Epidemiology of nosocomial fungal infection in the 1990s

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Nosocomial fungal infections have become increasingly common. This increase has been documented globally, i.e., in Europe [1], Asia [2,3], and North and South America [4,5]. In the United States, reports to the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infections Surveillance (NNIS) System document this increase in multiple clinical sites, including bloodstream, surgical wound, lower respiratory, and urinary tract [6]. Immunocompromised patients are susceptible to, and have a high mortality rate from, fungal infection. For example, the attributable mortality rate for patients diagnosed with invasive candidiasis may be as high as 38% [7] and the crude mortality of *Aspergillus* spp. infection in bone marrow transplant (BMT) recipients has been reported as high as 95% [8]. The emergence of nosocomial fungal infection and its associated high mortality rate underscore the need for prevention, early clinical recognition, and sensitive and specific laboratory tests for the diagnosis of invasive fungal infection. Early clinical diagnosis of invasive fungal infection often is delayed due to non-specific clinical signs and insensitive diagnostic testing. In this article, we will review the epidemiology and diagnosis of *Candida* and *Aspergillus* spp. infections, the emergence of non-albicans *Candida* spp. infections, and findings from recent investigations of outbreaks caused by less common fungal pathogens.

Candida albicans

During the 1980s, there was nearly a 500% increase in the number of nosocomial *Candida* bloodstream infections reported to the NNIS system [4]. This upward trend continued in the 1990s [9], predominantly at large referral centers [1,4]. Risk factors for invasive candidiasis as determined by multivariate analysis include use of intravascular devices, antimicrobial receipt, prolonged hospitalization, neutropenia, hemodialysis, or previous host colonization by *Candida* spp. (Table 1;[7,10-12]). *C. albicans* is the seventh most common isolate from all patients with nosocomial infection, accounting for 5% of all nosocomial infections [13]. Data from the NNIS intensive-care unit component demonstrate that while the percentage of fungal infections caused by *C. albicans* has remained stable, i.e., 58% in 1985 to 56% in 1996, the number of reported *C. albicans* infections has increased 526% during this period [unpublished data]. Of all clinical sites, the urinary tract has the highest rate (14.4%) of *C. albicans* infection per hospital discharge [14].

C. albicans commonly is present as normal gastrointestinal flora, and increased colonization has been demonstrated after receipt of antimicrobials [10]. Systemic introduction of colonizing organisms can occur after breakdown of normal host defenses (e.g., injury to the gastrointestinal mucosa, placement of intravascular devices, or immunosuppression). Hands of health care workers and hospital environment surfaces can become colonized or contaminated with *Candida* spp. [15], facilitating patient-to-patient nosocomial *Candida* spp. transmission. The relative contribution of pre-hospital colonization vs intra-hospital acquisition of *Candida* spp. to invasive candidiasis has not been determined. In addition, strain virulence factors and proven genetic diversity in geographically diverse regions [16] may influence patient outcome.

Table 1. Risk factors identified by multivariate analysis for invasive infection by either *Candida* or any fungal infection.

Candida	
Neutropenia	11
Intravascular device	7,11
Previous colonization	7,11
Antimicrobial receipt	10,12
Length of stay	12
Hemodialysis	7
Any Fungi	
Previous colonization	70
Antimicrobial receipt	71
Bacteremia	72,73
CMV infection or seropositivity	72,74-76
Increased blood product transfusion requirement	72-74

* References 72-75 studied liver transplant recipients.

