STICHTING WERKGROEP ANTIBIOTICABELEID

Dutch Working Party on Antibiotic Policy

SWAB Guidelines for the Management of Invasive Fungal Infections

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Chapter 1

Introduction

The Dutch Study Group on Antibiotic Policy (SWAB) has been established by the Infectious Diseases Society of the Netherlands (VIZ), the Netherlands Society for Medical Microbiology (NVMM) and the Netherlands Society for Hospital Pharmacists (NVZA). In cooperation with the National Center for Infectious Diseases Control (CIb), SWAB coordinates activities aimed at optimizing the quality of antibiotic use, monitoring the development of resistance, and at reducing the cost of antibiotic use in the Netherlands.
By way of 'evidence-based' development of guidelines, the SWAB offers local hospital antibiotic guidelines committees guiding principles for the development of antibiotic policies geared to prevailing local conditions. These guidelines also form the basis of SwabID, an on-line 'national antibiotics booklet' used by many hospitals as the platform on which, in cooperation with the SWAB, local antibiotics guidelines are formulated and made available on-line.

Invasive fungal infections are fungal infections of the blood or other normally sterile organs. These guidelines cover invasive fungal infection by *Candida* species, *Aspergillus* species, Cryptococci and Zygomycetes. As well as invasive infections, the policy as regards oro-pharyngeal candidiasis is also included in the guideline. Vulvovaginal candidiasis and dermatomycoses, however, are outwith the remit of the guideline. The guideline is applicable to adults, children and neonates and is intended for both intramural and extramural use. The members of the committee have been delegated by their respective professional bodies; the Netherlands Association Society Hospital Pharmacists, the Netherlands Society for Medical Microbiology, the Infectious Diseases Society of the Netherlands, including the pediatrics division, the Netherlands Society for Hematology and the Netherlands Society for Intensive Care.

Methods

The guidelines were drafted in accordance with the recommendations on evidence-based development of guidelines (EBRO) and reviewed in conformity with the AGREE instrument (www.agreecollaboration.org). The guidelines were derived from a systematic literature review based on essential research questions about the treatment of invasive fungal infections. The conclusions and recommendations have been provided with levels of evidential value in conformity with the handbook of the Dutch Institute for Healthcare Improvement CBO (Table 1.1- 1.2). The editor (AOL) conducted a systematic review of each of the research questions in the Pubmed database (January 1966 through January 2008). In addition, use was made of The Cochrane Library, Clinical Evidence and Sumsearch, and exploratory studies of existing guidelines were conducted. The draft guidelines were edited by the Guidelines Committee of delegates from the professional societies involved, and subsequently submitted to the members of the professional societies for comment. The final version was approved by the SWAB board of governors consisting of mandated representatives of the professional societies.

Table 1.1 Level of evidential value for articles relating to prevention or treatment

A1 Systematic reviews relating to at least a number of A2 level studies in which the results of individual studies are consistent

A2 Randomized comparative clinical studies of good quality and adequate scope and consistency (randomized, double-blind controlled trials).

B Randomized clinical trials of indifferent quality or insufficient scope or other comparative studies (non-randomized, comparative cohort studies, patient control studies)

C Non-comparative studies

D Expert opinion e.g. study group members

Table 1.2. Level of evidence of the conclusions

1 A systematic review (A1) or at least two A2-level studies conducted independently of each other

2 At least two B-level studies conducted independently of each other

3 An A2 or B-level study or C-level studies

4 Expert opinion e.g. study group members

Chapter 2

Invasive Aspergillosis

Introduction

Aspergillosis has emerged as a severe invasive infection in immunocompromized patients. Invasive aspergillosis generally affects the lower respiratory tract or sinuses. The disease may affect the central nervous system and other sites as a result of hematogenous dissemination. Saprophytic, non-invasive involvement includes pulmonary aspergilloma and allergic bronchopulmonary aspergillosis (ABPA). The latter manifestation is beyond the scope of these guidelines. Various classes of antifungal agents are active against *Aspergillus* species. Of the polyenes, conventional amphotericin B deoxycholate (c-AMB) is the oldest antifungal drug. Its registration is not based on comparative trials, but on clinical observations and open studies. The many side effects of c-AMB have resulted in the development of various lipid associated amphotericin B (LFAB) compounds: liposomal amphotericin B (L-AmB), amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD). Of the azoles, itraconazole, voriconazole and posaconazole are active against *Aspergillus* species. The echinocandins, caspofungin, micafungin and anidulafungin also are active against *Aspergillus* species.

To develop an optimal treatment recommendation for invasive aspergillosis, the committee has defined the core questions posed below. Answering these questions has provided the theoretical framework for rational management.

2.1. What is the optimal treatment for acute invasive pulmonary aspergillosis?
a. What is the optimal first-line therapy?
b. What is the second-line therapy following failure or (possible) toxicity?
c. What is the efficacy of adjunctive immunotherapy or surgery?
d. Which duration of therapy is required and what is the optimal secondary prophylaxis?

2.2. What is the optimal treatment for other forms of invasive aspergillosis?
a. What is the optimal treatment for *Aspergillus* sinusitis?
b. What is the optimal treatment for cerebral aspergillosis?
c. What is the optimal treatment for chronic pulmonary aspergillosis?
d. What is the optimal treatment for aspergilloma?

2.1. What is the optimal treatment for acute invasive pulmonary aspergillosis?

2.1.a. First-line therapy of pulmonary aspergillosis

Prospective randomized studies

Seven prospective randomized studies of invasive aspergillosis have been conducted. The majority of the patients had invasive pulmonary aspergillosis, although the studies were not restricted to this locus [1-7]. Unless otherwise stated, the European Organization on Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) definitions of proven, probable and possible invasive aspergillosis have been used in the studies discussed [8]. Response is defined as complete recovery (resolution of fever and disappearance of symptoms and radiological abnormalities) or partial recovery (resolution of fever and at least stabilization of symptoms and radiological abnormalities).
A number of studies, however, held stable disease to be a favourable response; in such cases, this is stated explicitly.

In a prospective, double-blind, randomized trial, Bowden et al. compared ABCD (6 mg/kg/d) with c-AMB (1.0-1.5 mg/kg/d) in the treatment of invasive aspergillosis [5]. This study included 174 immunocompromized patients (113 proven, 43 probable, 18 possible infections). Primary analysis of patients treated for at least 7 days showed no difference in response (complete and partial response and stable disease): ABCD 26/50 (52%) vs. c-AmB 27/53 (51%); 95%CI, –0.20 - 0.18. In the intent-to-treat group, no difference in response was observed between the two groups: 31/88 (35%) ABCD vs. 30/86 (35%) c-AmB; 95%CI, –0.15 - 0.14.
The confidence interval of the difference between both success percentages in the primary analysis (-0.20 – 0.18) is so large that non-inferiority of ABCD was not confirmed. Also, mortality was not significantly different (ABCD, 36% vs. c-AmB, 45%, p=0.4). Nephrotoxicity did occur significantly less often in the ABCD group (25% vs. 49%, p=0.002). Infusion-related toxicity was more frequent in the ABCD group (fever 27% vs. 16%; p=0.01, and chills, 53% vs. 30%; p=0.002).

In an open, randomized study, Leenders et al. [2] compared L-AmB (5 mg/kg/d) with c-AmB (1 mg/kg/d) in 106 patients with a range of proven, probable, or clinically suspected invasive fungal infections. The latter group included patients with unexplained fever and abnormal findings on chest imaging. In the total study population of 66 subjects with a variety of demonstrated or suspected pathogens, L-AmB was superior but in the group of 55 patients with proven or suspected invasive aspergillosis there was no significant difference between the two study arms (response at end of therapy (EOT), L-AmB 11/26 (42%) vs. cAmB, 6/29 (21%); p=0.14). Nephrotoxicity occurred significantly less often in the L-AmB group at EOT (11.5% vs. 40.7%, p<0.001).
Note: In this study, the EORTC/MSG criteria for proven or probable invasive infection were not applied; patients with unexplained fever also failed to comply with the EORTC/MSG definition of possible infection [8]. The outcomes in the group with proven invasive aspergillosis were not reported.

In 1998, the EORTC Invasive Fungal Infections Group has published a prospective dose finding study comparing L-AmB at 1 mg/kg/dag (L-AmB1) and 4 mg/kg/d (L-AmB4) [3], in which 120 patients with neutropenia (PMN <1000 x 10^6/l) induced by conventional chemotherapy or bone marrow transplantation and proven or probable invasive aspergillosis were included. In the subset of evaluable patients (n=87), no difference between the two groups was observed with respect to clinical (L-AmB1, 64% vs. L-AmB4, 48%; p=0.14) and radiological (58% vs. 54%; p=0.69) response. The mortality resulting from invasive aspergillosis at 6 months was also similar in both arms (22% vs. 20%). The number of evaluable patients (104) required to demonstrate a difference in efficacy between both study arms was not achieved.
A recent study compared L-AmB at 3 mg/kg/d (L-AmB3) with 10 mg/kg/d (L-AmB10) in 201 patients with a proven or probable invasive, filamentous fungal infection [6]. 14 days after start of treatment, the study dose was tapered to a consolidation treatment of 3 mg/kg/d. Of the 201 patients, 97% had an invasive aspergillosis. At end of treatment, there was no difference in response between the two groups (L-AmB3, 50% vs. L-AmB10, 46%; p>0.05) and no difference in survival at 12 weeks (72% vs. 59%; p=0.09). Greater toxicity was observed in the 10mg/kg/d group: nephrotoxicity (L-AmB3 14% vs. LAmB10 31%; p<0.01) and hypokalemia < 3.0 mmol/l (16% vs. 30%, p<0.02).

In a small randomized study, c-AmB (0.5-1 mg/kg/d) was compared with a combination of c-AmB (0.5-1 mg/kg/d) and flucytosine (5-FC, 150 mg/kg/d) in 18 neutropenic patients with a proven invasive aspergillosis [7]. The response was 1/9 in the monotherapy group and 2/9 in the group treated with c-AmB + 5-FC.

In a randomized comparative study of 32 neutropenic patients with proven or probable invasive fungal infections [1], itraconazole (oral capsules, 200mg bid) was compared with c-AmB (0.6 mg/kg/d). The main limitation of the study was the oral administration of the medication in neutropenic patients with unreliable resorption, which led to inclusion of a selected group only. In the patients with proven or probable invasive aspergillosis (n=13), the response was 75% (6/8) with itraconazole and 40% (2/5, p=0.21) with c-AmB.
Note: The committee has pointed out that, after completion of this study, itraconazole has become available as an oral solution with improved resorption. However, no prospective studies of its use in the treatment of invasive aspergillosis have been conducted.

A randomized, open label study by Herbrecht et al. compared voriconazole (4 mg/kg bid i.v. or 200 mg bid orally) with c-AmB (1.0-1.5 mg/kg/d) for the treatment of invasive aspergillosis in 277

immunocompromized patients with proven (n=108) or probable (n=169) acute invasive aspergillosis [4]. Both pulmonary and extra-pulmonary infections were included.
The diagnosis (proven vs. probable disease) and the response were established by a blinded data review committee (DRC). The success rate at 12 weeks was 52.8% in the voriconazole arm vs. 31.6% in the c-AmB arm (difference 21.2%; 95%CI, 10.4 - 32.9). Based on the confidence interval of the difference between the success rates, voriconazole (Vor) was superior to the standard treatment with c AmB. The survival at 12 weeks was 70.8% (Vor) vs. 57.9% (c-AmB, hazard ratio (HR) 0.59; 95%CI, 0.4 - 0.88, p=0.02). The favourable effect of voriconazole was independent of the site or certainty of diagnosis: success rates were 54.5% (Vor) vs. 34.2% (c-AmB) in pulmonary infections and 42.9% vs. 12.5% in extra-pulmonary infections. In patients with confirmed aspergillosis ("proven" according to the EORTC/MSG criteria), success rates were 44.8% (Vor) vs. 19.5% (c-AmB) and in patients with a likely infection ("probable") 59.7% vs. 37.0%. These results correspond to those of an earlier open, non-comparative study with voriconazole in patients with invasive aspergillosis [9].

In the trial described above [4], investigators were allowed to continue treatment with other licensed antifungal therapies (OLAT) in the event of intolerance to or failure of the randomized study drugs [10]. In patients randomized to c-AmB, the study drug had to be withdrawn and replaced with OLAT significantly more often, in a total of 80% (107/133, c-AmB) of subjects, vs. 36% (Vor, 52/144; p<0.001). Reasons for this were both intolerance (72/133, c-AmB, vs. 16/144, Vor) and failure (21/133, c-AmB, vs. 19/144, Vor). In patients originally randomized to c-AmB followed by OLAT (usually LFAB), the final response was only 19% in patients with an initial failure on c-AmB and 38% of patients intolerant to c-AmB. This suggests that initial treatment with c-AmB, even when followed by LFAB, is associated with a low response [10].

Retrospective studies with historic controls

First-line therapy with ABLC in 12 liver transplant subjects with invasive aspergillosis was compared to a historic cohort of 29 patients treated with c-AmB [11]. Mortality was 33% in the ABLC group and 83% (p=0.006) in the historic c-AmB group. Although the criteria for proven invasive aspergillosis were not reported, it is suggested that mortality in patients with proven invasive aspergillosis was 25% (1/4) in the ABLC group and 100% (11/11) in the c-AmB group.
White et al. compared ABCD (2-6 mg/kg/d) for the treatment of invasive aspergillosis in 82 hematology or oncology patients with a cohort of 261 historic controls treated with c-AmB [12]. The response was 49% (ABCD) vs. 23% (c-AmB, p<0.001). Mortality was 50% (ABCD) vs. 72% (c-AmB, p<0.001). Nephrotoxicity occurred less frequently in patients treated with ABCD (8%) than in the cohort treated with c-AmB (43%, p<0.001).
Singh et al. compared the combination voriconazole and caspofungin as primary therapy for proven or probable invasive aspergillosis (EORTC/MSG definitions) in 40 organ transplant subjects in a prospective multicenter study with a historic cohort (n=47) treated with LFAB [13]. The response at EOT was 70% in the combination thearapy group and 51% (p=0.08) in the historic controls; survival at 90 days was 67.5% (combination) vs. 51% (controls; p=0.12).
Kontoyiannis et al. retrospectively compared a group of 11 patients with hematological malignities and invasive aspergillosis who had initially been given the combination of LFAB and itraconazole with 101 patients that had initially been treated with LFAB as monotherapy [14]. Only patients who had been treated for at least 7 days were assessed. The response at EOT – defined as disappearance or major improvement of invasive aspergillosis, combined with a 75% improvement of radiological findings – was nil in the combination group vs. 10% (10/101) in the LFAB-group. Mortality at 2 weeks (18% vs. 13%) and at 4 weeks (36% vs. 34%) was similar in both groups.
Note: As these studies have used a historic control group, it is hard to dray any definite conclusions from these studies.

Non-comparative, retrospective studies

Two analyses retrospectively reported data collated by the manufacturers of LFAB on primary treatment of invasive aspergillosis [15, 16]. In a case series of 5 patients with invasive aspergillosis who had primarily been treated with L-AmB, response was favorable in 4 of the 5 patients [16]. The primary treatment with ABLC of 139 patients with invasive aspergillosis (not defined in accordance with the EORTC/MSG criteria) was described in the so-called CLEAR study. The response was 47% [15].

Note: Efficacy was assessed only in patients who had received a minimum of 4 doses of ABLC, likely resulting in a biased view of the true response in all patients treated, i.e., the (modified) intent-to-treat group given at least 1 dose of ABLC.

A recent study described 41 neutropenic patients with invasive aspergillosis who had been treated with caspofungin (loading dose 70 mg qd, followed by 50mg qd i.v.). In the subgroup of 12 patients with caspofungin as primary therapy, the response was 42% [17].

Kontoyiannis et al. described 17 patients given primary therapy consisting of L-AmB and caspofungin and 31 patients who had caspofungin added to L-AmB due to lack of efficacy (salvage therapy) [18]. In total, the response in patients with proven or probable infection was 22% (5/23). Success rates were and 33% (2/6) with primary therapy and 18% (3/17) with salvage therapy. In the 25 patients with a "possible" invasive aspergillosis, the response was 60%.

Primary therapy of invasive aspergillosis in children

The majority of studies on treatment of invasive aspergillosis have been conducted in adults or children > 12 years. The study carried out by Herbrecht et al. has included children aged over 12 years [4]. Unfortunately, the outcomes in the various age categories were not reported. Various studies have been conducted in neonates, children and adolescents with invasive aspergillosis [19-24]. None of these studies were randomized; all were compassionate use or salvage therapy studies, both prospective [19, 23] and retrospective [20-22, 24].
Wiley et al. retrospectively described the response in 69 children (< 20 years) with invasive aspergillosis who were treated with ABLC for at least 4 days [24]. The response was 39%, whereby it was not reported how many patients received primary treatment and how many (probably the majority) had salvage therapy.
Note: Data concerning primary therapy with ABLC in children have therefore not been published. Moreover, in this study [24], no (modified) intent to treat response was reported, but only a subgroup that had been treated with ABLC for at least 4 days, which likely yields a biased result.

Conclusions 2.1.a. – First-line therapy for acute invasive aspergillosis	
Conclusion 1	It has not been demonstrated that LFAB (ABCD or L-AmB), the combination of c-AmB with 5-FC or itraconazole are as effective as or better than c-AmB in the primary treatment of invasive aspergillosis. However, LFAB is associated with fewer side effects.
Level 2	Bowden, 2002 [5](A2); White, 1997 [12](B); Leenders, 1998 [2](B); Ng, 1995 [16](C); Verweij, 1994 [7](B); Van 't Wout, 1991 [1](B)
Conclusion 2	No difference in efficacy or mortality has been demonstrated in the treatment of invasive aspergillosis with 3 mg/kg/d L-AmB vs. 10 mg/kg/d L-AmB. Neither has it been shown that a lower dose (1 mg/kg) is as effective as 4 mg/kg/d of L-AmB.
Level 1	Ellis, 1998 [3](A2); Cornely, 2005 [6](A2)
Conclusion 3	It has not been demonstrated that caspofungin, ABLC or the combination of caspofungin/L-AmB are at least as effective as voriconazole or c-AmB in the primary treatment of invasive aspergillosis.
Level 3	Linden, 2003 [11](B); Chandrasekar, 2005 [25](C); Betts, 2006 [17](C); Kontoyannis, 2003 [18](C)
Conclusion 4	Voriconazole is superior to c-AmB in the treatment of invasive aspergillosis.
Level 3	Herbrecht, 2002 [4] (A2)
Conclusion 5	A 'step-up' policy with initial use of c-AmB followed by a second-line drug in the event of failure results in poorer results than primary therapy with voriconazole.
Level 3	Patterson, 2005 [10](A2); Denning, 2002 [9](C)
Conclusion 6	It has not been demonstrated that the combination therapies voriconazole/caspofungin or itraconazole/LFAB are as effective as or superior to monotherapy with LFAB in the treatment of invasive aspergillosis.
Level 3	Singh, 2006 [13](B); Kontoyannis, 2005 [14](B)
Conclusion 7	In spite of the absence of randomized comparative trials in children with invasive aspergillosis, ABLC and voriconazole are the most commonly used treatments for children with invasive aspergillosis.
Level 3	Walsh, 2002 [21](C) Wiley, 2005 [24](C).

Other considerations

For the treatment of invasive aspergillosis, voriconazole is superior to c-AmB. Formally, the efficacy of other agents, such as LFAB, echinocandins, itraconazole (intravenously or as an oral solution) or posaconazole has not been established. The committee therefore considers voriconazole to be the drug of choice in proven, probable or possible invasive aspergillosis. Several other agents mentioned are suitable as second-line therapies in the event of voriconazole toxicity or failure.
Although no data are available regarding the response of children with invasive aspergillosis to treatment with ABLC as primary therapy, experience with this drug is relatively extensive [24]. The committee emphasizes the absence of published data on the efficacy of ABLC for this indication, and consequently holds voriconazole, the efficacy of which has been demonstrated in adults, to be a rational first choice. Voriconazole is not licensed for children under 2 years of age.
There is evidence that the individual variations in the pharmacokinetics of voriconazole, posaconazole and itraconazole can have a major influence on treatment outcome. No consensus has been reached as to the need for therapeutic drug monitoring. The committee suggests that monitoring may be considered depending on individual patient characteristics, co-medication and the indication for treatment, especially in the event of toxicity or failure of therapy.

Recommendation 1	Primary treatment with voriconazole is recommended for patients with acute invasive aspergillosis.

Recommendation 2	Primary treatment with voriconazole is recommended for children with acute invasive aspergillosis. As an alternative, ABLC may be considered.

2.1.b. Second-line therapy in the event of treatment failure

Salvage therapy is defined as treatment given in the event of failure of first-line therapy, undue toxicity of first-line therapy or inability to treat using first-line therapy due to a variety of reasons (e.g., renal insufficiency). No double-blind controlled studies have been conducted in this category of patients.

Comparative studies in salvage therapy

In an open study, posaconazole was investigated as a salvage therapy for the treatment of 107 patients with invasive aspergillosis (proven or probable according to EORTC/MSG criteria) refractory (after at least 7 days of therapy, 88%) or intolerant (12%) to conventional antifungal therapy [26]. This group was compared to 86, partly historic, controls with invasive aspergillosis refractory to (79%) or intolerant of (21%) earlier therapy. Patients who had initially been treated with voriconazole or echinocandins or could not be assessed were excluded only from the control group. The response at EOT was 42% (45/107, posaconazole) vs. 26% (22/86, controls; OR 2.11; 95%CI, 1.14-3.92; p=0.018). In cases of failure on previous therapy, the response to posaconazole was 43% (40/94); in cases of intolerance of previous therapy, response was 38% (5/13). Response in the posaconazole group (42%) did not differ significantly from that in patients in the control group who had received newer, at that time non-licensed, agents (voriconazole or echinocandins) as salvage therapy (31%, p=0.22).

Prospective non-comparative studies

ABLC (5 mg/kg/d) was investigated in a large open-label salvage study of 556 patients with a proven or probable invasive fungal infection (EORTC/MSG criteria), refractory to or intolerant of the first-line antifungal therapy [27]. Reporting was restricted to only 291 patients who met the assessment criteria (at least 4 days of treatment with ABLC and sufficient follow-up). The response to salvage therapy in the subgroup with invasive aspergillosis was 42% (55/130).
Note: The response in the subgroups given salvage therapy because of toxicity or failure of earlier therapy was not reported and neither were the results for the entire intent-to-treat (ITT) population. At the time of the study, voriconazole was not yet used as primary therapy.

A prospective open-label study investigated salvage therapy with ABCD in patients with either kidney failure resulting from c-AmB use or pre-existing kidney failure [28]. Sixteen patients with invasive

aspergillosis (according to the then applicable IDSA/FDA definition) were assessed with a response of 62.5% (10/16).
Note: This appears to be a very favorable response, but only those patients who had been treated for at least 7 days were assessed with regard to efficacy. Thus, the treatment outcomes of patients with early failure or death were not reported.

The EORTC have studied liposomal nystatin (4mg/kg/d) in a prospective salvage trial in 26 patients with proven (n=3) or probable (n=23) invasive aspergillosis who were refractory to (n=24) or intolerant of (n=2) amphotericin B preparations. The response in 25 evaluable patients was 28% [29].

Caillot et al. described 31 immunocompromized patients with invasive pulmonary aspergillosis who were treated with intravenous itraconazole. Patients were allowed to receive follow-on treatment with oal itraconazole as capsules. The total response was 39%. In the subgroup of 21 patients who had failed on amphotericin B, the response was 52% [30].

Voriconazole as a salvage therapy was prospectively studied in 142 patients with invasive aspergillosis by Perfect et al. [31]. The response was 44%; following failure on previous therapy, the response was 41% (44/107) and in patients with pre-existing kidney failure or intolerance to prior antifungal therapy the response was 51% (18/35). Likewise, Denning et al. reported a response of 38% (21/56) in 56 patients with invasive aspergillosis who had received salvage therapy with voriconazole [9].

In an open, non-comparative multicenter study, Maertens et al. described caspofungin as a salvage therapy in 83 patients with invasive aspergillosis who had failed on (n=71) or were intolerant of (n=12) c-AmB [32]. At end of therapy, the total response was 45%. Following failure on previous therapy, the response was 39.4% and in patients who were intolerant of previous therapy it was 75%. The manufacturer of caspofungin further described salvage therapy with this drug in 45 patients with invasive aspergillosis who had failed on amphotericin B [33]. The total response was 44%. In a recent study by Betts et al., the response of 29 neutropenic patients with invasive aspergillosis to salvage therapy with caspofungin was 38% [17].

Retrospective studies

Twelve patients with proven invasive aspergillosis were given L-AmB salvage therapy [16]. The total response was 50% (6/12). The response to salvage therapy following failure of c-AmB was 1/3, vs. 5/9 in those treated after kidney failure or other adverse effects of various antifungal agents.
In a study by Mills et al., the response in 57 neutropenic patients given L-AmB salvage therapy for invasive aspergillosis was 56% [34]. The response following failure of previous antifungal therapy was 68% compared to 49% in intolerance of the previous therapy due to kidney failure or toxicity.
Chandrasekar et al. described 398 patients treated with ABLC for invasive aspergillosis, whereby criteria other than EORTC/MSG criteria were applied [25]. Efficacy was assessed in 368 patients following at least 4 doses of ABLC. The 216 patients given ABLC salvage therapy had a response of 44%. The response following failure on previous therapy was 38% (60/157), vs. 57.6% (34/59) in those with kidney failure or intolerance to primary therapy.
Note: It is important to note that reporting did not refer to the (M)ITT population but to a per-protocol cohort only.

In a cohort of 125 patients with invasive aspergillosis who were treated with oral itraconazole (capsules) Stevens et al. described a response of 63% [35]. No significant difference was reported between the response in the salvage therapy group (n=112) and the primary therapy group (n=13).
Note: Oral itraconazole was most likely prescribed to a selected subgroup of less seriously ill patients.

In a number of studies, combination therapy was studied as a second-line therapy [10, 13, 14, 18, 36, 37].
Marr et al. retrospectively compared 31 patients with invasive aspergillosis who, between 1997 and 2001, were treated with voriconazole as a salvage therapy, with 16 patients who were given the combination voriconazole and caspofungin as salvage therapy in 2001-2003 [36]. In a regression model, mortality at 90 days was lower in the combination group (p=0.048), as was the mortality directly attributed to invasive aspergillosis (p=0.024). As use was made of a historic control group, no definitive conclusions may be drawn from this study.

In the salvage therapy study conducted by Aliff et al., patients with acute leukemia and proven or possible invasive pulmonary aspergillosis were treated with L-AmB and caspofungin [37]. The response was 60% (48/60), and 83% (5/6) in the 6 patients with proven invasive aspergillosis.

Salvage therapy in children

In a compassionate use salvage study using voriconazole (4 mg/kg bid bid) as the primary therapy for 42 immunocompromized children with invasive aspergillosis (aged 9 months to 15 years) Walsh et al. noted a response of 43% [21]. Voriconazole salvage therapy (4 mg/kg bid) was also described retrospectively by Cesaro et al. in a small study of 7 patients (age 2-13 years) [22]. The response was 43% (3/7). All patients has previously received lengthy treatment with L-AmB (median 6 weeks, range 2-18).

Walsh et al. reported on the efficacy of ABLC (5.0 mg/kg/d) in an open-label salvage study of a subgroup of 25 young patients with proven invasive aspergillosis [19]. The age of the total study population (n=111) was 9.3 years, (range 21 days to 16 years) and the population largely consisted of patients with hematological malignities (80%). In patients who had been given ABLC for at least 4 days, the response was 56% (14/25) [19]. Wiley et al. retrospectively described the response of 69 children (< 20 years) with invasive aspergillosis who had been treated with ABLC for at least 4 days [24]. The response was 39%; Whether the patients received primary therapy or salvage therapy was not reported.
Note: It is likely that the patient groups of the latter two studies overlap [19, 24]. No
(modified) intent to treat response was reported in these groups but only a subgroup that had been treated with ABLC for at least 4 days.
A retrospective study from France assessed the outcomes in 23 children (≤18 years) with proven invasive aspergillosis who received ABLC (5mg/kg/d) as a salvage therapy following c-AmB [20]. The response was 78% (18/23), but 3 patients relapsed.

A prospective study of combination therapy using caspofungin (50 mg qd) and L-AmB (5-6 mg/kg/d) followed by voriconazole was conducted in 10 patients (median 13 years, 6-24 years) with invasive fungal infections and a hematological malignity; 8 of the patients had a proven or probable invasive aspergillosis infection [23]. Efficacy was assessed in patients who had received combination therapy for at least 7 days. The response to the L-AmB and caspofungin combination therapy was 50% (4/8). All 8 patients given voriconazole following the combination therapy were still alive 125 days (median) after end of therapy.

Conclusions 2.1.b. – Salvage therapy for acute invasive aspergillosis	
Conclusion 8	None of the studies demonstrated that any specific antifungal salvage therapy (or combination of 2 drugs) was comparable or superior to any other antifungal therapy for acute invasive aspergillosis.
Level 3	Walsh, 1998 (26); Chandrasekar, 2005 (15); Anaissie, 1998 (27); Ng, 1995 (16); Mills, 1994 (34); Walsh, 1999 (30); Herbrecht, 2001 (31) Caillot, 2003 (30); Stevens, 1997 (35); Denning, 2002 (9); Perfect, 2003 (31); Cesaro, 2003 (33) Maertens, 2004 (32); Kartsonis, 2005 (33); Betts, 2006 (17) Walsh, 2001 (25) Aliff, 2003 (37); Cesaro, 2004 (34) (C)
Conclusion 9	Liposomal nystatin has not been shown to be suitable as a salvage therapy**.**
Level 3	Offner, 2004 (28) (C)

Other considerations

Following failure of primary antifungal therapy for invasive aspergillosis, a number of causes should be taken into consideration. Firstly, it is possible that the infection has been caused by a zygomycete, alone or in combination with *Aspergilllus* species. Secondly, the infection may stem from an *Aspergillus* species that is intrinsically less susceptible to certain antifungal agents. It is known, for example, that *Aspergillus terreus* is less susceptible to (liposomal formulations of) amphotericin B [38, 39]. Thirdly, resistance to one or more azoles is known to exist in *A. fumigatus* [40]. For these reasons, the *Aspergillus* species and the susceptibility of the strain should be determined in the event of therapy failure.

