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Risk stratification for invasive aspergillosis in immunocompromised patients

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Severe prolonged neutropenia, allogeneic hematopoietic stem cell or solid-organ transplantation, corticosteroids or other T cell suppressive agents, and other severe immunosuppressive factors have for many years been considered to predispose patients to invasive aspergillosis. Other conditions such as impaired innate immunity, diabetes, renal impairment, progression of the underlying malignancy, prior respiratory disease, and nosocomial or environmental exposure to fungal spores or climatic factors have recently been considered additional risk factors of invasive aspergillosis. The multiplicity of risk factors as well as the obvious synergy between them renders risk stratification difficult. An international, large-scale, multicenter, epidemiological study is necessary to develop a risk score.

Keywords: invasive aspergillosis; leukemia; neutropenia; hematopoietic stem cell transplantation; risk factors

Introduction

In spite of more effective prophylaxis strategies, invasive aspergillosis remains the most common invasive fungal disease in allogeneic hematopoietic stem cell transplant recipients and in patients receiving induction or consolidation chemotherapy for acute leukemia.[1,2] With the development of new immunosuppressive therapy such as T cell inhibitors or monoclonal antibodies, patients with other hematological malignancies are now also at risk of invasive aspergillosis.[3,4] Among solid-organ transplant recipients, invasive aspergillosis is the second most common invasive fungal disease following invasive candidiasis.[5]

Invasive aspergillosis is still difficult to diagnose and to treat. Direct (microscopy, culture, histopathology) and indirect (*Aspergillus* galactomannan, β-D-glucan, PCR) confirmatory tests lack sensitivity. Therefore precise knowledge of the host factors predisposing to this infection is critical to suspect the diagnosis and to initiate early therapy before mycological confirmation can be obtained.

Incidence of invasive aspergillosis

Many studies have assessed the incidence of invasive aspergillosis in various groups of patients at risk of opportunistic infections. Table 1 lists the most frequent of these predisposing conditions and the range of incidence reported in the literature.[2,6–32] Incidence rates refer to the main underlying conditions and not to all the other factors associated with either a risk of colonization by the fungi or with a risk of tissue invasion by the pathogens. The impact of the combination of host group, risk of colonization and of the various conditions impairing the host response cannot appropriately be deducted from this table to stratify the risk.

How can we stratify the risk?

Identification of the patient population at risk for invasive aspergillosis may also be approached from the characteristics of patients included in recent major multicenter clinical trials conducted on invasive aspergillosis (Fig. 1).[33,34] Hematological malignancies and hematopoietic stem cell transplantations were the two most frequent underlying conditions,

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Table 1. Identified main underlying conditions predisposing to invasive aspergillosis, reported incidence, and specific patient and treatment-related risk factors[2,6–32]

Underlying conditions	Incidence (%)	Identified specific patient and treatment-related risk factors
Transplantation		
Allogeneic hematopoietic stem cells	2.7–23	Delayed neutrophil engraftment, secondary neutropenia, lymphocytopenia, monocytopenia, cord blood, T cell-depleted or CD34-selected stem cell products, unrelated or mismatched donor graft, acute or chronic graft versus host disease, corticosteroids, CMV disease, respiratory virus infections, renal failure, reduced-intensity conditioning regimen, purine analogs or monoclonal antibodies, history of invasive aspergillosis, iron overload, advanced age, donor toll-like receptor polymorphism
Autologous hematopoietic stem cells	0.5–6[a]	Neutropenia, purine analogs or monoclonal antibodies, lymphoproliferative malignancy as indication for transplantation
Lung or heart-lung	3–26	Airways colonization, single lung transplant, cystic fibrosis as indication for transplantation, rejection and increased immunosuppression, obliterative bronchitis, lymphocytopenia, corticosteroids, CMV disease, renal dysfunction, hypogammaglobulinemia, advanced age
Heart	0.4–15	Airways colonization, reoperation, Lymphocytopenia, corticosteroids, CMV disease, post-transplant hemodialysis, advanced age
Liver	0.7–10	Retransplantation, smoking, CMV disease, dialysis requirement, fulminant hepatic failure as indication for transplantation
Pancreas	1.1–2.9	None identified
Kidney	0.2–1	Graft failure requiring prolonged hemodialysis, lymphocytopenia, corticosteroids, sirolimus ± mycophenolate mofetil, advanced age
Small bowell	0–11	Lymphocytopenia, corticosteroids, CMV disease, renal dysfunction, advanced age
Malignancies		
Acute myeloid leukemia	5–24[b]	Neutropenia, monocytopenia, purine analogs or monoclonal antibodies, advanced age, iron overload, influenza H1N1 virus infection, lack of response to induction chemotherapy
Acute lymphoblastic leukemia	3.8	Lymphocytopenia, corticosteroids, advanced age
Multiple myeloma	2–3	Neutropenia, corticosteroids, advanced age
Non-Hodgkin's lymphoma	0.8	Corticosteroids, purine analogs or monoclonal antibodies, advanced age
Hodgkin's disease	0.4	None identified
Lung cancer	2.6	Stage IV disease, corticosteroids
Other		
AIDS	0–12	<50 $CD4^+$ cells/μL, neutropenia, corticosteroids
Chronic granulomatous disease	20–40[c]	None identified
Burns	1–7	Body surface area burn, full thickness burn, length of hospital stay, older age, inhalation injuries

