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. These guidelines also form the basis of SwabID, the national online antimicrobial guidelines (www.swab.nl).

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.

1.1. Scope and validity of the guidelines

These guidelines cover invasive fungal infection by *Candida* species, *Aspergillus* species, *Cryptococcus neoformans*, and mucorales. In addition to invasive infections, the policy for oropharyngeal candidiasis is also included in the guideline. Vulvovaginal candidiasis and dermatomycoses are beyond the scope of the guideline. The guidelines are applicable to adults, children and neonates, and are intended for both intramural and extramural use.
SWAB intends to revise their guidelines every 5 years. The potential need for earlier revisions will be determined by the SWAB board at annual intervals, on the basis of an examination of current literature. If necessary, the guidelines committee will be reconvened to discuss potential changes. When appropriate, the committee will recommend expedited revision of the guideline to the SWAB board.

1.2. Methods

The guidelines were drafted in accordance with the recommendations on evidence-based development of guidelines (Medical Specialties Guidelines 2.0, final report, 2011) by the Netherlands Federation of Medical Specialties. 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. For the original guidelines (published, September 2008), a systematic review was conducted on 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. For the present version, the an additional systematic review was performed, using the same sources, for January 2008 through December 2016. 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 executive board, consisting of mandated representatives of the professional societies.

1.3. Implementation

After final approval, the SWAB guidelines are published at www.swab.nl, and an executive summary is published in a peer-reviewed journal. The new guidelines form the basis of the treatment recommendations in the online national antimicrobial guide (SWAB-ID) for the prophylaxis and treatment of infectious diseases in hospitals. SWAB-ID is updated at least twice yearly, incorporating all SWAB guideline recommendations. Every hospital in the Netherlands has been offered the opportunity to obtain a custom, localized version of SWAB-ID as a local or regional online antimicrobial guide. Updates of the national version of SWAB-ID, including new guidelines, are distributed to the localized SWAB-ID guides. The implementation of national and local SWAB-ID antimicrobial guidelines and adherence to the recommendations are secured by the national Antimicrobial Stewardship Program that has been established by SWAB, the Health Inspectorate (IGZ) and the Ministry of Health (VWS) since 2013. In each hospital, an Antimicrobial Stewardship Team (A-team) is charged with implementation and monitoring of guidelines on a daily basis. Adherence to guidelines and recommendations is reported to the SWAB National Stewardship Monitor.

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1.4. Guidelines and Conflicts of Interest

All members of the guideline committee complied with the SWAB policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the guideline committee were provided the SWAB conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts are listed at the bottom of the guideline.

Table 1.1 Methodological quality of individual studies relating to prevention or treatment†

Evidence level	Definition
A1	Systematic review of at least two independent A2 level studies
A2	Randomised controlled trial (RCT) of sufficient methodological quality and power or Prospective cohort study with sufficient power and with adequate confounding corrections
B	Comparative study lacking the same quality as mentioned in A2 (including patient-control and cohort studies) or Prospective cohort study lacking the same quality as mentioned in A2, retrospective cohort study or patient-control study
C	Non-comparative study
D	Evidence based on the opinion of members of the Guideline committee

Table 1.2. Level of evidence

Evidence level	Definition
Level 1	Study of level A1, or at least two independent studies of level A2
Level 2	One study of level A2, or at least two independent studies of level B
Level 3	One study of level B or C
Level 4	Expert opinion

† Defined in: Handbook of the Dutch Institute for Healthcare Improvement CBO

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1.5. What is new compared to the 2008 version of the guidelines?

In view of the time elapsed since the release of the previous version of the guidelines, the majority of the paragraphs and recommendations have changed. Therefore, this paragraph will not attempt to summarize all changes, and readers are referred to the specific content of the present guidelines to carefully appreciate any changes in recommendations. Here, only major changes will be described globally.

Aspergillosis

Emerging azole resistance and changing epidemiology of invasive aspergillosis in non-hematological patients (e.g., in ICU patients and post-influenza) have significantly affected the treatment strategies for invasive aspergillosis, including diagnostic procedures, and the choice of primary therapy (Chapter 2).
To provide a background on epidemiology, diagnostic strategies and antifungal resistance, a specific chapter has been added (Chapter 2.1).
Separate recommendations are now provided for patients with *Aspergillus* isolates proven to be azole-susceptible (Chapter 2.2) and those with resistance or unknown susceptibility to azoles (Chapter 2.3).
A separate chapter has been added on special populations: ICU patients, patients with influenza pneumonia, and patients with chronic granulomatous disease (CGD) (Chapter 2.4).
A section on therapeutic drug monitoring has been added, as well as on oral step-down, duration of therapy, and adjunctive immunotherapy (Chapter 2.5).
The paragraphs on empirical and preemptive therapy (formerly Chapter 4) have been moved to the section on aspergillosis (Chapter 2.4).

Candidiasis

The accumulating evidence on the relative efficacy of echinocandin antifungals has led to major changes in the therapeutic strategy for patients with candidemia or invasive candidiasis (Chapters 3.1 – 3.2 and 3.5).
The section on empirical therapy of invasive candidiasis (formerly Chapter 4) has been moved to Chapter 3 (Chapter 3.6).
Finally, changing epidemiology and new insights have led to major changes in the paragraphs on prophylaxis of invasive candidiasis in patients in the ICU, transplant recipients and neonates (Chapters 3.12 – 3.14).

