Timing of treatment for invasive fungal disease (IFD) is critical for making appropriate clinical decisions. Historically, many centres have treated at-risk patients prior to disease detection to try to prevent fungal colonization or in response to antibiotic-resistant fever. Many studies have indicated that a diagnostic-driven approach, using radiological tests and biomarkers to guide treatment decisions, may be a more clinically relevant and cost-effective approach. The Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) defined host clinical and mycological criteria for proven, probable and possible classes of IFD, to aid diagnosis. However, some patients at risk of IFD do not meet EORTC/MSG criteria and have been termed Groups B (patients with persistent unexplained febrile neutropenia) and C (patients with non-definitive signs of IFD) in a study by Maertens et al. (Haematologica 2012; 97: 325–7). Consequently, we considered the most appropriate triggers (clinical or radiological signs or biomarkers) for treatment of all patient groups, especially the unclassified B and C groups, based on our clinical experience. For Group C patients, additional diagnostic testing is recommended before a decision to treat, including repeat galactomannan tests, radiological scans and analysis of bronchoalveolar lavage fluid. Triggers for stopping antifungal treatment were considered to include resolution of all clinical signs and symptoms. For Group B patients, it was concluded that better definition of risk factors predisposing patients to fungal infection and the use of more sensitive diagnostic tests are required to aid treatment decisions and improve clinical outcomes.

Keywords: diagnostic-driven therapy, immunocompromised patients, radiological triggers, galactomannan test

Introduction

Patients with haematopoietic malignancies and those patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) are at high risk of contracting invasive fungal disease (IFD). IFD may be considered to develop over three phases, beginning with colonization, progressing to infection and, finally, leading to manifestation of disease symptoms in the patient. A key consideration for the management of IFD is deciding which point is optimal for clinical intervention. For >50 years, a common treatment strategy has been to treat patients at risk of IFD at the point where they are potentially colonized with a possibly pathogenic fungus. Treatment may take the form of prophylaxis for patients at risk of IFD but without attributable signs and symptoms, or empirical treatment for those with antibiotic-resistant fever but without microbiological documentation, who may or may not have established clinical signs and symptoms. A number of trials have suggested that prophylactic treatment reduces the incidence of IFD and fungal deaths, but only two studies have demonstrated a significant impact on overall mortality. Slavin et al. found that fluconazole improved survival at day 110 in patients with fungal infections after bone marrow transplants and posaconazole was found to improve overall survival in patients with IFD who were undergoing chemotherapy for acute myelogenous leukaemia or myelodysplastic syndrome. A diagnostic-driven or pre-emptive approach, using clinical biomarkers and radiological imaging to detect early infection, has been found in many studies to be more effective, both clinically and in containing costs, although this approach is only applicable in centres where the appropriate equipment and expertise are available. When considering management approaches for high-risk patients with IFD, a combination of triggers for treatment should be used rather than individual ones and these will differ depending on the centre and country.

The Invasive Fungal Infections Cooperative Group of the European Organisation for Research and Treatment of Cancer/Mycoses Study Group
Group (EORTC/MSG) has published standard definitions for IFD to aid diagnosis for clinical and epidemiological research.\textsuperscript{11}

These definitions assign three levels of certainty to the diagnosis of IFD in immunocompromised patients with haematological malignancies and recipients of HSCT, namely proven, probable and possible. The clinical and mycological criteria for each of these categories are clearly defined. For proven IFD, fungal elements must be detected by direct tests on tissue or normally sterile fluids, e.g. by microscopy or by recovering the fungus by culture, but not from bronchoalveolar lavage (BAL) fluid obtained by bronchoscopy as this is not considered sterile. Cases of probable IFD require the presence of a host factor (such as neutropenia and allogeneic HSCT), together with clinical features and mycological evidence. For example, the clinical features of lower respiratory tract IFD include the presence of specific imaging signs (dense, well-circumscribed lesions, with or without a halo sign, air-crescent sign or cavity) on a CT scan.\textsuperscript{11,12} In this case, direct mycological evidence can include detection of fungal elements or recovery of a mould by culture from sputum or BAL fluid.\textsuperscript{11} Indirect tests that detect antigen or cell wall constituents of the fungus, such as the galactomannan (GM) antigen from plasma, serum, BAL fluid or CSF for aspergillosis, are also considered sufficient mycological evidence for this patient category. PCR tests for fungal elements are also being more widely used as indirect tests.\textsuperscript{13,14} but, as yet, PCR is neither validated nor standardized.\textsuperscript{15} To be diagnosed as having possible IFD, patients should have appropriate host factors and clinical signs of IFD, including typical radiological signs, but with no mycological evidence.

