

# **Guidelines for the use of antifungal agents in the treatment of invasive *Candida* and mould infections**

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## ***Summary of Recommendations for treatment***

### **A. Initial therapy for suspected or proven invasive fungal infection (IFI)**

- **Amphotericin B remains the empiric treatment of choice for invasive fungal infections except for those due to the fungi described in section C below, or in patients with pre-existing renal impairment described in section B (B111).**

Dose of amphotericin B: for a yeast infection 0.7 mg/kg/day (with the exception of *C. krusei* and *C. glabrata* where a dose of 1 mg/kg/day is recommended), for a mould infection 1 mg/kg/day.

To minimise renal impairment reduce the number of potentially nephrotoxic drugs co-administered and ensure the patient is well hydrated. Saline pre-hydration should be given if possible (A11).

- If mould infection is considered unlikely on clinical grounds, **fluconazole** 400 mg/day may be an alternative if not previously administered for prophylaxis (A1).
  
- **Voriconazole is an alternative to amphotericin B for the initial treatment of proven acute invasive aspergillosis in the immunocompromised patient (A1).**

Dose voriconazole: loading dose of 6 mg/kg/day IV bd for 2 doses and thereafter 4 mg/kg bd.

B. **Antifungal choice for patients who have developed amphotericin B nephrotoxicity or have pre-existing renal impairment**

- **Allow serum creatinine to rise to 0.23mmol/L before ceasing conventional amphotericin B (B11)**

**except** in patients where renal failure is expected to complicate management of underlying condition: eg renal transplant, haematopoietic stem cell transplant (HSCT), or chemotherapy for haematological malignancy where HSCT is ultimately planned. In these patients stop amphotericin B **if serum creatinine reaches 0.15 mmol/L on 2 consecutive days or the measured creatinine clearance falls by 50% or if the rate of creatinine increase has been rapid (e.g. doubling daily).**

- **Subsequent therapy if renal impairment reaches these thresholds will depend on clinical setting as follows:**

a. **For Fever of Unknown Origin (FUO) in neutropenic patients**

- **At low risk** for invasive mould infection **fluconazole** 400 mg/day may be an alternative if not previously administered for prophylaxis (A1).

- **At high risk** for invasive mould infection (eg allogeneic HSCT recipient, patients undergoing therapy for acute leukaemia, patient with >3 weeks Absolute Neutrophil Count (ANC)  $<0.5 \times 10^9/L$ )

**Liposomal amphotericin B** (AmBisome<sup>®</sup>) 1 mg/kg/day may be the preferred option (A1). The dose may be increased to 3 mg/kg/day in patients with poor response (B11).

**OR**

**Itraconazole** loading dose 200 mg IV bd for 2 days then 200mg IV/day in patients being treated for haematological malignancies who have not received itraconazole prophylaxis. After one week of intravenous itraconazole, oral itraconazole cyclodextrin solution 20 mls bd could be substituted. (Not studied in allogeneic HSCT recipients) (A1).

**OR**

**Voriconazole.** Loading dose of 6 mg/kg/day IV bd for 2 doses then 3 mg/kg IV bd or 200mg orally bd (B1).

The efficacy of lipid formulations other than AmBisome<sup>®</sup> are less well evaluated although **Amphotericin B lipid complex** (Abelcet<sup>®</sup>) 5 mg/kg/day or **Amphotericin B colloidal dispersion** (Amphocil<sup>®</sup>) 3-4 mg/kg/day are alternatives.

**Caspofungin** has not been evaluated for the empiric treatment of persistent fever in the setting of neutropenia

The agent of choice will depend on individual patient's tolerance, presence of hepatic impairment where liposomal amphotericin B may be better tolerated and requirement for drugs such as rifampicin, which induce metabolism of triazoles and the comparative drug costs. As itraconazole empiric therapy has not been evaluated in allogeneic HSCT recipients, liposomal amphotericin B or voriconazole would be preferred in this setting and itraconazole preferred in patients undergoing treatment for haematological malignancies who have not received itraconazole prophylaxis.

*b. For candidaemia or invasive candidiasis:*

- Neutropenic patient: **caspofungin** (B1), **liposomal amphotericin B** (A11) 3 mg/kg/day. If the organism is a non-*albicans Candida* species higher doses may be required. Amphotericin B lipid complex at 5 mg/kg/day or Amphotericin B colloidal dispersion 3-4 mg/kg/day are alternatives (C111).

- Not neutropenic and fluconazole-sensitive organism: **Fluconazole** 400 mg IV daily (A1).  
If the organism has intermediate susceptibility to fluconazole and the patient is stable, the dose can be increased to 800 mg/day. Doses should be adjusted for renal function.
- Not neutropenic and a fluconazole resistant organism: **caspofungin** (B1), **voriconazole** (C111), or a lipid preparation of amphotericin B (C111) may be used according to susceptibility of organism, patient tolerance and comparative cost. The maintenance dose of voriconazole is 3mg/kg IV bd for treatment of candidemia.

c. For suspected or proven acute invasive aspergillosis:

- **Voriconazole** loading dose of 6 mg/kg/day IV bd for 2 doses, followed by 4 mg/kg bd (A1).
- **Liposomal amphotericin B** at 3-5 mg/kg/day (B1). If patient not neutropenic and stable, liposomal amphotericin B at 3 mg/kg/day may be adequate (B1).
- **Caspofungin** 70mg load followed by 50 mg/day is an alternative (B11).
- Amphotericin B lipid complex at 5 mg/kg/day, Amphotericin B colloidal dispersion at 3-4 mg/kg/day (B111).

