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Review

Trends in the Epidemiology of Invasive Fungal Infections

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Abstract

Invasive fungal infections have increased in importance, largely because of the increasing size of the population at risk. *Candida* species remain the fourth most important cause of hospital-acquired bloodstream infections. Infections with *Candida* species other than *C. albicans* appear to have become more common, but significant geographic variation has been reported. Invasive aspergillosis and other mould infections are a leading cause of infection-related death in hematopoietic stem cell transplant recipients. Although *Aspergillus fumigatus* remains the most frequent cause of infection, *A. terreus* has emerged as an important pathogen, at least among certain populations. Despite marked reductions in the rates of AIDS-associated fungal infections, such as cryptococcosis, in the United States and other developed countries, the burden of these diseases in developing countries is large and increasing. Enhanced surveillance and reporting will be critical to improve our understanding of the importance of invasive fungal infections, to enable prioritization of research and prevention efforts, and to evaluate prevention strategies.

Key words: surveillance, candidiasis, cryptococcosis, aspergillosis, zygomycosis

Introduction

Over the last two decades, invasive fungal infections have assumed a much greater importance, largely because of the increasing size of the population at risk. This population includes persons with human immunodeficiency virus (HIV) infection, recipients of solid organ or haematopoietic stem cell transplants (HSCT), patients with hematologic malignancies, burns, or indwelling medical devices, and low-birth-weight infants. For all of its benefits, medical progress has led to an expanding population of susceptible hosts with impaired immunological defenses against infection. These individuals are at heightened risk for many invasive fungal infections, including aspergillosis, candidiasis, cryptococcosis, and zygomycosis.

The HIV epidemic is one of the major factors that have contributed to the dramatic increase in the prevalence of invasive fungal infections. Prior to the widespread usage of highly active anti-retroviral therapy (HAART) in developed countries, up to 80% of HIV-infected persons developed mucosal candidiasis, while others developed cryptococcosis, pneumocystosis, and other lethal fungal infections, such as penicilliosis. Throughout the developed world, the widespread use of HAART has led to a marked reduction in the rates of AIDS-associated opportunistic fungal infections. In contrast, in developing countries the burden of these diseases is large and increasing.

Among patients undergoing transplants or treatment for malignancies, more intensive regimens have resulted in more profound levels of immunosuppression that are sustained for longer periods. Likewise, the increasing use of invasive monitoring and aggressive therapeutic technologies in intensive care units has resulted in improved survival of individuals with life-threatening illnesses, but has also contributed to an increase in the number of persons at risk for invasive fungal infections.

In addition to infections acquired in hospitals and other healthcare settings, there has also been a marked increase in the incidence of several of the community-acquired mycoses that are endemic in the Americas, particularly

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coccidioidomycosis. Massive population growth, urban development, and consequent changes in land-use patterns in the endemic areas of the southwestern United States have resulted in increasing numbers of previously unexposed persons being infected. Many of these individuals are older, have underlying chronic illnesses and debilitation, and consequently are at greater risk of developing the more serious forms of coccidioidomycosis.

Surveillance

Despite general agreement that invasive fungal infections are becoming more important, our understanding of the public health burden of these diseases remains incomplete, mostly due to lack of adequate surveillance data. Epidemiologic surveillance (which should be distinguished from microbiologic surveillance) can be defined as the ongoing systematic collection, analysis and interpretation of information about a disease[1]. Surveillance data allow the burden of a disease to be measured and trends in its incidence to be determined. Changes in the incidence of particular infectious agents, as well as changes in their resistance to antimicrobial agents, can be monitored. Surveillance data also allow the effectiveness of interventions, designed to reduce the prevalence of an infection, to be monitored. Various surveillance systems have been used to assess the incidence and trends of fungal diseases and describe their epidemiology. They include population-based and sentinel surveillance systems, as well as review of hospital-based or national databases and passive reporting systems.

