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A multidisciplinary team approach to the management of patients with suspected or diagnosed invasive fungal disease

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Implementation of evidence-based guidelines for the treatment of invasive fungal disease (IFD) requires collaboration among numerous clinical and laboratory services, as partners in patient care. The multidisciplinary team (MDT) approach has emerged as a way of providing comprehensive medical care by bringing together professionals from a wide range of disciplines in a coordinated and effective manner. Here, we propose an MDT model for IFD management aimed at facilitating communication among consultants, adherence to clinical pathways and optimized use of resources available at each centre.

Keywords: aspergillosis, healthcare, immunocompromised hosts, haematological malignancy

Introduction

The rising incidence of invasive fungal disease (IFD) during the past two decades has had profound effects on the management of patients with haematological malignancies. Clinicians caring for these patients have had to familiarize themselves with an ever-increasing number of previously rare fungal pathogens, as well as the utilization and interpretation of novel diagnostic modalities, selection and appropriate use of systemic antifungal drugs and implementation of strategies to prevent infection. Published clinical practice guidelines summarize the best available evidence for managing patients with IFD.[1–6] However, efforts to translate such guidelines into effective management strategies at the institutional level often encounter logistical barriers, chiefly the lack of communication and cooperation between the many specialists and services that need to be involved in the care of patients with IFD. Moreover, the availability of specific diagnostic and therapeutic modalities, and expertise in their application, vary significantly among different centres.

This situation is by no means unique to IFD. Increasingly, the needs of patients with complex medical conditions cannot be met by a single healthcare provider, leading to the fragmentation of medical care among multiple consultants and services.[7,8] A potential further problem is that, in the absence of a clearly defined case manager, responsibility for the patient may become dispersed amongst numerous medical specialists, none of whom has a clear view of the patient as a whole.[7] Poor communication with patients and among healthcare providers, interrupted continuity of care and lack of accountability for the patient should be recognized as threats to patient safety.[8] The multidisciplinary team (MDT) approach has emerged as a way of providing comprehensive medical care by bringing together professionals from a wide range of disciplines in a coordinated and effective manner.[8,9] Here, we propose an MDT model for the management of IFD. This model aims to provide evidence-based medical care, while engaging the relevant specialties in the treatment plan and optimizing the use of resources available at each centre.

Some of the overarching principles that comprise the IFD-MDT management model are outlined in this review. The IFD-MDT is defined as a group of healthcare professionals, from different disciplines, who collaborate in the care of patients with suspected or proven IFD. The team consists of clinical services directly involved in patient care, such as haemato-oncology, infectious diseases (ID), pulmonary medicine, surgical specialists and nurses, as well as providers of supporting services, such as medical microbiology, histopathology, radiology and clinical pharmacology (Table 1, Figure 1). MDT performance is likely to be enhanced by a consistent team of professionals who are dedicated, knowledgeable and passionate about IFD.

Strong leadership is essential to the success of the MDT.[9] The role of the team leader is to identify patients for MDT discussion, to facilitate communication among team members and to act as the patient's advocate. In most cases, the haemato-oncologist, being the pivotal healthcare provider for this patient population, should lead the MDT and coordinate its actions.

Good communication and collaboration among team members are essential elements of the MDT model. While collaboration among team members can take many forms, physically meeting