Continued

Table 1. *Continued*

Underlying conditions	Incidence (%)	Identified specific patient and treatment-related risk factors
Chronic obstructive pulmonary disease with acute exacerbation	1.9	Systemic or inhaled corticosteroids, admission to the intensive-care unit, chronic heart failure, antibiotic treatment received in the three months prior to admission, airways colonization
Systemic lupus erythematous	0.5–2.1	Corticosteroids, other immunosuppressive drugs
Liver failure[d]	5.4	Multiple antibiotic use, frequent invasive procedures
Severe combined immunodeficiency	3.5	None identified

[a]Lower after transplantation of peripheral stem cells compared to bone marrow stem cells.
[b]Lower in acute lymphoblastic leukemia compared to acute myeloblastic leukemia.
[c]Lowered with itraconazole prophylaxis.
[d]Hepatitis B virus-related liver failure.

representing nearly 90% of primary predisposing factors of the host. Solid-organ transplantation, AIDS, and corticosteroid treatment each represented only 3–4% of primary predisposing conditions. Two further open-label studies assessing the efficacy of caspofungin were performed exclusively in patients with a hematological malignancy and in recipients of allogeneic stem cell transplantation.[35,36]

This approach of defining the patient population has certain limitations. In order to exhibit homogeneous patient populations in clinical trials, strict definition criteria are to be applied, with criteria usually based on or adapted from the European Organization for Research and Treatment of Cancer and the Mycosis Study Group (EORTC/MSG).[37] In general, the characteristics of patients included in the clinical trials reflect the inclusion and exclusion criteria, the consensus definition criteria if any exist, as well as the predominant population of patients admitted in the centers selected for the trial.

The real-life clinical setting, however, differs, as a significant proportion of patients seen in our daily practice would not qualify for inclusion in therapeutic clinical trials. In our experience, 22% of subjects in a cohort of 195 patients with documented invasive aspergillosis (probable or proven disease according to the EORTC/MSG definition) would not have been eligible for entry into the two largest clinical trials, notably the voriconazole versus amphotericin B trial

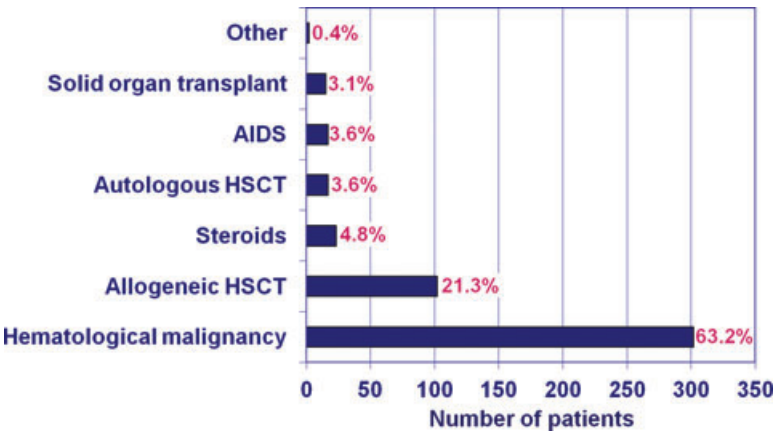

Figure 1. Distribution of primary host factors predisposing to invasive aspergillosis in the voriconazole trial and in the Ambiload trial (total number of patients = 478).[33,34]

and the Ambiload trial.[33,34,38] The main reasons for noneligibility would have been inappropriate renal function, the need for mechanical ventilation, or short life expectancy due to end-stage hematological malignancies (unpublished data). These noneligible patients generally exhibit more severe underlying conditions as well as concomitant single or multiple organ failure, thus creating a different environment for the development of invasive aspergillosis. Due to these comorbidities, these patients also display a poorer prognosis.

