Antifungal therapy in invasive fungal infections
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Early treatment of invasive fungal infections (IFIs) is essential for optimal clinical outcomes. Standard antifungal drugs (polyenes, azoles and echinocandins) are not predictably effective against emerging yeasts and filamentous fungi and may cause undesirable side effects. Species identification can guide antifungal selection for invasive candidiasis, but not less common moulds such as Scedosporium and Fusarium spp. Management strategies targeted to those at highest risk (prophylaxis), those with clinical signs of infection not responsive to antibacterials (empiric therapy) and those with occult infection (asymptomatic but with positive fungal biomarkers) produce better outcomes than therapy predicated on identification of a fungal pathogen, but require comparative evaluation. Appropriate dosing and consideration of pharmacokinetic parameters (including therapeutic drug monitoring) are important with newer triazoles. New therapies such as addition of the iron chelator, deferasirox, in the treatment of zygomycosis in diabetic patients, appear promising but additional agents with new targets of action are urgently needed.

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Introduction
Invasive fungal infections (IFIs) have increased steadily with the rise in at-risk immunocompromised patients and those with critical illness. Most are caused by Candida and Aspergillus fumigatus. However, previously uncommon or new pathogens, many of which are resistant to antifungal agents, are increasing; these include non-fumigatus Aspergillus spp., Zygomycetes, Scedosporium and Fusarium [1*,2*,3,4]. Despite antifungal therapy, mortality from IFIs is high (30–80%), with particularly poor outcomes in non-Aspergillus mould infections [1*,5]. Notably, only a single new drug class, the echinocandins, has been licensed (in 2001) for therapeutic use in the last decade. We here review contemporary evidence-based data for treatment of established IFIs in adult patients, and refer to recent practise guidelines, and the strength of recommendations (Table 1) [6], of the Infectious Diseases Society of America (IDSA). For consensus opinions on therapy of endemic fungal infections, the reader is referred to updated IDSA guidelines [7–9].

Treatment of Candida infections
Epidemiology of invasive candidiasis (IC)
There have been important changes in the epidemiology of IC, which, although it varies between different patient populations and geographic regions [10], is overall characterised by increasing incidence and a shift toward Candida spp. (particularly Candida glabrata) with reduced susceptibility to fluconazole [11–13].

The influence of empiric antifungal choice and timing
The crude mortality associated with IC is substantial (~30–60%), with much of this mortality reflecting underlying comorbidities and illness acuity [14,15,16*,17,18]. Nevertheless, a number of treatment-related variables influence IC-associated outcomes. In particular, the appropriateness and timing of empiric antifungal therapy appears to be an important predictor of outcome [17,19]. Retrospective studies have shown that appropriate antifungal therapy needs to be instituted within 12–24 hours of drawing the first ultimately positive blood culture for there to be substantial reduction in mortality. However, the major unmet challenge remains accurate clinical and microbiological support to guide early antifungal therapy, given that modern blood culture techniques still require 24–48 hours to signal ‘positive’ for yeasts.

Initial antifungal therapy
Although the polyenes (amphotericin B deoxycholate [c-AMB] and lipid formulations of amphotericin B [AMB]), the triazoles (e.g. fluconazole and voriconazole) and the echinocandins (caspofungin, micafungin and anidulafungin) have all proven efficacious for the treatment of IC in randomised clinical trials (RCTs), the choice of initial antifungal therapy — pending species identification and susceptibility results — usually lies between fluconazole and an echinocandin [20*,21]. Fluconazole has the advantages of low cost, low toxicity and its availability as both an oral and parenteral formulation, but it is not reliably effective against C. glabrata, which accounts for up to 20% of candidaemia episodes [10]. The echinocandins on the other hand are expensive, but have few drug interactions or toxicities and are broadly active againstazole-resistant Candida spp. The major consideration

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Candida

In practise, fluconazole dosed at 6 mg/kg daily should be mended in recent guidelines [20]. For C. glabrata infection include prior exposure to azoles and certain antibacterial agents, and gastrointestinal surgical procedures [22,23]. Knowledge of local epidemiological patterns is thus important for treatment decisions. In patients with haemodynamic instability, given the clinical imperative to provide initial coverage against all possible Candida spp., an echinocandin is generally recommended [20,21]. In this class, anidulafungin was demonstrably superior to fluconazole in a recent RCT [25], however it is generally accepted that the three echinocandins are of similar efficacy in IC.

