
Working Party Report

Therapy of deep fungal infection in haematological malignancy

Working Party of the British Society for Antimicrobial Chemotherapy*†

The treatment of deep fungal infection in haematological malignancy remains controversial due to the limited number of antifungal agents available and problems over their spectrum and dose-limiting side-effects. Difficulties in diagnosis mean that most treatments are begun empirically; amphotericin B remains the drug of choice. Emerging resistance may limit the usefulness of fluconazole and other azoles in some areas. Lipid preparations of amphotericin B have reduced the toxicity of this agent, but some issues of dosage and efficacy remain. Adjunctive treatments aimed at augmenting the host response to infection may have a role to play in deep fungal infection.

Introduction

Deep fungal infection (DFI) is an increasing problem in patients treated intensively for haematological malignancy. Fungal infection may be found in 25% of autopsies.¹ Most infections are with *Candida* or *Aspergillus* spp. or members of the order Mucorales, although reports of emerging pathogens such as *Fusarium* and *Trichosporon* spp. are increasing. Risk factors include prolonged neutropenia, broad-spectrum antibiotic and steroid use and central venous catheters. With disease- and treatment-related mucosal damage, reduced immunoglobulin levels and impaired cell-mediated immunity, defences to colonization and invasion are lost. In allogeneic marrow transplantation, graft rejection may be a significant predisposing factor for invasive pulmonary aspergillosis (IPA).²

Clinical presentation

Symptoms and signs of DFI are unreliable and often absent. The commonest single abnormality may be unremitting fever (>38°C) with a neutrophil count of $<0.5 \times 10^9/L$, despite broad-spectrum antibiotic therapy.³ Table I illustrates the wide spectrum of clinical presentation of DFI. *Candida* infection may present as pyrexia of un-

known origin (PUO) due to fungaemia or as involvement of any organ (e.g. kidney or lung) or as both during prolonged neutropenia. A specific syndrome of chronic disseminated candidosis (CDC), also known as hepato-splenic candidosis, usually occurs while neutrophils are regenerating.⁴ There is abdominal pain, persistent fever despite antibiotics, negative blood cultures, characteristic CT scan defects in liver and spleen, elevation of alkaline phosphatase out of proportion to other liver enzyme abnormalities and, sometimes, a positive needle biopsy.

Invasive aspergillosis occurs most often as thrombotic and haemorrhagic lung infection but also as invasive rhinosinusitis,⁵ cerebral infection or disseminated infection.⁶ Despite pulmonary symptoms, signs may be absent and chest radiographs normal. Thirty percent of patients whose autopsy reveals IPA have a normal chest X-ray in the last week of life.⁶ IPA should be suspected during neutropenic fever with pleuritic pain, cough, dyspnoea and abnormal pulmonary signs, even when the chest X-ray is normal or shows minimal or non-specific abnormalities.

Diagnosis

Objective diagnostic tests yield non-specific and variable results as the clinical presentation. *Aspergillus* spp. are

*Corresponding author: Dr Rosemary A. Barnes, Department of Medical Microbiology and PHL, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK.

†Rapporteurs: A. G. Prentice and R. A. Barnes. Members of the Working Party: T. R. F. Rogers (Chairman), Royal Postgraduate Medical School, London; R. A. Barnes, University of Wales College of Medicine, Cardiff; J. Cohen, Royal Postgraduate Medical School, London; D. W. Denning, University of Manchester; E. G. V. Evans, University of Leeds; R. J. Hay, Guy's Hospital, London; A. G. Prentice, Derriford Hospital, Plymouth; D. C. E. Speller, Central Public Health Laboratory, London; D. W. Warnock, Public Health Laboratory, Bristol; R. E. Warren, Royal Shrewsbury Hospital, Shrewsbury.

Table I. Clinical features associated with specific DFI in neutropenic patients

Clinical features	Associated fungi
Non-specific	
PUO unresponsive to antibiotics	any fungus (most often disseminated <i>Candida</i> or <i>Aspergillus</i> spp.)
Pulmonary	
cough	} <i>Aspergillus</i> spp. Mucorales <i>Candida</i> spp.
pleural pain	
haemoptysis	
focal infiltrates	
Head and neck	
facial pain	} <i>Aspergillus</i> spp. <i>Fusarium</i> spp. Mucorales
unilateral facial swelling	
proptosis	
sinusitis	
epistaxis	
dysphonia	<i>Candida/Aspergillus</i> spp.
Skin rash	
macronodular	<i>Candida</i> spp.
multiple pink nodules	<i>Candida/Trichosporon</i> spp.
erythematous	} <i>Fusarium/Aspergillus</i> spp.
necrotic	
maculopapular	
CNS	
epilepsy	} <i>Aspergillus</i> spp. <i>Pseudoallescheria/Scedosporium</i> spp.
stroke	
Liver and spleen	
nausea	} <i>Candida</i> spp. <i>Aspergillus</i> spp. <i>Trichosporon</i> spp.
abdominal pain	
neutrophil recovery	
hepatosplenomegaly	
rising liver enzymes	
CT scan multiple defects	

