

Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients

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Invasive fungal diseases are important causes of morbidity and mortality in immunocompromised patients. Patients with haematological malignancies and solid cancers, as well as those with allogeneic haematopoietic stem cell and solid organ transplants, are at high risk of developing such an infection. Many fungi can cause invasive disease, with *Aspergillus* spp. and *Candida* spp. being the prevalent fungal pathogens infecting susceptible patients. During the past few years, rare moulds (for example Zygomycetes and *Fusarium* spp.) have come into focus as the cause of devastating clinical disease. This review aims to analyse environmental factors and parameters related to impairment of the immune system that are thought to favour the onset of invasive mould infections. Some moulds are quite common among all categories of patients, while others appear to be limited to a given subset of patients, such as allogeneic haematopoietic stem cell or solid organ transplant recipients. In addition to an exploration of factors that predispose patients to the acquisition of an invasive mould infection, prognostic factors that help to predict the eventual outcome of these infections are identified.

Keywords: moulds, immune system, environment, risk factors, prognostic factors

Introduction

Fungi are opportunistic pathogens that can cause infections that evolve into invasive disease in critically ill patients as a result of the concurrence of multiple predisposing factors. An impaired immune system and exposure to filaments or spores in the environment are the most important factors. Until a few years ago, *Candida* spp. were held responsible for the majority of fungal infections, but over time a shift in the prevalent pathogens has been observed. At present, the majority of invasive fungal diseases (IFDs) in severely immunocompromised patients are attributed to moulds.^{1–3}

Many different fungi, including *Aspergillus* spp., Zygomycetes, *Fusarium* spp., *Scedosporium* spp. and *Acremonium* spp., have been associated with invasive mould diseases (IMDs), with invasive aspergillosis (IA) being the predominant infection.

Various studies involving large numbers of patients have identified categories of patients who are at high risk of IA and other IMDs, namely patients undergoing treatment for haematological malignancies, notably acute myeloid leukaemia (AML), and those who have undergone allogeneic haematopoietic stem cell transplantation (HSCT); those who have received a solid organ transplant (SOT); and a variety of patients with other severe immunosuppressive conditions.^{2–11} Table 1

summarizes the risk level for each category of immunocompromised patients at risk of IMD.

Risk factors

Genetic risk factors

In recent years it has been hypothesized that genetic variation within key innate or adaptive immune response genes may influence susceptibility to, as well as the outcome of, IFD.¹² Indeed, recent studies have demonstrated the possibility of a genetic predisposition to the onset of IFD when immune defences fail [for example, interleukin-10 (IL-10) production, Toll-like receptor (TLR) polymorphism and polymorphism in the plasminogen gene].^{12–18}

The production of IL-10, a cytokine that exerts regulatory activity in the inflammatory response, and that of tumour necrosis factor- α (TNF- α) has a role in the development of IA. It has been shown that patients with the ACC haplotype, which is associated with decreased IL-10 production, have a 9-fold lower risk of developing IA compared with control patients who have unaffected IL-10 production. Conversely, among those with the ATA haplotype (associated with increased IL-10 production) a significantly higher incidence of IA has been

Table 1. Stratification of immunocompromised patients in risk categories for invasive fungal disease according to incidence and mortality rates obtained from current literature^{2-7,9-11}

Low risk	Intermediate risk	High risk
autologous HSCT	acute lymphoblastic leukaemia	acute myeloid leukaemia (above all in first induction)
Hodgkin's lymphoma	chronic lymphocytic leukaemia	allogeneic HSCT (particularly with cord blood source)
chronic myeloproliferative disorders (CML and Ph- diseases)	lymphoma	heart, lung, liver transplantation
solid cancer	COPD	
myeloma	AIDS	
kidney transplantation	myelodysplastic syndromes	
chronic immunological disease		
systemic lupus erythematosus		

CML, chronic myeloid leukaemia; COPD, chronic obstructive pulmonary disease; Ph-, Philadelphia negative.

