An Overview of Changing Trends in Systemic Fungal Infections

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An Overview of Changing Trends in Systemic Fungal Infections

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Abstract

Background:
Invasive mycoses are a significant and growing public health problem. 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 number of persons at risk for fungal infections. This review discusses the changing patterns in the risk factors, epidemiology; the impact of changes in medical practice on the incidence of systemic fungal infection and the emergence of antifungal resistance.

Materials and Methods:
Relevant English-language articles were identified through search on four databases [PubMed, ProQuest, Medline and Embase (all, 2000-2011)] conducted in September 2011 using keywords “systemic fungal infection”, “aspergillosis”, “candidosis” and “antifungal”. Original research and review articles related to patients with systemic fungal infection were considered for the review.

Result:
Despite marked reduction in the rates of invasive fungal infections, in developed countries, the burden is increasing largely in developing countries. Infections with Candida albicans may be decreasing in frequency, the number of persons at risk for them continues to grow. Prolong and deep neutropenia and treatments neutralizing macrophage inflammatory cytokines have increased the likelihood of opportunistic infections. Extensive use of fluconazole in neutropenic patients has resulted in marked decrease in the incidence of invasive candidosis but it has resulted into a shift from highly susceptible to less susceptible Candida spp

Conclusion:
Continued research is required to meet the challenges associated with changes in epidemiology and resistance development.

Introduction

Emerging and re-emerging infectious diseases have shaped the landscape of medicine for the past three decades. Invasive fungal infections are a significant cause of morbidity and mortality in severely immunocompromised patients including those with human immunodeficiency virus (HIV) infection, hematologic malignancies, recipients of immunosuppressive therapies and solid-organ or hematopoietic stem cell transplantation (HSCT), burns or indwelling medical devices and low-birth-weight infants. These infections are being seen in increasing numbers and gained a much greater importance, largely because of the increasing size of the population at risk. In addition, advances in medical care are extending the survival of critically ill patients, rendering them more vulnerable to invasive fungal infections.

Prolonged prophylaxis or treatment with antifungal agents has reduced the incidence of a number of invasive fungal infections. Unfortunately, such strategies in some situations have iatrogenically driven the emergence of new fungal pathogens.

Although Aspergillus and Candida species remain the most common pathogens, the spectrum of invasive mycoses is changing with emergence of other opportunistic fungal pathogens such as Fusarium, Zygomycetes and Scedosporium. These invasive infections which are potentially life-threatening along with mold (aspergillosis) tend to be particularly serious.

Therapy for serious Candida infections has been difficult because of the limited number of available antifungal agents. Amphotericin B since its discovery has been the cornerstone of antifungal therapy due to its broad activity against a wide range of fungi including Aspergillus and Candida species. However, due to its lack of selective activity against fungal cell membranes, conventional amphotericin B (C-AMB) is toxic; significantly limiting its therapeutic utility.

The objective of this review is to discuss the changing patterns in the risk factors, epidemiology; changes in medical practice on the incidence of systemic fungal
Methods and Materials

In the review relevant English-language articles were identified through searches on three databases [PubMed, Medline and Embase (all, 2000-2010)] conducted in September 2011 using the keywords using the keywords “antifungals”, “aspergillosis”, “candidosis”. Original research and review articles related to patients with fungal infection were considered for the review.

Search strategy and selection criteria of the comprehensive literature review:

First, a literature search with special emphasis on research findings published over the ten years (2000 to 2011) years on Diabetes Mellitus was carried out using PubMed, Medline and Embase databases. PubMed and Medline contains citations published mostly from 2005-2008, whereas Embase database dates from 2008 to 2011. The following keywords were employed to search the above mentioned databases: “antifungals”, “aspergillosis” and “candidosis”.

Second, this search was complemented with an iterative proceeding in which we consistently reviewed reference lists of all those publications that were of relevance to address our main objective. The bibliographies of all these recovered manuscripts were retrieved again and the searching strategies repeated until no new information was forthcoming.

Third, we also performed search of the websites of the following organizations: National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC).

Fourth, dissertation abstracts were reviewed. They were searched in following databases (assessed on 04.07.2011 and 10.07.2011):

- www. google. com
- ProQuest Digital Dissertation

The same keywords as described before for the peer-reviewed literature search were used for this search.

*A flow chart of search strategy and selection criteria of the comprehensive literature review in given below in annexure 1

Emerging population at risk for fungal infections

The changing trend in the incidence of Aspergillus infection further illustrates that additional patient groups may be at risk for fungal infection that have not otherwise been categorized as having significant immune suppression by traditional criteria. Traditionally risk factors for invasive Aspergillus included significant neutropenia (<500 neutrophils/microlitre for >10 d), hematological malignancies, and bone marrow transplantation [7-9]. Although these individuals do represent the patient subset with the greatest risks of invasive Aspergillus, newer groups of patients in the intensive care unit (ICU) setting have been revealed to have intermediate or lower level of risk for this serious complication of immune suppression. The intermediate risk category include individuals with prolonged treatment with corticosteroids (.4 wk) before admission to the ICU; autologous bone marrow transplantation; chronic obstructive pulmonary disease, particularly if receiving systemic corticosteroids; liver cirrhosis with prolonged ICU stays; solid organ malignancy; advanced HIV/AIDS; lung transplantation; and individuals with systemic inflammatory diseases requiring immunosuppressive therapy, including prolonged corticosteroid therapies, chemotherapy, and newer immune suppressive agents [7-9]. The individuals at lower risk consist of severely burned or malnourished patients, individuals with other solid organ transplantation, those with prolonged stays in the ICU (>21 days), those receiving systemic corticosteroids for more than 7 days, and postcardiac surgical patients. Not only that reports indicate that patients in renal failure requiring renal replacement therapy and individuals with diabetes mellitus may also have risk for this serious complication [7-9].

