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REVIEW ARTICLE

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Current challenges in the management of invasive fungal infections

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Abstract The incidence of invasive fungal infections (IFIs) has increased over the past two decades, as the populations of patients at risk have continued to rise. Early and accurate diagnosis and the subsequent usage of appropriate antifungal therapy are difficult, which leads to a high mortality rate in patients with IFI. Along with the widespread use of antifungal prophylaxis, the epidemiology of invasive fungal pathogens has changed. Non-*albicans Candida*, Non-*fumigatus Aspergillus*, and molds other than *Aspergillus* have become more common pathogens causing invasive diseases, and most of these emerging fungi are resistant to or less susceptible than others to standard antifungal agents. Therefore, invasive infections due to these previously rare fungi are more difficult to treat. Advances in more potent and less toxic antifungal agents, such as second-generation triazoles and echinocandins, may potentially improve the outcomes of these infections. Recent advances in detecting fungal cell-wall components and genomic DNA also allow earlier diagnosis. This article reviews the changing spectrum of invasive fungal infections and the introduction of recent advances in diagnostic tools and antifungal agents.

Key words Invasive fungal infections · Epidemiology · Treatment

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Introduction

With the advances in medical care and successful treatment of most bacterial infections, the survival of patients with severe and life-threatening illnesses has improved in the past few decades. However, the emergence of human immunodeficiency virus infection, the development of newer intensive chemotherapy regimens for malignancy, and increases in the number of organ transplant recipients have resulted in more and more immunocompromised patients. The incidence of invasive fungal infections (IFIs) has also increased significantly and has emerged as a worldwide healthcare problem, as a result of the rapidly increasing numbers of patients at risk over the past two decades. The rate of sepsis due to fungal organisms in the United States increased by 207% during the period from 1979 through 2000.[1] These severe opportunistic fungal infections are also characterized by high morbidity and mortality. Despite the remarkable improvements that have been made in diagnostic modalities and antifungal agents in the past 10 years, the diagnosis of fungal infection is still difficult compared to the diagnosis of bacterial infections by conventional culture, and treatment remains a great challenge because of the limited availability of antifungal agents.

Candida albicans, *Cryptococcus neoformans*, and *Aspergillus fumigatus* were the most common causes of opportunistic IFIs in the past. However, changes in medical practice, such as the widespread use of antifungal prophylaxis, have led to a shift in the epidemiology of IFIs to non-*albicans Candida*, non-*fumigatus Aspergillus*, opportunistic yeast-like fungi (e.g., *Trichosporon* and *Rhodotorula* species), zygomycetes, and hyaline molds (e.g., *Fusarium* and *Scedosporium* species). The diagnoses of these emerging IFIs are more difficult, and most of these fungi are considered to be more resistant to standard antifungal drugs than the organisms that were the most common causes of IFIs in the past; hence, IFIs with these rare emerging fungi have a higher morality rate. Therefore, the management of IFIs with these rare fungi requires some newer diagnostic methods and antifungal agents.

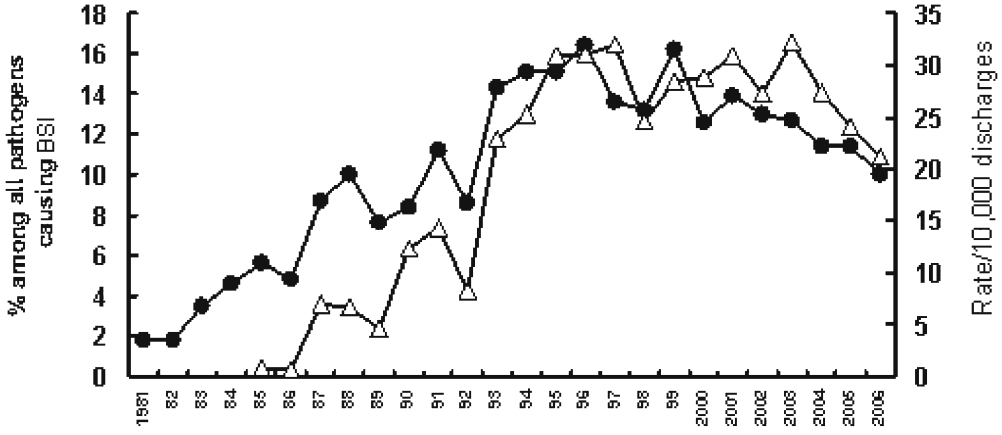

Fig. 1. Incidence of nosocomial bloodstream infections (*BSI*s) caused by *Candida* species in patients treated at the National Taiwan University Hospital, Taiwan, from 1981 to 2006. (In 2006, 21.6 patients per 10000 discharges had nosocomial candidemia, and 53.8% of these patients had candidemia caused by non-*albicans Candida* species (11.4 patients per 10000 discharges). *Black closed circles*, Percentage among all pathogens causing BSI; *open triangles*, rate/10000 discharges