Recommendations

No prospective comparative studies have been conducted to determine the optimal salvage therapy for invasive aspergillosis. On the basis of the available data, the committee has formulated the following recommendations:

Recommendation 3	On failure of a first-line therapy for (proven or suspected) aspergillosis, the cause of the failure should be investigated. In particular, resistance of *Aspergillus* species or a (co-)infection with zygomycetes should be taken into consideration. When these have both been reasonably excluded, the committee considers voriconazole to be the drug of first choice as a salvage therapy for patients who had received an amphotericin B or echinocandin preparation as first-line therapy.

Recommendation 4	On failure of voriconazole, the committee considers it to be of primary importance that resistance and a co-infection with zygomycetes be excluded. In view of this differential diagnosis, L-AmB is considered to be the drug of first choice. Caspofungin may be considered as the second choice if zygomycosis has been excluded and there is no evidence of intra-cerebral aspergillosis.

Recommendation 5	Although several case series with retrospective controls have report favourable results of combination therapy with voriconazole and edcaspofungin, the committee considers the use of combination therapy to have been insufficiently investigated.

Recommendation 6	Based on data from adults and children >12 years, voriconazole is recommended for children older than 2 years. ABLC is eligible as an alternative.

2.1.c. Adjunctive immunotherapy and surgery

Adjunctive immunotherapy

Although interferon (IFN)-γ has been studied as a prophylaxis in patients with chronic granulomatous disease (CGD) [41], no controlled trials have been conducted to investigate adjunctive therapy with IFN-γ as a treatment of invasive aspergillosis in patients with CGD. On the basis of theoretical considerations, many experts add IFN-γ to antifungal therapy for treatment of CGD patients with invasive aspergillosis.

Safdar et al. retrospectively investigated the effect of adding IFN-γ (50 µg subcutaneously qod) to antifungal therapy given to hematopoietic stem cell transplant patients with invasive fungal infections who did not respond sufficiently to antimycotic agents only [42]. Twenty-six of 32 patients had invasive aspergillosis. The response was 43.8% (7/16) in cases of probable and proven invasive aspergillosis. The mortality was 53.8% [42].

Surgery

A French study has described the effect of aggressive surgery in the treatment of invasive pulmonary aspergillosis in 26 neutropenic patients [43]. Prior to a subsequent neutropenic period, patients either underwent resection of the aspergillus mass to prevent massive hemoptysis resulting from arterial invasion, or lung resection on account of a diagnostic open lung biopsy; success rate 84%. All patients had already been treated pre-operatively with an amphotericin B preparation, itraconazole or a combination.
Two other case series [44, 45] further describe early surgical intervention in a group of patients with pulmonary aspergillosis. In 27 and 16 of the patients described, the survival was 70% and 69% respectively. The absence of a control group means that no conclusions can be drawn from these case series.

Conclusions 2.1.c. – Immunotherapy and surgery in acute invasive aspergillosis	
Conclusion 10	It has not been proven that addition of IFN-γ to antifungal therapy in hematological patients with invasive aspergillosis is useful.
Level 3	Safdar, 2005 [42](C)
Conclusion 11	It has not been shown that the efficacy of surgery in combination with medicinal therapy is equal or superior to antifungal therapy alone.
Level 3	Caillot, 2001 [43](C); Reichenberger, 1998 [44](C); Robinson, 1995 [45](C)

Recommendation 7	Despite the absence of formal studies, the committee is of the opinion that the addition of IFN-γ to conventional antifungal therapy should be considered in CGD patients with invasive aspergillosis.

Recommendation 8	Surgical resection of invasive pulmonary aspergillosis may be considered, especially when there is evidence of arterial invasion and a risk of pulmonary hemorrhage.

2.1.d. Which duration of therapy is required and what is the optimal secondary prophylaxis?

In general, primary treatment of invasive pulmonary aspergillosis is continued for 6 to 12 weeks. The decision to discontinue primary therapy is taken on the basis of the clinical response, laboratory cultures and the evolution of CT-scan findings. In patients with persistent immunosuppression, maintenance therapy may be considered following discontinuation of primary treatment. In neutropenic patients, a similar duration of therapy is recommended; in these patients, therapy should never be shorter than until 2 weeks after resolution of the neutropenia [46].

The term secondary prophylaxis denotes a preventive treatment following a previous episode of invasive aspergillosis, especially during (recurring) periods of immunosuppression.
An EORTC study has investigated the outcome of stem cell transplantation (HSCT) in patients who had suffered from invasive aspergillosis. In 48 patients with invasive aspergillosis (10 proven, 38 probable) HSCT was carried out within (median) 3 months of the episode [47]. Forty-one of the 48 patients received secondary antifungal prophylaxis around the time of the transplantation. The mortality was 48% (23/48). In total, 16 patients (33%) had a relapse of invasive aspergillosis within (median) 3 months (range 0-120 days) of the bone marrow transplant; 14 of these patients died.

No prospective studies of secondary prophylaxis of invasive pulmonary aspergillosis have been carried out. In a small study including 10 patients with leukemia who had invasive aspergillosis, however, treatment with voriconazole (400 mg qd) was prolonged at length to ensure that chemotherapy and allogeneic bone marrow transplantation were nor postponed [48]. None of the patients relapsed and voriconazole was reasonably well tolerated.

Other considerations

The choice of the antifungal agent for secondary prophylaxis of invasive aspergillosis has not been investigated. Based on the preference for posaconazole as primary prophylaxis (see chapter 5.1) and voriconazole for primary therapy, the committee considers both of these drugs to be eligible for secondary prophylaxis.

Conclusions 2.1.d. – Duration of therapy and secondary prophylaxis	
Conclusion 12	The duration of antifungal therapy has not been investigated. In general, treatment is continued for 6 to 12 weeks.
Level 4	Singh, 2003(D) [46]
Conclusion 13	Mortality is high in the event of relapse around the time of a bone marrow transplant.
Level 3	Offner, 1998(C) [47]

Conclusion 14	It has not been shown that secondary prophylaxis prevents relapse of invasive aspergillosis.
Level 3	Cordonnier, 2004 (C) [48], Offner, 1998 (C) [47]

Recommendation 9	The duration of therapy for patients with acute invasive pulmonary aspergillosis depends on the clinical course of the disease, laboratory culture and the evolution of CT-scan findings. Duration of therapy is at least 6 to 12 weeks and, in neutropenic patients, not less than 2 weeks subsequent to resolution of the neutropenia.

Recommendation 10	Despite the absence of studies, the committee is of the opinion that secondary prophylaxis is recommended after recent invasive aspergillosis in patients undergoing new immunosuppressive treatment (e.g., HSCT) or who are suffering from a specific primary immune deficiency (e.g., CGD). Voriconazole or posaconazole are eligible as oral prophylaxis.

2.2. What is the optimal treatment for non-pulmonary forms of invasive aspergillosis?

Aspergillus sinusitis, cerebral aspergillosis, chronic pulmonary aspergillosis and aspergilloma

No prospective comparative studies have been carried out with regard to specific forms of invasive aspergillosis as invasive sinusitis and cerebral aspergillosis. In the comparative study of voriconazole vs. amphotericin B [4], patients with extrapulmonary sites of invasive aspergillosis had a response of 43% in the voriconazole arm vs. 13% in the c-AmB arm ($p < 0.05$); this was, therefore, largely comparable to the outcomes in patients with invasive pulmonary aspergillosis [4]. In the absence of more detailed data and on the basis of this study, voriconazole would thus appear to be superior to c-AmB in invasive extrapulmonary aspergillosis. From the other comparative studies, no data relating to extrapulmonary invasive aspergillosis was reported [3, 5, 12].

Aspergillus sinusitis

An important distinction must be made between invasive and non-invasive *Aspergillus* sinusitis. Invasive *Aspergillus* sinusitis generally occurs in the immunocompromized patient and presents with fever, nasal mucosal ulceration, epistaxis, cough, facial pain, and headache. In addition, signs of invasion of the orbita may occur. Non-invasive *Aspergillus* sinusitis manifests as a sinusitis that does not respond to antibiotics in immunocompetent patients [49]. This non-invasive form will not be discussed here.

In the randomized comparative study of voriconazole and c-AmB [4], the response was 25% with voriconazole and 19% with c-AmB in patients with an invasive *Aspergillus* sinusitis.
In a number of open studies, the response of acute invasive aspergillosis was analyzed for separate anatomic sites [9, 27, 32, 33, 35, 50, 51]. In invasive sinusitis, response varied from 0% [9, 33] to 86% [27, 50, 51]. In this latter study, however, 11 of the 18 patients (61%) had relapsed, always in combination with a leukemia relapse and granulocytopenia. These studies cannot be properly compared with each other as some describe an intent-to-treat population whilst others refer to a subgroup of patients who had survived an initial period of treatment.

It is generally assumed that surgery makes a major contribution to the prognosis of invasive *Aspergillus* sinusitis. Surgical debridement is recommended to remove any necrotic tissue sustaining the growth of the *Aspergillus* species. In this area, however, no prospective studies have been conducted. In a retrospective case series in neutropenic patients, mortality following combined therapy (surgery and antifungal therapy; 8/10) was higher than in patients given only antifungal therapy (7/19). This was partly attributable to post operative bleeding in thrombopenia [52].
Note: In this historical series, the extent to which the thrombopenia had been adequately corrected is not clear.

Other considerations

Many experts recommend surgical treatment in combination with antifungal agents for invasive *Aspergillus* sinusitis [49, 53]. Despite the absence of studies, the committee considers this combined treatment to be useful. In pancytopenic patients, the risk of post-operative bleeding should be taken into consideration.
The choice of antifungal agents has not been specifically studied in this patient group. The subgroup of patients with sinusitis in the voriconazole trial [4] was very small. In the absence of further data, the committee has judged that, for *Aspergillus* sinusitis, there is no reason to deviate from the general recommendation that, based on the large randomized study by Herbrecht et al., invasive aspergillosis should be treated with voriconazole.

Cerebral aspergillosis

Cerebral aspergillosis is a common manifestation of disseminated aspergillosis. Its prognosis was poor, with mortality running to almost 100% until voriconazole became available [54-56]. In open case series of patients with invasive aspergillosis treated with voriconazole, the response in the subgroup with cerebral aspergillosis was 16% (3/19) [9], and 33% (4/12) [31], and 38% (3/8) in a small series treated with itraconazole [35]. In a retrospective survey of invasive aspergillosis, survival of patients with cerebral aspergillosis who were treated with c-AmB or itraconazole was only 9% (3/34) [56].
In a retrospective study of 81 patients with cerebral aspergillosis who were treated with voriconazole, the response was 35% (28/81), of whom 25% (7/28) recovered completely and 75% (21/28) recovered partially [57]. The aspergillosis-related mortality was 46% (37/81). In 31 of 81 patients, the treatment was combined with neurosurgery. Multivariate analysis showed neurosurgical intervention to be associated with improved survival (p=0.02).

Chronic pulmonary aspergillosis

Chronic aspergillosis is a generic term for a variety of diseases. In 2003, a new nomenclature for chronic aspergillosis was proposed: chronic cavitary pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis, and chronic necrotising pulmonary aspergillosis (also known as chronic invasive pulmonary aspergillosis). All patients described had an underlying lung disorder (COPD, emphysema, tuberculosis) but were not being treated with immunosuppressive drugs [58]. Treatment of the patients generally consisted of c-AmB, itraconazole or voriconazole, and the duration of treatment of these patients varied from several weeks to >10 years. The long term prognosis was poor.
In 3 of 4 patients, surgical resection led to complication and spread of the infection. In the only open prospective trial, 25 patients with subacute aspergillosis (duration of illness >1 month) or chronic pulmonary aspergillosis (illness >3 months) were treated with voriconazole (200 mg bid) [59]. There was only 1 complete recovery. At end of therapy, partial response had been achieved in 15/25 patients (60%).

Aspergilloma

An aspergilloma usually develops in an existing pulmonary cavity, e.g., following tuberculosis, or bronchiectasis. The major complication, hemoptysis, occurs in approximately 75% of the patients and is massive and life-threatening in 25%. Moreover, aspergilloma may develop into chronic necrotising pulmonary aspergillosis [53]. Consequently, treatment of both symptomatic and asymptomatic aspergilloma is held to be desirable. No randomized studies on treatment of aspergilloma have been conducted. Also, there is no international consensus as regards to its treatment or follow-up.
Surgery would appear to be the most appropriate treatment, but the mortality is high [60, 61]. Only retrospective studies on surgical treatment of aspergilloma have been published.
In 4 retrospective case series, a total of 144 patients (respectively 7, 24, 41 and 72) were described in whom an asperigilloma was resected [62-65]. In one study, itraconazole was added to the surgical treatment, from 2 weeks pre-operatively until 3 months post-operatively [62]. Postoperative complications were recorded in 24-42% of cases as well as a mortality of around 3% [62-65].
Other approaches such as bronchial artery embolization (BAE) or intracavitary administration of potassium iodide, sodium iodide, or antifungal agents have been described in case reports and retrospective studies in patients who were not eligible for surgery [66, 67]. CT-guided injection of

amphotericin B paste into the aspergilloma has been retrospectively analysed in 40 patients whereby a 1-year success rate of 50% was recorded [67].

Conclusions 2.2 – What is the optimal treatment of non-pulmonary forms of invasive aspergillosis?	
Conclusion 15	The optimal medicinal therapy and the value of surgical intervention in invasive *Aspergillus* sinusitis is not known.
Level 3	Herbrecht, 2002 [4]; Denning , 2002 [9]; Walsh, 1998 [27]; Maertens, 2004 [32]; Kartsonis, 2005 [33]; Stevens, 1997 [35]; Viollier, 1986 [51]; Iwen, 1997 [50], Denning, 1990 [52](C)
Conclusion 16	The optimal therapy for cerebral aspergillosis has never been the subject of prospective randomized studyies.
Level 3	Denning, 2002 [9]; Perfect, 2003 [31]; Stevens, 1997 [35](C)
Conclusion 17	Compared to historic controls, it is suggested that voriconazole is superior to c-AmB or itraconazole for the treatment of invasive cerebral aspergillosis.
Level 3	Schwartz, 2005 [57](C)
Conclusion 18	Compared to historic data, it is suggested that voriconazole results in reasonable treatment outcomes in sub-acute and chronic pulmonary aspergillosis
Level 3	Sambatakou, 2006 [59](C)
Conclusion 19	No comparative studies have been carried out on the treatment of aspergilloma. Surgical resection is considered to be the treatment of choice. It has not been demonstrated that intralesional administration of amphotericin B, potassium iodide or sodium iodide is equivalent or superior to surgery or bronchial artery embolisation in the treatment of aspergilloma.
Level 3	Gebitekin, 2005 [62]; Uflacker, 1983 [66]; Giron, 1998 [67]; Rumbak, 1996 [68]; Okubo, 2007[63]; Pratap, 2007 [64](C)

Recommendation 11	Despite the absence of specific studies into the treatment of invasive *Aspergillus* sinusitis, the committee favors the combination of surgery and antifungal therapy.

Recommendation 12	The committee considers voriconazole to be the drug of first choice for the medicinal treatment of *Aspergillus* sinusitis.

Recommendation 13	Despite the absence of randomized studies the committee considers voriconazole to be the drug of first choice for the treatment of cerebral aspergillosis.

Recommendation 14	Long-term treatment with voriconazole or another azole shown to be active in vitro (posaconazole or itraconazole) is recommended for subacute or chronic invasive aspergillosis.

Recommendation 15	Surgical resection is recommended for both symptomatic and asymptomatic aspergilloma.

Recommendation 16	Arterial embolisation and/or intralesional administration of c-AMB may be considered in inoperable patients with a symptomatic aspergilloma.

Chapter 3

Candidiasis

Introduction

Candida species cause both superficial and invasive infections. The superficial infections include oropharyngeal, oesophageal, vulvovaginal candidiasis and *Candida* dermatitis. This guideline is restricted to invasive candidiasis and oropharyngeal/oesophageal candidiasis. Untreated candidemia may result in a disseminated candidiasis and has a high mortality [69, 70]. Positive blood cultures taken via an intravascular catheter are also associated with a high mortality [71, 72]. Patients with a positive blood culture growing *Candida,* therefore, must always be treated with antifungal agents.

The epidemiology and incidence of invasive *Candida* infection has changed in recent decades. During a large scale surveillance study (>300 hospitals in the US from 1989 to 2000), Trick et al. found that the total incidence of candidemia within the ICU population had decreased [73]. Importantly, the incidence of candidemia due to *C. albicans* has fallen significantly in that period, while that of candidemia due to *C.* non-*albicans* has risen slightly. In particular, the role of *C. glabrata* candidemias has increased significantly.
Despite the virtual constancy of the absolute incidence of infection by non-*albicans* species, the decline of *C. albicans* incidence has consequenty brought about a shift in the relative incidence of species Thus, the chance that a patient with a candidemia is infected with a non-*albicans* species has doubled between 1989 and the year 2000. This changing epidemiology must be taken into account when making choices as regards the initial treatment of invasive candidiasis caused by an as yet not fully identified pathogen. In the Netherlands, the chance that a patient with candidemia has been infected with a *Candida* non-*albicans* species is around 50% [74]. Before 1994, this percentage lay between 25% [75] and 40% [76]. The main *C.* non-*albicans* species are *C. glabrata* and *C. parapsilosis*. *C. krusei* is inherently resistant to fluconazole, but is extremely rare (<1%), so that, in choosing an initial therapy, account need not be taken of this pathogen unless there are strong grounds for suspecting its involvement. *C. parapsilosis* most likely is less susceptible to the echinocandins, whereas 10-30% of *C. glabrata* display reduced susceptibility or resistance to fluconazole in vitro [77, 78].

To develop an optimal treatment recommendation for candidemia and acute disseminated candidiasis, the committee has defined the core questions posed below. Answering these questions has provided the theoretical framework for rational management.

3.1. What is the optimal treatment for candidemia and acute disseminated candidiasis?

a. What is the optimal initial treatment for unidentified *Candida* species of unknown susceptibility?
b. What is the optimal treatment for identified *Candida* species of known susceptibility?
c. What is the optimal treatment for candidemia and acute disseminated candidiasis in children?
d. What is the best method of catheter management?
e. Which diacnostics are required to diagnose hematogenous dissemination?
f. What is the optimal second-line therapy in the event of failure?
g. What is the value of adjunctive immunotherapy?

3.2. What is the optimal treatment for localised *Candida* infections?

a. Endophthalmitis
b. Candiduria
c. Oesophagitis
d. Peritonitis (Continuous Ambulatory Peritoneal Dialysis-related and surgical)

3.3. What is the optimal treatment of oropharyngeal candidiasis?

3.1. Treatment of candidemia and acute disseminated candidiasis

3.1.a. What is the optimal initial treatment for unidentified Candida species of unknown susceptibility?

Prospective randomized studies

In three prospective randomized studies, fluconazole (400 mg qd, loading dose 800 mg) was compared with c-AmB (0.5-0.6 mg/kg/d) in non-neutropenic patients with candidemia [79-81]. In these studies, no significant differences could be shown between the response to fluconazole and c-AmB. The response varied from 50-70% with fluconazole and 58-79% with c-AmB. In all three studies, significantly more toxicity was reported in the c-AmB arm.
In an open, prospective, randomized study, the combination of c-AmB (1.0-1.5 mg/kg every other day) plus 5-flucytosine (5-FC, 2.5 g tid) was compared with fluconazole (200 mg qd, loading dose 400 mg) in patients with candidemia or invasive candidiasis [82]. Response in the fluconazole arm was 67% vs. 69% in the c-AmB arm. Due to a lack of statistical power, no equivalence could be demonstrated.

A double-blind, randomized study has compared fluconazole (800 mg qd) combined with c-AmB (0.6-0.7 mg/kg/d) for the first 5 to 8 days, with fluconazole only (800 mg qd) combined with placebo in patients with candidemia [83]. The primary outcome parameter was time to failure (switch to other therapies, mortality, withdrawal from the study). The response on day 30 in the Kaplan-Meier time to failure analysis was 57% for fluconazole/placebo vs. 69% for fluconazole/c-AmB (p=0.08). Response at the last available study visit was 56% (60/107) vs. 69% (77/112, p=0.043). A disparity in persistently positive blood culture (fluconazole/placebo, 17%, vs. fluconazole/c-AmB, 6%; p=0.02) was also noted. The incidence of toxicity was found to be greater in the group with combined fluconazole/c-AmB (3% vs. 23%, p<0.001).
Note: In both arms of this study, fluconazole was administered in a dose of 800 mg qday [83]. The optimal dose of fluconazole as an initial treatment for candidemia (400 mg vs. 800 mg qd) has never been the subject of comparative studies. Based on the results from the fluconazole 800 mg qd monotherapy arm, there appears to be no convincing benefit to be gained from this higher dosage compared to the 400 mg qday fluconazole dose, as used in earlier studies [79-81].

In a large multicenter study, voriconazole (3 mg/kg bid i.v. or 200 mg bid orally, loading dose 6 mg/kg i.v. bid) was compared with c-AmB (0.7-1.0 mg/kg/d, during 4-7 days) followed by fluconazole (400 mg qd) in 370 non-neutropenic patients with candidemia [84]. The long term response at 12 weeks post treatment – the primary outcome measure in this study – was 41% in both study arms (p=0.96). Response at the last available study visit was 65% for voriconazole vs. 71% (p=0.25) in the c-AmB/fluconazole arm.
In a study published only as an abstract, itraconazole (200 mg i.v. od or 200 mg orally bid, loading dose 200 mg i.v. bid for 2 days) was compared with fluconazole (400 mg qd) in 197 non-neutropenic patients with candidemia [85]. The long term response at 12 weeks post treatment was 35% for itraconazole vs. 41% (p=0.41) for fluconazole. Statistically, the power of this study was insufficient to demonstrate equivalence, so that it could not be concluded that itraconazole is as effective as fluconazole in this indication.

Four comparative trials have been carried out using echinocandins in invasive candidiasis [86-88]. The first double-blind study compared caspofungin (50 mg qd, loading dose 70 mg qd) with c-AmB (0.6-0.7 mg/kg/d in non-neutropenic patients and 0.7-1.0 mg/kg/dag in neutropenic patients) in patients with candidemia or invasive candidiasis [86]. After at least 10 days, the treatment could be stepped down to oral fluconazole (400 mg qd). The response in the MITT population at end of treatment with the randomized i.v. medication (EOivT) was 73% (80/109) in the caspofungin arm and 62% (71/115, p=0.09) in the c-AmB arm. Only 24 neutropenic patients were included, with a response of 7/14 to caspofungin and 4/10 to c-AmB.
Anidulafungin (100 mg qd) was compared with fluconazole (400 mg qd) in 245 patients with candidemia and invasive candidiasis [87]. The response at end of treatment was 75.6% with anidulafungin vs. 60.2% with fluconazole (difference 15.42%, 95%CI: 3.85-26.99, p=0.009). Thus, anidulafungin was more effective than fluconazole. Remarkably, anidulafungin was more effective in the patients infected with *C. albicans* (success, 81% vs. 62%, p=0.015), than in those infected with

Candida non-*albicans* species (71% vs. 60%), despite the fact that all *C. albicans* isolates were found to be susceptible to fluconazole in vitro. The difference in mortality (anidulafungin 23%, fluconazole 31%) was not statistically significant (p=0.15). The greater efficacy of anidulafungin was observed in patients in all classes of APACHE II scores from 0 to 25, and therefore not related to disease severity [87].
Micafungin (100 mg qd) was compared with liposomal amphotericin B (3 mg/kg/d) for the treatment of invasive candidiasis [88]. The primary endpoint was the response in a subgroup of patients who had been treated successfully for at least 5 days. In this subgroup, the response was 89.6% (181/202) in the micafungin group vs. 89.5% (170/190) in the L-AmB group. In the more conventional analysis of the MITT population, the response at end of treatment was 74.1% (183/247) for micafungin vs. 69.6% (172/247) for L-AmB (p=0.27).
A 3-arm, randomized, double-blind study further compared micafungin in 2 different doses (100 mg qd and 150 mg qd) with caspofungin (50 mg qd, loading dose 70 mg) in 595 patients with candidemia or invasive candidiasis [89]. The response at EOivT was 76.4% for micafungin 100 mg qd, 71.4% for micafungin 150 mg qd and 72.3% for caspofungin. There were also no significant differences between the groups as regards response at end of total treatment and at 6 weeks post treatment.

Non-randomized studies

Fluconazole (200-600 mg qd) was compared to c-AmB (0.3-1.2 mg/kg/d) in a matched cohort study in neutropenic and non-neutropenic patients with candidemia [90]. The response was 73% (33/45) for fluconazole and 71% (32/45; p=0.78) for c-AmB. In patients who were neutropenic at start of treatment, the response was 64% in both groups. There was, however, significantly less nephrotoxicity and infusion-related toxicity in patients treated with fluconazole (9% vs. 67%, p<0.0001).
Fluconazole (median 200 mg qd) was compared with c-AmB in a non-randomized prospective study [91]. Thirty days after start of therapy, there appeared to be no difference in mortality between fluconazole and c-AmB (27% (18/67) vs. 31% (69/227), p=0.58).
Use of ABCD was reported in 88 immunocompromized patients with invasive candidiasis [92]. Response was 53%; 66% in 67 patients with candidemia and 14% in 21 patients with disseminated candidiasis.

Initial therapy in neutropenic patients

No randomized trials have been specificly conducted in neutropenic patients with candidemia or invasive candidiasis. Small numbers of neutropenic patients have, however, been included in several studies, but these studies are insufficiently powered to enable evidence-based judgement on the treatment of invasive candidiasis in neutropenic patients.

In the randomized study by Mora-Duarte et al., the response of patients who were neutropenic (neutrophil granulocytes <0.5 $x10^9$/l) at start of treatment was 7/14 (50%) for caspofungin vs. 4/10 (40%) for c-AmB [86]. For micafungin, this was 19/32 (59%) vs. 14/25 (56%) for L-AmB [88]. In the randomized study comparing micafungin and caspofungin, response among neutropenic patients was 18/22 (82%; micafungin 100 mg qd), 9/17 (53%; micafungin 150 mg qd), and 7/11 (64%; caspofungin) [89]. In an open retrospective study, the response in neutropenic patients with candidemia was 64% for both fluconazole and c-AmB [90].

The studies of empirical therapy in patients with neutropenia and fever also included patients who, in retrospect, were found to have blood cultures positive for *Candida* species on inclusion. The response in these patients was 8/11 (73%) with c-AmB vs. 9/11 (82%) with L-AmB [93], and in another study 8/12 (67%) with caspofungin vs. 5/10 (50%) with L-AmB [94].
In a retrospective case series, the efficacy of caspofungin was investigated in 27 neutropenic patients with invasive candidiasis [17]. The response was 63% (17/27): 58.3% (14/24) in patients undergoing primary therapy and 100% (3/3) in those on salvage therapy. In patients who had recovery of neutrophil granulocytes during treatment, the response was 77.8%, vs. 33.3% in patients with persistent neutropenia.
On the basis of these limited data, the outcomes of treatment in neutropenic patients appear not to be different from those in non-neutropenic patients.

Table 3.1. Antifungal therapy and response in randomized studies.