Epidemiology

In the recent years, many sentinel surveillance systems has been established, particularly for Candida blood stream infection (BSI). Although these programs have provided extremely valuable data but they may not be regarded as representative of general population as population-based surveillance systems. Nevertheless, the sentinel systems have the advantage of simple study design and methodology and less labour-intensive than population-based systems and, as such, can provide rapid reporting of results [10]. In the Mycotic Diseases Brach of CDC, efforts have focused on conducting active population-based surveillance for a range of invasive fungal infections [11,12].
Candidiasis

In the United States Candida species are ranked as the fourth most common cause of hospital-acquired BSI [10, 21, 22, 23, 24], with an incidence of 1.5 cases per 10,000 patient days or 8 infections per 10,000 hospital discharges [11]. 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 [15-18]. 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 [10]. 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 in hospitals of developing countries, limited numbers of health-care workers to assist patients in critical care units, and less aggressive practices for antifungal treatment of high risk patients.

Although the rates of Candida BSI were documented to be increasing among critical care patients in the United States during the 1980s, a more recent review of data from more than 300 hospitals participating in U.S NNIS system, showed that the incidence rate of Candida BSI in this patient group decreased between 1989 and 1999 [19]. This decline was mostly due to a reduction in the rate of Candida albicans infections, from 8 cases per 10,000 catheter days in 1989 to 2 cases per 10,000 catheter days in 1999. The rate of Candida 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. Data from U.S. NCHS suggest that the number of patients discharged from hospital with funga sepsis has tripled over the last decade, with Candida BSI being the most frequent cause [20].

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, 11, 17, 21]. 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, 11, 21, 22]. 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 [23, 24].

In the early 1990s, extensive use of fluconazole to treat HIV-infected persons with recurrent oropharyngeal candidiasis resulted in selection of Candida species gradually less susceptible to azoles, and in the emergence ofazole-drug-resistant strains in these patients due to acquisition of resistance by previously susceptible strains of C. albicans [25].

Candida glabrata has become the second most common cause of Candida BSI, accounting for 20-24% of cases in some recent reports [11, 25, 26]. One of the studies has demonstrated that among Candida species C. glabrata alone increased as a cause of BSI among U.S. critical care patients between 1989-1999 [19]. However, for reasons which are not well understood, C. glabrata remains an infrequent cause of Candida BSI in Latin America where C. tropicalis and C. parapsilosis are the most frequent etiologic agents followed by C. albicans [10]. C. glabrata BSI are rare among infants and children, but increases significantly in incidence with increasing age [27]. 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 [11, 21, 27, 28]. 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 [28].

Aspergillosis

Among HSCT recipients and high risk groups of solid organ transplant (SOT) recipients invasive aspergillosis has emerged as a leading cause of infection-related mortality. 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 mechanism make it difficult to compare the incidence rates reported in different studies. This problem is not only confined to aspergillosis but also applies to other invasive mould infections as well.

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 incorrect, 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 [29].

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 U.S. during a 22 month period in 2001 and 2002 [31]. The aggregate cumulative incidence of aspergillosis at 12 months was 0.5% after autologous HSCT, 2.3% after allogenic 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. The outcome at 3 months following the diagnosis of aspergillus infection was dismal, with mortality rates that ranged from 53.8% among autologous transplants to 84.6% among unrelated-donor transplants [31]. It suggested that the burden of risk for aspergillosis has shifted from the neutropenic pre-engraftment phase of allogenic 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[31]. The other species of aspergillus associated with infections after HSCT included A. flavus (19%) and A. terreus (16%) [31].

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. 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 [32]. Among HIV-infected persons, the rate was 95 per 100,000 and among persons living with AIDS, 14 per 1000 [33].

Zygomycosis

Zygomycosis is less common than other opportunistic invasive fungal infections. Over the past decades, however, zygomycosis has emerged as an increasingly important infection, particularly among HSCT recipients and patients with haematological malignancies [34,35,36]. 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 person with no apparent immunological impairment [34]. Voriconazole, a second generation triazole agent, which is the treatment of choice for invasive aspergillosis as well as antifungal prophylaxis in immunocompromised patients is inactive against the etiologic agents of zygomycosis [37]. Other emerging moulds are Fusarium spp. and Scedosporium spp (hyalohyphomycoses), which are also gaining importance due to capability of these organisms to cause wide variety of infections specially in immunocompromised patients, particularly HSCT and SOT recipients [38].

Changes in medical practice and its impact

Normally, anatomical barriers are the first line of defence. The skin and mucosal surfaces stop microorganisms entering the body and are themselves protected by acid pH, enzymes, mucus and other antimicrobial secretions. Changes in medical procedures have contributed to the increased incidence of fungal infections [38,39]. These barriers are broken down during surgery and when indwelling catheters are used and number of invasive procedures has increased in recent years. Moreover, burns, chemotherapy, radiotherapy and graft-versus-host disease can damage the skin or cause mucosal lesions thereby allowing fungal agents to reach the tissues and blood.

This scenario is different in case of healthy individuals as they are further protected by immune system. Many diseases cause immunodeficiency, the most notorious being AIDS or certain medications can cause immunosuppression. This can be deliberate with the use of immunosuppressive drugs, e.g: corticosteroids, cyclosporine, etc.

Conclusion

It is apparent that invasive fungal infections toll has increased tremendously 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 centres 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.
References

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