Clinical risk factors for invasive aspergillosis

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Despite improvements in the antifungal armamentarium and diagnostic modalities, invasive aspergillosis (IA) remains an important cause of morbidity and mortality in immunocompromised patients. There is an emergence of non-traditional groups at risk for IA, including intensive care unit (ICU) patients, post-operative patients, those with chronic pulmonary diseases, patients with AIDS and patients on immunomodulating drugs (TNF-α inhibitors). Identification of clinical risk factors for IA may help in determining which patients require risk modification and other prevention measures.

Keywords Aspergillus, clinical risk factors, invasive aspergillosis

Introduction

Invasive aspergillosis (IA) is an important cause of morbidity and mortality in immunocompromised patients. Despite improvements in the antifungal armamentarium and diagnostic modalities, mortality remains unacceptably high [1,2]. There is much interest in development of prevention measures, and identification of clinical risk factors will play a key role in focusing prevention efforts.

There are many risk factors for IA, which can be related to underlying disease of the host (malignancy, transplant type, age); co-morbidities (graft-versus-host disease, diabetes, cytomegalovirus infection, renal or liver dysfunction, COPD, post-surgery); medications (steroids, TNF-α inhibitors, chemotherapy); environment or nosocomial risk factors (air filtration, water, hospital construction), and those that deal with the host/pathogen interactions [3–12]. Risk factors for IA have been studied extensively in patients with hematologic malignancy and transplants; however, clinical risk factors are less well defined for non-traditional patient groups. Several emerging groups at risk for IA include intensive care unit (ICU) patients; patients with chronic obstructive pulmonary disease (COPD); post-operative patients; HIV patients and patients on newer immnosuppressive therapies (TNF-α inhibitors) [13–20]. Studies to identify clinical risk factors for IA are often difficult for several reasons: First, studies may be limited by small numbers of patients because of the low incidence of IA in some patient groups. Second, there are important methodologic issues, specifically regarding the impact of risk factors over time, and defining the period at risk. Finally, because of diagnostic limitations in non-traditional hosts, it is difficult to understand the true impact of IA in some groups. Herein, clinical risk factors for IA are reviewed, with a focus on emerging patient populations at risk for IA.

Hematopoietic stem cell transplant (HSCT) recipients

Because of the poor outcomes associated with invasive fungal infections in HSCT patients there has been much interest in prevention and treatment measures in hopes of improving survival. Identification of clinical risk factors for IA has been well studied in HSCT recipients, and important risk factors include prolonged neutropenia, corticosteroid use (dose and duration), underlying diseases and transplant-related variables (Table 1) [6,11,12,21–23]. In addition, the environment as a risk factor, including concentration of Aspergillus spore counts in air samples, and impact of hospital construction on nosocomial IA, has become important [9]. Recently, clinical risk factors for IA and other invasive fungal infections have been associated with timing of IA in relation to transplant (early, <40 days; or late, 40–80 or 100 days) [21,23–25]. For example, risk
Solid organ transplant recipients

Invasive aspergillosis in solid organ transplant patients continues to be a major cause of morbidity and mortality. Incidence of IA ranges from 2–40% and is dependent on the organ transplanted [29–32]. The most important risk factors for IA, common to all SOT patients, are the net state of immunosuppression and intensity of the immunosuppressive regimen, which may be affected by corticosteroid dose, treatment for rejection and immunomodulatory viruses such as CMV [31–33]. There are many other organ-specific clinical risk factors for IA, as described in Table 2; however, because of the rarity of IA in some transplant populations, studies evaluating clinical risk factors are uncommon [30–36].