Study	Therapy	Patients (n)	Response at EOT	Response at latest visit	All cause mortality
Candidemia 1 [79]	Fluconazole 400 mg qd c-AmB 0.5- 0.6 mg/kg/d	103 103	74% 83%	70% 79%	33% 40%
Canadian [80]	Fluconazole 400 mg qd c-AmB 0.6 mg/kg/d	50 58		57% 62%	38% 34%
Anaissie [81]	Fluconazole 400 mg qd c-AmB 0.67 mg/kg/d	22 21	59% 71%		
Abele-Horn [82]	Fluconazole 200 mg qd c-AmB 1.0-1.5 mg/kg/d + 5-FC 3 dd 2.5 g	17 18	59% 61%		
Candidemia 2 [83]	Fluconazole (800 mg qd) c-AmB (0.7 mg/kg/d) + fluconazole (800 mg qd)	107 112		56% 69%	39% 40%
Itraconazole [85]	Itraconazole 200 mg qd iv of bid 200 mg po Fluconazole 400 mg qd	96 97	67% 69%		40% 40%
Candidemia 3 [84]	Voriconazole 3 mg/kg bid c-AmB 0.7-1.0 mg/kg/d → fluconazole 400 mg qd	248 122	70% 74%	65% 71%	36% 42%
Caspofungin [86]	Caspofungin 50 mg qd c-AmB 0.6-1.0 mg/kg/d	109 115	73%* 62%		34% 30%
Anidulafungin [87]	Anidulafungin 100 mg qd Fluconazole 400 mg qd	127 118	76%* 60%	56%° 44%°	
Micafungin [88]	Micafungin 100 mg qd L-AmB 3 mg/kg/d	247 247	74% 70%		
Micafungin/Caspofungin [89]	Micafungin 100 mg qd Micafungin 150 mg qd Caspofungin 50 mg qd	199 202 192	75% (76%*) 68% (71%*) 70% (72%*)	47%° 45%° 43%°	29% 33% 26%

* response at end of *intravenous* therapy ° response after 6 weeks of follow-up

Conclusions 3.1.a. – Treatment of candidemia due to unidentified *Candida* species of unknown susceptibility	
Conclusion 1	Fluconazole is as effective as c-AmB for the treatment of candidemia in non-neutropenic patients.
Level 1	Rex, 1994 [79](A2); Philips, 1997 [80](A2); Anaissie, 1996 [81](B).
Conclusion 2	It has not been demonstrated that fluconazole and the combination c-AmB/5-FC are equivalent in the treatment of candidemia and invasive candidiasis
Level 3	Abele-Horn, 1996 [82](B)
Conclusion 3	Combination therapy with fluconazole and c-AmB appear to be more effective than fluconazole and placebo for the treatment of patients with candidemia
Level 3	Rex, 2003 [83](B)
Conclusion 4	It has not been demonstrated that fluconazole 800 mg qd is more effective than fluconazole 400 mg qd
Level 3	Rex, 1994 [79](B); Rex, 2003 [83](B)
Conclusion 5	In non-neutropenic patients with candidemia, voriconazole is as effective as c-AmB followed by fluconazole
Level 3	Kullberg, 2005 [84](A2)
Conclusion 6	It has not been demonstrated that itraconazole is as effective as fluconazole for the treatment of non-neutropenic patients with candidemia.
Level 3	Tuil, 2003 [85](B)
Conclusion 7	Caspofungin is as effective as c-AmB in patients with invasive candidiasis
Level 3	Mora-Duarte, 2002 [86](A2)
Conclusion 8	Anidulafungin is more effective than fluconazole for the treatment of non-neutropenic patients with invasive candidiasis.
Level 3	Reboli, 2007 [87](A2)
Conclusion 9	Micafungin is as effective as L-AmB for the treatment of patients with invasive candidiasis
Level 3	Kuse, 2007 [88](A2)
Conclusion 10	Micafungin (100 mg qd or 150 mg qd) is as effective as caspofungin for the treatment of patients with invasive candidiasis.
Level 3	Pappas, 2007 [89](A2)
Conclusion 11	It has not been demonstrated that fluconazole and c-AmB are equivalent in neutropenic patients with candidemia.
Level 3	Anaissie, 1996 [90](B).
Conclusion 12	It has not been demonstrated that ABCD is as effective as other antifungal therapies for the treatment of invasive candidiasis.
Level 3	Noskin, 1998 [92](C).
Conclusion 13	Little data is available with regard to the optimal choice of therapy for the treatment of invasive candidiasis in neutropenic patients; there is no evidence that the choice of agent for these patients should be other than that for non-neutropenic patients.
Level 4	(D)

Other considerations

The initial choice of therapy for candidemia is dictated by the risk of failure and of complications posed by non-susceptible *Candida* species. This risk partly depends upon the local epidemiology and the severity of the patient's illness.
Fluconazole and the broadspectrum antifungal agents (voriconazole, caspofungin, anidulafungin, micafungin and liposomal amphotericin B) are, on the basis of comparative studies of sufficient quality, considered to be equivalent. An exception to this is the study which, independently of the resistance spectrum and the severity of the illness, demonstrated that anidulafungin was more effective than fluconazole [87]. The committee considers the advantage of anidulafungin over fluconazole potentially relevant and, based partly on these data, gives preference to an echinocandin in seriously ill or hemodynamically unstable patients.
The committee considers the availability of evidence from additional studies desirable before recommending anidulafungin or other echinocandins as replacements of fluconazole as drugs of first choice for *all* patient groups with candidemia. Furthermore, more information is needed concerning the

relative efficacy of the other echinocandins, caspofungin and micafungin, compared to anidulafungin and fluconazole.
In an animal model, a possible relationship between micafungin and the development of hepatocellular tumors was reported. For this reason, the EMEA licensed micafungin for use only when other antifungal agents have not been found appropriate. For the time being, therefore, the committee sees no place for micafungin in antifungal therapy.
Based on the findings above, the committee considers all other above-mentioned drugs to be eligible for the initial treatment of candidemia. In this respect, the following considerations may be weighed: the risk of resistance and the consequent possibility of failure (fluconazole), few interactions and contra-indications (echinocandins), oral formulation and good penetration into the central nervous system and urine (fluconazole and voriconazole). In view of its high cost and nephrotoxicity, the committee does not consider the lipid formulations of amphotericin B to be a drug of choice.

In the view of the committee, conventional amphotericin B no longer has a place in the treatment of candidemia in adults, since, based on comparative studies, there are at least equally effective alternatives with significantly less toxicity. Based on their toxicity profile, combination therapy comprising c-AmB with fluconazole or sequential therapy with c-AmB followed by fluconazole are not preferred strategies, despite the possible greater efficacy of the combination c-AmB/fluconazole compared to fluconazole monotherapy described in one study.

Changing epidemiology with an increasing incidence of non-albicans *Candida* species raises the question whether fluconazole is still suitable in all situations for the initial treatment of unidentified *Candida* species. The committee points out that, statistically, none of the randomized studies had sufficient power to answer this question as to equivalence of fluconazole and broadspectrum drugs in specific non-albicans species.

For the choice of initial therapy for as yet unidentified *Candida* species, therefore, the committee has included the *Candida* epidemiology in the specific patient groups, the severity of the patient's illness and the consequent risk of mortality in the event of an erroneous initial choice in its considerations.
In seriously ill or unstable patients with a candidemia, the risk of mortality and complications due to failure of fluconazole caused by a *Candida* species that is less susceptible to fluconazole is considered to be too high. Also, the greater efficacy of anidulafungin compared to fluconazole [87] is held to be of potential importance, especially in this severely-ill patient group. In this specific group, an echinocandin is the first choice until the species and its susceptibility have been determined. Eligible drugs are caspofungin or anidulafungin. The contra-indication of the intravenous form of voriconazole when creatinine clearance is <50 ml/min and the possible interactions of voriconazole with other drugs form practical obstacles to choosing voriconazole, whilst the poorer penetration of echinocandins into urine and the CNS have to be taken into account in infections in these specific locations.

In addition, patients who have recently been pretreated with fluconazole should recieve initial treatment with an echinocandin (anidulafungin or caspofungin), until the species and its susceptibility have been determined.

In hemodynamically stable patients with uncomplicated candidemia who have not been pretreated (prophylactically or therapeutically) with an azole, the risk of failure on fluconazole is considered to be relatively low. In these patients, fluconazole is appropriate as an initial therapy. The committee points out that all studies with fluconazole were conducted using a dosage of 400mg qd (loading dose 800mg) whilst the Dutch package insert text advises a lower loading and maintenance dose, which the committee considers to be too low.

The committee is of the opinion that the initial choice of an echinocandin can be followed by a step-down therapy as soon as the patient is stable, and the *Candida* species and susceptibility are known. These choices are discussed later in 3.1.b.

As to initial therapy in neutropenic patients who have not undergone pretreatment with an azole, no consensus was reached by the committee on the choice between fluconazole and a broadspectrum drug. In this, the local epidemiology of *Candida* species and the stability of the patient form an important guideline. A major advantage of echinocandins as a primary therapy is their more favourable adverse effects and interaction profile. Unlike caspofungin, anidulafungin is not licensed for the treatment of candidemia in neutropenic patients. The committee notes that, statistically, neither the

investigation into caspofungin nor that into anidulafungin [86] [95] had sufficient power to show equivalence with the use of the older fungistatic agents in neutropenic patients, and the committee considers it likely that both drugs are equally effective in neutropenic patients.

Recommendation 1	In seriously-ill or unstable patients with a candidemia, echinocandins (anidulafungin (loading dose 200mg, followed by 100mg qd) or caspofungin (loading dose 70mg, followed by 50mg qd) are drugs of first choice.

Recommendation 2	Patients who have recently been pretreated with fluconazole should initially be treated with a broadspectrum drug such as anidulafungin (loading dose 200mg, followed by 100mg qd) or caspofungin (loading dose 70mg, followed by 50mg qd), until the species and its susceptibility have been determined.

Recommendation 3	For hemodynamically stable patients with an uncomplicated candidemia who have not been pretreated (prophylactically or therapeutically) with a azole, fluconazole (loading dose 800mg, followed by 400mg qd) is the preferred initial therapy.

Recommendation 4	In neutropenic patients with candidemia who have not been pretreated with azoles, a choice may be made between an azole (fluconazole, loading dose 800mg, followed by 400mg qd, or voriconazole, loading dose bid 6 mg/kg, followed by bid 3 mg/kg) or an echinocandin (caspofungin, loading dose 70mg, followed by 50mg qd, or anidulafungin (loading dose 200mg, followed by 100mg qd). In neutropenic patients who have been pretreated with an azole or are infected with *C. glabrata* or *C. krusei,* an echinocandin shoul be prescribed.

Recommendation 5	In stable patients, transition to fluconazole may be made, following identification of the *Candida* species as a fluconazole-susceptible strain.

Table 3.2. Recommended adult dose of antifungal agents for candidemia*

Antifungal agent	Loading dose	Maintenance dose
Fluconazole	800 mg iv/po	400mg /d iv/po
Voriconazole	bid 6 mg/kg iv or bid 400 mg po	3 mg/kg bid iv or 200 mg bid po
Liposomal AmB	-	3 mg/kg/d
Caspofungin	70 mg	50 mg qd, > 80kg: 70 mg qd
Anidulafungin	200 mg	100 mg qd

* The dosages in this table are specific for invasive candidiasis and candidemia; for other mycoses, different dosages may apply.

3.1.b. What is the optimal therapy for speciated *Candida* species of known susceptibility?

In general, data on the treatment of the individual *Candida* species and their susceptibility can be inferred from the randomized studies discussed earlier. Even for the treatment of *C. albicans* with a normal susceptibility pattern, however, these studies have insufficient statistical power to allow a formal judgement with regard to equivalence of the regimens studied. An exception to this is the comparative study of anidulafungin and fluconazole, in which anidulafungin was more effective than fluconazole in the group of patients with a fluconazole-susceptible *C. albicans* infection [87]. Similarly, none of the studies had sufficient statistical power to enable a judgement on the optimal treatment of *C. glabrata* infection.

C. albicans and other fluconazole susceptible strains

Taking the above restriction into account, the committee does not consider any of the drugs to be superior in the treatment of susceptible *Candida* strains. The committee considers the reported advantage of anidulafungin compared to fluconazole [87] potentially relevant, but is of the opinion that evidence from additional studies would be desirable before recommending echinocandins as drugs of first choice for *all* patients with *C. albicans* candidemia. On the basis of costs and its adverse effects profile, therefore, fluconazole is currently considered to be the drug of first choice in hemodynamically stable patients.

C. krusei and C. glabrata

C. krusei is usually inherently resistant to fluconazole. *C. glabrata* has a variable susceptibility to fluconazole; in a recent study, 69% of the *C. glabrata* strains were susceptible to fluconazole [96]. Although the in-vitro activity of voriconazole against *C. glabrata* is usually greater than that of fluconazole, 10% of the *C. glabrata* strains in the above-mentioned study were found to be resistant to voriconazole [96]. In 6 therapy studies of a total of 249 patients, *C. glabrata* had the highest average MIC value and the lowest success percentage with voriconazole (55%) [97]. In the light of the current availability of other classes of antifungals, the echinocandins in particular, the committee gives preference to an echinocandin for the treatment of *C. glabrata* and *C. krusei*, even in the case of in-vitro fluconazole susceptible strains. For oral treatment, voriconazole is preferred to fluconazole. In individual patients, fluconazole may be considered, if strict clinical and microbiological monitoring is carried out.

Candida parapsilosis and echinocandins

C. parapsilosis is generally less susceptible to echinocandins [86] than the other *Candida* strains. This appears to be a class effect, applying to all 3 echinocandins. Although the caspofungin vs. c-AmB study did not report any significant difference in treatment outcome between caspofungin and c-AmB in *C. parapsilosis* infected patients, this study has insufficient statistical power to demonstrate equivalence. Although *C. parapsilosis* accounted for only 19.8% of the infections in the caspofungin arm of this study, 5 of the 9 patients treated with caspofungin who had persistently positive blood cultures were infected with this pathogen. Similarly, in the comparative study of micafungin and caspofungin [89], 16 of 31 of the patients with persistently positive blood cultures were infected with *C. parapsilosis*. Based on these considerations, the committee gives preference to therapy with fluconazole in *C. parapsilosis* infections, even if the patient currently is being treated with an echinocandin.

Step down

In patients whose clinical and microbiological reaction to intravenous therapy is favourable, continuation of treatment with oral antifungal agents is feasible. In patients initially treated with an echinocandin, therapy may be continued with an orally administered azole. Although no studies to this effect have been conducted, the committee considers it acceptable – in hemodynamically stable patients infected with azole-susceptible *Candida species* (with the exception of *C. glabrata* and *C. krusei*) whose blood cultures have become negative – that treatment be continued using oral fluconazole or voriconazole.

Duration of therapy

The duration of therapy has never been investigated in prospective comparative studies. It may be assumed that in candidemia without proven metastatic foci, treatment lasting 14 days after the last positive blood culture is adequate in non-neutropenic patients who have responded well to therapy [79, 83, 84, 86, 98]. A retrospective study in 172 patients with candidemia reported that a short treatment of patients with candidemia was not associated with more complications than therapy lasting 2 weeks or longer [99]. Although there is no direct evidence, it is assumed that in neutropenic patients demonstrating favourable clinical response, treatment is desirable for up to 14 days after the last positive blood culture and 14 days following resolution of the neutropenia. In acute disseminated candidiasis, the treatment depends upon the clearing up of the metastatic foci. In general, a duration of treatment from 6 weeks to 6 months is necessary in those cases. Alongside surgical intervention, lengthy continuation of antifungal therapy is sometimes necessary in *Candida* endocarditis.

Conclusions 3.1.b. Therapy in identified *Candida* species of known susceptibility	
Conclusion 14	No randomized studies have been conducted that are of sufficient quality to support the choice of a specific antifungal agent for each individual *Candida* species.
Level 4	
Conclusion 15	*C. krusei* is usually resistant to fluconazole
Level 3	Pfaller, 2007 [96](B)
Conclusion 16	*C. glabrata* is generally less susceptible to fluconazole and voriconazole than the other *Candida* species.
Level 3	Pfaller, 2007 [96](C), Pfaller, 2006 [97](C).
Conclusion 17	Echinocandins are generally less active against *C. parapsilosis* and are possibly less effective against *C. parapsilosis*.
Level 3	Mora-Duarte, 2002 [86](C); Pappas, 2007 [89](C); Reboli, 2007 [87](C)
Conclusion 18	In patients demonstrating a favourable clinical and microbiological response to intravenous therapy, treatment may be continued using oral antifungal agents
Level 4	Claessen et al., unpublished data (D)
Conclusion 19	Optimal duration of therapy has not been clearly established. Although there is no direct evidence for this, clinical experience would appear to justify a treatment duration of 14 days after the last positive blood culture, unless there are proven metastatic foci.
Level 4	Pappas, 2004 [98]; Rex, 1994 [79]; Mora-Duarte, 2002 [86]; Kullberg, 2005 [84]; Rex, 2003 [83]; Oude Lashof, 2003 [99](C)

Recommendation 6	In hemodynamically stable patients who are not severely ill, fluconazole (loading dose 800mg, followed by 400 mg qd) is preferred for the treatment of *Candida albicans* candidemia.

Recommendation 7	Fluconazole (loading dose 800mg, followed by 400 mg qd) is preferred for the treatment of *Candida parapsilosis* candidemia.

Recommendation 8	An echinocandin (caspofungin (loading dose 70mg, followed by 50mg qd) or anidulafungin (loading dose 200mg, followed by 100mg qd) is preferred for the treatment of *Candida krusei* candidemia. Voriconazole or LFAB may be used as an alternative.

Recommendation 9	An echinocandin (caspofungin (loading dose 70mg, followed by 50mg qd) or anidulafungin (loading dose 200mg, followed by 100mg qd) is preferred for the treatment of *Candida glabrata* candidemia. LFAB can be used as an alternative.

Recommendation 10	In hemodynamically stable patients who are not seriously ill, fluconazole (loading dose 800mg, followed by 400 mg qd) is preferred for the treatment of candidemia caused by other fluconazole susceptible Candida species.

Recommendation 11	Non-neutropenic patients with an uncomplicated candidemia should be treated for up to 14 days after the last positive blood culture.

Recommendation 12	Neutropenic patients with a candidemia should be treated for up to 14 days after the last positive blood culture and for 14 days following after of the neutropenia.

Recommendation 13	Treatment in acute disseminated candidiasis depends on clinical and radiological findings and usually lasts from weeks to months. Where there are proven metastatic foci, the duration of therapy is at least 6 weeks.

3.1.c. What can be considered to be optimal catheter management?

A large retrospective analysis relating to the source of candidemia [100] suggested that the gut is a major portal of entry for *Candida,* and that there is little evidence pointing towards the skin or intravascular catheters as the source. Even if an intravascular catheter is not the primary focus of candidemia, it may be secondarily infected and subsequently lead to persistent candidemia and the formation of metastatic foci. Although the scarce published data are not unequivocal, in a retrospective, non-randomized study it appeared that removal of all intravascular catheters did shorten the duration of candidemia [101]. In this study, it appeared that replacement of a central venous catheter at the same site and in one session using a guidewire was associated with an unfavourable prognosis equal to that of not replacing the catheter. As regards mortality, an extensive review of retrospective studies into the effect of removing intravascular catheters in candidemia did not demonstrate any benefits of removal of catheters [102]; however, in a recent prospective comparative trial of micafungin and caspofungin [89], the success percentage (299/384; 78%) among patients in whom the catheter had been removed or replaced was greater than that among those in whom the catheter was left in place (91/144; 63%; p=0.001).

No studies have been conducted as to the optimal interval between removal of an intra–vascular catheter and the insertion of a new catheter. In view of the time involved with biofilm formation on a new catheter and the fact that the new catheter is inserted during antifungal therapy, the committee is of the opinion that there are insufficient grounds for observing a minimum interval before inserting a new catheter.

Other considerations

The removal and replacement of an intravascular catheter are not without risk, especially in patients who are thrombopenic or dependent on vasopressor drugs. The risks of leaving the catheter in place must therefore be weighed against those involved with replacement. Despite the absence of randomized studies, the committee considers the evidence that catheters remaining in place are associated with increased morbidity and mortality to be so compelling that it recommends removal or replacement of all intravascular catheters (central, peripheral and arterial) whenever logistically feasible. The committee wishes to emphsize that the primary consideration here is whether or not an intravascular catheter is still indicated. A new catheter should be inserted at a different site; catheter exchange using a guidewire appears to be inadequate.

Conclusions 3.1.c. – Catheter management	
Conclusion 20	Although intravascular catheters have not often been proven to be the primary source of candidemia, their removal appears to shorten the duration of candidemia.
Level 2	Rex, 1995 [101] , Pappas, 2007 [89](B)
Conclusion 21	Replacement of an intravascular catheter at the same site and using a guidewire has no demonstrably favourable effect on the duration of candidemia
Level 3	Rex, 1995 [101](B)
Conclusion 22	There are insufficient grounds for delaying the insertion of a new catheter following the removal of an intravascular catheter.
Level 4	

Recommendation 14	In patients with candidemia, all intravascular catheters (central, peripheral and arterial) should be removed or replaced whenever logistically possible.

3.1.d. Is investigation of secondary matastatic foci required in patients with candidemia?

There has been little prospective research into the incidence of the development of secondary metastatic foci in candidemia (acute disseminated candidiasis). It is assumed that *Candida* species cause dissemination relatively frequently. The most common metastatic foci are endophthalmitis and chorioretinitis.
In several studies, the incidence of *Candida* endophthalmitis or chorioretinitis was between 4 and 29 % [103-107]. In a prospective study in 370 patients with candidemia who were followed ophthalmologically, abnormal in fundo findings were noted in 16%; in 11% the anomalies were probably *Candida* related [107]. For many of the patients with ocular candidiasis (chorioretinitis or endophthalmitis), a longer duration of therapy is required than the standard treatment of uncomplicated candidemia, i.e., 14 days subsequent to the last positive blood culture. For this reason, these patients need to be identified. Prospective investigation shows that in candidemia, retinal lesions sometimes only develop in the course of 1-2 weeks [107]. The committee is of the opinion that fundoscopic examination of every patient is desirable before the duration of therapy is decided upon, but that this examination yields the most information when conducted shortly before the proposed end of therapy. Treatment of ocular candidiasis is described in chapter 3.2.

Frequently occurring manifestations of dissemination are spondylodiscitis, osteomyelitis [108], pulmonary metastatic foci [109] and renal abscesses [110]. Intravascular foci, such as endocarditis, an infected thrombus (at the site of an intravascular catheter or elsewhere) or a mycotic aneurysm may develop. In patients with candidemia, there appears to be a clear link between persistently positive blood cultures and the presence of an infected intravascular catheter or other intravascular foci. Specific diagnostic approaches to metastatic foci include echography, CT, MRI or nuclear techniques such as FDG-PET or leukocyte scanning. The FDG-PET-scan appears to be the most sensitive for this purpose [109].

The committee is of the opinion that, following removal of intravascular catheters, persistently positive blood cultures despite antifungal therapy ought to give rise to more detailed examination targeted at intravascular foci. Investigation aimed at metastatic foci in other organs should only be conducted on clinician indication or on the basis of positive deep tissue cultures. In the case of persistently positive blood cultures in children, it should be noted that the kidney is relatively often found to be the focus [111].

Conclusions 3.1.d. – Investigation of secondary metastatic foci in candidemia	
Conclusion 23	Ocular metastatic foci are found relatively often in candidemia.
Level 2	Donahue, 1994 [105], Rodriguez-Adrian, 2003 [106], Oude Lashof [107](B)
Conclusion 24	In candidemia, ocular metastatic foci sometimes only become manifest in the course of 1-2 weeks.
Level 3	[107] (B)
Conclusion 25	Ocular metastatic foci demand a longer duration of therapy than is the case in uncomplicated candidemia.
Level 4	(D)
Conclusion 26	In persistent candidemia, a persistent intravascular focus is often present.
Level 4	(D)
Conclusion 27	In children with persistent candidemia, the kidney should be investigated as a possible persistent focus.
Level 3	Zaoutis, 2004 [111] (C)

Recommendation 15	Fundoscopy is recommended in every patient with candidemia prior to discontinuation of the antifungal treatment.

Recommendation 16	In the event of persistently positive blood cultures with *Candida,* the existence of an underlying intravascular focus should be investigated.

3.1.e. What is the second-line therapy for invasive candidiasis in the event of failure of primary treatment?

In some patients with invasive candidiasis, first-line therapy fails. Second-line or salvage therapy has been investigated in several non-comparative studies. When failure occurs, a distinction must be made between patients who failed on first-line therapy and those who were merely intolerant of the first-line therapy and who have a considerably better prognosis than the first-mentioned group.

In a retrospective analysis, salvage therapy with ABLC was described in patients refractory to or intolerant of primary therapy [27]. In the subgroup of patients with invasive candidiasis the response was 71% (65/91). The proportion of these patients that was only intolerant of the primary treatment is not known.

Voriconazole has been described as a salvage therapy in invasive candidiasis [31, 112]. More than 90% of the patients had an infection that had proven refractory to earlier treatment. In patients with an invasive candidiasis the response was 56%; the response of patients previously exposed to azoles was 58% [112].

Salvage studies have been reported using both caspofungin and micafungin. In the caspofungin salvage study, the response in patients with invasive candidiasis was 60% (9/15); 14 of the patients had an infection that was refractory to earlier treatment [113]. In an open label study with micafungin, patients were described who had been given salvage therapy with micafungin, either alone or in combination with the antifungal drug first prescribed [114]. In patients on salvage therapy who had been given micafungin for at least 5 days, the response was 76% (22/29) with micafungin alone, and 72% (18/25) with the combination of micafungin and other antifungal therapy. The results for the total (modified intent to treat) population were not reported; usually these are considerably lower than the outcomes for the subgroup of patients treated successfully for at least 5 days.

Conclusions 3.1.e. – Second-line therapy for invasive candidiasis in the event of failure of the primary treatment	
Conclusion 28	It has not been demonstrated that ABLC is equivalent to or more effective than other forms of salvage therapy in the treatment of invasive candidiasis
Level 3	Walsh, 1998 [27](C)
Conclusion 29	It has not been demonstrated that voriconazole is equivalent to or more effective than other forms of salvage therapy in the treatment of invasive candidiasis
Level 3	Perfect, 2003 [31] Ostrosky-Zeichner, 2003 [112](C)
Conclusion 30	It has not been demonstrated that caspofungin is equivalent to or more effective than other forms of salvage therapy in the treatment of invasive candidiasis
Level 3	Kartsonis, 2004 [113](C)
Conclusion 31	It has not been demonstrated that micafungin alone or in combination with another antifungal drug is equivalent to or more effective than other forms of salvage therapy in the treatment of invasive candidiasis
Level 3	Ostrosky-Zeichner, 2005 [114](C)

Recommendation 17	In the event of failure of first-line therapy, second-line therapy can be instituted, once sources of persistent infection have been ruled out, using an echinocandin, LFAB or voriconazole and taking into account the treatment recommendations for the individual *Candida* species.

3.1.f. What is the value of adjunctive immunotherapy?

In 51 non-neutropenic patients with candidemia or invasive candidiasis, a small placebo-controlled study has investigated whether addition of recombinant human granulocyte-colony stimulating factor (rhG-CSF) to fluconazole is of value. Resolution of the infection at day 28 was 67% (14/21) in the rhG-CSF-group vs. 50% (15/30) in the placebo group. Patients treated with rGCSF cleared the candidiasis more rapidly (median 14 days) than the placebo group (median 21 days, HR 1.88; 95%CI 0.9-3.92). A leukocyte elevation to at least 15 x 10^9/l during therapy was associated with a greater chance of more rapid clearance of the infection (HR 2.77; 95%CI 1.3-5.92) and reduced mortality (HR 0.09; 95%CI 0.01-0.66) [115].

Efungumab, a recombinant monoclonal antibody against Heat Shock Protein 90, was compared with placebo during an open placebo-controlled study in 139 patients with candidemia or invasive candidiasis. Patients were treated with a lipid formulation of amphotericin B (LFAB; ABLC of L-AmB) and were given randomized and blinded adjuvant therapy with efungumab (bid 1 mg/kg, during 5 days) or placebo [116].
The primary response at day 10 of treatment in evaluable patients was reported as 47/56 (84%) in the efungumab arm vs. 29/61 (48%, p<0.01) in the placebo arm. Overall mortality at day 33 was 16% in the efungumab arm and 21% in the placebo arm (p=0.47).
This study is difficult to interpret for a variety of reasons. Firstly, patients were included who had been treated with another antifungal drug prior to randomization, as well as those with only a positive culture from the tip of an intravascular catheter or a surgical wound infection. Secondly, no intent-to-treat analysis was presented, data was not verified by an independent Data Review Committee and, in the efungumab arm, 3 patients were excluded from analysis – two of whom subsequently died. Furthermore, it is remarkable that almost 40% of the patients in the efungumab arm already had negative cultures at randomization compared to about 20% in the placebo arm, and that approximately 50% of patients in the LFAB/placebo arm were said to have persistently positive cultures for more than 21 days, a finding that has never been reported in any other candidiasis trial. This is remarkable in the light of the fact that LFAB are not licensed for primary treatment of invasive candidiasis, but were nevertheless used as such in this study, with a high reported failure percentage.
Finally, further analysis of the published data shows that there was higher mortality due to non-*Candida*-related causes in the efungumab arm (9/59, 15% vs. 2/61, 3%; p=0.02), which was not mentioned in the publication. The EMEA has not yet licensed efungumab.

Conclusions 3.1.f. – Adjunctive immunotherapy in candidemia	
Conclusion 32	In a study with insufficient statistical power, it was not proven that addition of rhG-CSF is of value in the treatment of patients with candidemia or invasive candidiasis
Level 3	Kullberg, 1998 [115](B)
Conclusion 33	It has not been shown that the combination of an antifungal agent with efungumab is as effective as or superior to monotherapy with an antifungal agent in patients with candidemia or invasive candidiasis
Level 3	Pachl, 2006 [116](B)

Recommendation 18	There is insufficient evidence upon which to base the routine use of adjunctive immunotherapy in invasive candidiasis.

3.1.g. What is the optimal treatment of candidemia and acute disseminated candidiasis in children?

In children with invasive candidiasis or candidemia, only one prospective randomized study has been conducted. The remaining data is based on open-label or retrospective studies.

Comparative studies

In 98 children (<15 years) with candidemia or invasive candidiasis, a double-blind, randomized study was conducted with micafungin (2 mg/kg/d) vs. L-AmB (3 mg/kg/d) [117]. The response at end of therapy was 73% in the micafungin arm vs. 76% (p=0.73) in the L-AmB arm. In pre-terms and children younger than 2 years, too, there was no difference between the two treatment arms. No information was given on adverse effects.

In a small open-label, randomized study in neonates, fluconazole (loading dose 10 mg/kg, followed by 5 mg/kg/d i.v. or orally) was compared with c-AmB (1 mg/kg/d) [118]. Where CSF (cerebrospinal fluid) culture was positive, 5-FC was added. Mortality was 33% (4/12) in the fluconazole group vs. 45% (5/11, p=0.55) in the c-AmB/5-FC group. Hepatotoxicity developed more often In patients treated with c-AmB than in the fluconazole group.
A prospective, open-label comparative study of fluconazole (10 mg/kg/d) and itraconazole suspension (10 mg/kg/d) in 43 children with candidemia showed equivalent results; a response of 82% (18/22) vs. 81% (17/21) [119].

In a study by Linder et al., two lipid formulations of amphotericin B, L-AmB (n=6) and ABCD (n=16), were compared with c-AmB (n=34) in 56 pre-term babies with candidemia [120]. The 3 groups were not comparable at the start of the study: patients in de ABCD arm had a significantly lower birth weight, had undergone a longer period of ventilation prior to start of therapy and had a poorer renal function compared to the 2 other groups. Also, the neonates in the LFAB arm were younger than those in the c-AmB group. The response was 67.6% for c-AmB, 83.3% for L-AmB and 57.1% for ABCD (not significant).

Open studies

In a large prospective study in more than 4500 neonates with 'extremely low birth weight' (<1000 g) there were 320 cases of invasive candidiasis (7%), of whom 27 had meningitis [121]. Almost all patients were treated with an AmB preparation; in this study, experience with fluconazole as the only therapy was limited to just 4 cases. Some of the patients were treated with LFAB, but the response to the various antifungal agents was not reported.

L-AmB appeared to be safe and effective at dosages from 2.5 to 7 mg/kg/d in 24 very low birth weight pre-terms and in 41 neonates with candidemia [122, 123]. ABLC showed a response of 81% (22/27) in a prospective, open-label study in pediatric patients with invasive candidiasis [19]. In 2 retrospective case series with ABLC a response of 37.4% (65/174) tot 58% (11/19) was reported in children with invasive candidiasis [20, 24] .