Cryptococcosis

During the past decade, major insights have led to better definition of optimal treatment of cryptococcal meningitis, including the value of combination therapy. Thus, treatment recommendations for all types of cryptococcosis have changed (Chapters 4.1 – 4.2). Also, studies on corticosteroid use, adjunctive immunotherapy, and initiation of combination antiretroviral therapy (cART) have led to new recommendations (Chapter 4.1).
Finally, the changing epidemiology has led to major changes in the paragraph on prophylaxis (Chapter 4.3).

Mucormycosis

For treatment of Mucormycosis (formerly Zygomycosis), the role of iron chelators, posaconazole, and isavuconazole have been added (Chapter 5.2).

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1.6. Summary of Recommendations

Aspergillosis

Diagnosis of invasive aspergillosis (IA) in patients with hematological malignancies

Recommendation 1	For early diagnosis, determination of serum *Aspergillus* galactomannan at least twice weekly should be considered in neutropenic patients with hematological malignancy or HSCT.
Recommendation 2	In neutropenic patients with hematological malignancy or HSCT, and a positive serum *Aspergillus* galactomannan index (≥0.5) or persistent unexplained fever, an HR-CT lung scan should be performed, regardless of chest radiograph results.
Recommendation 3	Bronchoalveolar lavage (BAL) to obtain specimens for both culture and galactomannan antigen assay should be performed in patients with suspected invasive pulmonary aspergillosis

Antifungal susceptibility

Recommendation 4	For all patients with suspected invasive aspergillosis, maximal efforts should be made to obtain samples for mycology culture and susceptibility testing.[1]
Recommendation 5	From patients with suspected invasive aspergillosis, clinical isolates should be tested for antifungal susceptibility.[1]
Recommendation 6	Resistance to azoles should be tested by MIC or 4-well screening agar screening followed by MIC testing.[1]
Recommendation 7	*Aspergillus* isolates tested to be resistant to one mould-active azole should be considered pan-azole resistant, unless otherwise proven
Recommendation 8	In case of negative fungal cultures in patients with invasive aspergillosis, Cyp51 PCR for resistance-associated genes on BAL fluid is strongly recommended

[1]See: Technical Note on fungal culture and susceptibility testing (www.nvmy.nl)

First-line therapy for acute invasive aspergillosis with proven voriconazole susceptibility

Recommendation 9	Primary treatment with voriconazole or isavuconazole is recommended for patients with acute invasive aspergillosis caused by isolates with confirmed susceptibility to azoles.
Recommendation 10	The committee recommends against the use of itraconazole or c-AmB for primary treatment of invasive aspergillosis
Recommendation 11	In case of contraindications to voriconazole or isavuconazole, L-AmB (3mg/kg/d) or posaconazole are suitable alternatives for patients with acute invasive aspergillosis with confirmed susceptibility to azoles.

First-line therapy for aspergillosis with unknown susceptibility to voriconazole or isavuconazole

Recommendation 12	For patients with invasive aspergillosis caused by isolates with unknown susceptibility to azoles, initial combination therapy with voriconazole/isavuconazole plus L-AmB, or voriconazole/isavuconazole plus an echinocandin is recommended. Monotherapy with L-AmB is considered as a second choice in these patients. In case of mixed azole-resistant and azole-susceptible mold infections, or suspected co-infection with mucorales, voriconazole/isavuconazole plus L-AmB is recommended.
Recommendation 13	If susceptibility or BAL Cyp51 resistance PCR results are expected shortly, initial monotherapy with voriconazole may be prescribed to patients with invasive aspergillosis of unknown azole susceptibility. Subsequent PCR results should guide escalation to L-AmB in case of resistance, and to combination therapy if susceptibility results are unavailable. Severely ill patients and patients in the ICU should receive initial combination therapy pending susceptibility results.

First-line therapy for aspergillosis with proven azole resistance

Recommendation 14	For patients with invasive aspergillosis caused by isolates with confirmed resistance to azoles, L-AmB is recommended. Echinocandin monotherapy is recommended as a second choice in these patients.

Invasive aspergillosis in ICU patients, patients with influenza, and patients with CGD

