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Triggers for driving treatment of at-risk patients with invasive fungal disease

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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).[1,2] 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.[3] 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.[2]

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.[4] 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.[5,6] Slavin *et al.*[5] 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.[6] 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,[7–9] although this approach is only applicable in centres where the appropriate equipment and expertise are available.[10] 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

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Group (EORTC/MSG) has published standard definitions for IFD to aid diagnosis for clinical and epidemiological research.[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.[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.[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,[13,14] but, as yet, PCR is neither validated nor standardized.[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.*[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.*[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,[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.*,[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 antibacterial 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 antibiotic therapy, there was only one death due to fungal infection.[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.[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 ($P=0.05$).[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.[21,22] Various antifungals have been tested for empirical therapy [fluconazole, itraconazole, liposomal amphotericin B (AmBisome®), caspofungin and voriconazole], but none was significantly more effective than liposomal amphotericin B, with the differences being based on lower toxicity.[23–27] Furthermore, most studies have used a very controversial composite clinical endpoint.[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.[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.[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.[32,33]

Diagnostic-driven therapy or pre-emptive antifungal therapy means initiating treatment in high-risk patients with some clinical

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Table 1. Patterns of invasive mould disease[a]

	Patient class							
	A	B	CI	CII	CIII	CIV	D	E
Radiological signs and clinical symptoms	no	no (persistent febrile neutropenia)	no	clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)	clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)	radiological signs on CT [dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign or cavity]	radiological signs on CT [dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign or cavity]	not considered necessary
Mycology results	negative	negative	positive biomarker, microscopy or culture from tissue	negative	positive biomarker, microscopy or culture from tissue	negative	positive biomarker, microscopy or culture from tissue	tissue positive
Disease	no	no	no	no	no	yes	yes	yes
Infection	no	no	yes	no	yes	no	yes	yes
Diagnosis of IFD	unclassified					possible	probable	proven

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.

[a]Table reproduced with permission from Maertens *et al.*[16]

or biomarker evidence of IFD. This approach aims to reduce the number of patients unnecessarily exposed to an antifungal drug and has not only been found to decrease morbidity and the length of hospital stay, but also to reduce treatment-related costs.[10] De-escalation of empirical treatment would have a major impact on IFD-attributable hospital costs.[31]

Maertens *et al.*[7] published the first non-comparative study on the feasibility of a pre-emptive approach using the combination of daily GM assays, pulmonary CT and BAL in 136 high-risk neutropenic patients given fluconazole as antifungal prophylaxis. They reported a reduction in the use of antifungal therapy from 35% (expected rate) to 7.7%. This strategy identified IFD in 10/19 neutropenic episodes without fever, which was equivalent to 7% of the study population. Similarly, Dignan *et al.*[33] found that their early treatment strategy [only treating patients with persistent antibiotic-resistant fever if they also had a positive high-resolution CT (HRCT) scan] reduced their overall use of parenteral antifungal drugs by 68%. These authors did not test serum for GM as they were concerned about obtaining false-positive results through their use of piperacillin/tazobactam as a first-line antibacterial agent and false-negative results through their use of itraconazole as prophylaxis against IFD. A rapid biomarker-based diagnostic strategy that relied on GM testing and *Aspergillus* PCR also led to a significant reduction of empirical antifungal therapy without a change in mortality.[14] Further studies have since confirmed that a diagnostic-based antifungal strategy is feasible, effective and reduces costs.[8,34]

In a trial of 293 high-risk neutropenic patients with febrile neutropenia conducted by Cordonnier *et al.*,[9] the incidence of IFD in patients treated with empirical therapy was 2.7% compared with 9.1% for patients treated with pre-emptive therapy. It was notable that 91% of patients who were still febrile and neutropenic after 4 days of antibacterial therapy did not develop IFD in the absence of empirical amphotericin B. The authors concluded that waiting for evidence of IFD decreased the use of antifungal treatment and did not increase mortality, although it did increase the incidence of IFD.[9]

Diagnostic-driven therapy is becoming more commonplace in many cancer centres, although no drug has currently been approved for this approach. Furthermore, there is no consensus on the definition of this approach. It is likely that many centres who consider their practice as a pre-emptive or diagnostic-driven, because they use CT scans and GM testing, actually use an empirical therapy approach, albeit in a different form from that originally deployed in the studies of Walsh and colleagues.[26–29]

