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Optimizing management of invasive mould diseases

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We describe an integrated care pathway (ICP) for the optimal management of invasive mould disease (IMD). The ICP is for use by health professionals involved in the care of patients with haematological malignancies and haematopoietic stem cell transplant recipients who are at increased risk of IMD. The ICP is not intended for use in other patient groups where the evidence base is more limited. The ICP involves the patient and their carers, as well as describing the roles and the complex interaction of healthcare professionals in different departments. Therefore, the management of IMD as described in the ICP must be appropriate for the overall organization, and will be dependent on the facilities [e.g. high-efficiency particulate air (HEPA) filtration] and services available. The ICP deals with risk stratification, diagnostic tests, prophylactic and treatment strategies and how to incorporate these into the ICP. Outpatient drug management after hospital discharge and cessation of therapy are outlined. Local implementation of this ICP will vary from centre to centre: the ICP is a generic template for guidance indicating the requirements for optimal IMD management and as such provides a standard against which local practice can be audited. For clinical governance, to minimize variation in practice and, ultimately, to improve patient outcomes, each centre should regularly monitor and document compliance with the local ICP, from provision of patient information, appropriate prescribing and diagnostic investigation to clinical outcomes.

Keywords: integrated care pathway, ICP, guidelines, moulds, audit, clinical governance

Introduction

The management of invasive mould diseases (IMDs) in patients with haematological malignancies and haematopoietic stem cell transplant (HSCT) recipients remains challenging. One significant problem is the lack of accurate diagnostic tools for making an early diagnosis. The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperation Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria, published in 2002[1] and revised in 2008,[2] were developed to facilitate clinical trial design and comparisons between different studies. They should not necessarily be used to guide the treatment of patients with IMD. Substantial differences in case mix and the availability (and turn-round time) of diagnostic tests means that integrated care pathways (ICPs) must be developed and tailored for each institution. The ICP provides a mechanism by which complex patients can be managed safely and effectively, and facilitates audit and other quality improvement programmes. Here, we describe a number of different approaches that may be appropriate.

Recently, there have been many changes in the different aspects of the management of IMD. There has been an improved understanding of risk stratification and diagnostic modalities and a broader range of mould-active drugs. The introduction of non-myeloablative conditioning regimens for allogeneic HSCT has extended allogeneic transplantation to older patients and those with comorbidities who would have previously been ineligible for transplantation.[3,4] The increasing use of T-cell immunosuppressants has influenced the risk of IMD in patient groups not previously considered to be at high risk [e.g. in chronic lymphocytic leukaemia treated with alemtuzumab (an anti-CD52 monoclonal antibody) and high-dose corticosteroids].[5,6] The importance of T cell immunity—not just innate immunity—in a successful host response to IMD was specifically recognized in the modification of host criteria in the EORTC/MSG 2008 update.[2]

The studies indicating the utility of CT scanning of the chest in the diagnosis of suspected IMD[7,8] have been translated into clinical practice with the widespread availability of routine CT scanning. Where available, whole-volume scanning with thin-slice reconstruction is preferable to high-resolution CT scanning. The key role of CT scanning in providing evidence of a clinically relevant disease process was emphasized in the EORTC/MSG 2008 update:[2] in the absence of characteristic CT findings, the combination of microbiological and host factors is no longer regarded as representing 'possible' IMD (see Figure 1 in Martens *et al.*[9] However,

radiological imaging cannot identify a specific pathogen and invasive procedures (such as a tissue biopsy) are often not possible in ill patients following chemotherapy. Of the biological markers, only serum measurement of the galactomannan index (GMI) has an extensive evidence base.[10] Nevertheless, both the GMI and (1→3)-β-D-glucan have been accepted as valid markers of microbiological evidence of IMD.[2] The use of these markers in tissue other than peripheral blood may be useful and, in particular, if a bronchoscopy can be performed, bronchoalveolar lavage fluid gives a better diagnostic yield using the GMI.[11] The various PCR approaches to the detection of IMD have not yet been translated into routine clinical practice, although studies have shown the feasibility of incorporating PCR detection of *Aspergillus* DNA into a management algorithm.[12,13]

