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Treatment options of invasive fungal infections in adults

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Summary

A panel of infectious disease specialists, clinical microbiologists and hospital epidemiologists of the five Swiss university hospitals reviewed the current literature on the treatment of invasive fungal infections in adults and formulated guidelines for the management of patients in Switzerland. For empirical therapy of Candida bloodstream infection, fluconazole is the drug of choice in non-neutropenic patients with no severe sepsis or septic shock or recent exposure to azoles. Amphotericin B deoxycholate or caspofungin would be the treatment option for patients with previous azole exposure. In neutropenic patients, empirical therapy with amphotericin B deoxycholate is considered first choice. In patients with severe sepsis and septic shock, caspofungin is the drug of first choice. For therapy of microbiologically-documented Candida infection, fluconazole is the drug of choice for infections due to *C. albicans*, *C. tropicalis* or *C. parapsilosis*. When infections are caused by *C. glabrata* or by *C. krusei*, caspofungin or amphotericin B deoxycholate are first line therapies. Treatment guidelines for invasive aspergillosis (IA) were stratified into primary therapy, salvage therapy and combination therapy in critically ill patients. Voriconazole is recommended for primary (ie upfront) therapy. Caspofungin, voriconazole (if not used for primary therapy) or liposomal amphotericin B are recommended for salvage therapy for refractory disease. Combination therapy with caspofungin plus voriconazole or liposomal amphotericin B should be considered in critically ill patients. Amphotericin B deoxycholate is recommended as initial therapy for the empirical therapy in patients with neutropenia and persistent fever with close monitoring of adverse events.

Key words: guidelines; candida; invasive aspergillosis; antifungal agents

Introduction

Candida and *Aspergillus* are the most common causes of invasive fungal infections, accounting for 70–90% and 10–20% of all invasive mycoses, respectively [1]. In the US, the incidence of fungal sepsis has increased three-fold between 1979 and 2000 [2]. Invasive candidiasis and aspergillosis are associated with substantial morbidity and high mortality (40–60% and 60–90%, respectively), prolonged hospital stay and increased health care costs [3–7]. Early diagnosis and prompt initiation of antifungal therapy are thus essential to reduce morbidity and mortality.

For decades, amphotericin B deoxycholate, has been standard therapy for invasive fungal infections. Unfortunately, amphotericin B deoxycholate is often poorly tolerated and associated with infusion-related acute reactions and nephrotoxicity. In the late 1970s and 1980s, the emergence of azoles (first miconazole and ketoconazole and then fluconazole and itraconazole), a new class of antifungal agents inhibiting the synthesis of the cell membrane, provided an alternative therapeutic strategy to amphotericin B deoxycholate. In recent years, several new antifungal agents have become available offering additional therapeutic options for the management of invasive fungal infections. These include lipid formulations (colloidal dispersion, lipid-complex and liposomal) of

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amphotericin B, new azoles (voriconazole, and posaconazole) and echinocandins (caspofungin, micafungin and anidulafungin) [8–12].

A recent publication has shown the utility of using treatment guidelines to improve the outcome of patients with invasive fungal infections [13]. Therefore the aim of the present article is to review the current literature on antifungal therapy and to formulate treatment recommendations for the management of the two most frequent invasive fungal infections occurring in surgical, critically ill or immunocompromised patients, namely invasive candidiasis and invasive as pergillosis and for empirical therapy of suspected fungal infections in patients with neutropenia and persistent fever.

Methods

The article was prepared by a group of infectious diseases specialists, clinical microbiologists and hospital epidemiologists from the five Swiss university hospitals with expertise in the diagnosis and the management of fungal infections. This group was founded in 2000 under the name of the Fungal Infection Network of Switzerland (FUNGINOS). The names of participating individuals and institutions of FUNGINOS can be found in the Appendix of the first article published by the group on the epidemiology of *Candida* infections [14]. FUNGINOS was created with the overall objective to promote biomedical research on invasive fungal infections in Switzerland. The recommendations were presented and discussed at meetings of the FUNGINOS group and of the Swiss Society of Infectious Diseases. Modifications were circulated electronically and agreed upon as part of an iterative process until consensus was reached by a majority of Steering Committee members. Treatment recommendations were rated according to a standard scoring scheme to illustrate the strength of the supporting evidence and the quality of the underlying data as follows: Level of recommendation: A = good evidence; B = moderate evidence; C = poor evidence, Quality of recommendation: I = randomised, controlled, clinical study; II = non-randomised, controlled clinical study or cohort study or case-control study; III = case series or expert opinion [15].

Invasive candidiasis

Epidemiology

Candida species are the most frequent cause of fungal infections (70 to 90% of cases) and account for 5 to 15% of health-care associated infections [16, 17]. Risk factors for fungal sepsis include prematurity, low birth weight, disruption of cutaneous or mucosal barriers (such as surgical wounds, burns or chemotherapy-induced mucositis), indwelling intravascular or urinary catheters, defects of cell-mediated immunity, broad-spectrum antibiotic therapy, parenteral nutrition, colonisation with *Candida* at multiple sites, surgery (especially gastrointestinal interventions) or haemodialysis [18–21]. Critically ill and severely immunocompromised patients are at particularly high risk of invasive candidiasis. Candidaemia, one of the most frequent clinical manifestations of candidiasis, is associated with significant morbidity, prolonged hospital stay, high crude and attributable mortality (40% to 60% and 20 to 40%, respectively) and increased health care costs [3, 6]. In a multivariate analysis of mortality associated with bloodstream infections, *Candida* was found to be the sole pathogen independently associated with fatal outcome [22]. A nationwide population surveillance study conducted in 50 hospitals in the US between 1995 and 2002 has confirmed that *Candida* is the fourth most common cause of bloodstream infections, representing 9.5% of all episodes [17]. In contrast, recent data from Europe have shown that *Candida* species were a less common cause of bloodstream infections. *Candida* species ranked number seven accounting for 3% of all bloodstream infections in a 10-year retrospective study carried out in Switzerland by the Fungal Infection Network of Switzerland (FUNGINOS) [14]. In this survey, one third of all episodes of candidaemia occurred in ICUs (intensive care unit), one third in medical wards, including haematology-oncology units, and one fourth in surgical wards [14].

Microbiology

Until recently, *C. albicans* was by far the predominant species causing up to two thirds of all cases of invasive candidiasis. However, a shift towards non-*albicans Candida* species with decreased susceptibility or resistance to azoles, such as *C. glabrata* and *C. krusei*, has been observed recently in some North-American and European centres [23–25]. The exact role of the increasing use of azoles in this epidemiological shift remains controversial [26]. In Switzerland the distribution of *Candida* species has remained stable between 1991 and 2000 with *C. albicans*, *C. glabrata* and *C. krusei* accounting for 66%, 14% and 2% of all cases of candidaemia, respectively [14].

Identification of *Candida* species and antifungal susceptibility testing are critical for selecting appropriate therapy. Indeed, studies have shown that *in vitro* susceptibility testing for *Candida* may increase the probability of good outcome [27–36]. So far, the clinical utility of *in vitro* testing has been demonstrated in experimental animal models of candidiasis and in HIV-positive patients with

oropharyngeal candidiasis [31; 37; 38]. A recent retrospective clinical study in 32 patients with candidaemia reported different success rates of fluconazole in infections with MIC ≤8 mg/L (ie susceptible: success in 14/21 (67%) cases), MIC 16 to 32 mg/L (ie dose-dependent susceptible: success in 1/5 (20%) cases), and MIC >32 mg/L (ie resistant: success in 0/6 (0%) cases) [30]. This study showed that a fluconazole dose/MIC ratio >50 was associated with a success rate of 74% (14/21 cases) compared to only 8% (1/13 cases) for a dose/MIC ratio ≤50. Antifungal susceptibility testing is also not routinely available in all centres, but identification of *Candida* species can be used to predict resistance and guide therapy (table 1). Indeed, *C. albicans* and other less frequent non-*albicans Candida* species, such as *C. tropicalis* and *C. parapsilosis* are in general susceptible to polyenes (amphotericin B), azoles (fluconazole, itraconazole, voriconazole, posaconazole), and echinocandins (caspofungin, micafungin, anidulafungin) [39]. In contrast, *C. glabrata*, the most frequent non-*albicans* species, is susceptible to amphotericin B and echinocandins, but displays reduced susceptibility to azoles [39]. A recent single-centre study reported high resistance rates in *C. glabrata:* up to 60% for fluconazole, 83% for itraconazole, and 44% for voriconazole, respectively [40]. *C. krusei* is susceptible to amphotericin B, voriconazole, and the echinocandins, but intrinsically resistant to fluconazole and itraconazole [39].

Antifungal therapy

Rapid initiation of appropriate antifungal therapy is essential for the control of systemic *Candida* infections and has been shown to reduce mortality [41–43]. Management guidelines have recommended that all patients with candidaemia, defined as the detection of *Candida* in at least one blood culture, should be treated with antifungal agents [20, 44, 45].

Polyenes

Amphotericin B deoxycholate, a fungicidal agent with broad-spectrum antifungal activity that acts on ergosterol of the fungal cell membrane, has been used for decades as the treatment of choice of invasive candidiasis. It is usually used at a dose ranging between 0.6 and 1 mg/kg/d i.v. Unfortunately, amphotericin B deoxycholate is often poorly tolerated being associated with infusion-related acute reactions (eg chills, fever, hypoxaemia, and hypotension), especially when administered over a short period of time (ie 4 to 6 hours), and with nephrotoxicity (decreased glomerular filtration and tubular wasting of potassium, magnesium, and bicarbonate). However, four recent studies have shown that administration of amphotericin B deoxycholate as a continuous infusion over 24 hours with saline loading reduced infusion-related reactions and renal impairment, including in allogenic stem cell transplant patients receiving cyclosporin A [46–49]. Also, a multivariate analysis on the epidemiology of renal toxicity in 494 patients receiving amphotericin B deoxycholate showed that male gender, body weight ≥90 kg, chronic renal disease, treatment with an aminoglycosides or cyclosporin and doses of amphotericin B ≥35 mg/day were independent risk factors for nephrotoxiciy. Of note, the incidence of nephrotoxicity rose with the increasing number of risk factors suggesting that alternative therapy might be appropriate in patients with 2 or more risk factors [50, 51].

Lipid formulations of amphotericin B (colloidal dispersion, lipid-complex and liposomal) are better tolerated than amphotericin B deoxycholate and have been used mainly in patients intolerant to conventional amphotericin B or unlikely to tolerate it because of already altered renal function [9, 52–55]. Only liposomal amphotericin B (AmBisome®) is available in Switzerland. Few studies have compared the efficacy of amphotericin B deoxycholate with that of lipid formulations for the treatment of patients with invasive candidiasis. Small non-comparative studies suggest that lipid formulations of amphotericin B are as efficacious as conventional amphotericin B [56–59]. High costs, a relative paucity of clinical data and the existence of alternative antifungal therapies (azoles and echinocandins) explain why lipid formulations have been generally used as second-line therapy in patients with refractory invasive candidiasis [20, 45].

Azoles

In the late 1980s triazoles rapidly became standard therapy for invasive candidiasis. Azoles inhibit the synthesis of ergosterol of the fungal cell membrane. *In vitro*, these compounds are fungistatic against *Candida* species. Several clinical studies have compared the efficacy and safety of azoles

Table 1

General pattern of susceptibility of Candida species (adapted from [20]).