seldom grown from blood culture⁷ except occasionally in endocarditis. Even with extensive candidosis involving several organs, blood cultures may be sterile. However, growth of candida in a single blood culture is sufficient proof of DFI⁸ and is an absolute indication for systemic antifungal therapy in the neutropenic patient. Fungal serology has little to offer in the diagnosis of DFI in neutropenia—antibody levels may have prognostic significance but are seldom diagnostic and current methods of antigen detection lack sufficient sensitivity except in the diagnosis of cryptococcal infections. Microscopy and culture of yeasts and hyphae in body fluids that are normally sterile and in biopsies implies DFI. Finding *Aspergillus* species on bronchoalveolar lavage (BAL), whilst specific, has poor sensitivity.⁹ BAL is superior to both bronchial washing and transbronchial biopsy (TBB) for IPA but may be negative in focal aspergillus infection², and TBB may be contraindicated by severe thrombocytopenia. CT scan appearances are more useful

diagnostically.² High resolution CT scans of the chest must be done early since nodular enhancing lesions showing cavitation, air crescent formation or a 'halo sign' are highly suggestive of IPA.¹⁰ The halo sign (low attenuation, perinfiltrates) is often the initial radiological abnormality and detection may enable an earlier diagnosis to be made.¹¹ Percutaneous needle aspiration from peripheral lesions guided by fluoroscopy or CT scan is 67% sensitive for IPA.¹³ CT scans may also identify CDC¹² and invasive rhinocerebral aspergillosis.⁵ In suspected aspergillus rhinosinusitis early biopsy or aspiration is essential because amphotericin B may prevent direct extension into the cranium.^{5,14}

Invasion of the gut wall by *Candida* spp. may be confirmed by endoscopy and brush or biopsy.¹⁵ Endoscopy alone is unreliable since mucositis has a similar appearance whether idiopathic or due to fungi, bacteria or viruses.

All biopsies should be cultured since fungal species and antifungal sensitivity cannot be determined by

histology. False-negative results are likely in the early stages of a DFI and repeat sampling may be needed. In cryptococcosis, organisms can usually be isolated from appropriate culture specimens and tests for detection of cryptococcal antigen in serum and CSF are reliable.

Treatment

Indications for starting systemic antifungal therapy are summarized in Table II. In practice, because current antifungal prophylaxis is not completely effective, most patients receive empirical treatment on suspicion of DFI because of a persistent, refractory PUO.

Empirical treatment

The drug of choice is iv amphotericin B because of its wide range of activity against systemic candidosis, aspergillosis, coccidioidomycosis, histoplasmosis, blastomycosis, mucormycosis and sporotrichosis.¹⁶ Fluconazole has been used in one study of PUO and shown to be equivalent.¹⁷ However, many episodes of PUO will be non-fungal in origin and much larger studies are necessary to identify differences in efficacy. Moreover, local variation in the spectrum of infections and widespread use of fluconazole mean that amphotericin remains the preferred choice for general recommendations, although local factors may dictate otherwise. The most appropriate timing for the start of empirical therapy is unclear. One retrospective review showed a significant reduction in iv catheter-associated persistent fungaemia when iv amphotericin B was used early.¹⁸ However, there are only two prospective, randomized, controlled studies of iv amphotericin B given at either 4 days³ or 7 days in patients with unresponsive PUO.¹⁹ Both showed a reduction in infective episodes and one showed an excess of deaths due to fungal infection in the non-amphotericin B arm,³ but neither showed a difference in overall survival. There have been no trials

comparing the efficacy of different start times, but it is likely that early start times confer an advantage in DFI, although this must be balanced against the fact that more patients will receive amphotericin B, some unnecessarily.

