Clinical Mycology

SECOND EDITION

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Clinical Mycology

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Preface

The first edition of *Clinical Mycology* established this text as an important, internationally recognized reference work for clinical mycology. Owing to numerous recent advances in the diagnosis and management of mycoses, a second edition is mandated to provide clinicians and laboratorians with a contemporary source of information. The second edition provides modern tools that will assist in the diagnosis, prevention and treatment of fungal infections in various patient populations. A group of internationally recognized experts was assembled to present this information in a comprehensive, authoritative manner with a clear focus on the clinical management of fungal infections.

All chapters in the second edition have been extensively revised and updated with current information and references. Obsolete and out-of-date material was eliminated to maintain this important textbook as a single volume. Two new chapters have also been added; one on pneumocystosis, in recognition of the reclassification of *Pneumocystis jiroveci* as a fungus and another covering anomalous fungal and fungal-like infections; that is, Lacaziosis and Rhinosporidiosis. Several new sections have been added to the chapter on fungal infections in cancer patients to reflect the formidable clinical challenges these infections continue to present.

The success of the first edition was due in part to the use of practical tools (algorithms, slides, graphs, pictorials, photographs, and radiographs) that have made the work clinically practical. A significant effort has been made in the second edition to enhance these reader-friendly features with a significant increase in the number of practical tools, algorithms and the expanded use of color for enhanced clarity.

The book is divided in 4 sections (32 chapters) covering the following topics:

I. Epidemiology, geographic medicine, pathogenesis, and laboratory diagnosis of fungal infections and antifungal agents.
II. Fungi that cause human disease (microbiology, pathogenesis, mycotoxicosis clinical syndromes, and in vitro and in vivo susceptibility to antifungal therapy)
III. Evaluation and management of fungal infections according to patient population (cancer, organ and stem cell transplantation, AIDS, pediatric).
IV. Presentation and management of organ system involvement (pulmonary, central nervous system, etc.).

We believe that the enormous efforts of all contributors to the second edition of *Clinical Mycology* have resulted in a state-of-the-art and clinically useful textbook that will guide clinicians in the diagnosis, prevention and treatment of fungal infections in various patient populations.

The editors wish to thank the remarkably talented authors who have contributed to *Clinical Mycology* and the superb Infectious Diseases team at *Elsevier*.

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CHAPTER 1

The epidemiology of fungal infections

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Fungal infections may be divided into two categories: nosocomial and community associated. Nosocomial fungal infections are defined as those acquired in a healthcare setting, and are almost always *opportunistic* mycoses. In contrast, community-associated fungal infections include not only opportunistic mycoses but also the *endemic* mycoses, for which susceptibility to the infection is acquired by living in a geographic area constituting the natural habitat of a pathogenic fungus and possessing risk factors that are predisposing.

Over the past two and a half decades, the incidence of both nosocomial and community-associated fungal infection has increased dramatically. An analysis of trends in infectious disease mortality in the United States found that fungal infections had risen from the tenth to the seventh most common cause of infectious disease related mortality between 1980 and 1997.[1]

Numerous factors have contributed to the increase in fungal infections. most notably a growing population of immunosuppressed or immunocompromised patients whose mechanisms of host defense have been impaired by primary disease states (e.g., AIDS, cancer), a mobile and aging population with an increased prevalence of chronic medical conditions, and the use of new and aggressive medical and surgical therapeutic strategies, including broad-spectrum antibiotics, cytotoxic chemotherapies, and organ transplantation.

Table 1-1 Nosocomial bloodstream infections: most frequent associated pathogens. Scope surveillance program, April 1995 to September 2002[a]

Rank	Pathogen	% of isolates[b]
1	Coagulase-negative staphylococci	31.3
2	*Staphylococcus aureus*	20.2
3	*Enterococcus* spp.	9.4
4	*Candida* spp.	9.0
5	*Escherichia coli*	5.6
6	*Klebsiella* spp.	4.8
7	*Pseudomonas aeruginosa*	4.3
8	*Enterobacter* spp.	3.9
9	*Serratia* spp.	1.7
10	*Acinetobacter baumannii*	1.3

[a]Data reproduced from Wisplinghoff et al.[6]
[b]Percent of a total of 24,179 infections.

