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Epidemiology of Nosocomial Fungal Infections

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INTRODUCTION: OVERVIEW OF FUNGAL INFECTIONS

Advances in medical and surgical therapy over the past two decades have changed the type of patients cared for in U.S. hospitals. Newer technologies and therapies, such as bone marrow or solid-organ transplants and chemotherapeutic agents, have become common at many medical centers, resulting in many immunocompromised individuals. Also, care in specialized units and the use of invasive monitoring devices, parenteral nutrition, broad-spectrum antimicrobial agents, and assisted ventilation have helped to treat patients suffering from previously devastating or fatal diseases and have provided life to premature neonates previously thought to be nonviable.

However, these successes have resulted in the proliferation of a severely ill, immunocompromised, hospitalized patient population. Furthermore, the AIDS epidemic has added to this growing population of immunocompromised individuals (28). These immunocompromised patients are highly susceptible to nosocomial infections caused by organisms such as fungi that were previously considered to be of low virulence or "nonpathogenic" (10). Fungal infections in these patients are often severe, rapidly progressive, and difficult to diagnose or treat (21). Fungi are eukaryotic cells; they are more complex than bacteria. A thorough appreciation and understanding of fungal infections, including diagnostic and therapeutic modalities, are needed among clinicians and microbiologists to provide better patient care. This paper briefly reviews current knowledge of

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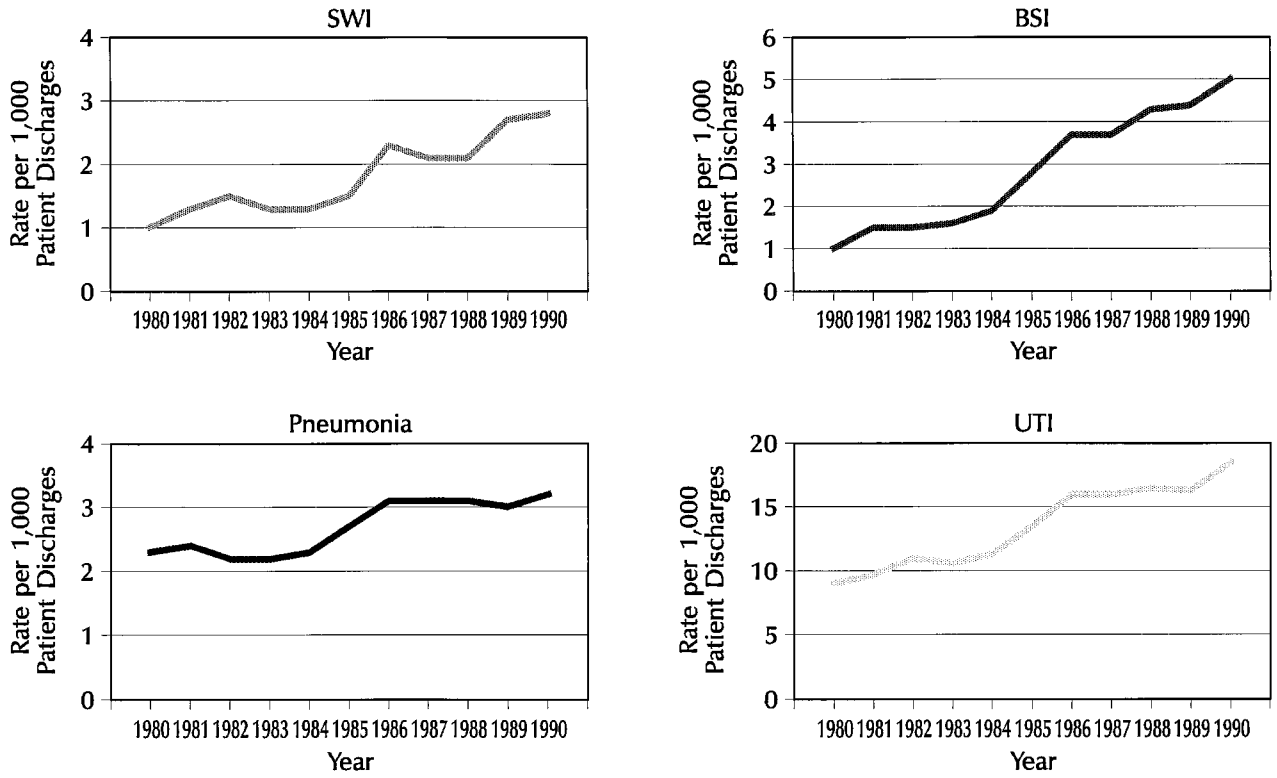

FIG. 1. Secular trend in the nosocomial fungal infection rate at U.S. hospitals, including surgical wound infection (SWI), bloodstream infection (BSI), urinary tract infection (UTI), and pneumonia, as reported to the NNIS system, by the site of infection, 1980 to 1990. Data from reference 8.

the epidemiology, modes of transmission, and therapeutic options for nosocomial fungal infections, with some emphasis on laboratory aspects of these diseases.

CLASSIFICATION OF FUNGAL INFECTIONS: ENDEMIC VERSUS OPPORTUNISTIC

In general, two populations have been at risk for acquiring invasive fungal infections. The first are persons at increased susceptibility of infection because of their geographic location. Their infections are referred to as endemic mycoses. Examples in the United States include infections with *Histoplasma capsulatum* var. *capsulatum* along the Mississippi River Valley, *Coccidioides immitis* in the Southwest, and *Blastomyces dermatitidis* in the central and southeastern states (73). The second population includes persons with increased host susceptibility (i.e., severely ill, immunocompromised, or malnourished individuals) who develop opportunistic infections.

The iatrogenic immunosuppression required for organ transplantation has been associated with a variable rate of fungal infections: <5% for renal transplant, 2 to 30% for bone marrow transplant, 10 to 35% for heart transplant, and 28 to 42% for liver transplant recipients (10). Thrush and esophageal candidiasis are extremely common among patients with AIDS, as is infection with *Cryptococcus neoformans*. Many immunosuppressed individuals present to the hospital with fungal infections, and others develop them while hospitalized. Although opportunistic fungal infections may be acquired outside of the hospital, many of them are included in this review of nosocomial fungal infections.

NOSOCOMIAL FUNGAL INFECTIONS

Scope of the Problem

In the mid-1980s, many institutions, including cancer research, university, and community hospitals, reported that fungi were becoming common pathogens in nosocomial infections (2, 10, 38). In addition, during 1980 to 1990, hospitals reporting data to the Centers for Disease Control and Prevention (CDC) National Nosocomial Infections Surveillance (NNIS) system reported a steady increase in the rate of nosocomial fungal infections, from 2.0 to 3.8 per 1,000 discharges (8). This increase was evident at all four body sites of nosocomial infection (Fig. 1). Although the rate varied by service, it increased with all services examined, including medicine, newborn nursery, and surgery. Hospitals participating in the NNIS system are mostly large, university-affiliated hospitals, and they may care for patients at higher risk for nosocomial infections compared with the average hospital in the United States. However, most, if not all, hospitals care for patients at risk for nosocomial fungal infections. This is suggested when examining the increase in the rate of nosocomial fungal infection by different wards at NNIS hospitals (Fig. 2). High rates of infection are not limited to oncology wards and high-risk nurseries but also occur on cardiac surgery and burn and trauma wards (Fig. 3). These data suggest that although nosocomial fungal infections may be more common at university-affiliated hospitals, the increase in the incidence of these infections may be evident in all types of hospitals.