With current information, voriconazole may be the preferred option. The limitations in the spectrum of activity of these agents should also be considered when treating suspected infection (eg. caspofungin is active against aspergillus and candida only, voriconazole is inactive against Zygomycetes, and amphotericin B is inactive against *Scedosporium spp.*)

**C. Other situations where agents other than amphotericin B may be considered:**

**a. For other moulds which may be less susceptible to amphotericin B:**

- *Scedosporium prolificans*: **voriconazole or itraconazole plus terbinafine 250mg** bd as first line treatment. (B111)
- *S. apiospermum* and its teleomorph *Pseudallescheria boydii*: **voriconazole or itraconazole**
- *Fusarium spp.*: **liposomal amphotericin B or other lipid preparation** at 5 mg/kg/day (C111) or voriconazole loading dose of 6 mg/kg/day IV bd for 2 doses followed by 4 mg/kg bd (C111).
- Zygomycetes: **liposomal amphotericin B or other lipid preparation** at 5 mg/kg/day (C111).

b. For failure of amphotericin B therapy

Failure is defined at day 7-14 of treatment with standard doses of amphotericin B, if there is no improvement in signs or symptoms of infection. (Note: CT changes often worsen in the first 2 weeks of treatment and a decision of failure should not be made on CT findings alone).

- Suspected or proven aspergillosis: **voriconazole** (B11) **caspofungin** (B11) **amphotericin B lipid complex** (B111), **liposomal amphotericin B** (C111) or combination of liposomal amphotericin B and caspofungin (C111).
- Cause of infection is unknown: voriconazole (B11), **amphotericin B lipid complex** at 5 mg/kg/day (B111) or **liposomal amphotericin B** at 5 mg/kg/day (C111) could be considered.

Voriconazole would be the preferred choice if the organism causing infection were unknown due to its broader spectrum of activity. If *Aspergillus* or *Candida* were suspected Caspofungin would be preferred. If a Zygomycete was suspected a lipid formulation of amphotericin B would be preferred.

c. For infusional toxicity of amphotericin B

eg fevers chills unable to be controlled by pre-medication.

Optimal pre-medication may include paracetamol 1g orally 1 hour prior to infusion, phenergen 12.5-25 mg IV, hydrocortisone 50-100 mg IV, pethidine 25 mg IV and anti-emetics (if nausea is a problem) just prior to start of infusion. During an infusion lasting more than 3 hours, more than one dose of pethidine may be required. An infusion may be ceased temporarily or slowed if reactions are problematic. Hydrocortisone may be omitted in appropriate clinical circumstances.

## Background

For 30 years, conventional amphotericin B (amphotericin B deoxycholate) has been the gold standard for treatment of invasive fungal infections (IFIs). Most fungi are susceptible to amphotericin B, although fungi with reduced susceptibility or resistance include *Trichosporon beigelii*, *Fusarium* spp and the dematiaceous fungi such as *Alternaria* spp, *Pseudallescheria boydii* and *Scedosporium* spp (1). In many clinical settings such as invasive aspergillosis in neutropenic or immunosuppressed patients the response to amphotericin B is poor. This may relate to late diagnosis, host defects or dose limiting toxicity.

The narrow therapeutic window and attendant toxicities of amphotericin B are well recognised. Infusional toxicity occurs in 60% of patients and renal impairment in 80% of patients receiving a 2 week course of amphotericin B (2). Although strategies to manage these toxicities have been developed (eg. saline loading, potassium sparing diuretics and premedication with antihistamines, steroids and pethidine), amphotericin B is often poorly tolerated particularly in patients requiring prolonged courses at doses above 0.5 mg/kg/day. Multivariate analysis of amphotericin B use and renal failure in over 200 transplant patients, showed that the degree of nephrotoxicity tolerated was secular with HSCT recipients most at risk of requiring hemodialysis (3). In another study of adults with amphotericin B associated renal failure, the mortality rate was higher and the mean length of stay was longer than in those without acute renal failure (4).

The number of available antifungals is increasing. Amphotericin B deoxycholate, three lipid formulations of amphotericin B, three triazoles as well as caspofungin are available in Australia. Different methods of administration such as 24 hour infusions of amphotericin B deoxycholate are under investigation. The following recommendations are based on currently available information and an attempt has been made to provide concordance with the treatment guidelines of the Infectious Diseases Society of America (IDSA) (5,6). The strength of recommendation and quality of evidence are rated according to the methods used in the IDSA guidelines (7), (Table 1).

