic pulmonary histoplasmosis. Itraconazole (200–400 mg/day for 12–24 months) is the drug of choice for most patients. Amphotericin B (0.7 mg/kg per day) is recommended for patients who require hospitalization because of ventilatory problems or general debilitation, or who are unable to take oral itraconazole because of drug interactions or impaired absorption. Amphotericin B should also be used in patients who fail to improve after at least 12 weeks of treatment with itraconazole. If patients cannot tolerate the full dosage of amphotericin B, it can be reduced to 0.5–0.6 mg/kg per day, or one of the lipid-based formulations can be used. If amphotericin B is used for the full course of treatment, a total dose of 35 mg/kg should be given over a 3–4-month period. In most individuals, however, treatment can be changed to itraconazole (200–400 mg/day).

Fluconazole (200–400 mg/day) is less effective than itraconazole or amphotericin B. It can be used in patients who cannot be given itraconazole, but the dose should be increased to 400–800 mg/day. Oral ketoconazole (200–400 mg/day) can also be used, but it is less well tolerated than itraconazole or fluconazole.

16.8.3 Disseminated histoplasmosis

Treatment is essential for all patients with disseminated histoplasmosis, even those with a single focal lesion.

HIV-NEGATIVE PATIENTS

Amphotericin B remains the recommended treatment for immunocompetent and immunocompromised patients without AIDS with disseminated histoplasmosis who require hospitalization. The usual regimen is 0.7–1.0 mg/kg per day. Most patients respond rapidly to amphotericin B and can then be treated with oral itraconazole. The transition can be made after the patient becomes afebrile, no longer requires blood pressure or ventilatory support, or parenteral fluids or nutrition. If amphotericin B is to be used over the full course, the total dosage should be 35 mg/kg given over 2–4 months.

Oral itraconazole (200–400 mg/day for 6–18 months) is the drug of choice for non-immunosuppressed individuals with the milder, non-meningeal forms of chronic disseminated infection who do not require hospitalization and for the continuation of treatment in those who have improved on amphotericin B treatment. Fluconazole should only be used in patients who cannot take itraconazole. The dosage should be at least 400 mg/day in immunocompetent individuals and 800 mg/day in immunosuppressed patients. Ketoconazole (200–400 mg/day) is reasonably effective, but less well tolerated than itraconazole or fluconazole.

HIV-INFECTED PATIENTS

The management of AIDS patients with disseminated histoplasmosis presents special problems. The recommended treatment regimen consists of an initial 12-week period of intensive induction treatment designed to induce a remission in the clinical illness followed by long-term maintenance treatment to prevent relapse.

Amphotericin B (0.7–1.0 mg/kg per day) is recommended as induction treatment in patients who are sufficiently ill to require hospitalization. It can be replaced with itraconazole (400 mg/day) when the patient no longer requires hospitalization or parenteral treatment to complete the 12-week period of induction treatment. Itraconazole (600 mg/day for 3 days and then 400 mg/day for 12 weeks) is the treatment of choice for individuals who have mild or moderate symptoms, or who do

not require hospitalization. Fluconazole (800 mg/day) is an alternative for patients who cannot take itraconazole.

It is recommended that all patients who survive beyond the initial induction treatment should receive lifelong maintenance treatment to prevent relapse. The drug of choice is oral itraconazole (200 mg twice daily). Amphotericin B (50 mg once weekly) is an alternative, but is not as well tolerated. Maintenance treatment with fluconazole (400–800 mg/day) should be considered in AIDS patients who cannot tolerate or fail to absorb itraconazole, and prefer not to be treated with amphotericin B. However, it is much less effective than itraconazole. Although patients with AIDS appear to be at low risk for relapse of histoplasmosis when their CD4 T-lymphocyte count rises to greater than 100 cells/μl in response to HAART, the number of individuals who have been evaluated is insufficient to warrant a recommendation to discontinue maintenance treatment.

16.8.4 CNS histoplasmosis

The optimal treatment for meningeal histoplasmosis is unclear, but aggressive management is recommended because of the poor outcome. Amphotericin B (0.7–1.0 mg/kg per day) is the usual drug of choice. It should be given to a total dose of 35 mg/kg over a 3–4-month period. Thereafter, fluconazole (800 mg/day) can be given for another 9–12 months to reduce the risk of relapse. Liposomal amphotericin B (3–5 mg/kg per day) is a potential alternative for patients who have failed on the conventional formulation. It should be given over a 3–4-month period.

Intrathecal or intraventricular administration of amphotericin B is an option for patients who relapse despite chronic maintenance treatment. However, the results have been poor and this approach is not recommended except for patients in whom all other forms of treatment have failed.

There are a few reports of successful treatment of focal brain lesions with amphotericin B. Treatment can be changed to oral itraconazole (400–600 mg/day) once the patient's condition has improved.

16.9 Prevention

Prevention of sporadic exposure to sources of *H. capsulatum* spores in areas of endemic disease is difficult. Nonetheless, it is feasible to prevent large-scale exposures during cleaning, construction work and so on. If a contaminated site must be disturbed, workers should be provided with personal protective equipment, such as masks and respirators, which should be worn during activities that can lead to aerosolization of infectious material. Dust-control measures, for example, wetting soils before disturbing the earth, should be used to decrease the amount of dust generated during construction, demolition or excavation.

Individuals at increased risk for severe infection, especially immunocompromised persons, should be advised to avoid sites, such as caves and bird roosts, that are often contaminated with *H. capsulatum*. These individuals should also be advised to avoid activities like spelunking, construction and soil excavation that are associated with increased risk of histoplasmosis. If, however, exposure cannot be avoided, individuals should be advised to wear masks and special protective equipment.

Disinfectants have been used to eliminate or reduce foci of *H. capsulatum* infection. Of the fungicidal and chemical agents that have been used, a 3% solution of formalin is the only disinfectant that has been proved to be an effective decontaminant. Formalin is inexpensive, but its use is associated with serious health hazards and precautions must be taken during its application. Decontamination is not a feasible option for bat-infested sites, because these animals can recontaminate the environment.

Although several trials have documented the effectiveness of prophylaxis with oral itraconazole (200 mg/day) to prevent histoplasmosis in HIV-infected persons, routine prophylaxis with this drug is not recommended. This is because of concerns about the high cost of such treatment, the lack of survival benefits associated with prophylaxis, and the potential for the development of drug resistance. It is, however, recommended that itraconazole prophylaxis be considered for HIV-infected persons who live, or have lived, in endemic disease

areas if their CD4 T-lymphocyte counts are less than 100 cells/μl, especially those who are at high risk because of occupational exposure. Fluconazole is not an acceptable alternative.

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17 Paracoccidioidomycosis

17.1 Definition

The term paracoccidioidomycosis (South American blastomycosis) is used to refer to infections due to the dimorphic fungus *Paracoccidioides brasiliensis*. Following inhalation this organism causes a benign and transient pulmonary infection in normal individuals. Later reactivation results in chronic infection of the lungs or other organs, in particular the skin and mucous membranes.

17.2 Geographical distribution

Paracoccidioidomycosis is a common endemic mycosis in Latin America. The endemic region extends from Mexico to Argentina, but the disease is more prevalent in South than Central America. The greatest number of reported cases have come from Brazil, Venezuela and Colombia. Cases of the infection have also been diagnosed outside Latin America among individuals who had earlier lived in an endemic region.

17.3 The causal organism and its habitat

P. brasiliensis is a dimorphic fungus. It exists in nature as a mould, but in tissue it forms large oval or globose cells with characteristic multiple buds encircling the mother cell.

Although *P. brasiliensis* has been isolated from soil, understanding of its precise natural habitat remains limited. In South and Central America, paracoccidioidomycosis is most frequently acquired in regions classified as subtropical upland rainforests, such as the Amazon river basin in Brazil. Further support for the hypothesis that *P. brasiliensis* is a soil-inhabiting fungus comes from the fact that it has been isolated from soil-digging armadillos found in regions where human paracoccidioidomycosis is prevalent.

17.4 Epidemiology

It is thought that inhalation of *P. brasiliensis* spores is the usual mode of infection in humans. However, in some cases infection might be the result of traumatic inoculation. The incubation period is unknown, but it is clear that the fungus can remain dormant for long periods in the lymph nodes following asymptomatic primary infection. Among 26 reported cases of imported paracoccidioidomycosis, the latent period ranged from 4 months to 60 yr with an average duration of asymptomatic infection of 14 yr.

Paracoccidioidomycosis is rare in children, accounting for around 5% of all reported cases. In contrast, skin testing of rural children living in certain endemic regions of Brazil has demonstrated that up to one-third have had an asymptomatic infection with *P. brasiliensis*. However, symptomatic disease is most prevalent in individuals over the age of 30 yr. Although skin testing has demonstrated that the rate of infection is similar in men and women, more than 90% of cases of symptomatic disease occur in men, most of whom have outdoor occupations such as farming.

Because paracoccidioidomycosis is not a notifiable disease in the countries in which it is endemic, information on the incidence and prevalence of the infection is limited. It has been estimated that throughout the endemic region, in which about 90 million people live, as many as 10 million individuals have been infected with *P. brasiliensis*. In Brazil, the annual incidence of symptomatic paracoccidioidomycosis has been estimated at 1–3 cases per 100 000 population. In Colombia, the annual incidence of the disease has recently been estimated at 0.05–0.2 cases per 100 000 population.

Alcoholism and smoking have been identified as risk factors for paracoccidioidomycosis. In recent years there has been an increase in the number of cases involving immunocompromised patients, including persons with human immunodeficiency virus (HIV) infection.

17.5 Clinical manifestations

The lungs are the usual initial site of infection, but the organism then spreads through the lymphatics to the regional lymph nodes. In most cases the primary infection

is asymptomatic. However, children and adolescents sometimes present with an acute disseminated form of infection in which superficial and/or visceral lymph node enlargement is the major manifestation. In these patients, pulmonary symptoms are minimal, and chest radiological signs are absent. This presentation is also seen in immunocompromised patients. It has a poor prognosis.

Most adults with paracoccidioidomycosis present with chronic progressive infection. In 80% of cases the disease involves the lungs. In some patients, the infection spreads to involve the mucosa, skin and other organs. The disease is slowly progressive and may take months or even years to become established. Most patients respond to antifungal treatment, but relapse is a common problem.

17.5.1 Chronic pulmonary paracoccidioidomycosis

In most cases, this illness is insidious in onset and the patient has been ill for weeks or months before diagnosis. The most frequent symptoms include persistent cough, purulent sputum, chest pain, weight loss, malaise, dyspnoea and fever.

The radiological findings are characteristic, but not diagnostic. Multiple bilateral interstitial infiltrates are often found. If left untreated, these will progress to fibrosis and cavitation. Hilar lymph node enlargement is found in 50% of cases, but calcification and pleural effusion are uncommon. The lesions must be distinguished from histoplasmosis and tuberculosis.

17.5.2 Mucocutaneous paracoccidioidomycosis

Ulcerative mucocutaneous lesions are the most obvious presenting sign of chronic disseminated infection with *P. brasiliensis*.

The mouth and nose are the commonest sites of mucosal infection. Painful, infiltrated, ulcerated lesions develop on the gums, tongue, lips or palate and can progress over weeks or months. Patients sometimes present with poor nutritional status due to dysphagia and/or impairment of mastication. Perforation of the palate or nasal septum may occur. Laryngeal lesions can lead to scar formation and ulceration resulting in hoarseness and stridor.

Cutaneous lesions often appear on the face around the mouth and nose, although patients with severe infection can have widespread scattered lesions. Small papular or nodular lesions enlarge over weeks or months into plaques with an elevated, well-defined margin. Verrucous lesions or ulcers with a rolled border may develop.

Lymph node involvement is a common manifestation of paracoccidioidomycosis. In the chronic form of the disease, it usually represents secondary involvement of lymph nodes draining the mucosal disease, whereas in the acute form it is assumed to be a primary involvement. In patients with head and neck disease, all lymph node chains may be involved, but the cervical and submandibular chains are most frequently affected. Magnetic resonance imaging (MRI) is helpful in evaluating lymph nodes which are inaccessible on clinical evaluation. It is not uncommon for infection of the cervical lymph nodes to result in abscess formation and the development of draining sinuses.

17.5.3 Other forms of disseminated paracoccidioidomycosis

Haematogenous and lymphatic spread of *P. brasiliensis* can result in widespread disseminated infection. Manifestations include nodular or ulcerative lesions of the small or large intestine, hepatic and splenic lesions, adrenal gland destruction, osteomyelitis, arthritis, focal cerebral lesions and meningitis, and infections of the male genitourinary tract.

17.6 Differential diagnosis

Mucocutaneous leishmaniasis is endemic in the same regions as paracoccidioidomycosis and can cause similar lesions. However, nasal lesions are seldom seen in paracoccidioidomycosis. Patients with histoplasmosis may also present with oropharyngeal and laryngeal ulcers that can be differentiated from paracoccidioidomycosis by their elevated borders and the absence of the typical fine granulation surface. Laryngeal tuberculosis is difficult to distinguish from paracoccidioidomycosis. The differential diagnosis of oropharyngeal and laryngeal lesions also includes squamous cell carcinoma and lymphoma. The cutaneous lesions of

paracoccidioidomycosis can resemble syphilis, psoriasis or lymphoma. The clinical and radiological manifestations of chronic *P. brasiliensis* infection of the lungs can be confused with tuberculosis or histoplasmosis.

17.7 Essential investigations and their interpretation

17.7.1 Microscopy

Microscopic examination of wet preparations of pus from draining lymph nodes, sputum, biopsies from ulcers, and other clinical material can permit the diagnosis of paracoccidioidomycosis if the characteristic large, round cells with multiple peripheral buds are seen. However these are usually present as single cells or chains of cells and often cannot be differentiated from other fungal pathogens, such as *C. neoformans* or *B. dermatitidis*.