Diagnosis of *Candida* spp. infection after health care providers' recognition of clinical manifestations of disseminated disease in conjunction with confirmatory laboratory evaluation has been ineffective for the early detection of invasive candidiasis [17,18]. New techniques with potential clinical applicability in the early diagnosis of *C. albicans* infection include detection of *Candida* cell wall (mannans,1,3-β–glucans) antigens [19-22], or cytoplasmic (enolase) antigens and DNA amplification and analysis by polymerase chain reaction (PCR) [23]. Therapeutic options to treat patients with *C. albicans* infection include polyenes (amphotericin), imidazoles, and triazoles. The emergence of antimicrobial-resistant fungal pathogens limits the few therapeutic options. Some acquired immune deficiency syndrome (AIDS) patients, particularly those with greater exposure to azole therapy or low CD4 counts, have developed azole-resistant

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C. albicans infections [24,25]. Resistance to azoles has not been well documented in human immunodeficiency virus (HIV)-negative patients. The appearance of azole-resistant *C. albicans* infection in AIDS patients portends resistance in other immunocompromised patient populations.

Non-albicans *Candida* species

Selective pressure from exposure to topical [26] or systemic antimicrobial agents can alter patients' colonizing flora and subsequently influence which organisms are responsible for invasive infection [10]. In BMT patients, fluconazole prophylaxis has been effective in decreasing the incidence of fungal infection and overall mortality [27-29]. However, prophylaxis with fluconazole may be responsible for the increased number of non-albicans *Candida* spp. infections in some facilities [30,31], and as reported to the NNIS system (Figure 1).

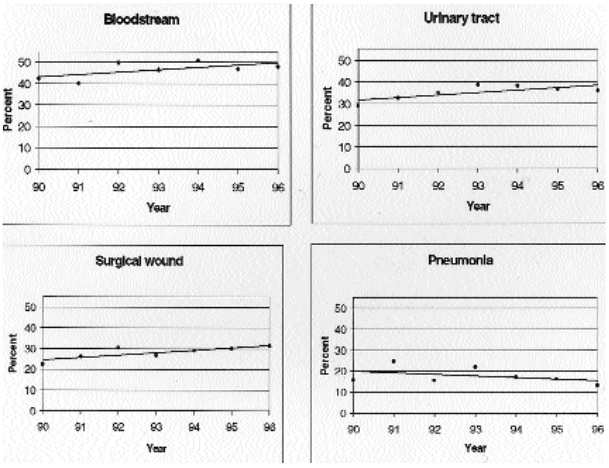

Figure 1. Secular trend in the proportion of *Candida* infections attributable to non-albicans *Candida* spp. from selected sites, reported to NNIS hospitals, 1990-1996.

Candida parapsilosis is a common nosocomial fungal pathogen in many hospitals and has been isolated in up to 25% of all *Candida* infections [32]. Infections due to *C. parapsilosis* are often associated with invasive devices, particularly intravascular [33,34], or peritoneal dialysis catheters [35], and are most common in high risk nursery patients [36-38]. Some *C. parapsilosis* isolates are capable of slime production, which may contribute to increased catheter adherence [39]. Catheter adherence combined with a propensity to grow well in glucose and total parenteral nutrition solutions [33] and the ability to colonize the hands of health care workers [40,41] may account for clusters of nosocomially transmitted *C. parapsilosis* infections.

Candida glabrata represents 8 to 14% of all *Candida* isolates cultured from infected hospitalized patients [3,30,42]. Patients with solid tumors and noncologic diseases are traditionally considered to be at greater risk than those with hematologic malignancy for infection with *C. glabrata* [43]. One study documented a high percentage of *C. glabrata* infections in BMT recipients after receipt of fluconazole prophylaxis [44]. Native resistance to azoles is common in *C. glabrata*, and fluconazole prophylaxis in select patient populations may increase the rate of *C. glabrata* infection [24,44].

C. tropicalis is another common non-albicans *Candida* species in many hospitals representing between 6-25 % of all *Candida* isolates [3]. A genotypic analysis of 89 isolates at seven U.S. medical centers revealed 49 different DNA types; serial isolates from the same individual patient were usually a similar genome type [45]. These data suggest that most *C. tropicalis* infections originate from the patient's colonizing flora. Probable episodes of nosocomial *C. tropicalis* transmission have been reported (Table 2)[46,47].