Table 1. Partners in the IFD-MDT model and their respective roles

Partner	Roles
Directly involved in patient care	
haemato-oncologist (MDT Leader)	(1) formulate clinical pathway for IFD management (2) detect patients with suspected IFD and propose who should be reviewed further by the team (3) decide which specialists and services should be involved in MDT discussions (4) facilitate communication amongst different consultants (5) harmonize MDT actions with haemato-oncology treatment plan (6) represent the patient's views and preferences in MDT discussions
infectious diseases specialist	(1) assist in formulating and implementing a clinical pathway for the management of patients with suspected or proven IFD (2) recommend appropriate diagnostic procedures (3) ensure correct collection and transport of specimens to the microbiology laboratory (4) prioritize tests when a limited amount of specimen is available (5) communicate with the microbiologist to optimize utilization of laboratory resources (6) assist in interpreting microbiology laboratory results (7) select appropriate antifungal drugs and dosages (8) review and revise therapy protocols based on local epidemiology and susceptibility patterns (9) design and implement an antifungal stewardship programme (10) continuously assess the need for novel diagnostic modalities and drugs and discuss these requirements with policy makers
pulmonologist	(1) select appropriate diagnostic strategy for LRT sampling (2) develop and implement a standardized protocol for FOB-BAL
surgical specialists	(1) assist in obtaining tissue for pathological and microbiological analyses (2) debride fungal foci unlikely to respond to medical treatment alone (3) in all cases, discuss risks and benefits of surgery with the MDT
nursing staff	(1) patient communication and education (2) adverse event monitoring (3) optimize specimen collection and transport to laboratory (4) minimize medication errors
Supporting services	
medical microbiologist	(1) formulate institutional protocols for processing and reporting specimens from patients with suspected or diagnosed IFD (2) report immediately by phone to MDT leader on specimens obtained from sterile sites, when: (a) fungal elements seen on microscopy (b) first detection of fungal growth (c) definitive fungal identification (3) discuss microbiology results with the MDT (4) ensure internal and external validation and quality control of fungal diagnostics (5) evaluate novel diagnostics as they become available
radiologist	(1) assist in formulating institutional guidelines that make optimal use of available imaging modalities (2) provide input on the selection of an imaging technique in specific cases (3) interpret imaging results, discuss differential diagnoses and suggest additional testing if appropriate (4) review novel imaging techniques and assess their role in the IFD-MDT management model as data become available
pathologist	(1) formulate institutional protocols for processing and reporting of specimens from patients with suspected or diagnosed IFD (2) report positive findings immediately by phone to the MDT leader (3) discuss histopathology results with the MDT (4) ensure internal and external validation, and quality control of fungal stains (5) evaluate novel diagnostics as they become available
clinical pharmacologist	(1) participate in MDT discussions on antifungal drug selection and dosing: evidence-based drug prescribing and TDM-guided dose adjustment (2) assist in design and implementation of antifungal stewardship programme (3) monitor antifungal drug prescribing, appropriateness and costs

IFD, invasive fungal disease; MDT, multidisciplinary team; LRT, lower respiratory tract; FOB-BAL, fibre-optic bronchoscopy with bronchoalveolar lavage; TDM, therapeutic drug level monitoring.

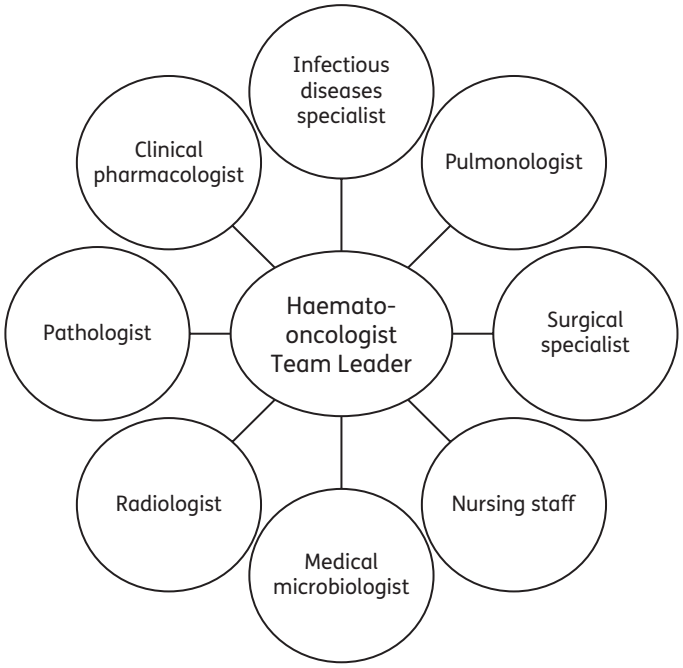

Figure 1. Diagram of the key members of the IFD-MDT.

to discuss patients and joint bedside rounds by core team members are strongly encouraged.