17.7.2 Culture

The definitive diagnosis of paracoccidioidomycosis depends on isolation of the fungus in culture. Mould colonies can be obtained after incubation at 30°C for 2–3 weeks on glucose petone (Sabouraud's) agar supplemented with cycloheximide (actidione). Cultures should be retained for 4 weeks before being discarded. Mycelial cultures seldom sporulate, but subculture of the isolate at 37°C on brain heart infusion agar, supplemented with glutamine, should result in production of the unicellular form. If more rapid identification is required (24 h), the initial mould culture can be subjected to an exoantigen test.

17.7.3 Serological tests

The complement fixation (CF) and immunodiffusion (ID) tests, using purified or recombinant antigens of *P. brasiliensis*, are useful for the diagnosis of paracoccidioidomycosis and monitoring the response to treatment. These tests are most helpful in cases with occult lesions in deep organs.

The ID test is simple to perform. It is highly specific and is positive in 65–100% of patients with active paracoccidioidomycosis. Although cross-reactions can occur in patients with histoplasmosis, these are uncommon.

The CF test with unpurified antigen is positive in 80–95% of patients, higher titres being obtained in those with more severe disease. A CF titre of at least 1:8 is considered presumptive evidence of paracoccidioidomycosis. However, 85–95% of patients with active disease have CF titres of 1:32 or greater. The CF test is not altogether specific and cross-reactions can occur with serum from patients with other mycotic infections, particularly histoplasmosis. Non-specific CF tests tend to give titres of 1:8. Titres of antibodies decline on successful treatment, precipitins being the first to disappear.

Other tests, such as indirect enzyme immunoassay (EIA) and immunoblotting, have been developed for the diagnosis of paracoccidioidomycosis. The indirect EIA measures IgG antibodies against a species-specific 43-kDa glycoprotein antigen of *P. brasiliensis*. It is simpler to perform, and more sensitive and specific than the CF test, provided the antigen is deglycosylated. The EIA test provides a quantitative measurement of titres for use in monitoring the response to treatment. A sensitive immunoblotting method for detection of *P. brasiliensis* antibodies has also been developed.

Tests for the detection of *P. brasiliensis* antigen in the urine are sometimes useful in immunocompromised patients, and for the evaluation of whether patients are cured.

17.8 Management

Patients with paracoccidioidomycosis require long-term antifungal treatment. The prognosis is good, but treated patients should be re-examined at regular intervals because relapse is a common problem. Along with antifungal treatment, supportive measures such as improved diet and rest are essential to improve the general health of the patient.

Oral itraconazole is the drug of choice for the treatment of both the adult and juvenile forms of paracoccidioidomycosis. The usual regimen is 100 mg/day given for 6 months. Late relapse has been uncommon, and relapsing patients have responded to further treatment with itraconazole. Oral ketoconazole is almost as effective, but less well tolerated than itraconazole. The usual dose is 200–400 mg/day given for 6–18 months (or for a

minimum of 6 months after all clinical signs of infection have disappeared). Treatment with ketoconazole requires regular follow-ups to prevent hepatic and gonadal dysfunction. If absorption of itraconazole or ketoconazole is a problem, oral or parenteral treatment with fluconazole (up to 600 mg/day for 6 months) is also effective. However, the need for higher doses and longer periods of treatment, together with frequent relapses, have limited its use for the treatment of this disease.

Amphotericin B remains a useful drug for the management of severe or refractory paracoccidioidomycosis. The usual regimen is 1.0 mg/kg per day for 4–8 weeks. Thereafter, treatment with an azole or a sulphonamide can be substituted. In the case of sulphonamides, either sulphadiazine or one of the long-acting compounds (sulphamethoxypyridazine or sulphadimethoxine) can be used. The usual adult dose of sulphadiazine is 4 g/day (500–1000 mg at 4–6-h intervals). Children should receive 60–100 mg/kg per day in divided doses. Treatment must be continued until clinical and mycological improvement is apparent. Then the dosage can be halved. The long-acting compounds should be administered at an adult dosage of 1–2 g/day for the first 2–3 weeks. If there is clinical improvement, the dose can be reduced to 500 mg/day. Sulphonamide treatment should be continued for 3–5 yr to prevent relapses, which occur in 20–25% of cases.

The prognosis in patients with paracoccidioidomycosis depends on the initial presentation. Cutaneous lesions will heal after a few weeks of azole treatment, but lymph node regression is slower. Radiographic improvement of pulmonary lesions does not occur until some months after the initiation of treatment. Regardless of the organs involved, paracoccidioidomycosis usually heals by fibrosis, with the formation of granulomata. These persist and constitute a source of *P. brasiliensis* that can lead to a relapse in the disease following cessation of treatment.

17.9 Prevention

It is rare for environmental sites that are contaminated with *P. brasiliensis* to be identified. For this reason, such sites can neither be avoided nor decontaminated. Avoid-

ance of outdoor activities in endemic regions is neither practical nor justified.

The prevalence of paracoccidioidomycosis in immunocompromised patients is too low to justify routine antifungal prophylaxis. The endemic regions of this disease overlap those of histoplasmosis. Therefore, the recommendation that itraconazole prophylaxis be considered in HIV-infected persons who live, or have lived, in areas endemic for histoplasmosis, if their CD4 T-lymphocyte counts are less than 100 cells/μl, might also provide protection against paracoccidioidomycosis.

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18 Chromoblastomycosis

18.1 Definition

The term chromoblastomycosis is used to refer to a chronic localized infection of the skin and subcutaneous tissue most often involving the limbs and characterized by slow-growing verrucous lesions. It is caused by a number of brown-pigmented (dematiaceous) moulds.

Chromoblastomycosis is distinguished from subcutaneous phaeohyphomycosis (see Chapter 26) and other superficial fungal infections due to dematiaceous fungi (see Chapter 6) by the finding of single or clustered, round, thick-walled, brown cells (termed muriform cells or sclerotic cells) on microscopic examination of material from lesions.

18.2 Geographical distribution

The disease has a worldwide distribution, but is most common in tropical and subtropical regions. It appears to be most prevalent in Central and South America, but it also occurs in southern Africa, Asia and Australia. The largest numbers of reported cases have come from Brazil, Costa Rica and Madagascar.

18.3 The causal organisms and their habitat

Chromoblastomycosis is caused by various brown-pigmented (dematiaceous) moulds, the most common of which are *Phialophora verrucosa*, *Fonsecaea pedrosoi*, *Fonsecaea compacta*, *Cladophialophora carrionii* and *Rhinocladiella aquaspersa*. However, sporadic cases of the disease have also been attributed to a number of other dematiaceous moulds, including *Exophiala jeanselmei* and *E. spinifera*. It should be noted that several of these organisms (including *F. pedrosoi* and *P. verrucosa*) have also been incriminated as aetiological agents of phaeohyphomycosis (see Chapter 26).

The aetiological agents of chromoblastomycosis are widespread in the environment, being found in soil, wood and decomposing plant matter.

18.4 Epidemiology

Infection follows the traumatic inoculation of the fungus into the skin or subcutaneous tissue. Minor trauma, such as abrasions or wounds due to thorns or wood splinters, is often sufficient to introduce the organism. The incubation period is unknown, but the disease is rare in children and adolescents exposed to the same environmental conditions as adults with the disease. This suggests a long latent period before signs of disease begin to appear.

Except in Japan, chromoblastomycosis is more common in men than women, reflecting the importance of occupational exposure. The disease is most prevalent among individuals over the age of 30 yr with outdoor occupations, such as farmers and gardeners. As with other subcutaneous fungal infections, affected individuals are otherwise normal and there does not appear to be any predisposition apart from exposure. In many instances, patients worked barefoot.

18.5 Clinical manifestations

The clinical manifestations of chromoblastomycosis are similar, regardless of the organism causing it. The lesions are usually unilateral and occur most frequently on the exposed parts of the body, particularly the feet and lower legs (about 50% of cases). Other less common sites include the hands, arms, buttocks, back, shoulders, neck and face. Most patients present with well-established disease.

The initial lesion is a small painless papule which develops at the site of implantation. If left untreated, this will usually enlarge only slowly to form a superficial nodule with an irregular friable surface. Established infections manifest as multiple large hyperkeratotic verrucous lesions sometimes separated from one another but clustered in the same region. Some lesions are flatter and appear plaque-like, and as they enlarge show central scarring. The lesions are seldom painful (unless bacterial superinfection occurs), but pruritus is frequent and can be severe.

Later in the disease, the lesions may become pedunculated. Autoinoculation from scratching or from superficial lymphatic spread can result in satellite lesions

around the original lesion. Bacterial superinfection can occur, resulting in ulceration and a malodorous discharge. Superinfection is also responsible for the lymphadenitis and lymphoedema that is sometimes seen in patients with long-standing chromoblastomycosis.

In rare cases, metastatic lesions develop in the lymph nodes, brain, liver, bones and other tissues. As with other proliferative epidermal processes, long-standing lesions of chromoblastomycosis can undergo carcinomatous transformation.

18.6 Differential diagnosis

Although the appearance and unilateral location of the lesions on a lower limb is often suggestive of chromoblastomycosis, the disease must be distinguished from a number of other fungal infections including blastomycosis, paracoccidioidomycosis, phaeohyphomycosis, lobomycosis, rhinosporidiosis and sporotrichosis. It must also be differentiated from protothecosis, leishmaniasis, verrucous tuberculosis, certain leprous lesions and syphilis. On the upper limbs the erythematosquamous lesions can be confused with psoriasis or subacute or discoid lupus erythematosus.

18.7 Essential investigations and their interpretation

By definition, chromoblastomycosis is characterized by the presence of typical muriform or sclerotic cells in scrapings or tissue samples. Microscopic examination of material from the lesions is therefore required to make a definitive diagnosis, and culture should be performed to identify the aetiological agent.

18.7.1 Microscopy

Direct microscopic examination of wet preparations of scrapings from the surface of lesions can permit the diagnosis of chromoblastomycosis if clusters of the characteristic small, round, thick-walled, brown-pigmented muriform cells are seen. These cells are often divided by longitudinal and transverse septa. Muriform cells can also be seen in stained sections of biopsy specimens.

18.7.2 Culture

Because the aetiological agents cannot be distinguished on the basis of microscopic examination of tissue, material from lesions should be inoculated on glucose peptone (Sabouraud's) agar and incubated at 25–30°C. Identifiable dark brown or olivaceous to black mould colonies should be formed within 1–2 weeks, but cultures should be retained for 4 weeks before being discarded. Identification of the individual causative agents can be difficult because they have different mechanisms of sporulation.

18.7.3 Serological tests

There are no reliable serological tests for chromoblastomycosis.

18.8 Management

It is rare for chromoblastomycosis to resolve without treatment: permanent scarring and disfigurement is a common problem, as is bacterial superinfection. Chromoblastomycosis is a difficult condition to treat. Surgical excision should be reserved for small lesions; it carries a high risk of local dissemination and should only be attempted in conjunction with antifungal treatment. Liquid nitrogen treatment and direct application of heat have been used with some success in patients with less extensive lesions.

There is no ideal antifungal treatment for chromoblastomycosis. The most effective drugs are itraconazole (200–400 mg/day for up to 12 months) and terbinafine (500 mg/day for 6–12 months), both of which can be combined with flucytosine in difficult cases. Higher response rates have been reported with prolonged treatment. Ketoconazole has been useful in some cases, but fluconazole appears to be ineffective.

Flucytosine (100–200 mg/kg per day given as four divided doses) has proved effective in more than 50% of reported cases, but incomplete lesion resolution, relapse and development of resistance are common problems. Much better results have been obtained when flucytosine is combined with oral thiabendazole (25 mg/kg per day given as three divided doses) or amphotericin B (0.5–1.0 mg/kg per day). Both regimens appear to

prevent the development of flucytosine resistance, but toxicities can be problematic. Treatment should be continued for at least 1 month after clinical cure is obtained.

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19 Entomophthoramycosis

19.1 Definition

The term entomophthoramycosis is used to describe a group of rare fungal infections caused by moulds belonging to the Order Entomophthorales of the Class Zygomycetes. The human pathogens in this Order include *Basidiobolus* and *Conidiobolus* species. Other pathogenic Zygomycetes belong to the Order Mucorales and cause mucormycosis (see Chapter 13). Two distinct clinical forms of entomophthoramycosis are recognized: rhinofacial conidiobolomycosis and basidiobolomycosis. These are usually subcutaneous infections that affect immunocompetent individuals and are transmitted through traumatic implantation.

19.2 Rhinofacial conidiobolomycosis

19.2.1 Definition

Rhinofacial conidiobolomycosis is a chronic localized subcutaneous fungal infection, caused by *Conidiobolus coronatus*. It originates in the nasal mucosa and spreads to the adjacent subcutaneous tissue of the face causing severe disfigurement.

19.2.2 Geographical distribution

The largest number of cases of this disease have been reported from West Africa, in particular Nigeria, but cases have also occurred in India and South and Central America.

19.2.3 The causal organism and its habitat

C. coronatus (*Entomophthora coronata*) is found in the soil and on decomposing vegetation in tropical rainforests. It causes a similar disease in horses and humans.

19.2.4 Epidemiology

In most cases the organism is introduced to the nasal mucosa on the soiled hands of the patient himself. In

some instances, the infection is thought to follow spore inhalation. The disease can occur at any age, but is uncommon in children. Most cases affect men with agricultural or outdoor occupations, living in the tropical rainforests of Africa. As with other subcutaneous fungal infections, affected individuals are otherwise normal, and there does not appear to be any predisposition apart from exposure.

19.2.5 Clinical manifestations

The infection may present with nasal obstruction, which is mostly unilateral, but is often not noticed until there is visible swelling on the upper lip or face. Nasal discharge is a common finding, but pain, tenderness and constitutional upset are rare. As the swelling spreads, it can involve the nasal bridge and upper and lower face, including the orbit. It is the resulting gross facial disfigurement that brings the patient for treatment.

The condition affects soft tissue, but the underlying bone is spared. The lesions have a distinct margin, but the mass is not movable over the underlying tissue. The skin is stretched, but remains intact.

19.2.6 Essential investigations and their interpretation

Even if, in advanced cases, the diagnosis is obvious from the typical clinical appearance, laboratory investigation is essential for its confirmation.