In the absence of better data, researchers have often resorted to retrospective analysis of large databases, such as deaths records and hospitalization data, to estimate the burden of fungal diseases. Analysis of U.S. National Center for Heath Statistics (NCHS) death records showed that fungal infections were the seventh most common cause of infectious disease-related mortality in 1992, and that mycotic disease-related fatalities had increased more than three-fold since 1980[2]. Additional analysis revealed that candidiasis and aspergillosis were the two specific diseases that accounted for most of these deaths[3] NCHS data also showed that, in 1994, fungal diseases resulted in 30,000 hospitalizations, and accounted for the fourth highest annual percentage increase (10%) since 1980[4]. Although helpful for investigating trends in various diseases, these databases tend significantly to underestimate the incidence of invasive fungal infections. In addition, validation of the fungal diagnosis is usually difficult since no medical records are available for review. U.S. national hospitalization data are derived from a representative sample of U.S. hospitals; in the case of the geographically restricted endemic mycoses, or the AIDS-associated mycoses, this sample may not be adequate to assess the burden of hospitalizations due to fungal infections.

Passive surveillance systems are not ideal for invasive fungal infections. Because these diseases are not notifiable and not usually transmissible from person to person, there is minimal incentive to report cases. In the United States, coccidioidomycosis is a reportable disease, but only in states where it is endemic[5]. In other countries, volunteer networks have sometimes been used to estimate the burden of fungal infections[6, 7]. Such systems do not usually provide complete estimates of disease burden, and reporting may vary for different diseases and risk groups. This can lead to inaccurate and biased descriptions of the epidemiological features of these diseases.

Most active surveillance for fungal infections has been conducted through sentinel systems. The National Nosocomial Infections Surveillance (NNIS) system, a sentinel surveillance system of U.S. hospitals, was established by the Centers for Disease Control and Prevention (CDC) in 1970 and provided much of the earlier data on the frequency of fungal pathogens as causes of health-care-associated infections[8, 9]. Hospital-based systems, such as NNIS, are important to quantify the mortality and morbidity associated with hospital-acquired fungal infections, especially in comparison with other hospital-acquired infections[8]. However, NNIS is a sentinel surveillance system of self-selecting hospitals and it may not be a representative sample of all hospitals. In addition, hospital-acquired infections constitute only a proportion of fungal infections. With recent changes in health care delivery, even infections historically considered to be acquired in hospitals are now being seen more commonly in the out-patient setting. As an example, population-based surveillance for candidemia, conducted between 1998 and 2000, demonstrated that 28% of all *Candida* bloodstream infections (BSI) were acquired outside hospitals[10].

In recent years, many sentinel surveillance systems have been established, particularly for *Candida* BSI. These programs have provided extremely valuable data, but may not be as

representative of the general population as population-based surveillance systems, especially when the institutions involved are mostly large academic or tertiary care referral centers. However, sentinel systems have the advantage of being simpler in study design and methodology and less labor-intensive than population-based systems and, as such, can provide rapid reporting of results. In addition, as these sentinel systems have become larger and involved more hospitals, the data they are generating have proven to be very similar to those obtained from population-based systems, especially in regards to trends in prevalence of antifungal drug resistance and species distribution among isolates causing *Candida* BSI.

In the Mycotic Diseases Branch of the CDC, efforts have focused on conducting active population-based surveillance for a range of invasive fungal infections[10-12]. This form of surveillance detects all cases of a disease within a given geographic area regardless of the location of the diagnosis. Although this type of surveillance can be expensive and labor-intensive, it has enabled accurate population-based incidence rates for several fungal infections, including *Candida* BSI and cryptococcosis, to be determined for the first time. In addition, population-based surveillance for candidemia has, for the first time, enabled us to conduct studies that adequately estimate the costs of hospitalization attributable to *Candida* BSI[13]. This form of surveillance has also allowed better risk factor studies to be conducted[14], because the cases detected are more truly representative of the population.

