Infectious Disease
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Duane R. Hospenthal
Michael G. Rinaldi *Editors*

Diagnosis and Treatment of Fungal Infections

Second Edition

Springer

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Editors

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ISBN 978-3-319-13089-7 ISBN 978-3-319-13090-3 (eBook)
DOI 10.1007/978-3-319-13090-3

Library of Congress Control Number: 2015937384

1st edition of this volume copyright 2008 year
Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Since publication of *Diagnosis and Treatment of Human Mycoses* in 2008 fungi have continued to emerge as important agents of human infection. Fungal infections (mycoses) continue to plague humankind as the at-risk population continues to expand with more immunosuppressive therapies, enlarging populations receiving cancer therapy, and continued support of our most ill in intensive care units and with broad-spectrum antibacterial agents. *Diagnosis and Treatment of Fungal Infections, 2nd Edition* again brings together globally recognized experts to guide readers in the use of our current knowledge to diagnose and treat patients with fungal infections.

In addition to basic and directed culturing techniques, histopathology, serological methods, and radiological studies, molecular biology techniques continue to improve our ability to diagnose fungal infection and identify the offending fungus. Genotypic identification has led to an expansion of our understanding of the fungal pathogens and has led to many new fungi being identified as the cause of human infection. This, and recent changes in taxonomy, can lead to confusion in keeping up with the most proper name for any recovered fungus and difficulty in identifying the appropriate medical literature to review.

We currently have three major classes of antifungal agents to choose from for systemic treatment of fungal infections. These include amphotericin B and the echinocandin and triazole antifungals. Selecting which drug to use can be difficult in the empirical setting and targeted therapy typically requires identification of the pathogen to species level. Antifungal susceptibility testing can assist in selecting the best antifungal drug to use, but clinical correlation of this testing with treatment success remains limited to the *Candida* species.

Diagnosis and Treatment of Fungal Infection, 2nd Edition is meant to be a concise text that will provide the busy infectious disease, hematology-oncology, pulmonology, or critical care specialist a practical tool to diagnose and manage fungal infections. In addition, the depth of the material in the text will provide these and other medical specialists and trainees an excellent reference and learning resource.

The text is divided into four parts to guide the reader. Part I provides a general introduction to the epidemiology of fungal infections and presents practical approaches for using patient risk factors, exposures, and site of infection to direct diagnostic evaluations. Part II introduces the science of mycology and the current tools available to diagnose fungal infections using basic clinical mycology laboratory techniques, with molecular biology, histopathology and immunology, and with radiological technologies. Part III provides a review of the available antifungal drugs, their use, and discussion of resistance and antifungal susceptibility testing. Part IV reviews fungal infections (mycoses) in 15 uniform, easy to read chapters, with accompanying tables and figures.

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Part I
Approach to Patients

Approach to Patients with Suspected Fungal Infections

1

Duane R. Hospenthal

Introduction

Fungal infections (mycoses) are increasing in incidence throughout the world as a result of modern medical practice and rise in the population of those at risk. Supporting this increase is the expanding use of immunosuppressive therapies, broad-spectrum antibiotics, and central venous access devices. Technology has led to the improved survival of persons with malignancies, transplanted organs, HIV infection, following trauma, and at the extremes of age. The medical community has met this challenge with the introduction of new antifungal agents, often with less toxicity and improved spectrums of activity. Additionally, newer, more sensitive and specific diagnostic strategies such as improved radiographic imaging and serological tests, have provided clinicians with better tools to detect fungal infections earlier, potentially influencing disease outcomes. Molecular techniques have been introduced in the last decade which can produce a more exact identification of recovered fungal pathogens and have the potential to improve diagnosis of fungal infection. Despite these advances, the approach to the diagnosis and management of fungal infections still relies on recognizing the interaction of the pathogen and the host. Although some fungal diseases have classic presentations, many of these occur so rarely that clinicians may not initially include them in their differential diagnoses. In the setting of immunosuppression, mycoses may produce nonspecific signs and symptoms, making their diagnosis a challenge. Early recognition and treatment is fundamental to modifying disease outcomes in many fungal infections, especially those in immunocompromised individuals. Increased awareness of key risk factors and clinical presentations of the human mycoses may enable clinicians to develop an inclusive approach to the diagnosis of these diseases.

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Epidemiology

Deaths associated with mycoses have increased in the USA, moving from the tenth most common infectious disease cause of death in 1980 to the seventh in 1997 [1]. Sepsis due to fungal infection increased over 200 % in the USA between 1979 and 2000 [2]. Fungal sepsis is chiefly secondary to candidemia. *Candida* continues to be the fourth most common organism recovered from bloodstream infections in the USA; associated with a crude mortality of about 40 % [3, 4]. Candidemia and disseminated (also termed systemic or invasive) candidiasis continues to be the most common cause of nosocomial fungal infections, responsible for more than 80 % of these infections and up to 15 % of nosocomial infections overall. Infections with *Candida* have declined in patients with cancer and undergoing hematopoietic stem cell transplantation (HSCT), likely in association with antifungal prophylaxis. Candidemia, after surging in numbers in the 1980s appears to have declined, at least in the intensive care setting [5]. This overall decline is chiefly due to fewer infections with *C. albicans,* as *nonalbicans Candida* (NAC) candidemia has increased over this same period, 1989–1999.

