Management

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The management of invasive fungal infection utilizes a variable multidisciplinary approach involving antifungals, appropriate surgery and immuno-correction. Conventional amphotericin B has been the mainstay of treatment but newer pathogens and poor outcomes has led to new formulations of this drug as well as to new and novel antifungals.

The final article in this symposium addresses therapeutic options, focusing on the two most common invasive fungal infections (IFI), namely invasive aspergillosis (IA) and candidiasis. Antifungals form the mainstay of treatment while surgery and immune augmentation are important adjuncts.

ANTIFUNGAL TREATMENTS

Amphotericin B

Sodium-deoxycholate colloid suspension of the polyene macrolide amphotericin B (conventional amphotericin B or CAB) induces lethal fungal cell membrane changes, forming transmembrane pores, and causing lipid peroxidation and proton ATPase inhibition while inflicting similar collateral damage on the host cell membrane. The latter results in substantial host toxicity, such as anaemia. Cytokine-mediated chills/rigors and glomerulo-tubular-mediated nephrotoxicity are extremely common (mainly in adults), particularly with rapid infusions (*Figure 1a,b*). This leads to significant underdosing and inappropriate use of immunosuppressant corticosteroids to limit these toxic events, which compromises therapeutic outcome (Gallis et al, 1990).

Crude overall response rates for IA in the immunocompromised host (ICH) are around 30% with eventual survival even lower: traditionally around 10% in bone marrow transplant patients (Denning and Stevens, 1990).

Lipidization of CAB has produced three commercial compounds (*Figure 2*) to counter the problems of toxicity (de Marie, 1996). They have a degree of reduced toxicity and provide the potential for successfully completing a course of

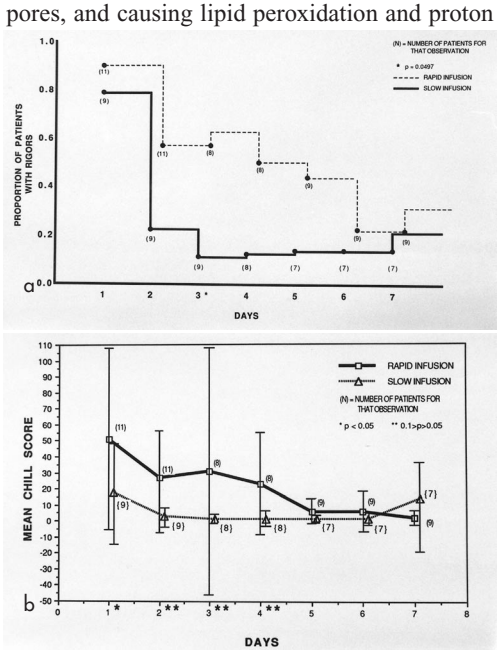

Figure 1. a. High proportion of patients experiencing rigors and chills with conventional amphotericin B; (b) reduced with slow infusions. From Ellis et al (1992).

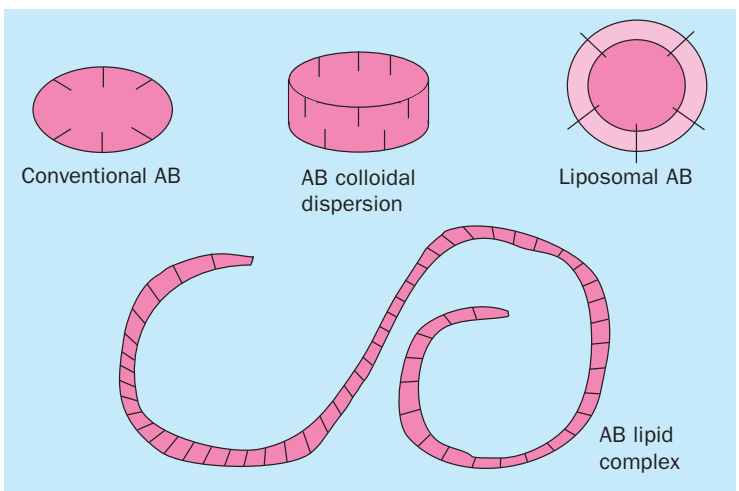

Figure 2. Pictorial representations of the lipid amphotericin B (AB) formulations.