The IFD-MDT model is patient centred and as such considers the patient an essential partner in the clinical decision-making process. Patients should be informed about MDT discussions, and patient demographics, comorbidities, supportive and palliative care issues, views and preferences should be presented at MDT discussions.

MDT discussions should be based upon written clinical pathways for IFD management. A clinical pathway is an algorithmic structure that translates guidelines into standardized local clinical practice and can be applied in a timely manner.[10,11] Clinical pathways must reflect both current scientific evidence and site-specific factors, such as drug availability and local susceptibility patterns. In proposing this model, we are keenly aware of the importance of country- and site-dependent factors. For example, in certain localities the role of the ID consultant is assigned to clinical microbiologists or haemato-oncologists with extensive knowledge and experience in this field. Therefore, our proposed model should be adjusted to local circumstances.

Finally, there should be periodic assessment of specific performance indicators associated with IFD-MDT activity. Auditable standards of care for IFD management have been proposed.[12] MDT members should be informed about regional and national trends in fungal infection rates in high-risk groups and antifungal susceptibility patterns, as well as process and outcome measures, such as the quantity and appropriateness of antifungal drug use and survival rates among patients diagnosed with IFD.

Clinical services involved in the IFD-MDT

Haemato-oncologist

The haemato-oncologist is the pivotal healthcare provider for patients with acute leukaemia and recipients of haematopoietic stem cell transplants (HSCTs), and as such is uniquely positioned to act as the MDT leader. Haemato-oncologists caring for these patients must familiarize themselves with clinical guidelines and important developments relevant to the prevention and treatment of infections in cancer patients.[1–6] Clinical pathways, based on evidence-based guidelines and adapted to local circumstances, should be formulated. Consensus statements issued by professional societies provide a useful reference,[1–6] but the specific epidemiology of IFD at each centre will have major implications for preventive and treatment strategies. For example, the baseline incidence of IFD may determine the appropriateness of antifungal prophylaxis versus a more selective diagnostic-driven clinical pathway.[13] Moreover, local antifungal susceptibility patterns will affect the selection of drugs for the prevention and empirical treatment of IFD.[14] Clinical pathways should be regularly reviewed and updated when changes occur in the local epidemiology or new scientific evidence becomes available.

A crucial element in the success of the IFD-MDT approach is the early detection of patients with suspected IFD, who should be reviewed by the team. To date, no single laboratory marker has been shown to be sensitive enough to reliably capture patients with incipient fungal infection; thus, it is often the haemato-oncologist, prompted by clinical cues, who alerts the team and initiates MDT discussions. Subsequently, it is up to the haemato-oncologist to decide which services should be involved in patient care, to facilitate communication among different consultants and to ensure that diagnostic and therapeutic interventions are performed within required time frames. Frequent updates and reassessments are often necessary as test results become available or the clinical situation evolves, particularly in severely ill and unstable patients. Moreover, as the clinician managing the patient's underlying malignancy, the haemato-oncologist must harmonize the actions of the IFD-MDT with ongoing oncological treatment. Common issues that arise during IFD management include the feasibility of diagnostic procedures, such as bronchoscopy and biopsy in frail patients with bleeding diathesis, interactions of antifungals with cancer drugs and the need to delay or adjust the dose of cancer treatment in patients with active IFD. Finally, in keeping with the patient-centred approach, the haemato-oncologist should involve the patient in the clinical decision-making process and accurately convey the patient's views and preferences to the MDT.

ID specialist

Consultation with an ID specialist has consistently been shown to improve the outcome of patients with life-threatening infections[15–19] and to reduce inappropriate use and costs of antibacterial and antifungal drugs in a range of clinical settings.[20–22] Nevertheless, the extent of involvement of ID physicians in managing IFD patients varies significantly among different hospitals. Given the complexity of such patients, we feel that an ID physician should be involved at all stages as a member of the IFD-MDT. The ID physician should have training and experience pertinent to the treatment of immunosuppressed patients. Moreover, he/she should be knowledgeable about cancer treatments, specifically their immune consequences, adverse effects and potential interactions with antimicrobial drugs.