Pharmacokinetic and pharmacodynamic considerations

Increasingly, antifungal pharmacokinetic and pharmacodynamic properties are proving important determinants of outcomes in IC. They are of direct relevance to dosing strategies and the potential role of therapeutic drug monitoring. In particular, with fluconazole, failure to achieve target pharmacodynamic targets of 25 (using Clinical Laboratory Standards Institutes [CLSI] minimum inhibitory concentration [MIC] methodology) or 100 (using European Union Committee Antimicrobial Susceptibility testing [EUCAST] MIC methodology) are associated with lower clinical success rates [26–29]. In practise, fluconazole dosed at 6 mg/kg daily should achieve such targets with susceptible Candida spp., as should, 12 mg/kg daily for C. glabrata infection, as recommended in recent guidelines [20,21]. Few data are available to guide dosing in critically ill patients with hyperdynamic sepsis and augmented renal clearance, or those managed with renal replacement therapies. Although of proven efficacy, voriconazole has few advantages over fluconazole for the treatment of IC, given that a significant proportion of fluconazole-resistant isolates of C. glabrata are also resistant to voriconazole. Voriconazole exhibits marked variations in individual pharmacokinetics and important drug interactions; where used for serious infections, therapeutic drug monitoring is recommended [30]. The echinocandins possess linear pharmacokinetics; from a pharmacodynamic viewpoint, the use of higher doses, or weight-based dosing, of echinocandins is of theoretical benefit. This hypothesis has not been tested in adequately powered clinical studies. In two recent trials different dosing strategies of micafungin (150 mg daily versus 100 mg daily) and caspofungin (70 mg on day 1 then 50 mg/day versus 150 mg daily) were assessed and neither demonstrated differences in efficacy [31,32].

Other treatment issues in IC

Recent IDSA and Australian treatment guidelines include recommendations on duration of antifungal therapy, management of intravascular catheters, investigation for deep/metastatic infective foci and need for careful assessment of clinical and microbiological responses [20,21]. In particular, the need to modify initial therapy based on species identification and antifungal susceptibility testing is not clear-cut. Although the identification of C. glabrata should prompt treatment with an echinocandin, where fluconazole has been initiated, its continuation is reasonable if there is clinical improvement and followup cultures are negative. Prompt initiation of an echinocandin, a lipid formulation of AMB or voriconazole is recommended following isolation of Candida krusei. For Candida parapsilosis infection, fluconazole, which has relatively greater in vitro activity, should be preferred to an echinocandin, however an echinocandin can be continued if clinical and microbiological responses are favourable.

Cryptococcosis

Emerging issues in management of cryptococcal meningitis (CM), the most severe form of cryptococcosis, include the recognition of new risk groups outside HIV/AIDS and organ transplantation (e.g. monoclonal antibody therapies) [33,34,35], the emergence of Cryptococcus gattii infections in new climatic zones (e.g. the Vancouver region of British Columbia, Canada and northwest USA [36], changes in treatment strategies and management of
complications such as raised intracranial pressure (ICP) and immune response inflammatory syndrome (IRIS)).

Meningoencephalitis in HIV/AIDS

RCTs of antifungal treatment of CM due to Cryptococcus neoformans in HIV/AIDS (Table 2) formalised the concept of induction, consolidation (clearance/eradication) and maintenance (suppression) therapy. Rapidly fungicidal induction therapy regimens have been correlated with favourable outcomes. In particular, combined AMB–flucytosine regimens sterilize the cerebrospinal fluid (CSF) most rapidly and result in superior clinical/mycological outcomes than AMB alone, AMB plus fluconazole or fluconazole alone [37,38**]. This superiority is most evident in patients with a high initial fungal burden and abnormal neurological manifestations; <14 days of flucytosine has been independently associated with treatment failure. A c-AMB dose of 1 mg/kg (cf. standard dose 0.7 mg/kg) daily has been used; however, drug toxicity may be problematic [37]. Duration of therapy depends on the treatment regimen (Table 2) and clinical response [39**]. Lipid AMB formulations (plus flucytosine) appear to be as effective as c-AMB (66–75% response rates).