Fluconazole was assessed during an open study in 40 children with candidemia. Of the 40 children, 34 were treated using a fluconazole monotherapy and 6 using combination therapy consisting of fluconazole and c-AmB; the response was 70% (28/40) [124].

Conclusions 3.1.g – Treatment of candidemia and acute disseminated candidiasis in children

Conclusion 34	Micafungin appears to be as effective as L-AmB in the treatment of invasive candidiasis in children.
Level 3	Queiroz-Telles, 2008 [117](B)
Conclusion 35	It has not been shown that fluconazole and c-AmB are equivalent in the treatment of candidemia in neonates.
Level 3	Driessen, 1996 [118](B); Huttova, 1998 [124](C)
Conclusion 36	It has not been shown that fluconazole and itraconazole are equivalent in the treatment of children with candidemia
Level 3	Mondal, 2004 [119](B)

Conclusion 37	It has not been shown that LFAB (L-AmB, ABLC or ABCD) are equivalent or superior to c-AmB in the treatment of candidemia in neonates and children
Level 3	Linder, 2003 [120](B) Walsh, 1999 [19](C), Wiley, 2005 [24](C), Herbrecht, 2001 [20](C), Juster-Reicher, 2000, 2003[122, 123](C)

Other considerations

As no studies of sufficient scope and quality have been carried out in children with candidemia or invasive candidiasis, the committee bases its therapy recommendations for children on those formulated for adults. The committee hereby notes that anidulafungin and caspofungin are not (yet) licensed for use in children* and voriconazole is licensed only for children above 2 years of age. Moreover, it should be remembered that *C. parapsilosis,* against which the echinocandins are less active, occurs more frequently in neonates. Keeping these factors in mind, use of echinocandins as a second choice may be considered in individual cases.
Micafungin has been licensed by the EMEA for children <16 years, but only when the administration of other antifungal agents is deemed inappropriate. This is based on the link with the development of hepatocellular tumours described from animal research. As yet, therefore, the committee sees no place for micafungin in antifungal therapy.
In the literature, there is little mention of the use of fluconazole in neonatal candidiasis. Nevertheless, based on clinical experience, the committee considers fluconazole to be an option in this condition. As an alternative, an amphotericin B preparation (c-AmB or LFAB) can be used in these patients.

Recommendation 19	For children with an uncomplicated candidemia who have not been pre-treated (either prophylactically or therapeutically) with an azole, fluconazole (loading dose 12 mg/kg, followed by 6 mg/kg/d) is preferred as the initial therapy. In pre-term neonates c-AmB (1.0 mg/kg/d) is eligible.

Recommendation 20	Children who have recently been pre-treated with fluconazole should initially be treated with a broadspectrum drug such as an amphotericin B preparation (c-AmB 1.0 mg/kg/d in neonates <3 months or LFAB 3 mg/kg/d) or voriconazole (7 mg/kg bid i.v.), until the species and susceptibility are known.

Recommendation 21	In unstable children with a candidemia, a broadspectrum antifungal agent should be the first choice until the species and its susceptibility are determined. Preference in this event is given to LFAB (3 mg/kg/d). In pre-term neonates c-AmB (1.0 mg/kg/d) is applicable.

Recommendation 22	In neutropenic children who have not been pre-treated with azoles, a choice can be made between fluconazole (loading dose 12 mg/kg, followed by 6 mg/kg/d) and a broadspectrum drug. The local epidemiology of *Candida* species forms an important guideline in this.

* Note added in proof (December 2009) – The recent approval of Caspofungin for use in children after release of these Guidelines may significantly affect the recommendations in this section in a subsequent revision of the guidelines.

3.2. What is the optimal treatment for other localised Candida infections?

a. Candida endophthalmitis
b. Candiduria
c. Candida oesophagitis
d. Candida-peritonitis (in Continuous Ambulatory Peritoneal Dialysis or surgical)

3.2.a. Candida-endophthalmitis

Candida endophthalmitis is a major complication of candidemia. In studies conducted in patients with candidemia, the incidence of ocular *Candida* infection is 4-29% [103-107, 125]. The optimal treatment of *Candida* endophthalmitis has never been investigated in comparative studies. The only data on the treatment of ocular candidiasis derive from studies with c-AmB or azoles; the use of echinocandins for this indication has only been described sporadically.
Where necessary, the treatment of ocular candidiasis comprises three components: administration of systemic antifungal therapy, intravitreal injection of antifungal agents and vitrectomy. Systemic therapy with amphotericin B does not penetrate well into the vitreous body; the azoles on the other hand do reach good concentrations there [126, 127]. Echinocandins reach only low concentrations in cerebrospinal fluid and in the eye and are therefore not considered to be a first choice in the treatment of *Candida* endophthalmitis or chorioretinitis [128].
The value of late vs. early vitrectomy was described In a series of patients with *C. albicans* endophthalmitis or chorioretinitis [129]. No complications developed in the 7 patients who underwent vitrectomy within 1 week. Other treatments (late vitrectomy or antifungal therapy only) almost all led to complications. In a large randomized trial comparing voriconazole and c-AmB followed by fluconazole, the patients participated in ophthalmological monitoring. Forty of the 370 patients with candidemia developed a probable *Candida* chorioretinitis or endophthalmitis. In 28/40 (70%), recovery was complete on systemic treatment with either voriconazole or with amphotericin B followed by fluconazole [107]. None of these patients underwent vitrectomy or were given intravitreal antifungal medication.

Conclusions 3.2.a – Treatment of *Candida* endophthalmitis and chorioretinitis	
Conclusion 38	The treatment of *Candida* endophthalmitis is, where necessary, based on a combination of systemic antifungal therapy, intravitreal injection of antifungal agents and vitrectomy.
Level 3	Brooks, 1989 [104], Parke, 1982 [103], Nolla-Salas, 1996 [125], Donahue, 1994 [105],Rodriguez-Adrian, 2003 [106] (C)
Conclusion 39	Early vitrectomy, within 1 week after the occurrence of *Candida* endophthalmitis, appears to improve the prognosis.
Level 3	Martinez-Vazquez, 1998 [129] (C)
Conclusion 40	Echinocandins do not reach adequate concentrations in the vitreous body.
Level 3	Goldblum D, 2007 [128] (C)
Conclusion 41	Fluconazole, voriconazole or the combination of AmB + flucytosine reach therapeutic concentrations in the vitreous body and have a role to play in the treatment of *Candida* endophthalmitis and chorioretinitis
Level 3	Brooks, 1989 [104], Parke, 1982 [103], Nolla-Salas, 1996 [125], Donahue, 1994 [105], Rodriguez-Adrian, 2003 [106], Oude Lashof, 2005 [107] (C)

Other considerations

No studies have been conducted into the additional effect of intravitreal c-AmB following vitrectomy or otherwise. The risk of the development of retina necrosis as a result of intravitreal c-AmB must be weighed against the potential favourable antifungal effect. In the light of the rather poor penetration of most systemic antifungal agents, the committee considers intravitreal c-AmB as an adjuvans to systemic antifungal therapy to be recommended for severe *Candida* endophthalmitis.

On the basis of preclinical data, it is assumed that the combination of flucytosine and amphotericin B is synergistic. Flucytosine reaches high concentrations in the eye. When amphotericin B is chosen for therapy, the committee considers its combination with flucytosine to be recommended for severe *Candida* endophthalmitis.
Little data is available with regard to the duration of therapy in ocular candidiasis. Based on clinical experience, a 2-4 week duration of treatment on resolution of fundus anomalies is usual in uncomplicated chorioretinitis. Depending on the clinical course of the infection, a treatment duration of 6 weeks to 3 months is usually required in endophthalmitis.

Recommendation 23	In view of good penetration into the vitreous body, *Candida* chorioretinitis or endophthalmitis should be treated systemically with an azole (fluconazole loading dose 800mg, followed by 400mg od, or voriconazole i.v. loading dose 6 mg/kg bid, followed by 3 mg/kg bid, or 200mg bid orally). In the event of invasion into the vitreous body, vitrectomy should be performed in combination with intravitreal c-AmB. Treatment duration is generally lengthy and depends on the clinical course of the infection.

3.2.b. Candiduria

Candida-positive urine cultures may be an expression of *Candida* colonization, of *Candida* cystitis, or of *Candida* pyelonephritis. During a prospective surveillance study in 530 patients with *Candida*-positive urine cultures, the urinary catheter was removed from 22% of the subjects; in 49%, antifungal therapy was initiated whether or not the catheter was removed and in 29%, no treatment was undertaken [130]. The candiduria resolved in 75.5% of the untreated patients, vs. 35.3% following catheter removal, vs. 50.2% following antifungal therapy. Candidemia developed in only 7 patients (1.3%).

Asymptomatic candiduria

In a placebo-controlled, double-blind study in 316 patients with asymptomatic candiduria, 200 mg fluconazole was compared with placebo for 14 days [131]. Removal of the urinary catheter alone led to clearance of the *Candida* in 20% of the cases. After 2 weeks of treatment, 50% of the fluconazole group had negative cultures, vs. 29% of those in the placebo arm ($p<0.001$). Two weeks after end of treatment, however, this difference was no longer present (68% vs. 65%) [131]. This applied to both patients with an indwelling catheter and those without a catheter. There was no difference in mortality and none of the patients developed candidemia.
Bladder irrigation with c-AmB (50-200 µg per ml) was compared with systemic antifungal therapy in a prospective, randomized study. Seven days after treatment there was no difference between the brief systemic treatment and bladder irrigations with AmB [132]. Another study compared fluconazole (200mg qd orally, 7 days) with c-AmB bladder washouts (50mg/l) for 1 or 7 days. There was no difference in response between the three groups [133].

Symptomatic candiduria and invasive renal candidiasis

No studies have been conducted as to the incidence and treatment of symptomatic *Candida* cystitis and pyelonephritis. In a large randomized study comparing voriconazole and c-AmB followed by fluconazole, 5 patients (1.4%) presented with a proven *Candida* pyelonephritis as source of the candidemia [84]. In an older series in a single center, 26/249 (10.4%) of the patients with a candidemia also had candiduria on admission [134]. The majority of these patients suffered from an obstruction of the ureter and had recently undergone a urological intervention.

Conclusions 3.2.b – Treatment of candiduria	
Conclusion 42	In patients with candiduria, removal of the urinary catheter or the initiation of antifungal therapy appears to have no measurable effect on the resolution of candiduria.
Level 3	Kauffman, 2000 [130](C)

Conclusion 43	It has not been shown that fluconazole is superior to placebo for the treatment of asymptomatic candiduria.
Level 3	Sobel, 2000 [131](A2)
Conclusion 44	Bladder irrigation with c-AmB is not more effective than systemic antifungal therapy.
Level 2	Leu, 1995[132](B); Fan-Havard, 1995 [133](B)
Conclusion 45	Symptomatic candiduria or invasive renal candidiasis, especially in the presence of a urninary tract obstruction, can lead to complications and should be treated.
Level 3	Kullberg, 2005 [84](C).

Other considerations

Asymptomatic candiduria is relatively common; it is not, however, associated with clinical consequences. The two prospective studies described here show that asymptomatic candiduria almost never leads to invasive candidiasis, that antifungal treatment is not very successful, and does not lead to eradication any more frequently than does removal or replacement of an indwelling catheter without antifungal treatment. Although there are no specific data, treatment of asymptomatic candiduria may be considered in patients with severe neutropenia, in kidney transplantation, in neonates with a low birth weight and prior to renal surgery.
Symptomatic ascending candidiasis in the urinary tract is relatively rare, is usually associated with an obstruction, and its course may be complicated. No studies have been conducted with respect to the specific treatment of this condition. The committee has considered that the echinocandins are not excreted in the urine and have barely been investigated for this indication and that, in view of its renal adverse effects, there is no place for c-AmB for this indication. For these reasons, it is recommended that symptomatic, invasive renal candidiasis be treated with an azole, and that the choice between fluconazole en voriconazole be made on the grounds of species and susceptibility. A duration of treatment of 2 weeks following removal of the urinary tract obstruction would seem to be adequate; where there are stones or other foreign bodies or persistent obstructions, a more prolonged treatment is necessary.

Recommendation 24	In asymptomatic candiduria removal or replacement of urinary catheters must be considered. There is no place for antifungal treatment, except in patients with severe neutropenia, in kidney transplantation, in low birth weight neonates and prior to renal surgery.

Recommendation 25	Symptomatic candiduria or invasive renal candidiasis should be treated with fluconazole.

3.2.c. Candida oesophagitis

The treatment of *Candida* oesophagitis has been investigated in various double-blind randomized studies, in particular in HIV-positive patients [135-142]. In these studies, fluconazole was compared with itraconazole capsules [136], itraconazole oral solution (OS) [141], itraconazole + flucytosine [135], voriconazole [137], caspofungin [139] and micafungin [140]. Caspofungin and c-AmB were also compared with each other [138, 142].

Fluconazole (bid 100 mg orally) was compared with itraconazole (capsules bid 100 mg) in an open, randomized study in 2213 HIV-positive patients [135]. The endoscopic response after 2 weeks of treatment was 81.2% (fluconazole) vs. 65.6% (itraconazole; p<0.001). In patients with persistent anomalies, the endoscopic response after 5 weeks of treatment was identical (97.0% vs. 97.6%, p=0.91). Treatment failed in 22.3% (fluconazole) vs. 26.6% (itraconazole; 95%CI for the difference, -7.9% to -0.7%, p=0.022).
In a similar study, fluconazole (3 mg/kg/d) was compared (double-blind) with a combination of itraconazole (capsules 3 mg/kg/d) plus 5-FC (100 mg/kg/d) and with placebo for 2 weeks in 85 AIDS patients with a *Candida* oesophagitis [136]. At 2 weeks, patients from the placebo group were randomized to either treatment arm and underwent 2 weeks of therapy. The endoscopic response after 2 weeks of treatment was 68.9% (fluconazole) vs. 72.4% (itraconazole + 5-FC; p=0.77), vs. a

partial response of 22.7% in the placebo arm. After 4 weeks (92.5% vs. 95%) and 3 months (89.8% vs. 94.8%), the endoscopic response still showed no significant difference.
Fluconazole (100 mg qd; loading dose 200 mg) was compared with itraconazole oral solution (100 mg qd; loading dose 200 mg) in 126 immunocompromized patients with *Candida* oesophagitis [141]. The clinical response at end of treatment (3-8 weeks) was 91% (fluconazole) vs. 94% (itraconazole; p=0.53). Similarly, no difference was found in the endoscopic (p=0.2) or mycological response (p=0.06) at end of treatment.

Ally et al. compared voriconazole (400 mg qd) with fluconazole (200 mg qd; loading dose 400 mg) in a double-blind study in 391 immunocompromized patients with *Candida* oesophagitis [137]. The patients were treated for 2 to 6 weeks depending on severity and response to therapy. The endoscopic response at end of therapy was 82.0% (164/200, voriconazole) vs. 83.2% (159/191, fluconazole; p=0.74). The clinical response 88.0% vs. 91.1% (p=0.31).

Caspofungin (50 mg i.v.) and fluconazole (200 mg i.v.) for the treatment of *Candida o*esophagitis were compared in 177 immunocompromized patients in a double-blind study [139]. The combined response (endoscopic and clinical) 5-7 days after end of treatment of patients who had received 5 days of therapy was 81% (66/81, caspofungin) vs. 85% (80/94, fluconazole; p=0.52). During 4 weeks of follow-up relapses occurred in 28% (18/64, caspofungin) vs. 17% (12/72, fluconazole; p=011).
In the double-blind 4-arm 'dose-finding' study, 3 different caspofungin doses were compared with c-AmB (0.5 mg/kg/d i.v.) in patients with oropharyngeal of oesophageal candidiasis [142]. In the 88 patients with oesophageal candidiasis, the endoscopic response 3-4 days after end of treatment was 67% (caspofungin 35 mg qd; n=21) vs. 90% (caspofungin 50 mg qd; n=20) vs. 77% (caspofungin 70 mg qd; n=2) vs. 61% (c-AmB; n=23). Caspofungin 50 mg qd was significantly better than c-AmB (p=0.03). In a double-blind 3-arm follow-up study, caspofungin (50 vs. 70 mg qd) was compared with c-AmB (0.5 mg/kg/d i.v.) for 14 days [138]. Combined (endoscopic and clinical) response 14 days after end of therapy was 74% (34/46, caspofungin 50 mg qd) vs. 89% (25/28, caspofungin 70 mg qd) vs. 63% (34/54; c-AmB). Caspofungin 70 mg qd was significantly better than c-AmB (p=0.012).

Double-blind comparison of micafungin in a variety of dosages and fluconazole was carried out in 245 HIV-positive patients with *Candida* oesophagitis [140]. The endoscopic response at end of therapy was 68.8% (44/64, micafungin 50 mg qd) vs. 77.4% (48/62, micafungin 100 mg qd) vs. 89.8% (53/59, micafungin 150 mg qd) vs. 86.7% (52/60, fluconazole 200 mg qd). Micafungin 50 mg qd was significantly poorer than fluconazole (p=0.021) and micafungin 150 mg qd (p=0.004). Two weeks after discontinuation of therapy, the response was 53.1%, 71.0% 84.7% vs. 81.7% for fluconazole. During follow-up 9 relapses occurred in the micafungin arm, vs. none in the fluconazole-arm (p=0.07).
Anidulafungin (50 mg qd; loading dose 100 mg) was compared double-blind with fluconazole (100 mg qd; loading dose 200 mg) in 601 patients with Candida oesophagitis [143]. The endoscopic response at end of therapy was 97.2% (242/249, anidulafungin) vs. 98.8% (252/255, fluconazole; p=0.19). Two weeks after withdrawal of therapy the endoscopic response was 64.4% (150/233, anidulafungin) vs. 89.5% (205/229, fluconazole; p <0.001).
Note: A combined analysis of the above studies by the committee suggests a significantly higher percentage of relapse following treatment with echinocandins compared to fluconazole (24 % vs. 10%; p<0.001).

The optimal duration of treatment in *Candida* oesophagitis has not been investigated. Treatment for at least 2 weeks is recommended. This duration can be prolonged on the basis of the clinical and endoscopic picture (where available).

Conclusions 3.2.c – Treatment of *Candida* oesophagitis

Conclusion 46	Fluconazole is more effective than itraconazole capsules for the treatment of *Candida* oesophagitis in HIV-positive patients.
Level 3	Barbaro, 1996 [135](A2)
Conclusion 47	It has not been shown that the combination of itraconazole + 5-FC is equivalent to fluconazole for the treatment of *Candida* oesophagitis in HIV-positive patients.
Level 3	Barbaro, 1996 [136](B)
Conclusion 48	Itraconazole oral solution and voriconazole are as effective as fluconazole for the treatment of *Candida* oesophagitis in immunocompromized patients.
Level 3	Wilcox, 1997 [141](A2); Ally, 2001 [137](A2)

Conclusion 49	Caspofungin (50-70 mg qd) is more effective than c-AmB for the treatment of *Candida* oesophagitis.
Level 3	Villanueva, 2001 [138](B); Arathoon, 2002 [142](B)
Conclusion 50	Caspofungin, micafungin and anidulafungin are as effective as fluconazole for the treatment of *Candida* oesophagitis in immunocompromized patients, but lead to relapse more often
Level 2	Villanueva, 2002 [139](A2); de Wet, 2004 [140](A2); Ally, 2001 [137](A2); Krause, 2004 [143](A2)

Recommendation 26	Fluconazole (loading dose 400mg, followed by 200 mg qd) for 2 weeks is the preferred treatment for *Candida* oesophagitis

Recommendation 27	For treatment of a *Candida* oesophagitis caused by fluconazole resistant *Candida* species, voriconazole (based on the susceptibility spectrum) is eligible, or, as a second choice, an echinocandin

3.2.d. Candida peritonitis

Candida peritonitis usually occurs following abdominal surgery, perforation of the gut or anastomotic leakage, or in patients undergoing continuous ambulant peritoneal dialysis (CAPD) [144, 145]. In a retrospective case control study, the mortality in *Candida* peritonitis was significantly higher than in peritonitis caused by other pathogens (48% vs. 28%, p<0.001) [146]. In a similar series of patients with acute necrotising pancreatitis with polymicrobial flora, mortality in the presence of *Candida* species was significantly higher (7/13 vs. 3/24, p<0.002).
No randomized trials have been conducted in which the treatment of *Candida* peritonitis has been specifically investigated. A number of patients with a *Candida* peritonitis were included in a comparative trial of caspofungin vs. c-AmB in invasive candidiasis. The response in peritonitis was 100% (caspofungin; 8/8) vs. 87.5% c-AmB, 7/8, not significant) and in intra-abdominal abscesses 75% (3/4) vs. 33.3% (3/9; not significant) [86].
In a comparative trial of micafungin vs. L-AmB, the response in patients with *Candida* peritonitis was 73% (14/17; micafungin) vs. 82% (8/11; L-AmB; p=0.54) [88]; in the randomized study of micafungin vs. caspofungin 62% (8/13; micafungin) vs. 40% (2/5; caspofungin; p=0.41) [89]. In the randomized study of anidulafungin vs. fluconazole, the response in *Candida* peritonitis and intra-abdominal abscesses was 75% (6/8, anidulafungin) vs. 50% (7/14; fluconazole; not significant) [87].
Important risk factors as regards the occurrence of a CAPD peritonitis caused by *Candida* species are the use of antibiotics and previously suffered peritonitis [147]. Treatment usually consists of removal of the CAPD catheter and i.v. administration of fluconazole or c-AmB. Comparative studies have not been conducted; more toxicity has been attributed to i.v. c-AmB. Amphotericin B may cause a chemical peritonitis and should not be administered intraperitoneally.

Conclusions 3.2.d – Treatment of *Candida* peritonitis

Conclusion 51	*Candida* peritonitis, both surgical and resulting from CAPD, is a potentially lethal condition which must be treated systemically using antifungal agents.
Level 4	Alden, 1989 [144](D), Calandra, 1989 [145](D), Hoerauf, 1998 [148](C), Montravers, 2006 [146](C)
Conclusion 52	Successful treatment of *Candida* peritonitis has been described using fluconazole, caspofungin, micafungin, anidulafungin, c-AmB and L-AmB.
Level 3	Mora-Duarte, 2002, [86](C), Kuse, 2007 [88](C), Pappas, 2007 [89](C), Reboli, 2007 [87](C)

Other considerations

No studies with sufficient statistical power have been conducted into the optimal treatment of *Candida* peritonitis. On the basis of published data and clinical experience, the committee recommends treatment of peritonitis caused by fluconazole-susceptible *Candida* species with fluconazole. In the

event of resistance, an echinocandin may be chosen on the basis of the susceptibility pattern. Voriconazole has not been investigated for this indication, but on the basis of its efficacy in disseminated candidiasis [84] the committee considers the choice of voriconazole as well as L-AmB to be justified in specific cases. On the grounds of its adverse effects profile, the committee sees no place for c-AmB in this indication.

Recommendation 28	Fluconazole (loading dose 800mg, followed by 400 mg qd) for at least 2 weeks is the treatment of preference in *Candida* peritonitis. Based on the susceptibility spectrum, an echinocandin is eligible in fluconazole resistant *Candida* species, or, as a second choice, voriconazole or L-AmB.

3.3. What is the optimal treatment of oropharyngeal candidiasis?

The treatment oropharyngeal candidiasis (OPC) has been investigated in several randomized trials in patients with cancer or HIV/AIDS. Miconazole in mucosal tablets (10 mg qd) was compared with ketoconazole (400 mg qd) in an open randomized study in 357 HIV-positive patients with OPC [149]. The clinical response after 7 days of treatment was 87% (miconazole) vs. 90% (ketoconazole; not significant).
Miconazole oral gel was compared with nystatin suspension in an open randomized study in 212 children <1 year with OPC [150]. The clinical response after 12 days of treatment was 96.2% (miconazole) vs. 44.9% (nystatin; p <0.01).
Note: no prospective comparison of miconazole and nystatin has been carried out in adults or older children. Clinical experience in these patient groups, however, does suggest greater activity of miconazole.

Fluconazole (50 mg qd) and ketoconazole (200 mg qd) were compared in a randomized double-blind study in 37 HIV-positive patients with OPC [151]. The response after 28 days of treatment was 100% (17/17; fluconazole) vs. 75% (12/16; ketoconazole; p=0.045).
Fluconazole suspension (100 mg qd) was compared with nystatin suspension (500.000U qid) in 167 HIV-positive patients with OPC in an open randomized study [152]. The clinical response after 14 days of treatment was 87% for fluconazole vs. 52% (p<0.01) for nystatin. Mycological eradication was 60% vs. 6% (p<0.001).
In an open randomized study, fluconazole suspension (50 mg qd) was compared to amphotericin B oral suspension (500mg tid) for 7-14 days in 305 patients with OPC [153]. The clinical response at end of therapy was 81% (fluconazole) vs. 87% (AmB; p=0.13). The mycological response was 35% (fluconazole) vs. 46% (AmB; p=0.08). Strictly speaking, this study has does not have sufficient statistical power to demonstrate equivalence.

Itraconazole oral solution (200 mg qd) was compared with clotrimazole (5dd 10mg) in 149 patients with OPC [154]. After 14 days of treatment, the combined clinical and mycological response was 53% (itraconazole) vs. 32% (clotrimazole; p <0.01).
In an open randomized study, itraconazole oral solution (200 mg qd, for 7 or 14 days) was compared with fluconazole (capsules 100 mg qd, 14 days) in 179 HIV-positive patients with OPC [155]. The clinical response was 87% (fluconazole) vs. 86% (itraconazole 7 days) vs. 97% (itraconazole 14 days; p=0.05 vs.fluconazole).
Itraconazole oral solution (200 mg qd for 7 days vs. 100 mg qd for 14 days) was compared with fluconazole (100 mg qd, 14 days) in a double-blind study in 196 HIV-positive patients with OPC [156]. The clinical response was 82% (51/62; itraconazole 7 days) vs. 90% (54/60; itraconazole 14 days) vs. 90% (65/72; fluconazole; p=not significant).
Itraconazole (capsules 200 mg qd, 15 days) was compared with fluconazole (100 mg qd, 10 days) in 252 cancer patients with OPC in an open randomized study [157]. The clinical response was 74% (fluconazole) vs. 62% (itraconazole; p=0.04). The mycological response was 80% vs. 68% (p=0.03).
In an open randomized trial, fluconazole (100 mg qd; loading dose 200 mg) was compared with posaconazole (100 mg qd; loading dose 200 mg) for 14 days in 350 HIV-positive patients with OPC

[158]. The clinical response after 14 days was 92.5% (fluconazole) vs. 91.7% (posaconazole; 95%CI, –6.61-5.04%).

In a double-blind study, caspofungin in 3 dosages (35 mg, 50 mg and 70 mg qd) was compared with c-AmB (0.5 mg/kg i.v.) in 52 patients with OPC. The clinical response was 84% (11/13; caspofungin 35mg qd) vs. 93% (13/14; caspofungin 50 mg qd) vs. 92% (12/13; caspofungin 70 mg qd) vs. 67% (8/12) for c-AmB [142].

Conclusions 3.3 – Treatment of oropharyngeal candidiasis (OPC)	
Conclusion 53	Fluconazole is more effective than nystatin suspension, miconazole oral gel, or ketoconazole in the treatment of OPC
Level 3	Van Roey, 2004 [149](A2), Hoppe, 1997 [150](A2), De Wit, 1989 [151](A2), Pons, 1997 [152](A2)
Conclusion 54	Miconazole oral gel is more effective than nystatin in the treatment of OPC in children <1 year
Level 3	Hoppe, 1997 [150](A2)
Conclusion 55	AmB suspension appears to be as effective as fluconazole in the treatment of OPC in non-immunocompromized patients
Level 3	Taillandier, 2000 [153](A2)
Conclusion 56	Itraconazole oral solution is more effective than clotrimazole for the treatment of OPC
Level 3	Murray, 1997 [154](A2)
Conclusion 57	Fluconazole is more effective than itraconazole capsules for the treatment of OPC in cancer patients.
Level 3	Oude Lashof, 2004 [157](A2)
Conclusion 58	Itraconazole oral solution is as effective as fluconazole in the treatment of OPC
Level 1	Graybill, 1998 [155](A2), Phillips, 1998 [156](A2)
Conclusion 59	Posaconazole is as effective as fluconazole in the treatment of OPC in HIV-positive patients
Level 3	Vazquez, 2006 [158](A2)
Conclusion 60	It has not been shown that caspofungin is equivalent to or more effective than c-AmB i.v. in patients with OPC
Level 3	Arathoon, 2002 [142](B)

Other considerations

Randomized studies of the treatment of OPC were to a large extent conducted among immunocompromized HIV-positive patients and patients with cancer. Treatment with miconazole gel has not been investigated in randomized studies in adults. Clinical experience, however, suggests that miconazole is often (initially) effective. In uncomplicated OPC, therefore, miconazole may be considered as a drug of first choice. Generally, initial therapy with fluconazole or itraconazole oral solution is preferred in severely immunocompromized patients.
Itraconazole in oral solution (OS) is absorbed better than itraconazole capsules. Itraconazole OS has been shown to be as effective as fluconazole capsules. Whether or not fluconazole oral suspension is even more effective than fluconazole capsules has not been investigated. In suspension, it may be assumed that, alongside their systemic effect, the local effect of both drugs makes a major contribution. In the majority of the randomized studies, no distinction has been made between initial or recurring episodes of OPC. The committee is of the opinion that the recommendations concerning fluconazole and itraconazole also apply to relapses of OPC. Of note, in breakthrough infections during therapy or recurrent relapse, the *Candida* species and its susceptibility should be determined.

Recommendation 29	In a first episode of oropharyngeal candidiasis, local treatment with miconazole may be chosen

Recommendation 30	Fluconazole 100 mg qd for 14 days is recommended for the treatment of oropharyngeal candidiasis in (severely) immunocompromized patients As an alternative, itraconazole oral solution 200 mg qd for 14 days may be considered. In breakthrough infections during therapy or in the event of recurrent relapse, the *Candida* species and its susceptibility should be determined.