As mentioned above, the local implementation of the ICP will be different in different centres. Other than published studies, relevant information in developing an ICP for the optimal management of IMD comes from the many national, international, pathogen-specific and haemato-oncology-specific guidelines that have been developed recently.[14–22] Another level of information—perhaps the level most clinically relevant to professionals and patients—is the existence of a huge number of local guidelines that interpret and translate the data from the available literature and peer-reviewed published guidelines to allow their practical implementation in a given clinical setting. However, rarely do such guidelines describe the minimum requirements needed to achieve successful implementation in both an objective and a comprehensive fashion. The aim of this article is to integrate the conclusions of the other articles in this issue[9,23–25] into an ICP for the management of patients with suspected IMD. The generic elements of an ICP are to provide a multidisciplinary approach indicating a pathway a patient could follow once their clinical features trigger initiation of the process.[26] The ICP should be designed with patients at its centre, and allow them and their carers to be informed and actively participate as far as is practically possible. The specific elements relating to the diagnosis and treatment of IMD have been dealt with in other articles in this Supplement,[9,23–25] and are brought together here, including specific timeframes, aiming to ensure appropriate and timely management. It must be emphasized that the ICP is for guidance and, in a specific case, clinical judgement and freedom take precedence over the pathway. The ICP should allow implementation into local daily practice of broader (inter)national guidelines and reduce variations in practice and patient outcomes. The ICP is an important document for clinical governance, embedding the various elements of IMD management into the overall organizational structure. Auditing of local practice against the ICP measures should provide robust data on compliance and evidence to support the resources used (i.e. drugs, investigations, etc.) and drive changes in practice if weaknesses are identified.

Stakeholders in the ICP

Who does the ICP involve? The starting point is the patient and the patient's carers. The management of IMD is only part of the overall management of infection in a patient with a haematological malignancy. Patients undergoing allogeneic HSCT, myeloablative chemotherapy for acute leukaemia and/or highly immunosuppressive treatment should be counselled, and given written information explaining the routine pathway of investigation and treatment for bacterial and fungal infections, particularly in terms of general advice on minimizing infectious risk, early presentation for signs and symptoms and the standards of care they can expect. Patient groups or other patient advocates should be consulted in the development of the local ICP.

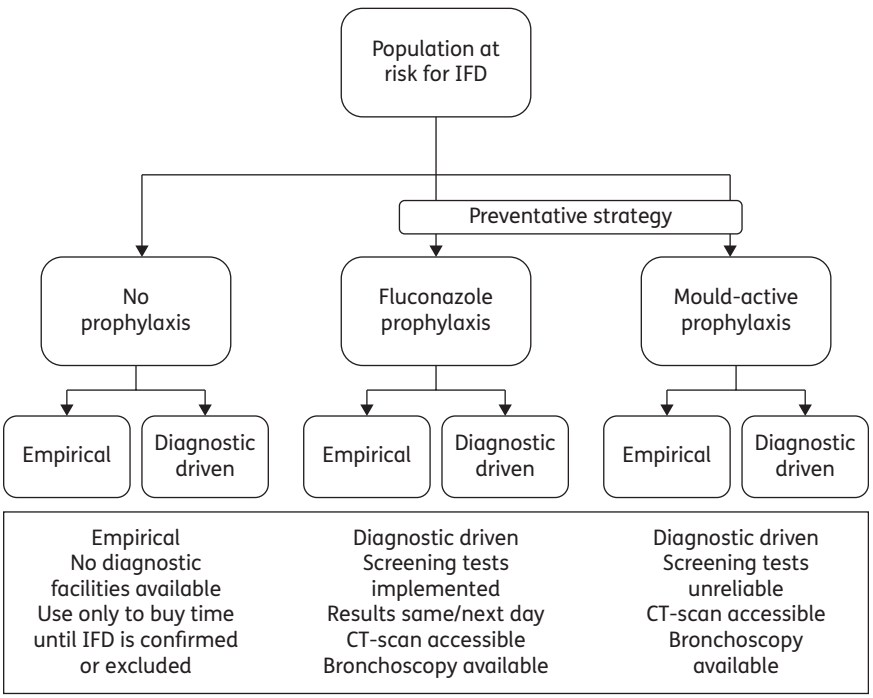

Figure 1. Antifungal strategies for patients at risk of invasive fungal disease (IFD).

The ICP involves a broad range of healthcare professionals. The development and subsequent dissemination of the ICP requires input from the nursing and medical teams looking after the patient: infection specialists, radiographers and radiologists, pharmacists, and respiratory physicians, as a minimum. A comprehensive set of standards for the management of invasive fungal disease has been previously published, incorporating minimum expectations in the areas of radiology, histopathology and microbiology, as well as treatment initiation, which can help to guide this process.[27] The stakeholders should jointly agree their roles, have written policies describing what is expected and specifying timelines for performing a task (e.g. a CT scan of the chest within 24 or 48 h of request). At the level of the overall organization, senior management must also be party to the development of the ICP, particularly in terms of the potential impact of the ICP on the existing infrastructure and service provision: the need for high-efficiency particulate air (HEPA)-filtered rooms, diagnostics in microbiology, turn-round times for CT scanning and the need for bronchoscopy services.