noted.¹³ TNF- α production is considered to be genetically determined in >60%–70% of cases; this factor may explain, at least in part, the interindividual differences in the risk of acquiring IFD in patients who undergo equally immunosuppressive treatment regimens.¹⁴

TLRs are transmembrane proteins expressed on the surface of immune cells, and they interact with several adaptor proteins to activate transcription factors, resulting in the production of inflammatory cytokines and the activation of adaptive immunity. Various polymorphisms in TLRs are thought to be allied to an increased risk of IFD. Meticulous attention has been paid to polymorphisms of TLR2 and TLR4 (gene haplotype S4). The absence or weakness of the signal in epithelial cells, not activated by TLR2 and TLR4 that are genetically abnormal, can lead to an increased risk of acquiring IA.^{14,15}

Similar observations have been reported in the presence of polymorphisms in TLR1 and TLR6.¹⁶ Other genetic factors that have been linked with increased susceptibility to IA are polymorphisms in the plasminogen gene and the mannose-binding lectin gene.^{17,18}

Risk factors related to the environment

Aspergillus spp., Zygomycetes and other moulds are ubiquitous saprophytes present in air, soil and water; therefore, exposure to these agents is almost universal. The primary mode of acquiring a mould infection is inhalation of fungal spores. After inhalation, spores are deposited in the mucous membranes of the upper and lower respiratory tract, and this may lead to pulmonary or sinus infection in extremely susceptible immunocompromised patients. Sources of potentially pathogenic fungi can be found both outside and inside the hospital walls. The epidemiology of mould infections, especially IA, that originate from the environment is influenced by meteorological conditions, which vary in regions of endemicity. Data from surveys indicate a high incidence of IA just after seasonal periods of dry weather with high temperatures (summer and autumn).^{19,20} In addition to the weather conditions, other predisposing factors, such as personal habits or lifestyle, have to be taken into account because a substantial number of patients who are diagnosed with haematological malignancy are already colonized at the time of the first clinical manifestation of their underlying

disease. Patients suffering from AML who smoke cigarettes ($P < 0.05$), live in the countryside ($P < 0.05$) or have been exposed to high concentrations of fungal spores ($P < 0.05$) have been found to be at increased risk of developing IFD.²¹ Likewise, farmers who inhale large quantities of mycotoxins, endotoxins and other toxic chemicals from contaminated silage have an increased risk of developing pulmonary mycotoxicosis.²² In consequence, such colonized patients are prone to developing IA when immune defences become deficient as a result of the treatment of the underlying haematological malignancy or subsequent immunosuppressive therapy. In the majority of environment-related cases, IFD constitutes a nosocomial infection. A recent review of 60 outbreaks of IA demonstrated that most resulted from contamination of the air due to building activities in the hospital.²³ Even reconstruction at sites remote from the patient's accommodation may increase the risk of infection. Malfunction or contamination of hospital ventilation systems without high-efficiency particulate air filters has also been reported as a cause of infection.^{24,25} Other possible sources of spores include potted plants, flowers and carpets, as well as water supplies, because spores present in the water are released during showering (Table 2).^{26,27}

Recent studies demonstrated also that dectin-1 deficiency is a novel susceptibility factor for aspergillosis in high-risk patients and identifies a previously unsuspected role for dectin-1 in anti-fungal immunity.²⁸

Risk factors related to the immune system

Neutropenia and impaired cell-mediated immunity are the most prominent defects in the immune system that predispose individuals to mould infections. The role of neutrophils in the control of fungal infections is fundamental. These cells are essential in the initiation and execution of the acute inflammatory response and subsequent resolution of infiltrates caused by the fungal infection. Usually neutrophils, together with monocytes/macrophages, internalize resting or swollen conidia, and use mechanisms such as respiratory burst to combat the growth of fungal elements in the body. A generally accepted tenet that also applies to IFD is that the longer and the deeper the neutropenia, the higher the incidence of serious infections. In 1966, Bodey²⁹ demonstrated that the frequency of infections