MICROSCOPY

The diagnosis is best established by microscopic examination of smears or tissue from the nasal mucosa. In stained tissue sections, the organisms appear as broad, non-septate, thin-walled, irregularly branched hyphae and in some cases are surrounded by eosinophilic material (Splendore–Hoeppli phenomenon).

CULTURE

Culture is difficult. To optimize the recovery of fungus from clinical material, specimens must be inoculated on the largest possible number of media; they should be incubated at between 25 and 35°C.

19.2.7 Management

Treatment of this condition is difficult, but patients often respond to itraconazole (200–400 mg/day), ketoconazole (200–400 mg/day), or fluconazole (200 mg/day). Treatment should be continued for at least 1 month after the lesions have cleared.

Saturated potassium iodide solution is useful for patients in developing countries because of its ease of administration and low cost. The starting dose is 1 ml three times daily, and this is increased up to 4–6 ml three times daily as tolerated. Treatment must be continued for at least 1 month after the lesions have disappeared. Allergic reactions and gastrointestinal intolerance are common complications, and relapse is common even long after successful treatment.

Surgical resection of infected tissue is seldom successful; it may hasten the spread of infection.

19.3 Basidiobolomycosis

19.3.1 Definition

The most common form of basidiobolomycosis is a chronic subcutaneous infection of the trunk and limbs. However, *Basidiobolus ranarum* has also caused rare cases of gastrointestinal infection.

19.3.2 Geographical distribution

The largest number of cases of subcutaneous disease has been reported from the tropical regions of East and West Africa and Indonesia. Sporadic cases have also been described from tropical or subtropical regions of Asia, Australia and South America. A small cluster of cases of gastrointestinal disease has been reported from the Desert South West of the USA.

19.3.3 The causal organism and its habitat

B. ranarum (*B. meristosporus, B. haptosporus*) has been isolated from soil and decomposing vegetation throughout the world. It has also been recovered from the intestines of several species of small reptiles and amphibians.

19.3.4 Epidemiology

It is still uncertain how the disease is acquired, but subcutaneous infection is thought to follow traumatic

inoculation. Minor trauma, such as a thorn prick or an insect bite, is often sufficient to introduce the organism. Basidiobolomycosis is unusual among subcutaneous fungal infections in that it is more common in children and adolescents than in adults. As with other subcutaneous fungal infections, affected individuals are otherwise normal, and there does not appear to be any predisposition apart from exposure.

It is thought that gastrointestinal disease is acquired through ingestion of soil, animal faeces, or food contaminated by either. Potential risk factors include prior ranitidine use.

19.3.5 Clinical manifestations

The most common sites of subcutaneous infection are the buttocks and thighs, but the hard, movable subcutaneous swellings that characterize this condition are also found on the arms, legs or shoulders. Pain and tenderness are unusual. This is a disfiguring infection, but the skin covering the lesions remains intact. The underlying bone and joints are not affected. Lymphatic obstruction may occur and can result in elephantiasis.

The presenting symptoms and signs of gastrointestinal basidiobolomycosis are non-specific. Most patients have a subacute onset of symptoms, usually beginning with abdominal pain. Abdominal computed tomographic scanning and barium enema examination will reveal gastrointestinal tract masses, indistinguishable from malignancies or inflammation. Most patients have elevated white blood cell counts with eosinophilia.

19.3.6 Essential investigations and their interpretation

The clinical appearance of the subcutaneous disease is distinctive, but a firm diagnosis requires mycological and histopathological confirmation to distinguish it from other causes of chronic cellulitis. The diagnosis of gastrointestinal basidiobolomycosis requires the microscopic examination and culture of biopsy specimens.

MICROSCOPY

Microscopic examination of histopathological sections of infected tissue will reveal focal clusters of

inflammation containing wide, irregular, non-septate hyphae or fragments thereof. The hyphae are usually surrounded by eosinophilic material (Splendore–Hoeppli phenomenon).

CULTURE

Specimens should be cultured on glucose peptone (Sabouraud's) agar at 30°C. Identifiable colonies should be obtained in less than 1 week.

19.3.7 Management

The treatment of choice appears to be oral traconazole (100–200 mg/day) which should be given for several months. Oral ketoconazole (400 mg/day) has sometimes been successful, but amphotericin B has seldom been helpful. Saturated potassium iodide solution is another alternative (see above). In some cases cotrimoxazole has been found to be more effective than potassium iodide. The recommended dose is two tablets three times daily (each tablet contains 400 mg sulphamethoxazole and 80 mg trimethoprim). As with potassium iodide solution, treatment should be continued for 1 month after the lesions have cleared.

Should a patient have an enlarged, useless limb resistant to medical treatment, amputation should be considered to forestall bacterial superinfection.

Patients with gastrointestinal basidiobolomycosis should undergo resection of all affected bowel and debridement of other involved tissues. This should be followed by at least 3 months of antifungal treatment with itraconazole.

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20 Lobomycosis

20.1 Definition

The term lobomycosis (keloidal blastomycosis) is used to refer to a rare chronic infection of the skin and subcutaneous tissue due to the fungus *Lacazia loboi*.

20.2 Geographical distribution

Most cases have been reported from countries in northern South America and Central America.

20.3 The causal organism and its habitat

The aetiological agent is now named *Lacazia loboi*, but so far all attempts to isolate this fungus in culture have failed. In tissue it appears as round or elliptical budding cells. The natural habitat of *L. loboi* is still unknown. It is, however, accepted that it is a saprobe in nature and that water has an important role in human infection. Lobomycosis has also been diagnosed in several species of marine and freshwater dolphins, supporting the hypothesis of an aqueous habitat of the aetiological agent.

20.4 Epidemiology

Most human infections have occurred in individuals who resided in, or travelled through, the tropical rainforest regions of Central America or northern South America. The disease is insidious in onset and notable for its long latent period. Some patients trace their infection to some traumatic incident such as an insect bite, cut or an abrasion. In many cases, however, the traumatic event is so minimal that it is not remembered. The disease is more common in men than in women or children. Affected individuals are otherwise normal, and there does not appear to be any predisposition apart from contact with water.

20.5 Clinical manifestations

The most common sites of infection are the legs, arms, face, ears and buttocks. The initial lesion is a papule or a

small nodule which slowly proliferates to form extensive keloidal or verrucous lesions. The lesions are located in the dermis, the normal tissue being replaced by granulomatous tissue. Autoinoculation can lead to the development of further lesions. In advanced cases, the lesions may cover an entire limb. In most instances the disease is symptomless. However, if the head is involved, the patient may be so grossly disfigured as to be completely excluded from social life.

20.6 Differential diagnosis

The vegetative lesions of lobomycosis must be distinguished from keloids, nodular lepromatous lesions, leishmaniasis and chromoblastomycosis.

20.7 Essential investigations and their interpretation

Histopathological examination of clinical material will reveal large numbers of the characteristic large, round or oval, thick-walled cells of *L. loboi* (over 10 μm in diameter). These can produce multiple buds that resemble the tissue form of *Paracoccidioides brasiliensis*. The cells are often formed in unbranched chains, the adjacent cells being joined together by bridge-like structures within the chain.

L. loboi has never been isolated in culture. This distinguishes it from *P. brasiliensis* to which it bears a marked resemblance.

20.8 Management

Antifungal treatment is ineffective, but oral clofazimine has given promising results in some patients. Provided the lesions are not too extensive, the treatment of choice is surgical excision. However, recurrence is common and patients should be followed up where possible.

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21 Mycetoma

21.1 Definition

Mycetoma is a chronic destructive disease that affects the skin, the underlying subcutaneous tissue and sometimes the adjacent bone. It usually affects the feet or hands and may be caused by various species of fungi (eumycetoma) or actinomycetes (actinomycetoma) which have been inoculated into subcutaneous tissue as a result of traumatic implantation. A characteristic feature of mycetoma is the production in infected tissue of abscesses which contain large compact masses of fungal or actinomycete filaments termed 'grains'. These are discharged to the outside through sinus tracts.

21.2 Geographical distribution

Mycetomas are most common in arid tropical and subtropical regions of Africa and Central and South America. The countries surrounding the Saharan and Arabian deserts (particularly Senegal, Sudan and Somalia) form the most important endemic region, but the disease is also endemic in the Indian subcontinent. Occasional sporadic cases have been reported from other parts of the world.

21.3 The causal organisms and their habitat

More than 20 species of fungi and actinomycetes have been implicated as aetiological agents of mycetoma. Many of these organisms have been isolated from the soil, plants or trees, or decomposing vegetation. About six species of fungi are common causes of eumycetoma and five aerobic actinomycetes are common aetiological agents of actinomycetoma.

The predominant causes of mycetoma differ from one part of the world to another (see Table 21.1). The most important factor responsible for this variation is believed to be the climate, particularly the annual amount of rainfall. Eumycetomas are the predominant form of the disease in Africa and the Indian subcontinent, while

actinomycetomas are more common in Central and South America. The fungi involved include *Leptosphaeria senegalensis*, *Madurella grisea*, *M. mycetomatis* (the most common fungal cause), *Neotestudina rosatii*, *Pyrenochaeta romeroi* and *Scedosporium apiospermum*. Other fungi that have sometimes been implicated as causes of eumycetoma include *Acremonium* species and *Aspergillus nidulans*. The actinomycetes include *Actinomadura madurae*, *A. pelletier*i, *Nocardia asteroides*, *N. brasiliensis* (the most common organism) and *Streptomyces somaliensis*.

21.4 Epidemiology

Infection results from the traumatic implantation of the pathogen into the skin or subcutaneous tissue. In some cases the organisms are introduced on thorns or wood splinters; in others infection is due to later contamination of the wound with soil organisms. The initial lesion appears several months after the traumatic incident, but patients most commonly present for medical attention with long-standing infection.

In some countries men are affected more frequently than women, but there is no consistent differential sex distribution. Most patients have outdoor occupations which expose them to soil and minor penetrating wounds. Mycetoma can affect all age groups, but is most common in individuals between 20 and 50 yr of age. As with other subcutaneous fungal infections, affected individuals are otherwise normal, and there does not appear to be any predisposition apart from exposure.

Mycetomas are most common on the feet (about 70–85% of cases), particularly among those who go barefoot, followed by the hands (about 5–10% of cases) and other parts of the body that come into contact with the soil or vegetation while working, sitting or lying. Other affected sites include the back, neck and back of the head, particularly in individuals who carry wood or loads contaminated with soil.

21.5 Clinical manifestations

The clinical features of the eumycetomas and actinomycetomas are similar, although eumycetomas tend to

follow a slower and less destructive course. Although most patients present with long-standing infections, the initial lesion consists of a small, firm, painless subcutaneous nodule that can either be moved under the skin or is attached to it. In general, eumycetomas tend to remain localized and swelling and destruction of adjacent anatomical structures is not marked until late in the course of the disease. In actinomycetoma infections, the lesions have less well-defined margins and tend to merge with the surrounding tissue. Progression is often more rapid and involvement of bone earlier and more extensive.

Mycetoma lesions present as swellings covered with hypo- or hyper-pigmented skin. With time, sinus tracts appear on the skin surface as small papules or pustules that discharge pus containing the characteristic grains. As old sinus tracts heal, new ones appear. In time, the infection spreads to the adjacent bone leading to a destructive form of osteomyelitis. Depending on the location and size of the lesion, and also on any bone involvement, movement of the joints in the affected parts may be impaired. In spite of their unpleasant appearance, most mycetomas are painless, even when well established. However, in about 20% of cases pain is the main complaint that brings patients to hospital. In most cases, pain heralds the impending rupture of a sinus onto the skin surface.

Radiological examination is useful in determining the extent of bone involvement. The most common and distinctive finding is focal bone destruction with formation of cavities. These are small and abundant in cases of actinomycetoma and larger and less numerous in eumycetoma. Early evidence of bone involvement can be provided by bone scan, magnetic resonance imaging (MRI) and echoscans, although the interpretation of the latter is difficult. MRI scans are helpful in delineating the extent of the lesions.

Mycetomas often spread to adjacent tissues. Spread to the regional lymph nodes and involvement of deep organs is rare. Although lymphatic spread is found in some cases of eumycetoma, it is encountered more often in cases of actinomycetoma where the grains are smaller. In both cases repeated surgical interference seems to be

an aggravating factor. Bacterial superinfection of the initial mycetoma lesion is common and is a frequent cause of regional lymph node enlargement and impairment of the general health of the patient.

21.6 Differential diagnosis

In most cases the diagnosis of mycetoma of the foot presents no problems, but it may be difficult if other body sites are involved, particularly if no grains have been discharged at the time of examination.

The characteristic feature of mycetoma is the presence in sinus tracts of grains which are found to contain actinomycotic or fungal filaments. This finding distinguishes mycetoma from chromoblastomycosis, botryomycosis, cutaneous tuberculosis and other conditions.

21.7 Essential investigations and their interpretation

21.7.1 Gross examination

The diagnosis of mycetoma depends on the identification of grains. These should, if possible, be obtained from an unruptured pustule (sinus) with a sterile needle by puncturing the roof of the lesion and squeezing the sinus contents onto a glass slide. The grains should be picked out, rinsed in 70% alcohol, and then washed in sterile saline before being cultured. Failing this, it is best to obtain material through a deep surgical biopsy. Superficial biopsies are seldom helpful.

Gross examination of the grains may afford a clue as to the aetiological agent (see Table 21.1). Black grains suggest a fungal infection; minute white grains often indicate a *Nocardia* infection; larger white grains the size of a pinhead may be of either fungal or actinomycotic origin. Small, red grains are specific to *A. pelletieri*, but yellowish-white grains may be actinomycotic or fungal in origin.

21.7.2 Microscopy

Direct microscopic examination of the grains will confirm the diagnosis of mycetoma and also reveal whether the causal organism is a fungus or an actinomycete. Actinomycotic grains contain very fine filaments (<1 μm in diameter) whereas fungal grains contain short

Table 21.1 Aetiological agents of mycetoma.