Opportunistic mold infections, most commonly caused by the *Aspergillus* species, continue to expand their range of hosts from severely neutropenic cancer patients to patients with other risk factors, including prolonged immunosuppressive therapies with corticosteroids and newer agents, including those that inhibit tumor necrosis factor alpha (TNF-α) [6]. *Aspergillus* is the second most common cause of nosocomial fungal infection and the most common mold to cause invasive mycosis. Other rare opportunistic molds (e.g., the Mucorales, *Fusarium,* and *Scedosporium*) and yeasts (e.g., *Trichosporon* and *Malassezia*) have emerged as more frequently causes of disease in patients with a wide range of risks [7–13].

Outbreaks of endemic mycoses, including coccidioidomycosis in association with the growing urbanization of the US Southwest, and on a smaller scale, histoplasmosis, continue to be reported more frequently, often affecting

D. R. Hospenthal, M. G. Rinaldi (eds.), *Diagnosis and Treatment of Fungal Infections,* Infectious Disease,
DOI 10.1007/978-3-319-13090-3_1,

greater numbers of persons. Outbreaks of endemic disease are occasionally diagnosed outside their known geographical areas, occurring in travelers to those locales. An outbreak of infection with the *nonneoformans Cryptococcus, C. gattii,* in mostly immunocompetent patients, has been going on in the US Northwest and Southwest Canada (Vancouver Island) over the past decade [14, 15].

Suspicion Based on Risk Factors

The risks for fungal infections are highly dependent on the combination of host immune competency and the specific exposures people have both within the health care system and in their communities.

Immunocompromise

Host immune status is probably the most import underlying factor determining whether people develop life-threatening, self-limiting, or no infection following exposure to fungi in their environment. Defense against invasive mycoses depends chiefly on intact mucosal barriers, the innate immunity provided by phagocytic cells, and cell-mediated immunity (CMI). The impact of humoral immunity is limited and remains poorly defined in defense against the fungi.

Neutropenia and Altered Phagocytic Function

Classically, neutropenia has been associated with candidemia and invasive candidiasis. With prolonged neutropenia, *Aspergillus* species become more common causes of infection. Infection with the Mucorales, *Fusarium, Scedosporium, Trichosporon,* and other rare species can also be seen with prolonged loss of neutrophils. The incidence of candidiasis in the highest-risk populations appears to have declined over the past decade in association with antifungal prophylaxis of these patients. This decrease has been associated with an increase in aspergillosis and other invasive mold infections. In addition to insufficient numbers of neutrophils, declination in phagocytic function also raises the risk of mycoses. The phagocytic dysfunction seen in chronic granulomatous disease (CGD) is associated with fungal infections, especially aspergillosis.

Impaired Cell-Mediated Immunity

Impaired CMI occurs in patients infected with HIV and those receiving many of the currently used immunosuppressive therapies. Impairment of CMI is associated with mucocutaneous candidiasis, *Pneumocystis* pneumonia, infection with *Cryptococcus,* and more severe and/or disseminated endemic mycoses. The specific mycoses associated with $CD4^+$ T lymphocyte decline as seen in HIV/AIDS have been carefully documented, allowing the clinician to increase their level of suspicion for particular fungal infections based on $CD4^+$ T lymphocyte counts of their patients (Table 1.1).

Table 1.1 Mycoses commonly associated with HIV infection

$CD4^+$ T lymphocyte cell count (cells/μl)	Fungal infections
>500	Candidal vaginitis
200–500	Thrush (oropharyngeal candidiasis)
<200	PCP, disseminated histoplasmosis, disseminated coccidioidomycosis
<100	Cryptococcosis, candidal esophagitis, penicilliosis

PCP Pneumocystis pneumonia

Table 1.2 Fungi associated with hematopoietic stem cell transplantation

Time period	Common fungi	Other fungi
Preengraftment (<30 days)	*Candida*	*Aspergillus*
Postengraphment (30–100 days)	*Aspergillus, Candida, Pneumocystis*	Mucorales, *Fusarium, Pseudallescheria* (*Scedosporium*)
Late (>100 days)	*Aspergillus, Pneumocystis*	

Organ Transplantation

Solid organ and HSCT recipients are at great risk for fungal infections [16–18]. In addition to immunosuppressive therapies, the mucosal damage and intensive therapy associated with these procedures place the persons who receive them at risk for the entire spectrum of fungal disease. Transplant medicine has seen substantial advancements in tailoring regimens to minimize the duration of neutropenia and to reduce immunosuppressive treatments used to control rejection. Unfortunately, most of these still place patients at a substantial risk for opportunistic infections. In solid organ transplantation, the risk of fungal infection is associated with risk surrounding the initial surgery and the use of immunosuppression to prevent rejection. This risk varies greatly based on organ transplanted and underlying condition of the recipient. As an example, in liver transplantation, the substantial risk of *Candida* infection in the first month is mostly associated with surgical manipulation of the gastrointestinal tract and the need for intensive care monitoring, as well as initial immunosuppressive agents given to control rejection (Table 1.2). Lung transplants are at high risk for invasive pulmonary aspergillosis, likely secondary to the route of inoculation and immunosuppression. Although a similar sequence of occurrence of fungal infection is seen in HSCT, the underlying factors creating risk differ from those of solid organ transplant (Table 1.3). In HSCT, initial conditioning commonly leads to neutropenia and breakdown of the mucosal surfaces. This neutropenia can be prolonged and as-