Table 2. Environmental risk factors

Risk factor	Reference(s)
Seasonal incidence	18,19
Weather variation	18,19
temperature	18,19
rainfall	18,19
humidity	18
wind speed	18
Personal habits	20,21
smoking	20
living in countryside	20
fungus exposure	20
type of work (e.g. farmer, agriculture)	21
Exposure outside	20–22
pets	
dusty household	20
construction work	
Exposure inside	22–26
potted plants	25
absence of HEPA-filtered rooms	22,23
water	26

HEPA, high-efficiency particulate air.

in patients with acute leukaemia was related to the levels of circulating leucocytes, more specifically neutrophils, and that the prevalence of all types of infection was inversely related to the level of neutrophils. The most important factor in predicting the risk of infection was actually the duration of neutropenia. If neutropenia persisted for 3 weeks, the risk of developing an infection, including those caused by fungi, was 60%, with a further rise to 100% when the neutrophil count dropped to levels of $<0.10 \times 10^9/L$. However, not only is the incidence of infections related to neutrophil count, but the outcome of bacterial and fungal infections also appears to be dependent on the evolution of the neutrophil count, with the highest fatality rate among patients with long-standing severe neutropenia ($<0.10 \times 10^9/L$). Recent studies have corroborated these classic observations.³⁰

The most common causes of neutropenia are cytotoxic or radiation therapy for a malignancy, but it may also be associated with autoimmune diseases, HIV infection, myelodysplastic syndromes, aplastic anaemia and drug-related bone marrow toxicity. In particular, patients affected by AML are considered to be at the highest risk. These patients develop neutropenia as a result of invasion of their bone marrow by leukaemic cells, as well as through the use of myeloablative cytotoxic therapy. Not only do patients with AML have a reduced number of neutrophils, but the function of the few remaining cells is usually debilitated, often due to a possibly coexisting myelodysplasia. A recent study has revealed that, in comparison with normal controls, dysplastic neutrophils display a lower fungicidal activity against yeasts and, presumably, moulds.³¹

It has become clear that it is not only neutropenia that must be seen as a factor that predisposes to IFD: lymphocytopenia

occurring after an allogeneic transplant procedure is another pertinent risk factor.³²

Drugs used to treat the underlying disease or its complications enhance the risk of IFD in immunocompromised patients. For example, steroids are a well-known major risk factor for the development of IFD. They suppress the ability of monocytes/macrophages to kill conidia through inhibition of non-oxidative processes and impairment of lysosomal activity.³³ Moreover, steroids inhibit polymorphonuclear cells in their chemotaxis, oxidative bursts and activity against hyphae. This may be an important trigger for the emergence of clinically relevant IA. For example, *in vitro* in the presence of hydrocortisone, *Aspergillus fumigatus* has an increased doubling time of 48 min.³⁴ Generally, steroids suppress macrophages, whereas cytotoxic chemotherapy decreases neutrophil numbers as well as their function. Furthermore, recent studies have shown that not only are the dose levels used important, but so is the duration of treatment.³⁵ Treatment regimens that involve new anti-neoplastic or immunosuppressive agents, particularly purine analogues (e.g. fludarabine) and antibodies targeted against T lymphocytes (anti-CD52 monoclonal antibodies, anti-thymocyte globulins, anti-CD3 monoclonal antibodies), are also thought to enhance the risk of IFD. These agents may not only cause a transitory deep neutropenia, but also induce prolonged lymphocytopenia with an inherent long-lasting impairment of cell-mediated immunity.^{36,37} Similarly, TNF- α blockade therapy (using anti-TNF monoclonal antibodies, e.g. etanercept) has been associated with the occurrence of IA in allogeneic HSCT recipients as well as in non-haematological patients who suffer from autoimmune diseases, such as rheumatoid arthritis or Crohn's disease.³⁸