Risk stratification

The starting point of the ICP is the risk assessment of the patient as discussed in an accompanying article,[23] and is summarized in Table 1. While the clinical scenario of different patients in the high-risk category may vary considerably (e.g. post-chemotherapy neutropenia compared with graft-versus-host disease-associated immunosuppression), for practical purposes of clinical implementation it was felt this assessment should be as simple as possible. A patient deemed at high risk of IMD enters the ICP (see Figure 1). All other patients were not considered candidates for mould-active prophylaxis, and were thought to be more appropriately managed with a diagnostic-driven approach [but without screening (in view of the low pre-test probability)] as opposed to an empirical approach (see Figure 3).

Table 1. Patient populations considered to be at high risk of invasive mould diseases

Patients	Example
With uncontrolled underlying disease	relapsed acute leukaemia
	prolonged MDS
Undergoing treatment	remission induction therapy for acute leukaemia or MDS
	monoclonal antibodies, e.g. etanercept, alemtuzumab
	prolonged treatment with corticosteroids (prednisolone or equivalent mean minimum dose of 0.3 mg/kg/day or for >3 weeks)
Receiving an allogeneic HSCT	
Post-allogeneic HSCT	corticosteroids to manage GVHD
	GVHD with or without CMV disease
History of previous invasive mould disease	probable or proven invasive aspergillosis

MDS, myelodysplastic syndrome; GVHD, graft-versus-host disease; CMV, cytomegalovirus.

Preventive strategy (Figure 1)

In addition to risk stratification, there are other factors to consider that influence the preventive strategy. The local incidence of IMD will have a significant impact on the appropriateness of any strategy, such that a low incidence can be managed with no drug prophylaxis combined with a diagnostic approach.[28] The availability of HEPA filtration offers prevention by minimizing exposure to airborne environmental spores.[29] Also, patient education—regarding diet, environmental and personal hygiene, signs and symptoms that require action and what actions to take, the need for isolation (if relevant), central venous access and care of catheters—should be incorporated into the management plan.

As shown in Figure 1, three approaches to prophylaxis can be used: (i) no prophylaxis; (ii) mould-inactive prophylaxis (i.e. fluconazole) and (iii) mould-active prophylaxis (e.g. itraconazole, voriconazole, posaconazole). Table 2 summarizes the therapeutic options for prophylaxis. For more detailed information, the reader is referred to a number of recent guidelines that have extensively reviewed the literature.[15,17,19,20] An important area of uncertainty with respect to management strategies is the potential for all mould-active drugs to interfere with the performance of biomarkers.[30–32] For all choices, the local incidence of IMD, the diagnostic strategies and the availability of HEPA filtration will need to be considered. No drug or mould-inactive prophylaxis is appropriate if the incidence of IMD is low (e.g. incidence <5%). If the incidence is higher, prophylaxis is more cost-effective, but issues of cost, variable tolerability, drug interactions, reduced efficacy of biomarker testing, the need for therapeutic drug monitoring (TDM)[33] and triazole resistance are all important considerations.[34,35]

Management strategies (Figures 2 and 3)

After risk stratification and choice of preventive strategy, the management strategy for IMD can follow two broad paths: empirical or diagnostic-driven. The empirical approach has been (and remains) the standard approach in many centres. It originally developed in an era of a lack of diagnostic tests for IMD and limited drug treatments, and is supported by evidence from two studies from the 1980s[36,37] and a systematic review, which includes more recent trials,[38] albeit with many caveats on the strength of the data. An empirical strategy is driven by unexplained persistent fever (for 3–7 days in most studies) despite broad-spectrum antibiotics and in the face of negative microbiological investigations. The limitations of this approach are discussed in an accompanying article.[9] The aim of empirical therapy for IMD is to begin treatment prior to clinical evidence of disease (other than fever), while instituting investigations to confirm or exclude the diagnosis. However, empirical therapy results in the treatment of patients who do not actually have IMD and high costs. In the absence of fever, which may occur because of the administration of corticosteroids, the empirical strategy may be inadequate.