Regardless of the type of surveillance system that is chosen, the quality of the data generated is heavily dependent on having a defined population, a clear case definition, a mechanism for reporting, and a sufficient incentive for all participants to conduct the surveillance. For mycotic diseases, several of these elements present distinct challenges. First, there are few standardized case definitions for invasive fungal infections and the limitations of currently available diagnostic tests for some diseases pose a major problem in developing such definitions. For example, for invasive aspergillosis, isolation of the organism is less than proof of disease, and histopathological evidence is often required. Obtaining adequate tissue samples from many of the patients at high risk for this disease can be difficult and may pose serious health risks. Secondly, fungal infections, especially the community-acquired endemic mycoses, such as coccidioidomycosis, have a wide spectrum of clinical manifestations, ranging from asymptomatic pulmonary infection to life-threatening disseminated disease. As a consequence, determining the overall burden of infection is very difficult and surveillance efforts usually concentrate on determining the burden of severe disease. Finally, health-care providers often feel that there is no need to report fungal infections, since no immediate public health action needs to be taken. As a result of these various factors, fungal infections are not only under-diagnosed, but also under-reported.

Candidiasis

Bloodstream infections with *Candida* species (candidemia) are the most common clinical presentation of invasive candidiasis, and are an important cause of morbidity and mortality in hospitalized patients. Although it is often difficult to compare incidence rates between different studies when different denominators are used, sentinel and population-based surveillance programs have helped to define the overall morbidity related to *Candida* BSI among the various groups at risk. Furthermore, they have served to highlight the relative importance of *Candida* species as compared with other common hospital-related pathogens. In the United States, *Candida* species are ranked as the fourth most common cause of hospital-acquired BSI[15-17], with an incidence of 1.5 cases per 10,000 patient days or 8 infections per 10,000 hospital discharges[10]. In comparable European studies, the incidence is slightly lower, at 0.5 - 0.7 cases per 10,000 patient days or 2 - 5 infections per 10,000 discharges from the hospital[18-21]. To date, the highest reported incidence of healthcare-associated candidemia (3.7 cases per 10,000 patient days) has come from an eleven-center sentinel surveillance program in Brazil[22]. Although the reasons for this high rate of infection are not clear, a number of factors could be involved, including limited resources available for medical care and training programs, difficulties in the implementation of infection control programs in hospitals of developing countries, limited numbers of health-care workers to assist patients in critical care units, and less aggressive practices for antifungal drug treatment of high-risk patients. As in the United States, *Candida* species are ranked as the fourth most common cause of hospital-acquired BSI in Brazil, indicating that these factors affect not just the candidemia rate, but the overall rates

of BSI [22].

Although hospital-based epidemiological studies have provided much useful information about candidemia, the data obtained may not be as representative as those derived from active population-based surveillance systems. Several population-based surveillance studies of *Candida* BSI have been reported from the United States [10, 23, 24] and Canada [25]. The annual incidence rates of candidemia, reported in recent U.S. studies, have ranged from 10 per 100,000 population in Baltimore and the state of Connecticut between 1998 and 2000 [10], to 8 per 100,000 in Atlanta and San Francisco during 1992 and 1993 [23], and 6 per 100,000 in the state of Iowa between 1998 and 2001 [24]. For reasons that are still unclear, the overall incidence of *Candida* BSI in the United States is higher than in a number of other countries, including Canada (2.9 per 100,000 population between 1999 and 2004) [25], Finland (2 per 100,000 population between 1995 and 1999) [26], and Spain (4.3 per 100,000 population between 2002 and 2003) [20]. These differences in rates between countries could be due, in part at least, to different distribution of risk factors in the populations studied, different age distributions, or differences in methodologies employed. For instance, the proportion of outpatient candidemia was lower in Spain than in the United States (11 versus 28% within 24 h of hospital admission), possibly due to a difference in the frequency of outpatient central venous catheter use [10, 20].