The ID specialist should be involved in the design and implementation of a clinical pathway for the management of patients with suspected or proven IFD. In addition, an ID specialist can

significantly enhance the interaction between the clinical team and the microbiology laboratory and optimize the utilization of laboratory resources. In this capacity, the ID specialist may recommend appropriate diagnostic procedures, ensure correct collection and transport of specimens to the microbiology laboratory, prioritize tests when a limited amount of specimen is available, communicate with the microbiologist and assist in interpreting the microbiology laboratory results.

The ID specialist should be charged with the selection and appropriate use of antifungal agents. Such decisions must take into account evidence from clinical trials, as well as local susceptibility data, risk of drug toxicity and interactions, and need for cost containment. The importance of appropriate and timely initiation of antifungal treatment is underscored by studies showing that delayed treatment is associated with increased mortality rates for candidaemia,[23,24] invasive aspergillosis[25] and mucormycosis.[26] The ID specialist should periodically review and revise prophylactic and empirical therapy protocols based on local epidemiology and susceptibility patterns.

The concept of antifungal stewardship is relatively new, although most hospitals restrict antifungal use because of cost considerations. The emergence of drug-resistant fungal species, such as *Candida glabrata*, *Candida krusei* and non-*Aspergillus* moulds,[27,28] and the spread of azole resistance among *Aspergillus* spp. in the Netherlands and elsewhere,[14] combined with a dwindling drug development pipeline, provide impetus for antifungal stewardship.[29] Strategies for optimizing antifungal use include adopting a diagnostic-driven approach instead of an empirical approach,[30–32] de-escalation of empirically initiated antifungals based on antifungal susceptibility testing[33] and switching intravenous azoles to oral formulations.[29] Importantly, these efforts should be supported by prospective surveillance of IFD incidence in high-risk patient populations, as well as audits of antifungal prescribing practices (timeliness and appropriateness) and IFD outcomes.[29]

Pulmonologist

The detection of pulmonary infiltrates in immunosuppressed patients with haematological malignancies is associated with increased mortality, with fungi predominating among the microbiologically determined causes.[34] Because lung infiltrates may result from numerous infectious and non-infectious aetiologies, accurate sampling and processing of the lower respiratory tract (LRT) is essential.[35,36] The most frequent diagnostic modality used for this purpose is fibre-optic bronchoscopy with bronchoalveolar lavage (FOB-BAL). Importantly, effective cooperation is achieved when a pulmonary specialist is engaged as a partner in patient care, rather than as a technologist who is only called upon to perform FOB-BAL. To that end, the pulmonologist should be involved in IFD-MDT discussions as soon as pulmonary infection is suspected. The primary role of the pulmonologist is to assess the diagnostic yield and risks of LRT sampling techniques and to recommend the most appropriate diagnostic strategy.

FOB-BAL is the most readily available LRT sampling method, but diagnostic yield is variable and depends on the underlying malignancy, extensiveness of pulmonary infiltrates and timing of the procedure.[36–38] Transbronchial biopsy is rarely performed in haematological patients because of the risk of bleeding due to thrombocytopenia and some uncertainty over the added value of this procedure. Computed tomography (CT)-guided lung biopsy shows promise in patients with peripherally located lesions and adequate platelet counts (>50 000/μL), with prothrombin and partial thromboplastin times within normal limits, especially if combined with molecular diagnostics.[39,40] Open lung biopsy is reserved for patients whose diagnosis remains elusive and who have failed to respond to empirical treatment. This procedure has a relatively high diagnostic yield and impact on patient care,[41–43] but is associated with significant morbidity.