Another limitation in qualifying for entry into clinical trials is the lack of host factors, as defined by the EORTC/MSG criteria.[37] While these criteria were designed to help select a homogeneous patient population in clinical trials, they exclude many patients with less typical predisposing factors. As stated in the consensus definition paper, host factor is not synonymous with risk factor. Thus, the lack of host factor may be an exclusion criterion for clinical trials but should not be a reason for deciding to not initiate treatment if clinical, radiological, or mycological data suggest invasive aspergillosis. As an example, in our center, the median duration of neutropenia prior to the first signs of invasive aspergillosis was 16 days in 91 patients with acute myeloblastic leukemia and invasive aspergillosis (unpublished data). However, 36 (40%) patients had neutropenia for less than 10 days before development of the fungal disease and would therefore not have qualified for the definition of possible, probable or proven invasive aspergillosis according to the EORTC/MSG criteria.[37] Nevertheless, the group of patients with a short duration of neutropenia prior to the first signs more frequently suffered from renal impairment, prior respiratory disease, or diabetes. These data strongly suggest that two or more risk factors may precipitate the occurrence of invasive aspergillosis in patients who do not meet the consensus criteria for host factors. This necessitates greater flexibility in these criteria, while seeking to consider a combination of risk factors in the consensus definitions. In an attempt to stratify the risk factors for invasive *Aspergillus* disease, we must distinguish patient-related factors and environmental factors (Fig. 2).

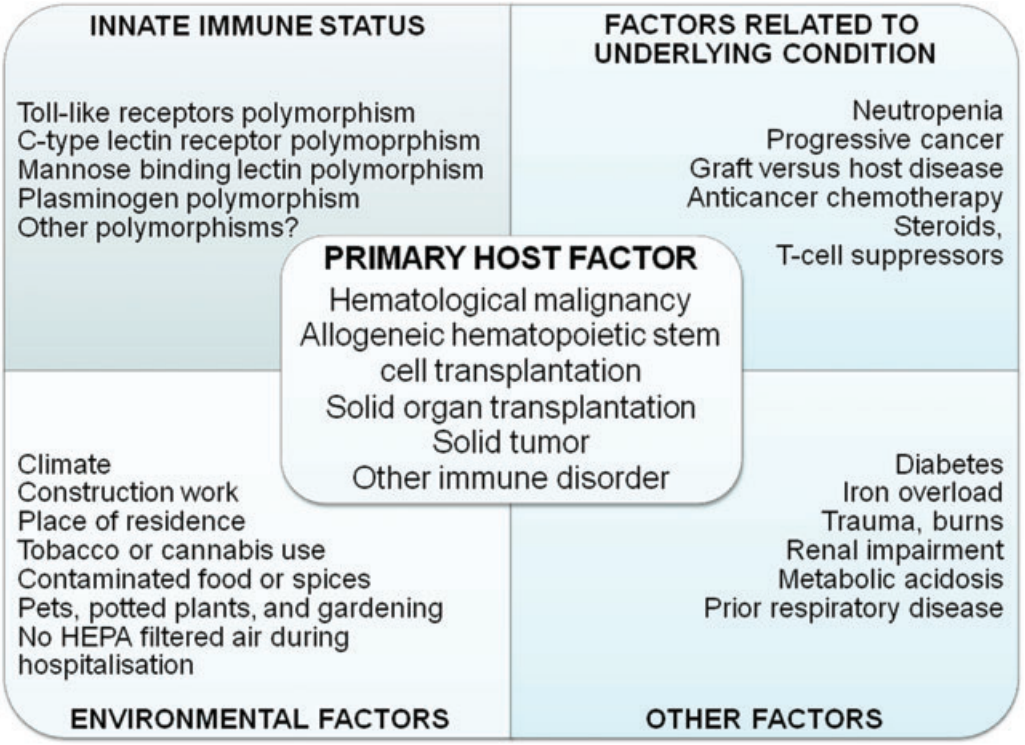

Figure 2. Diagram of the various risk factors affecting the primary host condition.