### ***Lipid formulations of amphotericin B***

The three lipid formulations are; *liposomal amphotericin B*, (AmBisome<sup>®</sup>), *amphotericin B lipid complex* (Abelcet<sup>®</sup>) and *amphotericin B colloidal dispersion* (Amphocil<sup>®</sup>). They are more expensive than conventional amphotericin B but generally have the advantage of less infusional and renal toxicity and provide the opportunity to administer higher doses of amphotericin B. Liposomal amphotericin B is less nephrotoxic than amphotericin B lipid complex (8). Whilst amphotericin B colloidal dispersion has less nephrotoxicity than conventional amphotericin B it has more infusional toxicity (9, 10). Animal studies (11) suggest similar efficacy between liposomal amphotericin B and amphotericin B lipid complex, as do retrospective comparisons of patient outcomes (12).

## ***Triazoles***

*Fluconazole* is a safe and effective drug for treatment and prevention of most yeast infections, but has no efficacy against moulds. Further, some *Candida* species are intrinsically resistant to fluconazole. Almost all *Candida krusei* are resistant and approximately 50% of *Candida glabrata* isolates are resistant or have intermediate dose-dependent susceptibility to fluconazole (13). Where patients have received fluconazole treatment or prophylaxis these species may become important pathogens, which limits the use of fluconazole in the empiric treatment of patients with fever and neutropenia.

*Itraconazole* has broad spectrum activity against both yeasts and moulds but its use has been previously limited by lack of an intravenous formulation. The serum concentrations achieved with the oral formulations have substantial interpatient variability. The capsule requires gastric acid for absorption. The cyclodextrin vehicle in the liquid formulation, whilst improving absorption, may cause diarrhoea. The long half-life leads to a one to two week delay in achieving adequate serum concentrations. An intravenous preparation is now available under the special access scheme and has been studied in empiric therapy of febrile neutropenic patients (14).

*Voriconazole* is the newest of the triazoles available and has activity against yeasts including those intrinsically resistant to fluconazole, as well as moulds such as *Aspergillus* spp, some

*Fusarium* spp and importantly *Scedosporium* spp. which are often resistant to amphotericin B (1). Voriconazole is both a substrate for, and inhibitor of the hepatic drug metabolising enzymes CYP2C9 and CYP2C19. Voriconazole has less affinity for CYP3A4 than some other azoles but this is an important source of many drug interactions (15). Drugs inducing hepatic enzymes such as *rifampicin* will increase its metabolism. Voriconazole may compete for metabolism with drugs such as *erythromycin* and *cyclosporine*, increasing blood levels of those drugs and interact with chemotherapy agents such as *cyclophosphamide* (with a potential reduction in levels of the active metabolite) and *vinca alkaloids* (with potential increase in levels). Use with *sirolimus* is contraindicated (15).

Newer triazoles with broad spectrums of activity such as *posaconazole* and *ravuconazole* are undergoing clinical trials. The only agent with *in vitro* activity against Zygomycetes is posaconazole (16).

All triazoles have side effects associated with this class including abnormal liver function tests and rash. However, voriconazole specifically causes visual disturbance in up to 30% of recipients, which is usually transient. All triazoles are metabolised by the hepatic microsomal enzymes and drug interactions are important considerations. The excipient for the intravenous formulation of voriconazole and itraconazole is cyclodextrin. As cyclodextrin is renally cleared (15), the intravenous formulation is not recommended in patients with a creatinine clearance of less than 50 ml/min.

## *Echinocandins*

These drugs have a different mechanism of action from polyenes and azoles, which act on the cell membrane. Echinocandins inhibit the synthesis of an essential component of the fungal cell wall, beta-(1,3)-D-glucan. This is not present in mammalian cell walls. *Caspofungin* has demonstrated most activity in the growing ends and branches of fungal hyphae and rapidly ceases hyphal growth and replication. A method of caspofungin susceptibility testing for moulds has not yet been established but from animal and clinical studies caspofungin has demonstrated activity against *Aspergillus* and *Candida*. It does not have activity against *Cryptococcus*, *Fusarium* or *Zygomycetes*. It is not recommended for use with cyclosporin as healthy subjects who received caspofungin together with cyclosporin developed transient elevations of transaminases. Caspofungin has thus far been relatively free of side effects.

## *Terbinafine*

*Terbinafine* (Lamisil<sup>®</sup>) is an allylamine with well documented activity when used both topically and systemically for infections of nails and skin. It is active *in vitro* against a wide range of fungi including dermatophytes, moulds, and some yeasts (17,18). Terbinafine inhibits squalene epoxidase which converts squalene to lanosterol. Lanosterol is eventually converted to ergosterol. Terbinafine leads to ergosterol deficiency and accumulation of intracellular squalene. Terbinafine appears to have low toxic potential in animal studies (17).

## ***Costs***

Costs will vary according to local pharmacy arrangements. As a guide costs per intravenous aspergillus treatment dose (in a 70 kg person) will range from \$23.75 for conventional amphotericin B to \$2,210 for liposomal amphotericin B. Costs of the newer agents are: Caspofungin \$750, Amphotericin B colloidal dispersion \$700, voriconazole \$531-760 depending on whether an opened vial is re-used.