There is no doubt that antifungal therapy should be initiated for a high-risk patient with a specific clinical presentation or when a biological marker of IFD is detected. Furthermore, an empirical approach should also be continued in centres in which appropriate diagnostic procedures are not available or are not well organized. Clinical signs or symptoms other than CT or GM that are used to initiate antifungal therapy are discussed later (Groups CI–IV and D). There are a few patient-related factors that may favour starting empirical antifungal therapy, such as the depth and duration of neutropenia, concomitant immunosuppressive treatment, evidence of systemic inflammatory response syndrome, underlying disease status, age and chronic obstructive pulmonary disease-like diseases. Environmental factors such as exposure to construction work and local epidemiology may also be taken into consideration. Results from a multistate model, applied to 185 high-risk patients

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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 'pre-emptive 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 β-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 ≥0.5 prompt a

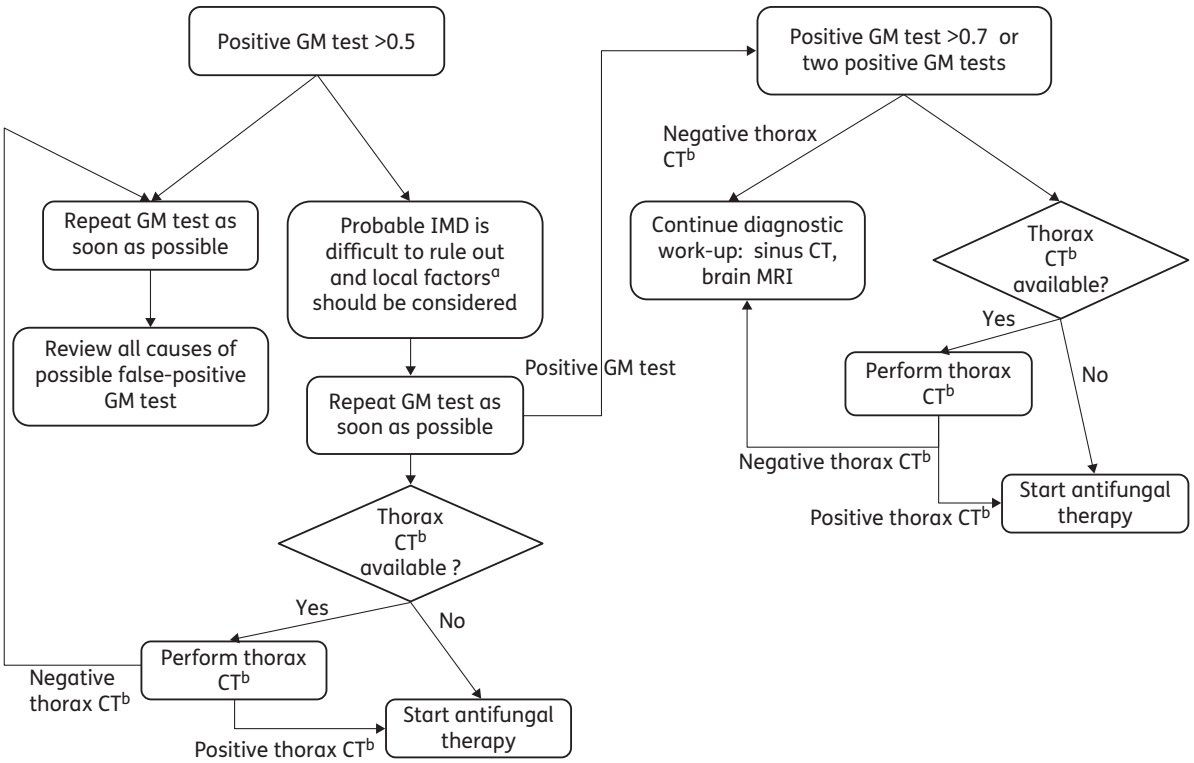


Figure 1. Triggers for driving treatment in asymptomatic patients with a positive galactomannan test. CT, computed tomography; GM, galactomannan; IMD, invasive mould disease; MRI, magnetic resonance imaging. [a]Host, environment, epidemiology, local infrastructure etc. [b]High-resolution computed tomography or multislice CT.