Table 2

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Therapy</th>
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<td>Induction therapy</td>
<td>Duration</td>
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<tr>
<td>HIV-infected individuals</td>
<td>c-AMB (0.7–1 mg/kg daily) plus flucytosine (100 mg/kg daily) (A-I) OR L-AMB (3–4 mg/kg daily) or ABLC (5 mg/kg daily) if renal function concerns plus flucytosine (100 mg/kg daily) (B-II) OR c-AMB, or L-AMB or ABLC (doses as above) for flucytosine-intolerant patients (B-II)</td>
</tr>
<tr>
<td>Organ transplant recipients</td>
<td>L-AMB (3–4 mg/kg daily) or ABLC 5 mg/kg daily plus flucytosine (100 mg/kg daily) (B-III) OR L-AMB (6 mg/kg daily) or ABLC (5 mg/kg daily) OR c-AMB (0.7 mg/kg daily) (B-III)</td>
</tr>
<tr>
<td>Non-HIV, non-transplant patients</td>
<td>c-AMB (0.7–1 mg/kg daily) plus flucytosine (100 mg/kg daily) (B-II) OR L-AMB (3–4 mg/kg daily) or ABLC (5 mg/kg daily) plus flucytosine (B-III) OR c-AMB or L-AMB or ABLC (in above doses) without flucytosine (B-III)</td>
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</table>

Abbreviations: c-AMB, amphotericin B deoxycholate; L-AMB, liposomal amphotericin B; ABLC, amphotericin B lipid complex.

Alternative induction regimens with fluconazole plus flucytosine, or fluconazole monotherapy are less effective and indicated only where first line drugs cannot be used. Fluconazole doses of 1200–2000 mg daily are recommended if given as a single drug [40]. On completion of induction/consolidation therapy, maintenance fluconazole (Table 2) should be continued until there is stable immune reconstitution with HAART [39**]. Voriconazole and posaconazole are reasonable options for salvage therapy in HIV/AIDS and other patient groups (see below) [39**].

Meningoencephalitis in organ transplantation

Given the risk of nephrotoxicity with concurrent use of c-AMB and calcineurin inhibitors, and that <25% of all organ transplant patients with cryptococcosis have renal dysfunction, lipid AMB formulations are preferred as induction therapy, in combination with flucytosine (Table 2). Furthermore, renal failure has been associated with higher mortality in solid organ transplant (SOT) recipients. Because CSF sterilisation may be prolonged (medianis ≥10 days), extension of induction therapy up to six weeks depending on whether flucytosine is given may be indicated [39**]. In a recent report, use of lipid AMB (versus c-AMB) independently predicted better outcomes [35*]. This study documented for the first time, the clinical benefit associated with lipid AMB in SOT recipients with CM. However, clinical outcomes were measured at 90 days and late complications of CM were not monitored. Further, the study was not designed to evaluate efficacy of different types of antifungal therapy.

Consolidation/maintenance therapy with fluconazole for 6–12 months is associated with low relapse rates (1.3%)
(Table 2). Most relapses in patients not given maintenance therapy occur within six months [41]. Clinicians should be vigilant regarding azole–drug interactions (see ‘Candida infections’). Any reduction in immunosuppressive therapy should be gradual to minimise risk of allograft loss and development of IRIS.

Neurocryptococcosis in non-immunocompromised hosts
There are no RCT data in this group. In uncomplicated C. neoformans meningitis, current opinion favours induction with c-AMB or a lipid formulation and flucytosine for two (favourable prognostic factors), or four weeks, provided two-week CSF cultures are negative, or six weeks in the present of neurological complications or positive cultures at two weeks [39**] (Table 2). Experts treating C. gattii meningitis favour four to six weeks of therapy. Whilst fluconazole (alone or combined with flucytosine) is not recommended for induction therapy, it is the drug of choice for eradication (eight weeks) and maintenance therapy (6–12 months). Compared with C. neoformans, intracranial C. gattii infection is associated with more neurological sequelae, more neurosurgical interventions and delayed responses to therapy. These differences are primarily because of a higher proportion of cerebral mass lesions (cryptococcomas) and late presentations in C. gattii infection.