Candidemia is often associated with disease outside of the bloodstream. In many cases the infection spreads from the gastrointestinal tract to other organs (invasive or disseminated candidiasis) and this helps to explain why *Candida* BSI is such a devastating disease. The attributable mortality rate for candidemia at one medical center in the United States between 1997 and 2001 was 49% [27], which was 11% higher than that observed in the same hospital between 1983 and 1986 [28]. Using data from a population-based, matched case-control study conducted in Baltimore and the state of Connecticut, Morgan *et al.* [13] estimated the attributable mortality rate of candidemia to be 19 - 24%, depending on the patient's age. When extrapolated to the entire U.S. population, the annual number of excess deaths was estimated to be 4256 - 5376, and the estimated excess hospital costs were $44 million - $320 million.

Interpretation of epidemiological studies that have evaluated the changing incidence of *Candida* BSI over time can be difficult, and it is here that we again find significant differences between the results from different countries and different centers. In Europe, the incidence rate of candidemia among hospitalized patients in The Netherlands increased from 0.37 to 0.72 cases per 10,000 patient days between 1987 and 1995 [29], but in Switzerland, it remained almost unchanged between 1991 and 2000 (median incidence: 0.5 cases per 10,000 patient days) [19]. With the exception of three recent reports from Nordic countries, most population-based studies do not report long-term trends in the incidence of *Candida* BSI. A report from Iceland, described a rise in annual incidence from 1.4 cases per 100,000 population between 1980 and 1984 to 4.9 cases per 100,000 population between 1995 and 1999 [30], and a study from Finland between 1995 and 1999 reported an increase in annual incidence from 1.7 to 2.2 cases per 100,000 population [26]. In Norway, the incidence of candidemia increased from 2 to 3 cases per 100,000 population between 1993 and 2003 [31].

Although the rates of *Candida* BSI were documented to be increasing among critical care patients in the United States during the 1980s [8, 9], a more recent review of data from more than 300 hospitals participating in the U.S. NNIS system, showed that the incidence rate of *Candida* BSI in this patient group decreased between 1989 and 1999 [32]. This decline was mostly due to a reduction in the rate of *C. albicans* infections, from 8 cases per 10,000 catheter days in 1989 to only 2 cases per 10,000 catheter days in 1999. The rate of *C. glabrata* infections, however, increased significantly (from 0.2 to 0.5 cases per 10,000 catheter days), while those of other *Candida* species remained stable. In contrast, data from the U.S. NCHS suggest that the number of patients discharged from hospital with fungal sepsis has tripled over the last decade, with *Candida* BSI being the most frequent cause [33]. Although candidemia is often associated with critical care, recent reports from the United States and Spain indicate that only one third of patients were in an intensive care unit when the infection was diagnosed [10, 20]. Furthermore, these population-based studies found that 11 - 28% of patients with *Candida* BSI had disease onset outside of the hospital. Clearly, the risk factors associated with candidemia (such as prior colonization, mucosal disruption, and use of central venous catheters and broad-spectrum antibacterial agents) are no longer limited to

critical care patients.

More than 200 species of *Candida* have been described, but only a few have been implicated in human disease. More than 95% of all *Candida* BSI worldwide are caused by five species: *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*[10, 20, 22, 34]. The remaining infections are caused by a number of other *Candida* species, including *C. dubliniensis*, *C. famata*, *C. guilliermondii*, *C. lusitaniae*, *C. norvegensis*, *C. pelliculosa*, and *C. rugosa*[10, 22, 31, 34]. Although these species are uncommon causes of candidiasis, several have been observed to occur in nosocomial clusters, or demonstrate innate or acquired resistance to one or more antifungal agents[35, 36].