Amphotericin B should be started at a dose of 1 mg/kg body weight/day given in 500 mL of 5% dextrose over 4 h as an iv infusion; there is no need to escalate from a lower dose over several days. Test doses (1 mg in 80 mL of 5% dextrose over 30–60 min) may identify hypersensitive patients. Alternatively, a small portion of the first dose may be infused slowly over 10 min and then, if there are no reactions after 20 min, the rest of the infusion can be given. Careful monitoring of patients during slow infusion is mandatory when initiating therapy.

Acute toxic reactions such as chills and fever are common and can be prevented or lessened by pethidine²⁰ (25–50 mg slow iv injection). Chlorpheniramine (12.5–25 mg iv) or ibuprofen (10 mg/kg orally) are also effective prophylactics.²¹ The widespread use of steroids for such reactions should be discouraged. Though often severe, acute toxicity may be self-limiting with tolerance to reactions developing in 7 days such that amphotericin B may be given more rapidly over 1–2 h. There is no need to protect the drug from light in infusion bags and lines as it is stable on exposure.²²

Renal blood flow, glomerular filtration rate and tubular reabsorption of electrolytes are all reduced by systemic amphotericin B. These effects are usually reversible, but can potentiate the nephrotoxicity of cyclosporin and aminoglycosides. Blood creatinine should be estimated on alternate days. When the creatinine exceeds 250 µmol/L or three times the pre-treatment baseline (less in children), it may be necessary to support renal function or change to a lipid-associated formulation (see below). Hypokalaemia and hypomagnesaemia commonly result from the amphotericin-induced tubular defect and loss of potassium and magnesium may be blocked by oral amiloride 10–20 mg daily.²³ In many cases intravenous

Table II. Indications for systemic antifungal therapy in neutropenic patients^a with haematological malignancy

PUO unresponsive to broad-spectrum antibiotics after 72–96 h
or
New pulmonary infiltrates/cavities on chest radiograph/CT scan
or
Positive fungal cultures from blood or other normally sterile sites
or
Positive aspergillus cultures from respiratory passages or skin biopsy
or
<i>C. tropicalis</i> cultures from any site in PUO
or
Specific clinical presentations as shown in Table I

^a Neutrophils <0.5 × 10⁹/L for >7 days.

supplements of these electrolytes will be needed. Serum magnesium levels should be measured weekly.²³ Less common side-effects of this drug are cardiotoxicity, hepatotoxicity and myelotoxicity.¹⁶

Documented invasive aspergillosis requires ≥ 1 mg/kg/day of amphotericin B and dosages up to 1.5 mg/kg/day have been tolerated.²⁴ Deterioration of renal function is inevitable but reversible. Therapy on alternate days may be considered but should not result in a significant reduction of total dose. Yeast infections require lower doses (0.7 mg/kg/day) although *Candida lusitanae* may develop amphotericin B resistance rapidly and higher doses should be used for *Candida krusei* infections. Appropriate duration of therapy is difficult to assess and guidelines for stopping iv amphotericin B are given in Table III. Using total cumulative dose as a guideline is unhelpful. Resolution of fever alone may be misleading as an indicator of response (and as a therapeutic end-point) because of the frequent concomitant use of anti-inflammatory agents. Since the response to iv amphotericin B depends on neutrophil regeneration,²⁵ it is often continued until the neutrophil count exceeds $0.5 \times 10^9/L$, and fever and other relevant symptoms and signs have resolved. Therapy should be continued until there is no further resolution of radiological changes. Minor radiological changes may persist due to post-infective scarring and do not necessarily require continued therapy. With no evidence of DFI other than PUO, iv amphotericin B can be stopped following resolution of fever and recovery of neutrophils. There is no evidence to support the common practice of using a longer duration of therapy for aspergillus than for candida infections, but a minimum of 2 weeks' treatment is necessary for survival.²⁶

While levels of circulating fungal antigen and antibody may correlate retrospectively with presumed infection,²⁷ serology has not been validated as a means of determining duration of therapy.

After treatment with iv amphotericin B, patients are at risk of relapse of DFI during subsequent periods of neutropenia (e.g. marrow transplant following conventional chemotherapy). This risk should not exclude further cytotoxic therapy because early empirical iv amphotericin B or continuous prophylaxis (amphotericin B 1 mg/kg/day starting with cytoreductive therapy and continuing until

neutrophil recovery) can successfully pre-empt recurrent DFI.²⁸ Elective surgical resection of one or more foci of pulmonary fungal infection is often successful and should be considered during a period of haematological recovery before any planned subsequent therapy with a high risk of fatality due to IPA.²

Alternative drugs, including new formulations of amphotericin B (Table IV)

Treatment failure occurs regularly and, in some cases, may be due to strains of fungi resistant to amphotericin B.²⁹ For the unresponsive patient, or for the patient with severe conventional amphotericin B toxicity, alternative therapy may therefore be needed.