Other management
A critical determinant of outcome in CM is control of CSF pressure, and early management of raised ICP with repeated lumbar puncture and if necessary, shunting, is of paramount importance. In the absence of cryptococcomas, the antifungal regimen should be as for meningitis.

Resection of large cerebral cryptococcomas should be considered early as response to antifungal drugs is poor. Multiple lesions are usually not amenable to surgical removal and require prolonged induction/eradication therapy. Corticosteroids are indicated if there is gross peri-lesional oedema on imaging, especially in the presence of neurological deficits. Duration of antifungal therapy depends primarily on clinical response. Re-imaging is indicated in apparent cases of relapse and may reveal new or enlarging lesions, and increased peri-lesional oedema despite effective antifungal therapy. This appears to result from an IRIS rather than poor control of infection [42]. Adjunctive recombinant interferon gamma has been tried in C. gattii infection unresponsive to repeated/prolonged courses of antifungal drugs. Its contribution to improving outcomes is uncertain.

Invasive mould infections (IMIs)
Immunocompromised patients are at particularly high risk of IMIs although healthy hosts may also be affected for example, following trauma (e.g. Zygomycetes and Scedosporium). Despite changes in haematopoietic stem cell transplantation (HSCT) practises, invasive aspergillosis (IA) remains the most common IMI [43]. Prompt surgical drainage (e.g. solitary abscesses), resection of devitalised tissue and control of underlying conditions, for example, with immune-modulatory therapies, are critical to management [44**].

Invasive aspergillosis
Impact of Aspergillus spp.
A. fumigatus (≥50% cases of IA) is usually responsive in vivo to AMB, voriconazole, posaconazole or caspofungin. IA caused by Aspergillus terreus and Aspergillus nidulans is refractory to AMB therapy. Species resistant to azoles and/or AMB include Aspergillus lentulus and multi-azole-resistant A. fumigatus has been reported [45,46]. Susceptibility testing, especially in the context of prior azole therapy, is advisable. Current IDSA treatment guidelines for IA detail antifungal and ancillary treatments and duration of treatments [47**].

Primary therapy
There is consensus that voriconazole is the primary treatment of choice in IA (A-I). In the landmark antifungal RCT for proven/probable IA, voriconazole was superior to c-AMB in efficacy (53% versus 32% response) and resulted in improved 12-week survival (71% versus 58%) [48]. Most cases in this study were invasive pulmonary aspergillosis (IPA). However, there is now sufficient experience to recommend voriconazole as primary treatment of extrapulmonary and disseminated IA. Oral voriconazole is preferred for ‘step-down’ or maintenance therapy. Preferred treatment regimens for IPA, CNS and eye infections are summarised in Table 3. As for Candida infections (above), therapeutic drug monitoring is recommended.

Where use of voriconazole is problematic, there is A-I evidence for L-AMB (3 mg/kg daily) as primary therapy. Notably, high dose L-AMB (10 mg/kg daily) has no clinical benefit over standard dose L-AMB (≤50% efficacy for both) but is more toxic [49]. Evidence for efficacy of other drugs is less robust. Caspofungin (B-II) was effective and well tolerated as primary therapy in recent phase II studies in patients with haematological malignancy/HSCT (response rates of 33–42% and 84-day survival rate of 53%) [50**,51**]; however, since only proven/probable IA cases [52] were included and patients had poor baseline characteristics, the patient cohorts are not comparable with those in the voriconazole and L-AMB trials. There are few data on micafungin, anidulafungin or posaconazole in primary therapy of IA.