Candida spp.	Fluconazole	Itraconazole	Voriconazole	Amphotericin B	Caspofungin
C. albicans	S	S	S	S	S
C. tropicalis	S	S	S	S	S
C. parapsilosis	S	S	S	S	S *
C. glabrata	S-DD to R	S-DD to R	S to I	S to I	S
C. krusei	R	S-DD to R	S	S to I	S
C. lusitaniae	S	S	S	S to R	S

Note: Interpretation based on the use of the NCCLS (CLSI) M27-A methodology
S: susceptible; S-DD: susceptible-dose dependent; I: intermediate; R: resistant
* MIC_{90} higher than in other *Candida* species, but clinical significance unknown (breakpoints not yet defined)

with that of amphotericin B deoxycholate for the treatment of candidaemia in non-neutropenic patients, but few data are available on the treatment of neutropenic patients.

Fluconazole (Diflucan®) is available as intravenous and oral formulations. Oral fluconazole is very well absorbed and the bioavailability is not influenced by H_2 blocking agents. The daily dose should be reduced by half in patients with creatinine clearance of less than 50 ml/min and by 75% if less than 20 ml/min. A loading dose of twice the daily dose is recommended. In a multicentre study of 206 non-neutropenic patients with candidaemia, fluconazole was found to be as efficacious as (success rates: 72% *vs* 79%, respectively) and better tolerated than amphotericin B deoxycholate [60]. Given the broad use of fluconazole, an increasing incidence of infections due to non-*albicans* *Candida* species with reduced, dose-dependent, susceptibility (*C. glabrata*) or intrinsic resistance (*C. krusei*) to azoles has been reported in the late 1990s [17, 25, 61]. Data on the efficacy of high doses (800 to 1200 mg) of fluconazole for the treatment of suspected azole-resistant *Candida* bloodstream infections are lacking.

Itraconazole is available as oral and intravenous formulations. However, the poor bioavailability (enhanced by food) of its original oral formulation has limited its use and no comparative clinical studies have been performed in patients with candidaemia. An intravenous formulation of itraconazole has recently become available, but few clinical data have assessed its efficacy and safety. Given the variation in its bioavailability and potential for drug-drug interactions (eg with rifampicin, anticonvulsants, protease-inhibitors, macrolides) it is recommended to monitor itraconazole blood levels during therapy.

Voriconazole is available as oral (bioavailability 60 to 100%) and intravenous formulations [10]. It is metabolised in the liver via the P-450 system (CYP2C9, CYP3A4 and CYP2C19), hence the potential for multiple drug interactions (eg with rifampicin, anticonvulsants, sirolimus, tacrolimus, cyclosporin, oral anticoagulants, statins, omeprazole, protease-inhibitors, NNRTI). There is no need to alter voriconazole doses in patients with renal impairment receiving the oral formulation. However, administration of intravenous voriconazole in patients with moderate renal insufficiency (creatinine clearance of less than 50 ml/min) may result in accumulation of the β-cyclodextrin used to solubilise voriconazole. Adverse events include transient and fully reversible, non-sight-threatening visual disturbances (in about 30 to 40% of patients), rash, hepatitis, and hallucinations. Voriconazole exhibits excellent *in vitro* and *in vivo* activities against *Candida* species [39]. Clinical data from immunocompromised (mainly HIV-positive) patients with oropharyngeal and/or oesophageal candidiasis suggest that voriconazole has excellent activity against fluconazole-susceptible and fluconazole-resistant *Candida* infections: 98% success of voriconazole versus 95% success of fluconazole [62]. Voriconazole salvage therapy showed an overall success rate of 55% in patients with refractory systemic candidiasis [63]. In a randomised, open-label, comparative multicentre non-inferiority trial in 422 patients with invasive *Candida* infections (of whom >95% had candidaemia), voriconazole was shown to be at least as effective as a regimen of amphotericin B deoxycholate followed by intravenous or oral fluconazole [64]. Of note, for C. *tropicalis* infections, success rates were higher with voriconazole than with amphotericin B/fluconazole ($P = 0.03$).

Posaconazole is a new azole with broad-spectrum antifungal activity against *Candida*, *Aspergillus*, and other emerging molds including *Fusarium* and the zygomycetes. The hepatic metabolic pathways of posaconazole differ from those of other azoles: glucuronation plays a major role, while enzymes of the CYP450 system are of secondary importance, which may decrease the risk of clinically significant drug-drug interactions [65]. The drug is available in oral form with variable bioavailability, which can be significantly improved (ie up to 90%) by food intake [66]. In 199 HIV-positive patients with azole-refractory oropharyngeal or oesophageal candidiasis, posaconazole 400 mg twice daily was clinically successful in 75% of cases (modified ITT analysis) and 81.6% of cases (evaluable population) [67]. In another clinical study, the success rate of posaconazole as salvage therapy in patients with invasive candidiasis was 47.8% [68]. In a long-term safety study in 102 patients treated with posaconazole for salvage therapy of invasive mycoses serious adverse events occurred in 12/102 (12%) patients, but only in one case posaconazole therapy was discontinued [69]. Although posaconazole will be soon approved for salvage therapy of refractory mycoses, clinical data from comparative studies on first-line therapy of candidiasis are needed.

Echinocandins

Echinocandins are a new class of parenteral antifungal agents that act by inhibiting the glucane synthase, the enzyme responsible for the synthesis of β-(1,3)-D-glucan in the fungal cell wall [12]. These compounds are fungicidal *in vitro* against *C. albicans* and non-*albicans* *Candida* species. No cross-resistance with azoles has been reported.

Caspofungin is the first echinocandin licensed for the treatment of invasive mycoses, including candidiasis [12]. It is only available as an intravenous formulation. Caspofungin is taken up by the liver and is slowly degraded by hydrolysis and N-acetylation. Therefore, there is no need for dose adjustments in patients with renal insufficiency, but dose reduction to 35 mg is recommended in patients with moderate hepatic dysfunction. No data are available in patients with severe impairment of liver function or in children. Safety profile of caspofungin is excellent with few reported adverse events (mostly abnormal liver

function tests, phlebitis or histamine-like reactions). Drug-drug interactions with some medications have been observed (eg with rifampicin, anticonvulsants, tacrolimus, cyclosporin, protease-inhibitors, NNRTI). In immunocompromised (mainly HIV-positive) patients with oropharyngeal and/or oesophageal candidiasis caspofungin was found to be as effective (success rates: 70 to 90%) as amphotericin B deoxycholate (success rate: 65%) or fluconazole (success rate: 80%) [70–72]. In a large multicentre trial that included 239 patients (of whom 24 were neutropenic) with invasive candidiasis, caspofungin was at least as efficacious as and less toxic than amphotericin B deoxycholate (success rates: 73% *vs* 62%; discontinuation for adverse events: 3% *vs* 23%) [73]. Of note, the success rates of caspofungin against *C. glabrata* and *C. krusei* were comparable to those obtained in azole-susceptible *Candida* species.

Micafungin and ***anidulafungin.*** Micafungin has been approved in Japan and recently by the FDA for prophylaxis of *Candida* infections in patients undergoing haematopoietic stem cell transplantation and for the treatment of oesophageal candidiasis. Approval in Europe is pending. Anidulafungin is in clinical development. In randomised, double-blind studies, the efficacy of micafungin (50, 100 or 150 mg/d; success rates: 70–90%, or anidulafungin (100 mg, followed by 50 mg/d; success rate: 97%) was found to be comparable to that of fluconazole (200 mg, followed by 100 mg/d; success 85–95%) for the treatment of oesophageal candidiasis in immunocompromised (mainly HIV-positive) patients [74, 75]. Micafungin was reported to yield 100% response rates in a small non-comparative series of six cases of candidaemia [76]. In an open-label, non-comparative, international study of patients with newly diagnosed or refractory candidiasis, micafugin was associated with an overall success rate of 83.3% [77]. Success rates of 84 to 90% have been observed in a phase II, dose-finding, study of anidulafungin for the treatment of 68 patients with invasive candidiasis [78]. In a randomised, double-blind phase III study of 245 adult patients with invasive candidiasis anidulafungin treatment was statistically superior to fluconazole (success rates at end of i.v. therapy 75.6% *vs* 60.2%, difference 15.4%, 95% CI 3.8 to 27). Persistence of candidaemia at the end of i.v. therapy was reported in 6.3% and 14.4% of patients receiving anidulafungin and fluconazole, respectively. Survival at 6 weeks was higher in the anidulafungin than in the fluconazole treatment group (75% *vs* 69%) [79].

Combinations of antifungal agents

Given the poor prognosis of *Candida* sepsis, clinicians have shown great interest for using combinations of antifungal agents of different classes for the treatment of critically ill patients. However, until now there have been relatively few studies on combinations of antifungal agents in invasive candidiasis. Some experts recommend the combination of amphotericin B deoxycholate and 5-flucytosine for the treatment of life-threatening *Candida* infections [20, 44, 45]. This recommendation is based on the demonstration of synergistic effects in *in vitro* studies and in experimental animal models of systemic candidiasis and *Candida* endocarditis [80–82]. Combinations of amphotericin B and 5-flucytosine have been shown to be superior to monotherapy for therapy with cryptococcal infections in immunocompromised patients, but there are few data in patients with invasive *Candida* infections [83–90]. Given the lack of evidence on clinical efficacy, concerns about toxicity (impairment of renal function by amphotericin B may lead to accumulation of flucytosine and increased toxicity) and the recent development of new therapeutic options in critically patients, combined amphotericin B deoxycholate and 5-flucytosine therapy is not recommended. Despite *in vivo* antagonism between amphotericin B and azoles in experimental models of aspergillosis [91–93], data obtained in animal models of invasive candidiasis and *Candida* endocarditis did not show antagonism, but also no synergism [91–93]. In a randomised, double-blind study in 219 non-neutropenic patients with candidaemia, fluconazole (800 mg/d i.v.) was compared to a combination of fluconazole (800 mg/d i.v.) and amphotericin B deoxycholate (0.7 mg/kg/d i.v.) [94]. At first glance, the efficacy of combination therapy was slightly superior to that of monotherapy (success 69% *vs* 56%). However, there were statistically significant differences in baseline covariates between the two treatment groups, such as diseases severity as measured by the APACHE II score, which was lower in the combination group. While awaiting the results of prospective, randomised clinical trials demonstrating that combinations of antifungals are superior to and no more toxic than treatment with single agents, the indiscriminate use of combined regimens should be discouraged.

Treatment recommendations

1. Empirical therapy for Candida bloodstream infections (table 2A and figure 1A)

An algorithm for choosing an empirical antifungal treatment for patients with Candida bloodstream infection (before information about species identification and susceptibility becomes available) is shown in figure 1A. Several factors should be taken into account that may help physicians when choosing an antifungal agent for empirical therapy. These includes local epidemiological data, prior exposure to antifungal therapy, presence of neutropenia, severity of the clinical pres-

entation (presence of sepsis, severe sepsis or septic shock) and presence of underlying diseases or organ dysfunctions that may affect drug metabolism or increase the risk of drug-related toxicities. Treatment recommendations have been developed for four clinical conditions covering most of the circumstances encountered by practicing physicians: 1) absence of neutropenia, of severe sepsis or septic shock, or of recent exposure to azoles, 2) previous exposure to azoles, 3) presence of neutropenia, and 4) presence of severe sepsis or septic shock.