Although the number of nosocomial infections caused by many pathogens has increased at U.S. hospitals over the past decade, it appears that the incidence of nosocomial fungal

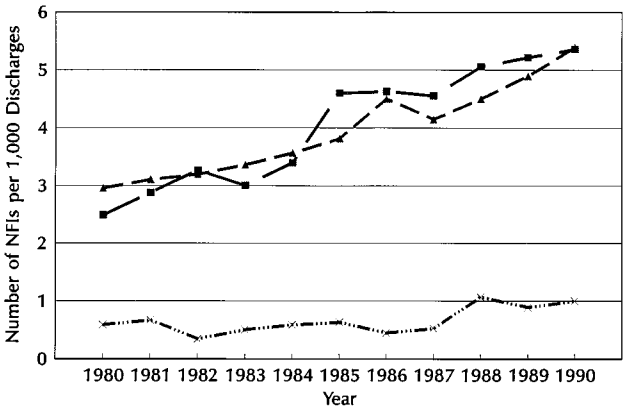

FIG. 2. Secular trend in the nosocomial fungal infection rate at U.S. hospitals, as reported to the NNIS system, by selected major services, 1980 to 1990. Modified from reference 8. Symbols: ▲, medical; x, newborn nursery; ■, surgery.

infections, specifically those caused by *Candida albicans*, has increased proportionally more. For example, the proportion of all nosocomial infections reportedly caused by *Candida* spp. increased from 2% in 1980 to 5% in 1986 to 1989 (85). Analysis of reports from NNIS hospitals from 1990 through 1992 show *C. albicans* ranking seventh among all hospital pathogens isolated from major infection sites (i.e., urinary tract infections, surgical site infection, bloodstream infection, pneumonia, and other sites) and fourth among all hospital pathogens isolated from nosocomial urinary tract infections alone (24). Of great concern to clinicians and hospital epidemiologists alike is the occurrence of the often devastating nosocomial fungal bloodstream infection. In studies of candidemia, the most common nosocomial fungal primary bloodstream infection (6), the estimated overall crude mortality rate is 50 to 60% and about one-third of infected patients will die as a result of the candidemia (13, 44, 46, 108). Among NNIS hospitals, there was a dramatic rise in the percentage of all nosocomial bloodstream infections caused by fungi, from 5.4% in 1980 to 9.9% in 1990. Furthermore, patients with fungemia were more likely to die during hospitalization than were patients with bloodstream infection due to nonfungal pathogens (relative risk, 1.8; 95% confidence interval, 1.7 to 1.9) (8).

In addition to what appears to be an increase in the incidence of endemic nosocomial fungal infections (i.e., those due to increased host susceptibility as a result of geographic location), there have been numerous reports of nosocomial fungal outbreaks (9, 30, 51, 77–79, 90, 91, 96, 104–106). A summary of the outbreaks investigated by the CDC is listed in Table 1. The modes of transmission vary and include environmental spread through air, carriage on the hands of hospital personnel, and contamination of medical products or devices before (i.e., intrinsic contamination) or after (i.e., extrinsic contamination) shipment to hospitals. Understanding the pathophysiology of pathogenic fungi is critical in determining the cause of an outbreak and implementing infection control measures to stop the outbreak.

Risk Factors

Numerous studies have identified common risk factors for patients developing fungal infections (Table 2). Most of these risk factors are very common in all hospitalized patients, and it is therefore difficult to determine which patients are at greatest risk for developing nosocomial fungal infections. Some exposures act primarily by inducing immunosuppression (e.g., corticosteroids, chemotherapy, malnutrition, malignancy, and neutropenia). Other exposures primarily provide a route of infection (e.g., extensive burns, indwelling catheter) or a combination of factors. For instance, infusion of broad-spectrum antimicrobial agents may allow fungi to proliferate in the gastrointestinal tract, subsequently colonize the skin, and enter the bloodstream via a central venous catheter. Another route of entry may be translocation of fungal pathogens from a patient's colonized gastrointestinal tract into the bloodstream. This process is supported by repeated findings that isolation of the fungus from a site of colonization elsewhere in the body is an independent risk factor for nosocomial fungemia (44, 109). Other exposures, such as the number of antimicrobial agents used before infection, administration of chemotherapy, presence of indwelling central venous or pulmonary artery catheters, and prior hemodialysis, have also been identified as risk

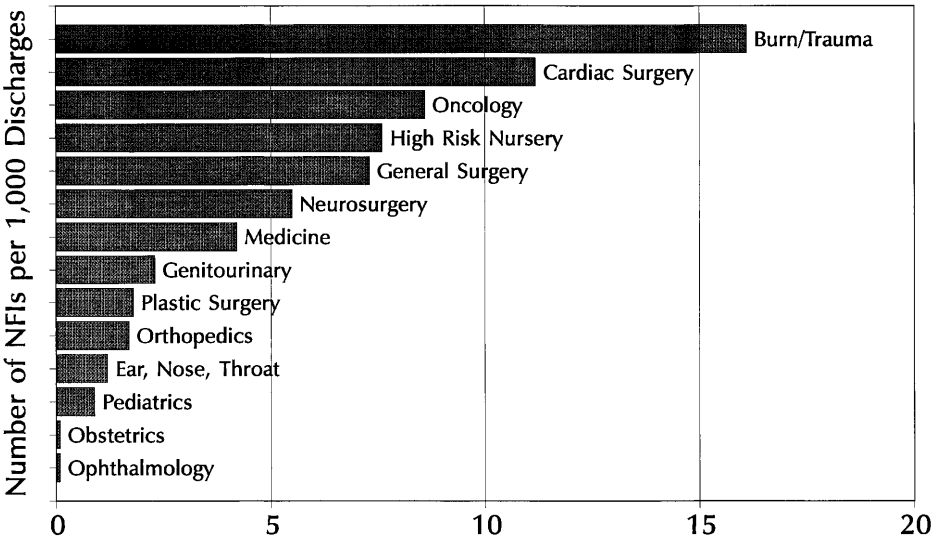

FIG. 3. Nosocomial fungal infection rate at U.S. hospitals, as reported to the NNIS system, by the type of hospital ward, 1980 to 1990.