These definitions have proved invaluable for clinical trials, but in the real world there are a number of groups of patients who may be suspected of having the early stages of IFD but who do not meet the EORTC/MSG criteria. For example, patients with a positive biomarker, e.g. the GM test, but no clinical symptoms or radiological signs of IFD. Maertens et al.\textsuperscript{16} further categorized these unclassified patient groups on a sliding scale of increasing likelihood of IFD that also includes the EORTC/MSG categories, creating Groups A–E (where A is no evidence of IFD), to aid the development of strategies for patient management (Table 1). This also emphasized the importance of determining the optimal triggers (clinical or radiological signs or biomarkers) for either further diagnostic tests or treatment in these patient groups. Other important considerations include which biomarkers should be used and the timing of diagnostic investigations or treatment. In this article, we discuss what might be appropriate triggers for driving treatment of patients potentially suffering from IFD in Groups B–E and whether they should be used in combination or sequentially, based on our experience of clinical practice. Patients in Group A are dealt with in the preceding article by Akan et al.\textsuperscript{17} in this Supplement.

**Empirical therapy in high-risk patients with persistent febrile neutropenia (Group B)**

Group B includes high-risk patients with persistent unexplained febrile neutropenia, despite treatment with broad-spectrum antibiotics, and negative mycology results, in whom fungal infection cannot be ruled out by any current clinical or mycological criteria. Empirical antibacterial therapy for febrile neutropenia has dramatically improved outcomes in these patients. In contrast, the difficulty in diagnosing fungal infection can cause delays in effective antifungal therapy, resulting in increased mortality.\textsuperscript{13,18} so the concept of empirical antifungal therapy with amphotericin B was developed.

Empirical amphotericin B therapy has been the standard of care in febrile neutropenic patients since the early 1980s. Its conceptual basis was established by the seminal study by Pizzo et al.\textsuperscript{19} in which, among other things, the effectiveness of empirical amphotericin B therapy was evaluated among patients whose fever and neutropenia persisted, despite ≥ 7 days of therapy with appropriate antibiotics. In this analysis, 6/16 patients who continued antibacterial therapy alone and 2/18 patients who continued antifungal therapy plus amphotericin B developed an infection. In the first group, five out of six infections were fungal, as were one out of two in the second group. Analysis of the post-mortem records of deceased patients revealed that when therapy with amphotericin B was initiated after 1 week of broad-spectrum antibacterial therapy, there was only one death due to fungal infection.\textsuperscript{18}

In 1989, the Invasive Fungal Infections Cooperative Group of the EORTC investigated the potential value of the empirical administration of amphotericin B in 132 patients with febrile neutropenia.\textsuperscript{20} In 64 patients who did not receive antifungal therapy, there were six documented fungal infections, compared with only 1/68 patients treated empirically with amphotericin B (P = 0.1). No deaths due to fungal infection occurred among patients who received empirical amphotericin B compared with four in the group who did not receive treatment (P = 0.05).\textsuperscript{20} The justification for using empirical antifungal therapy was based on these few limited data and the practice has never been supported by larger studies. Nevertheless, empirical antifungal therapy remains the standard of care for many cancer centres and is recommended in American and European guidelines.\textsuperscript{21,22} Various antifungals have been tested for empirical therapy (fluconazole, itraconazole, liposomal amphotericin B (AmBisome\textsuperscript{18}), caspofungin and voriconazole), but none was significantly more effective than liposomal amphotericin B, with the differences being based on lower toxicity.\textsuperscript{23–27} Furthermore, most studies have used a very controversial composite clinical endpoint.\textsuperscript{28} Indeed, it can be argued that none of these studies has explored the most pertinent question: would the outcome of empirical antifungal therapy be any better than that of a placebo?