1.1. Absence of neutropenia, severe sepsis or septic shock or recent exposure to azoles. Fluconazole is the drug of choice in haemodynamically-stable, non-neutropenic patients at low risk for azole-resistant *Candida* species. Alternative therapies are amphotericin B deoxycholate, caspofungin and voriconazole.

1.2 Recent exposure to azoles. A recent exposure to azoles increases the risk of an infection due to non-*albicans Candida*, such as *C. glabrata* or *C. krusei*, that exhibit reduced susceptibility (*C. glabrata*) or are resistant (*C. krusei*) to azoles. In patients in whom infections may be caused by azole-resistant non-*albicans Candida* species following previous therapy with azoles, amphotericin B deoxycholate or caspofungin are therefore rec-

Table 2A

Empirical therapy for Candida bloodstream infections.

Setting	First choice	Alternatives	Switch to oral therapy
Non-neutropenic patient			
No previous exposure to azoles	Fluconazole (Diflucan®) 800 mg i.v. (1st dose), then 400 mg/d i.v., **Grade: AI**	Amphotericin B deoxycholate (Fungizone®)* 1 mg/kg/d i.v., **Grade: AI**, or Caspofungin (Cancidas®) 70 mg i.v. (1st dose), then 50 mg/d i.v., **Grade: AI**, or Voriconazole (Vfend®) 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2×/d i.v., **Grade: AI**	According to species identification and susceptibility testing **Grade: CIII**
Previous exposure to azoles	Amphotericin B deoxycholate (Fungizone®)* 1 mg/kg/d i.v., **Grade: BI** or Caspofungin (Cancidas®) 70 mg i.v. (1st dose), then 50 mg/d i.v., **Grade: BI**	Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d i.v., **Grade: BII**	According to species identification and susceptibility testing **Grade: CIII**
Neutropenic patient	Amphotericin B deoxycholate (Fungizone®)* 1 mg/kg/d i.v., **Grade: CIII**	Caspofungin (Cancidas®)[1 (see Table 2B)] 70 mg i.v. (1st dose, then 50 mg/d i.v., **Grade: CIII** or Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d i.v., **Grade: CIII**	According to species identification, susceptibility testing and bone marrow recovery (see footnote 1, Table 2B), **Grade: CIII**
Severe sepsis or septic shock	Caspofungin (Cancidas®)[1,2 (see Table 2B)] 70 mg i.v. (1st dose), then 50 mg/d i.v. **Grade: CIII**	Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d i.v. **Grade: CIII** or IF NO PREVIOUS AZOLE EXPOSURE[1,3 (see Table 2B)]: Voriconazole (Vfend®) 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2×/d i.v., **Grade: CIII**	Continue i.v. therapy until patient is in stable condition, then adjust therapy according to species identification and susceptibility and susceptibility testing testing (see footnote 1, Table 2B)

* See general comments in the footnote of table 4.

Table 2B

Therapy for microbiologically-documented Candida infections.

Species	Susceptibility testing	First choice	Alternatives	Switch to oral medication
C. albicans *C. tropicalis* *C. parapsilosis*	Fluconazole S Fluconazole S Fluconazole S	Fluconazole (Diflucan®)[1] 800 mg i.v. (1st dose) then 400 mg/d i.v. Grade: AI (BI for *C. tropicalis* and *C. parapsilosis*)	Amphotericin B deoxycholate (Fungizone®)*,[2] 1 mg/kg/d i.v., **Grade: AI (BI for *C. tropicalis* and *C. parapsilosis*)** or Caspofungin (Cancidas®)[1,2], 70 mg i.v. (1st dose), then 50 mg/d i.v., **Grade: A (BI for *C. tropicalis* and *C. parapsilosis*)** or Voriconazole (Vfend®)[1], 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2x/d i.v., **Grade: AI (BI for *C. tropicalis* and *C. parapsilosis*)**	Fluconazole (Diflucan®) 400 mg/d[1] or generic formulations, **Grade: A (BI for *C. tropicalis* and *C. parapsilosis*)**
C. glabrata *C. krusei*	Fluconazole S/S-DD/R Fluconazole R	Amphotericin B deoxycholate (Fungizone®)*,[2], >1 mg/kg/d i.v. **Grade: BI** or Caspofungin (Cancidas®)[1, 2] 70 mg i.v. (1st dose), then 50 mg/d i.v.	Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d i.v., **Grade: BI** or Voriconazole (Vfend®)[1,3] **(only for *C. krusei*)** 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2×/d i.v., **Grade: BI**	Itraconazole (Sporanox®)[1,3,4] 400 mg/d, **Grade: CIII** or Voriconazole (Vfend®)[1,3,4] 400 mg/d, **Grade: CIII**

S: susceptible; S-DD: susceptible-dose dependent; R: resistant. The evidence that *in vitro* susceptibility of *C. glabrata* to fluconazole predicts clinical response is lacking.

* See general comments in the footnote of table 4.

[1] Few clinical data are available on the use of azoles and echinocandins in neutropenic patients with documented invasive candidiasis. *In vitro*, azoles are fungistatic, echinocandis are fungicidal. In some experimental models (eg *Candida* endocarditis, disseminated candidiasis in neutropenic animals), azoles are less efficacious than amphotericin B or echinocandins.

[2] Amphotericin B deoxycholate (Fungizone®) not recommended in critically ill patients with severe sepsis/septic shock: risk of acute nephrotoxicity or of underdosing due to infusion-related toxicity. Caspofungin (Cancidas®) = first choice or alternative, respectively, in this setting.

[3] According to susceptibility testing. Some experts would add voriconazole to the list of first choice agents for the treatment of *C. glabrata* infections.

[4] For *C. glabrata* switch to oral itraconazole or voriconazole only after resolution of clinical symptoms/signs of infection **and** only if susceptibility test shows MIC ≤0.5 mg/L for itraconazole) or ≤1.0 mg/L for voriconazole, respectively.

ommended as first choice agents for empirical therapy. Contraindications for using amphotericin B deoxycholate are listed in the footnote of table 4. Alternative therapies are caspofungin or liposomal amphotericin B.

1.3. Neutropenia. Few data are available on the clinical efficacy of antifungal agents in neutropenic patients with candidaemia. Data from experimental models in animals with *Candida* endocarditis or invasive candidiasis in the context of neutropenia suggest that fungicidal agents, such as amphotericin B or caspofungin, might be more efficacious than fungistatic drugs like azoles [93, 95]. Moreover, lower reponse rates have been reported in neutropenic compared with non-neutropenic patients with candidaemia [25, 96, 97]. Given that it might be preferable to use fungicidal agents in neutropenic patients, amphotericin B deoxycholate is proposed as first choice in patients without contraindications (see footnote table 4). Lipid formulations of amphotericin B and caspofungin are alternative therapies.

1.4. Severe sepsis and septic shock. Empirical antifungal therapy active against *albicans* and non-*albicans Candida* species (including species with decreased susceptibility to azoles accounting for 15% to 20% of all episodes in Switzerland) is required in patients with yeast bloodstream infections complicated by severe sepsis or septic shock [14]. Nephrotoxic agents should be avoided given the risk of development of renal failure in the haemodynamically unstable, septic patient. Despite limited clinical experience in this setting, caspofungin is the drug of first choice due to its excellent efficacy and safety profiles. Alternative therapies comprise lipid formulations of amphotericin B or voriconazole in patients not recently exposed to azoles.

2. Therapy for microbiologically-documented *Candida* infections (table 2B and figure 1B)

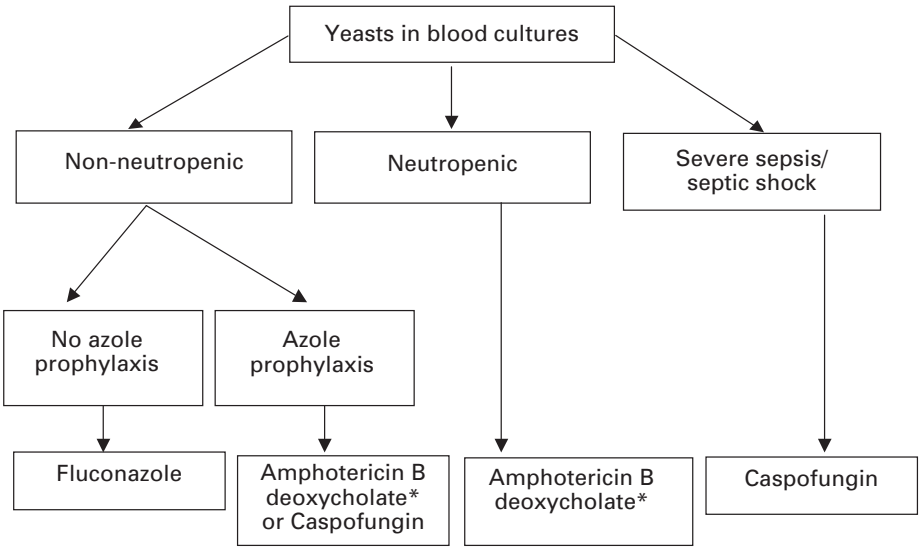
Although antifungal susceptibility tests are not performed routinely in all medical centres, susceptibility can usually be estimated upon identification of the *Candida* species.

For infections caused by *C. albicans*, *C. tropicalis* or *C. parapsilosis*, fluconazole is the drug of choice. Switch to oral therapy is recommended

Figure 1A

Detection of Candida in blood cultures: empirical antifungal therapy before identification of Candida species.

For dosages and alternative drugs see table 2A.

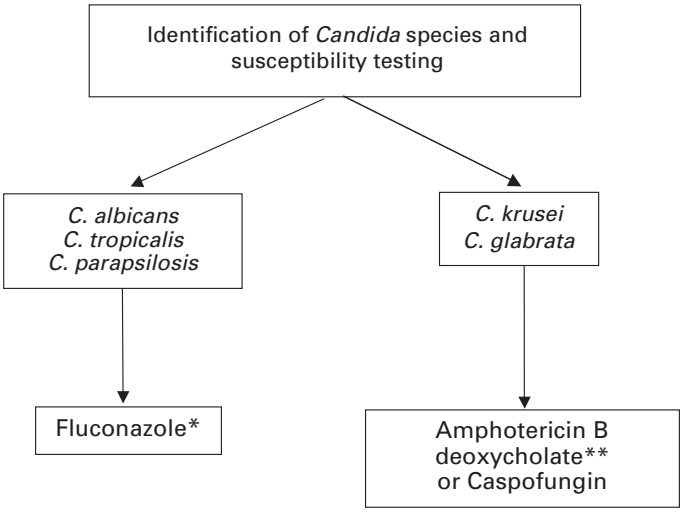


* Amphotericin B deoxycholate should not be used if contraindications are present (see general comments in the footnote of table 4).

Figure 1B

Invasive candidiasis: treatment options once species identity and susceptibility are known.

For dosages and alternative drugs see table 2B.