TABLE 1. Nosocomial outbreaks of fungal infections investigated by the CDC, 1981 to 1994[a]

Yr	Reference	Species	Infection	No. of patients	Unit or service[b]	Source[c]	Control measure
1981	91	*C. parapsilosis*	Fungemia	5	Medical/Surgical	Contaminated PN	Discontinue PN pump use
1983	90	*C. parapsilosis*	Fungemia	8	NICU	Contaminated PN	General infection control
1984	105	*Aspergillus* and *Mucor* spp.	Systemic infection	5	Heme/Oncology	Construction activity	Environmental control
	51	*C. parapsilosis*	Endophthalmitis	13	Ophthalmic surgery	Contaminated solution[d]	Discontinue product use
1985	104	*C. parapsilosis*	Fungemia	12	ICU	Contaminated PN	General infection control
1987	79	*M. furfur*	Systemic infection	3	NICU	Endogenous and personnel hand carriage	Identify at-risk patients; general infection control
1988	77	*Candida* spp.	Fungemia	24	Heme/Oncology	Endogenous	General infection control
	78	*A. fumigatus*	Wound infection	6	Cardiac surgery	Endogenous	Identify at-risk patients
1990	9	*Candida* spp.	Fungemia and endophthalmitis	29	Ophthalmic and general surgery	Contaminated IV anesthetic agent[e]	Discontinue product use; general infection control
1991	CDC[f]	*A. flavus*	Systemic infection	5	Heme/Oncology	Construction activity	Environmental control
	106	*M. pachydermatis*	Fungemia	5	NICU	Endogenous/hand carriage	General infection control
1992	CDC	*A. fumigatus*	Systemic infection	4	Cardiac transplant	Immunosuppression	General infection control
1993	30	*Acremonium* spp.	Endophthalmitis	4	Ophthalmic surgery	Humidifier	Environmental control
1994	CDC	*M. pachydermatis*	Fungemia	8	NICU	Endogenous/hand carriage	General infection control

[a] Modified from reference 52 with permission; not all-inclusive.
[b] ICU, intensive care unit.
[c] PN, parenteral nutrition; IV, intravenous.
[d] Intrinsic contamination.
[e] Extrinsic contamination.
[f] Unpublished data.

factors by multivariate analysis after factors such as underlying illness have been taken into account (8, 13, 44, 77, 87, 109).

Pathogens

The majority of nosocomial fungal infections are reported to be caused by *Candida* spp. (8, 64, 85) (Table 3). At hospitals reporting data to the NNIS system during 1980 to 1990, *Candida* infections accounted for 78.3% of nosocomial fungal infections, followed by *Torulopsis glabrata* (7.3%) (sometimes classified as *Candida glabrata*), and *Aspergillus* spp. (1.3%) (8).

Many institutions have reported newly recognized pathogenic fungi, previously thought to be nonpathogenic, including *Malasezzia* spp., non-*albicans Candida* spp., *Fusarium* spp., and *Trichosporon* spp. (3, 58, 92, 101, 103, 106, 107). However, the predominant fungi isolated from patients' blood are *Candida* spp. (6, 38, 64, 67). Very few blood cultures are reported to grow mycelial fungi, such as *Aspergillus* spp.; this may be due to the difficulty encountered in growing these fungi in premortem blood cultures (38).

Increased recognition of the importance of nosocomial fungal infections has led to increased research into newer diagnostic and therapeutic approaches for detecting and managing these infections (17, 34, 40, 62, 65, 66, 74, 86, 93, 94).

TABLE 2. Frequently identified risk factors for fungemia in hospitalized patients[a]

Risk factor	Reference(s)
Antimicrobial agents[b]	
Number	13, 77, 109
Duration	44, 77, 97, 109
Adrenal corticosteroid	44, 46
Chemotherapy[b]	44, 46, 87
Hematological/solid organ malignancy	46
Previous colonization[b]	13, 77, 87, 109, 111
Indwelling catheter[b]	
Central venous catheter	8, 13, 44, 46, 109
Pressure transducer/Swan-Ganz	44
Total parenteral nutrition	8, 44
Neutropenia (polymorphonuclear cells, $<500/mm^3$)[b]	44, 46, 77, 111
Extensive surgery or burns	44, 46
Assisted ventilation	13, 44
Hospitalization or intensive care unit stay	8, 13, 77, 97
Hemodialysis[b]	109
Malnutrition	109

[a] Studies involved either patients with hematologic or solid organ malignancies exclusively (44, 46, 87, 97, 111) or mixed patient population (8, 13, 46, 109).
[b] ≥1 multivariate analysis identified as independent risk factor.

CANDIDA SPECIES

Species Types and Human Disease

Although *Candida* spp. have become common human pathogens, relatively few of the more than 100 species of *Candida* previously identified have been isolated from humans (67). *C. albicans* is by far the most common *Candida* sp. causing infections in humans, followed by *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae*, and *T.* (*C.*) *glabrata*. All these *Candida* spp. may cause a similar spectrum of disease, ranging from thrush to invasive diseases such as arthritis, osteomyelitis, endocarditis, endophthalmitis, meningitis, or fungemia. However, there may be differences in severity and therapeutic options worth noting.

Candidemia is the most extensively studied nosocomial invasive fungal infection. The presentation of fungemia may vary, with pyelonephritis, peritonitis, arthritis, hepatosplenic abscesses, pneumonitis, myositis, macronodular skin lesions, osteomyelitis, endophthalmitis, meningitis, and/or multiorgan involvement (2, 10, 21). The organs involved in disseminated candidiasis may vary with the route of infection. If a previously colonized gastrointestinal tract is the source of infection through a breakdown in mucosal or epithelial tissue, liver and splenic abscesses will probably result. In contrast, if a colonized

TABLE 3. Relative proportions of common and emerging nosocomial fungal infections, by pathogen, 1980 to 1990[a]

Fungal pathogen	Estimated percentage
Candida albicans	61
Non-*albicans Candida* spp.	19
C. parapsilosis	
C. tropicalis	
C. krusei	
C. lusitaniae	
Torulopsis glabrata[b]	8
Aspergillus spp.	1
Other	11
Yeasts (*Malassezia* and *Trichosporon* spp.)	
Zygomycosis (*Mucor* and *Rhizopus* spp.)	
Hyalohyphomycosis (*Fusarium* and *Acremonium* spp.)	
Phaeohypomycosis (*Alternaria*, *Bipolaris*, and *Curvularia* spp.)	

[a] Data are from reference 8. The list of "other" pathogens is not all-inclusive.
[b] Also referred to as *C. glabrata.*

central venous catheter is the source, endocarditis or renal involvement is more likely (2, 10). Patients with candidemia and/or disseminated infection usually develop fever and leukocytosis, unless they are also on immunosuppressive medications.

More localized disease caused by *Candida* spp., including oral candidiasis and hospital-acquired or antibiotic-associated diarrhea, also occurs in hospitalized patients (20, 36). Patients receiving antimicrobial agents commonly develop a secretory nonbloody diarrhea, usually diagnosed as *Clostridium difficile*-associated diarrhea. However, some studies show that patients with *C. difficile* toxin-negative, antibiotic-associated diarrhea who have evidence of intestinal overgrowth of *Candida* spp. will respond to oral nystatin therapy despite persistent use of intravenous antimicrobial agents (19, 36).

The mortality attributable to invasive *Candida* infection is very difficult to ascertain, because the infections tend to occur in very ill patients. Various studies have estimated the attributable mortality at 38% (108), with crude mortality rates ranging from 50 to 60% (13, 44, 46, 108). Further evidence of the aggressive nature of invasive *Candida* infections is the high (67% to 88%) proportion of patients diagnosed with candidemia whose cause of death was attributed to *Candida* spp. infection at autopsy (29, 48, 108). Although transient cannula-associated candidemia lasting less than 24 h is commonly believed to be a benign event, there is evidence to suggest otherwise. In two studies, the crude mortality rate in patients with transient candidemia (<24 to 48 h) was 37 to 39% (46, 48), and if there was evidence of biopsy-proven organ involvement, this rate increased to 52% (46). Furthermore, there is evidence that a longer duration of candidemia is associated with a higher mortality (29). In patients with catheter-associated candidemia, catheter removal has been associated with a more favorable outcome than has treatment alone (48).