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Table 2. Recommended actions for triggers suggestive of IFD

Trigger	Action	Comments
Radiological signs (non-specific lung infiltrate)	diagnostic investigations [bronchoscopy, BAL, PCR[a], GM (serum/BAL fluid), culture/microscopy from tissue, tissue biopsy]	rule out bacterial, viral and non-infectious causes
Clinical symptoms (cough, chest pain, shortness of breath)	diagnostic investigations [bronchoscopy, BAL, PCR[a], GM (serum/BAL fluid), culture/microscopy, tissue biopsy]	rule out bacterial, viral and non-infectious causes
Any new lung infiltrate plus haemoptysis/chest pain/sudden respiratory deterioration/sinusitis	start antifungal therapy (continue with diagnostic investigations)	rule out bacterial, viral and non-infectious causes
New suggestive clinical symptom and radiological sign[b]	start antifungal therapy (continue with diagnostic investigations)	rule out bacterial, viral and non-infectious causes

BAL, bronchoalveolar lavage; GM, galactomannan.
[a]Where available.
[b]Other than pulmonary.

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 CII 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 cavity[11]) 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.[42] 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] PCR assays have been used mainly for diagnosis of invasive aspergillosis. Rogers *et al.*[3] 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

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as biomarkers may aid diagnosis of IFD in some patient groups and merits further investigation.[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.[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[11]) and with positive mycology results (biomarker, microscopy or culture from tissue).[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.[11] This group is defined by radiological signs detected via CT that fulfil 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).[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.).[43] 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.[53]

Patients with probable IFD (Group D)

The D group are patients with probable IFD according the EORTC/MSG 2008 criteria.[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).[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.[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.[11] This group is defined by positive mycology results (microscopy or culture from tissue).[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.[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, CI and CII, 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 CIII, 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.[33] Maertens *et al*.[22] 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

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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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References

1 Worth LJ, Slavin MA. Bloodstream infections in haematology: risks and new challenges for prevention. *Blood Rev* 2009; **23**: 113–22.

2 Marr KA, Carter RA, Crippa F *et al*. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2002; **34**: 909–17.

3 Rogers TR, Slavin MA, Donnelly JP. Antifungal prophylaxis during treatment for haematological malignancies: are we there yet? *Brit J Haematol* 2011; **153**: 681–97.

4 Zaragoza R, Peman J, Salavert M *et al*. Multidisciplinary approach to the treatment of invasive fungal infections in adult patients. Prophylaxis, empirical, preemptive or targeted therapy, which is the best in the different hosts? *Ther Clin Risk Manag* 2008; **4**: 1261–80.

5 Slavin MA, Osborne B, Adams R *et al*. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. *J Infect Dis* 1995; **171**: 1545–52.

6 Cornely OA, Maertens JA, Drew J *et al*. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.

7 Maertens J, Theunissen K, Verhoef G *et al*. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis* 2005; **41**: 1242–50.

8 Girmenia C, Micozzi A, Gentile G *et al*. Clinically driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. *J Clin Oncol* 2010; **28**: 667–74.

9 Cordonnier C, Pautas C, Maury S *et al*. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomised, controlled trial. *Clin Infect Dis* 2009; **48**: 1042–51.

10 Barnes RA, White PL, Bygrave C *et al*. Clinical impact of enhanced diagnosis of invasive fungal disease in high risk haematology and stem cell transplant patients. *J Clin Pathol* 2009; **62**: 64–9.

11 De Pauw B, Walsh TJ, Donnelly JP *et al*. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813–21.

12 Calliot D, Mannone L, Cuisenier B *et al*. Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients. *Clin Microbiol Infect* 2001; **7**: 54–61.

13 Maaroufli Y, DeBruyne JM, Duchteau V *et al*. Early detection and identification of commonly encountered *Candida* species from simulated blood cultures by using a real-time PCR-based assay. *J Mol Diagn* 2004; **6**: 108–14.