Species	Geographical distribution	Colour of grain
Eumycetomas		
Leptosphaeria senegalensis	West Africa	Black
Madurella grisea	Africa, Central and South America	Black
M. mycetomatis	Worldwide	Black
Neotestudina rosatii	Africa	White
Pyrenochaeta romeroi	Africa, South America	Black
Scedosporium apiospermum	North America	White
Acremonium species	Africa, Middle East	White
Aspergillus nidulans	Africa, Middle East	White
Actinomycetomas		
Actinomadura madurae	Worldwide	White/yellow
A. pelletieri	Africa	Red
Nocardia asteroides	Worldwide	White/yellow
N. brasiliensis	Central America	White/yellow
Streptomyces somaliensis	North Africa, Middle East	Yellow/brown

hyphae (2–4 μm in diameter) which are sometimes pigmented. This can be seen by direct microscopic examination of crushed grains in 20% potassium hydroxide, but is much more readily observed in stained histopathological sections.

21.7.3 Culture

Although the identification of the causal agents of mycetoma can often be deduced from the morphological characteristics of the grains, it is also important to isolate the organism in culture. Agar plates should be inoculated with several grains (or with secretion or tissue fragments) and incubated at 25–30°C and at 37°C. The most commonly used agar medium is glucose peptone (Sabouraud's) agar, without antibiotics but with cycloheximide (actidione) for isolation of actinomycetes, and with antibiotics but without cycloheximide for fungal agents. Alternative media for isolation of actinomycetes include brain–heart infusion or blood agar.

Cultures should be retained for up to 6 weeks before being discarded. The actinomycetes are much slower growing than the fungi.

21.7.4 Serological tests

Although serological tests are sometimes available, they are seldom sufficiently informative to be helpful in diagnosis. However, these tests are helpful in monitoring the therapeutic response and can provide the earliest clue to reactivation of infection, particularly with actinomycetomas.

21.8 Management

It is essential to distinguish eumycetomas from actinomycetomas because the treatment of these conditions is different, and the drugs used to treat one are ineffective in the other.

In most cases eumycetoma is unresponsive to antifungal treatment and radical surgical removal (amputation) is often the best option. Local excision is seldom effective. However, because the lesions are slow to spread, and because it appears possible to slow the progression of the infection, the decision regarding amputation must take into account the progress and symptoms, the availability of prostheses, and the circumstances of the individual patient. If the lesions affect the back, neck, back of the head, or other sites where amputation is impossible, little can be done to help the patient.

In a clinical trial in Sudan, oral treatment with ketoconazole (200 mg twice daily for 9–36 months) led to cure or marked improvement in more than 70% of patients with eumycetoma due to *M. mycetomatis*. The therapeutic response of *M. mycetomatis* to itraconazole (100 mg twice daily) has been less encouraging, but long-term treatment with this agent has sometimes resulted in improvement of black grain eumycetoma. Medical management is justified in patients without bone disease and where regular supervision of the patient over a number of months is anticipated. Should the lesions fail to respond to antifungal treatment, surgical intervention will be required.

Medical treatment is usually effective in all but the most advanced cases of actinomycetoma. The aetiological agent will determine the choice of antimicrobial agent but, in most cases, combination treatment is preferable to the administration of a single drug. In cases of

S. somaliensis actinomycetoma, the best combination is streptomycin (1000 mg/day; intramuscular injection) plus trimethoprim-sulphamethoxazole (cotrimoxazole) (1–2 tablets morning and evening; each tablet contains 400 mg sulphamethoxazole and 80 mg trimethoprim). Streptomycin treatment should be discontinued if ototoxic side-effects develop. In cases which are resistant to cotrimoxazole, this drug can be replaced with dapsone (diamino-diphenyl-sulphone, DDS) (100–200 mg/day). Cases due to *A. madurae* are best treated with streptomycin plus dapsone. In cases of actinomycetoma due to *Nocardia* species, the combination of choice consists of cotrimoxazole plus dapsone.

The average duration of treatment of actinomycetoma is about 9 months. Treatment must be continued until the pain and swelling diminish, the discharge of secretion and grains stops, and the sinuses close. Even if these signs have disappeared, it is prudent to continue treatment for the same period as was required to achieve these results.

In serious cases with difficult locations (such as the back or head), the best choice is amikacin (15 mg/kg per day). This should be administered as a single intramuscular or intravenous dose for 2–3 weeks followed by a similar resting period. Up to three pulses are recommended. This treatment should be combined with cotrimoxazole, and once the three amikacin pulses have been completed, long-term cotrimoxazole treatment should be prescribed. Amikacin treatment has proved to be one of the best treatments for *Nocardia* actinomycetomas, but is less successful in cases due to *A. madurae*.

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22 Rhinosporidiosis

22.1 Definition

The term rhinosporidiosis is used to refer to an uncommon chronic infection of the nasal and other mucosal surfaces and ocular conjunctiva. It is characterized by the development of large vegetative outgrowths. The causal agent is *Rhinosporidium seeberi.*

22.2 Geographical distribution

The disease is most common in southern India and Sri Lanka, but sporadic cases have been reported from East Africa, Central and South America, South East Asia and other parts of the world. A recent outbreak has been reported from Serbia.

22.3 The causal organism and its habitat

In tissue, *R. seeberi* forms characteristic abundant, large, thick-walled sporangium-like structures. Large numbers of endospores are produced within the sporangia and, when mature, these are released through a pore in the wall. Each spore may develop to produce a new sporangium. It has long been unclear whether this organism is a fungus, but sequencing of the *18S* small subunit ribosomal DNA sequence from *R. seeberi* has led to its recent reclassification as a member of a novel group of aquatic parasites, the protoctistan Mesomycetozoa clade. Attempts to isolate *R. seeberi* in culture have failed and thus far it has not been recovered from an environmental source. It is, however, believed that stagnant pools of fresh water are an important source.

22.4 Epidemiology

The mechanism by which human infection is acquired is not known, but it is believed that the organism is transmitted in water. The disease is most prevalent in rural districts, among persons bathing in public ponds or working in stagnant water, such as rice fields. Rhinosporidiosis is seen in all age groups, but is most common

in children and adolescents. Men are more commonly affected than women. Affected individuals are otherwise normal, and there does not appear to be any predisposition apart from contact with freshwater.

22.5 Clinical manifestations

The nose is the most common site of rhinosporidiosis, being affected in more than 70% of cases. The organism causes the production of large sessile or pedunculated lesions that affect one or both nostrils. The infection is insidious in onset and the patient remains unaware of its existence until symptoms of obstruction develop. Rhinoscopic examination will reveal papular or nodular, smooth-surfaced lesions that become pedunculated and acquire a papillomatous or proliferative appearance. The lesions are pink, red or purple in colour. If located low in the nostril, the polyps may protrude and hang on to the upper lip. In most cases the general health of the patient is unimpaired. Spontaneous remission is unusual and, left untreated, the polyps will continue to enlarge.

In some cases, lesions develop on the conjunctiva or the ears. Lesions may also appear on the penis and on the vulva or vagina in women. Cutaneous rhinosporidiosis is very rare and is usually due to spread from a neighbouring mucosal lesion. It presents as minute papillomas which enlarge and become pedunculated. In most cases, skin lesions are asymptomatic.

22.6 Differential diagnosis

The appearance of pedunculated or unpedunculated polyps or nodules on the nasal mucosa or the conjunctiva should suggest the diagnosis of rhinosporidiosis. The presence of small white dots on the surface of the lesions is also helpful; on microscopic examination these are seen to be sporangia.

The condition must be distinguished from cryptococcosis, cutaneous tuberculosis, leprous lesions, leishmaniasis and treponematoses. Lesions on the genitalia or anal region must be distinguished from warts, condylomata and haemorrhoids.

22.7 Essential investigations and their interpretation

The diagnosis is established by microscopic examination of biopsy specimens because the organism cannot be cultured. Microscopic examination of tissue sections or wet preparations of tissue or discharge will reveal large round or oval sporangia, 60–450 m or more in diameter, with a thick wall and an operculum. The sporangia may be filled with endospores.

The mature sporangia of *R. seeberi* resemble the spherules of *Coccidioides immitis*, but are much larger. In addition, flattened sporogenous cells are often present at the edge of the sporangium. Mature endospores of *C. immitis*, however, are round regardless of their location within the spherules.

22.8 Management

Spontaneous remission is unusual. The treatment of choice is surgical excision of lesions, with or without cauterization. No drug treatment has proved effective. Recurrence is common (more than 20% of cases) and patients should be followed up where possible.

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23 Sporotrichosis

23.1 Definition

The term sporotrichosis is used to refer to subacute or chronic infections due to the dimorphic fungus, *Sporothrix schenckii*. Following implantation this organism can cause cutaneous or subcutaneous infection which commonly shows lymphatic spread. Occasionally, infection of the lungs, joints, bones or other sites occurs in predisposed individuals.

23.2 Geographical distribution

Sporotrichosis is worldwide in distribution, but is most common in warm, temperate or tropical climatic regions. In recent years, the largest number of reported cases have been from North, Central and South America. Other regions where the infection is endemic include Africa, India, Japan and Australasia.

23.3 The causal organism and its habitat

S. schenckii is a thermally dimorphic fungus which is found in the soil, on decomposing vegetation and on plant materials such as wood and sphagnum moss. It exists in nature as a mould, but in human and animal tissue it forms small budding yeast cells.

23.4 Epidemiology

Infection usually follows the traumatic implantation of *S. schenckii* into the skin or subcutaneous tissue. Minor trauma, such as abrasions or wounds due to thorns or wood splinters, is often sufficient to introduce the organism. The initial lesion usually appears 1–4 weeks after inoculation. In occasional cases, infection follows spore inhalation.

Infection with *S. schenckii* occurs in all age groups, but is more common in adults than children. There is no clear sex or racial predilection. Infections are most often sporadic and associated with trauma during the course of outdoor work or recreational activities. The disease is

most prevalent among individuals whose occupation brings them into contact with soil, plants or plant materials, for example, gardeners, florists, mineworkers and carpenters. The precise incidence of sporotrichosis has not been determined, but active population-based surveillance, conducted in the USA in 1992 and 1993, indicated that fewer than 1 person per million developed sporotrichosis per annum.

Sporotrichosis has been shown to be hyperendemic in the south-central highlands of Peru. Between 1997 and 1999, active population-based surveillance showed that the disease developed in 98 persons per 100 000 per annum. Unlike other parts of the world, the incidence was three times higher among children (156 cases per 100 000) than among adults (52 cases per 100 000). Information on risk factors in this setting is limited, but recent work suggests that, among children living in Peru, factors that lead to increased environmental exposure and minor cutaneous trauma, such as living in homes with dirt floors, playing in crop fields or working oudoors, are associated with an increased risk of sporotrichosis.

Outbreaks of sporotrichosis have been well described and have led to important insights into the risk factors for acquisition of the disease. One of the largest outbreaks occurred in the South African gold mines in the 1940s when almost 3000 cases were recorded, the source of infection being contaminated timber used as pit props. In the USA, several recent outbreaks of sporotrichosis, involving up to 84 cases, have been associated with handling contaminated sphagnum moss.

23.5 Clinical manifestations

Sporotrichosis has a wide range of clinical manifestations. The most common presentation is a localized cutaneous or subcutaneous lesion. Lymphatic spread may then lead to the development of further cutaneous lesions. In contrast to adults where infection can occur at any anatomical site, the face and limbs, particularly the hands and fingers, are the most common sites of infection in children. Much less commonly, the fungus may cause infection of the lungs, joints, bones and other sites. Widespread disseminated infection has been

reported in diabetics and alcoholics, drug abusers and persons with the acquired immunodeficiency syndrome (AIDS). Extracutaneous forms of sporotrichosis are rare in children.

23.5.1 Lymphocutaneous sporotrichosis

Lymphocutaneous sporotrichosis is the most common clinical form of sporotrichosis. It tends to affect exposed sites such as the limbs, and in particular the hands and fingers. The right hand is affected more frequently than the left.

Following inoculation, the fungus replicates at the site of infection and then invades the regional lymphatics that drain the infected site. In about 25% of cases, however, the infection remains confined to the initial site of inoculation. Such 'fixed' infections are more common in children than in adults. Facial lesions also often behave in this manner.

The initial lesion is a small, firm, painless nodule that is at first movable, but later becomes attached to the neighbouring tissue. Over the ensuing weeks, the lesion slowly enlarges, and the skin and subcutaneous tissue surrounding the lesion become indurated and purplish red. The nodule becomes soft and breaks down to form a painless superficial ulcer which discharges a serous or purulent fluid. The edge of the ulcer is often irregular and may become oedematous and crusted.

In most cases, the infection spreads to the regional lymph nodes that drain the site of the primary infection. The resulting ascending chain of non-tender, mobile subcutaneous nodules with overlying erythematous skin is the characteristic clinical presentation of sporotrichosis. If left untreated, the nodules slowly enlarge, soften and evolve into painless draining ulcers.

Fixed cutaneous lesions can be plaque-like or verrous; ulceration is uncommon. Although these lesions sometimes remit, they usually return and can persist for years until treated.

In the disseminated cutaneous form of sporotrichosis, numerous small papular or nodular lesions that progress to necrotic ulcers are distributed over the trunk and limbs. This form of sporotrichosis occurs in less than 1% of patients, and is usually seen in individuals with

an underlying disease or predisposition. It generally follows lymphatic or haematogenous spread from an initial cutaneous or pulmonary site of infection, but may also be due to multiple cutaneous inoculations.

23.5.2 Extracutaneous sporotrichosis

Extracutaneous forms of sporotrichosis are most commonly seen in individuals with an underlying disease or predisposition, such as diabetes mellitus, alcoholism or AIDS. The most common sites of involvement are the lungs, joints and bones, but occasional cases of endophthalmitis and meningitis have been reported.

Pulmonary sporotrichosis is an uncommon, chronic infection. It is typically seen in middle-aged men with chronic obstructive pulmonary disease and alcoholism. It usually follows the inhalation of spores and is sometimes associated with enlargement of the hilar lymph nodes. In some cases, it follows haematogenous dissemination from another site of inoculation. The symptoms are non-specific and include productive cough, fever, weight loss, loss of appetite, breathlessness and haemoptysis. The latter can be massive and fatal. The most common radiological finding is upper lobe cavitation, similar to that seen in tuberculosis.