Breakthrough fungal infections occur in 2%–10% of cases treated with empirical therapy.\textsuperscript{29} Persistent antibiotic-resistant fever is not specific to IFD and may be related to chemotherapy, the use of growth factors or blood transfusions as well as drug reactions. Thus, the widespread use of empirical antifungal therapy is not without consequences as it leads to overtreatment, which, in turn, may result in increased antifungal toxicity and costs and a rising risk of emerging resistance. The relatively high costs of empirical antifungal treatment and length of hospital stay for patients with an IFD are an important consideration for many hospitals.\textsuperscript{30,31} Furthermore, an empirical approach may miss IFD that does not present with fever, especially in patients receiving corticosteroids (e.g. in patients with graft-versus-host disease (GVHD)), as these potent anti-inflammatory agents suppress the production of inflammatory cytokines and fever. Moreover, the early studies of empirical therapy may not be entirely representative of current patient populations, due to evolving risk factors, preventive strategies and diagnostic procedures, including CT scan, GM testing in serum or BAL fluid.\textsuperscript{32,33} Diagnostic-driven therapy or pre-emptive antifungal therapy means initiating treatment in high-risk patients with some clinical...
<table>
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<th>CII</th>
<th>CIII</th>
<th>CIV</th>
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<td>clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)</td>
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EORTC/MSG, Invasive Fungal Infections Cooperative Group of the European Organisation for Research and Treatment of Cancer/Mycoses Study Group; CT, computed tomography; IFD, invasive fungal disease.

*Table reproduced with permission from Maertens et al.*

Results from a multistate model, applied to 185 high-risk patients, showed that the incidence of IFD was increased by 91% for patients who were still febrile and neutropenic after 4 days of antibacterial therapy did not develop IFD. The authors concluded that empirical antifungal therapy should be initiated for such patients with a high clinical suspicion of IFD. However, there are concerns about the use of empirical antifungal therapy in patients with persistent fever and neutropenia without evidence of IFD. A rapid biomarker-based diagnostic strategy may help in this scenario. A randomized controlled trial conducted by Cordonnier et al. showed that patients with persistent fever and neutropenia who were treated with empirical antifungal therapy had a lower incidence of IFD compared to those who were not treated. The authors concluded that empirical antifungal therapy is effective in reducing the incidence of IFD in these patients. However, further studies are needed to confirm these findings. The use of empirical antifungal therapy has been associated with a reduction in the incidence of IFD, but it is important to balance the potential benefits against the risks of antifungal drug resistance.

There are a few patient-related factors that may favour starting antifungal therapy, such as the depth and duration of neutropenia. Other factors that may influence the decision to start antifungal therapy include the use of prophylactic agents, the presence of risk factors for IFD, and the severity of neutropenia. In a trial of 219 high-risk neutropenic patients, antifungal therapy was initiated for patients with persistent fever and neutropenia who did not develop IFD after 4 days of antibacterial therapy. The authors concluded that empirical antifungal therapy reduced the incidence of IFD in these patients. However, further studies are needed to confirm these findings. The use of empirical antifungal therapy has been associated with a reduction in the incidence of IFD, but it is important to balance the potential benefits against the risks of antifungal drug resistance.

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with acute myeloid leukaemia, suggested that the risk of invasive aspergillosis is a complex time function of neutropenia duration and risk management, and that using a quantitative PCR biomarker assay accelerated the early detection of invasive aspergillosis \( (P=0.01) \).\(^{35} \)

The most important question to ask is ‘do we feel safe enough to withhold antifungal therapy from a high-risk patient with persistent febrile neutropenia without classical CT findings and a negative GM?’ In order to answer this question, a prospective, randomized, multicentre, comparative study by the Infectious Diseases Group of the EORTC is currently underway in which the criteria for a ‘preemptive or diagnostic-driven’ approach and empirical approach are standardized along with the antifungal therapy to be used, the populations to be studied and the endpoint criteria (ClinicalTrials.gov identifier: NCT01288378). Another possibility is to improve the early laboratory diagnosis of occult fungal infection (fungal DNA with or without GM testing). Finally, a better definition of the risk factors predisposing patients to fungal infection would help to identify more precisely the population most likely to benefit from an empirical approach.

**Positive mycology results in asymptomatic patients (Group CI)**

The CI group of patients is defined by positive mycology results (either biomarker, microscopy or culture from tissue) without associated clinical symptoms and radiological signs.\(^{16} \) In daily practice, positive mycology for this group of patients usually means a positive GM test, as suitable specimens for microscopy and culture are seldom obtained from tissues of a patient at risk of IFD in the absence of signs or symptoms. Nucleic acid detection is not routinely performed due to the lack of a standardized test. The GM assay may be positive before there is any clinical suspicion of infection.