In a diagnostic-driven strategy, biological markers are combined with imaging to direct therapy for IMD. The rationale is

Table 2. Summary of drugs used for prophylaxis

Agent	Mould-active	Comments on administration	Impact on biomarkers[a]
Amphotericin B deoxycholate	yes	non-absorbable suspension or tablets	none
Liposomal amphotericin B	yes	given by inhalation	none
		intravenous	potentially negative
Fluconazole	no	minor drug interactions	none
Itraconazole	yes	poor tolerability gastrointestinal disturbance and elevated liver function tests multiple drug interactions to achieve serum trough concentration of at least 0.5 mg/L measured using HPLC	potentially negative
Posaconazole	yes	oral only absorption affected by gastric pH and food multiple drug interactions, though fewer than those of other triazoles (see review[43])	potentially negative
Voriconazole	yes	multiple drug interactions (see review[43]) TDM useful in certain clinical settings (see review[33])	potentially negative
Caspofungin	yes	intravenous only	unknown
Micafungin	yes	intravenous only	unknown

[a]All mould-active drugs have the potential to negatively affect biomarker assays.[26–28]

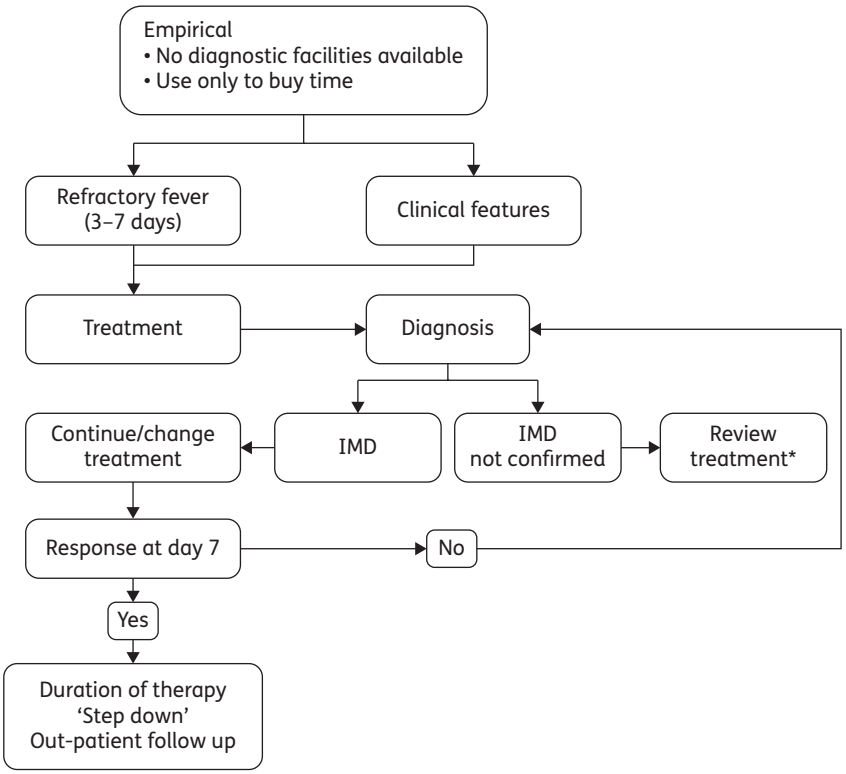

Figure 2. Empirical antifungal therapy integrated care pathway. *****Multidisciplinary team input important at this stage.

that an accurate and rapid assessment of the likelihood of IMD can be made, and only those patients with some evidence of disease (over and above fever alone) are treated—equally, this assumes that IMD can be effectively excluded when investigations are negative and treatment withheld. The efficacy of this approach has not been established, as discussed by Maertens *et al.*[9] in an accompanying article in this Supplement. Furthermore, if fever is the principal trigger for entry into the