## ***Clinical studies***

The use of a standard definition for IFI (19) and composite end-points for assessment of therapy for fever and neutropenia (20) have aided the interpretation of antifungal studies. When comparing efficacy in clinical studies, it is important to take account of the proportion of patients entering the study due to failure of prior antifungal therapy, the proportion of patients undergoing allogeneic HSCT, as well as those with disseminated or central nervous system (CNS) disease. These factors usually impact negatively on prognosis (21).

## ***Empirical antifungal therapy in febrile neutropenic patients***

### **Lipid Formulations**

All the comparative studies of lipid formulations in fever and neutropenia have used differences in toxicity as the primary endpoint, with the exception of the study by Walsh *et. al.* (20), which compares the efficacy of amphotericin B versus liposomal amphotericin B as the primary endpoint.

Two direct comparisons of amphotericin B lipid complex and liposomal amphotericin B have been undertaken. Both focus on differences in toxicity rather than efficacy (8,22). Three studies (9,20,23) have compared amphotericin B to the lipid products, liposomal amphotericin B or amphotericin B lipid complex. These three studies all detected less nephrotoxicity with liposomal amphotericin B in comparison to amphotericin B (20,23) or amphotericin B lipid complex (8). Whether this difference in renal toxicity translates into significant clinical benefit remains open to debate. No survival benefit for a lipid formulation in the treatment of fever and neutropenia has been demonstrated. Whilst amphotericin B colloidal dispersion has less nephrotoxicity compared to amphotericin B, infusional reactions, especially the rate of hypoxic reactions were of concern (9). In patients at highest risk of IFI, i.e. patients with prolonged neutropenia, liposomal amphotericin B at 3 mg/kg/day may be superior to amphotericin B or liposomal amphotericin B at 1 mg/kg/day (20,23).

## **Triazoles**

Triazoles studied in the setting of fever and neutropenia have been fluconazole, itraconazole and voriconazole. All have been compared with amphotericin B (14,24,25) or liposomal

amphotericin B (26). Two studies have compared fluconazole 400 mg daily to amphotericin B 0.5 mg/kg/day (24,25). Only one was powered to detect a difference in efficacy and showed a similar efficacy for both agents (24). Adverse events were more common with amphotericin B but there was no difference in the rate of hepatic dysfunction. However, these studies were in patient populations probably at a lower risk for IFI than those described above (9, 20). There were few allogeneic HSCT recipients and patients had not received prior fluconazole prophylaxis. An open-label, randomised comparison of itraconazole and amphotericin B in haematology patients, excluding allogeneic HSCT recipients, showed similar rates of death and breakthrough fungal infections (14). Less toxicity, including nephrotoxicity was observed in the itraconazole arm. After 2 days of intravenous itraconazole the level was therapeutic (>250 ng/ml) in 97% of patients and these levels were maintained on oral itraconazole when substituted for intravenous as early as day seven.

The largest study of a triazole in patients with fever and neutropenia, an open label study in 837 patients, compared voriconazole and liposomal amphotericin B (26). The overall success rates were 26% with voriconazole and 31% with liposomal amphotericin B. Voriconazole did not fulfil the protocol definition of non-inferiority which was an overall response rate within 10 percentage points of liposomal amphotericin B at the 95% confidence interval. There were fewer documented breakthrough fungal infections with voriconazole. This benefit was most marked in patients considered as high risk for fungal infection. No survival benefit was observed although survival was assessed at 7 days after completing therapy. At each of the 5 composite end-points other than breakthrough fungal infections the results favoured liposomal

amphotericin B over voriconazole. However, more patients receiving voriconazole were withdrawn from the study prematurely due to concerns regarding lack of efficacy with ongoing fever. The open study design may result in biases. There were fewer infusional reactions and less nephrotoxicity with voriconazole. The incidence of hepatic toxicity was similar but voriconazole recipients had more transient visual disturbances and hallucinations. These side effects of voriconazole while acceptable when treating IFI may be less acceptable in patients receiving empiric therapy.

These studies demonstrate that triazoles may be as effective as amphotericin B or liposomal amphotericin B in empiric therapy of patients with fever and neutropenia. When applying these results, the selective nature of the inclusion criteria used should be considered. For example, although itraconazole performed as well as amphotericin B (14), it should be noted that allogeneic HSCT recipients were excluded from this study. Similarly the study of Winston *et al.* (24) had few allogeneic transplants and included no patients receiving fluconazole prophylaxis. The role of voriconazole in the treatment of patients with fever and neutropenia requires further delineation but it is an alternative to amphotericin B especially in patients at high risk of IFI.