* Fluconazole is fungistatic in vitro and is less efficacious than amphotericin B and echinocandins in some experimental models of infection (eg *Candida* endocarditis, disseminated candidiasis in neutropenic animals). As clinical data on its efficacy in neutropenic patients with systemic candidiasis are lacking, some experts recommend the use of fungicidal drugs (ie amphotericin B, caspofungin) in this setting.

** If contraindications present / in critically ill patients (risk of acute nephrotoxicity / of underdosing due to infusion-related toxicity) amphotericin B deoxycholate should not be used (see general comments in the footer of table 4).

once the patient has improved and is able to take an oral medication. Amphotericin B deoxycholate, caspofungin or voriconazole are alternative treatment options. Although there are no clinical data to support this recommendation, some experts would prefer using fungicidal agents (caspofungin or amphotericin B) for treating neutropenic patients with *Candida* bloodstream infections or with invasive candidiasis. However, amphotericin B deoxycholate should be avoided in critically ill patients at high risk of developing renal failure or in whom infusion-related toxicity might delay administration of efficacious doses.

For infections caused by *C. glabrata* (independently of the results of *in vitro* susceptibility testing for fluconazole) or by *C. krusei*, caspofungin or amphotericin B deoxycholate are first choice therapies. Alternative therapies are lipid formulations of amphotericin B or voriconazole. However, fluconazole-resistant *C. glabrata* may be or may rapidly become cross-resistant to voriconazole [98] (J. Bille, unpublished observation). Susceptibility should therefore be checked before using voriconazole for the treatment of *C. glabrata* infections. As soon as the patient is clinically stable and is able to take an oral medication, a switch to either itraconazole or voriconazole should be considered, provided that the isolate is susceptible.

Duration of therapy. For primary bloodstream *Candida* infections, it is recommended to treat patients for two weeks after the last positive blood culture. In case of invasive candidiasis with involvement of one or more organs (eg liver, spleen, lung, skin, eye, or bone), therapy should be continued until complete resolution of clinical symptoms and signs at all sites of infection.

Invasive aspergillosis

Epidemiology

Invasive aspergillosis (IA) is the second most common invasive mycosis accounting for 10 to 20% of all cases. This potentially life-threatening infection occurs mainly in immmunocompromised hosts, including neutropenic cancer patients, haematopoetic stem cell (HSCT) or solid organ transplant recipients, especially those with severe graft-versus-host disease (GVHD), patients treated with immunosuppressive therapies (corticosteroids, cytotoxic agents or monoclonal antibodies acting as anti-immune mediators) [7]. The highest incidence (10 to 20%) and mortality (60 to 90%) rates of IA have been reported in allogeneic HSCT and in heart, lung or heart/lung transplant recipients [7, 99, 100]. Apart from the classical immunocompromised host, IA has been recently recognised to occur in a growing number of critically ill patients receiving corticosteroids for treatment of chronic lung diseases, including mechanically-ventilated intensive care unit patients [101]. In a recent report, 3.6% of 1850 medical ICU patients developed invasive aspergillosis, which was associated with a mortality of 80% [102]. Of note, several of these patients did not have classical risk factors, but various underlying conditions including liver cirrhosis. The most frequent site of IA is the lower respiratory tract accounting for about 80 to 90% of all cases. Other classical clinical manifestations include sinusitis, central nervous system (CNS) infections and disseminated infection involving multiple sites [7, 99].

Standardised definitions of IA were recently established by an expert panel of the EORTC and the MSG [103]. Based on clinical, radiological and microbiological criteria, cases of IA are classified into one of three categories: possible, probable or proven IA. However, these definitions have been primarily developed for clinical research, and their usefulness for management strategies remains to be determined.

Microbiology

A. fumigatus is the predominant *Aspergillus* species isolated in patients with IA (accounting for more than 90% of cases in many series), followed by *A. flavus*, *A. terreus* and *A. niger* [104]. However, a shift in the epidemiology of *Aspergillus* infections has been recently observed with an increasing frequency of infections caused by non-*fumigatus Aspergillus* species, such as *A. terreus* which is resistant to amphotericin B [105]. *A. terreus* is more often a health-care-associated than a community-acquired infection and has been associated with lower response rates to antifungal therapy when compared to *A. fumigatus* (28% versus 39%). Significant progress has been made in *in vitro* susceptibility testing for molds, including *Aspergillus* [106–109]. Yet, it is still a research tool performed in a few laboratories with special expertise in the field and clinical studies on *in vitro* and *in vivo* correlations remain to be conducted.

Antifungal therapy

Antifungal agents licensed for the treatment of invasive aspergillosis (IA) are amphotericin B deoxycholate, the lipid formulations of amphotericin B, voriconazole, itraconazole and caspofungin. Clinical data on their efficacy and safety profiles are mainly derived from patients with pulmonary aspergillosis, the most frequent form of IA. Since the mortality of IA ranges between 60 and 90%, an aggressive diagnostic approach (radiological imaging, cultures, determination of galactomannan and histopathological examinations of biological fluids or tissue biopsies), followed by prompt institution of an appropriate first-line antifungal therapy is critical [7, 104, 110, 111].

Polyenes

Amphotericin B

For decades, amphotericin B deoxycholate has been standard therapy of IA [112], but response rates have been disappointing, especially in patients with profound and persistent neutropenia or with graft-versus-host disease. In a review of 1941 cases, crude mortality rates of 60%, 26%, and 88% were reported in immunocompromised patients with pulmonary, sinus, and cerebral aspergillosis, respectively. In patients with invasive pulmonary aspergillosis, who had been treated for more than 14 days, response rates were 83% in heart or renal transplant recipients, 54% in leukaemic patients, 33% in HSCT, and 20% in liver transplant recipients [7]. Underdosing and treatment interruptions due to infusion-related and renal toxicity may affect the efficacy of amphotericin B deoxycholate therapy. In particular, nephrotoxicity requiring haemodialysis has been independently associated with death [113].

Lipid-based formulations of amphotericin B are better tolerated than amphotericin B deoxycholate. Outside clinical trials, lipid formulations of amphotericin B have been used primarily as salvage therapy in patients intolerant of or failing therapy with amphotericin B deoxycholate [52, 114, 115]. Although lipid formulations of amphotericin B have recently become the new standard comparator in clinical trials of empirical therapy in persistently febrile neutropenia, there are very few randomised studies comparing lipid forms to amphotericin B deoxycholate as first-line therapy of IA. In a randomised double-blind study in 174 immunocompromised patients with invasive aspergillosis similar success rates were obtained with amphotericin B colloidal dispersion (35%) and amphotericin B deoxycholate (35%) [116]. A study comparing a 1 to a 4 mg/kg/d i.v. dose of liposomal amphotericin B (AmBisome®) as first-line therapy of IA in 87 patients yielded similar survival rates (43 and 37%) [117]. Lastly, a recent prospective, randomised study comparing a high dose (10 mg/kg/d) to a standard dose (3 mg/kg/d) of liposomal amphotericin B for the treatment of invasive filamentous fungal infections yielded similar success and survival rates [118]. Overall, all the available data suggest that lipid formulations are at least as efficacious as and better tolerated than amphotericin B deoxycholate for the treatment of IA [53, 112].

Azoles

Itraconazole has been used as first-line treatment of invasive aspergillosis in few small non-comparative studies. In 76 patients with IA, oral itraconazole therapy resulted in a response rate of 39% [119]. A response rate of 48% was reported in a study of 31 patients with IA who were treated with itraconazole [120]. The highly variable bioavailability of oral itraconazole and risk of drug-drug interactions (eg with immunosuppressive drugs) also are serious drawbacks for the treatment of patients with life-threatening infections. Monitoring of blood levels is therefore mandatory. Itraconazole has thus been mainly used as step-down oral therapy in patients with IA who had responded to initial i.v. antifungal therapy [121].

Voriconazole is the present treatment of first choice for IA, and is available as intravenous and oral formulations. In a non-comparative study of first- or second-line treatment of IA in 116 patients, treatment with voriconazole was found to be associated with response rates of 48% [122]. The efficacy and safety of upfront therapy with voriconazole was compared to that of amphotericin B deoxycholate in the largest (277 patients), prospective, multicentre, randomised, comparative study of IA ever performed. After 12 weeks of protocol therapy with or without switch to other licensed antifungal agents due to failure or toxicity, success and survival rates were significantly better in the voriconazole group than in the amphotericin B group (53% versus 32% and 71% versus 58%, respectively) [123]. Moreover, fewer severe adverse events occurred in patients treated with voriconazole than in those treated with amphotericin B. There is substantial intra- and inter-individual variability in voriconazole blood levels: low levels have been observed, in particular in children, whereas elevated levels have been measured in patients with adverse events [122, 124–129]. Interactions with co-medications with hepatic metabolism (listed in the section on invasive candidiasis) may necessitate close clinical monitoring.

Posaconazole, a new azole antifungal agent was studied as salvage therapy of invasive aspergillosis in 107 patients refractory to or intolerant of first-line antifungal therapy [68]. Posaconazole was successful in 42% of patients. Response rates in high-risk subgroups were 24% in neutropenic patients and 31% in allogeneic HSCT recipients. Overall the 12-month survival was 45%. A salvage, open-label, compassionate study in 23 solid-organ transplant recipients with invasive mycoses refractory to or intolerant of standard therapy reported a complete or partial response in 57% of cases [130]. Drug-drug interactions increasing blood levels of cyclosporine or tacrolimus were observed in 3 cases and lead to discontinuation of posaconazole in one patient. A recent double-blind multicentre study in 600 allogeneic HSCT recipients compared posaconazole and fluconazole for prophylaxis of invasive mycoses [131]. The incidence of invasive aspergillosis during the 16-week study period was significantly lower in the posaconazole group (2% *vs* 7%). The mortality due to invasive mycoses was 1% *vs* 4%, respectively. Adverse events occurred in 33% of cases in both groups, and resulted in therapy discontinua-

tion in 3% of patients receiving posaconazole *vs* 8% in those receiving fluconazole. Awaiting results from comparative studies of first-line therapy of invasive aspergillosis, posaconazole will be soon available as salvage therapy of refractory invasive mycosis.

Echinocandins

Caspofungin has been licensed for salvage therapy of IA after it was shown to be efficacious and safe in 83 patients with haematological malignancies, allogeneic blood and marrow transplantation or solid organ transplantation, who were refractory (86%) to, or intolerant (14%) of conventional antifungal therapy [132]. Complete and partial responses to caspofungin were observed in 4 (5%) and 33 (40%) of these 83 patients. Treatment was well tolerated with minimal drug-related toxicity (clinical: 12%, laboratory: 14%). A non-comparative study on caspofungin for first-line therapy of invasive aspergillosis in 32 immunocompromised patients with haematological malignancies reported a complete or partial response in 56% of cases [133]. IA-related mortality was 22%. Comparative clinical studies of first-line caspofungin therapy for patients with IA are needed. The Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG) is currently conducting such a study.

Other echinocandins. In a non-comparative trial conducted in Japan in 19 patients with various forms of IA, success rates of micafungin were 60% to 67% [76].