Nosocomial fungal infections

Increasing incidence and mortality

For the past two decades, hospitals have been experiencing increasing problems with nosocomial fungal infections.[2-5] A recent study of the epidemiology of sepsis found that the annual number of cases of sepsis caused by fungal organisms in the United States increased by 207% between 1979 and 2000.[2] In the Surveillance and Control of Pathogens of Epidemiological Importance Study, a 49-center study of 24,179 nosocomial bloodstream infections recorded between 1995 and 2002, 9.5% of the infections were fungal in origin.[6] *Candida* spp. were the fourth leading cause of nosocomial bloodstream infections, surpassed only by staphylococci and enterococci (Table 1-1).[6]

Rates of invasive fungal infection vary by hospital and region because they are dependent upon local factors and practice patterns as well as underlying risk factors. However, the first population-based incidence rates of fungal infection were provided by an active laboratory surveillance program conducted in the San Francisco Bay area between 1992 and 1993.[7] The cumulative incidence of invasive mycoses in this study was 178 per million population. The most common nosocomial fungal pathogens were *Candida* (73 cases per million per year), *Aspergillus* (12 cases per million per year), and zygomycetes (~2 cases per million per year) (Table 1-2).[7] *Cryptococcus* was also a major cause of invasive mycoses in this study (65 cases

Table 1-2 Population-based incidence rates and case-fatality rates for opportunistic mycoses

Organisms[a]	No. cases per million per year[b]	Case-fatality ratio (%)[b]
Yeasts		
A. *Candida* species *C. albicans* *C. glabrata* *C. parapsilosis* *C. tropicalis* *C. krusei* *C. lusitaniae* *C. rugosa* *C. guilliermondii* *C. inconspicua* *C. norvegensis*	72.8	33.9
B. *Cryptococcus* species	65.5	12.7
C. Other yeasts		
Hyaline moulds		
A. *Aspergillus* species	12.4	23.3
B. Zygomycetes	1.7	30.0
C. Other hyalohyphomycetes	1.2	14.3
Dematiaceous moulds	1.0	0
Pneumocystis jiroveci		

[a]List not all-inclusive.
[b]Data reproduced from Rees et al.[7]
Table reproduced from Pfaller and Diekema.[21]

per million per year), which reflected the large number of patients at high risk due to HIV infection in the era prior to highly active antiretroviral therapy (89% of the patients with cryptococcosis were also HIV positive).[7]

The increasing rates of invasive fungal infection have also resulted in significant mortality. In one report, the number of deaths in the United States in which mycosis was listed on the death certificate increased fourfold between 1980 (1557 deaths) and 1997 (6534 deaths).[1] The crude mortality of fungal infections ranges from 27% to 77% but may exceed 90% in certain patient populations (e.g., aspergillosis or fusariosis in bone marrow transplant patients with persistent neutropenia). Although estimates of attributable mortality are confounded by the serious underlying diseases in many of these patients, matched cohort studies have confirmed that the mortality directly attributable to the fungal infection is extremely high.[8-10] A retrospective cohort study of fungal infections in Italian patients with hematologic malignancies placed the attributable mortality at 33% for candidemia, 42% for aspergillosis, 53% for fusariosis and 64% for zygomycosis.[11]

Risk factors

Although numerous risk factors for nosocomial fungal infection have been identified (Table 1-3), most are common in hospitalized patients and thus may not be useful in predicting those individuals who will develop invasive mycosis.[8,12,13] In an attempt to control for confounding factors such as underlying illness, several studies have used multivariate analysis to identify independent risk factors such as antimicrobial use, administration of chemotherapy, presence of indwelling catheters, colonization at other body sites, and hemodialysis (see Table 1-3).[8,13] The various exposures place individuals at risk for fungal infection primarily by inducing immunosuppression, promoting colonization or providing direct access to the bloodstream, lung or deep tissues (see Table 1-3).

Among patients at highest risk of fungal infection are solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients (Tables 1-4 and 1-5). For SOT recipients, the type of organ transplanted may predispose a patient to one type of fungal infection over another (Table 1-4)[14] while for HSCT recipients, risk for fungal infection depends upon the degree of immunosuppression (e.g., higher for allogeneic than for autologous transplants).[5,15,16] Risk factors for fungal infections in transplant recipients include the use of large doses of corticosteroids, multiple or acute rejection episodes (SOT), graft-versus-host disease (HSCT), hyperglycemia, poor transplant function, leukopenia, and advanced age.[17]