Candida albicans remains the predominant cause of candidemia worldwide, but the frequency with which this and other species of *Candida* are recovered from blood samples varies according to the geographic setting, and demographics of the population studied. In North America, *C. albicans* accounted for 45-55% of *Candida* BSI during the 1990s[10, 15, 23–25, 37]. In recent reports from hospital-based sentinel surveillance programs in Brazil and Japan, this species, while predominant, only accounted for 40% of *Candida* BSI[22, 34]. In contrast, 70% of candidemia cases in two Nordic countries during the 1990s were caused by *C. albicans*[26, 31].

In the early 1990s, extensive use of fluconazole to treat HIV-infected persons with recurrent oropharyngeal candidiasis resulted in selection of *Candida* species intrinsically less susceptible to azoles, and in the emergence of azole-drug-resistant strains in these patients due to acquisition of resistance by previously susceptible strains of *C. albicans*[38]. This phenomenon has led to the concern that widespread fluconazole use in broader patient populations could lead to similar selection for species and strains possessing inherent or acquired azole resistance. However, the incidence of fluconazole resistance among *C. albicans* bloodstream isolates, collected during population-based and sentinel surveillance programs worldwide, remains negligible[10, 20, 22, 24, 39].

Candida glabrata has become the second most common cause of *Candida* BSI in North America, accounting for 20-24% of cases in some recent reports[10, 24]. Trick *et al.*[32] have demonstrated that, among the *Candida* species, *C. glabrata* alone increased as a cause of BSI among U.S. critical care patients between 1989 and 1999. However, for reasons that are not well understood, *C. glabrata* remains an infrequent cause of *Candida* BSI in Latin America where *C. tropicalis* and *C. parapsilosis* are the second and third most frequent etiologic agents[22]. *C. glabrata* BSI is rare among infants and children, but increases significantly in incidence with increasing age[24]. The emergence of *C. glabrata* as an important cause of *Candida* BSI is of concern because of reports that 5-10% of incident bloodstream isolates of this species are resistant to fluconazole[10, 24, 34, 40]. In addition, cross-resistance to other azole agents has been well documented[40, 41]. Although increasing fluconazole usage might have contributed to the emergence of *C. glabrata*, it is likely that other host and healthcare factors have also had an effect on this trend[42].

Candida tropicalis has long been considered as an important cause of invasive candidiasis in HSCT recipients and patients with hematologic malignancies. Although it is only the third or fourth most frequent cause of *Candida* BSI in North America[10, 24, 37], it ranks second in Brazil[22] and is also more common than *C. glabrata* in the Asia-Pacific region[43]. The incidence of fluconazole resistance among *C. tropicalis* bloodstream isolates remains negligible[10, 20, 22, 24, 39].

Candida parapsilosis is more common than *C. glabrata* as a cause of BSI in European and Latin American countries[22, 43]. It is the most common *Candida* species found on the hands of health-care workers, and nosocomial clusters of infection have occurred in critical care patients, likely because of its association with indwelling vascular devices and parenteral nutrition[44–46]. Almost all bloodstream isolates of *C. parapsilosis* remain susceptible to fluconazole[10, 20, 22, 24, 39]. However, the emergence and subsequent transmission of a fluconazole-resistant strain has been associated with the use of prophylactic fluconazole in a neonatal intensive care unit[45].

Candida krusei is not a common cause of *Candida* BSI in most countries, accounting for fewer than 5% of cases in most population-based and sentinel surveillance programs[10, 20, 22, 24, 34, 37]. In longitudinal studies, the proportion of *C. krusei* BSI has remained almost constant over time[43]. Similar to *C. tropicalis*, *C. krusei* infections occur most frequently in HSCT recipients with neutropenia[47]. In addition to its intrinsic resistance to fluconazole, this species is also less susceptible to amphotericin B[10, 48]. However, it is susceptible to the extended-spectrum triazoles (posaconazole, ravuconazole, and voriconazole)[41, 49]. It should be noted that colonization and infection with *C. krusei* were apparent in certain medical centers before the introduction of fluconazole[50].