Salvage [53] and combination therapies
In patients failing voriconazole therapy, lipid AMB formulations (A-II), caspofungin or posaconazole (Table 3)
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Table 3

Summary of recommendations for treatment of invasive aspergillosis (adapted from [47**])

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary Therapy</th>
<th>Alternative or salvage therapya</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Invasive pulmonary aspergillosis (IPA)b</td>
<td><em>Initial</em>: Voriconazole 6 mg/kg IVb twice daily for one day, followed by 4 mg/kg IV twice daily; oral dose 200 mg twice daily (A-I); IV administration is recommended for very ill patients. <em>Maintenance</em>: Voriconazole 200 mg twice daily (A-I)</td>
<td>L-AMB 3–5 mg/kg daily IV (A-I) OR ABLC 5 mg/kg daily IV (A-II) OR Caspofungin 70 mg daily day 1, thereafter 50 mg daily IV (B-II) OR Posaconazole 200 mg four times a day initially then 400 mg twice daily orally (B-II)</td>
<td>Combination therapy is considered as salvage therapy in individual patients (B-II).</td>
</tr>
<tr>
<td>Aspergillosis of the CNS</td>
<td>Similar to IPA (A-II)</td>
<td>Similar to IPA; (B-II) except but caspofungin use as single agent not supported</td>
<td>Combination voriconazole–caspofungin may be used (C-III). Intrathecal agents are not recommended (C-III)</td>
</tr>
<tr>
<td>Aspergillus of the eye</td>
<td>Intraocular AMB with partial vitrectomy and IV AMB (B-III)</td>
<td>Voriconazole intravitreal and/or IV (B-III) OR Itraconazole6 orally together with intravitreal AMB (C-III)</td>
<td>Systemic therapy beneficial; surgical intervention if potential corneal perforation or disease progression</td>
</tr>
</tbody>
</table>

a For patients refractory or intolerant of primary antifungal therapy.
b Abbreviations: ABLC, amphotericin B lipid complex; CNS, central nervous system; IV, intravenous; IPA, invasive pulmonary aspergillosis; L-AMB, liposomal amphotericin B.

All yield response rates of 40–50% [47**,54]. Itraconazole is not recommended because of its similar mechanism of action to voriconazole and unreliable bioavailability. A change of drug class is required in breakthrough IA in the setting of mould-active azole prophylaxis. There are insufficient data to recommend antifungal combinations for primary or salvage therapy. Response rates for voriconazole–caspofungin (67.5% survival) or L-AMB–echinocandin (67% versus 27% response for L-AMB alone) have been reported [55]. A prospective RCT of voriconazole versus voriconazole–anidulafungin for initial treatment of proven/probable IA in haematology patients is underway.

Zygomycosis

Antifungal treatment strategies are evolving and focus on the roles of AMB formulations, posaconazole, combination therapies and newer therapeutic approaches. Posaconazole, the only orally active anti-zygomycete azole, generally has good in vitro activity against Zygomycetes (MIC<sub>90</sub> 1 to ≥ 4 μg/ml); however identification to genus/species level is important since *Cunninghamella, Absidia* and *Rhizopus oryzae* may be resistant both in vitro and in vivo [56,57].

Polyenes as standard treatment

Recent uncontrolled trial data have positioned AMB as the standard for primary treatment of zygomycosis [58]; c-AMB 1–1.5 mg/kg daily (B-II) is licensed for this indication but either ABLC (5 mg/kg daily) or L-AMB 5–15 mg/kg daily (B-II) are safer, effective alternatives, particularly with the prolonged treatment required. In SOT patients with zygomycosis and in rhino-orbital disease, 67–68% survival rates have been noted with L-AMB or c-AMB [59,60**]. High dose L-AMB (10–15 mg/kg daily) has been used for CNS or refractory disease, but its efficacy has not been compared systematically with the standard dose (5 mg/kg daily) and it is more toxic.

Role of posaconazole

There are no clinical data supporting single-agent posaconazole as primary therapy. Bioavailability is potentially problematic, with low serum levels (<1 μg/ml) reported in neutropenic patients dosed at 400 mg twice daily and steady state levels are achieved only after 7–10 days of therapy. Parameters for therapeutic drug monitoring [61] need further development. Posaconazole (200 mg four times daily with food) is useful as step-down therapy following AMB (B-II) and as salvage therapy (C-III: 60–70% response rates) [62,63].