Epidemiology: Endogenous versus Exogenous Acquisition

Most nosocomial candidemia is thought to be endogenous, acquired through prior colonization of the mouth, gastrointestinal tract, vagina, or skin, which acts as the source (2, 77). Evidence supporting this includes the occurrence of candidemia in patients cared for on special care units (e.g., bone marrow transplant and hematology/oncology units), private patient rooms, and positive-pressure rooms, with meticulous hand washing by hospital personnel and provision of specialized diets. In these situations, the possibility for cross-infection of *Candida* spp. from patient to patient should be minimal. In addition, previous colonization with *Candida* spp. is an independent risk factor for development of invasive disease (44, 109). Furthermore, characterization of the DNA of colonizing and infecting *Candida* strains by molecular techniques showed that strains causing infections were identical to strains previously colonizing the same patients (70, 72). This evidence supports the theory of endogenous acquisition of infection and has ramifications regarding the role of routine surveillance cultures or antifungal prophylaxis in these types of patients (35).

Unlike the specialized care settings described above, cross-infection (i.e., exogenous acquisition) appears to occur commonly in other areas of the hospital (9, 77, 79, 104–106). Molecular laboratory techniques have been used to identify a common strain type among infected patients, providing evidence that exogenous sources led to patient-to-patient transmission. Supporting evidence for cross-infection includes the physical setup of intensive care or burn units, which is different from that of bone marrow transplant units: multiple doors into and out of the patient's room, numerous health care workers caring for the patient, frequent transportation of the patient to different parts of the hospital for procedures, and, in some cases, a paucity of sinks for hand washing. All of these factors may contribute to cross-infection as the mechanism of transmission. However, some studies suggest that certain non-*albicans Candida* spp. (e.g., *C. lusitaniae*) may be spread by exogenous routes even in specialized care settings such as bone marrow transplant units (84).

Molecular Epidemiology

The differentiation between exogenous and endogenous acquisition is important for determining appropriate control measures to prevent the nosocomial transmission of *Candida* spp. Strain-typing studies are needed to avoid implicating an environmental source solely on the basis of the presence of a single species of *Candida*. Various typing methods have been developed (Table 4). Isolation of *Candida* spp. from the environment is not unusual; a recent multicenter culture survey found that the hands of health care workers are a potential reservoir for *Candida* spp. (e.g., the hands of 29% [range, 5 to 47%] of physicians were culture positive for *Candida* spp.) (71).

TABLE 4. Molecular methods for epidemiologic typing of fungal pathogens[a]

Method	Nosocomial fungal pathogen
DNA-based methods	
Southern hybridization analysis	*Candida* spp.
Pulsed-field gel electrophoresis (electrophoretic karyotyping)	*Candida* spp.
Restriction endonuclease analysis of genomic DNA	*Candida*, *Aspergillus*, and *Malassezia* spp.
Protein-based methods	
Immunoblot fingerprinting	*Candida* and *Aspergillus* spp.
Polyacrylamide gel electrophoresis of cellular proteins	*Candida* spp.
Multilocus enzyme electrophoresis	*Candida* spp.

[a] Data from references 64 and 65.

Previous typing systems for infectious pathogens have included analysis of phenotypic differences such as biotyping, enzyme profiles, susceptibility patterns to antimicrobial agents, biochemical analysis, serological agglutination reactions, and immunoblotting techniques (7). However, these methods lack sensitivity and reproducibility. Also, protein-based methods have not been successful in producing enough variation in banding patterns to permit adequate strain identification within a species (65). Newer molecular typing methods have included evaluation of genomic DNA by restriction enzyme analysis, electrophoretic karyotyping (pulsed-field gel electrophoresis of whole chromosomes), and the use of DNA probes (65, 81). These DNA-based methods include DNA fingerprinting by restriction endonuclease digestion of *Candida*. DNA followed by electrophoretic separation of this DNA on a gel. Isolates of genetically related strains have the same DNA fingerprint. These DNA typing methods, which have been used to type both *C. albicans* and non-*albicans Candida* spp., have been described elsewhere (7, 65). Although these methods may require specialized equipment and technical expertise, they are becoming the standard for determining the relatedness of *Candida* spp.

Prevention, Therapy, and Susceptibility

Prevention methods aimed at reducing identified risk factors for nosocomial fungal infection are being increasingly advocated. Although prior colonization has been shown to precede infection by the endogenous route, the role of routine prevalence cultures in detecting colonization and guiding prophylactic antifungal therapy has not been well established. However, recent studies do support the use of prophylactic fluconazole among selected leukemia or bone marrow transplant patients (35, 113).

Over the past decade, alternatives to amphotericin B, including the azoles fluconazole and itraconazole have become available to treat nosocomial fungal diseases. Most *Candida* spp. are susceptible to these antimicrobial agents, although there have been some reports of relative resistance among *C. lusitaniae* and *T. glabrata* isolates to amphotericin B (40, 61, 64, 69). *Candida* isolates obtained from patients undergoing prolonged amphotericin B therapy have been reported to be associated with elevated MICs of amphotericin B (74), although this finding was not reproduced in another study (70). In one experimental study, resistance to amphotericin B was associated with an increase in the number of fungal membrane sterols (40).

Although resistance to azole antifungal agents among *Candida* spp. is also very uncommon (40, 64), the frequent use of prophylactic antifungal therapy in chronically or transiently immunocompromised individuals has raised some concern. Two studies assessed the clinical utility of prophylaxis with fluconazole, a triazole, in patients with acute leukemia or bone marrow transplants. Prophylaxis prevented colonization and/or infection with all species of *Candida* except *C. krusei* (35, 113). Although various epidemiologic factors may affect the incidence of *C. krusei* infection in any one hospital, the routine use of prophylactic therapy in patients at highest risk for endogenous *Candida* infection may lead to the emergence of drug-resistant fungi, such as *C. krusei* (67), although this has not been a widespread observation.

Over the past decade, routine susceptibility testing has played a minimal role in the management of nosocomial *Candida* infections. Many difficulties have arisen in establishing a reliable and reproducible susceptibility testing method for *Candida* spp. Factors such as inoculum size, medium type, and temperature and time of incubation influence the results of such testing, and standardized methods have only recently been developed (74). A comparison of the relative susceptibilities of *Candida* spp. to antifungal agents, done in a blinded fashion, showed great intra- and interlaboratory variation in the results (31). However, a recent study found very good correlation between susceptibility tests involving Etest strips and National Committee for Clinical Laboratory Standards criterion M27-P (17, 54). Susceptibility testing standards for *Candida* spp. have been investigated most frequently, but a recent review article cautions that susceptibility testing should be considered a research tool and that clinical response to therapy should be used to guide therapeutic decisions (74). A National Committee for Clinical Laboratory Standards subcommittee currently is implementing a proposal describing standardized methods for susceptibility testing of yeast fungi. Until such methods are published and widely implemented, the routine use of susceptibility testing to guide therapy and to determine the extent to which antifungal resistance contributes to treatment failure will not be possible.