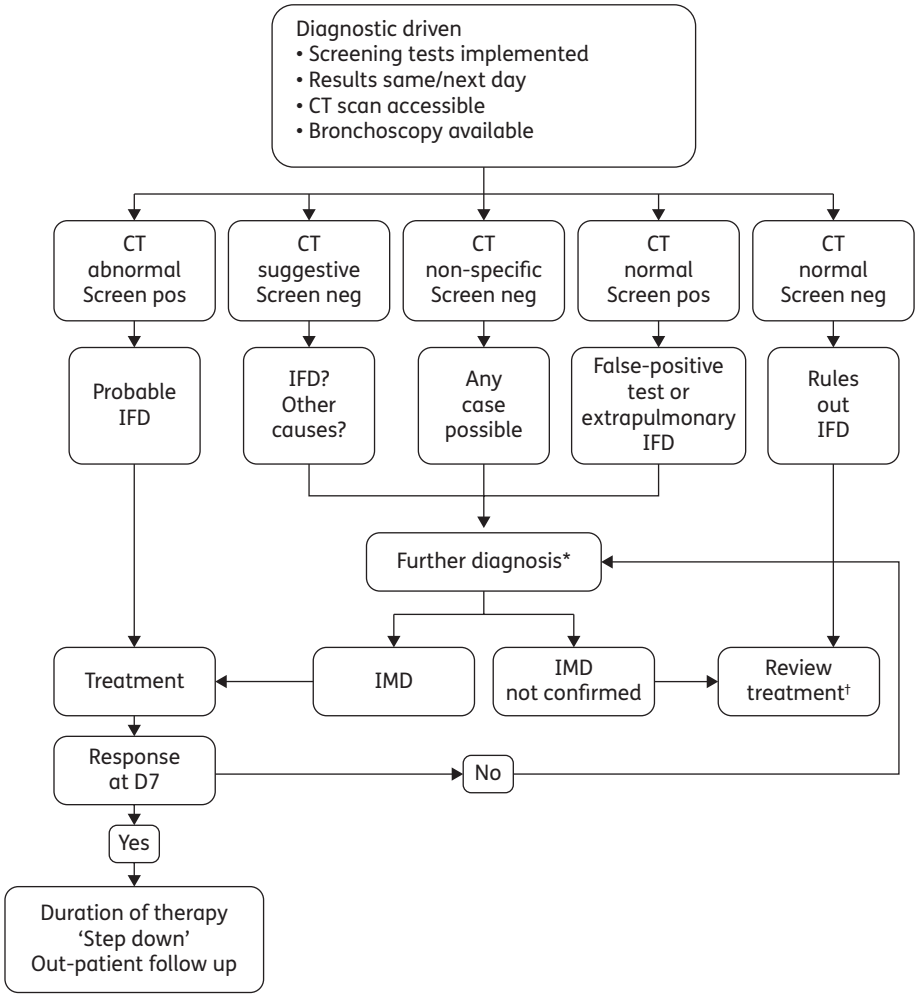

Figure 3. Diagnostic-driven antifungal therapy integrated care pathway. IFD, invasive fungal disease. *Further diagnosis could include bronchoscopy with bronchoalveloar lavage, calcofluor testing, galactomannan antigen, PCR and image-guided or surgical biopsy of any lesions. †Multidisciplinary team input important at this stage.

diagnostic-driven pathway, this will also be inadequate in IMD not associated with fever.[39] Consequently, a screening strategy based on regular blood tests for biological markers (principally GMI) is an alternative use of a diagnostic strategy (Figure 3) and can be used to trigger entry into the diagnostic algorithm along with clinical features.

Viewing these two broad strategies as mutually exclusive is not a true reflection of clinical practice. Some combination of the two is probably the commonest approach, for example CT scanning of the chest combined with a fever-driven approach.[40] Equally, in the knowledge that delayed treatment is associated with worse outcomes for IMD,[41] another approach would be to start antifungal treatment while awaiting the results of investigations even in a diagnostic-driven strategy, but then stop such therapy if investigations are not confirmatory. As discussed in an accompanying article,[24] if a mould-active prophylactic drug is used, this will have an impact on the efficacy of some diagnostic tests, further complicating the choice of management strategy.

These issues highlight the fact that no single algorithm will be universally appropriate and the ICP must be developed to be applicable locally. In principle, establishing a diagnosis and identifying the infective organism is the optimal management strategy. It should be borne in mind that both of these strategies may result in inappropriate antifungal agents being used to treat infection with unidentified fungi. However, in many centres the availability of rapid imaging with expertise in reporting, blood/serum biomarkers and early respiratory intervention for bronchoscopy may be the main determinants and limitations in developing the ICP.

Empirical strategy (Figure 2)

The empirical pathway is entered when a patient at high risk has persistent or relapsing fever refractory to broad-spectrum antibiotics, without an identified cause for 3–7 days. There is no consensus on the exact time frame that should be used, hence the wide range for the duration of fever. Although fever is clearly a clinical feature, other clinical findings are grouped separately (see Table 3) as per Ascioglu *et al.*[1] Entry into the ICP automatically triggers treatment with a systemic antifungal agent. At the same time, every effort should be made to investigate the

underlying cause of fever. Table 4 lists the relevant investigations with suggested time lines to be clinically useful. Positive results will support continued treatment. However, the ICP must define the approach for negative investigations—this will be influenced by the range of tests available and how fast they can be done in relation to starting mould-active treatment (which may negatively impact on biomarker and culture results), as well as the turn-round time of results. One option is to stop antifungal therapy if investigations are negative. One role for the ICP is to specify who needs to be involved in decision making and how and when their involvement is needed, i.e. a multidisciplinary team (MDT; the clinical team, radiologist and microbiologist as a minimum) approach, and this MDT review should be recorded for audit purposes.