### **Prolonged Amphotericin B Infusion**

A 24 hour infusion of amphotericin B has been compared to a 4 hour infusion at a dose of approximately 1 mg/kg/day on starting antifungal therapy (27). Continuous infusion had less overall infusional toxicity and nephrotoxicity and fewer deaths during treatment and at 3 months after end of treatment. Whilst this report is encouraging, this study was powered to detect changes in toxicity **not** efficacy. Also while the difference in death rates between the 2 arms was significant, there were no data on cause of death. Furthermore, the effectiveness of the 24 hour infusion strategy in protecting against further nephrotoxicity with established nephrotoxicity is unknown. More research is required to evaluate this mode of administration.

### ***Treatment of suspected/probable and proven fungal infection***

#### **Lipid formulations**

There are only two randomised comparisons of a lipid formulation to conventional amphotericin B. The first was between liposomal amphotericin B at 5 mg/kg/day and amphotericin B at 1 mg/kg/day (28). This small study compared neutropenic patients with a variety of IFIs but mostly suspected pulmonary aspergillosis. A complete response was seen in more patients receiving liposomal amphotericin B but there was no difference in the percentage of patients who failed therapy. The overall mortality was lower, and patients with progressive malignancy did better, with liposomal amphotericin B. The second was a randomised comparison of amphotericin B colloidal dispersion and amphotericin B for primary treatment of invasive aspergillosis (10). Although not powered to detect equivalence, similar outcomes

were seen in the 94 patients. There was less nephrotoxicity but more infusional toxicity with amphotericin B colloidal dispersion.

Two doses of liposomal amphotericin B, 1 versus 4 mg/kg/day, were compared for the treatment of proven or probable invasive aspergillosis (29). This study evaluated response in 87 neutropenic haematology or HSCT patients, the majority with probable rather than proven aspergillosis. The definition of probable aspergillosis was less stringent than that now used (19). Overall there was no difference in clinical or radiological response rates or survival at 6 months between the 2 doses. However, subgroups of patients with both proven invasive aspergillosis and prolonged neutropenia had better responses at 4 mg/kg/day and the power of the study to detect clinically meaningful differences in efficacy was very low given the small sample size.

The experience of one centre with amphotericin B lipid complex or liposomal amphotericin B in adult haematology and oncology patients was reported (12). Proven infection accounted for only 15 of 68 treatment courses. The occurrence of nephrotoxicity was similar but fever and chills were significantly higher with amphotericin B lipid complex. Overall response rates and survival were similar.

Data from several compassionate use programs have been reported. However, patients entering compassionate use programs are highly selected with inherent biases. They are rarely undergoing initial therapy. They have survived initial therapy and required treatment with

another antifungal agent due to toxicity or clinical failure. Walsh *et. al.* reported on the safety and efficacy of amphotericin B lipid complex in 556 patients (30). Just over half the patients entered due to failure of another antifungal, mostly amphotericin B. Although one third of patients entered due to nephrotoxicity, the mean serum creatinine fell on treatment. The overall response rate was 57% and this was identical for the 291 mycologically proven cases. Response rates for aspergillosis (42%), disseminated candidiasis (67%), zygomycosis (71%) and fusariosis (82%) were higher than would be expected from experience using amphotericin B. Perhaps these patients had a better than expected outcome because only 24% were neutropenic at baseline and almost half received amphotericin B lipid complex for intolerance of prior antifungals rather than clinical failure. Similar findings were reported in HSCT recipients with suspected or proven fungal infections who received compassionate use amphotericin B lipid complex or amphotericin B colloidal dispersion (31, 32). Analysis of the compassionate access program of amphotericin B colloidal dispersion revealed similar response rates of 58% for candidiasis and 34% for aspergillosis in 97 evaluable patients (33).

In summary, studies of lipid formulations in treatment of IFI reveal a relative lack of comparative data. Perhaps in the subgroup of patients with prolonged neutropenia or undergoing allogeneic transplant, liposomal amphotericin B at 4 mg/kg/day is a more effective treatment dose than 1 mg/kg/day. Liposomal amphotericin B may lead to more complete resolution of IFI than amphotericin B in haematology patients. The higher doses of lipid associated amphotericin B may be better than that of standard amphotericin for difficult to treat infections such as fusariosis and zygomycosis as well as for the non-*albicans Candida*

species such as *C. krusei*, *C. glabrata* or *C. lusitaniae* although no direct comparisons have been performed. There is a cost advantage for amphotericin B lipid complex and amphotericin B colloidal dispersion over liposomal amphotericin B. However, in patients undergoing solid organ or haematopoietic stem cell transplants and receiving potentially nephrotoxic drugs liposomal amphotericin B may be preferable as it has the lowest rates of nephrotoxicity and infusion reactions.

### **Caspofungin**

Two studies have compared caspofungin and amphotericin B in the treatment of oesophageal candidiasis in HIV infected patients (34,35). A randomised double blind study of caspofungin at either 50 or 70 mg/day and amphotericin B at 0.5 mg/kg/day showed higher success rates with caspofungin although this trial was not powered to test efficacy (34). Caspofungin was well tolerated with the most common adverse events described as fever, phlebitis, headache and rash. Significantly fewer patients receiving caspofungin than those receiving amphotericin B had impaired renal function. Similar response rates were seen in a double blind comparative study of caspofungin (doses of 35-70 mg/day) versus amphotericin B in 140 patients with oropharyngeal and oesophageal candidiasis (35).