Arthritis results from the spread of an adjacent subcutaneous infection, or from direct inoculation into the joint, or from haematogenous dissemination. It is an indolent, progressive infection which tends to affect the knee and other large weight-bearing joints, although the small joints of the hand and wrist are sometimes involved. The most common symptoms are stiffness, pain and swelling of the affected joint. It is not unusual for multiple joints to be involved.

In most cases, bone disease results from the spread of infection from an adjacent subcutaneous or joint lesion. In some cases, however, it occurs as a result of haematogenous dissemination. It is a chronic and indolent infection which tends to affect the long bones. Patients often complain of focal pain, with signs of focal tenderness and minimal swelling on examination. The most common radiological finding is a lytic lesion with a periosteal reaction. Most patients have concomitant arthritis.

Endophthalmitis, although rare, may result in blindness; chorioretinitis has also been reported. Occasional cases of meningitis have also been reported; the symptoms are identical to those of tuberculous meningitis. Cerebrospinal fluid findings are those of lymphocytic meningitis with an elevated protein concentration and a lowered glucose concentration.

23.6 Differential diagnosis

The diagnosis of sporotrichosis should be suspected in any patient with painless ulcerative lesions of the skin that are unresponsive to antibacterial treatment. The development of ipsilateral, ascending lymphatic nodules is also suspicious. Less typical manifestations must be differentiated from a wide range of infectious diseases, including blastomycosis, chromoblastomycosis, nocardiosis, paracoccidioidomycosis, leishmaniasis and cutaneous tuberculosis.

23.7 Essential investigations and their interpretation

23.7.1 Microscopy

Direct examination of clinical material, such as pus or tissue, is often disappointing because the organism is seldom abundant. However, the detection of typical oval or cigar-shaped cells or asteroid bodies of *S. schenckii* will confirm the diagnosis. Immunofluorescence staining has proved to be a sensitive and specific method for detecting low numbers of *S. schenckii* cells.

23.7.2 Culture

The definitive diagnosis of sporotrichosis depends on the isolation of the aetiological agent in culture. Clinical material should be inoculated on to several media, including glucose peptone (Sabouraud's) agar and brain–heart infusion agar, and incubated at 25–30°C. When exudate from draining lesions is unavailable, biopsies from the margin of an ulcer should be obtained. Identifiable mould colonies should appear in 3–5 days. The colour of the colonies usually changes from cream or light brown to dark brown or black with age. Confirmation of the identification depends on the morphological

characteristics of the mould form and its conversion to the yeast form on blood agar at 37°C.

23.7.3 Serological tests

At present, serological tests do not have a significant role in the diagnosis of sporotrichosis. Immunodiffusion (ID) and agglutination tests can be used to detect antibodies to *S. schenckii*, but are more helpful in diagnosing the unusual extracutaneous forms of sporotrichosis than in detecting cutaneous infection.

23.8 Management

It is rare for lymphocutaneous sporotrichosis to resolve without treatment: permanent scarring and disfigurement is a common problem, as is bacterial superinfection. Oral itraconazole is the drug of choice for patients with cutaneous and lymphocutaneous forms of sporotrichosis. It should be given at a dosage of 100–200 mg/day or 5 mg/kg per day for 3–6 months. Treatment should be continued for several months after the lesions have cleared. Fluconazole is less effective, and should be regarded as a second-line treatment for patients who do not tolerate or cannot absorb itraconazole. The minimum dosage should be 400 mg/day for 6 months. Oral ketoconazole is usually ineffective in lymphocutaneous sporotrichosis.

Saturated potassium iodide solution remains a useful treatment for patients in developing countries who contract lymphocutaneous sporotrichosis because of its ease of administration and low cost. However, it is inconvenient to take, and side-effects including allergic reactions and gastrointestinal intolerance are common. The starting dose is 5 drops three times daily, and this is increased as tolerated to 40–50 drops three times daily. Children can be treated with 50 mg or 1 drop three times daily, up to a maximum of 500 mg or 10 drops three times daily. Treatment should be continued for 4–6 weeks after the cutaneous lesions disappear, which may take 2–4 months. If adverse reactions occur, the drug should be discontinued for several days and then restarted at a lower dose.

Local application of heat is an effective alternative treatment for fixed cutaneous or lymphocutaneous

sporotrichosis in patients who are intolerant of the drugs used in these infections.

Itraconazole (200 mg twice daily) is the treatment of choice for patients with osteoarticular forms of sporotrichosis. Treatment should be continued for at least 12 months; shorter courses have led to relapse. Amphotericin B may be indicated for patients with extensive involvement, and for those in whom itraconazole is unsuccessful. Fluconazole is less effective and should be reserved for the occasional patient who cannot be treated with itraconazole or amphotericin B. The minimum dosage should be 800 mg/day. Potassium iodide is ineffective in osteoarticular sporotrichosis.

The treatment of pulmonary sporotrichosis is difficult and relapse is a common problem. Patients who are acutely ill should be treated with amphotericin B (1.0 mg/kg per day), but itraconazole (200 mg twice daily) may be substituted once their condition has improved. Patients who are not severely ill may be treated with itraconazole from the outset. The most effective approach to management appears to be a combination of amphotericin B and surgical resection. However, many patients with pulmonary sporotrichosis have severe underlying pulmonary disease that precludes surgical resection of lesions.

Patients with life-threatening disseminated sporotrichosis, including meningitis, require amphotericin B treatment (1.0 mg/kg per day). This should be continued until a total dose of 1–2 g has been administered. Patients with less acute forms of disseminated infection may be treated with itraconazole (400 mg/day) from the outset. HIV-infected individuals with sporotrichosis require lifelong maintenance treatment with itraconazole (200 mg twice daily) to prevent relapse.

23.9 Prevention

In adults, lymphocutaneous sporotrichosis appears to be an occupational risk for those who work outdoors. The wearing of protective clothing, such as long sleeves or gloves, during work should provides some protection against the disease.

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24 Hyalohyphomycosis

24.1 Definition

The term hyalohyphomycosis is used to refer to infections due to colourless (hyaline) moulds that adopt a septate hyphal form in tissue. This all-encompassing term was introduced in an attempt to stem the proliferation of new disease names each time an organism belonging to a new fungal genus was incriminated as the cause of infection. The number of organisms identified as causal agents of hyalohyphomycosis is increasing with over 70 different organisms, classified in more than 30 genera, being listed to date. The term hyalohyphomycosis is reserved as a general name for infections that are caused by unusual hyaline moulds that are not the cause of otherwise-named infections, such as aspergillosis or penicilliosis.

24.2 *Fusarium* infection

Fusarium species have long been recognized as a cause of nail and corneal infection in immunocompetent individuals (see Chapters 7 and 8). More recently, these moulds have emerged as the second most frequent cause of invasive fungal infection (after aspergillosis) among immunocompromised individuals, particularly in neutropenic cancer patients and haematopoietic stem cell transplant (HSCT) recipients.

24.2.1 Geographical distribution

Fusarium infection is worldwide in distribution. However, the largest number of cases of invasive *Fusarium* infection has been reported from North America.

24.2.2 The causal organisms and their habitat

The most frequent cause of human infection is *F. solani*, but *F. oxysporum*, *F. verticilloides (F. moniliforme)* and at least 12 other species have also been implicated. The identification of these moulds is difficult and often confusing even for specialists, and is not surprising that the

precise species of *Fusarium* involved has not been determined in many published reports.

Members of the genus *Fusarium* are common soil organisms and important plant pathogens. These moulds are often found in the indoor and outdoor air and on decomposing organic debris. *F. solani* and *F. oxysporum* have been recovered from water distribution systems in a number of North American hospitals, and have been found to persist for long periods of time.

24.2.3 Epidemiology

The mechanisms by which human infection is acquired are not well understood. The incubation period is unknown. There are several suggested routes of transmission, including inhalation, implantation following trauma, and acquisition via contaminated intravascular devices. In some cases, it has been found that the source of disseminated *Fusarium* infection in an immunocompromised individual was a pre-existing nail infection or a localized skin infection. The isolation of *Fusarium* species from hospital water distribution systems has led some specialists to suggest that inhalation of bioaerosols generated during showering could be an important source of invasive infection in HSCT recipients and other immunocompromised individuals.

Species of *Fusarium* are ubiquitous in the environment and the likelihood that infection will occur following inhalation or implantation of spores largely depends on host factors. Invasive *Fusarium* infection has emerged as a significant problem in several groups of immunocompromised individuals. Those at greatest risk include neutropenic cancer patients, particularly those with acute leukaemia, and allogeneic HSCT recipients. Less commonly, invasive *Fusarium* infection is seen in other groups of immunocompromised individuals, including burns patients and solid organ transplant recipients. The likelihood of infection developing in these individuals depends on a number of host factors, the most important of which is the level of immunosuppression, whether this manifests as profound or prolonged neutropenia, as graft-versus-host disease (GVHD) in HSCT recipients, or as rejection in organ transplant recipients.

Trauma is the major risk factor for localized *Fusarium* infection in the immunocompetent individual. Corneal infection is often the result of several factors including traumatic inoculation and local immunosuppression due to topical corticosteroid treatment. Localized deep *Fusarium* infection is rare in immunocompetent persons, but cases of endophthalmitis, osteomyelitis and arthritis have been reported following the traumatic introduction of the organism.

The overall mortality rate from invasive *Fusarium* infection is high, ranging from 50 to 80% in almost all groups of immunocompromised patients, and approaching 100% in patients who do not recover from neutropenia.

24.2.4 Clinical manifestations

Fusarium species cause a broad spectrum of human disease ranging from superficial infection of the nail and cornea in immunocompetent persons (see Chapters 7 and 8) to disseminated invasive infection in immunocompromised patients. Localized deep infections, including cases of endophthalmitis, osteomyelitis, arthritis, brain abscess and dialysis-associated peritonitis, have also been reported.

The clinical manifestations of invasive *Fusarium* infection are similar in several respects to those of acute invasive aspergillosis (see Chapter 10). Like the aetiological agents of aspergillosis and mucormycosis, *Fusarium* species have a predilection for vascular invasion, resulting in thrombosis, infarction and tissue necrosis. The lungs and paranasal sinuses are the most common initial sites of damage.

The usual initial presentation in the neutropenic patient is a persistent fever (greater than 38°C) that is unresponsive to antibacterial and antifungal treatment. Other presenting signs include pleuritic chest pain, nonproductive cough and haemoptysis. The radiological findings range from non-specific infiltrates to nodular or cavitating lesions, depending on the timing of the investigation.

Unlike aspergillosis, invasive *Fusarium* infection often leads to the development of cutaneous lesions, either as the initial site of involvement or as a metastatic site.

Cutaneous involvement has been described in about 70% of reported cases of *Fusarium* infections, particularly in immunocompromised persons, compared with less than 5% of patients with aspergillosis.

Among immunocompetent individuals, cutaneous *Fusarium* infections typically are localized and develop after skin breakdown at the site of infection. These infections most commonly present as necrotic lesions that complicate extensive burns or trauma, cellulitis adjacent to onychomycosis, or chronic ulcers and abscesses.

In contrast, most immunocompromised patients have disseminated skin lesions that evolve over a much shorter period of time (1–5 days), particularly in neutropenic individuals. Lesions in these patients consist of multiple painful, erythematous papules or macules with or without central necrosis. Necrotic lesions have an ecthyma gangrenosum-like appearance, while target lesions have a thin erythematous margin, 1–3 cm in diameter, surrounding the central papule. These disseminated lesions may result from skin breakdown in a patient with pre-existing onychomycosis.

24.2.5 Essential investigations and their interpretation

The definitive diagnosis of *Fusarium* infection depends on the isolation of the aetiological agent in culture from clinical specimens such as blood or material from cutaneous lesions. This is because the branching septate hyphal tissue form of these moulds cannot be distinguished from that of other agents of hyalohyphomycosis or aspergillosis on microscopic examination. Infection with *Fusarium* has been associated with a much higher rate of isolation from blood culture (about 40–60% of cases) than has been the case with *Aspergillus* and other mould infections. However, it has not been established whether lysis centrifugation is any more useful than other blood culture systems. *Fusarium* can usually be isolated from biopsies of cutaneous lesions.

No serological tests for the diagnosis of *Fusarium* infection are currently available.

24.2.6 Management

The most important factors influencing the outcome of *Fusarium* infection are the underlying immuno-

logical status of the patient and the extent of the infection.

Isolates of *Fusarium* are often resistant to amphotericin B and breakthrough infection has been reported during empirical treatment with this agent. Nonetheless, most specialists still regard amphotericin B as the drug of choice for patients with *Fusarium* infection. It should be given at the maximum tolerated dosage of 1.0–1.5 mg/kg per day (see Chapter 3). If the disease fails to respond to the conventional formulation, treatment should be changed to one of the lipid-based formulations of the drug at dosages of at least 5 mg/kg per day. Even with high-dose amphotericin B treatment, the prognosis is dismal unless the neutrophil count recovers.

Itraconazole and fluconazole are not active against *Fusarium* species, but limited animal data and some anecdotal clinical reports suggest that the new triazole antifungal agent voriconazole is effective against these moulds. The definitive assessment of this agent awaits more experience.

Immunological reconstitution is a critical factor in the treatment of *Fusarium* infection. Immunosuppressive and cytotoxic drugs should be reduced in dose or eliminated. Anecdotal reports suggest that shortening the duration of neutropenia with colony stimulating factors might be beneficial in treating disseminated *Fusarium* infection. Granulocyte transfusions have also been shown to be useful.

Non-immunosuppressed individuals with localized *Fusarium* infection of soft tissue or bone often respond to treatment. Amphotericin B (1.0 mg/kg per day) remains the agent of choice for patients with osteomyelitis, but successful management often requires aggressive surgical debridement of necrotic tissue. Patients with endophthalmitis require both medical and surgical treatment. Intravitreal concentrations of amphotericin B following parenteral administration are too low to treat this infection and intravitreal instillation is required. This will result in inflammation and retinal damage, but doses up to 10 μg can be tolerated. Surgical debridement is an essential part of the management of this infection.