Table 3. Entry into the empirical and diagnostic-driven pathways

Approach	Criteria
Empirical	persistent or refractory fever despite broad-spectrum antibiotics for 3–7 days and no alternative microbiological aetiology found
Diagnostic-driven	
Clinical evidence	respiratory—non-specific pulmonary infiltrates on chest X-ray, cough, chest pain, haemoptysis, dyspnoea, pleural rub or effusion
	sinonasal infection—rhinorrhoea, epistaxis, ulceration or eschar of nasal septum or hard palate, maxillary pain, periorbital swelling
	focal neurological signs or symptoms
	nodular or vesicular skin lesions
Mycological evidence	detection of galactomannan[39] or *Aspergillus* by PCR,[11] in a screening strategy (see text)

Diagnostic-driven strategy (Figure 3)

The diagnostic-driven pathway is entered as per the empirical entry criteria (see section above) with the addition of positive biomarkers if a screening approach is employed. The ICP must specify the biological, imaging and interventional examinations to be performed. Table 3 lists the investigations and time lines for clinical utility. The decision to start or to withhold antifungal treatment is determined by the outcome of these investigations. There is no consensus as to how a diagnostic-driven approach should be implemented in clinical practice. A truly biomarker-driven approach has been tested in two studies. Maertens *et al.*[39] performed daily GMI testing; a positive GMI (in addition to clinical triggers) led to CT scanning of the chest and a

Table 4. Investigations in both the empirical and the diagnostic-driven pathway

Investigation	Timelines and comments
Diagnostic investigations	
chest CT (preferably volume acquisition with thin slice reconstruction)	initial persistent fever
	repeat frequency no sooner than 2 weeks, unless significant clinical deterioration
CT/MRI other sites	according to clinical features
biopsy	according to clinical features
	every attempt should be made to obtain tissue (allows proven diagnosis to be made)
respiratory secretions	bronchoalveloar lavage should be undertaken following the earliest radiological evidence when a patient is unresponsive to antibiotics
blood cultures	during fever; if positive for fungus repeat daily until negative
serum/plasma galactomannan	this can be performed to provide support for the diagnosis of invasive aspergillosis
	several samples should be sent on consecutive days
Screening investigations	
serum/plasma galactomannan	pre-therapy and throughout the risk period
	twice weekly during admission
	can help exclude aspergillosis because of the high negative predictive value
	detection of galactomannan has been used as a criterion for starting therapy
whole-blood PCR	pre-therapy and throughout the risk period
	twice weekly during admission
	data suggest that some PCR tests can help exclude aspergillosis and candidosis because of the high negative predictive value
	detection of fungal nucleic acid might be useful as a criterion for starting therapy
	efforts are under way to define a standard for *Aspergillus* PCR
serum β-D-glucan	pre-therapy and throughout the risk period
	twice weekly during admission
	might help exclude aspergillosis and candidosis because of the high negative predictive value
	detection of β-D-glucan might be useful as a criterion for starting therapy

bronchoscopy and if these investigations were negative antifungal treatment was withheld. Hebart *et al.*[13] used an *Aspergillus* PCR approach (in addition to clinical triggers); however, treatment was also commenced in the 'diagnostic-driven' PCR arm for persistent fever, even if the PCR was negative. Other studies have initiated a diagnostic approach only after clinical triggers, as shown in Figure 3,[11,12,42] using both biomarkers and imaging, while one study has used a CT-only diagnostic algorithm.[40] The rest of the pathway is as for the empirical ICP.

Assessing response and duration of therapy

Assessing response is essentially clinical: routine repeat CT imaging raises issues of unnecessary radiation exposure along with difficulties in interpretation (i.e. apparent radiological worsening in the face of clinical response),[8] while monitoring with biomarkers cannot be regarded as standard even if available. In a well patient, whose fever or other clinical features have resolved, routine repeat investigation in the ICP needs to be justified (e.g. prior to an allogeneic transplant or a further cycle of chemotherapy). If biomarkers are measured and are persistently positive or worsening in a clinically responding patient, consideration should be given to a careful assessment of factors known to cause false positives, the choice of antifungal drug and TDM, as well as repeat/more extensive investigations. In a patient who is unwell, with persistent clinical signs/symptoms, repeat investigations (Table 3) should be performed after an adequate duration of antifungal treatment (i.e. approximately 7 days).