Combination therapy

Given the poor prognosis of IA in immunocompromised patients, using combinations of antifungal drugs would seem a logical approach to improve patient's outcome. However, there are few clinical data supporting this approach. A few reports (consisting mainly of case reports and subgroups of patients in case series) of combination therapy in patients with IA suggest that liposomal amphotericin B plus caspofungin or voriconazole plus caspofungin may improve the outcome of patients with refractory IA [82, 134–136]. A recent case-control study reported improved survival of patients with refractory, probable or proven IA treated with a combination of voriconazole and caspofungin compared with voriconazole monotherapy [137]. In a multicentre, noncomparative salvage study in 53 adult patients with proven or probable invasive aspergillosis refractory or intolerant to first-line antifungal therapy the combination of caspofungin with amphotericin B, itraconazole, or voriconazole was successful in 50%, 43%, and 60% of cases, respectively [138]. Success rates in patients with neutropenia or allogeneic haematopoietic stem cells transplant were 57% and 54%, respectively. The combinations were well tolerated, serious drug-related adverse events occurred in only 3% of cases. A case-control study compared the combination of voriconazole and caspofungin (n = 34) with a monotherapy with a lipid form of amphotericin B (n = 38) in solid organ transplant recipients with invasive aspergillosis [139]. A significant reduction of 90-day mortality in the combination group was reported (26% *vs* 50%). In high-risk patients (ie dialysis, retransplantation, or disseminated aspergillosis) mortality was 23% in the combination group and 79% in the control group. However, large, prospective, randomised, comparative studies are needed to determine whether combination therapy is indeed superior to monotherapy.

Treatment recommendations (table 3 and figure 2)

1.1. Primary (ie upfront) therapy for invasive aspergillosis. An intensive diagnostic work-up of the patient is recommended to determine the aetiology of infection in patients suspected of invasive aspergillosis. A recent report showing the limited efficacy of salvage antifungal therapy in patients suffering of IA has highlighted the importance of an appropriate upfront therapy [111]. Voriconazole is first choice for upfront therapy of IA. Keeping in mind the interindividual variations of voriconazole pharmacokinetics, monitoring blood levels may be considered in patients who do not respond to therapy or in those suspected of developing drug-related adverse events. Alternative therapies are liposomal amphotericin B and amphotericin B deoxycholate. It is recommended to continue therapy until complete clinical and radiological resolution of infection.

Switch to oral itraconazole or voriconazole should be considered as soon as the patient shows signs of improvement and is able to take oral drugs as it will significantly reduce treatment costs. Monitoring of itraconazole blood levels is routinely recommended.

1.2. Refractory invasive aspergillosis (ie salvage therapy). Caspofungin, voriconazole (if not used as primary therapy) and liposomal amphotericin B are treatment options for salvage therapy of IA in patients with refractory disease.

1.3. Combination therapy in critically ill patients. Combination therapy of caspofungin with either voriconazole or liposomal amphotericin B is recommended in critically ill patients presenting with severe (ie life-threatening) IA. A switch to either i.v. or oral antifungal monotherapy should be considered in patients with stable condition showing signs of clinical and/or radiological improvement.

Table 3

Treatment recommendations for invasive aspergillosis.

Setting	First choice	Alternatives	Switch to oral medication
Primary (i.e upfront) therapy of IA	Voriconazole (Vfend®) 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2×/d i.v., **Grade: AI**	Liposomal Amphotericin B (AmBisome®) 3–5 mg/kg/d i.v., **Grade: BI** or Amphotericin B deoxycholate (Fungizone®)* 1 mg/kg/d i.v., **Grade: CI**	Voriconazole (Vfend®) 400 mg/d **Grade: AI** or Itraconazole (Sporanox®) 400 mg/d, **Grade: BII**
Refractory disease (ie salvage therapy)	Caspofungin (Cancidas®) 70 mg i.v. (1st dose), then 50 mg/d i.v., **Grade: BII** or Voriconazole (Vfend®) if not used as primary therapy, 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2×/d i.v., **Grade: BII** or Liposomal Amphotericin B (AmBisome®) 3–5 mg/kg/d i.v., **Grade: BII**		Voriconazole (Vfend®) 400 mg/d, **Grade: AI** or Itraconazole (Sporanox®) 400 mg/d, **Grade: BII**
Combination therapy (i.e critically ill patient)	Caspofungin (Cancidas®) 70 mg i.v. (1st dose), then 50 mg/d i.v. plus Voriconazole (Vfend®)[1] 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2×/d i.v. or Liposomal Amphotericin B (AmBisome®) 3–5 mg/kg/d i.v., **Grade: CII**		Continue combination therapy until patient is in stable condition, then switch to i.v. or oral monotherapy (see above), **Grade: CIII**

* See general comments in the footer of table 4

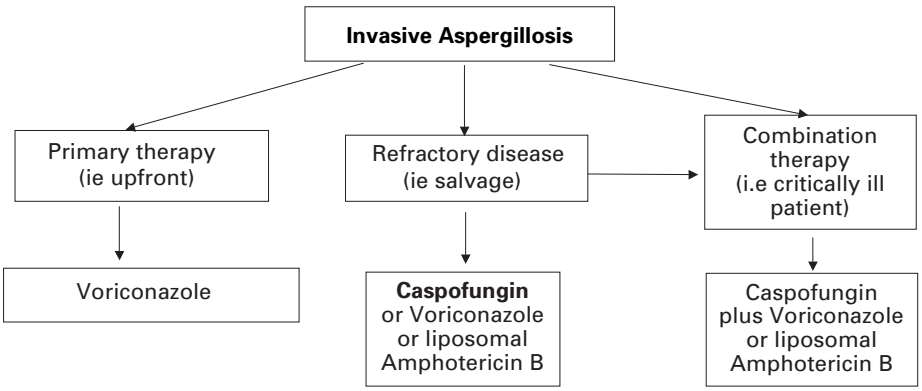
[1] Voriconazole: can be used in combination even if it was failing as monotherapy

Duration of treatment for invasive aspergillosis: stop after resolution of all clinical + radiological symptoms/signs of infection. **Grade: CIII**

Figure 2

Invasive Aspergillosis: Treatment Options.

For dosages and alternative drugs see table 3 and 4.



Empirical antifungal therapy in patients with neutropenia and persistent fever

Rationale

Cancer patients at high risk of fungal infections are those with acute leukaemia or with allogenic hematopoietic stem cell transplantation (HSCT) who have prolonged and profound neutropenia or immunosuppression for graft-versus-host disease. In contrast, patients with other haematological malignancies (myeloma, lymphomas, chronic myelogenous or lymphocytic leukaemia), solid tumours and recipients of an autologous HSCT are at low risk of invasive mycoses as neutropenia is typically of short duration and immunosuppression is rather moderate. Administration of empirical antifungal therapy has become a standard of care in patients with neutropenia and persistent fever despite treatment with broad-spectrum antibiotics. The rationale for early administration of antifungal agents in these patients has been that clinically occult fungal infections (primarily due to *Candida* or *Aspergillus*) are a frequent autopsy finding in neutropenic patients and that persistent fever is often the only early sign of an invasive mycosis.

Clinical trials

The concept of empirical antifungal therapy is supported by the results of two pioneer, albeit not placebo-controlled, randomised studies conducted in the 1980s, which showed that the empirical use of amphotericin B in neutropenic patients with prolonged fever of undetermined origin reduced the incidence of fungal infections and fungal-related mortality [140, 141]. The benefit was primarily observed in patients who were severely neutropenic, who had not received antifungal prophylaxis, or who had a clinically documented infection [141]. Based on the results of these initial studies, empirical administration of amphotericin B deoxycholate became standard therapy in these patients.

During the last two decades, more than 20 randomised controlled clinical trials of empirical antifungal therapy have been performed in patients with neutropenia and persistent fever [8, 9, 46, 117, 140–158]. The vast majority of these studies have compared the efficacy and safety of various doses or formulations (ie conventional versus lipid formulations) of amphotericin B with that of an azole (ketoconazole or fluconazole) in an usually limited number of patients and therefore lacked power to detect small differences of efficacy or toxicity. We will therefore review the results of the most recent clinical trials that included a larger patient population and that used a composite score of several clinical and laboratory criteria to evaluate the response to therapy. In a non-inferiority (± 10%) study of 702 patients, liposomal amphotericin B was shown to be as effective as amphotericin B deoxycholate (50% *vs* 49%), but was associated with fewer breakthrough fungal infections (3.2% *vs* 7.8%), less infusion-related fever (17% *vs* 44%), chills and rigors (18% *vs* 54%) and less nephrotoxicity (19% *vs* 34%) [8]. One should note, however, that the daily dose of amphotericin B deoxycholate (0.6 mg/kg/d) was moderate and that there was no mentioning of fluid loading to reduce amphotericin B deoxycholate toxicity.

Three clinical trials have compared the efficacy and safety of an azole (fluconazole, itraconazole or voriconazole) to that of amphotericin B deoxycholate or liposomal amphotericin B. In a study of 317 patients, favourable response rates occurred in 68% of the patients treated with intravenous fluconazole and in 67% of the patients treated with intravenous amphotericin B deoxycholate [153]. Progressive or new fungal infections occurred in a similar proportion of patients in the two treatment groups (8% *vs* 6%, respectively), but adverse events occurred more often in patients treated with amphotericin B than in the fluconazole group (81% *vs* 13%, P = 0.001). Overall mortality and fungal infection-related mortality were similar in both treatment groups. In a large, open, non-inferiority (± 15%) study that included 384 patients, itraconazole was found to exhibit at least equivalent efficacy in an intention-to-treat analysis (47% *vs* 38%, difference: 9%, 95%CI: –0.8 to 19.5%) and significantly fewer drug-related adverse events, including nephrotoxicity (5% *vs* 24%, P <0.001) than amphotericin B deoxycholate [155]. Interestingly, the response rate to itraconazole was superior to that of amphotericin B deoxycholate in patients who had previously received antifungal prophylaxis (48% *vs* 35%, difference: 13%, 95%CI: 1.6 to 24.8%). Breakthrough fungal infections and mortality were similar in both treatment groups. In the third study, a non-inferiority (± 10%) multicentre trial that included 837 patients, the overall success rates were 26% for patients treated with voriconazole and 31% for patients treated with liposomal amphotericin B [156]. However, voriconazole did not fulfill the statistical criteria for non-inferiority. Voriconazole was superior to liposomal amphotericin B for the prevention of breakthrough fungal infections (1.9% *vs* 5.0%, P = 0.02), especially in high-risk patients such as allogeneic transplants and patients with relapsed leukaemia. Fewer cases of infusion-related toxicity reactions (P <0.01) and of nephrotoxicity (P <0.001), but more cases of transient abnormal vision (P <0.001) and of hallucinations (P <0.001) occurred in the voriconazole group than in the liposomal amphotericin B group.

Finally, the results of a recent large, double-blind, multicentre study that included 1123 patients showed that caspofungin was as effective as (overall response rates: 33.9% *vs* 33.7%), and better tolerated than liposososmal amphotericin B [158]. Less infusion-related toxicity (35.1% *vs* 51.6%), nephrotoxicity (2.6% *vs* 11.5%), and premature discontinuation of study medication (10.3% *vs* 14.5%) occurred in patients treated with caspofungin than in those treated with liposomal amphotericin B. In addition, caspofungin was superior to liposomal amphotericin B for the successful outcome of baseline fungal infections (51.9% *vs* 25.9%) and for survival rates 7 days after therapy (92.6% *vs* 89.2%).