Cryptococcosis

An uncommon infection before the HIV epidemic, cryptococcosis emerged as an important cause of morbidity and mortality among persons living with AIDS throughout the developed and developing world in the 1980s and 1990s. In the United States, population-based surveillance for cryptococcosis, conducted between 1992 and 2000, enabled us to document the declining incidence of this infection among persons with AIDS, largely as a result of the widespread use of effective antiretroviral agents [12, 14]. The overall annual incidence of cryptococcosis in the general population of Atlanta, Georgia, declined from 5 cases per 100,000 in 1992, to 1.3 cases per 100,000 population in 2000 [12]. Almost 90% of cases occurred in persons known to be HIV-infected. The annual rate of cryptococcosis among persons living with AIDS in Atlanta, Georgia, declined from 66 cases per 1000 persons in 1992 to 7 cases per 1000 [12]. Cryptococcosis was the first AIDS-defining illness for 39% of the patients for whom this information was available. Despite the declining incidence of the disease during the 1990s, the annual case-fatality ratio did not change significantly among either HIV-infected or uninfected persons. The overall case-fatality ratio was 11.7% [12].

At the present time, sub-Saharan Africa carries the greatest burden of the global AIDS epidemic, with almost 64% of the world's HIV-infected population, around 24.5 million individuals, residing there [51]. Between 2002 and 2004, the CDC assisted the National Institute for Communicable Diseases of the National Health Laboratory Service of South Africa to conduct active population-based surveillance for cryptococcosis in the Gauteng Province, which includes the cities of Johannesburg, Pretoria and Soweto [52]. The province has a population of almost 9 million, of whom almost 1.5 million were estimated to be living with HIV-AIDS in 2002. The overall incidence of cryptococcosis in the general population of this South African province was 15 per 100,000, much higher than reported from the United States or other developed countries prior to the introduction of combination antiretroviral drug regimens (1.8-6.7 per 100,000 population) [6, 14]. Among HIV-infected persons, the rate was 95 per 100,000, and among persons living with AIDS, 14 per 1000 [52]. Although this last figure is lower than those reported from the United States in the early 1990s, it is almost certainly an underestimate of the true rate.

Aspergillosis

Invasive aspergillosis has emerged as a leading cause of infection-related mortality among HSCT recipients and certain high-risk groups of solid organ transplant (SOT) recipients. Assessing the incidence of invasive aspergillosis in these groups is difficult for a number of reasons. The lack of a consistent case definition and the absence of effective surveillance mechanisms make it difficult to compare the incidence rates reported in different studies. This problem is not confined to aspergillosis, but applies to other invasive mould infections as well. With the adoption of an agreed set of consensus definitions for clinical trials of invasive fungal infections [53], the situation is improving. However, because these definitions require the use of aggressive diagnostic procedures which may not be performed in all cases, it is likely that incidence figures will underestimate the true burden of disease.

There is a widespread perception that there has been a marked increase in the prevalence of aspergillosis over the past several decades. Although this belief may be correct, the evidence most frequently cited in its support has been derived from longitudinal studies conducted among HSCT recipients in one U.S. hospital and may not be representative of the situation in other patient groups, institutions or countries [54, 55]. However, there are other studies that support the perception that aspergillosis is increasing in incidence. Most of these have relied on retrospective analysis of large databases, such as hospital discharge and death records.

Although helpful for investigating trends, these databases tend to underestimate the incidence of fungal infections, such as aspergillosis. In addition, validation of the fungal diagnosis is usually difficult, because no medical records are available for review. Fraser *et al.* [56] reviewed discharge data from 1875 hospitals in the United States from the Commission on Professional and Hospital Activities. These authors reported that the incidence of aspergillosis as a hospital discharge diagnosis increased 158% between 1970 and 1976: from 1.87 cases per million population to 4.82 cases per million. To see if this upward trend was continuing, Reingold *et al.* [57] used identical methods to those of Fraser *et al.* [56]. Their results indicated that the incidence of aspergillosis as a discharge diagnosis almost doubled to 8.4 cases per million population between 1976 and 1980 - 1982.