Less common than the previously mentioned non-albicans *Candida* spp. (*C. glabrata*, *C. parapsilosis*, and *C. tropicalis*), *Candida krusei* has been reported to represent 1-4% of all *Candida* isolates [3,48]. *C. krusei* is frequently resistant to fluconazole and also may be less susceptible to amphotericin B [49]. There have been reports of an increase in *C. krusei* infection in patient populations that have received fluconazole prophylaxis [31]. Gastrointestinal colonization with *C. krusei* can precede infection; in most patients, colonizing and infecting strains in the same patient are genetically similar [49], confirming patients' colonizing flora as a source of invasive candidiasis. However, clustering of genotypically similar isolates from different patients has been demonstrated, suggesting nosocomial patient-to-patient transmission [49].

Aspergillus

Invasive *Aspergillus* infection is common in select patient populations, for example, BMT recipients. Data from the NNIS system indicate that although the number of reported *Aspergillus* infections has increased, the percent of nosocomial fungal infections due to *Aspergillus* spp. has remained stable at less than 2%. Pneumonia is the most common clinical site of *Aspergillus* infection, and up to 36% of all isolates from BMT patients with

Table 2. Examples of probable nosocomial transmission of non-albicans *Candida* species.

Ref.	Species	Patient population	Source/Evidence
[36]	*C. parapsilosis*	Neonatal ICU	Genotypically distinct isolates from mother/infant pairs. Vertical transmission unlikely
[37]	*C. parapsilosis*	Neonatal ICU	Multidose glycerin suppository, epidemiologic evidence
[38]	*C. parapsilosis*	Neonatal ICU	Genotypically similar strain infected multiple patients
[78]	*C. parapsilosis*	Ambulatory surgery	Intrinsically contaminated lot of ophthalmic irrigation solution
[46]	*C. tropicalis*	Neonatal ICU	Cluster of infections, hand carriage by staff *
[47]	*C. tropicalis*	Post-op wound infections	Culture-positive HCW epidemiologically implicated in the outbreak
[77]	*C. rugosa*	Burn ICU	Nine patients infected by a single strain

* No epidemiologic or molecular link to a specific health care worker (HCW).

pneumonia have been *Aspergillus* spp.[8]. The clinical consequences of invasive *Aspergillus* infection are devastating, with crude mortality rates reported as high as 95% [8]. A recent review of 158 BMT recipients diagnosed with invasive *Aspergillus* infection detected a bimodal distribution of infection, peaking 16 and 96 days after transplant; reported significant risk factors differed for early and late post-transplant infections (Table 3)[50]. The median time to *Aspergillus* infection for patients in laminar air flow rooms (LAF) was 78 days, compared to 40 days for patients not in LAF rooms [50], suggesting a protective effect from LAF. Early diagnosis is critical in preventing mortality from *Aspergillus* infection [51], but current diagnostic methods are not sensitive, making premortem diagnosis difficult. Clinicians have traditionally relied on histopathologic evidence of invasive disease. Diagnostic techniques to improve detection of early stage *Aspergillus* spp. infection include serologic assays for antigen detection, molecular probes, and PCR technology [52-54]. Evidence of clinical efficacy for these tests is needed.

Table 3. Multivariate analysis of risk factors for *Aspergillus* infection in bone-marrow transplant recipients in the early and late post-transplant periods [50].