Maintenance treatment in resistant or recurrent oropharyngeal candidiasis

In patients with recurrent oropharyngeal candidiasis, antifungal prophylaxis or maintenance treatment often is prescribed. There is, however, a theoretical risk that frequent use of fluconazole may lead to resistance.

Maintenance treatment with fluconazole (200 mg once weekly) was investigated during a double-blind, placebo-controlled study in 323 HIV-positive women [159]. Patients in the placebo arm were treated briefly during episodes of OPC. After follow-up of a median of 29 months, relapse of OPC was 44% (fluconazole) vs. 58% (placebo; p<0.001). Fluconazole resistance of *C. albicans* occurred in 4.8% (4/83 isolates; fluconazole) vs. 3.4% (4/116; placebo; p=not significant), and of non-albicans *Candida* species in 35% (29/84) vs. 31% (22/72; p=not significant). In another placebo-controlled study of secondary prophylaxis of OPC with fluconazole (150 mg 1 x per week) in 138 HIV patients, relapse occurred in 61% (fluconazole) vs. 90% (placebo; p<0.001). Resistance (MIC >64 mg/l) or clinical failure on therapeutic fluconazole occurred in 8 (fluconazole) vs. 4 (placebo) patients (not significant) [160].

In two prospective randomized studies, the differences in response and development of resistance were investigated in continuous or intermittent therapy with fluconazole for OPC. In the first small study among 44 HIV-positive patients, the patients on intermittent therapy were given fluconazole only on the occurrence of a new OPC episode [161]. Patients randomized to continuous therapy were given fluconazole (200 mg qd) for at least 3 months. Development of resistance was demonstrated in 56% (9/16; continuous therapy) vs. 46% (13/28; intermittent therapy; p=0.75).
In the second study, continuous treatment with fluconazole (200 mg thrice weekly) was compared with intermittent treatment on the occurrence of episodes of OPC in 829 HIV-positive patients [162]. The study was discontinued prematurely as there was no demonstrable difference after 42 months between the development of fluconazole-refractory episodes of OPC: (4.1%; continuous therapy) and intermittent group (4.3%; intermittent therapy; p=0.88).
Note: these studies do not have sufficient statistical power to demonstrate an effect on the epidemiology of fluconazole resistance.

Itraconazole oral solution (200 mg qd) for the treatment of fluconazole-refractory OPC was investigated in a prospective, open study in 36 HIV-positive patients [163]. The clinical response was 65%. During another study in 40 HIV-positive patients with fluconazole-resistant OPC, use of itraconazole oral solution resulted in a clinical improvement in 80%, but elicited mycological response in only 12% [164].

Conclusions 3.3. (continued) – Maintenance treatment of oropharyngeal candidiasis	
Conclusion 61	It has been demonstrated that secondary prophylaxis or maintenance therapy with fluconazole (150 or 200 mg twice weekly) can prevent relapse of OPC
Level 2	Pagani, 2002 [160](B) Schuman, 1997 [159](B)
Conclusion 62	It has not been shown that prophylaxis with fluconazole (once weekly) leads to the development of fluconazole resistance
Level 2	Pagani, 2002 [160](B) Schuman, 1997 [159](B). Baily, 1994 [165](C)
Conclusion 63	There is no difference between continuous maintenance therapy and intermittent therapy with fluconazole as regards the prevention of relapse or the development of fluconazole resistance
Level 2	Revankar, 1998 [161](B), Goldman, 2005 [162](A2)
Conclusion 64	The efficacy of itraconazole oral solution in patients with fluconazole-resistant OPC is limited
Level 3	Phillips, 1996 [163](C) Eichel, 1996 [164](C).

Other considerations

On the basis of studies and clinical experience, fluconazole is preferred for the treatment of recurrent OPC. In recurrent OPC, 3 treatment strategies are applicable: intermittent treatment linked to clinical episodes, daily maintenance therapy, or maintenance therapy with a dosage of (1-3 times weekly). The assumption that maintenance therapy with fluconazole is likely to lead to an increase in fluconazole resistance has not been not confirmed in published studies. The large ATCG/MSG study in particular [162] showed no difference in the incidence of fluconazole-refractory episodes between the patients treated with maintenance therapy and those treated only in the event of clinically manifest infection. As the statistical power of the study was calculated to demonstrate a clinical difference and not a difference in the in-vitro susceptibility (MIC) of the isolates, a difference in MIC between both arms cannot be excluded. However, should such a difference in fact exist, the clinical outcomes suggest that its clinical relevance is negligible.
No comparative studies have been conducted with regard to different dosing frequencies (once daily, thrice weekly, once weekly). On theoretical grounds, the committee prefers conservative use of fluconazole in recurrent OPC, i.e., the lowest appropriate dosing frequency for maintenance therapy.

Recommendation 31	Unless resistance has been demonstrated, fluconazole is the drug of first choice in recurrent oropharyngeal candidiasis.

Recommendation 32	In recurrent oropharyngeal candidiasis, intermittent treatment is preferred to maintenance treatment.

Recommendation 33	In case of frequent relapses of oropharyngeal candidiasis, maintenance therapy with fluconazole 200 mg once weekly, or, if necessary, thrice weekly or daily may be considered.

Chapter 4

Empirical and pre-emptive antifungal therapy

Introduction

Prolonged neutropenia is a major risk factor for the development of invasive fungal infections [166, 167]. In patients undergoing intensive chemotherapy, the mortality on occurrence of such infections is high [168], as it is in patients in intensive care. For this reason, empirical antifungal therapy is often prescribed; this is defined as treatment of unexplained symptoms (fever, sepsis) in specific risk groups (e.g., neutropenia), where there is no specific evidence of fungal infection. Pre-emptive therapy is defined as treatment started on specific signs of fungal infection (e.g. a positive antigen test) without proven invasive infection.
To develop an optimal recommendation for initiation of empirical antifungal treatment, the committee has defined the core questions posed below.

4.1. What is the efficacy of *empirical* antifungal therapy in febrile neutropenic patients?
4.2. What is the efficacy of *pre-emptive* antifungal therapy in high risk patients with signs of aspergillosis?
4.3. What is the efficacy of *empirical* or *pre-emptive* antifungal therapy in non-neutropenic patients?

4.1. What is the efficacy of empirical antifungal therapy in febrile neutropenic patients?

The administration of empirical antifungal therapy in neutropenic patients with fever despite the use of broadspectrum antibiotics was first suggested in 1982 [167]. 50 patients with persistent fever and neutropenia were randomized to: (i) withdrawal of all antibiotics (n=16), (ii) continuation of antibiotics (n=16) and (iii) addition of c-AmB (n=18). In the first group, an invasive mycosis occurred, in the second group 5 infections occurred, 4 of which were *Candida* infections (2 of which were mucosal), and in the third group there was a *Scedosporium* infection. In spite of the low numbers of patients included, it was this study suggested that empirical therapy did possibly have an effect on *Candida* infection. However, for filamentous fungal infection (one in each arm), not even a trend was demonstrated. In an open, randomized, non-placebo-controlled study by the EORTC, c-AmB was compared with no antifungal therapy in 132 patients with granulocytopenia and ≥4 days of fever in spite of administration of broadspectrum antibiotics [166]. There was no difference in the course of fever. In the c-AmB group, one candidemia occurred, vs. two candidemias, one aspergillosis and one zygomycosis in the untreated group (not significant).

Since the publication of these studies, empirical antifungal therapy has been recommended in neutropenic patients with persistent fever in spite of administration of broadspectrum antibiotics. Most of the studies conducted since then make use of a composite endpoint as outcome measure; for success, all of its five components are mandatory: survival of at least seven days, defervescence during neutropenia, successful treatment of any baseline fungal infection, no breakthrough infections, and no early withdrawal of therapy. These endpoints are subject of much discussion. Firstly, it is unclear whether or not a diagnosed 'breakthrough' infection is in fact a baseline infection that initially has remained undiscovered. Secondly, achieving defervescence during neutropenia as a requirement of a favourable outcome may be a flawed parameter, since this definition is dependent on the duration of the neutropenia. Moreover, in these patients, fever may not be caused only by infections.

4.1.a. Amphotericin B

L-AmB has been compared with c-AmB in two studies [93, 169]. A double-blind 3 arm study compared c-AmB (1.0 mg/kg/d) with L-AmB 1 mg/kg/d (L-AmB1) and 3 mg/kg/d (L-AmB3) in 338 neutropenic patients with fever [169]. L-AmB3 was significantly more effective than c-AmB in the composite

endpoint (resolution of fever and absence of breakthrough infections; p=0.03). For the individual endpoints, however, there were no differences: breakthrough infections (3 vs. 1 vs. 2) or mortality (1% vs. 1% vs. 1%). At both dosages, L-AmB had significantly fewer adverse effects than c-AmB; in particular, less nephrotoxicity.

In the double-blind study by Walsh et al. [93] in which L-AmB (3.0 mg/kg/d) was compared with c-AmB (0.6 mg/kg/d), there was no difference in response between both arms for the composite (5-factor) endpoint (50% vs. 49%). Although the total number of possible and proven breakthrough infections was similar, significantly fewer *proven* breakthrough infect–ions were seen in the L-AmB arm (11/343 vs. 27/344, p=0.009), in particular candidemia (3/343 vs. 12/344, p=0.03). There was no significant difference in mortality: 7.3% (25/343; LAmB) vs. 10.5% (36/344; c-AmB; p=0.18).

The publication of a doubleblind multicenter study of ABLC vs. c-AmB in patients with persistent fever and neutropenia was reportedly prevented by the manufacturer of ABLC [170]. In a subgroup of patients in this study of which the data are known, there was no difference in efficacy or toxicity between the two arms [171]. Subira et al. compared a low dose of ABLC (1.0 mg/kg/d) with c-AmB (0.6 mg/kg/d) in a randomized trial in 96 patients with neutropenia and fever desspite broadspectrum antibiotics [172]. The response was 72% (ABLC) vs. 48% (c-AmB; p=0.018), largely as a result of the withdrawal of c-AmB due to toxicity; there was, however, no difference in breakthrough infections, mortality, or infusion-related adverse effects (17%; ABLC vs. 19%; c-AmB; p=0.8). There was a difference in the incidence of kidney failure (8%, ABLC, vs. 32%, c-AmB; p=0.003).

White et al. compared ABCD (4.0 mg/kg/d) with c-AmB (0.8mg/kg/d) in 213 patients with neutropenia and fever [173]. In the 196 assessable patients (at least 7 days therapy) no difference in efficacy was found (50% vs. 43%, p=0.31). The incidence of nephrotoxicity was lower (p<0.001), but infusion-related toxicity in fact occurred more frequently in the ABCD-arm (82% vs. 65%, p<0.001).
L-AmB (3 and 5 mg/kg/d) and ABLC (5mg/kg/d) were compared with each other in 244 neutropenic patients with fever while on broadspectrum antibiotics in a double-blind, randomized study conducted by Wingard et al. [174]. The statistical power of the study was calculated to show a difference in the incidence of infusion-related toxicity at day 1. The L-AmB arms showed fewer infusion-related chills: 19% (L-AmB-3) vs. 24% (L-AmB-5) vs. 62% (ABLC; both p≤0.001), less fever (24% vs. 20% vs. 58%; p<0.001) and less nephrotoxicity (29% vs. 26% vs. 63%; p<0.01). The study was not designed to have sufficient statistical power to demonstrate differences in efficacy; response in the 3 treatment arms was 40% vs. 42% vs. 33% (not significant).

The Cochrane analysis of LFAB vs. c-AmB as empirical therapy in cancer patients with neutropenia reported that, with LFAB, there was less nephrotoxicity and fewer invasive fungal infections, but that there was no difference in mortality between LFAB and c-AmB [175]. This analysis is difficult to interpret because a large number of small toxicity studies with AmB in intralipid were included, as well as a study in which patients with proven infection were given targeted therapy in stead of empirical therapy.

The administration of c-AmB in 5% glucose was compared with administration in 20% intralipid in 51 neutropenic patients with fever [176]. Administration in intralipid did not result in less nephrotoxicity or infusion-related toxicity than c-AmB, but was associated with more respiratory adverse effects (p<0.05).
Note: the activity and efficacy of AmB in intralipid have never been investigated, and there are possible legal implications in view of the fact that the package insert texts of both preparations do not permit combination.

4.1.b. Azoles

In three randomised open-label studies, fluconazole (400mg qd) was compared with c-AmB (0.5-0.8 mg/kg/d) in a total of 529 neutropenic patients with fever. No difference in response could be found between the 2 arms, there were no differences in breakthrough infections or mortality; c-AmB was associated with significantly more adverse effects [177-179]. None of the studies had sufficient statistical power to demonstrate equivalence.
Boogaerts et al. compared itraconazole (i.v. followed by oral) with c-AmB in a randomized open-label study in 384 neutropenic patients with fever [180]. There were no significant differences in response as regards the composite endpoint (47% vs. 38%, 95% CI: -0.8-19.5), the course of the fever, efficacy,

breakthrough infections or mortality. On c-AmB, there were significantly more adverse effects (p=0.001), including nephrotoxicity.

Besed on the composite endpoint, it was not shown that voriconazole (success rate 26.0%) was equivalent to L-amB (success rate 30.6%) in a randomized open-label study compatring these drugs [181]. This was due to the fact that the 95% confidence interval around the difference was -10.6 to 1.6%, whilst -10% had been decided upon in advance as the lower limit of the difference to demonstrate equivalence [181]. There were no significant differences in four of the five separate endpoints; mortality, failure of resolution of baseline infection, persistent fever during neutropenia, and discontinuation of therapy due to adverse effects or failure. Breakthrough infections (the fifth endpoint) occurred significantly less with voriconazole: 1.9% vs. 5.0% (p=0.02), especially in patients with stem cell transplants or relapse of leukemia; 1.4% vs. 9.2%, (p=0.003). Voriconazole was withdrawn more frequently due to lack of efficacy (22 vs. 5 patients, p=0.001), most ofthen due to persistent fever (14 vs. 2, p=0.002). Voriconazole caused less infusion-related toxicity and less nephrotoxicity, but more visual disturbance and hallucinations.

4.1.c. Echinocandins

Caspofungin was compared with L-AmB in a doubleblind, randomized study in 1095 patients with persistent fever and neutropenia [94]. The response for the composite endpoint was the same in both groups (33.9% vs. 33.7%). For two of the five separate endpoints, caspofungin was more effective than L-AmB: in patients with a baseline fungal infection (response 51.9% vs. 25.9%, p=0.04) and in terms of early discontinuation of treatment. L-AmB caused significantly more nephrotoxicity and more infusion-related adverse effects and was more frequently associated with the early discontinuation of therapy. Survival 7 days after discontinuation appeared to be better in the caspofungin group (92.6% vs. 89.2%, p=0.05).

Conclusions 4.1 – Empirical antifungal therapy in patients with fever and neutropenia

Conclusion 1	It has not been shown that empirical antifungal therapy is effective in preventing invasive fungal infection in patients with persistent fever and neutropenia
Level 2	EORTC International Antimicrobial Therapy Cooperative Group, 1989; Pizzo, 1982 [166, 167] (B)
Conclusion 2	L-AmB is at least as effective as c-AmB in empirical therapy in neutropenia and fever, and causes fewer breakthrough infections than c-AmB
Level 2	Prentice, 1997 [169](A2), Walsh, 1999 [93](A2)
Conclusion 3	L-AmB causes less nephrotoxicity than c-AmB
Level 1	Prentice, 1997 [169](A2), Walsh, 1999 [93](A2)
Conclusion 4	It has not been shown that ABLC is equivalent to c-AmB or L-AmB as an empirical therapy in patients with neutropenia and fever
Level 3	Wingard, 2000 [174](A2), Subira, 2004 [172](B), Winston, 1999 [171](B)
Conclusion 5	In neutropenic patients with fever, L-AmB (3-5 mg/kg/dag) causes fewer infusion-related adverse effects and less nephrotoxicity than ABLC 5 mg/kg/d.
Level 3	Wingard, 2000 [174](A2)
Conclusion 6	There are no grounds for administering c-AmB in intralipid
Level 3	Schoffski, 1998 [176](B)
Conclusion 7	It has not been shown that fluconazole is equivalent to c-AmB for empirical therapy in neutropenic patients with fever. Fluconazole, however, does cause fewer adverse effects
Level 2	Viscoli, 1996 [177](B), Malik, 1998 [178](B), Winston, 2000 [179](B)
Conclusion 8	Itraconazole is as effective as c-AmB for empirical treatment in fever and neutropenia, but is associated with fewer adverse effects
Level 3	Boogaerts, 2001 [180](A2)
Conclusion 9	On the grounds of the chosen composite endpoint, it has not been shown that voriconazole is equivalent to L-AmB for empirical treatment in fever and neutropenia
Level 3	Walsh, 2002 [181](A2)
Conclusion 10	Caspofungin is as effective as L-AmB for the empirical treatment of neutropenia and is associated with fewer adverse effects; it also appears to be associated with a lower mortality
Level 3	Walsh, 2004 [94](A2)

Table 4.1. Comparison of endpoints in the studies by Walsh et al.

	c-AmB	L-AmB	Voriconazole	L-AmB	Caspofungin	L-AmB
Number of patients (reference)	343 [93]	344 [93]	415 [181]	422 [181]	556 [94]	539 [94]
No breakthrough fungal infection	307 89.2%	309 90.1%	407 98.1%	401 95.0%	527 94.8%	515 95.5%
Survival ≥ 7 dgn after [1]start or [2]end of Rx	308 89.5%[1]	318 92.7%[1]	382 92.0%[2]	397 94.1%[2]	515 92.6%[2]	481 89.2%[2]
No premature discontinuation	280 81.4%	294 85.7%	374 90.%	394 93.4%	499 89.7%	461 85.5%
Defervescence during neutropenia	200 58.1%	199 58.0%	135 32.5%	154 36.5%	229 41.2%	223 41.4%
Clearance of baseline infection	8/11 72.7%	9/11 81.8%	6/13 46.2%	4/6 66.7%	14/27 51.9%	7/27 25.9%
Composite endpoint (success)	172 50.1%	170 49.4%	108 26.0%	129 30.6%	190 33.9%	181 33.7%

Other considerations

Although the benefits of empirical therapy have not been proven, its use has become established in many centers. Recent randomized studies demonstrate no clinically relevant differences in the composite endpoints or mortality. The endpoints relating to baseline and breakthrough infection are difficult to interpret, as diagnosis was not standardised or state-of-the-art in all patients. Also, the course of fever as an outcome measure is debatable. If this criterion is left out of the considerations, voriconazole also complies with the endpoints.
In a comparative study, itraconazole was no better than c-AmB, whilst fewer breakthrough infections occurred with L-AmB than with c-AmB. Although no comparative study of itraconazole vs. L-AmB has been conducted, or of itraconazole vs. c-AmB and caspofungin, the committee considers L-AmB and caspofungin to be more effective than the other drugs on the basis of the available data.
The committee judges that refinement of diagnosis and use of pre-emptive therapy (described below) is preferable to empirical antifungal therapy in febrile neutropenia. If empirical therapy is nevertheless chosen, caspofungin or L-AmB are eligible on the grounds of their proven efficacy. Based on cost and its adverse effects profile, the committee prefers caspofungin. Based on the proven efficacy of voriconazole against *Aspergillus,* the most common pathogen among these patients, the committee considers that voriconazole is also eligible as empirical therapy in suspected aspergillosis.

Recommendation 1	Caspofungin, L-AmB and voriconazole are eligible for empirical therapy in adult patients with persistent fever and neutropenia

4.1.d. Empirical therapy in children

Splitting up of the results between the 133 adults and 202 children in the study comparing two dosages of L-AmB (1 and 3 mg/kg/d) with c-AmB, showed that the response in children was comparable to that in adults (children 64% vs. 63% vs. 51%, p=0.22) [169]. Similarly, with regard to adverse effects, there was no difference between the age groups. The study had insufficient statistical power to demonstrate a difference between the 3 treatment arms as regards the development of nephrotoxicity in children (8% vs. 11% vs. 21%, p=0.1), unlike in adults (12% vs. 13% vs. 31%, p=0.05). The other studies comparing LFAB and c-AmB either did not report the results for children specifically or did not include children.

Sandler et al. compared ABCD with c-AmB in children with neutropenia, fever and a high risk of invasive fungal infection [182]. In the ABCD arm, there was significantly less nephrotoxicity (12% vs. 52.4%, p=0.003), but for the other parameters there was no difference between the two groups.

Conclusions 4.1.d – Empirical antifungal therapy in children with fever and neutropenia	
Conclusion 11	No studies have been conducted with azoles or caspofungin aimed at the empirical treatment of children. Studies in children with LFAB and c-AmB have insufficient statistical power to confirm or refute that the data from the studies in adults are also applicable to children.
Level 3	EORTC International Antimicrobial Therapy Cooperative Group, 1989; Pizzo, 1982 [166, 167].

Other considerations

Voriconazole is assumed to be effective in children with invasive aspergillosis, the most common pathogen in these patients. For this reason, the committee considers that, alongside LFAB, voriconazole is also eligible as empirical therapy in suspected invasive aspergillosis in children.

Recommendation 2	In the absence of specific data, an LFAB preparation or voriconazole is recommended in children with persistent fever and neutropenia.

4.2. What is the efficacy of pre-emptive antifungal therapy in high-risk patients with suspected aspergillosis?

Pre-emptive antifungal therapy is treatment of patients in whom there is strong evidence of invasive aspergillosis based on certain diagnostic tests (radiological, serological or molecular) but in whom the infection has not been histologically or microbiologically demonstrated. The efficacy of initiating pre-emptive therapy in patients with a high risk of invasive aspergillosis had not been investigated in randomized studies before publication of these guidelines. The value of specific diagnostic tests prior to initiation of pre-emptive therapy, however, has been investigated.

Galactomannan

The diagnostic value of the circulating Aspergillus antigen galactomannan (GM) has been investigated in several studies. During serial monitoring twice weekly and with a cut-off value of 1.0, Maertens et al. found a sensitivity of 92.6% and a specificity of 95.4% for serum-GM in 186 patients with a hematological malignity in 243 treatment episodes [183]. The positive predictive value (PPV) was 92.6% (25/27) and the negative predictive value (NPV) was 95.4% (42/44). In a similar study in 50 neutropenic patients, the sensitivity was 100% (6/6) and specificity was 89% (31/35) at a cut-off value of 1.0 [184].

During a prospective study in 40 patients, Marr et al. found that the sensitivity of the GM-index at a cut-off value of 1.0 was poor [185]. Lowering the cut-off value to 0.5 raised the sensitivity from 18% to 82%, but reduced specificity from 100% to 77%. Similarly, in a retrospective study by Maertens et al., lowering the cut-off value from 1.5 to 0.5 raised the sensitivity from 76% to 97%, with a reduction in specificity from 98% to 91% [186].

The serum GM course during treatment with caspofungin was described in 17 patients with invasive aspergillosis and a GM-index ≥1.0. Of these patients, 4/5 with a favourable therapeutic response had a negative GM following discontinuation of the therapy. In 10/12 of the non-responders, the GM remained elevated [187].

In an observational study, serum-GM was determined daily during 136 episodes in 88 neutropenic patients [188]. At a GM of ≥0.5, HR-CT scan of the thorax and bronchoscopy were performed. An HR-CT scan was also carried out in patients with persistent fever, on discovery of clinical evidence of an invasive fungal infection, a new pulmonary infiltrate or isolation of fungi from respiratory materials. In the event of CT findings, a BAL (bronchoalveolar lavage) was carried out. In 19 episodes (13.9%) a positive serum-GM was noted twice; all these patients had proven or probable invasive aspergillosis (EORTC/MSG criteria). In 16 of 19 cases, the positive GM was a first sign of infection. In the remaining 117 episodes with a negative serum-GM, no proven or probable invasive aspergillosis was found; 1 patient did suffer from disseminated zygomycosis. Only 9 patients were pre-emptively treated,

whilst, according to pre-set criteria for empirical therapy, 41 episodes would have been judged eligible; a reduction in antifungal therapy of 35% to 7.7% [188].
Notes: The value of *Aspergillus* GM assay has been recorded only in patients with hematological malignities and neutropenia; the test characteristics of the assay in other patient groups do not appear to be universally comparable. False positive results due to the presence of galactomannan in certain antibiotics, e.g. piperacillin/tazobactam should also be taken into account [189], as well as reduced sensitivity during antifungal therapy with agents that are active against *Aspergillus* species.

Aspergillus PCR

The value of an *Aspergillus* PCR in peripheral blood has been described in several studies [190, 191]. In a prospective study in 84 patients who had undergone allogeneic HSCT, a PCR was carried out 2-4 times per week. In the 7 patients with an invasive aspergillosis, positive PCR preceded clinical diagnosis by median of 9 (2-23) days with a sensitivity and NPV of 100%. Specificity was only 65% and the PPV was 15.2% [191].
Einsele et al. reported a positive Aspergillus PCR in BAL samples from 7/134 patients who had undergone allogeneic HSCT, and of whom 5 patients developed an invasive pulmonary aspergillosis, at a median of 64 days (13-97) after transplantation [192]. The sensitivity and specificity for the prediction of invasive aspergillosis was 63% (5/8) and the specificity 98%. There was a significant association between a positive BAL at the time of HSCT and the development of invasive pulmonary aspergillosis ($p<0.001$).
Note: The *Aspergillus* PCR assay is not standardised and is, therefore, only applicable for experimental use.

HR-CT

Caillot et al. described the value of high-resolution CT-scanning of the lung in febrile neutropenic patients [193, 194]. Among 37 patients with proven or probable invasive aspergillosis, early HR-CT scanning showed a halo sign strongly suggestive of the diagnosis of invasive aspergillosis in 92%, and time-to-diagnosis was shortened from 7 to 2 days.
In a retrospective study of 161 episodes in 107 patients, galactomannan (≥0.5) was not positive significantly earlier than the appearance of anomalies on the HR-CT scan [195].
Greene et al. evaluated the use of HR-CT in 235 patients with proven or probable invasive pulmonary aspergillosis (EORTC/MSG criteria) [196]. In 95% of these patients, a “macro nodus” was visible on the HR-CT scan, and in 60.9% a halo-sign. The response of patients with a halo sign (75/143, 52%) was significantly better than that of patients with only a macro nodus (23/79, 29%, $p<0.001$), as was the 12 week survival (71% vs. 53%, $p<0.01$). The main conclusion to be drawn from this was that early diagnosis in the stage that the transient halo sign is still visible, is favourable for the prognosis.

Conclusions 4.2. – Diagnostic markers and pre-emptive therapy in neutropenic patients	
Conclusion 12	Determination of *Aspergillus* galactomannan in the serum has a major role in the early diagnosis of invasive aspergillosis
Level 1	Bretagne, 1997 [184], Maertens, 1999 [183] Maertens, 2005a [187], Maertens, 2005b [188](A2)
Conclusion 13	The diagnostic value of the *Aspergillus* serum galactomannan index is optimal at a cut-off value of 0.5
Level 2	Marr, 2004 [185], Maertens, 2005 [188](A2), Maertens, 2007 [186]
Conclusion 14	The course of the *Aspergillus* serum galactomannan index is a measure of response to therapy
Level 3	Maertens, 2005 [187](B)
Conclusion 15	The *Aspergillus* PCR assay is as yet insufficiently standardised for routine use in the diagnosis of aspergillosis
Level 4	(D)
Conclusion 16	A halo sign on an HR-CT lung scan has a high specificity for the diagnosis of early invasive pulmonary fungal infection
Level 2	Caillot, 1997 [193], Weisser, 2005 [195], Greene, 2007 [196](A2)
Conclusion 17	HR-CT scanning early in the course of the disease has an important role in the early discovery of invasive pulmonary aspergillosis.
Level 1	Caillot, 1997, [193], Greene, 2007, [196](A2)

Recommendation 3	In neutropenic patients with hematological malignities (acute myeloid leukemia, myelodysplastic syndrome, HSCT), it is recommended that determination of serum *Aspergillus* galactomannan be carried out at least twice weekly.

Recommendation 4	In neutropenic patients with hematological malignities (AML, MDS, HSCT), and a positive *Aspergillus* galactomannan index (≥0.5) or persistent unexplained fever, an HR-CT lung scan should be carried out.

Recommendation 5	Pre-emptive therapy against *Aspergillus* should be considered in the event of 2 x a positive GM >0.5 or findings consistent with invasive fungal infection on the HR-CT scan.

4.3. What is the efficacy of empirical or pre-emptive therapy against invasive candidiasis in non-neutropenic patients?

In view of the high mortality of candidemia, especially among severely ill patients, the option of empirical or pre-emptive therapy for patients in intensive care unit should be considered. In this context, empirical therapy is defined as antifungal therapy for patients with symptoms (fever, sepsis) in the absence of specific evidence of a *Candida* infection. Pre-emptive therapy is defined as treatment for patients with specific guiding signs (e.g., a positive culture from an i.v. catheter tip) in the absence of a proven invasive infection.

Empirical therapy

There is evidence that the sensitivity of a single blood culture for *Candida* is about 50% [197, 198]. This suggests that empirical antifungal therapy could be of value in the event of false negative cultures. In two retrospective studies, the effect of empirical antifungal therapy on mortality in candidemia was investigated [199, 200]. Morrell et al. found that initiation of antifungal therapy later than 12 hours after the taking of the blood culture sample was an independent predictor of mortality in patients in whom *Candida* species were eventually cultivated [199]. The second study also found the treatment outcome to be correlated with the interval between the taking of the blood culture sample and the start of the therapy [200]. In patients started on fluconazole on day 0 the mortality was 15%, compared to a mortality of 24% on day 1, 37% on day 2 and 41% on day 3 or later (p=0.009 for trend). A third study retrospectively described the correlation between mortality and the time interval between the start of septic shock and the first administration of effective antimicrobial therapy in 2731 ICU patients [201]. There was a strong correlation between the first dose of antimicrobial therapy and mortality in both bacterial sepsis and candidemia, with an odds ratio van 1.119 per hour of delay (95%CI, 1.103-1.136; p<0.0011), which suggests an increase in the mortality risk of 11.9% per hour of delay.