Treatment recommendations (table 4)

Clinical trials of empirical antifungal therapy for patients with neutropenia and persistent fever performed during the last two decades have not revealed a clear-cut superior antifungal agent in terms of efficacy. A consistent finding of many studies has been the increased risk of infusion-related reactions and nephrotoxicity in patients treated with amphotericin B deoxycholate and to a lower extent with lipid formulations when compared with azoles (fluconazole, itraconazole or voriconazole) or echinocandins (caspofungin). However, given that it is as active as and substantially less expensive than most other antifungal drugs on the market, amphotericin B deoxycholate is recommended as first choice therapy for patients with neutropenia and persistent fever. Close monitoring of the appearance of adverse events in patients treated with amphotericin B deoxycholate is mandatory. Should contra-indications be present at baseline or develop during therapy (see footnote table 4), liposomal amphotericin B, caspofungin, itraconazole, or voriconazole are alternative treatment options. However, azoles should not be used for empirical antifungal therapy in patients receiv-

Table 4

Empirical antifungal therapy in patients with neutropenia and persistent fever.

First choice	Alternatives	Switch to oral medication
Amphotericin B deoxycholate (Fungizone®)[1] 1 mg/kg/d i.v., **Grade: AI**	Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d i.v., **Grade: AI** or Caspofungin (Cancidas®)[2] 70 mg i.v. (1st dose), then 50 mg/d i.v. then 50 mg/d i.v., **Grade: AI** or Voriconazole (Vfend®)[2] 6 mg/kg q12h i.v. on day 1, then 4 mg/kg 2×/d i.v., **Grade: BI** or Itraconazole (Sporanox®) 200 mg/d q12h i.v on day 1, then 200 mg/d i.v., **Grade: BI**	Itraconazole (Sporanox®)[2] 400 mg/d, **Grade: AI** or Voriconazole (Vfend®)[2] 400 mg/d **Grade: BII**

[1] See general comments

[2] Few clinical data available on the use of azoles and echinocandins in neutropenic patients with documented systemic candidiasis. Few clinical data available on the use of caspofungin in neutropenic patients with documented invasive aspergillosis. Azoles and echinocandins are not active against zygomycetes. Due to the increased risk of azole-resistant *Candida* infections, azoles should not be used in patients receiving fluconazole prophylaxis.

Duration of empirical antifungal treatment for persistent fever during neutropenia : until recovery from neutropenia + resolution of clinical/microbiological/radiological symptoms/signs suggestive of invasive fungal infection. **Grade: CIII**

GENERAL COMMENTS

Contraindications for the use of amphotericin B deoxycholate (Fungizone®):

– Serum creatinine >150 micromol/L, **Grade: CIII**
– History of toxicity which required discontinuation of therapy, **Grade: CIII**
– Concomitant medication with nephrotoxic drugs (eg aminoglycosides, cyclosporin), **Grade: CIII**

Toxicity criteria for discontinuation of therapy in patients receiving amphotericin B deoxycholate (Fungizone®):

– Increase of serum creatinine: >2× baseline value (if normal at baseline), or >200 micromol/L (if baseline between upper normal limit and 150 micromol/L), **Grade: CIII**
– Debilitating infusion-related fever and chills persisting for >2 days despite infusion over 24 hours and symptomatic treatment including paracetamol + opioid + anti-histaminic, **Grade: CIII**

Monitoring of voriconazole blood levels should be considered if underdosing is suspected or in presence of clinical symptoms/signs suggestive of drug-related toxicity. **Grade: CIII**

Monitoring of itraconazole blood levels routinely recommended. **Grade: CIII**

Table 5

Daily hospital acquisition costs* of various antifungal agents.

* Calculated for a patient with a body weight of 70 kg (ex-factory prizes in Switzerland in 2005)

Generic drug name	Trade name	Daily dosing and route	Daily cost CHF
Amphotericin B deoxycholate	Fungizone®	1 mg/kg i.v.	76
Liposomal Amphotericin B	AmBisome®	3 mg/kg i.v.	1078
		5 mg/kg i.v.	1796
Fluconazole	Diflucan®	800 mg i.v.	185
		400 mg i.v.	92
		400 mg p.o.	41
	Generic formulations	400 mg p.o.	25–33
Itraconazole	Sporanox®	250 mg i.v.	243
		400 mg/d p.o. (suspension)	25
		400 mg/d p.o. (capsules)	19
Voriconazole	Vfend®	6 mg/kg 2× i.v.	932
		4 mg/kg 2× i.v.	699
		400 mg/d p.o.	125
Caspofungin	Cancidas®	70 mg i.v.	929
		50 mg/d i.v.	731

ing fluconazole prophylaxis, as infections due to azole-resistant non-albicans *Candida* species may occur in this setting.

Treatment costs of the available treatment options differ substantially and are summarised in table 5.

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References

1 Lamagni TL, Evans BG, Shigematsu M, Johnson EM. Emerging trends in the epidemiology of invasive mycoses in England and Wales (1990–9). Epidemiol Infect 2001;126:397–414.
2 Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–54.
3 Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia: the attributable mortality and excess lenght of stay. Arch Intern Med 1988;148:2642–5.
4 Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis 1995;20:1531–4.
5 Rentz AM, Halpern MT, Bowden RA. The impact of candidemia on lenght of hospital stay, outcome, and overall cost of illness. Clin Infect Dis 1998;27:781–8.
6 Gudlaugsson O, Gillespie S, Lee K, Vande BJ, Hu J, Messer S, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003;37:1172–7.
7 Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 2001;32:358–66.
8 Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. N Engl J Med 1999;340:764–71.
9 White MH, Bowden RA, Sandler ES, Graham ML, Noskin GA, Wingard JR, et al. Randomized, 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 Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis 2003;36:630–7.
11 Offner F, Krcmery V, Boogaerts M, Doyen C, Engelhard D, Ribaud P, et al. Liposomal nystatin in patients with invasive aspergillosis refractory to or intolerant of amphotericin B. Antimicrob Agents Chemother 2004;48:4808–12.
12 Denning DW. Echinocandin antifungal drugs. Lancet 2003;362:1142–51.
13 Patel M, Kunz DF, Trivedi VM, Jones MG, Moser SA, Baddley JW. Initial management of candidemia at an academic medical center: evaluation of the IDSA guidelines. Diagn Microbiol Infect Dis 2005;52:29–34.
14 Marchetti O, Bille J, Fluckiger U, Eggimann P, Ruef C, Garbino J, et al. Epidemiology of candidemia in swiss tertiary care hospitals: secular trends, 1991–2000. Clin Infect Dis 2004;38:311–20.
15 Kish MA. Guide to development of practice guidelines. Clin Infect Dis 2001;32:851–4.
16 Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274:639–44.
17 Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17.
18 Eggimann P, Garbino J, Pittet D. Epidemiology of Candida species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 2003;3:685–702.
19 Calandra T, Bille J, Schneider R, Mosimann F, Francioli P. Clinical significance of Candida isolated from peritoneum in surgical patients. Lancet 1989;1:1437–40.
20 Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161–89.
21 Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia. Arch Intern Med 1989;149:2349–53.
22 Pittet D, Li N, Woolson RF, Wenzel RP. Microbiological factors influencing the outcome of nosocomial bloodstream infections: a 6-year validated, population-based model. Clin Infect Dis 1997;24:1068–78.
23 Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 1991;325:1274–7.
24 Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis 1997;24:1122–8.
25 Viscoli C, Girmenia C, Marinus A, Colette L, Martino P, Vandercam B, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999;28:1071–9.
26 White MH. Editorial response: the contribution of fluconazole to the changing epidemiology of invasive candidal infections. Clin Infect Dis 1997;24:1129–30.
27 Nguyen MH, Clancy CJ, Yu VL, Yu YC, Morris AJ, Snydman DR, et al. Do in vitro susceptibility data predict the microbiologic response to amphotericin B? Results of a prospective study of patients with Candida fungemia. J Infect Dis 1998;177:425–30.
28 Powderly WG, Kobayashi GS, Herzig GP, Medoff G. Amphotericin B-resistant yeast infection in severely immunocompromised patients. Am J Med 1988;84:826–32.
29 Clancy CJ, Nguyen MH. Correlation between in vitro susceptibility determined by E test and response to therapy with amphotericin B: results from a multicenter prospective study of candidemia. Antimicrob Agents Chemother 1999;43:1289–90.
30 Clancy CJ, Yu VL, Morris AJ, Snydman DR, Nguyen MH. Fluconazole MIC and the fluconazole dose/MIC ratio correlate with therapeutic response among patients with candidemia. Antimicrob Agents Chemother 2005;49:3171–7.
31 Rex JH, Pfaller MA, Galgiani JN, Bartlett JA, Espinel-Ingroff A, Ghannoum MA, et al. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole and Candida infections. Clin Infect Dis 1997;24:235–47.
32 Baddley JW, Patel M, Jones M, Cloud G, Smith AC, Moser SA. Utility of real-time antifungal susceptibility testing for fluconazole in the treatment of candidemia. Diagn Microbiol Infect Dis 2004;50:119–24.
33 Antoniadou A, Torres HA, Lewis RE, Thornby J, Bodey GP, Tarrand JP, et al. Candidemia in a tertiary care cancer center: in vitro susceptibility and its association with outcome of initial antifungal therapy. Medicine (Baltimore) 2003;82:309–21.
34 Munoz P, Fernandez-Turegano CP, Alcala L, Rodriguez-Creixems M, Pelaez T, Bouza E. Frequency and clinical significance of bloodstream infections caused by C albicans strains with reduced susceptibility to fluconazole. Diagn Microbiol Infect Dis 2002;44:163–7.
35 Kovacicova G, Krupova Y, Lovaszova M, Roidova A, Trupl J, Liskova A, et al. Antifungal susceptibility of 262 bloodstream yeast isolates from a mixed cancer and non-cancer patient population: is there a correlation between in-vitro resistance to fluconazole and the outcome of fungemia? J Infect Chemother 2000;6:216–21.
36 Lee SC, Fung CP, Huang JS, Tsai CJ, Chen KS, Chen HY, et al. Clinical correlates of antifungal macrodilution susceptibility test results for non-AIDS patients with severe Candida infections treated with fluconazole. Antimicrob Agents Chemother 2000;44:2715–8.
37 Troillet N, Durussel C, Bille J, Glauser MP, Chave JP. Correlation between in vitro susceptibility of *Candida albicans* and fluconazole-resistant oropharyngeal candidiasis in HIV-infected patients. Eur J Clin Microbiol Infect Dis 1993;12:911–5.
38 Rex JH, Nelson PW, Paetznick VL, Lozano-Chiu M, Espinel-Ingroff A, Anaissie E. Optimizing the correlation between results of testing in vitro and therapeutic outcome in vivo for fluconazole by testing critical isolates in a murine model of invasive candidiasis. Antimicrob Agents Chemother 1998;42:129–34.
39 Ostrosky-Zeichner L, Rex JH, Pappas PG, Hamill RJ, Larsen RA, Horowitz HW, et al. Antifungal susceptibility survey of 2,000 bloodstream Candida isolates in the United States. Antimicrob Agents Chemother 2003;47:3149–54.
40 Malani A, Hmoud J, Chiu L, Carver PL, Bielaczyc A, Kauffman CA. Candida glabrata fungemia: experience in a tertiary care center. Clin Infect Dis 2005;41:975–81.
41 Nguyen MH, Peacock JE, Tanner DC, Morris AJ, Nguyen ML, Snydman DR, et al. Therapeutic approaches in patients with candidemia. Arch Intern Med 1995;155:2429–35.