A recent case-control study by Gavalda and colleagues, as part of the Spanish Network for Research on Infection in Transplantation, highlighted some important clinical risk factors for IA and the relationship of period of IA risk post-transplantation [37]. Controls included the two patients who underwent the same type of transplant before and after the enrolled IA case, provided a minimum of 18-month follow-up was documented. Overall, 156 cases of proven or probable IA were diagnosed; 80 (51.3%) in liver recipients, 47(30.1%) in heart recipients, 17(10.9%) in lung recipients, 10(6.4%) in kidney recipients, and 2(1.3%) in pancreas-kidney recipients. Independent risk factors for early IA (<3 months after transplantation) included use of vascular amines, additional ICU stay, post-transplantation renal failure or hemodialysis, CMV disease or >1 episode of bacterial infection. In contrast, older age, renal failure, immunosuppressive agents, CMV disease, >1 bacterial infection, chronic graft rejection and immunosuppressive-related neoplasm were independent risk factors for late IA (>3 months after transplantation) [37] Additional data on clinical risk factors for IA in solid organ transplant recipients, especially renal or heart transplant patients, is needed.

Intensive care unit patients

There has been increasing interest in the emergence of IA among critically ill patients, especially those admitted to the ICU [4,13,38,39]. Although IA incidence in the ICU...
has been reported to be as high as 7%, the true incidence is difficult to determine because of several important limitations of IA diagnosis in ICU patients [13]. For example, classic radiographic signs of IA (‘halo’ or ‘air crescent’) seen in neutropenic patients are not routinely present in ICU patients, determination of colonization vs. infection is problematic and diagnostic studies are less sensitive and have not been validated adequately in non-neutropenic patient populations [13]. Recently, Meersseman and colleagues, in a single-center study, investigated the use of bronchoalveolar lavage fluid (BAL) galactomannan testing as a diagnostic modality for ICU patients [40]. Among 110 patients eligible, 29 had proven IA [28]. BAL testing proved to be useful in this population, with sensitivity of 88% and 87%, respectively. Moreover, the sensitivity of serum galactomannan was only 42%. As diagnostic methods for IA improve and additional immunosuppressive agents are developed, an increased incidence of IA in ICU patients should be expected. Important non-traditional ICU patients at risk for IA include those with cirrhosis, COPD, solid-organ malignancy, HIV infection, malnutrition, and post-surgical patients and those on immunosuppressive therapies. Several of these groups will be discussed below.

**Post-operative invasive aspergillosis**

Post-operative IA is an uncommon and underestimated complication of surgery [17,18]. This entity is rare, but approximately 500 cases have been reported to date [17]. Jensen and colleagues estimated an incidence of 2 cases/10,000 surgical procedures [18]. Infection may arise after colonization of surgical sites from airborne Aspergillus spores, and the onset of disease is variable, ranging from days to months after the surgical procedure [17,18]. Because of the rarity of post-operative IA, it has been difficult to determine clinical risk factors. As noted in recent studies, post-operative IA usually occurs among patients without classic predisposing conditions for aspergillosis; however, in some cases, the disease has affected SOT patients and others receiving corticosteroids [17,18]. High-risk procedures appear to be cardiothoracic surgery, vascular surgery, and ophthalmologic or dental surgery. Although the presumed primary source of infection is colonization of surgical sites from airborne Aspergillus spores, it is unclear if elevated Aspergillus spore levels in operating rooms is a risk factor [18,41].

**Patients with COPD**

Among immunocompetent patients there have been increasing descriptions of the importance of COPD as a risk factor or an underlying co-morbidity in patients with IA [4,14,15, 42–44]. From these studies, mostly case reports, single-center case series, or reviews of published cases, it is estimated that up to 10% of cases of IA occur in patients with COPD, and that up to 5% of patients with COPD have IA. Moreover, the risk may have increased over the past decade [13,15,45]. An important limitation in identifying IA in COPD patients is related to the criteria used for diagnosis. Clinical manifestations are often non-specific, and diagnostic criteria have been adapted from standardized guidelines developed for immunocompromised patients [46]. Bulpa and colleagues have developed COPD-specific diagnostic criteria, but these require further validation [14]. Although the true incidence of IA among COPD patients is unknown, a recent single-center study documented a rate of 3.6 cases per 1000 COPD admissions, and determined that COPD was the most common predisposing condition for the development of IA at the hospital, representing 53% of all IA episodes [15]. This study screened COPD patients for IA only if respiratory tract cultures were positive for Aspergillus, perhaps missing cases with IA who did not have positive cultures, and likely underestimating the true rate of IA in the COPD population.