To optimize the diagnostic yield, techniques for FOB-BAL, as well as handling and processing of BAL fluid, should be standardized and clearly defined.[38,44] This may be especially true for quantitative tests performed on BAL fluid, such as the galactomannan index.[4,45] Unfortunately, there is a lack of high-quality clinical data to help formulate such a protocol. Variables that should be defined include the target area for FOB-BAL, type of fluid used, total volume infused and number of infusions. An example of a FOB-BAL protocol is provided in Table 2. The yield of FOB-BAL decreases dramatically when it is performed >24 h after clinical presentation.[36] Moreover, delayed FOB-BAL is associated with increased mortality rates.[36] Therefore, optimal utilization of FOB-BAL requires availability within 24 h of request.

Surgical specialists

Depending on the manifestations of IFD, surgical specialists may be involved in the MDT either for diagnosis or surgical debridement

Table 2. Example of a standardized fibre-optic bronchoscopy and bronchoalveolar lavage protocol[a]

(a) BAL technique
(1) Wedge the bronchoscope in the affected segment
(2) Infuse 40 mL of sterile saline solution[b]
(3) Manually aspirate the BAL fluid gently
(4) Infuse saline solution in 20 mL aliquots, aspirating after each aliquot, until 120 mL is infused
(5) If <40 mL effluent is retrieved, continue to infuse and aspirate 20 mL aliquots until 40 mL effluent is retrieved, up to a maximum of 200 mL infused
(6) Immediately transfer fluid to the laboratory for processing
(b) Tests performed on BAL fluid
(1) Cytospin and Giemsa stain to assess cell population in BAL fluid and infiltration by the underlying malignancy
(2) Gram's stain and bacterial culture
(3) Fungal stain (calcofluor white) and fungal culture
(4) Direct immunofluorescence for *Pneumocystis jirovecii*
(5) Direct immunofluorescence for *Legionella pneumophila*
(6) Ziehl–Neelsen/auramine stain and mycobacterial culture
(7) Respiratory virus assays: immunofluorescence for viral antigens or nucleic acid amplification
(8) Shell vial culture assay for cytomegalovirus
(9) Galactomannan EIA
(10) Optional: *Aspergillus*-specific or pan-fungal PCR, *P. jirovecii* PCR
(11) Optional: pan-bacterial (16S) PCR, mycobacterial PCR, *Legionella* PCR

BAL, bronchoalveolar lavage; EIA, enzyme immunoassay.
[a]Table reproduced with permission from Sampsonas *et al.*[38]
[b]Avoid using Plasma-Lyte® solution, as it may cause false-positive galactomannan results.[46]

of fungal foci that are unlikely to respond to medical therapy alone. Surgery of patients with haematological malignancies presents special challenges for the surgical team, including significantly increased risk of bleeding and perioperative infection. Hence, surgery should be carefully planned in close collaboration with the MDT and should always be preceded by assessment of potential risks and benefits. Clinical practice guidelines for the treatment of invasive aspergillosis define conditions where surgical resection of fungal foci should be considered, including disease contiguous to the heart or great vessels, persistent haemoptysis caused by a single fungal focus, pericardial infection, invasion of the chest wall, fungal empyema and endocarditis.[1] Resection of devitalized bone and skin may be required for cure of fungal osteomyelitis and cutaneous infection, respectively.[1] Surgical resection of a single pulmonary lesion in a patient who is scheduled for intensive chemotherapy or HSCT may also be considered.[1] The indications for surgical evacuation of fungal brain abscess remain poorly defined.[47,48] Hydrocephalus is a typical complication of fungal meningitis and requires drainage by insertion of a shunt.[48] Surgical debridement is recommended, if feasible, for mucormycosis involving rhino-orbital, cerebral and soft tissue, and for selected patients with localized pulmonary involvement.[49,50]

Pre-surgical planning and intervention should be performed without delay to prevent dissemination, due to the progressive nature of invasive mould infections.[51] The extent of surgical debridement will depend in many cases on the clinical judgement of an experienced surgeon during surgery. Intraoperative frozen sections may help guide such decisions.[52] Repeated assessment and debridement is often required, especially in patients with mucormycosis.[50,51]