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CAB and for administering higher doses. Less than 10% of patients have renal or systemic toxic events with liposomal AB compared to 80% with CAB. It is not surprising that their very different compositions, shapes, diameters, kinetics and bioavailabilities translate into variable degrees of toxicity and possibly efficacy. Liposomal AB and AB lipid complex are less toxic than AB colloidal dispersion. A recent study indicated that liposomal AB is superior to AB lipid complex in terms of toxicity (Wingard et al, 1999).

Animal data, case reports and open label retrospective studies (including salvage) suggest that the lipid AB products have improved efficacy over CAB as defined by observed responses in patients who had deteriorated on CAB, or improved survivorship compared to historical controls (Ellis, 2000). Three prospective randomized studies compared liposomal AB with CAB and found significantly improved response rates for liposomal AB in patients with neutropenic fever (Prentice et al, 1997), IFI (Leenders et al, 1998) and in the prevention of IFI (Walsh et al, 1999). Further information to support this contention is needed.

An unresolved issue is dosage. This subject has been reviewed in depth recently (Ellis, 2000). Scientific evidence currently does not support the use of 'high' doses of CAB or liposomal AB in achieving higher clinical response rates, despite better mycological eradication (Allende et al, 1994) (*Figure 3*). The only prospective randomized study that compared 1 *vs* 4 mg/kg/day of a liposomal AB preparation in IA showed equivalence of outcome (Ellis et al, 1998) (*Figure 4*). Further work is needed in this area — perhaps a maximum tolerated dose well above that currently used is needed. These compounds are expensive, but beneficial cost-efficacy outcomes from their use have nevertheless been demonstrated.

With the present vogue for use of liposomal AB, outcome for patients with IA appears to be better than it was previously (Ellis et al, 1998).

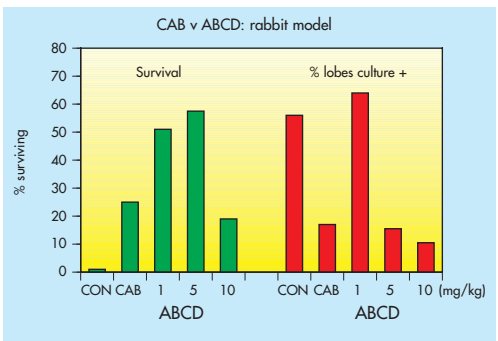

Figure 3. Disassociation of survival from fungal culture. From Allende et al (1994). ABCD = amphotericin B colloidal dispersion; CAB = conventional amphotericin B.

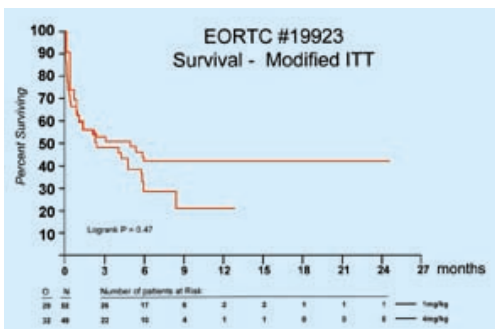

Figure 4. Equivalence of dose of liposomal amphotericin B on survival of patients with invasive aspergillosis. From Ellis et al (1998). EORTC = European Organisation for the Research and Treatment of Cancer; ITT = Intention to treat.

Practice points:

- Patients with ARNF (culture negative neutropenic unresponsive to broad spectrum antibiotics) should be treated early and empirically with AB to prevent overt IFI
- Current Infectious Diseases Society of America guidelines suggest initiating treatment on day 7–10 (Hughes et al, 1997). However, this delay could adversely affect outcome. Many physicians choose to start treatment on day 3. An ongoing European Organisation for the Research and Treatment of Cancer (EORTC) study is comparing outcome when starting liposomal AB treatment on day 3 *vs* day 6
- Dosage of CAB should be 0.8–1 mg/kg/day, if tolerated (Denning and Stevens, 1990)
- Liposomal AB is licensed for this at a dosage of 1–3 mg
- AB is administered until recovery from neutropenia, clinical/radiological response has occurred and a cumulative dose of at least 2 g has been given (Denning and Stevens, 1990)
- All patients with ARNF should undergo evaluation for overt IFI (see article on *Clinical and laboratory diagnosis*)
- In patients with presumptive/probable IA a dose of liposomal AB 1–5 mg is given (AB lipid complex 5 mg/kg), sometimes escalated further if disease is progressive on treatment.