Recently, the important role of iron overload in the emergence of IFD has been highlighted. Iron overload is seen in heavily transfused patients, such as patients with full-blown AML after a long episode of pre-existing myelodysplasia, or recipients of an allogeneic HSCT in whom erythropoiesis was slow to recover.^{39,40} Laboratory investigation has revealed that iron is essential for the growth and virulence of moulds. Moreover, high levels of free iron may enhance mucosal damage and may impair cellular antimicrobial systems. Kontoyiannis *et al.*³⁹ evaluated the bone marrow iron stores as a marker of iron overload and found a significantly higher proportion of patients with high bone marrow iron stores among the population with IA. Deferoxamine may be used to reduce the iron overload in these patients, but the benefit of this intervention is not obvious. In fact, some Zygomycetes, for instance *Rhizopus* spp., utilize this iron chelator as a siderophore to get access to previously unavailable iron, and subsequently the increased iron uptake by the fungus is linearly correlated with its growth.⁴¹ On the other hand, newer iron chelators, such as deferiprone and deferasirox, do not deliver iron to the fungus, and the use of these drugs in patients with an iron overload has been associated with improved fungicidal activity against Zygomycetes *in vitro*.⁴²

Some risk factors are specific to a limited group of patients, such as allogeneic HSCT recipients or those who have undergone SOT. Usually these procedures involve a prolonged period of immunosuppression in order to facilitate engraftment. Unfortunately, the drugs utilized for this purpose, as well as the transplant procedure itself, create circumstances that favour the onset of IFD. It is recognized that the type of transplant is

pivotal. For instance, the incidence of IFD in allogeneic HSCT recipients is very different from that found in patients who have undergone autologous transplantation.^{3,43}

The source of stem cells for allogeneic transplantation also has some bearing on the risk of IFD. Patients who are transplanted with stem cells harvested from cord blood are considered to be at higher risk; some authors report an IFD incidence of between 30% and 40% after such transplants.^{44,45} It is noteworthy that risk factors do differ depending on the time after a transplant procedure: an early (within the first 30 days of the procedure) and a late (after 100 days) phase can be distinguished. The early phase after an allogeneic HSCT is characterized by a low leucocyte count and a damaged mucosal barrier, and this implies that the main risk factors are neutropenia, lymphocytopenia and mucosal damage that can be aggravated by acute graft-versus-host disease (GvHD). During the late phase, impairment of cellular and humoral immunity usually prevails, supplemented by other risk factors that are related to chronic GvHD, relapsing underlying malignancy, cytomegalovirus infection and administration of steroids or immunosuppressant agents (e.g. sirolimus, ciclosporin and infliximab).^{8,32,46–48} Of note, if a patient acquires IA during pre-transplant conventional chemotherapy, the risk of recrudescence when a patient subsequently undergoes HSCT is extremely high.⁴⁹ Different risk factors have been identified for SOT patients. In general, the incidence of IFD in these patients is lower than in allogeneic HSCT recipients. IA has been observed mainly in lung and heart transplant recipients.^{6,7} In a large series of 153 cases of IA in SOT recipients, Gavalda et al.⁵⁰ classified the use of vascular amines, haemodialysis, more than one episode of bacterial infection and cytomegalovirus infection as risk factors for early IA after renal transplantation. Age over 50 years, relapsing bacterial infections, a relapsed malignancy and chronic graft rejection represent the most prominent risk factors for late IA.

The main immune system factors influencing the onset of IFD in each type of immunocompromised patient are listed in Table 3.

Risk factors for moulds other than *Aspergillus*

The factors that promote the onset of mould infections other than those due to *Aspergillus* do not differ from those that are held responsible for the emergence of IA, the most important factor being impairment of the immune system (Table 3).