Non-*albicans Candida* Species

Numerous reports have documented the increased incidence of *C. parapsilosis*, *C. lusitaniae*, *C. tropicalis*, and *T. glabrata* among hospitalized patients (11, 29, 61, 83, 84, 103). Little is known about the epidemiology of these infections in the non-outbreak setting. Some studies have provided evidence that exogenous infection, or cross-infection from staff to patient, may be common, even in specialized care units (83, 84). In one study, the hands of health care workers were documented as a reservoir (in 16 to 38% of surgical intensive care unit personnel) for *Candida* spp., 85% of which were non-*albicans Candida* spp. (71). However, there also is evidence that gastrointestinal colonization in neonates may precede infection (23).

Unlike *C. albicans* infection, invasive *C. parapsilosis* infection has been most commonly associated with total parenteral nutrition (55, 103, 104), intravascular devices (90), endocarditis in cardiac surgery patients (47, 56, 88), or intravenous drug use (103).

C. parapsilosis appears to proliferate in high concentrations of glucose and adheres to prosthetic materials (103). Recent studies have shown that 50 to 80% of *C. parapsilosis* blood isolates produce slime (12, 68) whereas only 25% of isolates obtained from the hands of health care workers do so (68). Although there are some conflicting reports, it appears that *C. parapsilosis* has enough genetic diversity that strain typing by pulsed-field gel electrophoresis and electrophoretic karyotyping should be useful as a component of epidemiologic studies to determine the mechanisms of nosocomial transmission (12, 68, 70).

The crude mortality rate associated with *C. parapsilosis* infection has been estimated to be 30%, lower than that reported for invasive infection with *C. albicans* (79%) or other non-*albicans Candida* spp. (mean, 78%) (39).

Outbreaks of *C. parapsilosis* have been commonly associated with parenteral nutrition (90, 91, 104); this organism also has been associated with postoperative endophthalmitis caused by intrinsically contaminated (e.g., contamination occurring before product manufacture is complete) intraocular lens-irrigating solution (51). Although other sporadic postoperative intraocular infections with *C. parapsilosis* have been reported, hematogenous endophthalmitis appears to be rare (103). In addition, there have been reports of sporadic nosocomial *C. parapsilosis* arthritis (associated with joint prostheses or arthrocentesis) and peritonitis (associated with chronic ambulatory

peritoneal dialysis) (60, 103). Risk factors for these sporadic incidents include diabetes mellitus, intravenous drug use, and immunosuppression.

C. tropicalis is an important pathogenic *Candida* sp. and has been reported to be a common cause of fungemia in both oncology and nononcology patients (46). The mechanism of acquisition appears to be similar to that of *C. albicans*; risk factors associated with *C. tropicalis* clinical illness appear to be similar to those for *C. albicans*. An outbreak of *C. tropicalis* fungemia in a neonatal intensive care unit (NICU) was traced to receipt of total parenteral nutrition and antimicrobial agents (26). *C. tropicalis* was isolated from the hands of two NICU workers but not from the environment. Although strain typing was not performed, the authors suspected cross-infection to be the cause of the outbreak and instituted strict hand-washing techniques.

C. krusei has been reported to cause fungemia and endophthalmitis; the mechanism of infection appears to be endogenous spread from the gastrointestinal tract in severely immunocompromised patients (112). Of concern is the apparent innate resistance of *C. krusei* to fluconazole and proliferation of this pathogen in patients receiving prophylactic fluconazole therapy in some centers (35, 113). Although *C. lusitaniae* had been considered part of the colonizing flora of the gastrointestinal and respiratory tracts, there have been reports of invasive infections similar to those with *C. albicans* in immunocompromised patients (84). Reports of strain typing by pulsed-field gel electrophoresis or electrophoretic karyotyping illustrate possible exogenous acquisition by cross-infection (69, 84). Finally, although *C. rugosa* is a common veterinary pathogen, it has not been a frequent cause of human disease. Proliferation of *C. rugosa* colonizing the wounds of patients in burn units has been associated with the routine use of topical nystatin in wound dressings (20). Although the isolated *C. rugosa* was resistant to nystatin, none of the 18 fungemias reported during the study were caused by *C. rugosa.*

ASPERGILLUS SPECIES

Epidemiology

Aspergillus spp. are ubiquitous, commonly occurring in soil, water, and decaying vegetation. Reservoirs in hospitals from which these fungi have been cultured include unfiltered air, ventilation systems, contaminated dust dislodged during hospital construction, carpeting, food, and ornamental plants (33, 78, 99). *Aspergillus* spp., especially *Aspergillus fumigatus*, *A. flavus*, and *A. terreus* (75), have become a common cause of nosocomial infection in highly immunocompromised patients such as those with hematologic malignancy undergoing bone marrow or solid organ transplantation or receiving corticosteroid therapy (2, 10).

Although data from the NNIS system indicate that only 1.3% of hospital-wide nosocomial fungal infections reported during 1980 to 1990 were caused by *Aspergillus* spp. (8) (Table 3), the incidence appears to be much higher in specialized care wards; for example, in one study, *Aspergillus* spp. was isolated in 20 (36%) of 55 patients with nosocomial pneumonia on a bone marrow transplant unit (57).

Outbreaks of nosocomial aspergillosis occur mainly among granulocytopenic patients (<1,000 granulocytes per mm^3) and have been associated with environmental disturbances such as hospital construction (4, 105), contaminated fireproofing material (1) or air filters (5) in the hospital ventilation system, and contaminated carpeting (33) (Table 1). There has been at least one pseudoepidemic which was caused by contamination of blood culture bottles processed in a utility room in which *Aspergillus* isolates were being stored (102).

The attributable mortality rate of invasive aspergillosis has been estimated to be high, but it is difficult to determine clearly because of the high mortality rate in susceptible patients. Attributable mortality has been estimated at 13 to 95%, with the higher rates being found in patients with aplastic anemia and recipients of allogenic bone marrow transplants (57).

Clinical Disease

Aspergillus clinical disease is predominately respiratory and includes necrotizing bronchopneumonia. Infection is commonly associated with vascular events (e.g., thrombosis or infarction of surrounding tissue, pulmonary embolus, or cerebral hemorrhage) and may disseminate (89). Cutaneous, sinus, and rhinocerebral involvement also may occur. Although rare, postoperative infections with *Aspergillus* spp., including endocarditis (43) and sternal wound infections (78), have been reported, as have infections associated with foreign bodies (e.g., aortic graft sites, peritoneal catheter sites, and corneal infections in patients with contact lenses) (2). A review of invasive infections from The Hospital for Sick Children in Toronto, Canada, showed a surprisingly high proportion of invasive cutaneous aspergillosis, with 41% cutaneous, 41% respiratory, 5% cerebral, 3% gastrointestinal, and 10% as asymptomatic infections found at autopsy (98). Cutaneous infections have been associated with the use of arm boards for patients with intravascular catheters and with the bandages or dressings used for these catheters.