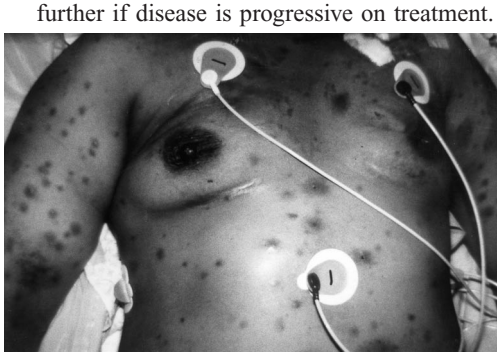

Figure 5. Disseminated fusariosis in patient with acute myeloid leukaemia.

Since the optimal dose is unknown, one approach is to administer 5 mg/kg/day and titrate downwards as response occurs

- For patients with candidiasis, a lower dose of 0.5–1 mg is used
- Some other fungal infections, e.g. fusariosis (*Figure 5*), are resistant mycologically and clinically to AB preparations
- All patients with 'isolated' candidaemia without a focal source should be treated to prevent late serious complications, e.g. ophthalmitis
- Intravenous line-associated candidaemia should be managed with antifungals and line removal to be certain of cure.

Azoles

These interfere with cell membrane ergosterol synthesis via inhibition of P450 dependent 14a demethylation of lanosterol. The triazoles are less toxic than ketoconazole. Limitations in their clinical applications include narrow spectrum (fluconazole), variable bioavailability (itraconazole), drug interactions, e.g. with cyclosporin (itraconazole), and emergence of resistance, e.g. of *C. albicans* or selection of inherently resistant organisms (fluconazole) (Sheehan et al, 1999).

Fluconazole is an alternative effective treatment for systemic candidiasis in non-neutropenic patients, hepatosplenic candidiasis, oropharyngeal candidiasis and for ARNF where IA is unlikely (Sheehan et al, 1999).

Itraconazole has a broader spectrum including *Candida*, *Aspergillus*, zygomycosis, histoplasmosis and blastomycosis, but is currently used in less ill patients who are tolerant of oral medications, following an initial response to CAB, for secondary prophylaxis of IA or as alternative/adjunctive therapy for progressive disease on CAB. It is more toxic than fluconazole, with hypokalaemia, oedema, nausea, abdominal pain and liver dysfunction being reported.

The addition of a glucose ring stabilizes itraconazole (itraconazole in cyclodextrin), and has improved the drug, optimizing bioavailability by 30%. Serum level monitoring of itraconazole is no longer required with this formulation. It should be used cautiously in patients with diminished renal function as cyclodextrin is excreted renally. An intravenous preparation is also available and offers further pharmacokinetic advantages including rapid steady state achievement and improved levels. These new formulations have proved successful as first-line therapy for IA (Caillot et al, 1999).

New azoles: Voriconazole (Sheehan et al, 1999), ravuconazole (Pfaller et al, 1999) and posaconazole (Pfaller et al, 1999) are in clinical trials. Voriconazole has enhanced and more specific inhibition of fungal 14a lanosterol demethylase. It is active against some fluconazole-resistant *Candida* spp., particularly *C. krusei*. Its activity against filamentous fungi including *Aspergillus* offers an alternative therapy to CAB. There are toxicity issues, e.g. renal and retinal problems, which need addressing. Posaconazole appears safe, has a broad spectrum including activity against *Fusarium* (usually highly resistant) and its once-daily dosing offers great promise.

Nucleoside analogues

5-fluorocytosine (5FC) is deaminated to 5 fluorouracil within fungi, and converted to deoxynucleoside which stops DNA synthesis via inhibition of thymidylate synthase. Resistance develops when 5FC is used alone. In combination with amphotericin B or fluconazole it is effective in disseminated candidiasis and cryptococcal meningitis. Mucositis and myelosuppressive toxicities are formidable if serum level monitoring is not used.