Zygomycosis is relatively rare but is seen with increasing frequency as the population at risk of IFD continues to grow. Patients who are treated for a haematological malignancy and allogeneic HSCT recipients are highly susceptible to these fungal infections. They represent the third leading cause of invasive fungal infections after *Aspergillus* spp. and *Candida* spp.²

Although several medical conditions have been associated with an increased risk of zygomycosis, two major factors clearly stand out, namely qualitative or quantitative defects in the phagocytic cells, and metabolic acidosis. As in all other IFDs, neutropenia represents a prominent risk factor for zygomycosis, while metabolic acidosis, which is frequently observed in ketoacidotic diabetes, constitutes a rather exceptional risk factor. Metabolic acidosis interferes with the ability of transferrin to bind iron, and this leads to high iron levels in tissue. High tissue levels of iron may enhance the growth of Zygomycetes, if they

are present. In addition, high concentrations of iron inhibit neutrophil chemotaxis and reduce their capacity for adhesion to hyphae.⁵¹

It has been suggested that the use of voriconazole could be a possible risk factor for the inception of zygomycosis, since an increased incidence of this fungal disease has been reported after prophylactic use of this compound, particularly in allogeneic HSCT recipients.^{52,53} However, recent prospective randomized studies, comparing prophylaxis with voriconazole and other azoles in a large series of allogeneic HSCT patients, did not show a significant increase in the incidence of zygomycosis.⁵⁴

Regarding fusariosis and scedosporiosis, the risk factors for their emergence are identical to those observed for IA.^{55–57} Neutropenia plays the key role in patients with haematological malignancies treated with conventional chemotherapy, while acute and chronic GvHD are the main risk factors in allogeneic HSCT recipients.

Risk factors for specific immunocompromised settings

In an evaluation of the risk factors for IFD in medical intensive care units (ICUs) in which most patients did not have haematological malignancies, chronic obstructive pulmonary disease (COPD) and liver failure were recognized as the main risk parameters. A recent study underlined that, in general, COPD may be an important additional risk factor in immunocompromised patients.^{58,59}

Mould infections are uncommon among AIDS patients, and since the introduction of effective antiretroviral treatment they have become even rarer. CD4 lymphocyte counts of <50 cells/mm³, neutropenia and steroid treatment are the most important factors to predict the onset of IA.⁶⁰

Prognostic factors

During the past few years, various studies have been performed in an attempt to identify the main prognostic factors that could help to forecast the outcome of mould infections. As is the case for risk factors that determine proneness to the disease, the key role is played by a defect in the immune system (Table 4). As a general rule, formulated on the basis of various studies, it can be stated that allogeneic HSCT recipients, patients not in remission of their malignancy and individuals with an uncontrolled disseminated disease will have the worst outcome if they have to be treated for IA.

In patients with haematological malignancy treated with conventional chemotherapy, the role of neutropenia is clear. Prolonged neutropenia caused by the lack of recovery of granulocytopenia after chemotherapy is strongly correlated with a poor prognosis.^{61–63} Usually, the lack of neutrophil recovery is due to progression of underlying malignancy that is unresponsive to chemotherapy. An increasing burden of leukaemic cells in the bone marrow will prohibit a return of normal neutrophils.^{61,62} Indeed, it has been reported that progression of underlying malignancy is more indicative than neutrophil recovery as such in the prediction of attributable mortality in patients with IA.⁶³ Recovery to adequate numbers and normal function of the neutrophils are also extremely important factors for a favourable outcome of IA in allogeneic HSCT recipients.^{46,62–66} Like neutrophils, monocytes are components of the cellular defence system; therefore, it is not surprising that in various statistical

Table 3. Common risk factors for IFDs observed in the different groups of patients (including aspergillosis, zygomycosis, fusariosis)