Pathogenesis

Inhalation of fungal conidia is thought to be the primary means of acquiring aspergillosis (75). Pulmonary infections are thought to arise by local tissue invasion, and there is subsequent dissemination to other deep organs (115). Increased host susceptibility is thought to be the primary factor leading to infection. Like endogenous *Candida* infections, prior colonization with *Aspergillus* spp. may be necessary before infection. Colonization of the lower respiratory tract predisposes patients, especially patients with chronic lung disease (e.g., chronic obstructive lung disease, cystic fibrosis, inactive tuberculosis, and α_1-antitrypsin deficiency), to acquire pulmonary or disseminated infections (2, 115). However, the role of colonization of the upper respiratory tract has not been well established. Although most cases of aspergillosis are thought to arise in susceptible patients as a result of exposure during hospitalization, one study suggests that colonization in the community may predispose some patients with chronic lung disease who undergo coronary bypass surgery to *A. fumigatus* sternal wound infections (78).

Another proposed route of acquisition of *Aspergillus* spp., especially *A. flavus*, is through ingestion of contaminated food (75). This concern arises from the ability to cultivate *A. flavus* from grain products. However, no outbreak of aspergillosis has been traced to contaminated food. Localized infections have been associated with extrinsic or intrinsic contamination of adhesive tape or gauze (presumably by airborne contamination) used with intravascular catheters (2). The pseudoepidemic resulting from blood cultures processed in a utility room in which *Aspergillus* isolates were being stored (102) demonstrates that contamination of patient care items can occur in such rooms.

Diagnosis

The diagnosis of aspergillosis can be difficult to establish premortem. A clinical diagnosis may be suspected in susceptible patients with fever and characteristic single or multiple rounded densities on the chest radiograph (10). Blood cultures are very insensitive for detecting *Aspergillus* spp. (43), and systemic antibody responses are poorly predictive in high-risk patients. Histopathologic demonstration of tissue invasion by fungal hyphae in skin or lung biopsy specimens may be needed to confirm a diagnosis. Culture of *Aspergillus* spp. from bronchoalveolar lavage specimens, sputum samples, or endotracheal aspirates may represent colonization, but in conjunction with a clinical diagnosis, positive cultures probably indicate pulmonary aspergillosis (116). The role of routine surveillance cultures of immunocompromised patients has not been well established. In one study, routine surveillance by using lower respiratory cultures failed to detect *Aspergillus* spp. even though 15 study patients eventually developed invasive aspergillosis (57).

Risk Factors

Infections with *Aspergillus* spp. appear to be the result of both host susceptibility and environmental exposure to the fungus. The major risk factor related to the host is severe granulocytopenia. The longer the duration of severe granulocytopenia ($<$1,000 polymorphonuclear leukocytes/mm^3), the greater the risk of invasive disease.

This fact places patients with autologous bone marrow transplants at great risk, because they tend to be severely granulocytopenic longer than patients with induction chemotherapy or allogenic bone marrow transplants. In addition, patients with autologous bone marrow transplants may develop graft versus host disease, which requires immunosuppressive therapy that may further increase their susceptibility to invasive aspergillosis. Patients receiving solid organ transplants also are at risk for invasive aspergillosis as a result of immunosuppression by corticosteroid therapy. However, the use of cyclosporine and FK-506 has helped to decrease the degree of immunosuppression of these patients. Attempts to establish the efficacy of decreasing the period of severe granulocytopenia in these patients by administration of granulocyte-stimulating factor or cytokines are under way (49, 99). In addition, the role of prophylactic intranasal, oral, or systemic antifungal drugs is being evaluated.

Contaminated air or ventilation systems have been associated repeatedly with outbreaks of nosocomial aspergillosis (1, 4, 33, 75, 76). The cause of the contamination is not always clear, although nearby construction activity, renovation, cleaning, and moist environments within the ventilation system ducts (1) or air filters (5) have been commonly cited. Although a "safe" airborne concentration of conidia has not been well established, at least one study documents a correlation between clinical disease and increasing conidial counts (5). In one investigation (75), *Penicillium* spp. were found to proliferate in rotting wood beneath a leaky sink, indicating that *Aspergillus* growth may be promoted in a similar way.

In general, wet organic debris should be avoided in hospital ventilation systems serving high-risk patients (75). This point is also important in the outpatient setting, because patients, even those with severe immunosuppression, are increasingly being cared for in outpatient clinics. Construction guidelines for ventilation systems should be followed when renovating or building new patient care facilities (1a). These guidelines emphasize the need for routine maintenance of these ventilation systems to avoid potential contamination with *Aspergillus* spp.

Prevention and Control

Aside from maintenance of ventilation systems and minimization of host risk factors, the single most important infection control measure to prevent nosocomial transmission of invasive aspergillosis is a heightened awareness of the pathogenesis and epidemiology of aspergillosis. The CDC has published revised recommendations for preventing nosocomial pulmonary aspergillosis (Table 5) (95). Periodic review of microbiology, histology, and autopsy data is recommended as routine surveillance for nosocomial aspergillosis, especially in specialized units where high-risk patients are treated. If aspergillosis is diagnosed in multiple patients, the likelihood of an environmental source of the *Aspergillus* spp. is increased. Components of a protected environment commonly include a sealed room capable of achieving $\geq$15 air changes per hour, use of filtered air ($\geq$95% efficacy at removing 0.3-μm particles), maintenance of positive pressure relative to the hallway, and occasionally the use of directed airflow within the room (Table 5).

Although routine environmental cultures, such as gravity settle plate cultures, did not help prevent an outbreak of invasive aspergillosis in one study (41), the use of environmental cultures directed by an epidemiologic study during an outbreak may be very useful. Hospital epidemiologists are now able to supplement epidemiologic studies with genomic typing data comparing environmental and patient isolates. Various techniques are being used to type *Aspergillus* spp. isolates (Table 4), and they appear to be superior to phenotypic differentiation in identifying an environmental source. Fingerprinting methods include analysis of restriction fragment length polymorphism of digested total cellular DNA (65), randomly amplified polymorphic DNA markers, and moderately repetitive DNA sequences (34). Although it is unclear which single method is best, particularly for different *Aspergillus* spp., it is clear that isolates should be typed in parallel under identical conditions and that the tests should include epidemiologically unrelated strains as control isolates (65).

When an environmental source of an outbreak is identified, the source should be eliminated and the ventilation system should be modified when appropriate. Sporadic infections may be associated with bursts of fungal conidia in the air. Attempts to prevent exposing high-risk patients to bursts of fungal conidia include installation of protected environments such as (i) special units constructed to minimize fungal conidium counts in the air by filtration of incoming air with high-efficiency particulate air filters, (ii) directed room or laminar airflow (intake on one side of the room and exhaust on the opposite side), (iii) positive room air pressure relative to the corridor, (iv) well-sealed rooms, and (v) high rates of room air changes ($>$15 air exchanges per h (95).