Recommendation 15	ICU patients with a positive *Aspergillus* culture from respiratory samples, who have chest radiology abnormalities and risk factors for ICU-related aspergillosis should undergo BAL and serum galactomannan testing. A positive galactomannan index in either sample prompts for antifungal therapy, covering azole-resistant *Aspergillus*, unless the isolate has been proven susceptible.
Recommendation 16	ICU patients with clinically relevant unexplained chest radiology abnormalities and risk factors for ICU-related aspergillosis who are not *Aspergillus* culture-positive should undergo serum and BAL galactomannan testing. A positive galactomannan index in either sample in the absence of other explanations prompts for antifungal therapy, covering azole-resistant *Aspergillus*. Patients who have clinically improved after 2 weeks, are stable and have unknown azole resistance may be stepped down to azole monotherapy under strict follow-up.
Recommendation 17	ICU patients with confirmed influenza should undergo sampling for serum galactomannan. It is recommended that ICU patients with confirmed influenza and radiologic abnormalities on chest X-ray should undergo bronchoscopy and BAL for galactomannan and culture. In case of tracheobronchitis, a positive serum galactomannan or a positive BAL galactomannan (index ≥0.8), patients should be treated with combination azole+echinocandin or azole+L-AmB therapy. Monotherapy with L-AmB is considered as a second choice in these patients. If cultures reveal no *Aspergillus* growth, galactomannan-positive BAL material should be tested by PCR for the presence of Cyp51 mutations. ICU patients with influenza and negative *Aspergillus* serum and bronchoscopy/BAL screening, and non-ICU influenza patients should undergo (repeat) serum and bronchoscopy/BAL diagnostics if new respiratory complications or clinical worsening occur, or if sputum/tracheal *Aspergillus* colonization cultures are positive.
Recommendation 18	Serum galactomannan should not be used to screen for or rule out invasive aspergillosis in CGD patients

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Therapeutic drug monitoring (TDM) and oral stepdown

Recommendation 19	TDM is strongly recommended for patients using itraconazole. For prophylaxis, trough levels of >1 mg/l (itraconazole + hydroxy-itraconazole) should be achieved; for therapy, trough levels should be 2 to 4 mg/l. For oral administration, itraconazole suspension is preferred over tablets.
Recommendation 20	TDM is recommended for patients using voriconazole. Trough levels should be 1.5-2 to 6 mg/l. Concentrations should be assessed 2–3 days after first administration, and repeated during therapy, regardless of previous concentrations.
Recommendation 21	TDM should be considered for patients using posaconazole tablets or iv. For patients using posaconazole suspension, TDM is required. Posaconazole suspension should only be used if tablets are contraindicated. For prophylaxis, trough levels of >0.7 mg/l should be achieved; for therapy, trough levels should be >1 mg/l. Concentrations should be assessed 3 days after first administration using a loading dose, and repeated during therapy.
Recommendation 22	Pending further evidence, TDM should be considered for patients using isavuconazole. Trough levels of 2 to 4 mg/l should be achieved for therapy. Using a loading dose, concentrations should be assessed 3 days after first administration.
Recommendation 23	For children, TDM is strongly recommended for all mould-active azoles.
Recommendation 24	Patients may be stepped down from an iv to oral azole, provided that they can tolerate oral therapy, and with TDM where appropriate.

Streamlining, duration of therapy and secondary prophylaxis for acute invasive aspergillosis

Recommendation 25	The duration of therapy for patients with acute invasive pulmonary aspergillosis depends on the clinical course of the disease and the evolution of serum galactomannan index and CT-scan findings. Duration of therapy is at least 6 to 12 weeks and, in neutropenic patients, not less than 2 weeks after resolution of neutropenia.
Recommendation 26	Secondary prophylaxis is recommended after recent invasive aspergillosis in patients undergoing new immunosuppressive treatment (e.g., HSCT) or patients with a specific primary immune deficiency (e.g., CGD). In case of proven/probable aspergillosis, the susceptibility pattern should guide the choice of prophylaxis. Voriconazole or posaconazole are eligible as oral prophylaxis for azole-susceptible isolates, with appropriate TDM.

Immunotherapy and salvage therapy for acute invasive aspergillosis

Recommendation 27	Testing for IFN-γ production defects by a reference lab should be considered, to guide the decision to start rIFN-γ immunotherapy in non-neutropenic patients with invasive aspergillosis with fulminant or refractory disease. Adjunctive IFN-γ therapy should be considered in all CGD patients, and in other patients with proven or suspected Th1/Th17 host defense pathway defects and invasive aspergillosis.
Recommendation 28	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 (co)-infection with mucorales should be taken into consideration.
Recommendation 29	On failure of voriconazole or isavuconazole, the committee considers it to be of primary importance that azole resistance and a co-infection with mucorales be excluded. In view of this differential diagnosis, L-AmB is recommended. An echinocandin may be considered as the second choice if mucormycosis has been excluded and there is no evidence of cerebral aspergillosis.

Diagnostic-driven (preemptive) and empirical antifungal therapy in leukemia/HSCT patients

Recommendation 30	In neutropenic patients with hematological malignancies or HSCT, a diagnostic-driven antifungal strategy is recommended, based on screening serum *Aspergillus* galactomannan at least twice weekly.
Recommendation 31	In neutropenic patients with hematological malignancies or HSCT and a positive serum *Aspergillus* galactomannan index (≥0.5) or persistent unexplained fever, an HRCT lung scan should be carried out. Preemptive therapy against *Aspergillus* should be given in the event of x a positive GM >0.5 or findings consistent with invasive fungal infection on the HRCT scan.
Recommendation 32	The committee recommends the use of a diagnostic-driven antifungal strategy as opposed to symptom-driven empiric strategy. If circumstances require an empiric strategy in patients with persistent fever and neutropenia, L-AmB or caspofungin may be used.