Early risk factors (1-40 days)
Summer season
Outside laminar air flow
Underlying disease
Donor type
Late risk factors (> 40 days)
Graft vs host disease
Neutropenia
Corticosteroid use
Construction activity
Underlying disease
Donor type

Host or environmental factors can be altered to prevent *Aspergillus* infection. The time at risk for acquisition of *Aspergillus* can be minimized by administering colony-stimulating factors and shortening the duration of neutropenia. Pharmaceutical prevention of aspergillosis has been reported as successful [55], but there is no consensus on an effective regimen. Environmental manipulation to decrease the concentration of ambient spores can be accomplished by specialized construction of units for high risk patients and anticipation of construction projects with implementation of infection control measures [56]. Active surveillance to determine baseline rates and detect increased rates of infection can be accomplished by episodic review of hospital microbiology, histopathology, and autopsy records. Diagnosis of *Aspergillus* infection often is missed pre-mortem, and therefore review of post-mortem data is essential [57]. If surveillance data indicates an increase in the incidence of invasive aspergillosis, an investigation to identify an environmental source should be initiated. Often, outbreaks can be traced to recent construction or renovation activity. Possible environmental sources include unfiltered outside air entering the hospital through gaps in filters, windows, or backflow of contaminated air [58,59], or moist environments (e.g., plumbing leaks, rainwater exposure, or condensate from air conditioning systems). Ceiling tiles, carpet, fireproofing material, and particleboard frames of air filters have all been *Aspergillus* culture positive in hospitals [60-62]. Timely intervention when an epidemic is detected and appropriate construction of rooms housing high risk patients are paramount in decreasing infection in at-risk patient populations [56].

The percentage of fungal isolates reported to the NNIS system classified as "other" fungi, i.e., those isolates which are not *Candida* or *Aspergillus* spp., increased from 9.1% in 1986 to 16.0% in 1996 [unpublished data]. Environmental transmission of these less commonly encountered fungi has been identified in several clusters of infection (Table 4)[63-65]. As the number and geographic distribution of immunocompromised patients increase, the emergence of less commonly identified fungi, novel modes of transmission, unique environmental reservoirs, and an increase in the number of fungi documented as human pathogens is likely. Many patients do not respond to current pharmaceutical antifungal therapeutic options. Therefore, new antifungal agents are being developed. These agents either have antifungal activity [66] or augment the host immune system to improve the efficacy of conventional therapy [67,68]. Since many nosocomial fungal infections are associated with intravascular devices, these devices have been modified to decrease infection rates by coating the lumens with anti-infective agents. One study demonstrated *in vitro* inhibition of *C. albicans*; however, clinical trials have not yet shown a reduction in device-related fungal infections [69].

Increased rates of nosocomial fungal infection likely will continue as aggressive treatment options and technologic advancements that prolong the survival of immunocompromised and critically ill patients become available to more people. Minimizing the increase depends on developing a better understanding of the epidemiology of, and risk factors for, acquisition of nosocomial fungal infection. In particular, determining the relative importance of pre-hospital vs intra-hospital colonization of patients and the events necessary for the transition from colonization to infection. Some well-known risk factors can be reduced by implementing effective infection control measures, e.g., appropriate use of broad-spectrum antimicrobials and invasive devices. Patient-to-patient transmission of pathogens may be minimized by implementation and adherence to current barrier infection control measures. Continued active surveillance will be important to detect changes in the distribution of fungal pathogens, and to monitor the emergence of antimicrobial-resistant fungi. In addition, combined epidemiologic and laboratory investigation of outbreaks and large-scale epidemiologic and therapeutic studies should advance our knowledge of these infections and lead to enhanced preventive interventions.

Table 4. Examples of uncommon fungal organisms responsible for recent clusters of nosocomial infections, with identified environmental reservoirs.

Ref.	Organism	Reservoir	Patient population
[63]	*Rhizopus microsporus*	Tongue depressors*	Neonatal ICU
[64]	*Paecilomyces lilacinus*	Skin lotion	Bone marrow transplant recipients
[65]	*Acremonium kiliense*	Ventilation system	Ophthalmologic ambulatory surgery patients

*Tongue depressors were used as intravascular device splints. Microbiologic surveillance of 44 wooden tongue depressors at a separate facility yielded the following fungal organisms, and number identified: *Penicillium* 31, *Aspergillus* 11, *Alternaria* 6, *Rhizopus* 4, *Chaetomium* 1 [79].

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