14 Morrissey CO, Chen SC, Sorrell TC *et al*. Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. *Lancet infect Dis* 2013; **13**: 519–28.

15 White PL, Bretagne S, Klingspor L *et al*. Aspergillus PCR; one step closer to standardization. *J Clin Microbiol* 2010; **48**: 1213–40.

16 Maertens JA, Nucci M, Donnelly JP *et al*. The role of antifungal treatment in hematology. *Haematologica* 2012; **97**: 325–7.

17 Akan H, Antia VP, Kouba M *et al*. Preventing invasive fungal disease in patients with haematological malignancies and the recipients of haematopoietic stem cell transplantation: practical aspects. *J Antimicrob Chemother* 2013; **68** Suppl 3: iii5–15.

18 Von Eiff M, Roos N, Schullten R *et al*. Pulmonary aspergillosis: early diagnosis improves survival. *Respiration* 1995; **62**: 341–7.

19 Pizzo PA, Robichaud KJ, Gill FA *et al*. Empirical antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* 1982; **72**: 101–11.

20 EORTC International Antimicrobial Therapy Cooperative Group. Empirical antifungal therapy in febrile granulocytopenic patients. *Am J Med* 1989; **86**: 668–72.

21 Hughes WT, Armstrong D, Bodey GP *et al*. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; **34**: 730–51.

22 Maertens J, Marchetti O, Herbrecht R *et al*. Third European Conference on Infections in Leukemia. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 update. *Bone Marrow Transplant* 2011; **46**: 709–6.

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23 Winston DJ, Hathorn JW, Schuster MG *et al*. A multicenter, randomised trial of fluconazole versus amphotericin B for empirical antifungal therapy of febrile neutropenic patients with cancer. *Am J Med* 2000; **108**: 282–9.

24 Boogaerts M, Winston DJ, Bow EJ *et al*. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad spectrum antibacterial therapy. A randomized controlled trial. *Ann Intern Med* 2001; **135**: 412–22.

25 Walsh TJ, Finberg RW, Arndt C *et al*. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999; **340**: 764–71.

26 Walsh TJ, Pappas P, Winston DJ *et al*. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346**: 225–34.

27 Walsh TJ, Teppler H, Donowitz GR *et al*. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004; **351**: 1391–402.

28 Marchetti O, Cordonnier C, Calandra T. Empirical antifungal therapy in neutropenic cancer patients with persistent fever. *Eur J Cancer Suppl* 2007; **5**: 32–42.

29 Madureira A, Berganon A, Larcoix C *et al*. Breakthrough invasive aspergillosis in allogeneic haematopoietic stem cell transplant recipients treated with caspofungin. *Int J Antimicrob Agents* 2007; **30**: 551–4.

30 Turner SJ, Chen SC, Slavin MA *et al*. Pharmacoeconomics of empirical antifungal use in febrile neutropenic haematological malignancy and haematopoietic stem cell transplant. *Expert Rev Pharmacoecon Outcomes Res* 2013; **13**: 227–35.

31 Amanda-Rajah MR, Morrissey CO, Spelman T *et al*. Attributable hospital cost and antifungal treatment of invasive fungal diseases in high-risk haematology patients: an economic modelling approach. *Antimicrob Agents Chemother* 2011; **55**: 1953–60.

32 Maertens J, Groll AH, Cordonnier C *et al*. Treatment and timing of invasive mould disease. *J Antimicrob Chemother* 2011; **66** Suppl 1: i37–43.

33 Dignan FL, Evans SO, Ethell ME *et al*. An early CT-diagnosis-based treatment strategy for invasive fungal infection in allogeneic transplant recipients using caspofungin first line: an effective strategy with low mortality. *Bone Marrow Transplant* 2009; **44**: 51–6.

34 Aguilar-Guisado M, Martín-Peña A, Espigado I *et al*. Universal antifungal therapy is not needed in persistent febrile neutropenia: a tailored diagnostic and therapeutic approach. *Haematologica* 2012; **97**: 464–71.

35 Schwarzinger M, Saganon-Teyssier L, Cabaret O *et al*. Performance of serum biomarkers for the early detection of invasive aspergillosis in febrile, neutropenic patients: a multi-state model. *PLoS One* 2013; **8**: e65776.