Nursing staff

Engaging the nursing staff in team discussions is an essential but frequently overlooked component in the success of an IFD-MDT model. An involved and knowledgeable nursing team is likely to enhance patient safety and outcomes by facilitating the implementation of MDT decisions, reducing errors in obtaining and transporting specimens to the microbiology laboratory and minimizing medication errors. Nurses are frequently the first to become aware of early signs or symptoms of fungal disease, as well as adverse effects associated with antimicrobial treatment. Moreover, nurses play a central role in patient education. Of importance to IFD prevention, involved nurses can promote avoidance of exposure to fungal spores, maintenance of personal hygiene and self-monitoring for early signs of infection.[53]

Supporting services

Medical microbiologist

Centres caring for patients at high risk of IFD should have rapid access to a microbiology laboratory that can perform detection, identification and susceptibility testing of medically relevant fungi. All three components are essential to guide patient management and should ideally be available onsite. Some services, however, such as susceptibility testing and genomic sequence-based identification, may require specimens to be sent to a reference laboratory.

Because saprophytic fungi are ubiquitous in the environment, the clinical significance of their detection in respiratory samples depends to a large degree on host factors.[54] Therefore, hospitals should apply a scheme for prioritized handling of specimens from high-risk patients, e.g. through specimen labelling. The importance of exchange of information between the clinical team and the microbiologist cannot be overstated. The clinical team should alert the microbiologist to high-priority specimens and share their clinical suspicion. It is the responsibility of the microbiologist to guide correct specimen collection and transport, as well as to alert the clinicians in the event of fungal detection in prioritized samples. Positive results should be reported by phone to the responsible physician at the first detection of hyphae by microscopy, first detection of growth on culture and final fungal identification. Fungi cultured from sterile-site specimens, including blood, CSF and vascular catheter tips, as well as those cultured from urine, should be identified to the species level.[4,12] BAL fluid is considered sterile for this purpose.

It should be noted that fungal identification has undergone transformation in recent years, with traditional morphological identification being replaced by DNA-based methods.[55] Traditional identification requires extensive experience and training, whereas DNA-based methods are not universally available; thus, both methodological approaches may be delegated to a specialist reference laboratory.

Non-culture assays have gained importance in management algorithms for high-risk patients due to the limited sensitivity of culture for the detection of IFD. The use of galactomannan (in serum) and cryptococcal antigen (in serum and CSF) are supported by strong evidence, whereas there is moderate evidence to support β-D-glucan testing.[3] PCR-based assays, although promising, have yet to be appropriately standardized.

Radiologist

Imaging studies have assumed a crucial role in the clinical assessment of patients with suspected IFD. In particular, findings on CT of the chest often serve as a trigger to initiate antifungal treatment and to conduct additional diagnostic testing. Recent advances in CT technology include the replacement of single detector scans with multidetector scans and the advent of thin-section multislice CT and low-dose CT.[56] Information is emerging regarding the use of additional modalities, such as magnetic resonance imaging and fluorodeoxyglucose positron emission tomography.[56,57] Proper use of imaging technology must be addressed within the IFD-MDT protocol, taking into consideration diagnostic accuracy, radiation dose and cost.

The modality of choice to diagnose invasive pulmonary aspergillosis (IPA) is chest CT. Thin-section multislice CT (slice section 1 mm, beam pitch 1.5–2) is superior to high-resolution CT.[4,56–58] The typical findings in IPA are single or multiple macronodules. The halo sign is an early transient clue to the diagnosis of IPA that is most likely to be seen during the first week after presentation.[59] Initiating treatment during this early phase is associated with improved survival.[25] Therefore, in centres implementing a diagnostic-driven approach, CT imaging should be performed and interpreted within 1 day of requisition. The air-crescent sign and cavitation represent late radiological manifestations of IPA.[59] Preliminary data suggest that CT angiography may have improved specificity for angioinvasive mould disease as compared

Table 3. Suggested template for standardized reporting of histopathology[a]