24.2.7 Prevention

Measures to reduce the incidence of *Fusarium* infection should focus on protecting high-risk individuals from exposure to the organisms, and prompt diagnosis and treatment of localized skin and nail infection in patients awaiting immunosuppressive or cytotoxic treatment.

Although invasive *Fusarium* infection is an uncommon condition, it appears to be more prevalent in some hospitals than in others. Housing high-risk patients in rooms provided with high efficiency particulate air (HEPA) filtration has not eliminated the problem of nosocomial *Fusarium* infection in these institutions, and it has been suggested that ingestion of contaminated tap water, or inhalation of spores released during showering, is another potential source of *Fusarium* infection. Should hospital water be found to be contaminated with *Fusarium*, it has been recommended that immunosuppressed patients be provided with sterile (boiled) water for drinking to reduce the risk of infection. It has also been suggested that patients should use bed baths instead of showering. If individuals insist on showering during periods of intense immunosuppression, showerheads, and bathroom floors and walls should be cleaned before use.

Because the skin is an important source for disseminated *Fusarium* infection, it is essential that patients who require immunosuppressive or cytotoxic treatment be evaluated by a dermatologist before commencing immunosuppression. All sites of tissue breakdown should be identified and suspicious skin and nail lesions cultured. Local debridement should be performed and topical antifungal agents, such as natamycin and amphotericin B, considered if *Fusarium* species are isolated. If possible, immunosuppressive treatment should be delayed until the lesions have healed.

There is currently no effective antifungal prophylaxis available for prevention of *Fusarium* infection.

24.3 *Scedosporium apiospermum* infection

S. apiospermum is the most frequent cause of fungal mycetoma in immunocompetent individuals residing in temperate regions (see Chapter 21). In addition, this ubiquitous mould has emerged as a significant cause of

invasive infection in immunocompromised patients, individuals with impaired anatomical barriers (trauma, burns, etc.), and cases of massive inoculation (near drowning in polluted water).

24.3.1 Geographical distribution

These infections are worldwide in distribution.

24.3.2 The causal organism and its habitat

S. apiospermum (the current name for the anamorph or asexual state of the ascomycete *Pseudallescheria boydii*) is a ubiquitous fungus found in the soil, sewage and polluted freshwater. A related pathogen, *Scedosporium prolificans*, is an important cause of phaeohyphomycosis (see Chapter 26).

24.3.3 Epidemiology

Infection with *S. apiospermum* is thought to follow traumatic implantation, inhalation or aspiration of contaminated water. There are also several reports of acquisition via contaminated intravascular devices. The incubation period is unknown.

S. apiospermum is ubiquitous in the environment and the likelihood that infection will occur following inhalation or implantation of spores largely depends on host factors. Disseminated infection has emerged as a significant problem in several groups of immunocompromised individuals. Those at greatest risk include neutropenic cancer patients, particularly those with acute leukaemia, and allogeneic HSCT recipients. Less commonly, disseminated *S. apiospermum* infection has been seen in other groups of immunocompromised individuals, including persons with the acquired immunodeficiency syndrome (AIDS) and solid organ transplant recipients.

Trauma is the major risk factor for localized *S. apiospermum* infection in the immunocompetent individual. Localized deep infection is rare in immunocompetent persons, but cases of endophthalmitis, osteomyelitis and arthritis have been reported following the traumatic introduction of the organism. Unlike other opportunistic mould pathogens, *S. apiospermum* can cause pneumonia in immunocompetent individuals following

aspiration of polluted water. Haematogenous dissemination to the brain is a frequent complication.

The incidence of serious *S. apiospermum* infection appears to have increased in recent years, particularly among those undergoing allogeneic HSCT. Infections have also been reported in persons with AIDS and solid organ transplant recipients. The mortality rate in immunocompromised patients with disseminated disease is 100%.

24.3.4 Clinical manifestations

The most common clinical presentation of *S. apiospermum* infection in immunocompetent individuals is cutaneous and soft tissue mycetoma. This chronic infection results from the traumatic implantation of the fungus into subcutaneous tissue (see Chapter 21). The feet and hands are the most common sites of infection. The initial lesion, which appears several months after the traumatic incident, is a small, painless, subcutaneous nodule. This enlarges and ruptures to the surface forming sinus tracts which discharge white grains, then spreads into adjacent tissue and bone, causing disfiguring, swelling and tissue destruction.

The lung is the second most common site of *S. apiospermum* infection in humans. In the immunocompetent individual, isolation of these moulds from sputum most commonly represents transient (or prolonged) colonization of the bronchi or lungs or both. Underlying cavitating or cystic lung disease is a major factor predisposing an individual to *Scedosporium* colonization. Fungus ball formation has been described in patients with residual tuberculous or bronchiectatic cavities.

S. apiospermum pneumonia is rare in immunocompetent individuals. However, it has been seen following the aspiration of contaminated water. Fatal dissemination to the brain is a frequent complication.

In immunosuppressed patients, the clinical manifestations of *S. apiospermum* infection of the lungs are similar to those of invasive aspergillosis (see Chapter 10). The most common presentation in the neutropenic patient is a persistent fever (greater than 38°C) that is unresponsive to broad-spectrum antibacterial treatment. The radiological findings range from non-specific infiltrates to

areas of consolidation which can evolve to cavitation. Haematogenous dissemination to other organs is quite common.

In immunocompetent persons, *S. apiospermum* infection of the central nervous system (CNS) is most often due to spread from the paranasal sinuses, due to penetrating trauma or due to spread from the lungs following near drowning in polluted water. In immunocompromised individuals, CNS infection tends to follow haematogenous dissemination. Most CNS infections have presented as a brain abscess, but ventriculitis and meningitis have also been reported.

24.3.5 Essential investigations and their interpretation

The definitive diagnosis of *S. apiospermum* infection rests on the isolation of the fungus from clinical specimens. This is because the branching septate hyphal tissue form of this mould cannot be distinguished from that of other aetiological agents of hyalohyphomycosis or aspergillosis in wet preparations or sections. This distinction is important because *S. apiospermum* is resistant to amphotericin B.

S. apiospermum can usually be isolated from infected organs, but blood cultures are seldom positive.

24.3.6 Management

Surgical resection remains the preferred treatment for patients with localized cavitating lesions of the lung. Other localized forms of *S. apiospermum* infection, such as sinusitis, arthritis and osteomyelitis, have also been eradicated following surgical debridement of infected tissue. In some cases cure has resulted when debridement has been combined with antifungal treatment.

The prognosis for patients with *S. apiospermum* CNS infection is poor. Surgical drainage, when possible, is essential. Many strains of this mould are resistant to amphotericin B and CNS disease is best treated with an azole. Parenteral miconazole, despite being effective in some patients with CNS involvement, is no longer available. Anecdotal clinical reports suggest that the new triazole antifungal agent, voriconazole, is effective in the treatment of patients with different forms of

invasive *S. apiospermum* infection, including meningitis and brain abscess. The definitive assessment of this agent awaits more experience.

24.4 Other agents of hyalohyphomycosis

Many other colourless moulds have been incriminated as occasional aetiological agents of human hyalohyphomycosis. Isolation of these organisms alone is insufficient grounds for making a diagnosis because many are common culture contaminants. Even when the same organism is recovered on more than one occasion, the diagnosis must remain in doubt unless the fungus is demonstrated in histopathological sections of biopsy specimens.

Acremonium species have long been recognized as an occasional cause of nail and corneal infection (see Chapters 7 and 8). More recently, several members of this genus, including *A. kiliense* and *A. strictum*, have been implicated as causing localized deep infections in immunocompetent persons, including osteomyelitis, endocarditis, meningitis and peritonitis in dialysis patients. Successful clinical outcomes have been reported after surgical intervention and treatment with amphotericin B or itraconazole.

The two most common species of *Paecilomyces* are *P. lilacinus* and *P. variotii*. In immunocompetent individuals, these environmental moulds have been implicated as aetiological agents of corneal infection (see Chapter 8), endocarditis following heart valve replacement, and peritonitis in dialysis patients. Disseminated infection has been reported in immunocompromised individuals. *P. lilacinus* has caused outbreaks of endophthalmitis in surgical patients following its inadvertent administration in contaminated irrigation fluids. Successful clinical outcomes have been reported after treatment with itraconazole, voriconazole and caspofungin.

In immunocompetent persons, *Scopulariopsis brevicaulis* has been reported to cause onychomycosis (see Chapter 7), invasive sinusitis and prosthetic valve endocarditis. In neutropenic individuals and organ transplant recipients, this mould has caused localized invasive infection of soft tissues and lungs, as well as widespread disseminated disease. As in patients with *Fusarium*

infection, cutaneous lesions adjacent to infected toenails have been identified as the source of a subsequent disseminated infection. Invasive infections may require surgical and medical treatment and are frequently fatal.

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25 *Penicillium marneffei* infection

25.1 Definition

Penicillium marneffei infection has become one of the most frequent opportunistic infections encountered in human immunodeficiency virus (HIV)-infected persons who reside in South East Asia or southern China. Infection is thought to follow inhalation, but widespread disseminated disease is the most common clinical presentation.

25.2 Geographical distribution

P. marneffei has a limited geographical distribution, affecting persons residing in countries in South East Asia, including southern China, eastern India (Manipur state), Indonesia, Laos, Malaysia, Myanmar, Taiwan, Thailand and Vietnam. Imported cases have been diagnosed worldwide among individuals who had earlier resided in or visited the endemic region.

25.3 The causal organism and its habitat

P. marneffei is a thermally dimorphic fungus. It exists in nature as a mould, but in tissue it forms small round to elliptical yeast cells which divide by fission.

Although *P. marneffei* has been isolated from soil, understanding of its precise natural habitat remains limited. Further support for the hypothesis that *P. marneffei* is a soil-inhabiting fungus comes from the fact that it has been isolated from four different species of soil-digging bamboo rats, found in regions of South East Asia where human infection is prevalent.

25.4 Epidemiology

Infection with *P. marneffei* is thought to follow inhalation of spores that have been released into the air. The incubation period is variable, but it is clear that the fungus can sometimes remain dormant for long periods following asymptomatic primary infection. In contrast, cases have been reported in infants and children with

the acquired immunodeficiency syndrome (AIDS) in which disseminated infection occurred within a few weeks of exposure to the organism.

The likelihood that an infection with *P. marneffei* will develop after inhalation depends, in major part, on host factors. Even before the spread of AIDS to South East Asia, the disease tended to occur in individuals with T-cell-mediated immunological defects, such as are found in persons with lymphoproliferative disorders, or those receiving corticosteroid or cytotoxic treatment. HIV infection is now the single most common predisposing illness among patients with penicilliosis. In HIV-infected persons, *P. marneffei* infection is associated with severe immunological impairment, as reflected by CD4 T-lymphocyte counts of less than 100 cells/μl. It has been reported that the risk of symptomatic *P. marneffei* infection is greater in HIV-infected individuals with recent occupational or other contact with soil. In contrast, exposure to, or consumption of, bamboo rats is not a risk factor for infection.

Until the late 1980s few natural human infections with *P. marneffei* had been reported, and these had all occurred in individuals living in South East Asia or in visitors to the region. However, following the spread of AIDS to this region, penicilliosis has become much more common. It is the fourth most prevalent opportunistic infection among HIV-infected individuals living in Chiang Mai province in northern Thailand, accounting for 7% of AIDS-defining illnesses reported between 1994 and 1998. In northern Thailand, the disease has a case–fatality ratio of 11%.

25.5 Clinical manifestations

The lungs are the usual initial site of infection, but most affected individuals present with widespread disseminated infection closely resembling acute disseminated histoplasmosis (see Chapter 16).

The most common presenting symptoms of AIDS-associated *P. marneffei* infection include fever, marked weight loss, non-productive cough and debilitation. About 60–70% of patients present with multiple papular skin lesions, some of which show a central necrotic umbilication, resembling molluscum contagiosum.

These are often found on the face, neck, trunk and upper limbs. Molluscum contagiosum-like lesions are also commonly present on the oral mucosa and throat.

Other presenting signs include generalized lymphadenitis, hepatosplenic enlargement, anaemia and thrombocytopenia. Chest radiographs often reveal diffuse reticulonodular or localized alveolar infiltrates. Pleural effusion and hilar lymph node calcification are uncommon. Some patients have osteolytic bone lesions or subcutaneous abscesses. The illness is usually fatal if left untreated.

25.6 Differential diagnosis

Histoplasmosis and cryptococcosis are endemic in the same regions as *P. marneffei* infection and can cause similar necrotic skin lesions in persons with AIDS. The radiological signs of *P. marneffei* infection can be confused with those of pulmonary tuberculosis.

25.7 Essential investigations and their interpretation

It is recommended that HIV-infected persons who have visited South East Asia should be investigated for signs of *P. marneffei* infection if they present with fever, cutaneous lesions, lung disease, generalized lymphadenitis or hepatosplenic enlargement.

25.7.1 Microscopy

Microscopic examination of Wright-stained bone marrow smears or touch smears of skin or lymph node biopsies can permit the rapid diagnosis of *P. marneffei* infection if the characteristic round, oval or elliptical yeast cells, often with prominent cross walls, are seen (often within macrophages). *P. marneffei* cells can, however, be confused with those of *Histoplasma capsulatum*. However, unlike the latter, *P. marneffei* cells often possess cross-walls, but never produce buds.

25.7.2 Culture

The definitive diagnosis of *P. marneffei* infection depends on isolation of the fungus in culture. The organism has been isolated from skin and lymph node biopsies, pus, bone marrow aspirates, sputum, broncho-

alveolar lavage (BAL) fluid and other clinical materials. It has been recovered from blood cultures in over 70% of cases in persons with AIDS.

Identifiable mycelial colonies can be obtained on glucose peptone (Sabouraud's) agar after incubation at 25–30°C for 1 week, but cultures should be retained for up to 3 weeks before being discarded. *P. marneffei* colonies produce a distinctive red pigment which diffuses into the agar. However, some other non-pathogenic species of *Penicillium* can also produce a similar pigment.