The incidence of aspergillosis as a hospital

discharge diagnosis has continued to increase. By 1996, there were an estimated 10,190 aspergillosis-related hospitalizations annually in the United States, resulting in 1970 deaths and $633 million in costs[58]. These cases represent 38 hospitalizations per million population or 0.03% of all hospital discharges. Although the sample of hospitals in this database differs from those included in the earlier reports, there is nonetheless a clear upward trend in disease incidence. The number of aspergillosis-related hospitalizations and hospital days appear to have increased about eight-fold since 1970[56]. Furthermore, even though aspergillosis-related hospitalizations account for only a small portion of hospitalizations, the burden of the disease is significant. The average hospitalization with aspergillosis lasted 17.3 days and cost $62,426. This represents an average excess length of hospitalization of 12.3 days and excess cost of $51,779 compared with patients without aspergillosis[58].

The strength of the Healthcare Cost and Utilization Project database used by Dasbach *et al.*[58] is that it provides a national estimate of aspergillosis-related hospitalizations, across a broad spectrum of U.S. hospitals. However, as with any retrospective analysis of a database not designed to look at a particular problem, there are limitations. In particular, in these analyses, some patients may have been categorized as having aspergillosis on the basis of microbiological rather than on histopathological evidence: on grounds that we would now regard as insufficient. This may partially account for the mortality rate of 19.3% for aspergillosis, which is much lower than the rates reported in other studies.

Conducting surveillance to assess the incidence of aspergillosis in high-risk groups is important to establish the burden of disease. However, it has been difficult for several reasons. As discussed earlier, these include the lack of a consistent case definition and the absence of effective surveillance mechanisms. The problem of consistent case definitions has been solved, at least in part, with the advent of consensus definitions for proven and probable infection[53]. In the United States, the Transplant Associated Infections Surveillance Network (TransNet) was established in 2000 as a cooperative effort among academic institutions and the CDC. Its objective was to monitor trends in the incidence of invasive fungal infections (including aspergillosis) in transplant recipients through a nationwide network of hospitals, and to develop estimates of the national incidence of these infections. By aggregating data from different sites, it was hoped to develop better estimates of the national incidence of these infections, to determine risk factors for different groups of patients, and to assess the impact of prevention programs.

In an interim analysis of TransNet data, the incidence of invasive aspergillosis was estimated among 4621 HSCT and 4110 SOT recipients at 19 hospitals dispersed throughout the United States, during a 22 month period in 2001 and 2002[59]. Cases were identified using the consensus definitions for proven and probable infection[53]. The aggregate cumulative incidence of aspergillosis at 12 months was 0.5% after autologous HSCT, 2.3% after allogeneic HSCT from an HLA-matched related donor, 3.2% after transplantation from an HLA-mismatched related donor, and 3.9% after transplantation from an unrelated donor. These figures are lower than those published in earlier reports[55, 60–62]. Many factors could account for this, including changes in transplantation practices, diagnostic methods, and supportive care. However, the outcome at 3 months following diagnosis of *Aspergillus* infection was dismal, with mortality rates that ranged from 53.8% among autologous transplants to 84.6% among unrelated-donor transplants[59].

Analysis of TransNet data showed that more than 50% of autologous transplant recipients developed their *Aspergillus* infection within one month of transplantation and only 15% developed the infection more than four months after transplant[59]. Among the matched-related donor and unrelated donor allogeneic transplant recipients, 36% and 23% of cases, respectively, occurred more than four months after transplantation. These data are consistent with earlier reports from single institutions[55, 60] which suggested that the burden of risk for aspergillosis has shifted from the neutropenic pre-engraftment phase of allogeneic HSCT, to the later post-engraftment phase where the immunosuppression of graft-versus-host disease is predominant, and T-cell function is still diminished.