Pathological section	Morphological features	Comments
Permanent section		
hyphal fungal organism	septate non-pigmented hyphal elements identified[b]	morphological findings suggestive of *Aspergillus* spp. differential diagnosis includes other septate moulds, such as *Fusarium*, *Scedosporium* and *Paecilomyces*, as well as non-septate moulds (*Mucorales*); correlation with culture results is recommended
	non-septate (or pauciseptate) non-pigmented hyphal elements identified[b]	morphological findings suggestive of *Mucorales*; differential diagnosis includes septate moulds; correlation with culture results is recommended
yeast-like fungal organism	yeast with pseudohyphae[c]	morphological findings suggestive of *Candida* spp.; differential diagnosis includes other filamentous fungi; correlation with culture results is recommended
	yeast without pseudohyphae[c]	morphological findings suggestive of *Candida* spp.; differential diagnosis includes *Cryptococcus*, *Sporothrix*, *Histoplasma*, *Coccidioides* and *Blastomyces*; correlation with culture results is recommended
	pigmented septate hyphal or yeast-like elements identified	morphological findings suggestive of a dematiaceous fungus; differential diagnosis includes other filamentous and yeast-like fungi (including *Cryptococcus*); correlation with culture results is recommended
additional relevant comments		(1) quantity of fungal elements (2) angioinvasion (3) perineural invasion (4) tissue necrosis (5) inflammatory exudate (neutrophilic, mononuclear) (6) granuloma formation
Intraoperative frozen section	hyphal elements identified yeast-like elements identified	

[a]Table reproduced with permission from Sangoi *et al.*[64]
[b]Other features relevant to filamentous fungi: hyphal width, regularity and branching pattern (acute or right angle).
[c]Other features relevant to yeast-like fungi: size, budding (broad or narrow-based), capsule, intracellular localization within macrophages (*Histoplasma capsulatum* and *Penicillium marneffei*), presence of spherules (*Coccidioides immitis*).

with standard CT,[60] but further validation is required before this modality can be recommended.

The above imaging techniques are only effective if findings are accurately interpreted and reported to the MDT. Specifically, macronodules, ground glass opacities and cavitation should be clearly described. Use of non-specific language to report findings, e.g. 'findings consistent with an infectious aetiology' or 'fungal infection cannot be ruled out', is unhelpful and should be discouraged.

Follow-up imaging can provide important information on response to therapy, but inappropriate use of serial CT scans can lead to misleading results and unnecessary treatment changes. Radiologists and clinicians should be aware that IPA lesions tend to increase in volume during the first 10 days of therapy and during recovery from neutropenia[59] and that these phenomena do not correlate with treatment failure. Therefore, in patients who are clinically stable, CT imaging should not be repeated within 3 weeks of treatment initiation. Low-dose CT produces granular images and may be suboptimal for assessing febrile neutropenic patients.[56] It can, however, be used for follow-up of patients with known pulmonary findings, in order to minimize the radiation dose from multiple scans. Serial imaging is generally unnecessary in patients who are clinically stable and appear to be responding to treatment. Criteria for repeating chest imaging include: (i) clinical evidence of progressive or relapsing disease (fever, dyspnoea or haemoptysis); (ii) possible cessation of antifungal therapy; (iii) commencement of an additional cycle of chemotherapy; and (iv) prior to allogeneic stem cell transplantation.[11]

Utilization of chest imaging is not without risks to patients. Cumulative radiation dose is a concern in patients undergoing multiple scans. Moreover, transportation of immunosuppressed patients to and from the radiology suite may place them at risk of acquiring nosocomial infections. HSCT recipients and neutropenic patients may benefit from wearing N-95 respirators during transport, particularly during periods of hospital renovation.[53,61] Healthcare workers in contact with these patients should adhere to strict hand-hygiene practices and regulations should be in place to avoid unnecessary delays in the radiology suite.[53]

Pathologist

Detection of fungal elements within diseased tissue is the principal means of establishing a definitive diagnosis of IFD.[62] Moreover, pathology may provide the only evidence of fungal disease in the case of non-culturable organisms.[52] Significantly, pathological case series have shown that incorrect reporting of fungal elements found in specimens occurs in ~20% of cases.[63] Frequent errors

include misidentification of septate and non-septate organisms and yeast forms, resulting from the use of inappropriate terminology, incomplete knowledge of mycology and the presence of morphological mimics.[63] Thus, the IFD-MDT should ideally include a pathologist who is experienced in IFD diagnosis.