New antifungal targets

Unravelling cellular and molecular profiles of fungi in conjunction with computer-aided drug modelling are providing exciting new possibilities for antifungal drug developments (*Figure 6*). For example the candins (Onishi et al, 2000) target cell wall 1,3-β-D glucan synthase, an enzyme unique to fungi. Capsofungin is active against *Candida*, including strains resistant to other antifungals, and a selected spectrum of filamentous fungi (but not *Fusarium*). Several others are in the process of development. Over 15 other potential targets for antifungals have been identified. These include cell wall chitin synthase (nikkomycin antibiotics), cell wall mannoproteins (calcium dependent benanomicin/pradimicins), plasma membrane ergosterol (oxidosqualene cyclase inhibitors), elongation factors (sordarins), proton ATPase (folimycin) and

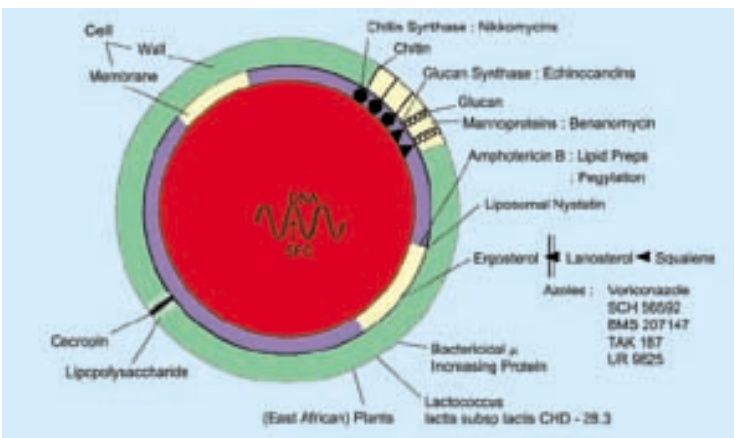

Figure 6. Antifungal targets.

signal transduction/cell cycle kinases/phosphatases (Georgopapadakou and Walsh, 1996).

SURGICAL MANAGEMENT

This has been reviewed in detail (Denning and Stevens, 1990; Ellis, 1999). Excision of well-defined fungal masses is associated with superior outcome over medical therapy alone for:

- Fungal endocarditis (valve replacement together with antifungal therapies giving a better survival than medical therapy alone; *Figure 7*)
- Endophthalmitis, bone and joint disease
- Early bleeding from mycotic lung sequestrum (primary aspergilloma)
- Invasive fungal sinusitis.

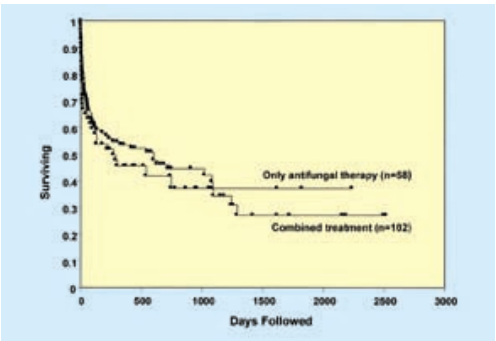

Figure 7. Improved survival of antifungal and surgical therapy compared to antifungal therapy alone in fungal endocarditis (Ellis, 2000).

TABLE 1.
Impact of growth factors on mortality from invasive fungal infection

	Total no (%) of patients dying	
Organism	GMCSF (*n*=52)	Placebo (*n*=47)
Aspergillus	1/4 (25)	5/7 (71)
Candida	0/3	3/4 (75)
Other	0/1	1/1 (100)
Total	1/8 (13)	9/12 (75) (*P*=0.02)

From Rowe (1998). GMCSF = granulocyte monocyte colony-stimulating factor

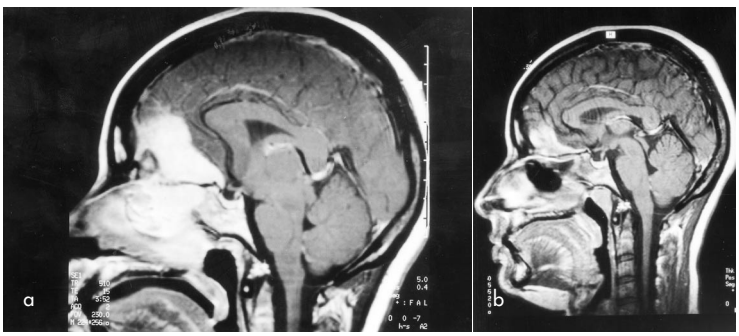

Figure 8. Sagittal SE T1 magnetic resonance imaging post gadolinium showing (a) extensive Aspergillus *disease of paranasal sinuses, and through cribriform plate to frontobasal brain, (b) same view 7 months later after antifungal and immunomodulatory treatment.*

Its role is less clearly defined for:

- Prevention of bleeding in well-circumscribed mycotic lung sequestrum
- Cases refractory to medical treatment
- Prevention of future relapses in patients initially surviving IA who undergo further immunosuppressive treatment of their underlying disease.