Table 1.3 Fungi associated with solid organ transplantation. (Table produced from data in reference [16])

Time period	Common fungi	Other fungi
First month	*Candida*	
1–6 months	*Aspergillus, Pneumocystis, Cryptococcus*	Endemic fungi[a]
>6 months	Endemic fungi[a]	*Cryptococcus*

[a] Chiefly, coccidioides and histoplasma

sociated with life-threatening mold infections. In allogeneic HSCT, graft-versus-host disease (GvHD) and its treatment may put the patient at risk for fungal infection for a prolonged period of time following engraftment.

Health Care Exposure (Nosocomial)

A multitude of risk factors for nosocomial fungal infections have been identified (Table 1.4) [6, 19, 20]. Unfortunately, many of these health care-associated risk factors overlap with those associated with bacterial infections or are risks that are common to many or most hospitalized patients. This is especially true for those patients hospitalized in intensive care units, the majority of whom have central venous catheters and are receiving broad-spectrum antibiotics [21, 22]. In addition to the use of vascular catheters, other procedures including urinary catheterization and intubation establish portals of entry for fungal pathogens. Other risk factors include immunosuppression seen with the use of corticosteroids and chemotherapy, and with malnutrition and malignancy. Infusion of contaminated infusates, inclusion of lipids in parenteral nutrition, and construction within the hospital are additional exposures that can lead to fungal infections. A few specific risks allow the clinician to suspect certain fungi. Ketoacidosis and deferoxamine therapy has been clearly shown to be a risk for mucormycosis (zygomycosis). Unfortunately, given the overlapping nature of most of these risk factors with those associated with bacterial infections, it is often difficult to apply these risk factors to differentiate patients at higher risk of fungal versus bacterial infection.

Community Exposure

The fungi that cause community-acquired infections commonly originate in the environment and are "true pathogens" (i.e., cause disease in persons with normal immune status). Most are restricted to certain geographic environments or exposure risks (Table 1.5). The source of disease includes inhalation, ingestion, or traumatic inoculation of the fungi. Diseases most commonly afflict the lungs, paranasal sinuses, skin, and soft tissues. Rarely, disseminated, central nervous system, or osteoarticular disease occurs. The most commonly recognized community-acquired infections are the endemic mycoses, each with their limited geographical areas of exposure. With the extensive use of antibiotics, corticosteroids, and other immune modulators in the community, as well as the increased number of elderly, and population of immunocompromised persons receiving their care outside of the hospital, the boundaries between community-acquired and health care-associated infection have become blurred.

Table 1.4 Risk factors commonly associated with health care-associated invasive mycoses (Table produced from data in reference [17])

Mycosis	Risk factors
Candidiasis	*Candida* colonization, surgery (especially abdominal), acute renal failure, parenteral nutrition, central venous catheters, neutropenia, broad-spectrum antibacterial antimicrobials, mucosal surface disruption
Aspergillosis	Prolonged neutropenia, corticosteroids, neutrophil dysfunction, hematologic malignancy, cytotoxic drugs, AIDS, HSCT (highest in allogeneic), solid organ transplantation (highest heart-lung), underlying lung disease, GvHD, GvHD therapies (TNF-α blockers)

HSCT hematopoietic stem cell transplantation, *GvHD* graft-versus-host disease, *TNF*-α tumor necrosis factor alpha

Other Risks

Other risks or probable risks associated with immune competency or genetic disposition include gender and race. The role of gender and potentially inhibitory effect of estrogen has been postulated to be important in the risk of clinical paracoccidioidomycosis. A clear risk exists for disseminated coccidioidomycosis in women when disease is acquired in pregnancy. Disseminated and severe coccidioidomycosis has also been associated with Filipino and African descent.

The use of antifungal therapy or prophylaxis in populations at risk should also be kept in mind when evaluating patients for potential fungal infections. The last decade has seen an emergence of NAC, *nonfumigatus Aspergillus* infection, and increased numbers of infections with the more rare yeasts and molds. This shift appears to reflect our greater usage of antifungals and use of the newer agents. Included in this change in epidemiology is the emergence of fluconazole-resistant *Candida* (i.e., *C. krusei*) and recent increase in *non-Aspergillus* molds (e.g., the Mucorales, *Fusarium,* and *Scedosporium*) which have decreased susceptibility or resistance to many of the currently available antifungal agents.

Suspicion Based on Organs Involved

Although the fungi may and often do cause disease in more than one organ system, many of these are associated with certain organ system infections. The presentation of disease