Lipid-associated amphotericin B. Three lipid-based preparations are currently available in clinical practice. Incorporation of amphotericin B in liposomes allows daily 30 min iv infusion of up to 6 mg/kg body weight with no undue acute toxicity and a marked reduction in nephrotoxicity.^{30,31} When 3–5 mg/kg liposomal amphotericin B was used for suspected or confirmed DFI in 133 neutropenic episodes in 116 patients not tolerating or not responding to conventional amphotericin, acute reactions occurred in only five and there was no significant nephrotoxicity. There was a 61% response in suspected DFI and a 77% response in proven IPA.³² This and other forms of lipid-associated amphotericin B (e.g. amphotericin B colloidal dispersion, amphotericin B lipid complex) are now available. Each is likely to exert a different degree of reduction in toxicity with equal or potentially greater efficacy.³³ The major advantage of these agents is their enhanced therapeutic index, owing not only to reduced toxicity (enabling higher dosaging regimens) but also, possibly, to the organ distribution, resulting in targeting of the drug to the reticular endothelial system and sites of inflammation (such as liver, lung and spleen).³⁴ Consequently lipid-associated forms are recommended (i) for infections where effective concentrations are not readily achievable using conventional amphotericin B (Mucorales infections, *Fusarium* spp., some *Aspergillus* spp.), (ii) for infections where conventional amphotericin B appears to be failing and (iii) when renal and other toxicities preclude the use of conventional amphotericin B.

The recommended dosages of lipid preparations are under review. EORTC studies have suggested that 1 mg/kg of liposomal amphotericin B is as effective as 4 mg/kg in the treatment of aspergillosis,³⁵ and similar data suggest the use of lower dosages for the treatment of PUO.³⁶ Conversely, higher doses may be required in the treatment of candidiasis,³⁷ particularly in neutropenic patients where drug efficacy may depend, in part, on phagocyte delivery.³⁸ Further randomized studies are required to determine the optimum therapeutic dosages;

Table III. Guidelines for stopping empirical systemic antifungal therapy in neutropenic patients

Recovery of neutrophils ($>0.5 \times 10^9/L$)
Resolution of fever
Resolution of other symptoms and signs
Abnormal radiology becomes normal
No further improvement in radiological abnormalities
Positive cultures become consistently negative

Table IV. Antifungal drugs for DFI in haematology malignancy

Indication	First-line	Adult dosage	Contraindications/ side-effects	Second-line	Notes
Suspected DFI	amphotericin B	1 mg/kg/day	progressive renal failure; acute allergy	lipid-associated amphotericin B	
Invasive aspergillosis	amphotericin B or lipid-associated amphotericin B	1–1.5 mg/kg/day ≥3 mg/kg/day	as above	itraconazole 400 mg/day	
<i>C. albicans</i> e.g. line-associated, CDC, candidaemia Non- <i>albicans</i> yeast	amphotericin B or fluconazole amphotericin B	0.7–1.0 mg/kg/day ≥400 mg/kg/day 0.7–1.0 mg/kg/day	as above minor as before	fluconazole ≥400 mg/day itraconazole 400 mg/day liposomal amphotericin B ≥3 mg/kg/day itraconazole 400 mg/day fluconazole	remove line 400 mg/day remove line identify fully add flucytosine 75–100 mg/kg/day for meningitis surgical debridement often needed
Cryptococcosis	amphotericin B	0.7 mg/day	as before		
Mucorales	lipid-associated amphotericin B	≥3 mg/kg/day			
<i>Fusarium</i> sp.	lipid-associated amphotericin B	≥3 mg/kg/day		itraconazole	
Trichosporonosis	fluconazole	≥400 mg/day		lipid-associated amphotericin B	
Pseudallescheriosis	miconazole	600–120 mg tds	anaphylaxis; cardiotoxicity	itraconazole	

CDC = chronic disseminated candidiasis.

until then lower dosages are not recommended in fulminant fungal infection. Because of the high cost of these lipid forms, the suspension of amphotericin B in 20% Intralipid has been compared with the conventional suspension in 5% dextrose: reductions in allergic reactions and nephrotoxicity were noted with Intralipid use, but there was no difference in efficacy. Neither Intralipid nor amphotericin B is licensed for such use, and this practice is not recommended.³⁹