	Neutropenia depth and duration	Monocytopenia	Lymphocytopenia	Steroids	Iron overload	GvHD	CMV infection	Purine analogue or monoclonal antibodies	Renal failure	Advanced age
Haematopoietic transplantation										
allogeneic HSCT	+	+	+	+	+	+	+	-/+	+	+
autologous HSCT	-	-	-	+	-	-	-	-/+	-	-
Solid organ transplantation										
lung or heart- lung	-	-	+	+	-	+	+	-	+	+
small bowel	-	-	+	+	-	+	+	-	+	+
kidney	-	-	+	+	-	+	+	-	+	+
liver	-	-	+	+	-	+	+	-	+	+
heart	-	-	+	+	-	+	+	-	+	+
Haematological malignancy										
acute myeloid leukaemia	+	+	-	-	+	-	-	+	-	+
acute lymphoid leukaemia	-	-	+	+	+	-	-	-	-	+
multiple myeloma	-	-	-	+	-	-	-	-	-	+
Non-Hodgkin's lymphoma	-	-	-	+	-	-	-	+	-	+
Hodgkin's disease	-	-	-	+	-	-	-	-	-	+
chronic myeloid leukaemia	-	-	-	-	-	-	-	-	-	+
chronic lymphoid leukaemia	-	-	+	-	-	-	-	+	-	+
solid tumour	-	-	-	-	-	-	-	-	+	+
AIDS	-	-	-	-	-	-	-	-	-	-
chronic immunological disease	-	-	-	+	-	-	-	-	-	-

CMV, cytomegalovirus.

Table 4. Prognostic factors in the different categories of patients for different IMDs

	Neutropenia recovery	Monocytopenia	Uncontrolled underlying malignancy	Steroid administration	Probable or proven versus possible IA	Uncontrolled graft-versus-host disease	Disseminated disease (including CNS)	Renal failure	Prior respiratory disease
Haematopoietic transplantation									
allogeneic HSCT	+	+	+	+	+	+	+	+	+
autologous HSCT	+	-	-	-	+	-	+	-	-
Solid organ transplantation									
lung or heart- lung	-	-	-	+	+	+	+	+	+
small bowel	-	-	-	+	+	+	-	-	-
kidney	-	-	-	+	+	+	-	-	-
liver	-	-	-	+	+	+	-	+	-
heart	-	-	-	+	+	+	-	+	+
Haematological malignancy									
acute myeloid leukaemia	+	+	+	-	+	-	+	+	+
acute lymphoid leukaemia	-	-	+	+	+	-	+	-	+
multiple myeloma	-	-	+	-	-	-	+	+	+
Non-Hodgkin's lymphoma	-	-	-	+	-	-	+	-	-
Hodgkin's disease	-	-	-	+	-	-	-	-	-
chronic myeloid leukaemia	-	-	+	-	-	-	+	-	-
chronic lymphoid leukaemia	-	-	+	-	-	-	+	-	+
solid tumour	-	-	-	-	-	-	-	+	+
AIDS	-	-	+	-	-	-	+	+	+
chronic immunological disease	-	-	-	+	-	-	-	+	-

models a low monocyte count is correlated with a poor outcome, especially in allogeneic HSCT patients.⁶⁶ In the light of this, it is not surprising that the use of steroids, which can inhibit neutrophil chemotaxis, oxidative bursts and antihyphal activity, is correlated with a substantial negative impact on the prognosis of transplant recipients with IA.^{63,65,66}

Other well-established negative prognostic factors, underlined by all authors, are disseminated disease (particularly when CNS involvement is observed) and proven IFD.^{62–66} Dissemination of IA is correlated with serious impairment of the immune defence systems, which are obviously unable to control the progression of the life-threatening infection. Some authors have hinted at a possibly unfavourable outcome of IA in patients who have been transplanted with stem cells harvested from peripheral blood compared with bone marrow-derived stem cells, but the mechanism behind this putative difference remains obscure.⁶⁴

In a recent report from the University of Seattle,⁶⁵ 405 cases of proven/probable IA in allogeneic HSCT recipients were analysed in order to detect the main prognostic factors for outcome. In general, that study corroborated earlier observations, and renal and liver insufficiency were added as parameters suggestive of a poor outcome. The conclusion of the authors from Seattle has been confirmed by a recent Transplant-Associated Infection Surveillance Network (TRANSNET) study on 415 allogeneic HSCT recipients.⁶⁶ Moreover, TRANSNET extended the findings to SOT recipients. Renal insufficiency and liver insufficiency are markers of organ failure and signify that the patient is severely ill; multiple co-morbidities will limit the potential of antifungal therapy.