36 Mennink-Kersten MA, Donnelly JP, Verweij PE. Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. *Lancet Infect Dis* 2004; **4**: 349–57.

37 Wheat LJ. Approach to the diagnosis of invasive aspergillosis and candidiasis. *Clin Chest Med* 2009; **30**: 367–77.

38 Mikulska M, Furfaro E, Del Bono V *et al*. Piperacillin/tazobactam (Tazocin™) seems to be no longer responsible for false-positive results of the galactomannan assay. *J Antimicrob Chemother* 2012; **67**: 1746–8.

39 Cummings JR, Jamison GR, Boudreaux JW *et al*. Cross-reactivity of non-*Aspergillus* fungal species in the *Aspergillus* galactomannan enzyme immunoassay. *Diagn Microbiol Infect Dis* 2007; **59**: 113–5.

40 Martín-Rabadán P, Gijón P, Fernández RA *et al*. False-positive *Aspergillus* antigenemia due to blood product conditioning fluids. *Clin Infect Dis* 2012; **55**: e22–7.

41 Hashiguchi K, Niki Y, Soejima R. Cyclophosphamide induces false-positive results in detection of *Aspergillus* antigen in urine. *Chest* 1994; **105**: 975.

42 Georgiadou SP, Sipsas NV, Marom EM *et al*. The diagnostic value of halo and reverse halo signs for invasive mould infections in compromised host. *Clin Infect Dis* 2011; **52**: 1144–55.

43 Arendrup MC, Bille J, Dannaoui E *et al*. ECIL-3 classical diagnostic procedures for the diagnosis of invasive fungal diseases in patients with leukaemia. *Bone Marrow Transplant* 2012; **47**: 1030–45.

44 Marchetti O, Lamoth F, Mikukska M *et al*. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. *Bone Marrow Transplant* 2012; **47**: 846–54.

45 Marková M, Brodská H, Malíčková K *et al*. Substantially elevated C-reactive protein (CRP), together with low levels of procalcitonin (PCT), contributes to diagnosis of fungal infection in immunocompromised patients. *Support Care Cancer* 2013; **21**: 2733–42.

46 Villarroel M, Avilés CL, Silva P *et al*. Risk factors associated with invasive fungal disease in children with cancer and febrile neutropenia: a prospective multicenter evaluation. *Pediatr Infect Dis J* 2010; **29**: 816–21.

47 Kikuchi M, Nakasone H, Mitani K *et al*. Retrospective assessment of secondary prophylaxis for invasive aspergillosis in neutropenic hematology patients and identification of risk factors for relapse of fungal disease. *Scand J Infect Dis* 2013; **45**: 531–6.

48 Artz AS, Wickrema A, Dinner S *et al*. Pre-treatment C-reactive protein (CRP) is a predictor for allogeneic hematopoietic cell transplantation outcomes. *Biol Blood Marrow Transplant* 2008; **14**: 1209–16.

49 Blijlevens NM, Donnelly JP, DePauw BE. Inflammatory response to mucosal barrier injury after myeloablative therapy in allogeneic stem cell transplant recipients. *Bone Marrow Transplant* 2005; **36**: 703–7.

50 Koya J, Nannya Y, Ichikawa M *et al*. The clinical role of procalcitonin in hematopoietic SCT. *Bone Marrow Transplant* 2012; **47**: 1326–31.

51 Pagano L, Fianchi L, Leone G. Fungal pneumonia due to molds in patients with hematological malignancies. *J Chemother* 2006; **18**: 339–52.

52 Hori A, Kami M, Kishi Y *et al*. Clinical significance of extra-pulmonary involvement of invasive aspergillosis: a retrospective autopsy-based study of 107 patients. *J Hosp Infect* 2002; **50**: 175–82.

53 Avni T, Levy I, Sprecher H *et al*. Diagnostic accuracy of PCR alone compared to galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis: a systematic review. *J Clin Microbiol* 2012; **50**: 3652–8.

54 Barnes A. Directed therapy for fungal infections: focus on aspergillosis. *J Antimicrob Chemother* 2013; **68**: 2431–2434.

55 Dellinger RP, Levy MM, Rhodes A *et al*. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **14**: 580–637.

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