Flucytosine. Flucytosine is well absorbed orally and has good tissue penetration, but it has a narrow spectrum of activity and resistance can develop rapidly if it is used alone. Reported synergy between flucytosine and amphotericin B has led to the combined use of these agents, especially in the treatment of candidosis. However, clinical results do not support this and there have been no large, randomized, prospective trials of amphotericin B alone versus amphotericin B plus flucytosine in DFI in haematological malignancy. Flucytosine may slow down the recovery of neutrophil counts in neutropenic patients because it is myelotoxic,⁴⁰ particularly if amphotericin B produces renal toxicity and higher flucytosine concentrations. Flucytosine may be used in CDC where, in some studies, it has shown advantages when used in combination with amphotericin B,⁴¹ and it is still recommended as adjunctive therapy in cryptococcal meningitis. In combination the dose of amphotericin B should be 0.7 mg/kg/day and flucytosine 75–100 mg/kg/day with weekly monitoring of serum concentrations of the latter.

Azoles. Ketoconazole has no place in the treatment of DFI in neutropenic patients.⁴² Intravenous miconazole given in combination with initial iv antibiotics in a randomized, prospective, placebo-controlled, double-blind trial of 208 courses of treatment in 180 neutropenic patients with PUO significantly reduced episodes of DFI.⁴³ This trial could be described as partly prophylactic, and there have been no trials comparing iv miconazole versus iv amphotericin B in suspected or proven DFI during neutropenia, and the intravenous preparation is not readily available in the UK.

Triazoles. Fluconazole is active against most *Candida* spp. and *Cryptococcus neoformans*. A daily iv dose of at least 400 mg is recommended in systemic fungal infection. Prophylactic trials using smaller doses suggest that it may be effective against *Candida albicans* and *Candida tropicalis* but not against *C. krusei* or *Aspergillus* spp. in neutropenic patients with haematological malignancy.⁴⁴ In addition, some isolates (e.g. *Candida glabrata*) may develop resistance rapidly during treatment.⁴⁵ It may be an effective drug in CDC when amphotericin B is ineffective or stopped because of toxicity.^{46,47} Fluconazole has been compared with amphotericin B as empirical therapy for suspected

DFI in febrile, neutropenic patients and shown to be equivalent.¹⁷ Similarly, open studies, including some neutropenic patients, have shown it to be as effective and less toxic in the treatment of candidosis.^{48,49} However, caution is needed in interpreting these trials, as they used low doses of amphotericin B and were conducted before the widespread emergence of azole resistance. Fluconazole may be unsuitable for treatment in centres where azole prophylaxis is used. Fatal aspergillus superinfections have been reported in neutropenic patients given fluconazole.⁴⁶

Itraconazole is active against *Candida* and *Aspergillus* spp. It may be fungicidal at achievable serum concentrations for 60% of fungal isolates and inhibitory for most of the remainder.⁵⁰ Amphotericin B-resistant deep aspergillus infections may respond to oral itraconazole.⁵¹ Oral itraconazole has been shown to be as effective as iv amphotericin B in one very small, prospective, randomized study⁵² and has been successfully used in profoundly neutropenic patients with IPA.⁵³ The solution form (5 mg/kg/day) will give higher and more reliable serum concentrations⁵⁴ than the capsule form (400 mg daily).⁵⁵ Side-effects are few,⁵⁶ although vincristine toxicity may be exacerbated.⁵⁷ Serious interaction with cyclosporin has not been seen in allogeneic marrow transplantation.⁵⁸

New azoles, most notably voriconazole, are under development. Voriconazole is a novel triazole with a wide spectrum of activity *in vitro* including fungicidal action against *Aspergillus* spp. Results from phase II studies are encouraging and the drug is being evaluated in comparative phase III trials.

Azoles are now widely used for antifungal prophylaxis but may fail in suspected or proven fungal infection during neutropenia. If iv amphotericin B is started it would be rational, but not essential, to stop the azole. Theoretically azoles and polyenes could be antagonistic, but *in-vitro* studies have shown both antagonism⁵⁹ and synergy⁶⁰ and the clinical consequences of these interactions are unknown.

Rare fungal infections

Increasingly, uncommon fungi that cause superficial and treatable infections in the non-immunocompromised host are presenting as unresponsive DFI in haematological malignancy. Those most often reported are *Cryptococcus*, *Fusarium*, *Pseudallescheria* and *Trichosporon* spp. and members of the order Mucorales. Haemato-oncologists should be aware of the main clinicopathological features of such infections.