In a responding patient, the optimal duration of antifungal treatment for IMD is not known. Many factors will impact on the management of an individual patient: baseline features (large fungal load, e.g. presence of a mycotic lung sequestrum), persistent neutropenia, ongoing immunosuppression (e.g. post-transplant or for graft-versus-host disease), presence of diarrhoea, further chemotherapy, underlying disease status of the haematological malignancy, etc. Clinical practice varies considerably and prior to the current era of effective, well-tolerated oral mould-active agents several weeks (6–12) of intravenous amphotericin B deoxycholate was standard for invasive aspergillosis. Now, with increasing demands on inpatient beds, pressure to discharge patients early and the availability of oral antifungals for effective outpatient management, an additional decision is when to change from an intravenous to an oral agent ('step-down' therapy). One to 2 weeks of intravenous therapy for proven/probable IMD followed by oral treatment is a practical approach when the patient is clinically stable and, if performed, biomarkers and imaging are compatible with response. If antifungals are given as an outpatient prescription, controls must be instituted to avoid unnecessary prolonged treatment and drug wastage (e.g. hospital dispensing limited to a 2 week supply of drug). Close outpatient follow-up of patients is essential during treatment for IMD—in order to assess continued response, to undertake TDM if appropriate, to repeat prescriptions and to stop therapy as clinically indicated.

Conclusions

The complex management of IMD in patients with haematological malignancies undergoing a variety of myelosuppressive and immunosuppressive therapies requires a coordinated approach across different specialties. To ensure optimal management in every case, a system must be implemented at local level providing clear and simple instructions to patients, carers, doctors, nurses and other healthcare workers. Here, we have attempted to describe the global aspects of an ICP for the management of IMD. Translation of this into local clinical practice will vary from centre to centre. By defining specific processes and actions and educating all users of the ICP, this should reduce variation in practice and improve outcomes. It is important to audit adherence to the ICP. This information will allow changes to be made to improve any identified weaknesses, including the allocation of resources to enable optimal IMD management, from the introduction of biomarker testing to building a HEPA-filtered unit.

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References

1 Ascioglu S, Rex JH, de Pauw B *et al*. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; **34**: 7–14.

2 De Pauw B, Walsh TJ, Donnelly PJ *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.

3 Giralt S, Estey E, Albitar M *et al*. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukaemia without myeloablative therapy. *Blood* 1997; **89**: 4531–6.

4 Slavin S, Nagler A, Naparstek E *et al*. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and non-malignant hematologic diseases. *Blood* 1998; **91**: 756–63.

5 Rieger K, Von Grünhagen U, Fietz T *et al*. Efficacy and tolerability of alemtuzumab (CAMPATH-1H) in the salvage treatment of B-cell chronic lymphocytic leukemia—change of regimen needed? *Leuk Lymphoma* 2004; **45**: 345–9.

6 Wendtner CM, Ritgen M, Schweighofer CD *et al*. German CLL Study Group (GCLLSG). Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission—experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). *Leukemia* 2004; **18**: 1093–101.

7 Caillot D, Casanovas O, Bernard A *et al*. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997; **15**: 139–47.

8 Caillot D, Couaillier J-F, Bernard A *et al*. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol* 2001; **19**: 253–9.

9 Maertens J, Groll AH, Cordonnier C *et al*. Treatment and timing in invasive mould disease. *J Antimicrob Chemother* (this Supplement).

10 Leeflang MM, Debets-Ossenkopp YJ, Visser CE *et al*. Galactomannan detection for invasive aspergillosis in immunocompromized patients. *Cochrane Database Syst Rev* 2008; **8**: CD007394.

11 Maertens J, Maertens V, Theunissen K *et al*. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. *Clin Infect Dis* 2009; **49**: 1688–93.

12 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.

13 Hebart H, Klingspor L, Klingebiel T *et al*. A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT. *Bone Marrow Transplant* 2009; **43**: 553–61.

14 Böhme A, Ruhnke M, Buchheidt D *et al*. Treatment of invasive fungal infections in cancer patients—recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2009; **88**: 97–110.

15 Cornely OA, Bohme A, Buchheidt D *et al*. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. *Haematologica* 2009; **94**: 113–22.