One prospective study has been conducted relating to empirical therapy in non-neutropenic patients with a high risk of invasive candidiasis [202]. Schuster et al. compared fluconazole (800mg od for 14 days) with placebo in 270 ICU patients with unexplained fever for >4 days who complied with the following selection criteria: duration of stay in ICU >4 days, APACHE II score ≥16, broadspectrum antibiotics ≥4 days and presence of a central venous catheter >1 day. The primary outcome measure was success 4 days after end of treatment, defined as absence of documented invasive mycosis and resolution of fever. Discontinuation of the treatment due to adverse effects or the prescription of other antifungal medication was classified as failure. Empirical treatment with fluconazole had no significant effect on success (36%; 44/122, fluconazole, vs. 38%; 48/127, placebo; RR 0.95; 95%CI, 0.69-1.32), on documented invasive fungal infection (5%; 6/122, fluconazole, vs. 9%; 11/127, placebo; RR 0.57, 95%CI, 0.22-1.49), or on mortality (24%; 29/122, fluconazole, vs. 17%; 22/127, placebo; RR 1.36; 95%CI, 0.23-1.67) [202]. *Note:* The definition of the composite endpoint may have negatively affected the outcome, as defervescence was required to define a success, and this has been the driver of the majority of failures.

Indicators for initiation of pre-emptive therapy

Pre-emptive therapy is initiated on the basis of positive markers that may indicate an invasive *Candida* infection. In a prospective cohort study, Pittet et al. investigated the colonization index as an indicator of invasive candidiasis [203]. Patients admitted to the ICU were included if ≥3 screening cultures (from the oropharynx, the trachea or the stomach) had been positive for *Candida* species on at least 2 consecutive days. Of the 29 patients included, 11 developed candidemia and 3 an invasive candidiasis (38%). The remaining 18 patients remained colonized without any evidence of invasive infection. The corrected colonization index (CCI) was defined as the number of sites that were quantitatively highly colonized by *Candida*, divided by the number of sites examined. In colonized patients without an invasive infection, the CCI was on average 0.16, and in patients with invasive candidiasis 0.56 ($p<0.01$); all patients who were only colonized had a CCI of ≤0.35, and in all infected patients the CCI was ≥0.4. In this study, the CCI made a full distinction between the 2 groups and had a 100% positive predictive value [203].
Note: It is striking that only colonization of the upper alimentary and respiratory tracts were chosen for determination of the CCI and not colonization of urine or feces.
Multicenter studies, however, did not show any relationship between colonization of any site and invasive infection [204].

In a study including 1699 patients who had been in ICU for >7 days, León et al. determined the risk factors for developing invasive candidiasis in a logistic regression analysis [205]. The principal risk factors were assigned a weight factor: colonization with *Candida* at multiple sites (in weekly screening of the upper GI tract, the trachea and in urine) (1 point), total parenteral nutrition (1 point), surgery on admission to the ICU (1 point) and severe sepsis (not defined by the authors) (2 points). A score of ≥3 had a sensitivity of 81% and a specificity of 74% (PPV 16%; NPV 98%) for presence of candidemia.
Note: In practice, this score suggests that in patients with severe sepsis (2 points), only one of the other risk factors (TPN, surgical patient or multifocal colonization (1 point)) would have to be positive to predict the existence of a candidemia with a PPV of 16%; in the absence of these risk factors, candidemia is unlikely with a NPV of 98%.
Note: The committee notes that these data have been obtained exclusively for patients with an ICU stay of >7 days, and that these predictive values are strongly dependent on the incidence of candidemia in the de patient group, which was relatively high in the population studied (97/1699, 5.8%). The authors did not prospectively evaluate the score in another population.*

Retrospectively applied to an Australian cohort of ICU patients, the PPV was only 2% (G. Playford, written communication). With reference to this and other single center studies, Wenzel et al. [206] have pointed out the important role played by the local epidemiology and argued in favour of a more formal, model-based approach using validated mortality figures. The committee agrees that, in general, currently published studies are based on local situations with a high incidence of candidemia, and are therefore not suited to generalisation.

(1→3)-β-D-glucan (β-glucan) is a circulating fungal polysaccharide that may possibly be useful as a marker for invasive fungal infection. Obayashi et al. investigated β-glucan during 202 febrile episodes in 179 patients [207]. Sensitivity (β-glucan >20pg/ml) for invasive mycoses was reported as 31/41 (76%) in the first specimen and 37/41 (90%) on repeated testing. In patients free of invasive mycoses, the test was positive in 26/138 (19%, specificity 81%). However, patients with only a positive culture from a catheter tip were also held to have an invasive mycosis. In small control groups with a resolved invasive fungal infection, fungal colonization, pulmonary cryptococcosis or allergic bronchopulmonary aspergillosis, specificity was reported as 100%. In this highly selected population with a 23% incidence of "invasive" mycoses, a positive predictive value of 59% (37/63) was recorded and a negative predictive value of 97% (135/139).
Note: The committee remarks that, on the basis of these data, the positive predictive value would be only 5% in a population with a 1% incidence of invasive mycosis (as is the case in ICUs in the Netherlands).

* Note added in proof (December 2009) – After release of these Guidelines, a prospective validation study conducted in Spain among 1107 patients with an ICU stay of > 7 days was published, yielding similar results (León et al., Crit Care Med 2009).

Odabasi et al. investigated β-glucan (Glucatell assay) in the serum of 30 neutropenic patients with proven candidemia and in 30 healthy controls [208]. At a cutoff value of 60 pg/ml, the sensitivity was 97% and specificity was 93%. Next, β-glucan was determined in 2070 specimens from 283 patients with AML or MDS who were receiving chemotherapy and antifungal prophylaxis. Sixteen patients developed a proven invasive fungal infection, 4 a probable and 33 a possible infection. The β-glucan was positive median 10 days before the clinical diagnosis proven or probable fungal infection was made. When on collecting an average of 7 (2070/283) specimens per patient, one positive specimen was considered to be proof, the sensitivity was 100%, decreasing to 60% if 3 sequential positive specimens were required. The NPV in this population was thus 96% with an incidence of 7% proven or probable invasive mycoses. Specificity was 90% (positive predictive value, 43%) and increased as more sequential specimens were evaluated.

Ostrosky-Zeichner et al. determined β-glucan (Glucatell assay, cut-off 60 pg/ml) in specimens from 107 patients with proven candidemia or invasive candidiasis [209]. The sensitivity was 87/107 (81.3%), and was not significantly different for the various *Candida* species, although there seemed to be a trend towards a slightly lower sensitivity to *C. parapsilosis*. In 170 healthy subjects and clinical controls the specificity was only 87%. The committee remarks that the specificity is based on a poorly detailed population that comprised both volunteers and clinical patients. It may be assumed that the specificity in a clinical population is lower, due to false positive results in postoperative patients and those undergoing renal replacement therapy.

Conclusions 4.3. Empirical or pre-emptive therapy against invasive candidiasis

Conclusion 18	Retrospective studies suggest that delay of effective antifungal therapy in candidemia leads to a higher mortality.
Level 3	Morrell, 2005 [199](C); Garey, 2006 [200](C); Kumar, 2006 [201](C).
Conclusion 19	Empirical therapy with fluconazole in patients with fever and risk factors for candidemia in the ICU had no significant effect on outcome or survival using a composite endpoint.
Level 3	Schuster, 2008 [202] (A2)
Conclusion 20	Although in several studies previous colonization had a high predictive value for the development of invasive candidiasis, this was not confirmed in all studies.
Level 3	Pittet, 1994 [203](B); Blumberg, 2001 [204](B)
Conclusion 21	Determination of β-glucan in serum offers reasonable sensitivity, its sensitivity for the discovery of candidemia, however, is only moderate.
Level 2	Obayashi, 1995 [207], Odabasi, 2004 [208], Ostrosky-Zeichner, 2005 [209](B).
Conclusion 22	In patients who have been in ICU for longer than 7 days and are not subject to such risk factors as colonization with *Candida* in several sites, total parenteral nutrition (TPN), or recent surgery, the chance of invasive candidiasis in severe sepsis would appear to be low.
Level 3	León, 2006 [205](A2)

Other considerations

The value of β-glucan testing has only been properly investigated for the diagnosis of invasive candidiasis. For other mycoses, including invasive aspergillosis, the data are insufficient. The two, last-mentioned studies differ in the number of investigated specimens per patient, and suggest that the sensitivity is extremely high when an average of 7 specimens per patient are investigated, but lower if only *one* specimens is collected.
The committee notes that, in clinical practice, positive and negative predictive value have to be viewed in the real population. In an ICU population with an incidence of candidemia of 1%, the positive predictive value on the grounds of these data is 6% [209], this means that 94% of the positive tests would be false-positive. Even for the initiation of prophylaxis, (let alone pre-emptive therapy) a positive predictive value of >10% is considered desirable.
Also, account must be taken of false-positive results in patients undergoing renal replacement therapy and immunoglobulin treatment, as well as in postoperative patients due to the use of gauzes containing β-glucan. These populations were not investigated in the studies referred to.

On the other hand, the high negative predictive value (95-100%) suggests that with a negative test, the diagnosis invasive candidiasis can be excluded. In the studies cited, however, these values are based on use of the test for screening in the entire (ICU or hematological) population. If the test is used as a specific diagnostic tool in a selected symptomatic patient group (e.g. in febrile neutropenia

or ICU patients with sepsis and receiving broadspectrum antibiotics) the a priori chance (incidence) is altered and the negative predictive value declines. Thus, in the last mentioned patient group with a 25-50% a priori chance of candidemia, 7-18% of the infections would still be missed (NPV 82-93%). The value of β-glucan determination, however, has not yet been investigated in the relevant clinical populations (febrile neutropenia, septic shock), in which its use as a marker for pre-emptive therapy would be desirable. Also, insufficient data are available concerning the use of this determination in invasive aspergillosis.

There is evidence that early empirical therapy prior to receiving results of blood culture might improve the prognosis in non-neutropenic ICU patients. The indications for initiation of empirical therapy are controversial, and a recent randomized trial demonstrated no favourable effects of empirical fluconazole in suspected candidemia in ICU patients [202]. The committee is of the opinion that the initiation of empirical therapy in selected cases may be considered in ICU patients with a lengthy duration of stay (>7 days) and unexplained sepsis, if this is based on a combination of the following factors: (1) significant colonization with *Candida* and (2) clinical risk factors (e.g. abdominal surgery, anastomotic leakage, broadspectrum antibiotics, a central venous line). Currently, none of these criteria has been adequately investigated and the committee is aware of the dilemma surrounding the potential benefits of early treatment of candidemia, versus overtreatment of a large group of patients. Essential is that enough cultures are taken prior to the initiation of treatment and that empirical therapy is discontinued if blood cultures prove negative.

Recommendation 6	Determination of β-glucan in serum is not yet sufficiently validated for use in the diagnosis of invasive mycoses.

Recommendation 7	The indication of empirical therapy on suspicion of candidemia in non-neutropenic patients is controversial. Empirical therapy may be considered in selected cases.

Chapter 5

Antifungal prophylaxis

What is the efficacy of antifungal prophylaxis
5.1. in patients with hemato-oncological conditions and those undergoing hematopoietic stem cell transplantation (HSCT)?
5.2. in patients who have undergone a solid organ transplantation?
5.3. in patients in intensive care?
5.4. in patients with a primary immune deficiency and in neonates?

5.1. Antifungal prophylaxis in patients with hemato-oncological conditions and those undergoing hematopoietic stem cell transplantation (HSCT)

5.1.a. Hematological malignancies and autologous stem cell transplantation

Several meta-analyses have been carried out that assessed oral or intravenous antifungal prophylaxis studies in neutropenic patients with hematological malignancies. A Cochrane meta-analysis included both prophylaxis studies and empirical antifungal therapy. As the design of prophylaxis studies and that of empirical therapy studies is very different, this meta-analysis cannot be used to make judgements on prevention of invasive fungal infection [210, 211]. A larger meta-analysis (7014 patients) by Bow et al. in 2002, which included 38 studies with itraconazole, fluconazole, miconazole, ketoconazole or i.v. c-AmB, reported a significant reduction of invasive fungal infection (OR, 0.44; 95% CI, 0.35– 0.55) and fungal infection-related mortality (OR, 0.58; 95% CI, 0.41– 0.82), not only in stem cell transplant patients but also in other risk groups [212].

Placebo-controlled studies

The effect of antifungal prophylaxis was investigated in a number of double-blind, placebo-controlled studies. A distinction has to be made here between effects on *Candida* colonization and superficial infection on the one hand, and on the incidence of invasive fungal infection on the other.
In two studies, prophylaxis with c-AmB (1mg/kg/48hrs) in 95 patients [213] or with liposomal amphotericin B (3 x per week 2mg/kg) [214] in 161 patients, did not lead to any significant reduction of invasive fungal infection or mortality when compared to placebo.

In several studies, prophylaxis with fluconazole has been compared with placebo in neutropenic patients [215-217]. The first double-blind, randomized study with fluconazole (400 mg qd) in 257 patients with acute leukemia did show a significant effect on *Candida* colonization and the development of superficial candidiasis, but no significant reduction of invasive fungal infection (5/123 (4%) vs. 10/132 (8%), p=0.23) or of mortality [215]. Similarly, in an open study in 68 patients with refractory acute myeloid leukemia, no significant reduction of invasive fungal infection or mortality was recorded [216].
A larger, double-blind, placebo-controlled study in 304 patients with a hematological malignity or who had undergone autologous stem cell transplantation, showed fewer invasive fungal infections (3/141, fluconazole, vs. 10/133, placebo; p=0.03) and lower mortality resulting from invasive fungal infection (1/15, fluconazole, vs. 6/15, placebo; p=0.04), but no significant difference in total mortality [217].

In a double-blind placebo-controlled study with itraconazole oral solution (2 dd 2.5 mg/kg/d) in 405 neutropenic patients, there was no difference in the incidence of proven invasive fungal infection (5/201, itraconazole, vs. 9/204 placebo; p=0.28), or of invasive aspergillosis, or in the total mortality [218]. The authors did report a significant reduction in proven and “probable” invasive fungal infection (48/201 (24%) vs. 68/204 (33%); p=0.035), but, in this study, patients with fever that was not

responsive to broadspectrum antibiotics were also counted as having a probable fungal infection [218]. Similarly, in two smaller double-blind, placebo-controlled studies with itraconazole capsules, no significant effect was demonstrated as regards the incidence of invasive fungal infection [219, 220]: during a study in 92 patients in the Netherlands, 9/46 proven or probable invasive infections developed during treatment with itraconazole (2 dd 200mg) vs. 15/46 in the placebo-arm (p=0.15) [219]. Here too there was no difference as regards mortality (10/46 vs. 14/46; p=0.34). In the other study there was no significant difference in invasive mycoses (5 vs. 9; p=0.28), but in the subgroup of patients with lengthy (>7 days) and deep neutropenia (<0.1x10^9 neutrophil granulocytes) significantly fewer invasive fungal infections developed (3/50 (6%) vs. 9/46 (19%), 95%CI; 0.3-27; p=0.04) [220].

Comparative studies

In addition to placebo-controlled studies, a number of trials has been carried out in which two prophylaxis regimes were compared with each other.
In studies with insufficient statistical power, fluconazole was compared with i.v. c-AmB [221], ABCD [222], oral AmB or nystatin [223, 224], while combinations of fluconazole and itraconazole have been compared with liposomal amphotericin B [225] in hemato-oncological patients.
In an unblinded randomized study of fluconazole (400 mg qd) and c-AmB i.v. (3 x per week 0.5mg/kg) in 77 patients, there was no significant difference in the incidence of proven invasive mycoses (4/41 vs. 6/36) or probable and possible pulmonary fungal infection (3 vs. 7) [221]. C-AmB was discontinued significantly more often (20% vs. 42%; p<0.05), especially as a result of nephrotoxicity. A double-blind, randomized study of fluconazole (200mg qd) and nystatin suspension (6 million IU/day) in 164 patients showed no difference in invasive infection (2/56 (4%) vs. 6/53 (11%); p=0.21) [223], and there was also no difference in invasive infection (6/256 vs. 9/255) in an unblinded study of fluconazole (100mg qd) and oral AmB (2g/d) or nystatin [224] or in a randomized study of fluconazole (150mg qd) and oral AmB (2 dd 500mg suspension) in 820 neutropenic patients: 11/420 (2.6%) vs. 8/400 (2.0%; p=0.56) [226].
In an unblinded randomized study in 137 patients, the combination fluconazole (200mg bid) and itraconazole capsules (200mg bid) was compared with liposomal amphotericin B (L-AmB 3mg/kg i.v. 3 x per week) [225]. There was no difference in invasive fungal infection (3/67 vs. 3/70) or mortality (8/67 vs. 10/70; p=0.69). The patients in the L-AmB group developed adverse effects significantly more often [225]. Retrospectively compared with L-AmB in the earlier study, a follow-up study with ABLC (2.5mg/kg/d) in 131 patients showed no difference in invasive fungal infection (6/131 (5%) vs. (3/70 (4%) p=0.92), nor in mortality (8% vs. 14%; p=0.37) [227]. An unblinded, randomized prophylaxis study of fluconazole (200mg qd) and ABCD (2 mg/kg/d i.v.) had to be prematurely discontinued due to too many infusion-related adverse effects and toxicity in the ABCD group (6/12 vs. 0/12) [222].
In a meta-analysis of 16 randomized studies of oral fluconazole prophylaxis in a total of 3734 neutropenic patients, fluconazole was found to be effective only in the prevention of invasive fungal infection in patients who had undergone a stem cell transplantation [228].

A double-blind, placebo-controlled study comparing itraconazole oral solution 2.5 mg/kg bid with AmB capsules (4dd 500mg) in 557 patients undergoing chemotherapy for a hematological malignity or autologous stem cell transplantation [229] found no difference in invasive aspergillosis (5 vs. 9; p=0.26), invasive fungal infection (8/281 vs. 13/276; p=0.25) or mortality (18/281 vs. 23/276; p=0.38). The study was designed as a superiority trial; for this reason, it cannot be concluded statistically that AmB is as effective as itraconazole. In an open study of itraconazole oral solution (100mg bid) and the combination of AmB capsules (500mg tid) and nystatin (2MU 4dd) in patients undergoing chemotherapy for AML or HSCT [230], no difference in invasive fungal infection was demonstrated (7/144 vs. 7/133; p=0.88).

In 4 studies in patients undergoing chemotherapy for acute leukemia or an autologous or allogeneic bone marrow transplantation, itraconazole was compared with fluconazole. During a randomized study, itraconazole (200mg oral solution bid or 200mg i.v. qd) was compared with fluconazole (400mg qd) in 195 patients [231]. There was no difference in the development of invasive fungal infection (8/96 vs. 9/99; p=0.85). A double-blind, randomized study compared itraconazole capsules (100mg bid) with fluconazole (50mg bid) in 213 patients [232]. There was no difference in the development of invasive fungal infection (4/101 vs. 4/101; p=1.0) or mortality (11/101 vs. 7/101; p=0.32). An open study [233] compared itraconazole oral solution (5 mg/kg/d) with fluconazole (100mg qd) in 445 patients. There was a trend towards fewer cases of proven invasive aspergillosis in the itraconazole arm (1/227 vs. 6/218 (3%); p=0.06). No difference in the development of invasive fungal infection or in mortality was found (25/218 vs. 29/227; p=0.67) [233]. Similarly, in a fourth open randomized study, there was no

difference between itraconazole (2.5 mg/kg bid) or fluconazole (400mg qd) as regards the development of invasive fungal infection (4/248 vs. 5/246, 95%CI, -2.8-1.9; p=0.694) or mortality (25/248 vs. 28/246; p=0.68) [234].

In an open, randomized study comparing itraconazole (200mg qd i.v.) and caspofungin (50mg qd i.v.) in 192 patients undergoing chemotherapy for AML or MDS, there was no difference in the incidence of proven invasive fungal infection (5/86 vs. 7/106; p=0.82) [235].
Note: Unlike fluconazole, itraconazole and caspofungin are active in vitro against *Aspergillus* species, but none of these studies was designed with sufficient statistical power to demonstrate a difference in the incidence of invasive aspergillosis.

A meta-analysis of 13 randomized studies with itraconazole prophylaxis (3597 neutropenic patients) by Glasmacher et al. demonstrated a significant reduction in invasive fungal infection (relative risk reduction 40% ± 13%; P=0.002) and invasive fungal infection-related mortality (reduction 35% ± 17%; p=0.04). Only in studies with itraconazole oral solution and not itraconazole capsules, was there a significant effect on the incidence of invasive aspergillosis (48% ± 21%; P=0.02) [236-238].

Posaconazole (200mg tid, n=304) was recently compared with fluconazole (400mg qd per os, -n=240) or itraconazole oral solution (200mg bid, n=58) in a randomized, non-blinded study during consecutive neutropenic episodes in patients with AML or MDS [239]. Proven or probable invasive fungal infection developed in 7 patients (2%) in the posaconazole arm and in 25 patients in the control arm during treatment (8%, 95%CI, -9.7 to -2.5; p<0.001), and in 14/304 vs. 33/298 within 100 days following randomization (p=0.003). Invasive aspergillosis was proven or probable in 2/304 (1%) vs. 20/298 (7%; p<0.001). Mortality within 100 days following randomization was 44/304 (14%) in the posaconazole arm vs. 64/298 (21%) in the control arm (p=0.025). There were more serious adverse effects in the posaconazole arm (19 (6%) vs. 6 (2%) patients; p=0.01) [239]. In a post-hoc analysis of the subgroups in the control arm who had received fluconazole or itraconazole, it appeared that posaconazole was superior to fluconazole (invasive fungal infections 4/239 (2%) vs. 19/240 (8%), 95%CI, –12.1% to –2.9%; p=0.001), but there was no difference in invasive fungal infection between posaconazole and itraconazole (3/65 (5%) vs. 6/58 (10%), 95%CI, –0.2% tot 0.04%; p=0.22).

Conclusions 5.1.a. – Antifungal prophylaxis in AML/MDS or autologous HSCT	
Conclusion 1	It has not been shown that prophylaxis with c-AmB or L-AmB in neutropenic patients leads to fewer invasive fungal infections or a lower mortality.
Level 3	Karthaus, 2000 [213](B); Kelsey, 1999 [214](A2)
Conclusion 2	Prophylaxis with fluconazole prevents invasive fungal infection in neutropenic patients undergoing chemotherapy for acute leukemia or autologous stem cell transplantation.
Level 3	Rotstein, 1999 [217](A2)
Conclusion 3	It has not been shown that fluconazole, i.v. c-AmB, L-AmB, ABLC and nystatin are equivalent in the prevention of invasive fungal infection in patients undergoing chemotherapy for acute leukemia.
Level 3	Bodey, 1994 [221]; Young, 1999 [223], Philpott-Howard, 1993 [224]; Mattiuzzi, 2003[225]; Mattiuzzi, 2004 [227](B)
Conclusion 4	Fluconazole (150mg qd) is as effective as oral AmB suspension (500mg bid) in the prevention of invasive fungal infection in neutropenic patients
Level 3	Menichetti, 1994 [226]. (A2)
Conclusion 5	It has not been shown that oral c-AmB is equivalent to itraconazole for the prophylaxis of invasive fungal infection in neutropenic patients.
Level 2	Harousseau, 2000 [229](A2); Boogaerts, 2001 [230](B)
Conclusion 6	Itraconazole is effective in the prevention of invasive fungal infection and fungal infection-related mortality
Level 1	Glasmacher, 2003 [236]; Prentice, 2006 [232, 238)]; Morgenstern, 1999 [233]; Glasmacher, 2006 [234]; Oren, 2006 [231]; Mattiuzzi, 2006 [235](A1); Harousseau, 2000 [229](A2); Boogaerts, 2001 [230](B)
Conclusion 7	Itraconazole oral solution is more effective than itraconazole capsules or fluconazole as a prophylaxis for invasive aspergillosis
Level 1	Glasmacher, 2003, 2005 [236, 237]; Prentice, 2006 [238](A1)
Conclusion 8	Posaconazole is more effective than fluconazole in the prevention of invasive fungal infection in neutropenic patients
Level 3	Cornelly, 2007 [239](A2)

5.1.b. Allogeneic or autologous bone marrow or stem cell transplantation

In patients undergoing myeloablative allogeneic stem cell transplantation, the incidence of invasive mycoses is considerably higher than among patients undergoing autologous HSCT or chemotherapy [240]. For this reason, antifungal prophylaxis in patients undergoing stem cell transplantation has been investigated separately in these guidelines.

Placebo-controlled studies

In a small, double-blind, randomized study comparing L-AmB (1 mg/kg/d) and placebo in 84 HSCT recipients (69 allogeneic, 15 autologous), fungal colonization occurred significantly less often in the L-AmB arm, but there was no difference in the incidence of invasive fungal infection (1/36, LamB; vs. 3/40, placebo; p=0.36) [241].

In two large studies, fluconazole was compared with placebo in patients undergoing HSCT [242, 243]. In a double-blind, randomized study in 356 HSCT recipients, fluconazole prophylaxis (400mg qd given from the start of the conditioning regimen until granulocyte recovery (>1000/µl) reduced both superficial (8.4% vs. 33.3%; p<0.001) and proven invasive fungal infection (2.8% (5/179) vs. 15.8% (28/177; p<0.001)) as well as fungal infection-related mortality (1 vs. 10 deaths; p<0.001), but not the overall mortality [242]. All invasive *Candida* infections in patients from the fluconazole group were caused by *C. krusei.*
In a double-blind study, Slavin et al. compared fluconazole (400mg qd) with placebo in 300 HSCT recipients (88% allogeneic) from the start of conditioning until the first 75 days post-transplantation [243]. Fluconazole reduced both superficial (77% vs. 86%; p=0.037) and proven invasive fungal infection (10/152, 7%, fluconazole; vs. 26/148, 18%, placebo; p=0.004) as well as overall mortality (20% vs. 35%; p=0.004).
In a follow-up study, Marr et al. demonstrated that – even after 8 years of follow-up – this prolonged prophylaxis (up to 75 days after transplantation) still had an effect on survival (68/152, fluconazole; vs. 41/148, placebo; p<0.002) [244]. This effect was largely caused by more invasive candidiasis in the placebo group (8% vs. <1%; p= 0.007). Also, the severity of gastrointestinal graft-versus-host disease (GVHD) in the fluconazole group was less (p=0.019), which possibly explains the lower incidence of candidemia.

Comparative studies

Fluconazole was compared with c-AmB as prophylaxis in HSCT recipients in 2 prospective, randomized open studies [245, 246]. Prophylaxis was given from the start of conditioning until granulocyte recovery > 500/µl. In the first study with fluconazole (200mg qd) vs. c-AmB i.v. (0.2 mg/kg/d) [245], no effect was seen on the incidence of invasive fungal infection (12/100, 12%, fluconazole; vs. 11/86, 12.8%, c-AmB; p=0.5) or mortality due to invasive fungal infection (6% vs. 7%; p>0.05). In the second study [246] with fluconazole (400mg qd) vs. c-AmB (0.2mg/kg/d) in 355 HSCT patients, again no effect was seen as regards fungal infection (8/196, 4.1%, fluconazole; vs. 12/159, 7.5%, c-AmB; p=0.16) or on mortality resulting from invasive fungal infection.

Fluconazole 400mg qd was compared with itraconazole in patients undergoing allogeneic HSCT in two studies [247, 248]. In the study by Marr et al., prophylaxis with itraconazole (oral solution 2.5 mg/kg tid, or i.v. 200mg qd) was continued until 180 days after the stem cell transplantation. There was a significant difference in invasive fungal infection (fluconazole 15% vs. itraconazole 7%; p=0.03), particularly due to a reduction in invasive aspergillosis (18/148,12%; vs. 8/151, 5%; p=0.03). There was no difference in mortality. Itraconazole caused more adverse effects (16% vs. 36%; p<0.001) [247].
In de study carried out by Winston et al. with itraconazole oral solution 200mg bid or i.v. 200mg qd in 138 patients undergoing allogeneic HSCT, fewer invasive fungal infections developed with itraconazole (9%, 6/71, itraconazole; vs. 25%, 17/67, fluconazole; 95% CI, -29.2;-4.7; p=0.01) [248]. There was no significant reduction of invasive aspergillosis (4.2% vs. 11.9%; p=0.09), fungal infection-related mortality (9% vs. 18%; p=0.13) or overall mortality.
Note: There is some debate with regard to the chosen endpoints in this study. Furthermore, in comparison with other studies, there is a strikingly high percentage of invasive fungal infection in the fluconazole arm.

An open, randomized study in 253 patients undergoing HSCT compared two fluconazole dosage regimens (400mg qd vs. 200mg qd) during the neutropenic phase, and demonstrated no significant differences in the incidence of invasive fungal infection or mortality [249].

A double-blind, placebo-controlled randomized study compared posaconazole (suspension 200mg tid) with fluconazole (400mg qd) in patients with a severe graft-versus-host disease (GVHD) [250]. Patients undergoing allogeneic HSCT were given prophylaxis during 112 days in the event of an acute (grade II-IV) or an extensive chronic GVHD, or if they were undergoing intensive immunosuppressive therapy. The primary endpoint, incidence of invasive fungal infection within 112 days, demonstrated no significant difference between posaconazole and fluconazole (5.3% vs. 9.0%; 95%CI 0.3-1.07; p=0.07). The difference in incidence of invasive aspergillosis, however, was significant (2.3%, posaconazole vs. 7.0%, fluconazole; 95%CI 0.13-0.75; p=0.006) [250]. Also, the incidence of invasive fungal infection in the posaconazole group during the actual use of the prophylaxis (often less than 112 days) was significantly lower (2.4% vs. 7.6%; p=0.004, including that of invasive aspergillosis, 1.0% vs. 5.9%; p=0.046).