ADJUNCTIVE TREATMENTS

White cell transfusion

Recovery from IFI in neutropenic patients is linked to neutrophil recovery. Efficacy of white cell transfusions has only been seen for bacterial infections in cancer patients. Improvement in donor harvest technology to increase cell yield, quality, reduce apoptosis and infection is prompting reassessment (Chanock and Gorlin, 1996).

Cytokines

Since recombinant haematopoietic growth factors reduce neutropenia duration and improve neutrophil, macrophage and monocyte functions they could play a role in reducing frequency and severity of IFI. There is scant literature on this. Gamma interferon also enhances fungal hyphal damage and significantly reduces IFI in patients with chronic granulomatous disease. Recently the addition of growth factors to antifungal therapy significantly reduced death from IFI in leukaemia patients (*Table 1*) (Rowe, 1998) which indicates their use should be further explored. Gamma interferon and granulocyte monocyte colony-stimulating factor (GMCSF) have been used successfully to treat hepatosplenic candidiasis in patients with acute leukaemia (Poynton et al, 1998).

In a recent case of invasive cranial aspergillosis in an apparent normocompetent patient, a response was only seen when gamma interferon and GMCSF were used in addition to high-dose liposomal AB (*Figure 8a,b*). The indications for their use are not clearly defined. However, it is suggested that they are used in persistently neutropenic patients with an established IFI.

Cytokines offer exciting therapeutic possibilities, e.g. in an animal model of IA 70% of mice were cured when treated with soluble interleukin-4 receptor therapy, associated with a pronounced TH2 to TH1 shift (Cenciu et al, 1997).

Hyperbaric oxygen

This enhances white cell-mediated fungal killing, optimizes tissue oxygenation, reduces oedema and acidosis, and promotes tissue survival. There is some benefit in zygomycosis and possibly other fungal infections. Where the facility is available selected cases might benefit (*Figure 9a,b*).

Intensive care

Surprisingly there is virtually no information assessing the contribution of this aspect of patient management. One review before the general use of growth factor treatment and newer antifungals portrayed a grim outcome. The survival rate for patients with IA in respiratory failure was only 8% (Janssen et al, 1996). Evaluation of the indications, outcome and role of intensive care in these patients is needed.

CONCLUSIONS

The increasing numbers of patients with IFI is a great impetus to therapeutic development. The current escalation of interest in this area, not just with modifications of existing antifungals but with innovative approaches, is exciting. Detailed knowledge of fungal cell structure, identification of virulence, adhesion and other factors and genome sequencing opens the possibility for new candidate targets and interventions including vaccine development and extracellular signalling manipulation. Nevertheless some fundamental problems remain including approaches to empirical therapy, optimal doses and duration of drugs, cost issues and combination regimens. International groups such as the EORTC and mycoses study group are important in facilitating communication between interested individuals and providing structure for investigating these complex areas. HM

Conflict of interest: none.

Allende MC, Lee JW, Francis P et al (1994) Dose-dependent antifungal activity and nephrotoxicity of amphotericin B colloidal dispersion in experimental pulmonary aspergillosis. *Antimicrob Agents Chemother* **38**: 518–22

Caillot D, Basaris H, Seifert WF et al (1999) Efficacy, safety, and pharmacokinetics of intravenous followed by oral itraconazole in patients with invasive pulmonary aspergillosis. Abstract 1646. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco

Cenciu E, Perito S, Enssle KH et al (1997) Th1 and Th2 cytokines in mice with invasive aspergillosis. *Infect Immunol* **65**: 564–70

Chanock SJ, Gorlin JB (1996) Granulocyte transfusions; time for a second look. *Infect Dis Clin N Am* **10:** 327–43

de Marie S (1996) Liposomal and lipid based formulations of amphotericin B. *Leukemia* **10** (Suppl 2): s93–96

Denning DW, Stevens DA (1990) Antifungal and surgical treatment of invasive aspergillosis: Review of 2,121 published cases. *Rev Infect Dis* **12:** 1147–201

Ellis M (1999) Therapy of Aspergillus fumigatus related diseases. In: Brakhage AA, Jahn B, Schmidt A, eds. Contrib Microbiol. *Aspergillus fumigatus: Biology, Clinical Aspects and Molecular Approaches to Pathogenicity.* Basel, Karger: 105–29