42 Nolla-Salas J, Sitges-Serra AL-GC, Martinez-Gonzales J, Leonb-Regodir M, Ibanez-Lucia P, Torres-Rodriguez J, et al. Candidemia in non-neutropenic critically ill patients: analysis of prognostic factots and assessment of systemic antifungal therapy. Intensive Care Med 1997;23:23–30.

43 Morrell M, Fraser VJ, Kollef MH. Delaying the Empiric Treatment of Candida Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality. Antimicrob Agents Chemother 2005; 49:3640–5.

44 Edwards JE Jr, Bodey GP, Bowden RA, Buchner T, De Pauw BE, Filler SG, et al. International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections. Clin Infect Dis 1997;25:43–59.

45 Rex JH, Walsh TJ, Sobel J, Filler SG, Pappas PG, Dismukes WE, et al. Practice guidelines for the treatment of candidiasis. Clin Infect Dis 2000;30:662–78.

46 Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. BMJ 2001;322:579–82.

47 Furrer K, Schaffner A, Vavricka SR, Halter J, Imhof A, Schanz U. Nephrotoxicity of cyclosporine A and amphotericin B-deoxycholate as continuous infusion in allogenic stem cell transplantation. Swiss Med Wkly 2002;132:316–20.

48 Imhof A, Walter RB, Schaffner A. Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. Clin Infect Dis 2003;36:943–51.

49 Peleg AY, Woods ML. Continuous and 4 h infusion of amphotericin B: a comparative study involving high-risk haematology patients. J Antimicrob Chemother 2004;54:803–8.

50 Harbarth S, Pestotnik SL, Lloyd JF, Burke JP, Samore MH. The epidemiology of nephrotoxicity associated with conventional amphotericin B therapy. Am J Med 2001;111:528–34.

51 Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DR, et al. Correlates of acute renal failure in patients receiving parenteral amphotericin B. Kidney Int 2001;60:1452–9.

52 Walsh TJ, Hiemenz JW, Seibel NL, Perfect JR, Horwith G, Lee L, 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.

53 Ostrosky-Zeichner L, Marr KA, Rex JH, Cohen SH. Amphotericin B: time for a new "gold standard". Clin Infect Dis 2003; 37:415–25.

54 Hiemenz JW, Walsh TJ. Lipid formulations of amphotericin B: recent progress and future directions. Clin Infect Dis 1996;22(Suppl 2):S133–S144.

55 Barrett JP, Vardulaki KA, Conlon C, Cooke J, za-Ramirez P, Evans EG, et al. A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. Clin Ther 2003;25:1295–320.

56 Bowden RA, Cays M, Gooley T, Mamelok RD, van Burik JA. Phase I study of amphotericin B colloidal dispersion for the treatment of invasive fungal infections after marrow transplant. J Infect Dis 1996;173:1208–15.

57 Noskin GA, Pietrelli L, Coffey G, Gurwith M, Liang LJ. Amphotericin B colloidal dispersion for treatment of candidemia in immunocompromised patients. Clin Infect Dis 1998;26: 461–7.

58 Juster-Reicher A, Leibovitz E, Linder N, Amitay M, Flidel-Rimon O, Even-Tov S, et al. Liposomal amphotericin B (AmBisome) in the treatment of neonatal candidiasis in very low birth weight infants. Infection 2000;28:223–6.

59 Lopez Sastre JB, Coto Cotallo GD, Fernandez CB. Neonatal invasive candidiasis: a prospective multicenter study of 118 cases. Am J Perinatol 2003;20:153–63.

60 Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE Jr, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. N Engl J Med 1994;331:1325–30.

61 Nguyen MH, Peacock JE, Morris AJ, Tanner DC, Nguyen ML, Snydman DR, et al. The changing face of candidemia: emergence of non-Candida albicans species and antifungal resistance. Am J Med 1996;100:617–23.

62 Ally R, Schürmann D, Kreisel W, Carosi G, Aguirrebengoa K, Hodges M, 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.

63 Perfect JR, Marr KA, Walsh TJ, Greenberg RN, Dupont B, Torre-Cisneros J, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003;36:1122–31.

64 Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366: 1435–42.

65 Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. Eur J Pharmaceutical Sciences 2004;21:645–53.

66 Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. Br J Clin Pharmacol 2003;57:218–22.

67 Skiest DJ, Vazquez JA, Graybill JR, Reynes J, Ward D, Corcoran GR, et al. Open-label trial of posaconazole for azole-refractory oropharyngeal ans oesophageal candidiasis in HIV/AIDS subjects: final analysis. 44th ICAAC, Washington D C 2004;Abs # M-1027.

68 Raad I, Chapman SW, Bradsher R, Morrison VA, Goldman M, Graybill JR, et al. Posaconazole salvage therapy for invasive fungal infections. 44th ICAAC, Washington D C 2004;Abs # 669.

69 Graybill JR, Raad I, Negroni R, Corcoran GR, Pedicone L. Posaconazole long-term safety in subjects with invasive fungal infections. 44th ICAAC, Washington D C 2004;Abs # M-1025.

70 Villanueva A, Arathoon E, Gotuzzo E, Berman R, DiNubile M, Sable C. A randomized double-blind study of caspofungin versus amphotericin B for the treatment of candidal esophagitis. Clin Infect Dis 2001;33:1529–35.

71 Villanueva A, Gotuzzo E, Arathoon EG, Noriega LM, Kartsonis NA, Lupinacci RJ, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. Am J Med 2002;113:294–9.

72 Arathoon EG, Gotuzzo E, Noriega LM, Berman RS, DiNubile MJ, Sable CA. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiases. Antimicrob Agents Chemother 2002;46:451–7.

73 Mora-Duarte J, Betts R, Rotstein C, Lopes-Colombo A, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020–9.

74 de Wet N, Llanos-Cuentas A, Suleiman J, Baraldi E, Krantz EF, Della Negra M, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis 2004;39:842–9.

75 Krause DS, Simjee AE, van RC, Viljoen J, Walsh TJ, Goldstein BP, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. Clin Infect Dis 2004;39:770–5.

76 Kohno S, Masaoka T, Yamaguchi H, Mori T, Urabe A, Ito A, et al. A multicenter, open-label clinical study of micafungin (FK463) in the treatment of deep-seated mycosis in Japan. Scand J Infect Dis 2004;36:372–9.

77 Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, Mullane KM, Vazquez J, Anaissie EJ, et al. International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. Eur J Clin Microbiol Infect Dis 2005;24:654–61.

78 Krause DS, Reinhardt J, Vazquez JA, Reboli A, Goldstein BP, Wible M, et al. Phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in invasive candidiasis and candidemia. Antimicrob Agents Chemother 2004;48:2021–4.

79 Reboli A, Rotstein C, Pappas PG, Schranz J, Krause D, Walsh T, et al. Anidulafungin vs. fluconazole for treatment of candidemia and invasive candidiasis. 45th ICAAC Washington D C 2005;Abs. # M-718.

80 Polak A. Combination therapy of experimental candidiasis, cryptococcosis, aspergillosis and wangiellosis in mice. Chemotherapy 1987;33:381–95.

81 Thaler M, Bacher J, O'Leary T, Pizzo PA. Evaluation of single-drug and combination antifungal therapy in an experimental model of candidiasis in rabbits with prolonged neutropenia. J Infect Dis 1988;158:80–8.

82 Kontoyiannis DP, Lewis RE. Combination chemotherapy for invasive fungal infections: what laboratory and clinical studies tell us so far. Drug Resist Updat 2003;6:257–69.

83 Bennett JE, Dismukes WE, Duma RJ, Medoff G, Sande MA, Gallis H, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptoccal meningitis. N Engl J Med 1979;301:126–31.

84 Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 2000;30:710–8.

85 Smego RA Jr, Perfect JR, Durack DT. Combined therapy with amphotericin B and 5-fluorocytosine for Candida meningitis. Rev Infect Dis 1984;6:791–801.

86 Goldman M, Pottage JC Jr, Weaver DC. Candida krusei fungemia. Report of 4 cases and review of the literature. Medicine (Baltimore) 1993;72:143–50.

87 Abele-Horn M, Kopp A, Sternberg U, Ohly A, Dauber A, Russwurm W, et al. A randomized study comparing fluconazole with amphotericin B/5-flucytosine for the treatment of systemic Candida infections in intensive care patients. Infection 1996;24:426–32.

88 Brouwer AE, Rajanuwong A, Chierakul W, Griffin GE, Larsen RA, White NJ, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet 2004;363:1764–7.

89 van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med 1997;337:15–21.

90 Larsen RA, Leal MA, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. A randomized trial. Ann Intern Med 1990;113:183–7.

91 Pahls S, Schaffner A. *Aspergillus fumigatus* pneumonia in neutropenic patients receiving fluconazole for infections due to *Candida* species: is amphotericin B combined with fluconazole the appropriate answer? Clin Infect Dis 1994;18:484–6.

92 Schaffner A, Frick PG. The effect of ketokonazole on amphotericin B in a model of disseminated aspergillosis. J Infect Dis 1985;151:902–10.

93 Sanati H, Ramos CF, Bayer AS, Ghannoum MA. Combination therapy with amphotericin B and fluconazole against invasive candidiasis in neutropenic-mouse and infective-endocarditis rabbit models. Antimicrob Agents Chemother 1997;41:1345–8.

94 Rex JH, Pappas PG, Karchmer AW, Sobel J, Edwards JE, Hadley S, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis 2003;36:1221–8.

95 Marchetti O, Entenza JM, Sanglard D, Bille J, Glauser MP, Moreillon P. Fluconazole plus cyclosporine: a fungicidal combination effective against experimental endocarditis due to Candida albicans. Antimicrobial Agents & Chemotherapy 2000;44:2932–8.

96 DiNubile MJ, Hille D, Sable CA, Kartsonis NA. Invasive candidiasis in cancer patients: observations from a randomized clinical trial. J Infect 2005;50:443–9.

97 Bodey GP, Mardani M, Hanna HA, Boktour M, Abbas J, Girgawy E, et al. The epidemiology of Candida glabrata and Candida albicans fungemia in immunocompromised patients with cancer. Am J Med 2002;112:380–5.

98 Drago M, Scaltrito MM, Morace G. In vitro activity of voriconazole and other antifungal agents against clinical isolates of Candida glabrata and Candida krusei. Eur J Clin Microbiol Infect Dis 2004;23:619–24.

99 Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002;100:4358–66.

100 Singh N. Antifungal prophylaxis for solid organ transplant recipients: seeking clarity amidst controversy. Clin Infect Dis 2000;31:545–53.

101 Denning DW. Aspergillosis in "nonimmunocompromised" critically ill patients. Am J Respir Crit Care Med 2004;170: 580–1.

102 Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, Van WE. Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med 2004;170:621–5.

103 Ascioglu S, Rex JH, De Pauw BE, Bennet JE, Bille J, Crokaert F, 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.