Therapy of other forms of invasive aspergillosis

Recommendation 33	For the treatment of invasive *Aspergillus* sinusitis, the combination of surgery and systemic antifungal therapy are recommended, except for a non-invasive fungal ball, which can be removed surgically without systemic antifungals.
Recommendation 34	For cerebral aspergillosis, combination antifungal therapy with voriconazole and L-AmB is recommended pending confirmation of voriconazole susceptibility, and, if feasible, surgical debridement.
Recommendation 35	Uncomplicated *Aspergillus* otitis externa should be treated with topical antifungals or boric acid. For invasive aspergillosis of the ear, the combination of surgery and prolonged systemic antifungal therapy are recommended.
Recommendation 36	For chronic pulmonary aspergillosis (CPA), prolonged azole therapy is recommended. Echinocandins are an acceptable alternative if azoles are not suitable.
Recommendation 37	Surgical resection is recommended for both symptomatic single aspergilloma with bleeding. In patients not eligible for surgical therapy, prolonged antifungal therapy and bronchial arterial embolization should be considered in case of bleeding.
Recommendation 38	For patients with complicated cranial or pulmonary aspergillosis, consultation with the National Mycology Expertise Center should be considered.

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Antifungal prophylaxis in in patients with hematological malignancies or HSCT

Recommendation 39	In patients with neutropenia following chemotherapy for AML/MDS or HSCT, posaconazole (until resolution of the neutropenia, or during treatment of severe GVHD, and monitored by TDM where appropriate) may be considered for antifungal prophylaxis, depending on the local incidence of invasive mycoses.

Candidiasis

Treatment of candidemia due to unidentified Candida species of unknown susceptibility

Recommendation 1	For adult patients with candidemia or invasive candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is the preferred initial therapy. This recommendation applies to all non-neutropenic and neutropenic patients, except those with *Candida* meningitis, endophthalmitis, or invasive urinary tract candidiasis, and neonates.
Recommendation 2	For patients who have *Candida* endophthalmitis, or invasive urinary tract candidiasis, fluconazole is recommended as initial therapy.
Recommendation 3	A follow-up blood culture sample should be obtained daily from patients with candidemia, until negative.
Recommendation 4	Initial echinocandin therapy should be continued until the patient has stabilized, regardless of *Candida* species.
Recommendation 5	Stable patients may be stepped down from an echinocandin to fluconazole after ≥5 days, provided that follow-up blood cultures during therapy are still negative, the patient is clinically improving, the isolate has been confirmed fluconazole-susceptible, and the patient has no *Candida* endocarditis, intravascular candidiasis, unchanged vascular catheters, or prosthesis-associated candidiasis.

Therapy of candidemia with identified Candida species of known susceptibility

Recommendation 6	For *Candida albicans* or *C. parapsilosis* candidemia/invasive candidiasis in stabilized patients, step-down to fluconazole is preferred after initial echinocandin treatment, provided that follow-up blood cultures during therapy are negative, the patient is clinically improving, the isolate has been confirmed fluconazole-susceptible, and the patient has no *Candida* endocarditis, intravascular candidiasis, unchanged vascular catheters, or prosthesis-associated candidiasis.
Recommendation 7	For *Candida krusei* candidemia/invasive candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is preferred. Voriconazole or L-AmB may be used as an alternative.
Recommendation 8	For *Candida glabrata* candidemia/invasive candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is preferred. L-AmB may be used as an alternative.
Recommendation 9	Patients with an uncomplicated candidemia should be treated for 14 days after the last positive blood culture. Treatment of acute disseminated candidiasis depends on clinical and radiological findings. In case of proven metastatic foci, the duration of therapy is at least 4 to 8 weeks.
Recommendation 10	In patients with candidemia, all intravascular catheters (central, peripheral and arterial) should be removed or replaced.

Secondary metastatic foci in candidemia

Recommendation 11	Fundoscopy should be considered for patients with candidemia, and is strongly recommended for patients with signs of disseminated infection, ocular symptoms, or patients unable to communicate about visual symptoms.
Recommendation 12	A search for intravascular and metastatic foci, using ophthalmoscopy, echocardiography (TEE) and FDG PET-CT, should be considered for all patients with candidemia who have persistently (≥96h) positive blood cultures during therapy, or signs of disseminated candidiasis, ocular symptoms, or cardiac valve disease, a valve prosthesis, or an intravascular device, prosthesis, or thrombus.
Recommendation 13	For patients with chronic disseminated candidiasis, prolonged therapy with either L-AmB or an echinocandin is recommended, followed by fluconazole or voriconazole, until radiographic resolution of all lesions. In patients with signs of immune reconstitution inflammatory syndrome (IRIS), corticosteroids may be considered.
Recommendation 14	For patients with complicated disseminated candidiasis, *Candida meningitis, endocarditis or osteomyelitis,* consultation with the National Mycology Expertise Center should be considered.

Treatment of candidemia and acute disseminated candidiasis in children

Recommendation 15	In neonates, treatment of candidemia or invasive candidiasis should be targeted at potential hematogenous *Candida* meningoencephalitis. Fluconazole or L-AmB is the preferred initial therapy for candidemia or invasive candidiasis in neonates.
Recommendation 16	For treatment of children with candidemia or invasive candidiasis, caspofungin or micafungin is the preferred initial therapy. L-AmB, fluconazole or voriconazole are second-line alternatives.
Recommendation 17	For children who have *Candida* meningitis, endophthalmitis, or invasive urinary tract candidiasis, fluconazole is recommended as initial therapy.
Recommendation 18	Recommendations for children to step down from echinocandin to fluconazole, for catheter management, treatment duration, follow-up, and management of complications are similar to those for adults (sections 3.1 and 3.2).