In allogeneic HSCT recipients, both acute and chronic GvHD are instrumental in the onset of IFD, although they do not seem to have an impact on the outcome of IFD.^{62–66} However, when uncontrolled GvHD coincides with IA, the prognosis will be dismal, as suppression of the host defence mechanisms to control GvHD will be inevitable and devastating.^{46,65}

Besides HSCT itself, high doses of steroid and proven infection are also regarded as ominous prognostic factors in SOT recipients, while the type of organ transplant, notably liver or lung, and malnutrition play a marginally negative role.⁶⁶

In addition to factors associated with the host immune system, other parameters that refer to clinical practice can influence the outcome of IFD. An appropriate therapeutic approach is correlated with a better prognosis in all patients. Treatment with voriconazole or lipid amphotericin B is correlated with an improved prognosis in all statistical models for the assessment of outcome of IA.^{62–66} However, recent studies have hinted at acquired azole resistance by some *Aspergillus fumigatus* isolates. So far, this phenomenon is only an *in vitro* laboratory finding of low prevalence without any clinical counterpart, but, if it were to be accompanied by clinical resistance, its presence would imply a potential adverse prognostic factor.⁶⁷ Another decisive factor is treatment delay, i.e. the time that elapses between suspicion of the diagnosis and the initiation of an effective antifungal therapy. The importance of early institution of appropriate therapy has been well demonstrated in a retrospective survey of treatment of patients with zygomycosis.⁶⁸ Interestingly, an analysis of 88 immunocompromised patients with IA suggested that the mortality rate was higher among non-neutropenic patients than among neutropenic patients.⁶⁹ The authors

hypothesized that this was probably because the non-neutropenic patients may have been monitored for IA less closely than their neutropenic counterparts, and that this, in turn, led to suboptimal management and delayed antifungal therapy. However, it is tempting to speculate that non-neutropenic patients who develop aspergillosis may suffer from severe immunosuppression that is more difficult to diagnose and control, from which recovery might be difficult or impossible.

A recent study evaluated persistently high serum galactomannan levels during antifungal treatment as a predictive index of poor outcome in patients with proven/probable galactomannan-positive IA.⁷⁰ The authors concluded that the course of the galactomannan decay is indicative of the eventual outcome, independent of other, more traditional, risk factors for mortality. Some opinion leaders argue that the level of galactomannan could serve as a surrogate endpoint in future antifungal therapeutic trials.

Prognostic factors for other mould infections

Factors that determine the outcome of infections by other, more obscure, moulds, such as those causing zygomycosis, fusariosis and scedosporiosis, do not differ from the factors in patients with IA (Table 4). Uncontrolled underlying disease, proven zygomycosis, lack of neutrophil recovery, severe lymphopenia, use of steroids and delay in targeted therapy are correlated with a poor prognosis.⁶⁸ Another potential adverse prognostic factor is the failure to perform aggressive surgical debridement when possible. Low albumin levels, fungaemia, the need for admission to an ICU and, most of all, persistent neutropenia and use of steroids have been found to be prominent predictors of mortality in patients with fusariosis.^{55,56}

In a recent review, all parameters that might influence the outcome of infections due to *Scedosporium* spp. were analysed and produced no surprises. As for all IFDs, uncontrolled malignancy, disseminated disease, lack of recovery from neutropenia and treatment with potent immunosuppressive agents were heralds of a poor prognosis.⁷¹

Conclusions

Various cofactors may influence the onset and the outcome of mould infections. In addition to well-defined parameters, such as neutropenia, new factors that need our attention, including genetic predisposition and iron overload, have been added in recent years. Correct identification of the main risk factors for developing an IFD is essential in the evaluation of patients to allow timely institution of appropriate antifungal therapy in this vulnerable group.

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