104 Patterson TF, Kirkpatrick WR, White M, Hiemenz JW, Wingard JR, Dupont B, et al. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. Medicine (Baltimore) 2000;79:250–60.

105 Hachem RY, Kontoyiannis DP, Boktour MR, Afif C, Cooksley C, Bodey GP, et al. Aspergillus terreus: an emerging amphotericin B-resistant opportunistic mold in patients with hematologic malignancies. Cancer 2004;101:1594–600.

106 Espinel-Ingroff A, Bartlett M, Bowden R, Chin NX, Cooper C Jr, Fothergill A, et al. Multicenter evaluation of proposed standardized procedure for antifungal susceptibility testing of filamentous fungi. J Clin Microbiol 1997;35:139–43.

107 Espinel-Ingroff A. Clinical utility of in vitro antifungal susceptibility testing. Rev Esp Quimioter 2000;13:161–6.

108 Espinel-Ingroff A, Rezusta A. E-test method for testing susceptibilities of Aspergillus spp. to the new triazoles voriconazole and posaconazole and to established antifungal agents: comparison with NCCLS broth microdilution method. J Clin Microbiol 2002;40:2101–7.

109 Espinel-Ingroff A. Evaluation of broth microdilution testing parameters and agar diffusion Etest procedure for testing susceptibilities of Aspergillus spp. to caspofungin acetate (MK-0991). J Clin Microbiol 2003;41:403–9.

110 Denning DW. Therapeutic outcome in invasive aspergillosis. Clin Infect Dis 1996;23:608–15.

111 Patterson TF, Boucher HW, Herbrecht R, Denning DW, Lortholary O, Ribaud P, et al. Strategy of following voriconazole versus amphotericin B therapy with other licensed antifungal therapy for primary treatment of invasive aspergillosis: impact of other therapies on outcome. Clin Infect Dis 2005;41:1448–52.

112 Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW, et al. Practice guidelines for diseases caused by Aspergillus. Infectious Diseases Society of America. Clin Infect Dis 2000;30:696–709.

113 Wingard JR, Kubilis P, Lee L, Yee G, White M, Walshe 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.

114 Mills W, Chopra R, Linch DC, Goldstone AH. Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients: a single-centre experience of 133 episodes in 116 patients. Br J Haematol 1994;86:754–60.

115 Ng TT, Denning DW. Liposomal amphotericin B (AmBisome) therapy in invasive fungal infections. Evaluation of United Kingdom compassionate use data. Arch Intern Med 1995;155:1093–8.

116 Bowden R, Chandrasekar P, White MH, Li X, Pietrelli L, Gurwith M, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. Clin Infect Dis 2002;35:359–66.

117 Ellis M, Spence D, de Pauw B, Meunier F, Marinus A, Collette L, 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.

118 Cornely OA, Maertens J, Bresnik M, Herbrecht R and on behalf of the AmBiLoad Trial Study Group. Liposomal amphotericin B as initial therapy for invasive filamentous fungal infections: a randomized, prospective trial of a high loading regimen vs. standard dosing (AmBiLoad Trial). Blood 2005; 106:900a, Abstract 3222 (ASH 2005).

119 Denning DW, Lee JY, Hostetler JS, Pappas P, Kauffman CA, Dewsnup DH, et al. NIAID Mycoses Study Group Multicenter Trial of Oral Itraconazole Therapy for Invasive Aspergillosis. Am J Med 1994;97:135–44.

120 Caillot D, Bassaris H, McGeer A, Arthur C, Prentice H, Seifert WF, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematological malignancies, chronic granulomatous disease, or AIDS. Clin Infect Dis 2001;33:e83–e90.

121 Utili R, Zampino R, De VF, Maiello C, Andreana A, Mormone G, et al. Improved outcome of pulmonary aspergillosis in heart transplant recipients with early diagnosis and itraconazole treatment. Clin Transplant 2000;14:282–6.

122 Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002;34: 563–71.

123 Herbrecht R, Denning DW, Patterson TF, Bennet JE, Greenfield LD, Oestmann J, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408–15.

124 Anonymous.FDA ADAC. Briefing document for voriconazole. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_01_Pfizer pdf 2001;

125 Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab Dispos 2003;31:540–7.
126 Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther 2004;75:587–8.
127 Walsh TJ, Karlsson MO, Driscoll T, Arguedas AG, Adamson P, Saez-Llorens X, et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. Antimicrob Agents Chemother 2004;48: 2166–72.
128 Boyd AE, Modi S, Howard SJ, Moore CB, Keevil BG, Denning DW. Adverse reactions to voriconazole. Clin Infect Dis 2004;39:1241–4.
129 Pascual A, Bolay S, Marchetti O. Monitoring of Voriconazole Blood Levels: 1-Year Experience at a University Hospital. 45th ICAAC New Orleans 2005;Abs. # M-2164.
130 Alexander B, Perfect JR, Daly J, Restrepo A, Tobon A, Patino H, et al. Posaconazole as salvage therapy in patients with invasive fungal infections following solid-organ transplant. 45th ICAAC Washington D C 2005;Abs # M-959.
131 Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo S, et al. Posaconazole versus fluconazole for prophylaxis of invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease: results of a multicenter trial. 45th ICAAC Washington D C 2005;Abs # M-716.
132 Maertens J, Raad I, Petrikkos G, Boogaerts M, Selleslag D, Petersen FB, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. Clin Infect Dis 2004;39:1563–71.
133 Candoni A, Mestroni R, Damiani D, Tiribelli M, Michelutti A, Silvestri F, et al. Caspofungin as first line therapy of pulmonary invasive fungal infections in 32 immunocompromised patients with hematologic malignancies. Eur J Haematol 2005; 75:227–33.
134 Marr K. Combination antifungal therapy: where are we now, and where are we going? Oncology (Williston Park) 2004;18: 24–9.
135 Cuenca-Estrella M. Combinations of antifungal agents in therapy – what value are they? J Antimicrob Chemother 2004;54:854–69.
136 Kontoyiannis DP, Hachem R, Lewis RE, Rivero GA, Torres HA, Thornby J, et al. Efficacy and toxicity of caspofungin in combination with liposomal amphotericin B as primary or salvage treatment of invasive aspergillosis in patients with hematologic malignancies. Cancer 2003;98:292–9.
137 Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. Clin Infect Dis 2004;39:797–802.
138 Maertens J, Glasmacher A, Herbrecht R, Aoun M, Thiébaut A, Cordonnier C, et al. Multicenter, noncomparative study of caspofungin combined with other antifungals in adults with invasive aspergillosis refractory or intolerant to prior therapy: final data. 45th ICAAC Washington D C 2005;Abs. # M-954.
139 Singh N, Limaye A, Safdar N, Forrest G, Pursell K, Munoz P, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients. 45th ICAAC Washington D C 2005;Abs. # M-717.
140 Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982;72:101–11.
141 EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med 1989;86:668–72.
142 Fainstein V, Bodey GP, Elting L, Maksymiuk A, Keating M, McCredie KB. Amphotericin B or ketoconazole therapy of fungal infections in neutropenic cancer patients. Antimicrob Agents Chemother 1987;31:11–5.
143 van't Wout JW, Novakova I, Verhagen CA, Fibbe WE, De Pauw BE, van der Meer JW. The efficacy of itraconazole against systemic fungal infections in neutropenic patients: a randomised comparative study with amphotericin B. J Infect 1991;22:45–52.
144 Walsh TJ, Rubin M, Hathorn J, Gress J, Thaler M, Skelton J, et al. Amphotericin B vs high-dose ketoconazole for empirical antifungal therapy among febrile, granulocytopenic cancer patients. A prospective, randomized study. Arch Intern Med 1991;151:765–70.
145 Caillot D, Reny G, Solary E, Casasnovas O, Chavanet P, Bonnotte B, et al. A controlled trial of the tolerance of amphotericin B infused in dextrose or in Intralipid in patients with haematological malignancies. J Antimicrob Chemother 1994;33:603–13.
146 Viscoli C, Castagnola E, Van Lint MT, Moroni C, Garaventa A, Rossi MR, et al. Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. Eur J Cancer 1996;32A:814–20.
147 Prentice HG, Hann IM, Herbrecht R, Aoun M, Kvaloy S, Catovsky D, 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.
148 Malik IA, Moid I, Aziz Z, Khan S, Suleman M. A randomized comparison of fluconazole with amphotericin B as empiric anti-fungal agents in cancer patients with prolonged fever and neutropenia. Am J Med 1998;105:478–83.
149 Leenders AC, Daenen S, Jansen RL, Hop WC, Lowenberg B, Wijermans PW, 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.
150 Silling G, Fegeler W, Roos N, Essink M, Buchner T. Early empiric antifungal therapy of infections in neutropenic patients comparing fluconazole with amphotericin B/flucytosine. Mycoses 1999;42(Suppl 2):101–4.
151 Nucci M, Loureiro M, Silveira F, Casali AR, Bouzas LF, Velasco E, et al. Comparison of the toxicity of amphotericin B in 5% dextrose with that of amphotericin B in fat emulsion in a randomized trial with cancer patients. Antimicrob Agents Chemother 1999;43:1445–8.
152 Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. 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. L Amph/ABLC Collaborative Study Group. Clin Infect Dis 2000;31:1155–63.
153 Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. 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.
154 Fleming RV, Kantarjian HM, Husni R, Rolston K, Lim J, Raad I, et al. Comparison of amphotericin B lipid complex (ABLC) vs. ambisome in the treatment of suspected or documented fungal infections in patients with leukemia. Leuk Lymphoma 2001;40:511–20.
155 Boogaerts M, Winston DJ, Bow E, Garber G, Reboli AC, Schwarer AP, 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.
156 Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, 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.
157 Subira M, Martino R, Gomez L, Marti JM, Estany C. Sierra J. Low-dose amphotericin B lipid complex vs. conventional amphotericin B for empirical antifungal therapy of neutropenic fever in patients with hematologic malignancies – a randomized, controlled trial. Eur J Haematol 2004;72:342–7.
158 Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 2004;351: 1391–402.

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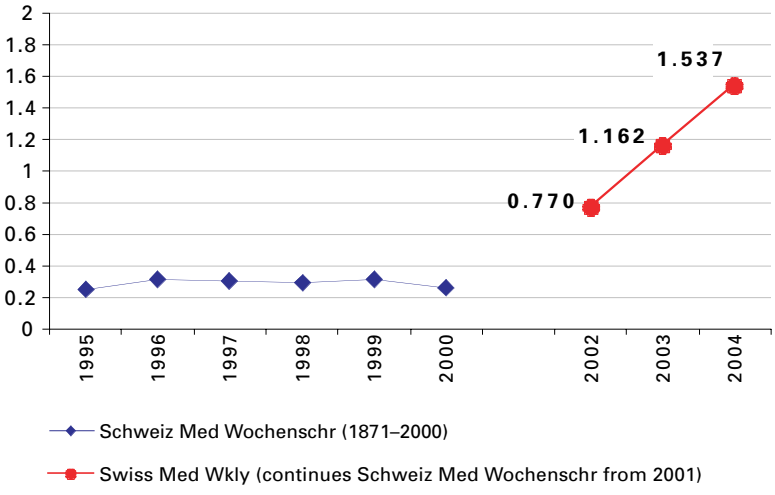

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