A recently published study compared caspofungin and amphotericin B for invasive candidiasis or candidaemia in predominantly non-neutropenic patients (36). Treatment was for 14 days

after last positive culture. Dosing for caspofungin was 50 mg/day after a 70 mg loading dose and amphotericin B doses ranged between 0.6-1.0 mg/kg/day. Caspofungin was at least as effective as amphotericin B with fewer adverse events. The overall favourable response rate on modified intention to treat analysis at end of therapy was similar in both arms at 73% for caspofungin and 62% for amphotericin B. It is important to note that favourable response included microbiological and clinical criteria as well as remaining on study drug. Approximately 23% of patients in the amphotericin B arm as compared to 3% of patients receiving caspofungin withdrew due to an adverse event. The most frequent drug-related adverse events for caspofungin were hypokalemia (11%) and doubling or increase baseline serum creatinine by more than 0.088 mmol/L (8.4%). Both of these were significantly less common with caspofungin than amphotericin B (36).

A salvage therapy study for invasive aspergillosis was approved in the US and Australia has been published as an abstract (37) and also appears in the product information and on the FDA web site (<http://www.fda.gov/>). This an open label, non-comparative study of caspofungin was in patients with proven or probable invasive aspergillosis according to standard definitions (19). Patients were intolerant to, or had progressed or failed to improve, despite 7 days of other antifungal agents. Treatment was with a single loading dose of 70 mg followed by 50 mg IV daily. A favourable response was either complete cure or partial response defined as clinically meaningful improvement of all clinical signs, symptoms and radiological findings. Stable disease was classified as a treatment failure. Of the 90 enrolled patients, 83 were evaluable. Most patients had refractory disease and 77% had pulmonary disease. A

favourable outcome was seen in 45% of patients who received at least one dose of caspofungin. The favourable response rate was higher in patients with toxicity on other therapy. Favourable response rates were 50% in patients with pulmonary disease and 26% in patients with extrapulmonary disease.

These studies suggest that caspofungin is as efficacious as amphotericin B in treating candidaemia or oesophageal candidiasis, but with fewer adverse events including nephrotoxicity. For invasive aspergillosis, the evidence for use is based on a single open label non-comparative study. However, the presence of well documented infection, seriousness of the infection (pulmonary infection as well as disseminated and CNS infection), the high proportion of patients entering the study due to failure of prior therapy and the presence of 28% of patients who had allogeneic HSCT indicate that this study group was one where a low success rate would be expected. It is not possible to extrapolate the success of this single study in aspergillosis to other settings e.g. fever and neutropenia, although such studies are underway. Further, caspofungin lacks *in vitro* activity against *Cryptococcus*, *Fusarium* spp and Zygomycetes, limiting its use for broader clinical indications.

### **Voriconazole**

Herbrecht (38) *et. al.* conducted an open randomised comparison of voriconazole 6 mg/kg loading dose 12 hourly and then 4 mg/kg 12 hourly or 200 mg orally bd versus amphotericin B 1 mg/kg in 392 patients with invasive aspergillosis. Aspergillosis was defined according to

standard definitions (19) as definite or probable. Satisfactory outcome was a complete response of clinical or radiological findings or partial response, which was significant clinical and  $\geq 50\%$  radiological improvement. The primary end-point was response at week 12. Patients remained on study if they were changed to other licensed antifungal therapy before week 12. Patients were assessed for outcome at week 12 and at end of study therapy. Most patients had undergone HSCT or were undergoing treatment for haematological malignancy and had pulmonary invasive aspergillosis. At week 12, satisfactory outcome occurred in 53% voriconazole and 32% amphotericin B recipients (95% CI for difference 33% to 10%). Survival of patients receiving voriconazole was 71% versus 58% receiving amphotericin B (Hazard ratio 0.59, 95% CI 0.40 to 0.88). The median duration of study drug was 77 days in voriconazole recipients and 11 days for amphotericin B. This study suggested voriconazole was more effective than amphotericin B followed by other licensed antifungal therapy and may result in improved survival. However, the open label study design creates potential bias and not all confounders can be easily controlled.

An open label non-comparative study of efficacy and safety of voriconazole in the treatment of definite or probable invasive aspergillosis in 116 patients was reported by Denning *et. al.* (39). Aspergillosis was definite if a histological diagnosis was made or if a positive culture was obtained from a sterile site. The definition of probable invasive aspergillosis and failure of therapy was more lenient than in the above study (38). Treatment was with intravenous loading followed by 3 mg/kg/day bd for 6-27 days followed by 200 mg bd orally for up to 24 weeks. Overall good responses were seen in 48%, and failure in 31%. Immunosuppression and site of

infection influenced the response rate. Better outcome was seen in those with pulmonary disease, with haematological disorders and those receiving initial rather than salvage therapy.

Voriconazole 200 mg bd and fluconazole 200 mg daily were compared in 391 immunocompromised patients with biopsy and mycologically proven oesophageal candidiasis (40). The primary end-point was response as assessed by oesophagoscopy and equivalency was demonstrated.