Pathogens

Candida species

Although the array of fungal pathogens known to cause nosocomial infection is extremely diverse, most of these infections are due to *Candida* spp.[6] *Candida* spp. accounted for 88% of all nosocomial fungal infections in the United States between 1980 and 1990 and were the fourth leading cause of nosocomial bloodstream infection (BSI).[5,12] A more recent multicenter surveillance program found that *Candida* species caused over 70% of invasive fungal infections in hospitalized patients (Fig. 1-1).[18,19] Between 1995 and 2002, the frequency of nosocomial candidemia rose significantly from 8% to 12% of all reported BSIs.[6] Wenzel and Gennings, extrapolating from these data, estimate the annual burden of candidemia to be 10,500–42,000 infections in the United States, associated with between 2800–11,200 deaths per year.[20] National Hospital Discharge Survey (NHDS) data estimates of invasive candidiasis incidence have been steady or increasing between 1996 and 2003 at 22–29 infections per 100,000 population (Fig. 1-2).[21] These data include not only candidemia but also other forms of invasive candidiasis that may not be associated with positive blood cultures, which may partially explain why the estimates are higher than several recent population-based studies of candidemia incidence (Table 1-6).[22-30] Combined with data from the NNIS system, which show an overall decline in frequency of candidemia among ICU patients in the US,[4] these data suggest that the burden of invasive candidiasis is shifting from the ICU to the general hospital (and even outpatient) setting.

Table 1-3 Risk factors for fungemia in hospitalized patients

Risk factor	Possible role in infection
Antimicrobial agents[a]	
Number	Promote fungal colonization
Duration	Provide intravascular access
Adrenal corticosteroid	Immunosuppression
Chemotherapy[a]	Immunosuppression
Hematologic/solid organ malignancy	Immunosuppression
Previous colonization[a]	Translocation across mucosa
Indwelling catheter[a]	
Central venous catheter	Direct vascular access
Pressure transducer/ Swan–Ganz	Contaminated product
Total parenteral nutrition	Direct vascular access Contamination of infusate
Neutropenia (polymorphonuclear cells <500/mm^3)[a]	Immunosuppression
Extensive surgery or burns	Route of infection Direct vascular access
Assisted ventilation	Route of infection
Hospitalization or intensive care unit stay	Exposure to pathogens Exposure to additional risk factors
Hemodialysis[a]	Route of infection Immunosuppression
Malnutrition	Immunosuppression

[a]Independent risk factor.

The excess (or attributable) mortality due to *Candida* spp. bloodstream infection is high (20–50%), and two studies performed at the University of Iowa Hospital demonstrate that this mortality did not change substantially between 1983 and 2001.[9,10] In addition, among patients who survive an episode of candidemia, the mean excess length of stay in the hospital attributable to the infection is 30 days.[9] Population-based mortality burden due to invasive candidiasis is available from National Center for Health Statistics (NCHS) multiple cause of death data, which reveal that the mortality associated with invasive candidiasis has remained steady since 1997 at approximately 0.4 deaths per 100,000 population (Fig. 1-3).[21]

Although more than 100 species of *Candida* have been identified, fewer than 20 species have been implicated in nosocomial infections. *C. albicans* is the species most commonly isolated from clinical material and accounts for 40–70% of cases of invasive candidiasis.[21,23,31-35] The second and third most frequently isolated species of *Candida* causing nosocomial candidiasis are dependent upon the age of the patient and the geographic location of the hospital (Table 1-7). In the NICU setting in the United States *C. parapsilosis* is the second most frequently isolated organism while in the general ICU setting it is *C. glabrata*. Despite reports suggesting that shifts have occurred in the distribution of infections caused by species of *Candida* other than *C. albicans*, many of these reports are isolated to specific institutions, and we have observed that the rank order of species distribution has been stable over 12 years of global surveillance.[36]

Accumulated knowledge about the epidemiology of nosocomial candidemia is summarized in Figure 1-4. Certain hospitalized patients are at increased risk of contracting nosocomial candidemia because of their underlying medical conditions, while medical interventions such as antibiotic use, the presence of a central venous catheter, and hemodialysis further increase the risk of contracting candidemia (Table 1-8).[37] The available epidemiologic data indicate that between 5 and 10 of every 1000 high-risk patients exposed to any of the preceding risk factors will contract *Candida* bloodstream infection, which comprises 8–10% of all nosocomial bloodstream infections.[38] Approximately 35% of these patients will die as a result of the infection, and an additional 30% will die because of their underlying disease.[9] In a recent matched cohort study of nosocomial candidemia, 49% of the patients died as a result of their infection while an additional 12% died of their underlying disease.[10]

Because delays in the administration of appropriate antifungal therapy are important contributors to the unacceptably high associated mortality, considerable efforts are now being made to develop risk stratification strategies to guide antifungal therapy (prophylaxis and early empiric therapy) to improve outcomes.[21]