Cryptococcal infection is normally associated with AIDS, but occurs occasionally in leukaemia and lymphoma. Meningitis is the commonest presentation but 25% of patients may also have radiological evidence of asymptomatic pulmonary infection.⁶¹ The CSF will contain the organisms and free antigen, which is also detectable

in serum. Treatment is iv amphotericin B 0.7 mg/kg/day plus iv flucytosine 75–150 mg/kg/day. Triazoles have not been evaluated in cryptococcosis in haematological malignancy.

Rhizopus, *Rhizomucor* and *Absidia* spp. belonging to the order Mucorales are the organisms most commonly associated with mucormycosis. Infection presents as rhinocerebral, pulmonary or disseminated disease.⁶² Desferrioxamine treatment is a specific risk factor.⁶³ The organisms invade and spread along blood vessels and into the surrounding parenchyma, producing necrosis. Blood cultures remain negative despite the fact that in haematological malignancy, over half the cases have disseminated infection.⁶⁴ Pulmonary radiology mimics bacterial pneumonia, invasive aspergillosis, other pulmonary infections, haemorrhage and tumour masses. Few patients recover from infection without neutrophil regeneration. Treatment is more likely to succeed if high-dose amphotericin B is started early and extensive surgical debridement may also be needed. Surgical resection is particularly beneficial in pulmonary mucormycosis and should be considered early in the course of the disease.⁶⁵ There may be a role for using a lipid-associated amphotericin B preparation in doses of >3 mg/kg daily.

Fusarium infection, like aspergillosis, presents as an antimicrobial-resistant PUO during neutropenia. Cutaneous lesions are common and culture of *Fusarium* spp. is more likely from skin and blood.⁶⁶ The organisms are indistinguishable from *Aspergillus* spp. on histology. Most neutropenic patients die despite full doses of iv amphotericin B, and antifungal susceptibilities are variable.

Pseudallescheria infection presents during neutropenia as pulmonary, disseminated or intracerebral forms.⁶⁷ Diagnosis is by fungal isolation as it is often indistinguishable from *Aspergillus* and *Fusarium* spp. on histology. Most strains are resistant to amphotericin B, so iv micafungin or oral itraconazole⁶⁸ are the drugs of choice although survival is poor.

Trichosporon beigeli disseminates during neutropenia in the same way as candida, presenting as PUO resistant to antibiotics with widespread involvement of liver, spleen, gut and lungs and multiple, erythematous, maculopapular skin lesions.^{67,69} It is essential to culture blood, urine or exudates from skin since trichosporonosis is often diagnosed only at autopsy. Microscopy is suggestive but not diagnostic. Amphotericin B 1 mg/kg/day iv seldom arrests infection unless neutrophils regenerate and many strains of *T. beigeli* are resistant to the drug. Some activity of fluconazole has been reported in non-neutropenic patients,⁷⁰ and limited data support the use of fluconazole as first-line therapy of trichosporonosis in haematological malignancy.

Even less frequently reported in these patients are DFIs due to other hyaline fungi (*Histoplasma*,^{71,72} *Coccidioides*,⁷³ *Penicillium*, *Paecilomyces*, *Blastoschizomyces* and *Scopulariopsis* spp.), phaeohyphomycoses (*Alternaria*, *Bipolaris* and *Curvularia* spp.), *Sporothrix* spp., *Malassezia*

furfur, *Geotrichium candidum*, *Hansenula anomala* and *Rhodotorula* spp.

Future developments

Treatments aimed at augmenting host immune defence mechanisms have potential in the therapy of fungal infections in patients with haematological malignancies. Growth factors (G-CSF, GM-CSF, M-CSF) have been used to reduce the duration of neutropenia, and hence the risk period, but there is little evidence that they prevent DFI, although there is a retrospective report that M-CSF in combination with amphotericin B may reduce candida DFI.⁷⁴ More interesting is the potential of these cytokines as adjunctive therapies in established infections.⁷⁵ GM-CSF appears most active in this respect and small studies have suggested a role in DFI.^{76,77} Prospective trials are under way. Gamma-interferon is an established treatment of fungal infection in chronic granulomatous disease and may also be useful particularly in the treatment of DFI in haematological malignancy.⁷⁸ In addition the use of growth factors to prime blood donors has enabled granulocyte transfusions to regain some popularity as a treatment modality for fungal infection.

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