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Empirical or pre-emptive therapy against invasive candidiasis

Recommendation 19	The predictive value of nonculture diagnostic tests is not sufficiently validated for use in the diagnosis of invasive candidiasis.

Recommendation 20	The indication of empirical therapy on suspicion of candidemia in non-neutropenic patients is controversial. Empirical therapy may be considered in selected individual cases, such as patients >7 days in the ICU and unexplained sepsis, with a combination of the following factors: (1) significant colonization with *Candida* and (2) clinical risk factors (e.g., abdominal surgery, anastomotic leakage, broadspectrum antibiotics, central venous line).

Treatment of Candida endophthalmitis and chorioretinitis

Recommendation 21	*Candida* chorioretinitis or endophthalmitis should be treated systemically with an azole (fluconazole or voriconazole i.v.) in case of proven or presumed azole susceptibility. For proven or potentially azole-resistant cases, liposomal AmB combined with 5-FC is recommended. In the event of invasion into the vitreous body, vitrectomy should be performed in combination with intravitreal voriconazole or c-AmB. Treatment duration is generally lengthy and depends on the clinical course of the infection.

Treatment of candiduria

Recommendation 22	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, kidney transplant, in low birth weight neonates, and prior to renal surgery.

Recommendation 23	Symptomatic candiduria or invasive renal candidiasis should be treated with fluconazole (loading dose 800mg, followed by 400 mg qd for 2-4 weeks). In case of fluconazole-resistance, local irrigation with c-AmB is a suitable alternative for lower urinary tract candidiasis. Fungal balls or persistent obstructions require surgical intervention.

Management of abdominal candidiasis

Recommendation 24	For patients with invasive abdominal candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is the preferred initial therapy. L-AmB is an appropriate alternative in case of echinocandin resistance. Appropriate source control, including surgical debridement and drainage is crucial in treatment of abdominal candidiasis. The duration of treatment depends primarily on surgical and radiological resolution of infected foci. Stable patients may be stepped down from an echinocandin to fluconazole after ≥5 days, provided that all infected foci have been drained, the patient is clinically improving, the isolate has been confirmed fluconazole-susceptible, and the patient has no vascular or prosthesis-associated candidiasis.

Treatment of esophageal candidiasis

Recommendation 25	For esophageal candidiasis, fluconazole (loading dose 400mg, followed by 200 mg qd) for 2 weeks is the preferred treatment. In case of fluconazole resistance, voriconazole (based on the susceptibility spectrum) is eligible, or, as a second choice, an echinocandin.

Antifungal prophylaxis

Recommendation 26	Prophylaxis with fluconazole in intensive care is not recommended, except in specific situations, such as relaparotomy following anastomotic intestinal leakage in units with an unacceptably high local incidence of invasive candidiasis.

Recommendation 27	Fluconazole (400 mg qd) anti-*Candida* prophylaxis is recommended for allogeneic HSCT recipients during the neutropenic phase who do not receive anti-mold prophylaxis. Prolonged prophylaxis up to 100 days post transplant may be considered

Recommendation 28	Fluconazole (400 mg qd) is only recommended for patients undergoing liver transplantation who have an elevated risk of invasive mycoses, i.e., those with renal insufficiency, re-transplantation, choledochojejunostomy, perioperative massive blood transfusion, or proven perioperative colonization with *Candida*.

Recommendation 29	In premature neonates with a very low birth weight, fluconazole prophylaxis (3 mg/kg twice weekly) should only be considered in settings in which there is a proven high incidence of invasive candidiasis.

Cryptococcosis

Treatment of cryptococcal meningitis

Recommendation 1	Cryptococcal meningitis should be treated with L-AmB (3 mg/kg/d) plus 5-FC (100 mg/kg/d) for at least 2 weeks. Thereafter, the treatment of stable and favorably responding patients may be continued with fluconazole (loading dose 800mg, followed by 400 mg qd), for a total of at least 10 weeks, followed by chronic maintenance therapy.

Recommendation 2	For patients with contraindications to 5-FC, induction therapy with L-AmB (3 mg/kg/d) plus fluconazole (400 mg twice daily) for at least 2 weeks is an acceptable second choice.

Recommendation 3	Adjunctive therapy with rIFN-γ (100µg) on days 1 and 3 may be considered for patients with cryptococcal meningitis. In patients with a slow clinical response, rIFN-γ may be continued twice weekly.

Recommendation 4	Control of CSF pressure is a critical determinant of outcome, and repeated therapeutic lumbar punctures are required for patients with elevated intracranial pressure or clinical deterioration.

Recommendation 5	Dexamethasone adjunctive therapy is contraindicated in patients with cryptococcal meningitis.

Recommendation 6	In cART-naïve HIV-infected in patients with cryptococcal meningitis, the initiation of cART should be deferred until 5 weeks after start of antifungal therapy.

Recommendation 7	In apparently immunocompetent patients with *C. gattii* infection auto-antibodies against GM-CSF should be tested, to guide initiation of rGM-CSF immunotherapy.