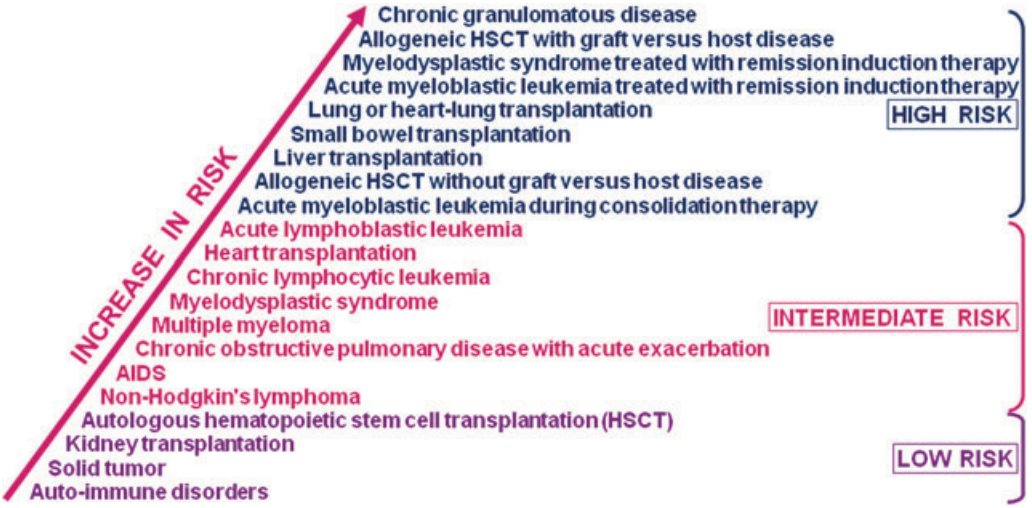

Figure 3. Risk of invasive aspergillosis based on the primary host factor.

Patient-related risk factors

Patient-related risk factors primarily concern the underlying condition, such as allogeneic hematopoietic stem cell transplantation, solid-organ transplantation, prolonged neutropenia occurring in a patient with hematological malignancy or any type of other significant immune disorder (Fig. 3). The treatment given for the underlying disease may be as central as the disease itself. Corticosteroids, T cell suppressors like calcineurin inhibitors (cyclosporine, tacrolimus, sirolimus), monoclonal antibodies with anti-T cell activity (e.g., alemtuzumab), antithymocytes globulins, anti-TNF-α monoclonal antibodies (e.g., infliximab or adalimumab) or other TNF-α inhibitors (etanercept), purine analogs (e.g., fludarabine) are well-known risk factors for fungal diseases in general and invasive aspergillosis in particular.[6,7,37]

The impact of the underlying condition and the type of therapy are affected by other patient-related factors (Table 1). Most critical of these factors are as follows:

- The progression of the hematological malignancy is associated with poor outcome in invasive aspergillosis, while being also likely to lead to an increased risk of developing the disease.[33,38]
- More episodes of fungal infections occur in patients with acute myeloblastic leukemia during remission induction chemotherapy as compared to consolidation chemotherapy.[39]
- Higher bone marrow iron stores increase the risk of invasive aspergillosis in patients with leukemia and in hematopoietic stem transplant recipients.[32] A role of iron overload in increasing the risk of dissemination of the invasive aspergillosis has been suggested in liver transplant recipients.[40]
- Graft versus host disease in allogeneic stem cell transplant recipients requiring an increase in immunosuppressive therapy with or without corticosteroids results in a higher risk of aspergillosis.[41] Corticosteroid-refractory graft versus host disease is a major factor for developing opportunistic infections, including aspergillosis.
- A higher risk of aspergillosis is associated with allograft or renal insufficiency, transplantation or retransplantation for fulminant hepatic failure in liver transplant recipients.[42]
- Neutropenia, prior cytomegalovirus infection, and renal dysfunction are risk factors for aspergillosis in lung transplant recipients.[43]
- Renal impairment possibly also plays a role in patients with acute myeloblastic leukemia (personal unpublished data).
- Prior non-*Aspergillus* respiratory disease (such as chronic obstructive pulmonary disease, pulmonary fibrosis, residual lesion after tuberculosis or sarcoidosis, asthma, lung involvement by the malignancy, prior lung irradiation, recent respiratory virus infection. . .) was found in a high proportion of onco-hematologic

patients with invasive aspergillosis, suggesting that this condition may be a risk factor.[38,44]