In a double-blind study, prophylaxis with micafungin was compared with fluconazole in 882 neutropenic HSCT recipients [251]. Micafungin 50mg qd (or 1mg/kg/d) or fluconazole 400mg qd (or 8mg/kg/d) were given to both children and adults until 5 days after granulocyte recovery (≥ 500/µl). There was no significant difference in the numbers of invasive fungal infections (7/425, 1.6%, micafungin; vs. 11/457, 2.4%, fluconazole; p=0.48), invasive aspergillosis (1 vs. 7; p=0.07) or in mortality (18 vs. 26; p=0.32).
Note: The study had insufficient statistical power due to the fact that the incidence of invasive fungal infection in the population studied was extremely low (1-2%). The committee points out that, in Europe, micafungin is only indicated for use when other antifungal agents cannot be used, in view of the risk of hepatocellular tumours found in animal research. Hence, the committee does not recommend the use of micafungin for antifungal prophylaxis.

Conclusions 5.1.b – Antifungal prophylaxis in patients undergoing HSCT	
Conclusion 9	There is no proof that L-AmB is effective as prophylaxis against invasive fungal infection in patients with neutropenia who are undergoing HSCT.
Level 3	Tollemar, 1993 [241](A2)
Conclusion 10	Fluconazole protects against invasive fungal infection in patients undergoing HSCT.
Level 1	Goodman, 1992 [242](A2); Slavin 1995 [243](A2)
Conclusion 11	Fluconazole prophylaxis up to 75 days post HSCT has a persistent benefit as regards mortality in patients undergoing allogeneic HSCT.
Level 3	Marr, 2000 [244](A2)
Conclusion 12	No difference has been demonstrated between the efficacy of fluconazole and c-AmB in the prevention of invasive fungal infection in HSCT patients.
Level 1	Koh, 2002 [245](A2); Wolff, 2000 [246](A2).
Conclusion 13	Itraconazole is superior to fluconazole for the prevention of invasive fungal infection in allogeneic HSCT patients but causes more toxicity than fluconazole
Level 1	Marr, 2004 [247](A2); Winston, 2003 [248](A2).
Conclusion 14	There is no proof that fluconazole prophylaxis using 400 mg qd is better than 200 mg qd in HSCT patients.
Level 3	MacMillan, 2002 [249](A2)
Conclusion 15	Posaconazole is equivalent to fluconazole in the prevention of invasive fungal infection and superior to fluconazole in the prevention of invasive aspergillosis in patients with severe graft-versus-host disease.
Level 3	Ullmann, 2007 [250](A2)
Conclusion 16	There is no proof that micafungin is superior to fluconazole in the prevention of invasive fungal infection in HSCT patients.
Level 3	van Burik, 2004 [251](A2)

Other considerations

Whether or not antifungal prophylaxis is indicated in patients with hematological malignancies depends on the efficacy of the prophylaxis and the risk of invasive infection. The incidence of invasive mycoses in patients undergoing chemotherapy for hematological malignancies or autologous stem cell transplantation is relatively low. In patients who have undergone myeloablative allogeneic HSCT, the incidence of invasive mycoses is considerably higher, particularly in the group with severe GVHD and/or undergoing immunosuppressive therapy.
Based on its in-vitro activity, it may be assumed that itraconazole is more effective than fluconazole in preventing invasive aspergillosis, but this has not been demonstrated convincingly in individual comparative studies. A meta-analysis suggests that, on reaching adequate serum concentrations, itraconazole is more favorable [236]. That antifungal prophylaxis with posaconazole is active and more effective than fluconazole, is strongly suggested in two recent randomized investigations [239, 250]. Whether or not its use as prophylaxis is also efficient, depends on the incidence in the specific patient group, the costs, adverse effects and interactions. The committee considers the indication to be strongly dependent upon the local incidence of invasive aspergillosis and patient population.

Recommendation 1	In patients with neutropenia following chemotherapy for AML/MDS or HSCT, posaconazole (200 mg tid, until resolution of the neutropenia, or during treatment of severe GVHD) may be considered for antifungal prophylaxis, depending on the local incidence of invasive mycoses.

5.2. Antifungal prophylaxis in solid organ transplantation

Lung transplants

During an open, non-comparative study with fluconazole (400mg qd) in combination with aerosolised c-AmB (0.6 mg/kg/d), none of the 52 lung transplant recipients developed an invasive fungal infection in the course of prophylaxis (1 month); during the follow-up period, however, invasive aspergillosis was diagnosed in 4 patients [252]. In 100 lung transplant recipients, prophylaxis with c-AmB aerosol (25mg qd) was randomly compared with ABLC aerosol (50mg qd) [253]. Apart from more adverse effects in the c-AmB group, no difference was found in failure of primary prophylaxis (pulmonary invasive fungal infection, 6/49, 12.2%, c-AmB; vs. 5/51, 9.8%, ABLC; p=0.7).

Liver transplants

A reduction or a trend towards reduction of invasive mycoses in liver transplant patients was shown in various studies. In a prospective, placebo-controlled study in 77 liver transplant patients with L-AmB (1 mg/kg/d for 5 days), there was a significant difference in the development of invasive fungal infection (0/40 vs. 6/37; 16%; p<0.01) [254]. Furthermore, an open study with ABLC (5 mg/kg/d) compared to a historic control group described a trend towards fewer invasive fungal infections (3/250, 1%; vs. 3/58, 5%; p=0.08) [255]. In a double-blind, placebo-controlled study in 212 liver transplant patients, significantly fewer invasive fungal infections (6/108, 6%; vs. 24/104, 23%; p<0.001) occurred in the group randomized to fluconazole 400 mg qd up to 10 weeks after transplantation [171]. There was no effect on total mortality (11%, fluconazole; vs. 14%, placebo; p= 0.2) but there was a reduction in fungal infection-related mortality (2% vs. 13%; p=0.003).
Note: compared with other studies, this study found a strikingly high percentage of invasive fungal infections in the placebo group.
In several smaller studies, no significant difference was found between the treatment groups:
itraconazole oral solution vs. placebo (0/25 vs. 0/37) [256], fluconazole vs. nystatin (2/76 vs. 6/67, p=0.12) [257], fluconazole vs. itraconazole oral solution (4/91 vs. 7/97, p=0.25) [258], fluconazole vs. untreated historic controls (3/45 vs. 8/72, p=0.42) [259], or sequential prophylaxis with itraconazole preceded by L-AmB (n=42) or fluconazole (n=43) vs. placebo (n=45) [260].
A meta-analysis of antifungal prophylaxis in liver transplant patients included both placebo-controlled studies and comparative studies with polyenes and azoles [261]. No reduction of mortality could be demonstrated (RR, 0.84; 95%CO 0.54-1.3). Fluconazole, however, did result in a significant reduction of invasive mycoses (RR, 0.28, 95%CI 0.13-0.57).

Factors associated with an increased risk of invasive mycoses in liver transplant patients include terminal kidney failure or hemodialysis, mechanical ventilation prior to surgery, re-transplantation, choledochojejunostomy, perioperative massive blood transfusion, or fungal colonization around the day of transplantation (day -2 until 3) [261]. In an observational study, the risk in this group was 5% vs. 0.5% in the other patients [255]. However, no comparative studies have been carried out in this specific, high risk patient category.

Pancreas transplants

In a retrospective study among 445 patients undergoing pancreas transplantation, the incidence of invasive mycoses was 7/108 (6%) in patients given fluconazole prophylaxis (400 mg qd for 7 days), vs. 33/327 (10%, p=0.2) among patients without prophylaxis [262]. The 1-year donor organ survival was 17% in patients with an invasive fungal infection vs. 65% (p<0.01) in those infection. Prospective studies have not been carried out in this patient group.

Heart or kidney transplants

The incidence of invasive mycoses in patients undergoing kidney or heart transplantation is low [263], and studies of the possible effect of antifungal prophylaxis have not been conducted in these patient groups.
A Cochrane review relating to prophylaxis against invasive fungal infection in patients undergoing solid organ transplantation [264] confirmed that fluconazole reduces the incidence of invasive fungal infection compared to placebo (or no prophylaxis) in patients undergoing liver transplantation (RR 0.28; 95%CI 0.13-0.57). This could not be demonstrated for itraconazole or L-AmB. Due to the low incidence, no conclusion could be drawn on kidney or heart transplantation.

Conclusions 5.2 – Antifungal prophylaxis in solid organ transplantation	
Conclusion 17	The efficacy of AmB aerosol or fluconazole as antifungal prophylaxis in lung transplantation has not been demonstrated.
Level 3	Drew, 2004 [253](B); Calvo, 1999 [252](C)
Conclusion 18	Fluconazole and L-AmB are effective in the prevention of invasive mycoses in lung transplant patients.
Level 2	Winston, 1999 [171](A2); Tollemar, 1995 [254](B); Sharpe, 2003 [256](B); Lumbreras, 1996 [257](B); Winston, 2002 [258](A2); Kung, 1995 [259](B); Biancofiore, 2002 [260](B); Playford, 2006 [261](A1)
Conclusion 19	Fluconazole is effective in the prevention of invasive candidiasis in patients undergoing pancreas transplantation.
Level 3	Benedetti, 1996 [262](C)
Conclusion 20	The incidence of invasive mycoses in patients undergoing kidney transplantation or heart transplantation is low, and a favourable effect of antifungal prophylaxis has not been demonstrated in these groups.
Level 3	Grossi, 2000 [263), 264](C)

Recommendation 2	fluconazole (400 mg qd) is recommended for use among patients undergoing liver transplantation and who have an elevated risk of invasive mycoses, (i.e., those with terminal kidney failure or hemodialysis, re-transplantation, choledochojejunostomy, perioperative massive blood transfusion, or proven perioperative colonization with *Candida*). In pancreas transplantation, prophylaxis with fluconazole (400mg up to 7 days postoperative) may be considered, depending on the local incidence of invasive mycoses.

5.3. Antifungal prophylaxis in the intensive care unit

The practice of antifungal prophylaxis in the intensive care unit has been investigated in subgroups of (usually surgical) ICU patients with a high risk of invasive candidiasis.
In a double-blind, placebo-controlled study, Pelz et al. investigated prophylaxis with flucoklm hnazole (400mg qd; loading dose 800mg) in surgical patients with an estimated duration of stay in the ICU of

at least 3 days [265]. Of the 1282 ICU patients, 260 complied with these inclusion criteria. In the fluconazole arm, 11/130 (8.5%) invasive *Candida* infections occurred, vs. 20/130 (15%) in the placebo group (P=0.01; RR 0.45, 95%CI 0.21-0.98), including 3 vs. 8 *Candida* peritonitis. The differences in the number of candidemias (1 vs. 3) and in mortality (11% vs. 12%) were not significant.
Garbino et al. investigated prophylaxis with fluconazole (100mg qd) in a double-blind, placebo-controlled study in 204 ICU patients who had been mechanically ventilated for at least 48 hours and in whom the expected duration of ventilation was at least another 3 days [266]. All patients underwent selective gut decontamination (polymyxin B, neomycin, and vancomycin). No significant difference was found in the incidence of invasive candidiasis (fluconazole, 4/103, 4%; vs. placebo, 10/101, 10%), but there was a significant difference in the incidence of candidemia (1/103, 1%; vs. 9/101, 9%; RR 0.1; 95%CI 0.02-0.74, p=0.008). There was no significant difference in mortality (39% vs. 41%).

In 109 patients with perforation of the gut, mortality was higher (8/33, 24%) in patients with positive perioperative *Candida* cultures of the abdominal fluid than in those with negative cultures (4/76, 5%; OR 11.5; p=0.007) [267]. The efficacy of a perioperative dose of fluconazole (400mg) in this group was investigated in a double-blind placebo-controlled study. A single dose of fluconazole had no significant effect on mortality (4/53, fluconazole; vs. 8/56, placebo; p=0.059).
In a placebo-controlled study, Eggimann et al. investigated the effect of fluconazole prophylaxis (400mg qd for an average of 15 days) in a small group of 49 patients who underwent re-laparotomy following anastomotic leakage or intestinal perforation [268]. Invasive candidiasis occurred in 2/23 (9%) in the fluconazole group vs. 7/20 (35%) in the placebo group (RR 0.25;95%CI, 0.06-1.06; p=0.06). The difference in the incidence of *Candida* peritonitis (1 vs. 7) was significant (RR 0.12; 95%CI, 0.02-0.93; p=0.02).
Note: The incidence of *Candida* peritonitis in the control group (35%) suggests that there was a specific risk of invasive candidiasis in the department under study.

Meta-analyses

Four meta-analyses and a Cochrane review have been published on the subject of the practice of antifungal prophylaxis in severely ill, immunocompetent patients [261, 269-272]. In a meta-analysis of 15 studies, non-absorbable antifungal prophylaxis with amphotericin B or nystatin (either as part of selective gut decontamination or otherwise) had no significant effect on the incidence of invasive mycoses [272].
Two meta-analyses of studies with azoles as prophylaxis in various patient categories in the intensive care setting suggest that prophylaxis with azoles (fluconazole in 7 of the 9 studies) is associated with a reduction of candidemia (fluconazole, RR 0.21, 95%CI 0.06-0.72, p=0.01), but not of mortality [269, 270].
Note. The value of these meta-analyses is limited by the fact that the studies included are heterogeneous (some including patients with a prolonged ICU stay and protracted mechanical ventilation [265, 266], patients with anastomotic leakage [268], gut perforation [267] or pancreatitis [262]. Also, the dosage and duration of administration of fluconazole (single dose or 100 – 400 mg qd) varied widely. The value of the Cochrane review, too, [261] is limited, as 12 randomized studies in highly diverse populations were included, including 4 studies with ketoconazole, which is no longer in use and for which the license for these indications has been withdrawn. In this analysis, the studies with ketoconazole did exert a significant effect on mortality, unlike those with fluconazole which recorded no significant effect on mortality (RR 0.77, 95%CI 0.56-1.07, p>0.05).

Which patients in the intensive care setting are eligible for prophylaxis?

Prophylaxis with fluconazole is possibly efficient in a subgroup of ICU patients with a high risk of invasive candidiasis. Identification of this group has not yet been sufficiently investigated.
Independent risk factors for candidemia in 4276 patients in a surgical intensive care unit were: presence of a central venous catheter (RR 1.42), recent surgery (RR 7.3), acute kidney failure (RR 4.2), total parenteral nutrition (RR 3.6), or a triple lumen catheter (RR 5.4) [204].
Ostrosky-Zeichner et al. have proposed a number of empirically determined prediction rules with which patients with a high risk of candidemia can be identified in the intensive care setting [273, 274]. Using a prediction rule based on a combination of factors (at least 4 days in the ICU, use of antibiotics, a central venous line, surgery, administration of immunosuppressive drugs, pancreatitis, total parenteral nutrition and use of steroids), a subgroup with a 9.9% incidence of invasive candidiasis was identified in a retrospective series of 2890 patients.

Note: The Committee has noted that the rule identified only 30/117 (26%) of all patients with candidemia in the ICU, or 30/88 (34%) of the candidemias after day 4. Applying the prediction rule, therefore, will fail to identify the majority of the patients who develop candidemia in advance.

In a prospective study, Piarroux et al. [275] described the effect of antifungal prophylaxis with fluconazole (400mg qd) in patients who were in a surgical ICU for >4 days. Prophylaxis was initiated as soon as ≥2 of the 5 colonization cultures (rectum, oropharynx, urine, stomach and trachea) became positive for *Candida* species. With this regimen, the incidence of candidemia was 18/478 (4%), vs. 32/455 (7%) in a historic control group (p = 0.03).

Conclusions 5.3 – Antifungal prophylaxis in patients in the intensive care setting	
Conclusion 21	Fluconazole prophylaxis (100-400mg qd) in a predefined category of high-risk ICU patients reduces the incidence of invasive candidiasis.
Level 1	Pelz, 2001 [265](A2); Garbino, 2002 [266](A2)
Conclusion 22	Fluconazole prophylaxis (400 mg qd) is effective in preventing intra-abdominal candidiasis in patients undergoing relaparotomy for anastomotic lintestinal eakage in circumstances characterised by a high incidence of candidiasis
Level 2	Eggimann, 1999 [268](B)
Conclusion 23	Fluconazole reduces the occurrence of invasive fungal infection in specific, selected subgroups with a high incidence of invasive candidiasis in the intensive care unit.
Level 1	Shorr, 2005 [271](A1); Ho, 2005 [270](A1); Playford, 2006 [261](A1)
Conclusion 24	Patient selection based on risk factors as well as on the basis of colonization with *Candida* both appear able to contribute to indication decisions as to antifungal prophylaxis in the intensive care. The effect of this selection approach on the incidence of candidemia, however, has not been investigated in prospective randomized studies.
Level 3	Paphitou, 2005 [274](C); Ostrosky-Zeichner, 2007 [273](C); Piarroux, 2004 [275](C)

Other considerations

The committee considers prophylaxis with fluconazole to be effective in certain specific high-risk situations, such as those involving patients undergoing relaparotomy following anastomotic intestinal leakage in units with a very high incidence of invasive candidiasis. Selection criteria for other risk groups eligible for prophylaxis in the intensive care unit have not been adequately established. Strategies based on colonization require large numbers of surveillance cultures, are associated with high costs, and with delays resulting from the duration of culture incubation. For this reason, patient selection baed on epidemiological risk factors would appear to be more attractive; however, the sensitivity of the criteria examined up till now is very limited, and modelling of the prediction rules published by Ostrosky-Zeichner et al. suggests that only 13% of candidemias would be prevented in a Dutch ICU (unpublished data). For the time being, therefore, the committee recommends that fluconazole prophylaxis be reserved for strictly selected subgroups of patients in local situations with a proven high incidence of invasive candidiasis.

Recommendation 3	Prophylaxis with fluconazole in intensive care is not recommended, except in specific situations in which it has been established that there is an unacceptably high local incidence of invasive candidiasis.

5.4. Antifungal prophylaxis in patients with a primary immune deficiencies and in neonates

Antifungal prophylaxis in chronic granulomatous disease

Due to a specific granulocyte defect, patients with chronic granulomatous disease (CGD) have an elevated risk of aspergillosis. Prophylaxis with recombinant interferon-γ (rIFNγ; 3 times weekly 50μg/m^2) was investigated in 128 patients with CGD in a randomized, double-blind placebo-controlled study [41]. With rIFNγ, the number of severe infections was 14/63 (22%) in 1 year vs. 30/65 (46%) with placebo (p<0.0001). Invasive aspergillosis occurred in 2 vs. 4 episodes (p>0.05) [41]. In an open, non-

randomized series in the same period 1/23 (4%) of the patients treated with rIFNγ developed a proven invasive fungal infection vs. 9/37 (24%) of those not given prophylaxis [276].
In a randomized, double-blind, placebo-controlled cross-over study, prophylaxis with itraconazole capsules (100 to 200 mg qd) was investigated in 39 patients (≥5 years) with CGD [277]. The follow-up ran to a total of 113 patient years. There was a significant difference in the incidence of invasive fungal infection (7/63 episodes, placebo; vs. 1/61, prophylaxis; p=0.05).
In an open, prospective study, prophylaxis with itraconazole (capsules, 10 mg/kg/d) was compared in 30 CGD patients with 64 historic controls with CGD not given prophylaxis [278]. During a follow-up of median 35 months, (6-64 months) 3/30 patients (10%) developed a pulmonary aspergillosis, vs. 24/64 (34.4%, p=0.013) in the historic control group.

Antifungal prophylaxis in premature neonates with a low birth weight

Prophylaxis with fluconazole was investigated during 3 placebo-controlled studies in premature neonates with a birth weight <1500g ('very low birth weight', VLBW) or <1000g ('extremely low birth weight', ELBW). The dosage schedules used varied (3-6 mg/kg) and, in the majority of the studies, the administration frequency rose (every 3rd dag in week 1 to every other day or daily in week 4–6).
In 100 children with ELBW, fluconazole prophylaxis resulted in 0/50 invasive fungal infections vs. 10/50 (20%) in the placebo group (p=0.008) [279]. In a second study in 103 neonates with VLBW, 2/53 invasive fungal infections occurred with fluconazole vs. 2/50 in the placebo arm (p>0.05) [280]. In a Cochrane meta-analysis of these studies, a relative risk of invasive fungal infection of 0.20 (95%CI; 0.07-0.64) was calculated, with a number needed to treat (NNT) of 8, and for mortality an RR of 0.44 (95%CI; 0.21-0.91) [281]. In a more recent 3-arm multi-center study, (fluconazole 3 mg/kg, 6 mg/kg, vs. placebo) in 322 neonates with VLBW or ELBW, invasive fungal infection occurred in 4/104 (3.8%; 3 mg/kg) and in 3/112 (2.7%; 6 mg/kg) with fluconazole prophylaxis vs. 14/106 (13.2%) in the placebo arm (p<0.02) [282].

In an open study, fluconazole prophylaxis in neonates with VLBW resulted in 0/136 invasive fungal infections, vs. 9/119 in a historic control group (p=0.003) [283]. In a similar study in neonates with VLBW, the incidence with prophylaxis was 5/225 (2%) vs. 27/240 (11%, p<0.001) in the historic control group [284], and in a study among neonates with ELBW 15/206 (7%) vs. 4/240 (2%, p=0.01) in historic controls [285].

In a small, double-blind study with insufficient statistical power, no significant difference was shown between two fluconazole dosage regimens in 81 neonates with ELBW: 3 mg/kg every 3rd day in weeks 1 and 2, 3 mg/kg every other day in weeks 3 en 4, and 3 mg/kg/d during weeks 5 and 6; 2/41 invasive mycoses vs. 2 x per week 3 mg/kg; 1/40 mycoses [286].

Antifungal prophylaxis in the neonatal and pediatric intensive care

In a neonatal intensive care unit (NICU), oral nystatin prophylaxis was compared with no prophylaxis in an open, randomized study in 3991 neonates, of whom 24% had a VLBW. Prophylaxis with oral nystatin appeared to lead to a significant reduction of the number of candidemias (17/1996 vs. 131/1516) [287].
Note: Due to its combination of VLBW and heavier neonates, its statistical methodology and non-blinded character, this study is difficult to interpret.
A retrospective, non-randomized study with historic controls in children who had been mechanically ventilated and treated in a pediatric intensive care unit for >7 days, described a 2.7% (5/185) incidence of candidemia in prophylaxis with 50 mg oral amphotericin B suspension tid vs. 10.7% (21/196); p=0.004) in the historic control group [288].

Conclusions 5.4 – Antifungal prophylaxis in primary immune deficiencies and neonates

Conclusion 25	Prophylaxis with recombinant IFNγ appears to lower the incidence of invasive fungal infection in patients with CGD.
Level 2	International CGD Study Group, 1991 [41](A2); Gallin, 1991 [276](B)
Conclusion 26	Itraconazole prophylaxis is effective in the prevention of invasive aspergillosis in patients with CGD.
Level 2	Gallin, 2003 [277](A2); Mouy, 1994 [278](C)
Conclusion 27	Fluconazole prophylaxis is effective in the prevention of invasive candidiasis in children with a birth weight <1500g.
Level 2	Kaufman, 2001 [279](A2); Manzoni, 2007 [282](A2), Bertini, 2005 [283](B); Healy, 2005

	[285](B), Manzoni, 2006 [284](B)
Conclusion 28	There is no convincing evidence from placebo-controlled studies that prophylaxis with oral nystatin or amphotericin B suspension lowers the incidence of candidemia in patients admitted to the NICU or PICU
Level 3	Ozturk, 2006, [287](B), Ben-Ari, 2006 [288](C)

Recommendation 4	In patients with chronic granulomatous disease (CGD), prophylaxis with itraconazole (10 mg/kg/d , max. 200mg bid) is recommended. In addition, prophylaxis with recombinant interferon-γ (50µg/m^2 3 x per week) may be considered.

Recommendation 5	In neonates with a birth weight <1500g, fluconazole prophylaxis may be considered in situations in which there is a proven significant incidence of invasive candidiasis.

Chapter 6

Cryptococcosis

Introduction

Immunocompromised patients, e.g., HIV/AIDS patients or those who have undergone organ transplantation, have an increased risk of cryptococcal infection. In AIDS-patients with cryptococcosis, 75-90% present with subacute meningitis or meningoencephalitis [289]. To develop an optimal treatment recommendation with regard to cryptococcosis, it is necessary to formulate answers to the core questions below.

6.1. What is the optimal treatment of cryptococcal meningitis?
6.2. What is the optimal treatment at other sites of cryptococcal infection?
6.3. What is the optimal primary and secondary prophylaxis?

6.1. What is the optimal treatment of cryptococcal meningitis?

Prospective comparative studies

In a prospective comparative study, c-AmB (0.4 mg/kg/d for 10 weeks) was compared with a combination therapy of c-AmB (0.3 mg/kg/d) with flucytosine (150 mg/kg/d) for 6 weeks in 66 patients with proven cryptococcal meningitis [290]. The response was 47% (15/32, monotherapy) vs. 68% (23/34, combination therapy; p=0.088). The time to sterilisation of the CSF was shorter in the combination therapy group than in the monotherapy group (p<0.001). The ultimate mortality was significantly lower in the combination group (47% (15/32) vs. 24% (8/34), p=0.047).
In a double-blind, prospective study c-AmB (0.7 mg/kg/d) monotherapy was compared with c-AmB (0.7 mg/kg/d) plus 5-FC (100mg/kg/d) as the initial treatment (2 weeks) for cryptococcal meningitis in 381 AIDS patients [291]. After 2 weeks of therapy, the CSF was sterile in 51% (91/179, c-AmB monotherapy) vs. 60% (122/202, combination therapy; p=0.06). If the response was favourable, oral consolidation therapy was given by further randomization between fluconazole (400 mg qd, loading dose 800 mg) or itraconazole capsules (600mg qd for 3 days, followed by 400mg qd for 8 weeks). After 8 weeks of consolidation therapy, the CSF was sterile in 72% (109/151, fluconazole) vs. 60% (93/155, itraconazole, p=0.024). At 10 weeks, the combined mycological and clinical response was 42% vs. 47%.
Multivariate analysis showed that sterilisation of the CSF within 2 weeks was significantly associated with combination therapy (OR 1.92, p=0.01), and sterilisation within 10 weeks with fluconazole consolidation therapy (OR 1.78, p=0.02) [291].

In an open randomized study, L-AmB (4mg/kg/d) was compared with c-AmB (0.7 mg/kg/d) for the treatment of primary cryptococcal meningitis in 28 AIDS patients [292], followed after 3 weeks by fluconazole (400mg qd) for 7 weeks in both arms. Clinical response after 3 weeks of treatment was 12/15 (80%) for L-AmB vs. 11/13 (85% p=1.0) for c-AmB; after 10 weeks this was 87% vs. 83%.
The CSF was sterile within 14 days in 10/15 (L-AmB) vs. 1/9 patients (c-AmB; p=0.01). Nephrotoxicity occurred more frequently in the c-AmB arm (p=0.003). *Note:* compared to other studies [291, 293] the CSF sterilisation observed in the c-AmB group at 2 weeks is very low in this study (11%).

In an open dose comparison study with insufficient statistical power, no difference in response was demonstrated between ABLC (1.2 vs. 2.5 vs. 5.0 mg/kg/d) and c-AmB (0.7 mg/kg/d) in 55 AIDS patients with cryptococcal meningitis [294].

In a randomized study among 64 AIDS patients with a first episode of cryptococcal meningitis, four treatment strategies were compared: c-AmB (0.7mg/kg/d), c-AmB/5-FC (100mg/kg/d), c-AmB/ fluconazole (400mg qd) or c-AmB/5-FC/fluconazole, all for 2 weeks [295]. After 2 weeks, consolidation therapy followed with fluconazole 400 mg qd for 8 weeks. Patients were severely immunocompromised with a median CD4-count of 9 cells/µl (range, 6-32). Combination therapy

consisting of c-AmB with 5-FC was the most effective in sterilising the CSF compared with monotherapy c-AmB (p<0.001), c-AmB/fluconazole (p=0.02) and c-AmB/5-FC/fluconazole (p=0.02). There was no significant difference in mortality between the 4 arms. Early mortality was associated with cerebral dysfunction and a high cryptococcal load in the CSF on presentation.

In a randomized study, fluconazole (200mg qd, loading dose 400mg) was compared with c-AmB (at least 0.3 mg/kg/d) in 194 patients with AIDS-associated cryptococcal meningitis [296]. Patients were randomized 2:1 to fluconazole and c-AmB. After 10 weeks, the CSF was sterile in 34% (44/131; fluconazole) vs. 40% (25/63; c-AmB; p=0.4). The median time to negative CSF culture was 64 days (fluconazole) vs. 42 days (c-AmB, p=0.25). Fluconazole was significantly less toxic than c-AmB (27% vs. 64%, p<0.001) but discontinuation of therapy was rarely necessary (2% vs. 8%, n.s.). The mortality following 2 weeks of treatment tended to be higher in the fluconazole group (15% vs. 8%, p=0.25), but mortality at 10 weeks was similar (18% vs. 14%; p=0.48).

In a small, open study in 20 AIDS patients with cryptococcal meningitis, fluconazole (400mg qd, loading dose 800mg) was compared with combination therapy c-AmB (0.7 mg/kg/d for 7 days, and 3 x per week thereafter) plus 5-FC (150 mg/kg/d) in a 2:1 ratio [293]. At week 10, 57% (8/14) failed with fluconazole vs. 0% (0/6) with c-AmB/5-FC (difference 57%, 95%CI 29-82%, p=0.04). The time to CSF sterilisation was 40.6 ± 5.4 days for fluconazole vs. 15.6 ± 6.6 days for c-AmB/5-FC (p=0.02). The study was prematurely discontinued as all patients who failed turned out to be randomized to fluconazole.

In a randomized study, itraconazole (200mg capsules bid) led to a complete response less often than c-AmB (0.3 mg/kg/d) plus 5-FC (150 mg/kg/d): 5/12 (42%, itraconazole) vs. 10/10 (100%, c-AmB/5-FC; p<0.01) [297]. All patients (6/6) treated with itraconazole in whom there was only a partial response, showed symptoms of relapse with positive cultures in the period following 6 weeks of treatment.
Combination therapy consisting of fluconazole (200mg qd, loading dose 400mg; 2 months) plus 5-FC (150 mg/kg/d; 2 weeks) was no more effective than fluconazole monotherapy (200mg qd, loading dose 400mg): the response after 2 months was 14/30 (47%, combination therapy) vs. 9/28 (32%, fluconazole; p=0.26). Mortality during the first 2 weeks of treatment was 13% (combination) vs. 36% (fluconazole, p=0.05) [298].