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Treatment of nonmeningeal cryptococcosis

Recommendation 8	Nonmeningeal or disseminated cryptococcosis should be treated with L-AmB (3 mg/kg/d) plus 5-FC (100 mg/kg/d) for at least 2 weeks. Consolidation therapy of stable and favorably responding patients should follow with fluconazole (loading dose 800mg, followed by 400 mg qd, for 6 to 12 months).
Recommendation 9	Fluconazole (loading dose 800mg, followed by 400 mg qd, for 6 to 12 months) may be a reasonable alternative for patients with mild, localized, nonmeningeal infection, and less severe immunosuppression. Before considering this option, a lumbar puncture and blood cultures are required in all patients, to rule out cryptococcal meningitis, disseminated disease and cryptococcemia.
Recommendation 10	Adjunctive therapy with rIFN-γ (100µg twice weekly) may be considered for all patients with severe meningeal, pulmonary or disseminated cryptococcosis, and for patients in whom T-cell immunity cannot be restored by cART or withdrawal of immunosuppressive therapy.

Secondary prophylaxis of cryptococcosis

Recommendation 11	Chronic maintenance therapy with fluconazole (200mg qd) is required for patients who have suffered from invasive cryptococcosis and continue to have an underlying immune defect. In solid organ transplant recipients, maintenance therapy with fluconazole (200-400mg qd) for 6-12 months is recommended.
Recommendation 12	After a minimum of 1 year after successful treatment of cryptococcosis, chronic maintenance therapy can be discontinued in solid organ transplant recipients, and in HIV-positive patients with CD4 counts ≥100 cells/µL, who have undetectable viral loads on cART for >3 months.

Mucormycosis

Recommendation 1	Direct microscopy of clinical specimens followed by culture is strongly recommended for the diagnosis of mucormycosis.
Recommendation 2	Invasive mucormycosis should be treated with L-AmB in a dosage of at least 5 mg/kg/day.
Recommendation 3	Where possible, the antifungal treatment of invasive mucormycosis should be combined with surgical debridement and correction of underlying risk factors.
Recommendation 4	For salvage treatment of invasive mucormycosis on failure or intolerance of L-AmB, posaconazole or isavuconazole may be considered.

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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, and may disseminate hematogenously. 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. The many side effects of c-AMB have resulted in the development of various lipid associated amphotericin B (LFAB) compounds, such as liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC). Of the azoles, itraconazole, voriconazole, isavuconazole and posaconazole are active against *Aspergillus* species. The echinocandins (caspofungin, micafungin and anidulafungin) have fungistatic activity against *Aspergillus* species. In recent years, emerging resistance against azoles has become a major problem in Europe. This has led to reconsideration of optimal treatment strategies in the current guidelines.

2.1. Diagnosis and antifungal susceptibility

Definitions

The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the former National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group (Now: Mycoses Study Group Education and Research Consortium (MSGERC)) have published standard definitions for invasive fungal infections for clinical and epidemiological research (1). These EORTC/MSG definitions have been used in major trials of antifungal drug efficacy, in strategy trials, for the formulation of clinical practice guidelines, for validation of diagnostic tests, and for performance of epidemiologic studies.
The definitions assign 3 levels of probability to the diagnosis of invasive fungal infection: proven, probable, and possible. While proven infection requires microbiologic or histologic proof of infection, probable and possible invasive fungal infections hinge on 3 elements—namely, a host factor that identifies the patients at risk, clinical and radiological signs and symptoms consistent with the disease, and mycological evidence including culture, microscopy or antigen detection. Whereas the EORTC/MSG definitions have been primarily developed for clinical studies, they are used as to define patient populations in the present guidelines.

Diagnosis of invasive aspergillosis

While the EORTC/MSG definitions require a histopathologic diagnosis or a positive culture of a normally sterile site (excluding sputum or bronchoalveolar lavage (BAL)) to define *proven* invasive aspergillosis, this issue is challenging in clinical practice. In the majority of patients, a diagnosis of *probable* invasive aspergillosis will be established by combining clinical risk factors (e.g., immunosuppression, underlying disease) with clinical and radiological signs, and mycological data such as a positive culture from a nonsterile site (e.g., BAL) or antigen detection.
In clinical practice, patients often do not fulfill the 2008 EORTC/MSG definition of proven, probable or possible invasive aspergillosis. Typically these unclassifiable patients fulfill the host as well as the microbiological criterion but do not fulfill the radiological signs described in the EORTC/MSG definition (e.g. pulmonary infiltrate present but not a well-described nodule nor a cavity or halo sign). Pending the update of the EORTC/MSG criteria addressing this issue, these patients are treated in a similar way as patients who fulfill the EORTC/MSG probable category.

Importantly, the diagnostic techniques described in this section have been predominantly validated in patients with hematological malignancies. In other patients groups, such as ICU patients and non-immunocompromized hosts, the test performance may be different. Those patients groups are specifically discussed in Chapter 2.4.