These studies indicate that voriconazole will be a useful treatment of acute invasive aspergillosis. It may be more effective than amphotericin B in the treatment of invasive aspergillosis especially as amphotericin B is commonly used as first line therapy with a change to another agent on development of toxicity or lack of improvement. The study of Herbrecht *et. al.*, was designed to test the initial treatment of aspergillosis in immunocompromised patients only and it should be remembered that patients on the amphotericin B arm remained on this treatment for a median of 11 days only before changing to other licensed antifungal therapy.

### **Combination therapy**

With the availability of antifungal agents acting on different targets in the fungal cell, the possibility of combination therapy exists. *In vitro* testing suggests combination therapy produces synergy. Its role has been explored in difficult to treat infections such as

scedosporiosis and aspergillosis as well as candidiasis and cryptococcosis. However, there is limited clinical experience to confirm these *in vitro* observations apart from case reports.

*In vitro* testing of *Aspergillus* species revealed potent synergy with the combination of terbinafine and a triazole (18). Synergy was most notable with itraconazole and voriconazole, but was also found with fluconazole, an agent that has no activity against *Aspergillus* species. With *Scedosporium prolificans*, testing revealed synergy between itraconazole and terbinafine in 95% of isolates (41).

Combinations of caspofungin with fluconazole, flucytosine and amphotericin B have also been tested *in vitro*. Synergy was noted for these combinations with *Cryptococcus neoformans* which is not susceptible to caspofungin alone (42). Synergy was also noted for amphotericin B and caspofungin against *Aspergillus* spp. and *Cryptococcus* spp. (43). A series describing use of combination liposomal amphotericin B and caspofungin in leukaemic patients with proven or suspected aspergillus pneumonia refractory to amphotericin B treatment has recently been published (44). Although the response was encouraging in 75% of the 30 patients, most of the patients included had possible rather than proven or probable aspergillosis. Currently combination therapy can only be recommended for difficult infections such as with *Scedosporium prolificans*.

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## References

1. Espinel-Ingroff A. *In vitro* fungicidal activities of voriconazole, itraconazole and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. *J Clin Microbiol* 2001;39: 954-58
2. Butler WT, Bennett JE, Alling DW et al. Nephrotoxicity of amphotericin B: early and late effects in 81 patients. *Ann Intern Med* 1964; 61:175-87
3. Wingard JR, Kubilis P, Lee L et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis* 1999; 29:1402-7
4. Bates DW, Su L, Yu DT et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin Infect Dis* 2001; 32:686-93
5. Rex JH, Walsh TJ, Sobel JD et al. Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2000; 30:662-78.
6. Stevens DA, Kan VL, Judson MA et al. Practice guidelines for diseases caused by *Aspergillus* *Clin Infect Dis* 2000; 30:696-709.

7. Sobel JD for the Mycoses Study Group. Infectious Diseases Society of America. Practice guidelines for the treatment of fungal infections. Clin Infect Dis, 2000; 30:652.
8. Wingard JR, White MH, Anaissie E et al. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. Clin Infect Dis 2000; 31:1155-63.
9. White MH, Bowden RA, Sandler, ES et al. Randomised, double-blind clinical trial of Amphotericin B colloidal dispersion vs Amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 1998; 27:296-302
10. Bowden R, Chandraseker P, White MH et al. A double blind randomized controlled trial of amphotericin B colloidal dispersion versus amphotericin B for the treatment of invasive aspergillosis in immunocompromised patients. Clin Infect Dis 2002; 35:359-66.
11. Clemons KV, Stevens DA. Comparison of Fungizone, Amphotericin B colloidal dispersion, Liposomal amphotericin B and Amphotericin B lipid complex for

treatment of systemic murine cryptococcosis. *Antimicrob Agents Chemother* 1998; 42:899-902.

12. Clark AD, McKendrick S, Tansey PJ, Franklin IM, Chopra R. A comparative analysis of lipid-complexed and liposomal amphotericin B preparations in haematological oncology. *Br J Haematol* 1998; 103:198-204.
  
13. Pfaller MA, Diekema DJ, Jones RN et al. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program, *J Clin Microbiol* 2001; 39:3254-9
  
14. Boogaerts M, Winston DJ, Bow EJ et al. Intravenous and oral itraconazole versus intravenous Amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy, *Ann Intern Med* 2001; 135: 412-22
  
15. Johnson LB, Kaufman CA. Voriconazole: A new triazole antifungal agent. *Clin Infect Dis* 2003;36:630-7

16. Espinel-Ingroff A. Comparison of in vitro activities of the new triazoles SCH56592 and echinocandins MK-0991 and LY 303366 against opportunistic filamentous and dimorphic fungi and yeasts. *J Clin Micro* 1998;36:2950-6.
17. Petranyi G, Meingassner JG, Mieth H. Activity of terbinafine in experimental fungal infections of laboratory animals. *Antimicrob Agents Chemother* 1987; 31:1558-61.
18. Ryder NS, Leitner I. Synergistic interaction of terbinafine with triazoles or amphotericin B against *Aspergillus* species. *Med Mycol* 2001; 39:91-5.
19. Ascoglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; 34:7-14
20. Walsh TJ, Finberg RW, Arndt C et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999; 340:764-71.
21. Patterson TF, Kirkpatrick WR, White M et al Invasive Aspergillosis – Disease spectrum, treatment practices and outcomes. *Medicine* 2000; 79: 250-60.