There are few well-controlled studies detailing clinical risk factors for IA among patients with underlying COPD [3,4,15]. Rello and colleagues reported a summary of eight cases and a review of the literature and noted that corticosteroid treatment, usually at daily oral doses of >20 mg of prednisone, and previous antibiotic use were common among IA patients [3]. In several other review articles, late-stage COPD, prolonged steroids, viral infection, and inhaled steroids are suggested as possible risk factors; however, these findings were derived from anecdotal case reports and not controlled studies [45,47,48]. Guinea and colleagues, describing a large retrospective cohort of patients from a single institution, determined four independent risk factors for probable IA among patients with COPD: admission to the ICU (OR 2.4, 95% CI 1.19–5.29); previous antibiotic treatment (OR 2.57, 95% CI 1.2–5.49); and cumulative steroid dose in past 3 months prior to admission (OR 2.98, 95% CI 1.26–7.06) or from admission to diagnosis (OR 2.02, 95% CI 1.2–5.49) [15]. Clearly, there is a great need to identify risk factors for IA among patients with underlying COPD, and larger, adequately powered multi-center studies will be necessary.

**HIV-infected patients**

Invasive aspergillosis is a relatively uncommon infection in patients with acquired immune deficiency syndrome (AIDS), with an incidence rate of 3.5 cases per 1000 person-years [19]. A recent study using 2003 National Inpatient Sample (NIS) administrative data reported that HIV infection was an underlying condition in 3.7% of total aspergillosis cases, with an incidence of 0.43% [49]. Fortunately, it does not appear that the incidence if IA in HIV-infected patients is increasing. In fact, as the population of AIDS patients with
Patients receiving newer immunosuppressive agents

The number of patients receiving immunosuppressive agents has increased over the past decade and is expected to increase substantially in the near future. Newer biologic medicines, including the tumor necrosis factor (TNF)-α inhibitors infliximab, adalimumab, etanercept, certolizumab and golimumab, have been approved for the treatment of one or more of a number of diseases including rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn’s disease, juvenile idiopathic arthritis and ankylosing spondylitis. Moreover, immunosuppressive agents such as abatacept, anakinra and rituximab are used increasingly. TNF-α plays an important role in regulation of the immune response, and use of TNF-α inhibitors is associated with an increased incidence of serious infections caused by a broad spectrum of pathogens, including viral, bacterial, mycobacterial, fungal, and protozoal organisms [20,54,55]. There have been numerous case reports describing IA among patients receiving TNF-α inhibitors, recently summarized by Tsiodras and colleagues [20,56,57]. The authors reviewed published reports from January 1966 through 1 June 2007 to determine the association of fungal infections with TNF-α blockade. The authors identified 64 cases of proven or probable aspergillosis, mostly pulmonary disease in HSCT patients. The most common TNF-α inhibitor was infliximab, used in 75% of cases. Among cases with data available, overall mortality was 82%. Currently, data regarding impact of these agents on risk of IA are limited; however, vigilance in the care of these patients is warranted while studies are ongoing.

Conclusions and future perspectives

There has been much improvement in the care of patients with IA in the past decade. In concert with improved antifungal therapy, newer diagnostic modalities are decreasing the time to diagnosis, and improving the sensitivity of diagnosis of IA. We have benefited from recent research into clinical risk factors for IA, especially the importance of a well-defined risk period among transplant patients. An enormous future challenge will be identification of precise clinical risk factors in non-traditional patient populations, including patients in the ICU setting, those with COPD or HIV-infection and those receiving newer immunosuppressive therapies. Because of the rarity of IA in some of these non-traditional host groups, large, observational studies or case-control studies may be required to elucidate clinical risk factors and will help to focus prevention efforts.

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References

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