- Corticosteroid therapy increases the risk of both bacterial and fungal infections in patients with chronic obstructive pulmonary diseases.[44]
- Diabetes is a well-known risk factor for mucormycosis, although this condition has not been recognized as a risk factor for aspergillosis when occurring alone. In our patient cohort with invasive aspergillosis, diabetes was present in 55 out of 303 patients (18%).[38] This rate of diabetes cases proved to be much higher than that usually encountered among patients admitted to our department of oncology and hematology, suggesting that diabetes is an additional risk factor for aspergillosis in cancer patients.

Innate immunity plays a critical role in the defense against various pathogens, including *Aspergillus* spp., in insects, while its key role has also been recognized in mammals.[45] Pathogen-associated molecular patterns (e.g., mannan, glucan, chitin, DNA, and RNA) are recognized by pattern recognition receptors (PRRs). Polymorphism in PRRs (e.g., Toll-like and C-type lectin receptors) and downstream signaling molecules, such as defensins, chemokines, cytokines, and reactive oxygen species, was reported to be associated with increased or decreased susceptibility to infections, including invasive aspergillosis.[45–47] Several studies confirmed the crucial role of innate immunity in human aspergillosis.[31,48–50]

Environmental risk factors

The patient's environment at home and during hospitalization is likely critical. Outbreaks of invasive aspergillosis were reported during construction work inside or outside of the hospital.[7] The hospitalization of highest-risk patients in units with filtered high-efficiency particulate air, with or without laminar air flow, was shown to efficiently prevent the occurrence of nosocomial invasive aspergillosis. The control of the patient's environment at home proved more difficult. Renovations, gardening, repotting house plants, activities involving exposure to dust that potentially contains fungal spores, and contact with food or spices rich in fungal spores (e.g., pepper) are all contraindicated for highly immunosuppressed patients. While restricting these activities reduces the risk of exposure to a high amount of fungal spores, this does not prevent exposure to low counts of spores in the air, which we permanently face.

A seasonal effect was observed in a large study performed in Seattle, with patients receiving allogeneic hematopoietic stem cell transplantations during the summer being more likely to develop invasive aspergillosis.[51] Climate is known to strongly depend on geography, which may account for the large between-center differences in the incidence of invasive aspergillosis. Changes in global climatic conditions (global warming) may also exhibit an impact, which needs to be further investigated.

Personal habits, such as smoking, increases the risk by exposing the lower respiratory tract to the fungal spores contained in tobacco or cannabis.[52,53] Furthermore, the impact of the residence place, i.e., countryside versus cities or semiurban areas, has not yet been analyzed.

Risk factor or prognostic factor?

Unsurprisingly, several risk factors for invasive aspergillosis are also factors associated with a higher risk of death, the most common being the presence of corticosteroid-refractory graft versus host disease in allogeneic hematopoietic stem cell transplant recipients, severe prolonged neutropenia in leukemia patients, progression of the underlying malignancy, and corticosteroid exposure.[38,54] Impaired renal function or prior respiratory disease is very likely also a risk and prognosis factor.[38,55]

Impact on therapeutic strategies and conclusion

The early initiation of antifungal therapy is the most critical factor toward a favorable outcome. Initiating treatment as preemptive therapy prior to the mycological documentation of the disease (possible invasive aspergillosis according to the EORTC/MSG consensus criteria as opposed to probable or proven invasive aspergillosis) was reported to significantly improve the 12-week survival rate.[38] Risk stratification helps identify the patients likely to suffer from invasive aspergillosis, even if they do not present the classical risk factors, as defined in the guidelines or clinical trials. However, the multiplicity of risk factors identified in patients with invasive aspergillosis as well as the obvious synergy between these factors renders the stratification of risk factors

more difficult. International, large-scale, multicenter, epidemiological studies with the inclusion of environmental and climatic conditions are necessary in order to elaborate a risk score.

Conflicts of interest

The authors declare no conflicts of interest.

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