Although aspergillosis is rare among hospitalized patients overall, current understanding of the epidemiology of nosocomial aspergillosis enables hospital epidemiologists to focus efforts on high-risk populations, to use newer diagnostic and laboratory techniques to quickly identify the reservoir associated with an outbreak, and to decrease the morbidity and mortality associated with invasive aspergillosis. However, despite these control measures, invasive aspergillosis remains a devastating disease with continuing high mortality rates.

ZYGOMYCETES

Mucor, *Absidia*, and *Rhizopus* Species

Fungi of the class *Zygomycetes* reported to cause hospital-acquired infection include several of the genera in the order

TABLE 5. CDC Recommendations for the prevention and control of nosocomial pulmonary aspergillosis[a]

Recommendation	Category[b]
Staff education, especially care providers for immunocompromised patients	IA
Surveillance, with focus on	
High-risk patients (<1,000 granulocytes/mm^3 for 14 days, <100 granulocytes/mm^3 for 7 days)	IB
Periodic review of microbiological, histopathologic, and postmortem data	IB
Periodic surveillance cultures of high-risk patients	Unresolved
New construction of specialized care unit for high-risk patients	
Minimization of fungal spore counts by HEPA filtration, directed airflow, positive pressure, proper seals, high rates of room-air changes	IB
Ultra-high air change rates (100 to 400/h), laminar airflow	Unresolved
Minimization of exposure of high-risk patients to construction and carpet and floor cleaning	IB
Prophylactic use of copper-8-quinolinolate biocide in fireproofing material	Unresolved
Existing facilities with no cases of nosocomial aspergillosis	
Minimize fungal spore counts as above	IB
Minimize exposures as above	IB
Conduct routine maintenance of the heating, ventilation, and air-conditioning system, including prevention of bird access to air intake ducts	IB
Minimize time and wear mask when high-risk patients are outside the area	IB
Eliminate potential *Aspergillus*-contaminated food, potted plants, and flowers	II
During construction use, erect barriers, direct pedestrian traffic away and clean new areas before entry by high-risk patients	IB
After a case of nosocomial aspergillosis occurs	
Begin a retrospective review and prospective search for other cases	IB
If continuing infection occurs, conduct an environmental investigation	IB
Contact the local or state health department if assistance is needed	IB
Modifying host risk for infection	
Use of cytokines to decrease the duration of granulocytopenia	II
Intranasal amphotericin B or oral antifungal agents prophylactically	Unresolved

[a] Adapted from reference 95.

[b] Each recommendation is categorized as follows: IA, strongly recommended for all hospitals and supported by well-designed experimental or epidemiologic evidence; IB, strongly recommended for all hospitals and viewed as effective by experts on the basis of strong rationale and suggestive evidence; II, suggested for implementation in many hospitals, supported by suggestive clinical or epidemiologic studies with a strong theoretical rationale or definitive studies applicable to some but not all hospitals; Unresolved, practices for which insufficient evidence or consensus regarding efficacy exists.

Mucorales (e.g., *Mucor*, *Absidia*, and *Rhizopus*). Clinical illness usually occurs in immunocompromised hosts and is similar to that seen in patients with aspergillosis. Risk factors include hematologic malignancy, myelosuppression, renal failure, diabetes mellitus, receipt of antimicrobial agents, severe underlying disease, and exposure to hospital construction activity (2). Zygomycosis tends to present with pulmonary, renal, and/or rhinocerebral involvement, although disseminated infections may occur in patients with hematologic malignancy.

While the reservoir and mechanisms of transmission of members of the *Zygomycetes* are similar to those of *Aspergillus* spp., there are some unique mechanisms as well. Most impressive were reports of primary zygomycosis of the skin associated with elasticized surgical bandages (45). Such infections also have been associated with trauma, hemodialysis, and postoperative wounds. The clinical presentation is a rapidly developing bullous cellulitis associated with necrosis and systemic toxicity (16). However, there have also been reports of disease with a low rate of progression without systemic toxicity (58). The treatment of choice for zygomycosis is usually amphotericin B, with the addition of wound debridement for wound mucormycosis.

EMERGING NOSOCOMIAL FUNGAL PATHOGENS

Yeasts Other than *Candida* Species

As the patient population has changed over the past decade, several types of yeasts have become recognized pathogens in hospitalized patients. As with most fungal infections, the major reason is the change in host susceptibility. Unlike aspergillosis, diagnosis of these yeast infections commonly is made by blood culture. However, the epidemiology and modalities of treatment for these pathogens are still under study.

***Malassezia* species.** *Malassezia* spp., specifically *Malassezia furfur* and *M. pachydermatis*, are being observed more frequently as nosocomial pathogens, especially in NICU patients. For example, reports of invasive infections with *M. furfur*, which is well established as the etiologic agent of pityriasis (tinea) versicolor (80), have increased over the past 15 years (50, 79, 92).

(i) Growth requirements. *M. furfur* is not able to synthesize medium- and long-chain fatty acids and requires exogenous lipid for growth. Thus, detection of this organism is enhanced by growing the specimen at 35 to 37°C on Sabouraud agar covered with a thin layer of sterile olive oil (3). One study suggests that supplementation of Peds Plus blood culture bottles (Becton-Dickinson Diagnostic Instruments Systems, Sparks, Md.) with palmitic acid (3%) improves the recovery of *Malassezia* spp. in the BACTEC NR 660 instrument (55).

(ii) Epidemiology. The dependence on exogenous lipid helps explain some of the epidemiology of invasive *M. furfur* infections. Exposure to intravenous lipid through a central venous catheter is a common factor in reports of *M. furfur* fungemia in both neonates and adults (3, 50, 92). Among neonates, other established risk factors include low birth weight, early gestational age, and length of hospital stay. However, studies of neonate skin colonization demonstrate that administration of lipid emulsions does not predispose infants to skin colonization; it is thought that the presence of lipid in a central venous catheter assists pathogen migration via the catheter hub into the intravascular system, causing infection (92). Although most infections appear to be sporadic, an investigation of one outbreak of invasive pulmonary infections involving neonates

identified the duration of antimicrobial therapy as a risk factor for disease among very low birth weight infants (<1,000 g), most of whom received intravenous lipids. This investigation provided evidence that *M. furfur* can be transmitted from an infected or colonized infant to other infants via the hands of health care workers (79).

(iii) Invasive infections. Signs of infection with *M. furfur* in neonates range from asymptomatic to symptoms of temperature instability, bradycardia, thrombocytopenia, and worsening respiratory function (18, 79, 92). Adults, in particular those who have undergone recent abdominal surgery, those with gastrointestinal abnormalities, or those in an immunocompromised state, usually develop mild illness with fever (18, 50, 80). Cultures of blood from the central line used for infusion of the lipid emulsion tend to grow *M. furfur*, whereas peripheral blood cultures rarely do (92).

(iv) Treatment. Treatment of *M. furfur* infections includes removal of the catheter and cessation of lipid infusion. Systemic antifungal treatment, including amphotericin B, ketoconazole, or miconazole, should be reserved for patients with persistent infection, although the choice of systemic agent is controversial (92).