25.7.3 Serological tests

Several tests have been described for the detection of antibodies to *P. marneffei*, including immunodiffusion (ID), indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA). These methods are specific, but less sensitive than culture. Promising methods have also been developed for the detection of *P. marneffei* antigen in serum and urine. Antigen detection tests have proved to be more sensitive for the detection of penicilliosis in HIV-infected persons, while antibody detection tests have been more helpful in HIV-negative individuals. However, none of these tests is widely available at present.

25.8 Management

Patients infected with *P. marneffei* have a poor prognosis without antifungal treatment. Even with treatment, the case-fatality ratio from disseminated infection in persons with AIDS is 11 % in northern Thailand. Furthermore, 50% of patients will relapse within 6 months of the successful completion of treatment,.

Amphotericin B remains the drug of choice for patients with severe *P. marneffei* infection. The usual regimen is 0.6–1.0 mg/kg per day for 2 weeks. Patients can then be changed to itraconazole (200 mg twice daily) for a further 10 weeks, provided their condition has improved on amphotericin B treatment. In milder infections, an azole agent can be used from the outset. Fluconazole appears to be less effective than itraconazole, but it may be useful in patients who fail to absorb the latter drug. The new triazole agent, voriconazole, is active against *P. marneffei in vitro*.

Long-term maintenance treatment with oral itraconazole (200 mg/day) is safe and well tolerated, and has been shown to prevent relapse of *P. marneffei* infection in patients with AIDS.

25.9 Prevention

A controlled trial demonstrated that long-term prophylactic administration of itraconazole (200 mg/day) to persons with advanced HIV infection residing in northern Thailand was well tolerated and prevented the development of *P. marneffei* infection (and cryptococcosis), especially in those with CD4 T-lymphocyte counts of less than 100 cells/μl. The use of combination antiretroviral treatments, including highly active antiretroviral therapy (HAART), has greatly reduced the incidence of opportunistic fungal infections among HIV-infected persons in developed countries. However, until these drugs become available in the developing countries where *P. marneffei* infection is endemic, it is recommended that itraconazole prophylaxis be used in persons with CD4 counts below 100 cells/μl living in districts where there is a high burden of the disease.

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26 Phaeohyphomycosis

26.1 Definition

The term phaeohyphomycosis is used to refer to cutaneous, subcutaneous and systemic fungal infections caused by brown-pigmented (dematiaceous) moulds that adopt a septate mycelial form in host tissue. This term was introduced in an attempt to stem the proliferation of new disease names each time an organism belonging to a new fungal genus was identified as the cause of human infection. It was also created to segregate various clinical infections caused by dematiaceous moulds from the distinctive subcutaneous infection known as chromoblastomycosis (see Chapter 18). However, it is now clear that several organisms (including *Fonsecaea pedrosoi* and *Phialophora verrucosa*) can cause both chromoblastomycosis and subcutaneous phaeohyphomycosis.

26.2 Geographical distribution

Phaeohyphomycosis has a worldwide distribution, but subcutaneous infection is most often seen in the rural population of tropical and subtropical regions of Central and South America. The largest numbers of cases of cerebral or paranasal sinus infection have been reported from North America.

26.3 The causal organisms and their habitat

The number of organisms implicated as aetiological agents of phaeohyphomycosis is increasing. More than 100 different moulds, classified in 60 different genera, have been incriminated. Often these fungi have been given different names at different times and there is therefore a great deal of confusion in the nomenclature used in various reports.

Among the more important aetiological agents can be included *Alternaria* species, *Bipolaris* species, *Cladophialophora bantiana*, *Curvularia* species, *Exophiala* species, *Exserohilum* species, *Ochroconis gallopava*,

Phaeoacremonium parasiticum, *Phialophora* species, *Ramichloridium mackenziei* and *Scedosporium prolificans*. Many of these organisms are found in soil, wood, polluted water and decomposing plant matter; others are plant pathogens.

26.4 Epidemiology

Subcutaneous infection is the most frequently reported form of phaeohyphomycosis. It is thought to result from the traumatic implantation of the causative fungus into the subcutaneous tissue. Minor trauma, such as abrasions or wounds due to thorns or wood splinters, is often sufficient to introduce the organism. The incubation period is unknown. The principal aetiological agents include *Exophiala jeanselmei*, *E. dermatitidis* (*Wangiella dermatitidis*), *Phialophora* species and *Bipolaris* species. However, many less common moulds have also been reported to cause this condition. Unlike other subcutaneous fungal infections, immunocompromised individuals (particularly solid organ transplant recipients) appear to be at increased risk of infection.

Dematiaceous moulds are important causes of both chronic invasive sinusitis and allergic fungal sinusitis. Infection is thought to follow inhalation. The organisms most commonly implicated include *Alternaria* species, *Bipolaris spicifera*, *B. hawaiiensis*, *Curvularia lunata* and *Exserohilum rostratum*. Chronic invasive sinusitis can occur in normal individuals, but it is more commonly seen in persons who have received corticosteroid treatment for some other condition or have diabetes mellitus. Allergic fungal sinusitis occurs in young immunocompetent adults with chronic relapsing rhinosinusitis, 50–70% of whom are atopic. The reported incidence of this disorder ranges from 5–10% of patients with chronic rhinosinusitis in some reports to a much higher proportion in others.

Cerebral phaeohyphomycosis may follow haematogenous dissemination of infection from the lungs or it may result from direct spread from the paranasal sinuses. It is the most frequently reported systemic infection caused by dematiaceous fungi. More cases have been reported in men than women, but a particular occupational predisposition has not been noted. The

age range of reported cases is wide, but most patients are young adults. Although cerebral phaeohyphomycosis has been reported in immunocompromised patients, the disease is most commonly encountered in immunocompetent individuals with no obvious risk factors predisposing them to this infection. The mortality rate is high (about 80%).

The most common cause of cerebral phaeohyphomycosis is *Cladophialophora bantiana*. This mould is found worldwide, however, it is a rare cause of cerebral infection in Far East Asia. *Exophiala dermatitidis* also occurs worldwide, but has only been reported to cause cerebral infection in East Asia. *Ramichloridium mackenziei* is limited to the Middle East; no other neurotropic fungus has been reported from this region. Other aetiological agents include *Bipolaris* species and *Ochroconis gallopava*.

Disseminated phaeohyphomycosis is an uncommon infection, but recent reports suggest that its incidence might be increasing, particularly in immunocompromised patients. *Scedosporium prolificans* is by far the most commonly reported cause of this disease, the largest number of cases being described from Spain. Other aetiological agents include *Bipolaris spicifera* and *Exophiala dermatitidis*. Those at greatest risk for infection include neutropenic cancer patients, particularly those with acute leukaemia, haematopoietic stem cell transplant (HSCT) recipients, solid organ transplant recipients and persons with the acquired immunodeficiency syndrome (AIDS). Most cases of *S. prolificans* infection have been associated with prolonged neutropenia. The overall mortality rate is about 84% in immunocompromised patients, compared with 65% in immunocompetent individuals. However, *S. prolificans* infection has a mortality rate of 100% in patients with persistent neutropenia.

Several nosocomial outbreaks of phaeohyphomycosis have been reported. An outbreak of *Exophiala jeanselmei* fungemia in a Brazilian hospital was associated with contamination of hospital water used to prepare antiseptic solutions that were used for intravascular catheter-site care. More recently, five cases of *Exophiala dermatitidis* infection in four hospitals in North

Carolina were traced to contaminated injectable steroids from the same source.

26.5 Clinical manifestations

Phaeohyphomycosis can be divided into a number of distinct clinical forms, including subcutaneous infection, sinusitis, central nervous system (CNS) infection, localized systemic infection and disseminated infection. In addition, dematiaceous moulds have been implicated as causes of superficial cutaneous infection (see Chapter 6), onychomycosis (see Chapter 7), keratitis (see Chapter 8) and mycetoma (see Chapter 21).

26.5.1 Subcutaneous phaeohyphomycosis

The clinical manifestations of subcutaneous phaeohyphomycosis are similar regardless of the organism causing it. The most common sites of infection are the feet, legs and hands; other sites include the arms, buttocks, neck and face.

The usual clinical presentation is the asymptomatic development of a single subcutaneous nodule at the site of prior trauma. If left untreated, the nodule will slowly increase in size to form a painless cystic abscess. In most cases the lesions remain localized; the overlying skin usually remains unaffected. Purulent fluid can be aspirated from well-developed abscesses.

Draining sinuses sometimes develop in immunocompromised patients with subcutaneous phaeohyphomycosis.

26.5.2 Sinusitis

Dematiaceous moulds are a frequent cause of chronic invasive sinusitis (see also Chapter 10). This is a slowly progressive, destructive condition that may remain confined to the sinuses or spread to the orbit and brain. Affected individuals usually complain of long-standing symptoms of allergic rhinitis or chronic bacterial sinusitis. Thick nasal polyposis and thick mucopurulent mucus are common. If left untreated, the infection can spread from the ethmoid sinuses into the orbit, leading to impaired vision and restricted ocular movement. Proptosis can also occur. Posterior spread from the ethmoid sinus can result in cavernous venous thrombosis.

Non-contrast computed tomographic (CT) scans will reveal a hyperdense mass within the involved sinus with erosion of the sinus walls.

Dematiaceous moulds are the most frequent cause of allergic fungal sinusitis (see also Chapter 10). The criteria for diagnosis of allergic sinusitis have undergone numerous revisions, however, most specialists now agree on the following: the presence in patients with chronic rhinosinusitis of characteristic allergic mucin containing clusters of eosinophils and their by-products, and the presence of non-invasive fungal elements within that mucin detectable on staining or culture. In addition, most experts require the presence of type 1 (IgE-mediated) hypersensitivity to fungi, and nasal polyposis.

Patients with allergic fungal sinusitis often present with unilateral nasal polyposis and thick yellow-green nasal or sinus mucus. The nasal polyposis may form an expansive mass that causes bone necrosis of the thin walls of the sinus. Should the ethmoid bone be traversed, allergic mucin can enter the orbit and cause proptosis. Polypoid material can also push the nasal septum into the contralateral airway. Sinus radiographs show mucosal thickening. CT scans often reveal a characteristic serpiginous sinus opacification of more than one sinus, mucosal thickening and erosion of bone, but this does not represent tissue invasion.

26.5.3 Cerebral phaeohyphomycosis

The symptoms of cerebral phaeohyphomycosis are gradual in onset. Persistent headache is the most common presenting symptom. The most frequent clinical findings include focal neurological signs, haemiparesis and fits. Fever is minimal or absent. Chest radiographs are normal.

CT scans of the head will often reveal a unilateral, well-circumscribed lesion with a contrast-enhancing margin. The frontal lobes of the brain are the most common location. The cerebrospinal fluid (CSF) findings are varied. The opening pressure may be raised, the protein concentration increased, the glucose concentration reduced, and pleocytosis present. It is most unusual to recover the fungus from the CSF. The diagnosis is

seldom established until neurological resection is performed.

26.5.4 Other forms of phaeohyphomycosis

Dematiaceous moulds have been reported to cause endocarditis after valve insertion or replacement, and peritonitis in patients on continuous peritoneal dialysis. Posttraumatic osteomyelitis and arthritis have also been reported. Affected individuals are often immunocompromised, but both localized and disseminated disease have been seen in immunocompetent individuals.

S. prolificans was initially reported to cause bone and joint infections and locally invasive disease in immunocompetent individuals. More recently, however, cases of disseminated infection have become more common, particularly in immunocompromised, usually neutropenic, patients.

In immunosuppressed individuals, the clinical manifestations of disseminated phaeohyphomycosis are similar to those of invasive aspergillosis (see Chapter 10). The most common presentation in the neutropenic patient is a persistent fever (greater than 38°C) that is unresponsive to broad-spectrum antibacterial treatment. Many patients have developed widespread disseminated infection, the most common sites of involvement including the heart, skin, brain and kidneys. The liver, spleen, lymph nodes, bones and joints have been less frequently reported as sites of infection.

26.6 Differential diagnosis

The lesions of subcutaneous phaeohyphomycosis can be confused with the small initial lesions of chromoblastomycosis, sporotrichosis, blastomycosis, coccidioidomycosis and paracoccidioidomycosis, as well as with cutaneous leishmaniasis. Lymphangitic spread of sporotrichosis and the development of verrucous lesions in the other conditions makes the distinction easier.

In immunocompetent individuals, the clinical presentation of chronic invasive phaeohyphomycotic sinusitis is indistinguishable from that of *Aspergillus* infection (see Chapter 10). In immunosuppressed patients, *Aspergillus* sinusitis is a fulminant, often lethal, condition unlike phaeohyphomycosis. However, both groups of

organisms have caused black necrotic lesions of the nasal septum in patients with leukaemia or AIDS.

The presenting symptoms of cerebral phaeohyphomycosis are similar to those of an untreated bacterial brain abscess, but the fungal infection is often more indolent in onset. In occasional patients, the diagnosis of cryptococcosis, histoplasmosis, coccidioidomycosis or sporotrichosis must be excluded.

26.7 Essential investigations and their interpretation

26.7.1 Microscopy

One common factor among these fungi is their melanin formation in the cell wall in culture and, in most cases, in human tissue. Microscopic examination of stained histopathological sections or wet preparations of clinical material, such as pus or skin scrapings, can permit the diagnosis of phaeohyphomycosis if brown-pigmented, septate hyphae with occasional branching are seen.

26.7.2 Culture

Identification of the aetiological agent is essential for correct management, and this depends on its isolation in culture. Clinical material should be inoculated on glucose peptone (Sabouraud's) agar and incubated at 25–30°C. Identifiable dark brown or olivaceous to black mould colonies should be formed within 1–2 weeks, but cultures should be retained for at least 4 weeks before being discarded.

Infection with *S. prolificans* has been associated with positive blood cultures in 80% of reported cases of disseminated phaeohyphomycosis.

26.7.3 Serological tests

There are no reliable serological tests for phaeohyphomycosis.

26.8 Management

26.8.1 Subcutaneous phaeohyphomycosis

Incision and drainage of subcutaneous lesions is seldom successful. Complete surgical excision is required. Treatment with amphotericin B has cured or improved lesions

that are not amenable to resection, but later relapse after discontinuation of treatment has been common. Itraconazole (100–400 mg/day) has been found to produce a good response in some cases. The optimum duration of antifungal treatment that should be given has not been defined, but several months' treatment is usually required.