The GM assay in neutropenic patients has a high negative predictive value (>85%).\(^ {36} \) However, in many patients (24% of patients with HSCT in one study), false-positive results have been recorded particularly due to the following:\(^ {37} \)

- Concomitant administration of certain batches of the \( \beta \)-lactam antibiotics piperacillin/tazobactam or amoxicillin/clavulanate and ampicillin has in the past been found to be responsible for positive GM results, but may no longer be a problem.\(^ {35,38} \)
- Cross-reactivity with fungal species other than the *Aspergillus* species that are responsible for IFD, including *Penicillium marneffei*, *Histoplasma capsulatum*, *Cryptococcus neoformans* and *Trichosporon* species.\(^ {39} \)
- Cross-reactivity with transfused blood or antiglobulin sera.\(^ {40} \)
- Treatment of patients with cyclophosphamide.\(^ {41} \)
- Patients with intestinal mucositis caused by chemotherapy and irradiation, which allows for extra absorption of dietary GM.\(^ {37} \)
- GM in the diet, especially of children, e.g. from a milk-based diet or nutrient supplements containing soya bean proteins.\(^ {37} \)
- Cross-reactivity with *Bifidobacterium bifidum* in neonates.\(^ {37} \)

In a clinical setting that includes serial monitoring, one or two GM test results with optical density (OD) readings of \( \geq 0.5 \) prompt a

**Figure 1.** Triggers for driving treatment in asymptomatic patients with a positive galactomannan test. CT, computed tomography; GM, galactomannan; IFD, invasive mould disease; MRI, magnetic resonance imaging. \(^ {a} \) Host, environment, epidemiology, local infrastructure etc. \(^ {b} \) High-resolution computed tomography or multislice CT.
radiological investigation (Figure 1). In addition, thorax CT (HRCT or multislice CT) should be considered.

**Patients with atypical radiological signs of IFD with negative mycology results (Group CII)**

The CI group of patients is defined by radiological signs (any new infiltrate distinct from the sort of infiltrates that meet the EORTC/MSG 2008 criteria: dense, well-circumscribed lesions with or without a halo sign, air-crescent sign, or cavity11) and clinical symptoms, with negative mycology results (biomarker, microscopy or culture from tissue).16 As for the CI group, there are several conditions to consider before the initiation of antifungal therapy, such as the patient, the environment and the clinician’s experience.

The role of typical versus non-typical radiological signs of fungal disease in HRCT patients is currently under review. The EORTC/MSG definitions specifying the presence of CT signs are accepted as contributing to diagnosis in the neutropenic setting, but are not necessarily applicable in the non-neutropenic setting.11 The incidence of the halo sign among neutropenic patients with haematological malignancies varies widely, ranging from 25% to 95%; therefore, any infiltrate should be further investigated to confirm or exclude IFD.43 Furthermore, in contrast to adults, typical radiological signs are not usually seen in children, in whom multiple nodules or fluffy masses and infiltrates that look like mass lesions are often seen. Consequently, in children, even atypical pulmonary infiltrates (e.g. fluffy masses) may support the diagnosis of invasive pulmonary fungal disease in high-risk patients.

Radiological examinations are normally carried out for patients with respiratory symptoms such as cough, chest pain and shortness of breath. Persistent fever, typically of 4–5 days duration, is also usually a trigger for radiological investigations. Despite the negative results of initial mycology investigations (GM test, β-D-glucan test, culture from tissue or microscopy) in this subgroup, any new infiltrate found on a CT scan of these high-risk patients should be a trigger for attention and action.

The course of action should always include steps to exclude other causes of pneumonia, such as bacteria, viruses or non-infectious aetiology (Table 2). We suggest bronchoscopy with BAL should be performed as soon as possible, ideally before or soon after the initiation of antifungal therapy.43 This is to allow direct microscopy, culture and GM testing of BAL fluid and, if possible, to obtain a tissue sample via bronchoscopy or by the transthoracic approach (e.g. CT-guided, fine-needle biopsy).

For GM testing of BAL fluid, use of an OD >1 as a cut-off (tests with OD >1 are viewed as positive) is advised pending recommendations from the manufacturer.44 GM may be detected in BAL fluid in cases where the serum or plasma GM test was negative. Such a finding is also valuable for non-neutropenic patients with haematological malignancies who are susceptible to IFD (e.g. allogeneic stem cell transplant recipients with GvHD), where typical CT signs are not always present. However, GM screening is still regarded as necessary and should also be continued. The sensitivity of GM testing is reduced in patients receiving antimould prophylaxis and therefore a new infiltrate detected by CT should prompt further diagnostic investigations (bronchoscopy with BAL or biopsy), to exclude breakthrough of IFD.