Culture and PCR

Culture is critical for species identification and susceptibility testing. The taxonomy of *Aspergillus* species has changed dramatically in the past decade mainly due to the use of molecular techniques for classification. *Aspergillus fumigatus*, previously classified on the basis of morphological characteristics, includes now over 55 different species, referred to as sibling species. Identification of these sibling species often requires sequencing of household genes such as calmodulin and beta-tubulin. Species identification in the clinical microbiology laboratory is therefore a challenge, although automated identification by MALDITOF spectrometry is emerging as a useful tool. The Netherlands Society for Medical Mycology (NVMy) will provide a Technical Note on fungal culture and susceptibility testing (www.nvmy.nl).

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New sibling species have been identified for other *Aspergillus* species as well, including *A. niger*, *A. flavus*, *A. terreus*, etc. When phenotypic methods are used for strain identification often the term 'species complex' is added to highlight that the strain might be one of the sibling species.
Tissue obtained by CT-guided percutaneous lung biopsy for direct staining, PCR and culture has a high diagnostic yield (2). In contrast, the sensitivity of *Aspergillus* cultures from respiratory materials is low, and a negative respiratory culture does not exclude the diagnosis of invasive aspergillosis.

The specificity of positive cultures from respiratory samples yielding *Aspergillus* is limited, as cultures cannot differentiate invasive disease from colonization (3). Therefore, positive cultures from sputum, tracheal aspirate or BAL only constitute a probable invasive aspergillosis when found in combination with appropriate clinical risk factors and clinical or radiological signs. The same limitation applies to a positive *Aspergillus* PCR from respiratory samples. In a systematic review of 9 studies adherent to the EORTC/MSG criteria, the sensitivity of BAL PCR was 62–88%, and the specificity 91 to 96%, resulting in a positive predictive value of 60–80% in the study populations (4). As PCR assays for *Aspergillus* have not yet been standardized, the characteristics of various PCR assays may vary.

Serum galactomannan
The *Aspergillus* galactomannan serum antigen test has been associated with reasonable sensitivity (around 70%) in children and adults with hematological malignancies or HSCT, and the optimal cutoff has been set at ≥0.5 (5–8). In high-risk hematology patients (AML, MDS, HSCT) monitoring of serum galactomannan has been successfully used as part of a diagnostic driven (or pre-emptive) strategy, in combination with lung CT in galactomannan positive patients. In nonneutropenic patients, the sensitivity is substantially lower, and in solid organ transplant recipients or patients with chronic granulomatous disease (CGD), the galactomannan sensitivity is less than 20% (9,10). In patients receiving anti-*Aspergillus* prophylaxis, the sensitivity of serum galactomannan was reduced (11,12). However, the test remained useful as diagnostic tool in patients suspected of invasive fungal disease. False positive results have been reported due to the presence of galactomannan in transfused blood products and certain antibiotics, e.g. piperacillin/tazobactam, although recent studies indicate that current batches are galactomannan-negative (13,14).

The course of the serum galactomannan index has been found to be a measure of response to therapy (5). In patients enrolled in a large prospective trial (15), a serum galactomannan index reduction of >35% between baseline and week 1 predicted a probability of a favorable clinical response, and an increase during therapy was significantly associated with failure (16).
Twice-weekly galactomannan serum antigen screening has been demonstrated an effective strategy to guide diagnostic-driven therapy in patients hematological malignancies or HSCT at risk for invasive aspergillosis (11,17) (see chapter 2.4).

BAL galactomannan
The detection of galactomannan in BAL fluid has been shown to have a sensitivity of 70–92% in several studies, which significantly exceeds the sensitivity of cultures (50–58%) (18–21). The optimal threshold for BAL galactomannan positivity has not been determined. In an analysis of 251 consecutive BAL galactomannan tests ordered for patients at risk, an OD index of ≥0.8 resulted in an optimal performance in diagnosing proven/probable invasive aspergillosis of 86.4%, and a specificity of 90.7% (20). In the population tested at Leuven University Hospital, the positive predictive value was 81% and the negative predictive value 93.6% at this cutoff. Patients with an OD index of >3.0 all had confirmed proven/probable invasive aspergillosis (100% specificity and positive predictive value irrespective of the pretest probability). Conversely, an OD cutoff of <0.5 led to a sensitivity of 93.2%, corresponding with a negative predictive value of 92-97% in the population tested (20).

Radiology
In patients with hematological malignancies or HSCT, the value of radiologic imaging has been well established.
High-resolution CT (HRCT) scan is more sensitive than chest radiograph to identify lesions of invasive aspergillosis. Combined screening by twice-weekly serum galactomannan and early HRCT scan in patients with positive serum galactomannan results or fever while neutropenic led to early identification of invasive diagnosis and a shorter time to diagnosis (11,17,22). A halo sign as identified on HRCT scanning is an early sign of invasive aspergillosis and can be seen in 61–92% of neutropenic patients. Early detection of a halo sign is associated with an improved prognosis (23,24). In a prospective study, vascular occlusion detected by CT angiography was more sensitive than standard HRCT evaluation in patients with hematological malignancies (25).