In an open randomized prospective study, the duration of combination therapy with c-AmB/5-FC was investigated in 194 patients with cryptococcal meningitis [299]. All patients were treated for 4 weeks with c-AmB 0.3 mg/kg/d and flucytosine 150 mg/kg/d. After 4 weeks of induction therapy, 91 non-high risk, stable and favourably responding patients were randomized to either discontinuation (n=45) or continuation of therapy until a total of 6 weeks (n=46). Treatment was successful in 76% (34/45, 4 weeks vs. 85% (39/46, 6-weeks, n.s.). Relapse of cyptococcal meningitis occurred in 24% (11/45) vs. 16% (7/46; n.s.). There was no difference in toxicity between the groups.

Retrospective comparative studies

In a retrospective descriptive analysis of 106 AIDS patients with cryptococcosis, combination therapy c-AmB (approx. 0.5 mg/kg/d) plus 5-FC (75-100 mg/kg/d) was compared with c-AmB monotherapy (approx. 0.5 mg/kg/d). In the 89 patients with cryptococcal meningitis, median survival was 186 days (combination) vs. 144 days (monotherapy; p=0.21) [300].
In a retrospective analysis c-AmB, (n=43) was compared with fluconazole (n=40) for the treatment of cryptococcosis in HIV-negative patients [301]. In patients with meningitis, the response was 74% (26/35) for c-AmB vs. 68% (17/25; p=0.59) for fluconazole. As the dosages varied, no judgement can be made with respect to difference in efficacy. Another retrospective study described 44 HIV-negative patients with cryptococcosis who were treated with fluconazole (200-400 mg qd) [302]. Among the 19 patients with cryptococcal meningitis, treatment was successful in 58% (11/19).

Immunotherapy

There is evidence that endogenous interferon-γ (IFN-γ) production is associated with the rate of clearance of cryptococci from CSF [303, 304]. Immunotherapy with recombinant IFN-γ was therefore investigated in a double-blind, placebo-controlled study of adjuvant rIFN-γ (100µg vs. 200µg vs. placebo; 3 x per week, for 10 weeks) in 70 AIDS patients with cryptococcal meningitis receiving

standard therapy (c-AmB 0.7 mg/kg/d + 5-FC 4dd 25 mg/kg/d) [305]. After 2 weeks, the CSF cultures were sterile in 13% (placebo) vs. 36% (rIFN-γ, 100 µg, p=0.072) and 32% (rIFN-γ, 200 µg, p=0.14). There were no significant differences in the clinical outcomes.

Intraventricular therapy

In a very small, retrospective series, the intraventricular administration of c-AmB added to systemic antifungal therapy (c-AmB, 1mg/kg/d plus 5-FC, 100mg/kg/d) was compared with systemic therapy only in 13 patients with cryptococcal meningitis [306]. Sterilisation of the CSF was achieved in 6/6 (combination) vs. 3/7 patients. Mortality during therapy was 1/6 vs. 6/7 (p=0.025). The two groups were not properly comparable; the patients given combination therapy were younger and had been symptomatic for a longer period of time.

Elevation of intracranial pressure in cryptococcal meningitis

Elevated intracranial pressure in patients with cryptococcal meningitis is associated with a less favourable prognosis [307]. In the Van der Horst study, [291] a high opening pressure was associated with headache, loss of hearing, meningism, altered states of consciousness and the level of cryptococcal antigen in the CSF [308]. Mortality in patients with an opening pressure >250mm H_2O was 33% (39/119) vs. 21% (21/102, at pressure <250mm; p=0.04), clinical failure after 2 weeks was 20% vs. 2% (p<0.001), and mycological response after 2 weeks was 45% vs. 67% (p=0.002) [308]. Lowering the pressure by means of repeated CSF drainage improved the prognosis.
Administration of steroids in patients with high opening pressures (>350 mm H_2O) turned out to be associated with a poorer outcome (mortality 4/13, 31%, steroids) vs. 1/39 (3%, without steroids; p=0.003) [308].
A double-blind, placebo-controlled study investigate acetazolamide (4dd 250mg) for the treatment of elevated intracranial pressure (≥200 mm H_2O) in 22 patients with cryptococcal meningitis [309]. The study had to be prematurely discontinued due to adverse effects occurring in the treatment arm.

Non-comparative studies

Monotherapy with c-AmB (0.7 mg/kg/d, for at least 2 weeks) followed by maintenance therapy with an azole was described in 106 AIDS patients with cryptococcal meningitis [310]. Of these patients, only 38% had negative CSF cultures after 2 weeks of therapy, and 56% after 4 weeks. In an open, prospective study with L-AmB (3.0 mg/kg/d, for at least 6 weeks), the response in 19 AIDS patients with cryptococcal meningitis was 74% (14/19) and the mortality was 16% (3/19) [311]. In a retrospective analysis of 78 patients with cryptococcal meningitis and treated with ABLC, the response was 65% (51/78) [312].

In an open study with high-dose fluconazole (800-1000mg qd) in 14 AIDS patients with cryptococcal meningitis, the response after 10 weeks of treatment was 55% (6/11), at end of therapy it was 73% (8/11) [313]. Time to negative CSF cultures appeared to depend on the MIC for fluconazole (MIC 4 µg/ml, 56 days; MIC <4 µg/ml, 16 days).
An open, non-comparative study investigated the combination of fluconazole (400mg qd) plus 5-FC (150 mg/kg/d) in 32 AIDS patients with cryptococcal meningitis [314]. The response after 10 weeks of therapy was 63%. Itraconazole (200mg bid) was studied in 20 immunocompromised patients with cryptococcal meningitis; the response was 65% (13/20) [315].

Conclusions 6.1 – Treatment of cryptococcal meningitis

Conclusion 1	Combination therapy with c-AmB plus 5-FC leads to more rapid sterilisation of CSF and better survival than monotherapy with low dose c-AmB (0.3 mg/kg/d).
Level 1	Bennett, 1979 [290](A2); van der Horst, 1997 [291](A2)
Conclusion 2	In the initial treatment of cryptococcal meningitis, there is no difference in clinical outcome between monotherapy with c-AmB (0.7mg/kg/d) and combination therapy consisting of c-AmB plus 5-FC
Level 3	van der Horst, 1997 [291](A2)
Conclusion 3	It has not been shown that L-AmB and ABLC are equivalent to c-AmB for the treatment of cryptococcal meningitis. L-AmB does sterilise the CSF more rapidly than c-AmB in the treatment of cryptococcal meningitis.
Level 2	Sharkey, 1996 [294](B); Leenders, 1997 [292](B); Coker, 1993 [311](C); Baddour, 2005 [312](C)
Conclusion 4	Fluconazole is as effective as amphotericin B monotherapy in the treatment of cryptococcal

	meningitis. However, fluconazole was associated with a trend towards higher mortality during the first 2 weeks of treatment.
Level 3	Saag, 1992 [296](A2)
Conclusion 5	Combination therapy with c-AmB plus 5-FC is more effective than fluconazole or itraconazole monotherapy for the treatment of cryptococcal meningitis.
Level 2	Larsen, 1990 [293](B); de Gans, 1992 [297](B); Denning, 1989 [315](C)
Conclusion 6	Combination therapy with c-AmB/5-FC sterilises the CSF more rapidly than c-AmB alone, c-AmB/fluconazole, or c-AmB/fluconazole/5-FC in cryptococcal meningitis.
Level 3	Brouwer, 2004 [295](A2)
Conclusion 7	Initial combination therapy with fluconazole/5-FC is more effective than monotherapy with fluconazole for the treatment of cryptococcal meningitis.
Level 3	Mayanja-Kizza, 1998 [298](A2)
Conclusion 8	It has not been proven that a high dose of fluconazole (800mg qd) sterilises the CSF more rapidly than 400mg qd.
Level 3	Menichetti, 1996 [313](C)
Conclusion 9	It has not been proven that consolidation therapy with fluconazole is more effective than itraconazole in the treatment of AIDS-associated cryptococcal meningitis.
Level 3	van der Horst, 1997 [291](A2)
Conclusion 10	It has not been proven that the combination of c-AmB plus rIFN-γ is more effective than conventional treatment of cryptococcal meningitis. However, addition of rIFN-γ does lead to more rapid sterilisation of CSF.
Level 3	Pappas, 2004 [305](A2)
Conclusion 11	The value of additional intraventricular administration of c-AmB in the treatment of cryptococcal meningitis has not been demonstrated.
Level 3	Polsky, 1986 [306](C)
Conclusion 12	Elevated intracranial pressure is associated with a less favourable prognosis in cryptococcal meningitis. Steroids or acetazolamide do not improve the prognosis; lowering of the pressure by means of CSF drainage does.
Level 3	Graybill, 2000 [308](A2); Newton, 2002 [309](C)

Other considerations

Older studies of the treatment of cryptococcosis and cryptococcal meningitis by Bennett [290], Chuck [300], Dismukes [299], Saag [296] and De Gans [297] have utilised a very low dose of c- AmB (0.3-0.4 mg/kg/d). For this reason, the results of these studies are difficult to extrapolate to current practice. In later studies [291, 293] higher doses of c-AmB were used (0.7 mg/kg/d) which better outcomes. The small study by Larsen et al., in 20 AIDS patients, suggested that the combination c-AmB/5-FC is more effective than fluconazole for the initial treatment of cryptococcal meningitis. This is in agreement with the finding that the combination c-AmB/5-FC leads to more rapid CSF sterilisation [295]. The study by Saag et al. [296], which showed no significant difference between monotherapy with c-AmB and fluconazole, has, due to a (non-significant) difference in mortality during the first 2 weeks of treatment (15% vs. 8%), led to a preference for c-AmB as the basis for the initial treatment of cryptococcal meningitis. On the grounds of the study by Larsen et al. [293], the committee considers that the combination c-AmB/5-FC is generally preferable to fluconazole for the treatment of cryptococcal meningitis.

No studies of the treatment of cryptococcal meningitis have been carried out in children. In the absence of such data, the committee recommends that the treatment of cryptococcal meningitis in children should be based on the treatment guidelines for adults.

Recommendation 1	Cryptococcal meningitis should be treated with c-AmB (0.7 mg/kg/d) plus 5-FC (100 mg/kg/d) for at least 2 weeks. Thereafter, the treatment of stable and favourably responding patients may be continued with fluconazole (loading dose 800mg, followed by 400 mg qd; in children, a loading dose of 12 mg/kg, followed by 6 mg/kg/d), for a total of at least 10 weeks.

6.2. What is the optimal treatment at other sites of cryptococcal infection?

Extrameningeal cryptococcal infection occurs mainly in patients not infected with HIV [316, 317]. In a retrospective analysis, c-AmB (n=43) was compared with fluconazole (n=40) for the treatment of cryptococcosis in HIV-negative patients [301]. In patients with extrameningeal cryptococcosis, the response was 75% (6/8, c-AmB) vs. 93% (14/15, fluconazole; p=0.21). As the dosage of the antifungal therapy per patient per dag was not uniform, it is not possible to make any judgement on the efficacy of either drug.
In a retrospective descriptive study in 106 AIDS patients with cryptococcosis who had been treated with c-AmB or c-AmB/5-FC, 14 patients had an extrameningeal infection; the median survival was 187 days, and relapse occurred in 20% [300]. Other descriptive studies reported results in patients with extrameningeal cryptococcosis treated with ABLC (response 16/23, 70%) [312], fluconazole (response 11/14, 79%) [318] or itraconazole (response 9/9; 100%, of which 2/9 relapsed after discontinuation of therapy) [315].
In a cohort study, 83 transplant patients with cryptococcosis were prospectively followed [319]. The choice of therapy was LFAB (39/83, 47%), c-AmB (17), fluconazole (24) or itraconazole (3). Furthermore, 31/84 (37%) patients were given 5-FC, mainly in combination with AmB. Amphotericin B was given more often to patients with a proven CNS localisation, a disseminated cryptococcosis, or cryptococcemia. Fluconazole was given more often to patients with pulmonary infections. There was no difference in 6-months' mortality in patients with extrameningeal cryptococcosis who had been treated with AmB (2/18, 11%) vs. fluconazole (2/21, 10%) [319]. Virtually all patients were then given maintenance therapy with fluconazole (51/54, 94%). Relapse occurred in only 1 patient.

Children

The incidence of cryptococcosis in children infected with HIV was described in a retrospective study [320]. 473 patients, of whom 4 developed cryptococcosis (0.85%), were prospectively followed for 8 years; an annual incidence of 0.1%. All 4 patients had a low CD4-count (median, 15 cells/µl, range 6-66) despite antiretroviral therapy.

Conclusion 6.2 – Treatment of extrameningeal cryptococcosis

Conclusion 13	The sparse data available suggest that there is no significant difference in outcome between c-AmB, c-AmB/5-FC, ABLC, and fluconazole for the treatment of extrameningeal cryptococcosis. However, it has not been proven that c-AmB and fluconazole are equivalent for the treatment of extrameningeal cryptococcosis.
Level 3	Aberg, 1999 [317](B); Chuck, 1989 [300](C); Baddour, 2005 [312](C); Meyohas, 1996 [318](C); Singh, 2005 [319](C); Dromer, 1996 [301](B).

Other considerations

No studies of sufficient quality have been conducted in patients with extrameningeal cryptococcosis. The sparse data available from prospective studies usually relate to HIV-positive patients. In HIV-negative patients, extrameningeal cryptococcosis accounts for a far greater percentage of all cryptococcal infections. In patients with extrameningeal cryptococcosis, it is important to exclude cryptococcal meningitis and cryptococcemia by means of a lumbar puncture and blood cultures [321]. In the absence of specific studies, the committee bases its recommendations on studies of cryptococcal meningitis. The duration of antifungal therapy in non-meningeal cryptococcosis has not been investigated, but lengthy treatment is assumed to be necessary.

Recommendation 2	In patients with extrameningeal cryptococcosis, a cryptococcal meningitis should be excluded by means of lumbar puncture.

Recommendation 3	Treatment of extrameningeal cryptococcosis depends on the severity of the illness. In severely ill patients, initial therapy with c-AmB/5-FC is recommended. For patients with mild symptoms, fluconazole (400mg qd, in children 6 mg/kg/d) may be prescribed.

6.3.a. Prophylaxis of cryptococcosis

Primary prophylaxis

Comparative studies

In a Cochrane analysis of the primary prophylaxis of cryptococcosis in adults with HIV, 5 studies were included [322]. In 2 studies, fluconazole was given and in the remaining 3, itraconazole. Prevention of cryptococcosis was the primary objective in only one study, in the others, the objective was the prevention of histoplasmosis or of all invasive fungal infections. Furthermore, there were more differences between the studies, including limits of CD4 count (<100 up to <300), the use of HAART, and the duration of follow-up.
Both fluconazole and itraconazole were found to be effective in the primary prophylaxis of cryptococcosis in patients in an advanced stage of HIV infection (relative risk compared to placebo 0.21; 95%CI 0.09-0.46). In this meta-analysis, however, no effect on mortality was demonstrated [322].

In a placebo-controlled study, itraconazole (capsules, 200mg qd) as primary prevention of invasive fungal infection was investigated in 129 HIV patients with a CD4 count < 200 cells/µl [323]. In the interim analysis, the study was prematurely discontinued due to a significant difference between the 2 arms. Invasive fungal infection was demonstrated in 1/63 (1.6%, itraconazole) vs. 11/66 (17%, placebo, p=0.003). The incidence of cryptococcosis was 0/63 vs. 7/66 (p<0.001). There was no difference in mortality.
In another double-blind, placebo-controlled study, itraconazole (capsules, 200mg qd) was investigated in 295 HIV-positive patients with a CD4 count <150 cells/µl (without HAART) as a prophylaxis against fungal infection [324]. Cryptococcosis occurred in 1 patient (0.7%, itraconazole) vs. 8 patients (5.5%, placebo; p<0.001). There was no significant difference in mortality (32, itraconazole vs. 21, placebo, p= 0.11).
A double-blind placebo-controlled study investigated fluconazole prophylaxis (400mg/week) in 90 HIV patients with a CD4 count <100 cells/µl [325]. Cryptococcosis occurred in 3/44 (6.8%, fluconazole) vs. 7/46 (15.2%, placebo; p=0.32), and there was a difference in mortality in favour of fluconazole (2 vs. 9, p=0.029).
In a multicenter, double-blind, randomized study (CCTG-trial), fluconazole 200mg qd was compared with fluconazole once weekly 400mg in 636 HIV patients with <100 CD4-cells/µl [326]. There was no difference in the incidence of cryptococcosis (2/318, 0.6%, 200mg qd) vs. 5/318 (1.6%, 400mg/week; 95%CI of the difference, -0.7%–2.6%, p=0.25).
An open prospective, randomized study (ACTG-trial) compared fluconazole (200mg qd) with clotrimazole (5dd 10mg; not licensed in the Netherlands) in 428 HIV patients [327]. Cryptococcosis occurred in 2/217 (0.9%, fluconazole) vs. 15/211 (7.1%, clotrimazole, p=0.004). The estimated cumulative 2-years risk of cryptococcosis in patients with a CD4 count of ≤50 was 1.6% (fluconazole) vs. 9.9% (clotrimazol; p=0.02).
A retrospective analysis compared fluconazole prophylaxis (100mg qd) in 329 HIV patients with CD4 <68 cells/µl with a historic control group (n=337) without prophylaxis [328]. One patient (fluconazole, 0.7/100 patient years) vs. 16 patients (placebo, 10.2/100 patient years) developed cryptococcosis.

Non-comparative studies

In an open, non-randomized study, fluconazole (200 mg, 3 x weekly) was prescribed as primary prophylaxis in 218 HIV patients with a CD4 count ≤100 cells/µl (without HAART) [329]. Cryptococcal meningitis developed in 1/218 (0.4%) patients with a median follow-up of 12.1 months (0.5-30 months).

Conclusions 6.3.a – Primary antifungal prophylaxis of cryptococcosis	
Conclusion 14	Both fluconazole (200mg qd) and itraconazole (capsules, 200mg qd) are effective in the prevention of cryptococcosis in HIV-positive patients.
Level 1	Chang, 2005 [322](A1); Chariyalertsak, 2002 [323](A2); McKinsey, 1999 [324](A2); Nightingale, 1992 [328]
Conclusion 15	No difference in efficacy has been demonstrated between fluconazole 200mg qd or 400mg weekly for the prevention of cryptococcosis.
Level 3	Havlir, 1998 [326](A2)
Conclusion 16	Fluconazole (200mg qd) is more effective than clotrimazole (10mg 5 times qd) as prophylaxis against cryptococcosis.
Level 3	Powderly, 1995 [327](A2).

Secondary prophylaxis

A double-blind placebo-controlled study investigated secondary fluconazole prophylaxis in 61 HIV-positive patients who had suffered a cryptococcal meningitis [330]. At interim-analysis, the percentage of relapses was 3% (1/34, fluconazole) vs. 37% (10/27, placebo; 95%CI 15-53, p<0.001). Following this interim-analysis, the study was discontinued.
In an open, randomized study, fluconazole (200 mg qd) was compared with c-AmB (1 mg/kg/week i.v.) for the prevention of cryptococcal meningitis relapse in 189 HIV-positive patients [331]. The incidence of cryptococcosis relapses at the last follow-up (median, 286 days) was 2/111 (fluconazole) vs. 14/78 (c-AmB; p<0.001).
A double-blind, randomized study compared fluconazole (200mg qd) with itraconazole (200mg qd) as secondary prophylaxis in patients with HIV-positive [332]. The percentage of patients with relapsing cryptococcal meningitis was 4% (2/51; fluconazole) vs. 23% (13/57; itraconazole; difference 19%, 95%CI 8-29%). Due to this significant difference, the study was discontinued at the interim analysis.

Discontinuation of secondary prophylaxis during HAART

A prospective, randomized trial investigated the discontinuation of secondary cryptococcal prophylaxis (fluconazole 200mg qd) in 60 patients with a CD4 count of >100/µl and an HIV RNA that remained undetectable for 3 months during HAART [333]. Patients were randomized to either continuation or discontinuation of antifungal prophylaxis. After 48 weeks there was no cryptococcal meningitis relapse in either group.
Three small prospective, descriptive reports each descrribed 6 HIV-positive patients with a CD4 count of >100/µl, who discontinued secondary prophylaxis during HAART. During the 12-24 month follow-up, none of the patients relapsed [334-336].
In a retrospective multicenter study in 100 HIV-positive patients, a cryptococcal meningitis relapse occurred in 2 patients, and extrameningeal cryptococcosis in 2 others, at a median of 28 months (range 6.4-64.5) after discontinuation of secondary prophylaxis (incidence, 1.53 / 100 patient years; 95%CI 0.42-3.92) [337].

Conclusions 6.3.b – Secondary prophylaxis of cryptococcosis	
Conclusion 17	Fluconazole (200 mg qd) is effective in the prevention of cryptococcosis relapse in HIV-positive patients.
Level 1	Bozzette, 1991 [330](A2); Powderly, 1992 [331](A2); Saag, 1999 [332](A2)
Conclusion 18	Fluconazole (200 mg qd) is more effective than c-AmB (1mg/kg/week) in the prevention of cryptococcosis relapse.
Level 3	Powderly, 1992 [331](A2)
Conclusion 19	Fluconazole is more effective than itraconazole in the prevention of relapse of cryptococcal meningitis.
Level 3	Saag, 1999 [332](A2)
Conclusion 20	It is safe to discontinue secondary antifungal prophylaxis in patients having had cryptococcal meningitis,who have a favourable immunological and virological response to HAART (CD4 >100 cells/µl and HIV load < 50 copies/ml, for at least 3 months).
Level 3	Vibhagool, 2003 [333](A2); Aberg, 2002 [334](C); Martinez, 2000 [335](C); Rollot, 2001 [336](C); Mussini, 2004 [337](C).

Other considerations

The incidence of cryptococcosis in HIV-positive patients in the Netherlands is relatively low. Although many patients with <200 CD4-cells/µl use fluconazole for mucosal candidiasis, primary prophylaxis of cryptococcosis is not routinely given to these patients in the Netherlands [338], despite the favourable results of randomized studies.
Discontinuation of prophylaxis on achieving a CD4 count of >100/µl following cryptococcosis has been investigated in various studies. In practice, however, a limit of 200 CD4-cells/µl is held to for the discontinuation of secondary prophylaxis; this is analogous to the criteria for discontinuation of prophylaxis against *P. jiroveci, T. gondii*, and CMV [338].

Recommendation 4	In HIV-positive patients with a CD4 count of <100 cells/µl, fluconazole prophylaxis (200mg qd) against primary cryptococcosis may be considered.

Recommendation 5	In HIV-positive patients who have suffered cryptococcosis, fluconazole maintenance therapy (200mg qd) is recommended.

Recommendation 6	In HIV-positive patients with a favourable immunological response to HAART (CD4 count >200 cells/µl, for ≥3 months) discontinuation of fluconazole prophylaxis may be considered.

Chapter 7

Zygomycosis

Introduction

Zygomycosis, also known as mucormycosis, is a severe and often fatal infection caused by fungi belonging to the order of the zygomycetes. The most common sites of zygomycosis are the paranasal sinuses and adjacent areas (rhinocerebral, sino-orbital and sinopulmonary zygomycosis), the lungs, the skin, and the brain [339, 340]. In children, zygomycosis may occur in the gastro-intestinal tract [341].
The incidence of invasive zygomycosis appears to be rising (from 0.09% to 0.17%) in recent years, especially in hematological patients [342, 343]. Some investigators relate this rising incidence to the increasing use of voriconazole [344].
The conduct of prospective, randomized studies of the treatment of zygomycosis is not possible due to its low incidence. Data on the treatment of zygomycosis are therefore based on clinical experience and retrospective analyses.

7.1. What is the optimal treatment for invasive zygomycosis?

Most experience in the treatment of invasive zygomycosis has been gained with c-AmB [345]. The treatment results with this drug have not been systematically collected and published.
In a retrospective analysis of 64 patients with zygomycosis treated with ABLC (approx. 5 mg/kg), 52% had a complete (13%) or partial (39%) response after median 16 days of therapy (range 5-180) [346, 347].
ABLC (5 mg/kg/d) was investigated in a large open-label salvage study in 556 patients who had a proven or probable (per EORTC/MSG criteria) invasive fungal infection, refractory to or intolerant of the first-line antifungal therapy, and who met the assessment criteria (treatment for at least 4 days with ABLC and sufficient follow-up) [27]. The response in the subgroup of 24 patients with invasive zygomycosis was 71% (17/24), of whom 38% (9/24) had complete response.
Note: The response in the subgroups receiving salvage therapy due to toxicity or as a result of failure of earlier therapy was not recorded and neither were the results of the full intent-to-treat (ITT) population.
In a retrospective series of 6 kidney transplant patients with invasive zygomycosis treated with ABLC (> 5mg/kg/d), the mortality was 50% (3/6). These patients died within 30 days after the diagnosis had been made [348].
Herbrecht et al. described 21 patients with zygomycosis who were treated with ABCD [349]. Primary therapy with ABCD (approx. 5 mg/kg/d) was initiated because of pre-existing kidney failure. Salvage therapy with ABCD was initiated because of failure or the development of kidney failure on use of c-AmB. In 13 patients, the therapy was combined with surgery. The response (complete or partial) was 12/20 (60%). In combination with surgery the response was 8/13 (62%), of whom 7/13 (54%) had complete response. Without surgery, a complete response was seen in only 1/7 patients [349]. A retrospective analysis of 16 patients with invasive zygomycosis and treated with c-AmB or LFAB revealed an overall mortality of 25% (4/16) [350].

Posaconazole (800mg qd) as salvage therapy was investigated retrospectively in 91 patients with proven or probable invasive zygomycosis [351]. Patients were intolerant (n=10) of or had infections that were refractory (n=81) to other antifungal therapies. 77/91 (85%) had been pre-treated with LFAB, 24/91 (26%) had been treated with c-AmB. The response at 12 weeks was 60% (14% complete, 46% partial). There was no difference in response between patients treated either with (39/64; 61%) or without surgical debridation (16/26; 62%). Mortality at 1 month of follow-up was 35/91 (38%) [351].
Another retrospective salvage study with posaconazole (800mg qd) in 24 patients with invasive zygomycosis described a response of 79% (19/24) [352]. There was no difference in response between patients with refractory infections (79%) and intolerance to standard therapy 80% (4/5).

Children

Wiley et al. described 4 pediatric patients treated with ABLC for an invasive zygomycosis, with a response of 2/4 (complete and partial response) [24].

Other considerations

The absence of randomized comparative studies on the treatment of invasive zygomycosis has resulted in the choice of therapy being based on retrospective analyses and expert opinion. It is assumed that the relatively poor response to c-AmB is at least partially due to the small amounts of AmB that can be safely administered. It is generally assumed, therefore, that a lipid formulation of amphotericin B in a daily dosage of at least 5 mg/kg is to be preferred.
There is still little experience with posaconazole; this drug has only been investigated in patients with refractory infections and appears to have reasonable efficacy in these circumstances.
In view of the poor prognosis of invasive zygomycosis despite antifungal and surgical treatment, it is assumed that correction of underlying risk factors (e.g. immunosuppression, ketoacidosis) is of great importance.

Conclusions 7 – Treatment of invasive zygomycosis	
Conclusion 1	Lipid formulations of amphotericin B are effective for the treatment of invasive zygomycosis
Level 3	Larkin, 2003 [346](C); Perfect, 2005 [347](C); Forrest, 2007 [348](C); Herbrecht, 2001 [349](C); Sims, 2007 [350](C)
Conclusion 2	Antifungal treatment of invasive zygomycosis combined with surgical debridement leads to a better response than antifungal therapy only.
Level 3	Herbrecht, 2001 [349](C)
Conclusion 3	Posaconazole appears to be effective as a salvage therapy in refractory invasive zygomycosis
Level 3	van Burik, 2006 [351](C); Greenberg, 2006 [352](C)

Recommendation 1	Invasive zygomycosis should be treated with a lipid formulation of amphotericin B in a dosage of at least 5 mg/kg/day.

Recommendation 2	Where possible, the antifungal treatment of invasive zygomycosis should be combined with surgical debridement and correction of underlying risk factors.

Recommendation 3	For salvage treatment of invasive zygomycosis on failure or intolerance of LFAB, administration of posaconazole may be considered.

Potential conflicts of interest

The SWAB employs strict guidelines with regard to potential conflicts of interests as described in the SWAB Format for Guideline Development (www.swab.nl). Members of the preparatory committee reported the following potential conflicts of interest:
Drs A.M.L. Oude Lashof: no conflicts of interest reported.
Prof Dr B.J. Kullberg: received support for conference attendance from Pfizer and participated in CME courses with unrestricted support from Astellas, Janssen-Cilag, MSD and Pfizer; his department received contributions for consultancy services from Basilea, Novartis, Pfizer and Schering-Plough.
Dr J.J.W.M. Janssen: received support for conference attendance from Amgen, Novartis and Roche, and speakers' fees from Novartis; he also provided consultancy services for Schering-Plough.
Dr J.F.G. Meis: participated in CME courses with support from Janssen-Cilag, received support for conference attendance from Gilead and Pfizer and speakers' fees from Pfizer and Schering-Plough; he also provided consultancy services for Basilea and MSD and his department received contributions for scientific research from Basilea, Cephalon, MSD and Schering-Plough.
Dr S. Natsch: no conflicts of interest reported.
Prof Dr P.E. Verweij: received support for conference attendance from Gilead and Merck, speakers' and consultancy fees from Gilead, Merck, Pfizer and Schering-Plough, and his department received contributions for scientific research from Basilea, Gilead, Merck, Pfizer and Schering-Plough.
Dr A. Warris: organised CME with support from Gilead and Pfizer, received support for conference attendance from Pfizer and provided consultancy services for Pfizer and Schering-Plough.
Dr J.W. van 't Wout: participated in CME with support from Janssen-Cilag
Dr A. van Zanten: received support for conference attendance from MSD and Pfizer and speakers' fees from Pfizer; he also provided consultancy services for Neutec, MSD and Pfizer.

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