16 Pappas PG, Kauffman CA, Andes D *et al*. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503–35.

17 Slavin MA. Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2008. *Intern Med J* 2008; **38**: 457–67.

18 Walsh TJ, Anaissie EJ, Denning DW *et al*. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46**: 327–60.

19 Prentice AG, Glasmacher A, Hobson RP *et al*. 2008. *Guidelines on the Management of Invasive Fungal Infection During Therapy for Haematological Malignancy*. http://www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf (15 October 2010, date last accessed).

20 Maertens J, Frère P, Lass-Flörl C *et al*. 2009. *Antifungal Prophylaxis in Leukemia Patients 2009 Update of the ECIL-1 and -2 Guidelines*. http://www.eortc.org/home/IDG/ECIL/ECIL3_Antifungal_prophylaxis_update_2009.pdf (15 October 2010, date last accessed).

21 Herbrecht R, Flückiger U, Gachot B *et al*. 2009. *Antifungal Therapy in Leukemia Patients 2009 Update of the ECIL-1 and -2 Guidelines*. http://www.eortc.org/home/IDG/ECIL/ECIL3_Antifungal_therapy_Update_2009.pdf (15 October 2010, date last accessed).

22 Marchetti O, Cordonnier C, Calandra T 2009. *Empirical Antifungal Therapy 2009 Update of the ECIL-1 and -2 Guidelines*. http://www.eortc.org/home/IDG/ECIL/ECIL3_Empirical_Antifungal_Therapy_Update_2009.pdf (15 October 2010, date last accessed).

23 Pagano L, Akova M, Dimopoulos G *et al*. Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. *J Antimicrob Chemother* 2011; **66** Suppl 1: i5–14.

24 Cuenca-Estrella M, Bassetti M, Lass-Flörl C *et al*. Detection and investigation of invasive mould disease. *J Antimicrob Chemother* 2011; **66** Suppl 1: i15–24.

25 Freemantle N, Tharmanathan P, Herbrecht R. Systematic review and mixed treatment comparison of randomized evidence for empirical, pre-emptive and directed treatment strategies for invasive mould disease. *J Antimicrob Chemother* 2011; **66** Suppl 1: i25–35.

26 Bandolier 2010. *Integrated Care Pathways*. http://www.medicine.ox.ac.uk/bandolier/booth/glossary/ICP.html (15 October 2010, date last accessed).

27 Denning DW, Kibbler CC, Barnes RA, British Society for Medical Mycology. British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. *Lancet Infect Dis* 2003; **3**: 230–40.

28 De Pauw B, Donnelly P. Prophylaxis and aspergillosis—has the principle been proven? *N Engl J Med* 2007; **356**: 409–11.

29 Wald A, Leisenring W, van Burik JA *et al*. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; **175**: 1459–66.

30 Marr KA, Balajee SA, McLaughlin L *et al*. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. *J Infect Dis* 2004; **190**: 641–9.

31 Francesconi A, Kasai M, Petraitiene R *et al*. Characterization and comparison of galactomannan enzyme immunoassay and quantitative real-time PCR assay for detection of *Aspergillus fumigatus* in bronchoalveolar lavage fluid from experimental invasive pulmonary aspergillosis. *J Clin Microbiol* 2006; **44**: 2475–80.

32 Marr KA, Laverdiere M, Gujel A *et al*. Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. *Clin Infect Dis* 2005; **40**: 1762–9.

33 Hope WW, Billaud EM, Lestner J *et al*. Therapeutic drug monitoring for triazoles. *Curr Opin Infect Dis* 2008; **21**: 580–6.

34 Howard SJ, Cerar D, Anderson MJ *et al*. Frequency and evolution of azole resistance in *Aspergillus fumigatus* associated with treatment failure. *Emerg Infect Dis* 2009; **15**: 1068–76.

35 Verweij PE, Howard SJ, Melchers WJG *et al*. Azole-resistance in *Aspergillus*: proposed nomenclature and breakpoints. *Drug Resist Updat* 2009; **12**: 141–7.

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

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

38 Goldberg E, Gafter-Gvili A, Robenshtok E *et al*. Empirical antifungal therapy for patients with neutropenia and persistent fever: systematic review and meta-analysis. *Eur J Cancer* 2008; **44**: 2192–203.

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

40 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.
41 von Eiff M, Roos N, Schulten R *et al*. Pulmonary aspergillosis: early diagnosis improves survival. *Respiration* 1995; **62**: 341–7.
42 Cordonnier C, Pautas C, Maury S *et al*. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis* 2009; **48**: 1042–51.
43 Cronin S, Chandrasekar PH. Safety of triazole antifungal drugs in patients with cancer. *J Antimicrob Chemother* 2010; **65**: 410–6.