22. Fleming RV, Kantarjian HM, Husni R et al. Comparison of Amphotericin B Lipid Complex (ABLC) vs liposomal amphotericin B in the treatment of suspected or documented fungal infections in patients with leukemia. *Leuk Lymphoma* 2001; 40: 511-20
  
23. Prentice HG, Hann IM, Herbrecht R et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol.* 1997; 98:711-8.
  
24. Winston DJ, Hathorn JW, Schuster MG et al. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. *Am J Med* 2000; 108:282-9.
  
25. Malik IA, Moid I, Aziz Z, et al. A randomised comparison of fluconazole with amphotericin B as empiric anti-fungal agents in cancer patients with prolonged fever and neutropenia. *Am J Med* 1998; 6:478-83
  
26. Walsh TJ, Pappas P, Winston DJ et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; 346: 225-34.

27. Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *Br Med J* 2001; 322:579-82.
28. Leenders ACAP, Daene S, Jansen RLH et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *Br J Haematol* 1998; 103:205-12
29. Ellis M, Spence D, de Pauw B et al. An EORTC international multicenter randomized trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. *Clin Infect Dis* 1998, 27:1406-12
30. Walsh TJ, Hiemenz JW, Seibel NL et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis* 1998; 26:1383-96
31. Wingard JR, Efficacy of amphotericin B lipid complex injection (ABLIC) in bone marrow transplant recipients with life-threatening systemic mycoses. *Bone Marrow Transplant* 1997; 19:343-7

- 32.** Noskin G, Pietrelli L, Bowden R. Treatment of invasive fungal infections with amphotericin B colloidal dispersion in bone marrow transplant recipients. *Bone Marrow Transplant* 1999; 23:697-703.
- 33.** Oppenheim BA, Herbrecht R, Kusne S. The safety and efficacy of amphotericin B colloidal dispersion in the treatment of invasive mycoses. *Clin Infect Dis* 1995; 21:1145-53.
- 34.** Villanueva A, Arathoon EG, Gotuzzo E et al. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. *Clin Infect Dis* 2001; 33:1529-35
- 35.** Arathoon EG, Gotuzzo E, Noriega LM et al. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiasis. *Antimicrob Agents Chemother* 2002; 46:451-7
- 36.** Mora-Duarte J, Betts R, Rotstein C et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *New Engl J Med* 2002; 347:2020-9
- 37.** Maertens J, Raad I, Pettrikos G et al. Update of the multicenter noncomparative study of caspofungin in adults with invasive aspergillosis refractory or intolerant to

other antifungal agents: analysis of 90 patients. Abstract M-868, 42<sup>nd</sup> ICAAC Abstracts, American Society for Microbiology, September 27-30, 2002 San Diego, CA, page 388.

38. Herbrecht R, Denning DW, Patterson TF et al. Voriconazole versus Amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347:408-15
39. Denning DW, Ribaud P, Milpied N et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002; 34:563-71
40. Ally R, Schurmann D, Kreisel W et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. *Clin Infect Dis* 2001; 33:1447-54
41. Meletiadis J, Mouton JW, Rodriguez-Tudela JL et al. In vitro interaction of terbinafine with itraconazole against clinical isolates of *scedosporium prolificans*. *Antimicrob Agents Chemother* 2000; 44:470-2
42. Franzot SP, Casadevall A. Pneumocandin L-743,872 enhances the activities of amphotericin B and fluconazole against *Cryptococcus neoformans* in vitro. *Antimicrobial Agents Chemother.* 1997; 41:331-6

- 43.** Bartizal K, Gill CJ, Abruzzo GK et al. In vitro preclinical evaluation studies with the echinocandin antifungal MK-09991 (L-743,872). *Antimicrob Agents Chemother.* 1997; 41:2326-32
- 44.** Aliff TB, Maslak PG, Jurcic JG et al. Refractory aspergillus pneumonia in patients with acute leukemia. Successful therapy with combination caspofungin and liposomal amphotericin. *Cancer* 2003;97:1025-32

## **Table1: Categories of levels of evidence**

### **Categories for strength of evidence for or against a recommendation**

A: good evidence to support a recommendation for use

B: moderate evidence to support a recommendation for use

C: poor evidence to support a recommendation for or against use

D: good evidence to support a recommendation against use

### **Categories indicating the quality of evidence for recommendations**

- I. evidence from at least one properly randomised controlled trial
- II. evidence from at least one well-designed clinical trial without randomisation eg from cohort or case controlled studies (preferably from >1 centre), from multiple time series or dramatic results in uncontrolled experiments
- III. evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.