There are an increasing number of centres using PCR assays for biomarkers for diagnostic investigations, despite the lack of standardization and interlaboratory reproducibility.44,45 PCR assays have been used mainly for diagnosis of invasive aspergillosis. Rogers et al.43 demonstrated that for two quantitative PCR assays of blood and serum from high-risk HSCT patients, the negative predictive value was good (>80%-90%) and the overall biomarker performance was improved by combining PCR with GM testing. We suggest that positive PCR results can be a trigger for further diagnostic investigations in centres where quantitative PCR assays are well established, but not for starting antifungal therapy until assays have been standardized and the results of a prospective evaluation are available.

C-reactive protein (CRP) levels have been considered as a biomarker for fungal infections, having been found to be elevated in patients with IFD, as well as in those with bacterial infection.45,46 A high serum CRP level (≥ 10 mg/L) was found to be a risk factor for patients not achieving a complete response to secondary antifungal prophylaxis in a retrospective study of Japanese haematology patients with invasive aspergillosis.47 However, CRP levels were also found to be elevated in recipients of allogeneic HSCT during neutropenia as well as during GvHD and in those with hepatotoxicity.48,49 A combined approach using serum procalcitonin (high predictive value for bacterial infections, but low for IFD) and CRP...
as biomarkers may aid diagnosis of IFD in some patient groups and merits further investigation.\textsuperscript{45,50}

Fungal pneumonia is the most common presentation of IFD in high-risk patients, but clinicians should consider that other sites may be involved (e.g. paranasal sinuses, gastrointestinal tract, CNS etc.) and therefore adequate radiological and mycological investigations should be carried out when suspicious clinical symptoms occur.\textsuperscript{51,52}

For the group of patients with clinical respiratory symptoms, new lung infiltrates and negative direct or indirect microbiological tests, in whom bacterial or viral causes have been excluded, we recommend antifungal therapy be initiated when there are clinical signs suggestive of infection, haemoptysis, chest pain, sudden respiratory deterioration or sinusitis. Other triggers would be a suggestive clinical symptom confirmed by radiological signs (e.g. new neurological symptoms with focal lesions on CT or magnetic resonance imaging; painful nasal ulcer with black eschar).

**Patients with radiological signs of IFD and positive mycology results (Group CIII)**

The CIII group of patients is defined by radiological signs (any new infiltrate distinct from the types of infiltrates described in the EORTC/MSG 2008 criteria\textsuperscript{13}) and with positive mycology results (biomarker, microscopy or culture from tissue).\textsuperscript{16} Signs of IFD on CT may be non-specific in immunocompromised patients who are not neutropenic and in other groups such as children. Steroid and immunosuppressive treatment may also result in the absence of typical signs of infection.

The best approach for this subgroup is to start antifungal therapy according to the mycology results. Appropriate diagnostic investigations in blood, BAL etc. should be performed as soon as possible to detect the fungal pathogen and to exclude concomitant bacterial or viral infection or non-infectious causes of pulmonary lesions.

**Patients with possible IFD (Group CIV)**

The CIV group are patients with possible IFD according the EORTC/MSG 2008 criteria.\textsuperscript{11} This group is defined by radiological signs detected via CT that fulfill the EORTC/MSG 2008 criteria [dense, well-circumscribed lesion(s), with or without a halo sign, air-crescent sign or cavity] and clinical symptoms, with negative mycology results (biomarker, microscopy or culture from tissue).\textsuperscript{16}

In this group, therapy with effective anti-Aspergillus antifungals (voriconazole or liposomal amphotericin B) should be initiated. Early bronchoscopy (before or just after the start of therapy) with mycological investigation of BAL fluid is recommended to detect azole-resistant fungal pathogens (e.g. Mucorales, Fusarium spp. and Scedosporium spp.).\textsuperscript{4,6} A systematic review of patients with invasive aspergillosis according to EORTC/MSG definitions suggested that the diagnostic performance of PCR on BAL fluid was similar to that of GM tests and that performing both tests resulted in optimal sensitivity with no loss of specificity.\textsuperscript{53}