(v) *M. pachydermatis*. *M. pachydermatis* has also been implicated as a nosocomial pathogen. Unlike *M. furfur*, *M. pachydermatis* is a nonobligatory lipophilic yeast, since fatty acids stimulate but are not required for growth (50). This yeast is commonly found on dogs and is a common cause of canine otitis externa. However, human infections have been reported only sporadically, usually in premature, low-birth-weight infants with multiple complications of prematurity. Investigation of two outbreaks of *M. pachydermatis* infections in NICU patients found associations between *M. pachydermatis* fungemia and receipt of parenteral nutrition and intravenous lipids (15, 106) and longer exposure to antimicrobial agents (15). Molecular analysis of *Malassezia* isolates in these studies has been helpful in determining that transmission occurs from person to person via the hands of health care workers.

***Trichosporon* species.** *Trichosporon beigelii* (formally referred to as *Trichosporon cutaneum*) causes a superficial infection of hair shafts known as white piedra. However, deep infections, i.e., trichosporonosis, are becoming more common in hospitalized patients. The occurrence appears to be sporadic and involves severely immunocompromised patients (e.g., patients with hematologic malignancy, corticosteroid use, or burn trauma). Recent reviews describe the clinical manifestations of trichosporonosis, including bloodstream infections, severe skin infections, endocarditis, and peritonitis associated with a dialysis catheter (37, 101). Also, at least one cluster of trichosporonosis has been reported in a NICU (27). Diagnosis of invasive disease is usually made by performing a blood culture. Trichosporonosis appears to be a difficult disease to treat, and it is associated with high morbidity and mortality rates (37). In vitro susceptibility does not always correlate with in vivo response; laboratory studies have shown that the minimum lethal (fungicidal) concentrations of amphotericin B were much higher than the MICs (100). Walsh et al. (100) also noted that blood isolates were more resistant to amphotericin B than were skin isolates. The optimal antifungal therapy for these infections is unclear; some reviewers suggest empirical treatment with amphotericin B and flucytosine or rifampin pending susceptibility testing (37, 101). However, most mycologists think that rifampin offers little, if any, benefit in the treatment of fungal infections.

Hyalohyphomycosis

Many nondematiaceous molds cause opportunistic fungal infections, but this review will discuss only a few genera that have recently been recognized as emerging nosocomial pathogens.

***Fusarium* species.** *Fusarium* spp. are common soil fungi that cause localized infections of the eyes (e.g., endophthalmitis, keratitis), nails, and skin (2, 3, 82). *Fusarium* spp. involved in such infections include *Fusarium solani*, *F. oxysporum*, and *F. moniliforme*. Most severe disease occurs in severely immunocompromised patients and may become disseminated or involve major organs (3). The mechanism of infection may include inhalation into the lungs or upper airways or breaks in the skin or mucous membranes. The clinical manifestations of severe disease are like those seen in patients with disseminated aspergillosis, except that there is an increased incidence of subcutaneous lesions in patients with *Fusarium* infections. The pathogen is also more readily isolated from cultures of blood than are *Aspergillus* spp. (2). Diagnosis is usually made by culture of biopsy specimens or other normally sterile sites.

Most localized infections are not considered nosocomial but, rather, are due to increased host susceptibility and acquisition from the environment outside of the hospital. However, postoperative endophthalmitis and peritonitis associated with dialysis catheters has been considered nosocomial, even though the *Fusarium* sp. was probably acquired outside of the hospital (82, 114).

***Acremonium* species.** *Acremonium* spp. (previously known as *Cephalosporium* spp.) are ubiquitous soil fungi and have been found in Europe, Asia, Egypt, and North and Central America. This pathogen has been reported to cause mycetoma, hypersensitivity pneumonitis, locally invasive disease (paranasal sinus, arthritis, hemodialysis access graft, endocarditis), and posttraumatic keratitis (25).

Acremonium spp. usually grow within 5 days on Sabouraud agar at 30°C. Molecular studies have not been reported, but environmental and clinical isolates have been compared for phenotypic and biochemical similarities (30).

True nosocomial transmission of *Acremonium* spp. has rarely occurred. Extrinsic contamination of multidose vials of an injectable radioactive solution for nuclear medicine procedures has been reported, although this was not associated with any clinical disease (32). There have been at least three reports of disseminated *Acremonium* infections in mild or severely immunocompromised individuals (14, 25, 42), two of which demonstrated azole resistance (14, 42). The mechanism of disseminated infection is thought to be secondary to increased host susceptibility with prior colonization.

Recently, an outbreak of *Acremonium kiliense* endophthalmitis was reported following cataract surgery in an ambulatory surgical center in which the reservoir was determined to be a contaminated humidifier within the heating, ventilation, and air-conditioning system located directly above the operative suite (30). This was somewhat surprising since, historically, only *Aspergillus* spp. and zygomycetes have been implicated as major airborne fungal pathogens in health care settings, usually associated with hospital construction or renovation and occurring in immunocompromised patients (22).

Optimal treatment of these infections has not been well defined. Locally invasive disease has been treated by surgery and systemic therapy with amphotericin B. Several patients with endophthalmitis were treated with vitrectomy, instillation of intravitreous amphotericin B, and oral fluconazole for at least 4 weeks (30). By using nonstandardized methods of susceptibility testing, one study found amphotericin B to be the

most consistently active agent (compared with ketoconazole, fluconazole, and itraconazole) against six *Acremonium* isolates tested (25).

Other fungi. Another fungus associated with infection in hospitalized patients is *Paecilomyces lilacinus*. This ubiquitous saprobic mold with low pathogenicity is found in the soil. It has been associated with intrinsic contamination of a neutralizing solution for synthetic intraocular lenses, which resulted in postoperative endophthalmitis (63), and with contamination of skin lotion, which caused skin infections in a bone marrow transplant unit (110).

Lastly, *Pseudallescheria boydii* has emerged as a possible nosocomial pathogen. This fungus can cause corneal ulcers, endophthalmitis, otitis, sinusitis, pneumonia, endocarditis, meningitis, arthritis, osteomyelitis, and abscesses (3). Diagnosis is usually made by culturing normally sterile body sites, including the blood. In the literature, pseudallescheriasis may be referred to as allescheriasis or monosporiosis. This pathogen may cause disease in immunocompromised hosts and is commonly resistant to amphotericin B but susceptible to miconazole and newer azoles (3, 59). Again, the mechanism of infection is thought to be secondary to colonization of the lungs or skin from the environment, as with aspergillosis, and the exact extent of true nosocomial "exogenous" infection is unclear.

CONCLUSION

It is apparent that nosocomial fungal infections are becoming more prominent. There are an increasing number of immunocompromised patients and patients receiving a broader range of antimicrobial agents in U.S. hospitals today compared with previous years. Consequently, infections due to previously obscure fungi are being seen more commonly in hospitalized patients. Although diagnostic and therapeutic modalities for some fungi are improving, such as those used for candidiasis or aspergillosis, there is still much to learn about many of the other fungi discussed above. Molecular typing for non-*albicans Candida* spp. is in its infancy, and typing methods for fungi other than *Candida* and *Aspergillus* spp. are mostly experimental. In addition, standards for susceptibility testing are currently being developed and should help guide clinicians and hospital epidemiologists in the management of nosocomial fungal infections. However, continued epidemiologic and laboratory research is needed to better characterize these pathogens, allowing for improved diagnostic and therapeutic strategies in the future.

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