26.8.2 Sinusitis

Invasion of adjacent structures is a common complication of chronic invasive fungal sinusitis. For this reason, extensive surgical debridement, with removal of all necrotic material, combined with amphotericin B treatment (1.0 mg/kg per day) is recommended. The optimum duration and total dose of amphotericin B that should be given have not been defined, and it is not uncommon for this condition to recur, necessitating further surgical intervention. The role of the newer triazole antifungal agents, such as itraconazole and voriconazole, is unclear but promising. There is limited evidence that long-term suppressive treatment with itraconazole can reduce the rate of recurrence following surgical resection and amphotericin B treatment.

In patients with allergic fungal sinusitis, treatment consists of surgical debridement to remove polyps and the allergic mucin containing fungal debris which is thought to be the cause of the immune reaction in the sinus mucosa. More than one surgical procedure may be required to accomplish this goal. Despite surgical debridement and post-operative systemic corticosteroid treatment, the condition recurs in up to two-thirds of patients. There is no published evidence that oral or topical antifungal treatment is of benefit in allergic fungal sinusitis. However, there is anecdotal evidence that a 6-week post-operative course of itraconazole can reduce the rate of recurrence. Post-operative endoscopic follow-up is recommended because there is a poor correlation between subjective improvement and presence of objective regression of disease.

26.8.3 Cerebral phaeohyphomycosis

The clinical outcome of cerebral phaeohyphomycosis is dismal, with long-term survival being reported only

when complete surgical resection of solitary lesions is possible. Treatment with amphotericin B on its own is ineffective. Lesions that have not been completely removed have usually proved fatal.

26.8.4 Disseminated phaeohyphomycosis

Too few patients have been treated to make firm recommendations. However, many dematiaceous moulds are resistant to amphotericin B *in vitro* and the response to this agent in patients with disseminated phaeohyphomycosis has been partial at best. Among the available azole agents, itraconazole and voriconazole have been shown to be active against many dematiaceous moulds *in vitro*. However, their role in treating disseminated infections is unclear at present. On the basis of published reports, combination treatment with amphotericin B and an azole does not appear to improve the outcome of cases of disseminated phaeohyphomycosis.

S. prolificans appears to be resistant to all available antifungal agents and the prognosis for immunocompromised patients with disseminated infection is dismal.

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27 Other invasive yeast infections

27.1 Introduction

In recent years, a number of yeast species that had previously been thought to represent contamination or harmless colonization when isolated from humans have been recognized as significant pathogens in compromised patients. Establishing the diagnosis is difficult and depends on the detection of the organism in tissue sections or smears of clinical material as well as isolation in culture.

27.2 Systemic *Malassezia* infection

Malassezia is a genus of lipophilic yeasts responsible for various common forms of skin infection in humans, including pityriasis versicolor (see Chapter 6). Less frequently, these organisms have caused life-threatening systemic infection in low-birth-weight infants and other immunocompromised and debilitated individuals, all of whom had received lipid-supplemented parenteral nutrition through an indwelling vascular catheter.

27.2.1 Geographical distribution

These infections are worldwide in distribution.

27.2.2 The causal organisms and their habitat

Until recently, only three *Malassezia* species were recognized: two lipid-dependent species, *M. furfur* and *M. sympodialis*, and one non-obligate lipophile, *M. pachydermatis*. Following genomic and ribosomal sequence comparisons of a large number of human and animal isolates, the genus has now been enlarged into seven species comprising the three former taxa, *M. furfur*, *M. pachydermatis* and *M. sympodialis*, and four new taxa named *M. globosa*, *M. obtusa*, *M. restricta* and *M. slooffiae*. With the exception of *M. pachydermatis*, six of the seven *Malassezia* species are lipid-dependent.

27.2.3 Epidemiology

Malassezia species form part of the normal microbial flora of the skin of humans and other warm-blooded animals and most infections are endogenous in origin. The prevalence of skin colonization with these organisms is dependent upon age, anatomical site and, to a lesser degree, race. Although *Malassezia* species are not found on the skin of healthy newborn infants, up to 50% of pre-term infants who reside in neonatal intensive care units become colonized by their second week of life. High temperatures and high humidity appear to be the most important exogenous risk factors affecting the colonization status of infants.

Exposure to lipid-rich intravenous infusions through a central venous catheter is the single most important risk factor for systemic *Malassezia* infection in both adults and infants. Among neonates, other risk factors include low birth weight, early gestational age and length of hospitalization. An investigation of one outbreak of *M. furfur* infection among low-birth-weight infants, most of whom received intravenous lipids, identified the duration of antimicrobial treatment as an additional risk factor for disease.

Although most infections appear to be sporadic, nosocomial outbreaks of systemic *Malassezia* infection have been reported. An investigation of one outbreak of *M. furfur* infection among low-birth-weight infants provided evidence that the organism can be transmitted from an infected or colonized infant to other infants via the hands of healthcare workers. Nosocomial outbreaks of *M. pachydermatis* infection have also been reported. In one outbreak, patient-to-patient transmission of the organism was documented in a neonatal intensive care unit, but the source of the outbreak was not identified. In a more recent outbreak the organism was introduced into the unit on healthcare workers' hands after being colonized from pet dogs at home. The organism persisted in the unit through patient-to-patient transmission.

27.2.4 Clinical manifestations

In infants, *Malassezia* fungaemia usually presents as fever and/or apnoea and bradycardia. Interstitial

pneumonia and thrombocytopenia are common findings in this patient group. The most common symptoms of systemic infection are fever and respiratory distress with or without apnoea. Less frequent symptoms and signs include poor feeding and hepatosplenic enlargement. No signs of infection have been noted at catheter insertion sites, nor has a skin rash been evident in infants with systemic *Malassezia* infection.

The few reported adult cases of catheter-associated *M. furfur* sepsis have occurred in conjunction with a range of underlying illnesses. All patients had been receiving parenteral lipid emulsions through central venous catheters for periods ranging from a few days to many months. Fever was the consistent presenting symptom.

The predominant pathological changes noted in patients with catheter-associated *Malassezia* infections have involved the heart and lungs. These have included mycotic thrombi around the tips of indwelling catheters, endocardial vegetations, vasculitis of vessels, and inflammation of alveoli, bronchi and bronchioles.

27.2.5 Essential investigations and their interpretation

The diagnosis of *Malassezia* fungaemia should be considered in any febrile patient (particularly if there is clinical and radiological evidence of pneumonia) who is receiving lipid-containing parenteral nutrition through an indwelling vascular catheter, especially if routine blood cultures are sterile.

Malassezia fungaemia has sometimes been diagnosed following detection of the organism in stained smears prepared from catheter blood specimens. However, the diagnosis is most often based on isolation of the organism from blood taken through the catheter. In instances where the catheter can be removed, the tip of the catheter should be inoculated on to glucose peptone (Sabouraud's) agar overlaid with sterile olive oil or another lipid-enriched medium. The lipid concentration of conventional broth and agar media is usually insufficient to support the growth of *Malassezia* species (with the exception of the non-lipid-dependent species, *M. pachydermatis*), but it would appear that the blood of patients receiving parenteral nutrition often contains

sufficient lipids to support initial growth of these organisms in culture. Subculture of broth on to an agar medium containing, or overlaid with, a lipid source should ensure isolation of the organism. Identifiable colonies can be obtained after incubation for 1–4 days at 35–37°C.

27.2.6 Management

The most important factor in the successful management of *Malassezia* fungaemia in pre-term infants is the prompt removal of the infected vascular catheter, whether or not antifungal treatment is given. Lipid supplements should be discontinued in almost all patients, and an antifungal azole, such as parenteral fluconazole (5 mg/kg per day), should be administered. More stable patients may be able to receive fluconazole or itraconazole by mouth. The duration of treatment depends on persistence of fungaemia, presence of metastatic foci of infection and removal of the catheter.

27.3 Trichosporonosis

In addition to causing white piedra, an uncommon asymptomatic infection of the scalp, facial and pubic hair (see Chapter 6), *Trichosporon* species, can also cause a systemic infection known as trichosporonosis in immunocompromised individuals.

27.3.1 Geographical distribution

These infections are worldwide in distribution.

27.3.2 The causal organisms and their habitat

Until recently, the genus *Trichosporon* encompassed a heterogeneous group of species that were the anamorph (asexual) stages of both ascomycetous and basidiomycetous fungi. Two species were associated with systemic infection in humans: *T. beigelii* and *T. capitatum*. Following genomic and ribosomal sequence comparisons of a large number of human, animal and environmental isolates, the genus is now considered to be a basidiomycetous yeast genus consisting of 19 species. Two of these newly delineated taxa (*T. asahii* and *T. mucoides*) are associated with systemic infections in humans, while four (*T. asteroides*, *T. beigelii*, *T. inkin*

and *T. ovoides*) have mostly been associated with superficial infection, most commonly white piedra. Three species associated with humans have been transferred to other genera. *T. capitatum* has been reclassified as *Blastoschizomyces capitatus*, while *T. penicillatum* and *T. fermentans* have been transferred to the genus *Geotrichum*. Identification of the different species of *Trichosporon* can be accomplished using temperature requirements, assimilation reactions and cycloheximide (actidione) resistance.

Trichosporon species have a widespread natural distribution, being found in soil, water and on plants. They are also common commensal inhabitants of the skin and gastrointestinal tract of humans.

27.3.3 Epidemiology

Most cases of trichosporonosis appear to be endogenous in origin. Like candidosis, *T. asahii* infection has been acquired through invasion from the gastrointestinal mucosa, through aspiration of gastrointestinal tract contents, and via indwelling vascular catheters.

The likelihood that trichosporonosis will develop in a colonized individual depends, in major part, on host factors. Those at greatest risk include neutropenic cancer patients receiving cytotoxic treatment. Less commonly, disseminated infection has been seen in solid organ transplant recipients, burns patients, low-birth-weight infants, and persons with the acquired immunodeficiency syndrome (AIDS). Factors that enhance mucosal colonization and subsequent invasive infection include broad-spectrum antibiotic treatment and breaks in anatomical barriers.

The overall mortality rate is high, ranging from 60 to 80% in earlier reports. Some improvement has been achieved with recent developments in diagnosis, treatment and prevention.

27.3.4 Clinical manifestations

The clinical manifestations of disseminated trichosporonosis are similar in most respects to those of disseminated candidosis (see Chapter 11). Like candidosis, trichosporonosis may take the form of an acute or chronic infection. The former often presents as a

persistent fever that fails to respond to broad-spectrum antibacterial treatment. Multiple cutaneous lesions, similar to those seen in disseminated candidosis, occur in up to two-thirds of patients. These evolve from maculopapules to necrotizing ulcers. Chorioretinitis has also been described. The liver, spleen, brain and heart are among the other organs which may be involved, but the lungs are the most common site of end-organ disease. In patients with *Trichosporon* pneumonia, chest radiographs will reveal reticulonodular or diffuse infiltrates.

Chronic hepatosplenic trichosporonosis has been described in leukaemic patients who recover from neutropenia. Like chronic disseminated candidosis (see Chapter 11), this infection often begins while the patient is neutropenic, but does not become apparent until after the neutrophil count has recovered. The patient remains febrile and unwell, developing an enlarged liver and spleen.

27.3.5 Essential investigations and their interpretation

The diagnosis of trichosporonosis is seldom suspected until the fungus is isolated from blood, urine or cutaneous lesions. Often, however, patients have died and the infection has remained unrecognized until material obtained post-mortem has been investigated.

MICROSCOPY

Microscopic examination of smears and histopathological sections of cutaneous lesions will reveal branching hyphae with numerous rectangular arthrospores and budding blastospores. If arthrospores are sparse in tissue, *T. asahii* can resemble *Candida albicans*. However, *T. asahii* sometimes produces more true hyphae and fewer pseudohyphae than *C. albicans*.

CULTURE

In culture, members of the genus *Trichosporon* form white to cream, heaped colonies that consist of hyaline hyphae with arthrospores and blastospores. In neutropenic patients, blood cultures are often positive and the organisms can also be recovered from biopsies of cutaneous lesions. Isolation from these specimens provides more reliable evidence of deep-seated infection than

does isolation from bronchoalveolar lavage (BAL) fluid, sputum or urine.

SEROLOGICAL TESTS

Trichosporon species produce a heat-stable antigen which shares antigenic determinants with the capsular antigen of *Cryptococcus neoformans*. Several reports have appeared indicating that with serum the latex particle agglutination (LPA) test for *C. neoformans* antigen is positive in patients with disseminated trichosporonosis and could be useful in making the diagnosis. However, negative results have also been obtained in LPA tests with serum and urine specimens from patients dying with disseminated trichosporonosis.

27.3.6 Management

Isolates of *T. asahii* are often resistant to amphotericin B *in vitro*. Anecdotal case reports suggest that neutropenic patients with disseminated trichosporonosis are best treated with fluconazole (400 mg/day) or itraconazole (200 mg twice daily). The new triazole agent, voriconazole, may also be effective.

27.4 Other yeast infections

Blastoschizomyces capitatus is commonly found in the environment and can be recovered from the skin, gastrointestinal tract and respiratory tract of healthy individuals. In neutropenic patients, *B. capitatus* produces a pattern of infection similar to that of trichosporonosis, but with more frequent central nervous system involvement. Chronic disseminated infection can occur in patients who recover from neutropenia. The diagnosis of *B. capitatus* infection is usually made by culture of blood. The optimum approach to treatment remains to be defined, but fluconazole is a reasonable option.

Other unusual yeasts that have been reported to cause invasive infections in profoundly immunocompromised patients include *Saccharomyces cerevisiae*, *Rhodotorula rubra* and *Hansenula anomala*. These organisms may present with a wide range of clinical manifestations, ranging from fungaemia to localized deep or disseminated infection. The approach to successful management is necessarily individual, but includes

antifungal treatment and removal of potentially colonized vascular catheters. Most isolates are susceptible to amphotericin B and flucytosine. Of note, however, there are reported instances of *in vitro* fluconazole resistance and clinical failure of fluconazole treatment.

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