Pathology laboratories should establish standard procedures for the handling of specimens from immunocompromised patients suspected of IFD. Reducing the turnaround time for biopsy specimens from haemato-oncology patients is a priority as the rapid availability of results can dramatically influence treatment decisions. Labelling and prioritizing biopsy specimens from haemato-oncology patients, automation of specimen processing and optimization of workflow can help achieve this goal.[52]

All tissue specimens from immunocompromised patients should be stained with fungal stains in addition to standard stains such as haematoxylin/eosin.[12] It is important that specialized fungal and standard stains are performed in parallel rather than sequentially, to prevent unnecessary delays.[12] The choice of fungal stain often depends on local expertise and experience. Silver impregnation stains, such as Gomori or Grocott methenamine silver, provide excellent visualization of fungal hyphal walls but overstaining of surrounding tissue can be problematic.[12,52] Melanin stains, such as Fontana–Masson, are particularly useful for dematiaceous fungi and *Cryptococcus*.[52] Periodic acid Schiff, which stains glycogen in fungi and tissue, may offer better visualization of surrounding tissue.[12] Control sections are essential to ensure adequate staining, e.g. *Mucorales* spp. require longer staining times than *Aspergillus* spp.[52]

It is important to recognize that histopathological examination alone does not allow for fungal identification beyond that provided by general morphological features. With these caveats in mind, histopathological findings may be sufficient to guide treatment until definitive identification by culture. To avoid over-reporting, results of fungal detection on histopathology should be standardized, emphasizing morphological appearance: hyphae (septate or non-septate; pigmented or non-pigmented) and yeast or yeast-like forms (with or without pseudohyphae) (Table 3). The presence of fungal elements should be immediately reported by phone. Immunohistochemical and molecular methods have shown promise for the identification of fungi directly from pathological specimens,[52,65–68] but are not yet widely available to clinical laboratories.

Clinical pharmacologist

The expanded use of antifungal drugs in immunocompromised patients presents important challenges, namely the selection of drug-resistant fungi, the need for therapeutic drug level monitoring (TDM), surveillance of adverse events, drug–drug interactions and the rising cost associated with these drugs.[29] Thus, there is a need to optimize antifungal use with the aim of improving patient outcomes and reducing adverse sequelae. Suboptimal exposure to fluconazole, voriconazole and posaconazole is frequent and associated with treatment failure and increased mortality.[69,70] Partnership with a clinical pharmacologist can facilitate evidence-based drug prescribing and TDM-guided dose adjustment. Moreover, a clinical pharmacologist is a key player in the development and implementation of an institutional antifungal stewardship initiative. The essential elements of such a programme have been laid out[29,71] and include the implementation of locally adapted guidelines, formulary restriction and ongoing monitoring of the appropriateness of antifungal use.

Summary

The IFD-MDT model proposed here is aimed at improving outcomes in patients with IFD by optimizing the use of expertise available to each medical centre. We have avoided discussing specific clinical care pathways, such as antifungal prophylaxis and empirical versus diagnostic-driven strategies for initiating antifungal treatment in high-risk patients. These approaches depend to a large degree on site-specific factors, such as the incidence of IFD in various patient populations, availability of non-culture diagnostics and the ability to rapidly perform CT scans and FOB-BAL and analyse the results. In bringing together an MDT and formulating clinical pathways, physicians may become aware of gaps in the local availability of critical services. Thus, the IFD-MDT model can serve as a catalyst for achieving adequate standards of care for the management of patients with IFD.

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