Ellis M (2000) Amphotericin B preparations: a maximum tolerated dose in severe invasive fungal infections? *Transpl Infect Dis* **2:** 51–61

Ellis ME, al-Hokail AA, Clink HM et al (1992) Double-blind randomized study of the effect of infusion rates on toxicity of amphotericin B. *Antimicrob Agents Chemother* **36:** 172–9

Ellis M, Spence D, de Pauw B et al (1998) An EORTC international multicenter randomised trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. *Clin Infect Dis* **27:** 1406–12

Gallis HA, Drew RH, Pickard WW (1990) Amphotericin B: 30 years of clinical experience. *Rev Infect Dis* **12:** 308–29

Georgopapadakou NH, Walsh TJ (1996) Antifungal agents: chemotherapeutic targets and immunologic strategies. *Antimicrob Agents Chemother* **40**: 279–91

Hughes WT, Armstrong D, Bodey GP et al (1997) 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* **25:** 551–73

Janssen JJ, Strack van Schijndel RJ, van der Poest Clement EH, Ossenkoppele GJ, Thijs LG, Huijgens PC (1996) Outcome of ICU treatment in invasive aspergillosis. *Intens Care Med* **22:** 1315–22

Leenders ACAP, Daenen S, Jansen RLH et al (1998) Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *Br J Haematol* **103:** 205–12

Onishi J, Meinz M, Thompson J et al (2000) Discovery of novel antifungal (1,3)-beta-D-glucan synthase. *Antimicrob Agents Chemother* **44:** 368–77

Pfaller MA, Jones RN, Doern GV et al (1999) International surveillance of blood stream infections due to Candida species in the European SENTRY Program: species distribution and antifungal susceptibility including the investigational triazole and echinocandin agents. SENTRY participant group (Europe). *Diagn Microbiol Infect Dis* **35:** 19–25

Poynton CH, Barnes RA, Rees J (1998) Interferon γ and granulocyte-macrophage colony stimulating factor for the treatment of hepatosplenic candidosis in patients with acute leukemia. *Clin Infect Dis* **26:** 239– 40

Prentice HG, Hann IM, Herbrecht R et al (1997) A randomised comparison of liposomal *vs* conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* **98**: 711–18

Rowe JM (1998) Treatment of acute myeloid leukemia with cytokines: effect on duration of neutropenia and response to infections. *Clin Infect Dis* **26**: 1290–4

Sheehan DJ, Hitchcock CA, Sibley CM (1999) Current and emerging azole antifungal agents. *Clin Microbiol Rev* **12**: 40–79

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

Wingard JR, White MH, Anassie EJ et al (1999) A randomised double blind study of AmBisome and Abelcet in febrile neutropenic patients. Abstract # 015. 9th Focus on fungal infections, San Diego, California

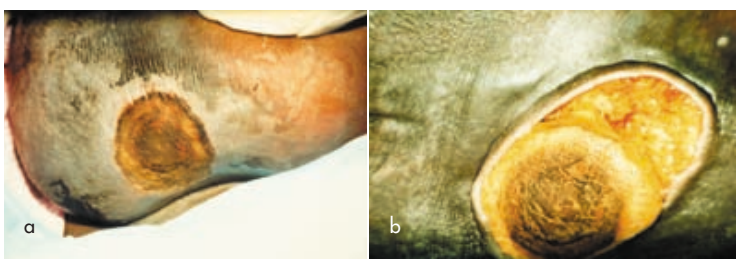

Figure 9. Patient with acute myeloid leukaemia (a) showing extensive skin necrosis, infiltration and oedema from Aspergillus, (b) after hyperbaric oxygen treatment. Note resolution of diffuse infiltration and oedema and circumscription of lesion.

KEY POINTS

- Conventional amphotericin B has a low therapeutic index leading to incomplete treatments.
- Lipidization improves its therapeutic index, by reducing the toxic denominator and possibly by directly improving efficacy.
- The optimal dose of amphotericin B is unknown, and is a major concern particularly when using the expensive lipid formulations.
- Several new antifungals are being developed including voriconazole, the candins and others consequent to new information on fungal structure.
- Interest has been regained in the use of white cell transfusions in neutropenic patients.
- Various cytokines are showing promise in clinical trials.