Epidemiology

Candida species

Candida species are the most common IFI pathogens among the fungi, and bloodstream infection (BSI) is the most common clinical presentation of invasive candidiasis. The annual incidences of *Candida*-associated BSIs were 6–23 per 100000 persons in the United States[2,3] and 2.53–11 per 100000 persons in Europe.[4] At the National Taiwan University Hospital,[5] the incidence of nosocomial candidemia gradually increased in early 1990, and it has remained at around 20 to 32 patients per 10000 discharges since 1993 (Fig. 1). In 2006, 21.6 patients per 10000 discharges had nosocomial candidemia and 53.8% of these patients had candidemia that was caused by non-*albicans Candida* species (11.4/10000 discharges). In the past two decades, the incidence of candidemia has been increasing throughout the world.[3–6] Several studies have investigated the risk factors associated with invasive candidiasis and candidemia.[7,8] A susceptible host and the existence of portals of entry are the two major risk factors for developing candidemia. The overall crude mortality rate remains high, ranging from 30% to 50%.[2–4]

C. albicans is the most common species involved in candidemia and it accounts for more than half of the cases.[3–6] *C. albicans* and four other major species (i.e., *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*) cause more than 95% of *Candida*-associated BSIs.[3,4,9,10] The remaining, rare, species are *C. lusitaniae*, *C. guilliermondii*, and *C. rugosa*.[11,12] The epidemiology of *Candida*-related BSIs is different in various patient groups.[4] *C. parapsilosis*-associated BSIs are more common in premature neonates and in patients with vascular catheters.[13–15] In contrast, *C. glabrata* infections are rare in pediatric patients, but are common in the elderly.[16–22] In a medical intensive care unit, *C. glabrata* was the second most common species and accounted for 45 (30%) episodes of candidemia.[5] In patients with hematological malignancy, *C. tropicalis* is an important pathogen causing invasive diseases.[23–27] Overall, the non-*albicans Candida* species are now causing many more IFIs than before,[2,28] and a 10% to 11% increase over a 6.5-year period was reported in a global study.[28] Continuously increasing incidences of *C. glabrata* and *C. krusei* infections were reported in the United States.[29–31] In contrast to the incidence in the United States, the frequency of *C. glabrata* causing BSI has decreased from 12.3% to 8.8% in Europe and from 10.2% to 4.7% in Latin America.[31]

Antifungal susceptibility varies significantly among different species of *Candida*. *C. albicans* remains susceptible to polyenes, flucytosine, the azoles, and the echinocandins.[32–36] *C. parapsilosis* and *C. tropicalis* are susceptible to both azoles and polyenes. In contrast to *C. albicans*, *C. glabrata* and *C. krusei* are inherently or secondarily resistant to fluconazole. Furthermore, a decreased susceptibility of *C. krusei* to amphotericin B has also been reported.[36] Second-generation triazoles and the echinocandins appeared to be more active than amphotericin B and fluconazole against *C. glabrata* and *C. krusei*.[33,34,36]

Aspergillus species

The incidence of invasive aspergillosis (IA) has increased significantly in highly immunocompromised patients, such as neutropenic patients, patients with acquired immunodeficiency syndrome, transplant recipients, and patients on aggressive immunosuppressive regimens (such as steroids and chemotherapy).[37–40] Following environmental exposure to *Aspergillus* conidia, primary infection usually involves the respiratory tract.[41] In severely immunocompromised patients, it may involve other organs, such as brain and sinus, or even cause disseminated infection.[37] *A. fumigatus* and *A. flavus* are the most common causative species of invasive mold infections. Other species of *Aspergillus,* such as *A. niger* and *A. terreus*, have also been identified as rare causes of invasive infections. The majority of *Aspergillus* species, except for *A. terreus,* are susceptible to amphotericin B.[6] New antifungal agents, such as extended-spectrum triazoles and the echinocandins, remain active against most of the *Aspergillus* species, including *A. terreus*.[42–44] IA is