Aspergillus fumigatus remains the most frequent cause of invasive aspergillosis. However, it only accounted for 56% of isolates recovered from cases in the recent interim analysis of the TransNet surveillance program[59]. The other species of *Aspergillus* associated with infections after HSCT included *A. flavus* (19%) and *A. terreus* (16%). This differs from data from the 1990s, when 90% of cases in which isolates

were recovered were due to *A. fumigatus*[63, 64]. There have been few longitudinal studies, but one U.S. hospital recorded an increase in the proportion of *Aspergillus* infections caused by *A. terreus* from 2.1% of all cases in 1996 to 10.2% in 2001[65]. The emergence of *A. terreus* is a cause for concern because it is less susceptible to amphotericin B than *A. fumigatus*[66, 67], and has the potential to cause fulminant invasive infections in immunocompromised patients[65, 68, 69]. Several newer antifungal agents, including voriconazole, posaconazole, and caspofungin are active against a range of *Aspergillus* species, including *A. terreus*[70].

Zygomycosis

Zygomycosis is less common than other opportunistic invasive fungal infections, such as aspergillosis and candidiasis. In a population-based surveillance program, conducted in San Francisco during 1992 and 1993, the annual incidence rate of zygomycosis was reported to be 0.17 cases per 100,000 population[11]. If extrapolated to the entire U.S. population, this would translate to approximately 500 cases per annum. Over the past decade, however, zygomycosis has emerged as an increasingly important infection, particularly among HSCT recipients and patients with hematological malignancies[71–73]. In addition to causing disease in these severely immunocompromised individuals, zygomycosis can also cause lethal infections in a broader population, including patients with diabetes mellitus, patients receiving deferoxamine treatment, injection drug users, and persons with no apparent immunological impairment[72].

Voriconazole, a second-generation triazole agent, has become the treatment of choice for invasive aspergillosis. It has also become an attractive option for empiric treatment, as well as for antifungal prophylaxis in immunocompromised patients. However, voriconazole is inactive against the etiologic agents of zygomycosis[70], and a number of U.S. transplant centers have documented increases in the number of cases of the disease following the introduction of this agent[73–76]. According to these reports, less than 1% of HSCT recipients at these centers developed zygomycosis before voriconazole prophylaxis was started, compared with ～4% following the introduction of the drug. This increase may not be entirely attributable to voriconazole. It may be associated with an unrelated temporal fluctuation in the environmental reservoir, or an increase over time in the patients' underlying susceptibility to infection. Marr *et al.*[64] noted that twice as many transplant recipients at their center developed zygomycosis during the period between 1995 and 1999 compared with the period between 1985 and 1989. Similar increases occurred for both aspergillosis and fusariosis, suggesting that the increase may have had more to do with patient susceptibility than selection pressure for zygomycosis.

The TransNet surveillance program has reported an interim analysis of pooled data from 16 U.S. transplant centers showing an increase since 2001 in the number of reported cases of zygomycosis, despite stable numbers of fusariosis cases, and declining numbers of aspergillosis cases. However, these data require proper adjustment (e.g. calculation of incidence by risk groups) to reflect true trends in incidence. It remains an open question as to whether the rate of zygomycosis is increasing simply because more patients are surviving longer to become infected, or because the microbial flora of these individuals is being altered. In either case, the likelihood is that more cases of zygomycosis will be seen among transplant recipients and patients with cancer during the coming decade.

Conclusion

It is apparent that invasive fungal infections exact a tremendous toll in terms of human life and healthcare costs, despite the fact that these diseases are still under-diagnosed and under-reported. Establishing and maintaining surveillance programs for a range of fungal diseases, both on a national basis and within individual medical centers, will be essential if we are to determine the true magnitude of the burden posed by these infections, and to prioritize research and prevention efforts. Together with risk-factor studies and cost-effectiveness analyses of proposed interventions, this should provide the information needed to develop appropriate intervention and prevention strategies.

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