**Patients with probable IFD (Group D)**

The D group are patients with probable IFD according the EORTC/MSG 2008 criteria.\textsuperscript{11} This group is defined by radiological signs on CT fulfilling the EORTC/MSG 2008 criteria [dense, well-circumscribed lesion(s) with or without a halo sign, air-crescent sign or cavity] and clinical symptoms with positive mycology results (biomarker, microscopy or culture from tissue).\textsuperscript{16} PCR assays combined with GM testing have also been shown to have clinical utility in this patient group (as well as in those with proven IFD), as in one study positive results preceded clinical signs and symptoms in 85% of haematology and stem cell transplant patients, and may be a trigger for further diagnostic investigations.\textsuperscript{54}

Targeted therapy is indicated according to mycology results, the pharmacokinetics and pharmacodynamics of antifungals and the potential for toxicities and drug–drug interactions.

**Patients with proven IFD (Group E)**

The E group are patients with proven IFD according the EORTC/MSG 2008 criteria.\textsuperscript{11} This group is defined by positive mycology results (microscopy or culture from tissue).\textsuperscript{16}

As with Group D, targeted therapy is indicated according to mycology results, the pharmacokinetics and pharmacodynamics of antifungals and the potential for toxicities and drug–drug interactions.

In all groups, adequate radiological and mycological investigations should be continued after initiation of antifungal therapy to monitor the course of infection and effectiveness of antifungal treatment.

**Triggers for stopping the antifungal treatment**

Triggers for stopping antifungal treatment in each of the groups treated with an antifungal also need to be considered. A de-escalation approach similar to that used for managing sepsis/septic shock may prove useful.\textsuperscript{55} Criteria for stopping or de-escalating the treatment can be divided into two groups: (i) early de-escalation/stopping of antifungal treatment after negative diagnostic results; and (ii) de-escalation/stopping of the therapy after response to treatment or resolution of IFD.

After appropriate intervention for confirmation/exclusion of IFD, for Groups B, C and D, antifungal treatment can be stopped if no mycological evidence is found. For centres where empirical/fever-driven therapy is used, antifungal treatment should be continued until there are no signs of infection (e.g. fever) and at least the major host risk factor (e.g. neutropenia) has been resolved. For patients in Groups CII, CIV, D and E, where IFD cannot be excluded or be classified by the EORTC/MSG 2008 criteria, antifungal treatment should continue until all clinical symptoms are resolved and there is no mycological evidence of active IFD; in addition, recovery of immunity should be apparent. Theoretically, de-escalation of antifungal therapy in this setting means either stopping the antifungal therapy, changing the route of administration (e.g. intravenous to oral), changing to maintenance therapy (in cases where a drug combination has been used) or switching to secondary prophylaxis.

**Conclusions**

The host factors, clinical features and mycological criteria proposed by the EORTC/MSG provide guidance to determine possible, proven and probable IFD for clinical and epidemiological research.\textsuperscript{33} Maertens et al.\textsuperscript{32} extended this approach to categories of patients at risk of IFD in which the patient’s illness does not satisfy the EORTC/MSG definitions. We based our conclusions about the most appropriate triggers (clinical or radiological signs
or biomarkers) for the treatment of all patient groups, especially the unclassified B and C groups, on our clinical experience.

Overall, for patients with no definitive signs of IFD (Group C), additional diagnostic testing, including repeated GM tests, radiological imaging and analysis of BAL fluid, is recommended before deciding to treat. However, for Group CIV, i.e. patients with possible IFD by EORTC/MSG criteria, therapy with effective anti-Aspergillus antifungals (voriconazole or liposomal amphotericin B) is recommended in parallel with early bronchoscopy with mycological investigation of BAL fluid to detect azole-resistant fungal pathogens (e.g. Mucorales, Fusarium spp. and Scedosporium spp.). For Groups D and E, i.e. patients with proven or probable IFD, targeted therapy is indicated according to mycology results, the pharmacokinetics and pharmacodynamics of antifungals and the potential for toxicities and drug–drug interactions. Triggers for stopping antifungal treatment were also considered and thought to be resolution of all clinical signs and no mycological evidence of active IFD.

Finally, better definition of risk factors predisposing patients to fungal infection and more sensitive and specific diagnostic tests are required for patients with persistent unexplained febrile neutropenia (Group B), to aid treatment decisions. Further standardization and evaluation of indirect mycological tests, such as quantitative PCR assays, alone or in combination with other biomarkers (including GM tests) may lead to improvements in the diagnosis and, ultimately, the outcomes of patients with IFD.

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