Aspergillus species

Aspergillus species are ubiquitous fungi that may be isolated from a variety of environmental sources, including soil, grain, leaves, grass, and air.[39,40] Reservoirs in hospitals from which aspergilli have been cultured include unfiltered air, ventilation systems, dust dislodged during construction, carpeting, food, and ornamental plants.[39-42] Although several hundred species of *Aspergillus* have been described, relatively few are known to cause disease in humans. *Aspergillus fumigatus* remains the most common cause of aspergillosis, although the proportion of aspergillosis cause by *A. fumigatus* has fallen from ~90% of cases in the 1980s to ~50–60% of cases in the 1990s into the 2000s.[5] The other species of *Aspergillus* commonly causing nosocomial infections include *A. flavus*, *A. terreus*, *A. niger*, *A. versicolor*, and *A. nidulans*.[16,39,40,43]

Aspergillus infections occur worldwide and appear to be increasing in prevalence.[39,40] National Hospital Discharge data from the 1990s reveal that there are approximately 10,000 aspergillus-related hospitalizations annually in the United States.[44]

Table 1-4 Compiled incidence of fungal infections among organ transplant recipients, 1980–1999[a]

Organ transplant	Incidence of invasive fungal infection	Proportion of invasive fungal infection			
		Aspergillus	Candida	Cryptococcus	Other
Renal	0–20%	0–26%	76–95%	0–39%	0–39%
Heart	5–21%	77–91%	8–26%	NA	NA
Liver	4–42%	1–53%	35–91%	3–7%	3–15%
Lung and heart-lung	10–36%	20–50%	42–73%	18–26%	11%
Small bowel	33–59%	0–4%	80–100%	NA	0–11%
Pancreas and pancreas-kidney	6–38%	0–3%	97–100%	NA	NA

NA, data not available.
[a]Adapted from Fungal infections.[14]

Table 1-5 Most common opportunistic mould infections in organ transplant and hematopoietic stem cell transplant recipients

Fungus	Percentage of invasive mould infections	
	SOT[a]	HSCT[b]
Aspergillus fumigatus	55%	51%
Other *Aspergillus* species	15%	26%
Non-*Aspergillus* hyalohyphomycetes and phaeohyphomycetes	18%	14%
Zygomycetes	6%	9%
Other	6%	-

[a]Data based on a multicenter study 1998–2002 by Husain et al.[38]
[b]Data reproduced from Marr et al.[5]

Although the total number of nosocomial infections due to *Aspergillus* spp. is small compared with those caused by *Candida* spp., *Aspergillus* spp. are particularly important causes of nosocomial infections in patients who are immunocompromised as a result of burn injury, malignancy, leukemia, and bone marrow and other organ transplantation.[39,40]

Although invasive aspergillosis is a devastating complication for SOT recipients,[39] the incidence of *Aspergillus* spp. infections in these patients has been lower than in HSCT recipients, probably because of the greater degree of granulocytopenia among HSCT recipients. Most studies place the cumulative incidence of invasive aspergillosis among allogeneic HSCT recipients at between 3% and 15%.[16,45,46] However, the incidence of aspergillosis increases in relation to the type of donor used for transplantation (Table 1-9).[16] Major risk factors for invasive aspergillosis include neutropenia, broad-spectrum antibacterial therapy, administration of corticosteroids, antitumor necrosis factor therapy, and grade III–IV graft-versus-host disease (see Table 1-3).[39,40] The most important extrinsic risk factor is the presence of aspergilli in the hospital environment. Nosocomial transmission of *Aspergillus* to patients occurs primarily by the airborne route, but contact transmission (e.g., direct inoculation from occlusive materials) has also been implicated.[41] Outbreaks of nosocomial aspergillosis occur most commonly among granulocytopenic patients ($<1000/mm^3$) and have been described in association with exposure to *Aspergillus* conidia aerosolized by hospital construction, contaminated air-handling systems, and insulation or fireproofing materials within walls or ceilings of hospital units.[39-41]

The crude mortality associated with invasive aspergillosis is high, but the attributable mortality has been difficult to determine given the high mortality rate in susceptible patients. A recent case review of nosocomial aspergillosis placed the attributable mortality rate at approximately 58%.[47] The highest attributable mortality rates have been observed among patients with aplastic anemia and after bone marrow transplantation. The survival rate of patients diagnosed with aspergillosis has been steadily increasing, especially in HSCT patients. The mortality rate in 1990 was >95% but by the end of that decade the mortality rate had decreased to between 55% and 80%.[39]

Prevention of nosocomial aspergillosis is a difficult issue and requires active surveillance for cases of aspergillosis, minimization of host risk factors, and maintenance of an environment as free as possible of *Aspergillus* spp. spores for patients with severe granulocytopenia.[48] For those at highest risk of invasive aspergillosis, provision of high-efficiency particulate air (HEPA) filtered environments is recommended.[49] Revised guidelines for prevention of nosocomial aspergillosis have been published by the CDC;[48] however, despite these efforts, invasive aspergillosis remains a constant threat to the survival of immunocompromised patients.