Other therapies

Combination antifungals cannot be recommended as primary therapy for zygomycoses. Although promising results were reported with polyene–echinocandin combinations in rhino-orbital disease in retrospective clinical studies, benefit from the echinocandin (caspofungin) combination was observed principally with ABLC [60**]. Use of polyene–posaconazole combinations is not supported by pre-clinical data [63] but addition of the iron chelator, deferasirox (see below) to AMB, or as salvage therapy appears promising; a phase II clinical trial...
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is ongoing [58]. Colistin is fungicidal against *R. oryzae* and protected mice with lung infection against death [64].

**Scedosporium**
Amongst pathogenic *Scedosporium* spp., *Scedosporium prolificans* is resistant to all licensed antifungal agents whilst voriconazole and posaconazole demonstrate good activity against *Scedosporium apiospermum*, *Pseudallescheria boydii* and *Scedosporium aurantiacum*. Voriconazole is more potent in vitro (MICs 0.12–0.5 μg/ml for *S. apiospermum*, *S. aurantiacum*) and in vivo [65,66].

On the basis of current opinion, voriconazole (6 mg/kg twice daily on day 1 then 4 mg/kg twice daily; B-II) is the treatment of choice for *S. apiospermum*, *P. boydii* and *S. aurantiacum* infections (B-II) [66*,67,68]. In a recent series of 107 patients with scedosporiosis given voriconazole as primary or salvage/compassionate therapy, the global response rate was 57% (43% in CNS infection) [66*]. AMB-based therapies are inferior toazole-based therapies [67]. Combined voriconazole–terbinafine (250 mg daily orally) treatment is preferred in *S. prolificans* infections based on strong in vitro synergy and anecdotal successes using voriconazole in combination with terbinafine (B-III) [67]. Azole–echinocandin synergy has also been reported; promising results with the novel antifungal agent miltefosine remain to be confirmed [69,70]. Posaconazole is an alternative to voriconazole in *S. apiospermum/P. boydii* infections in salvage therapy (B-III). For eye infections, topical plus systemic voriconazole is recommended.

**Fusarium**

Since there are no clinical studies comparing the efficacy of different antifungal agents in fusariosis, therapeutic decisions are often guided by outcome data from subgroup analyses of drug comparison studies. *Fusarium* spp. are resistant to echinocandins, whilst susceptibility to AMB, voriconazole and posaconazole is variable [71].

High dose lipid AMB formulations remain the treatment of choice including in patients with haematologic disease (B-III) with 46% response rates reported for ABLC [72]. Although there are limited data supporting voriconazole or posaconazole as initial therapy, some authors suggest voriconazole (6 mg/kg twice daily on day 1 then 4 mg/kg twice daily as an alternative to AMB (B-III). Both azoles are useful, as are combined polyene–azole regimens, as salvage therapy (responses rates of 46–63% (C-III) [73*]).

Fusarial keratitis/endophthalmitis has been treated successfully with topical plus systemic voriconazole — voriconazole MICs against *Fusarium* are 1–8 μg/ml [74,75] thus high drug concentrations in the aqueous humour are required for efficacy. Salvage therapy with posaconazole or combined L-AMB–voriconazole regimens have been used with good response [72,76].

**Newer antifungals**

**Isavuconazole**

Isavuconazole is a triazole in late-stage clinical development for treatment of IA and candidiasis. It is active against other moulds except for *Fusarium* (MICs 4 ≥8 μg/ml) and Zygomycetes (MICs 1–>8 μg/ml) [77]. A RCT comparing isavuconazole with standard antifungal therapy for the treatment of IC is nearing completion.

**Iron chelators**

That iron is essential for virulence of Zygomycetes and *Aspergillus* spp. is supported by clinical data that iron overload in malignancy predisposes to infection due to these fungi [78]. Iron chelation therapy is a promising adjunctive strategy to improve outcomes of zygomycosis, and has been used successfully as salvage therapy [79]. Unlike deferoxamine, other chelators do not supply iron to the fungus (thereby increasing risk of zygomycosis). Oral deferasirox (US FDA-approved) is fungicidal against Zygomycetes at concentrations well below serum levels, protects mice with mucormycosis against death and is undergoing systematic clinical study; used alone or in combination with L-AMB, it is also effective in treatment of experimental IA [80**,81]. Deferiprone is licensed for clinical use in India and Europe and is effective in experimental *R. oryzae* infection [78].

**Conclusions**

Treatment of IFIs requires understanding of the epidemiology of specific infections. Azoles and the echinocandins are the cornerstones of anti-*Candida* treatment and should be guided by species identification and susceptibility testing. Broad-spectrum azoles have proven effective in treating IA and other IMIs whilst lipid AMB formulations are the preferred drug for zygomycosis. e-AMB/lipid AMB drugs are recommended for CNS cryptococcosis, preferably in conjunction with flucytosine. The challenge resides in translating promising exploratory or pre-clinical results with newer agents into proven clinical efficacy, either in addition to, or in synergy with, existing treatments.

**Acknowledgement**

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**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

+ of special interest
+ + of outstanding interest

The results of the PATH registry, a prospective multicentre database of invasive fungal infections in stem cell recipients, are presented. A key study finding is that although the survival of patients with invasive aspergillosis appears to be improving, that of those with non-Aspergillus moulds remains poor. This underscores the need to direct efforts towards the early diagnosis and treatment of these emerging moulds.


The authors provide a comprehensive review of novel risk factors for, and biomarkers of, invasive mould infections in stem cell recipients, and discuss the relative merits of prophylactic, empiric, pre-emptive and definitive antifungal treatment strategies.


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35. Sun HY, Alexander BD, Lortholary O, Dormer F, Forrest GN, Lyon GM, Somani J, Gupta KL, Busto RD, Pruettl TL et al.: Lipid formulations of amphotericin B significantly improve outcome in solid organ transplant recipients with central nervous system cryptococcosis. Clin Infect Dis 2009, 49:1721-1729. This study prospectively assessed clinical and mycological (two-week cerebrospinal fluid cultures) variables influencing mortality among solid organ transplant recipients with central nervous system cryptococcosis, including the effects of induction antifungal treatment regimen. The key finding is the observation for the first time of the clinical benefit (lower mortality) with lipid amphotericin B formulations, which provides data necessary to support the recent practice guidelines that preferentially recommend lipid amphotericin B formulations as induction therapy for severe disease (see Ref. [39**]).


This large study provides further evidence supporting earlier findings that combined amphotericin B plus flucytosine regimens are the best strategy for induction therapy in patients with cryptococcal meningoencephalitis and in all those with high fungal burden and abnormal neurology. This was found for both HIV-positive and HIV-negative populations.


44. Pyrgos V, Shoham S, Walsh TJ: Pulmonary zygomycosis. Semin Respir Crit Care 2008, 29:111-120. Aspects of pulmonary, and other clinical features of zygomycosis are succinctly discussed together with the epidemiology, pathogenesis and treatment of infection. Updated evidence (or lack of) for adjunctive treatments including surgery, hyperbaric oxygen and management/ reversal of underlying immune deficiency using cytokines and growth factors are reviewed.


This is the first published randomised controlled trial evaluating caspofungin as first-line monotherapy of proven/probable invasive aspergillosis in patients with haematological cancers and autologous stem cell transplant recipients. Caspofungin achieved an end-of-treatment response rate of 33% in the modified-intention-to-treat population and day-54 survival of 52%.


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65. Troke P, Aquilabensos K, Artega C, Ellis D, Heath C, Lutsar I, Rovira M, Nguyen Q, Slavin M, Chen S: Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob Agents Chemother 2008, 52:1743-1750. This large case series summarises the efficacy of voriconazole in the primary, as well as compassionate/named and salvage treatment of Scedosporium infection. Voriconazole demonstrated clinically useful activity in the treatment of both S. apiospermum and S. prolificans infection and was well tolerated. Efficacy and patient survival were dependent on species and type of infection.