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Conclusions 2.1. – Diagnosis of invasive aspergillosis (IA) in patients with hematological malignancies	
Conclusion 1	Whereas no randomized studies comparing diagnostic strategies have been performed, determination of serum *Aspergillus* galactomannan (cut-off, OD index ≥0.5) twice weekly can be used for the early diagnosis of invasive aspergillosis in patients who are not on anti-mold prophylaxis.
Level 1	Maertens, 2005a (B); Maertens, 2005b (B); Maertens, 2007 (A2); Steinbach, 2007 (A2), Morrissey, 2013 (A2); Duarte, 2014 (A2)
Conclusion 2	The sensitivity and specificity of BAL *Aspergillus* galactomannan for the diagnosis of IA exceed those of BAL culture and PCR.
Level 1	Meersseman, 2008 (A2); Maertens, 2009 (A2); D'Haese, 2012 (A2)
Conclusion 3	The cut-off for BAL *Aspergillus* galactomannan for the diagnosis of IA has not been formally established. An OD index ≥0.8 is associated with an optimal predictive value.
Level 2	Guo, 2010 (A2), D'Haese, 2012 (A2)
Conclusion 4	The course of the *Aspergillus* serum galactomannan index is a measure of response to therapy.
Level 2	Maertens, 2005 (B); Chai, 2012 (A2)
Conclusion 5	HR-CT scanning has an important role in the early discovery of invasive pulmonary aspergillosis.
Level 1	Caillot, 1997 (B), Maertens, 2005b, (B); Greene, 2007 (A2); Morrissey, 2013 (A2)
Conclusion 6	A halo sign on an HR-CT scan has a high specificity for the diagnosis of early invasive pulmonary fungal infection in neutropenic patients.
Level 2	Caillot, 1997 (B); Greene, 2007 (A2)

Recommendations

Most diagnostic studies have been performed in patients with hematological malignancies. In other patients groups, such as ICU patients and non-immunocompromized hosts, the test performance may be different. For example, HR-CT scan findings may be less specific in nonneutropenic patients, and the sensitivity of serum galactomannan in hematology patients without neutropenia (e.g. GVHD), solid organ transplant recipients or patients with chronic CGD (see Chapter 2.4) is very low.

As studies comparing the outcome benefits of various combinations of diagnostic strategies (e.g., HRCT, serum galactomannan screening) are sparse, the committee cannot make a formal evidence-based recommendation for a specific screening strategy. In addition, diagnostic strategies should be adapted to local policies, such as use of antifungal prophylaxis, which reduces the sensitivity of serum galactomannan. In the absence of antifungal prophylaxis, both BAL galactomannan index of <0.8 (20) and twice-weekly serum galactomannan screening (index <0.5) corresponded with a negative predictive value of 92-99% in the populations tested.

Recommendation 1	For early diagnosis, determination of serum *Aspergillus* galactomannan at least twice weekly should be considered in neutropenic patients with hematological malignancy or HSCT.

Recommendation 2	In neutropenic patients with hematological malignancy or HSCT, and a positive serum *Aspergillus* galactomannan index (≥0.5) or persistent unexplained fever, an HR-CT lung scan should be performed, regardless of chest radiograph results.

Recommendation 3	Bronchoalveolar lavage (BAL) to obtain specimens for both culture and galactomannan antigen assay should be performed in patients with suspected invasive pulmonary aspergillosis

Antifungal susceptibility

Primary antifungal drug resistance may be found in *Aspergillus* species. *A. terreus* is intrinsically resistant to amphotericin B, and azole therapy is recommended. Furthermore, sibling species might exhibit different resistance profiles compared with other members of the species complex. For instance *A. tubingensis*, which is a sibling species within the *A. niger* species complex, is less susceptible to the triazoles compared with *A. niger*. As identification to the species level may not be available in clinical microbiology laboratories, in vitro susceptibility testing of clinically relevant isolates may help to guide antifungal therapy in individual patients.

Acquired triazole resistance of *A. fumigatus* has been rapidly rising in the Netherlands, and had increased to 12.9% in 2016, as reported from centers that screened unselected isolates, with local prevalences up to 35% in specific ICU and hematology departments in the Netherlands (26). Azole resistance has now been reported worldwide, in Europe, the Middle East, Asia, Africa, Australia and, most recently, North and South America (27). For updates on the prevalence of azole resistance in the Netherlands, readers are referred to the yearly NethMap reports (26).

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Two routes of resistance development are distinguished: through long-term azole therapy in patients, and via the application of azole fungicides in the environment. While data from patients with aspergilloma or chronic aspergillosis indeed have confirmed that *A. fumigatus* can undergo multiple genetic changes leading to azole resistance (28), the main burden of resistance is through resistance selection in the environment. The use of azole fungicides is assumed to be an important factor in the selection of azole resistance in the environment, and patients are colonized by azole-resistant strains outside the hospital, which may subsequently cause invasive disease once patients undergo immunomodulating therapies (28). This is in agreement with the observation that two-thirds of patients with resistant disease have no previous history of azole therapy (29). Thus, environmental resistance is characterized by a lack of patient risk factors. Only residency in or visiting of a geographic area with known environmental resistance can be considered a risk.

Mechanisms of azole resistance
Surveillance studies in the Netherlands indicate that environmental mutations are responsible for over 80% of clinical infections with azole-resistant strains. Environmental azole resistance is caused by a limited number of resistance mechanisms associated with the Cyp51A-gene, including TR34/L98H, TR53, and TR46/Y121F/T289A (28). Most environmentally azole-resistant *Aspergillus* isolates are resistant to all azoles. Hence, isolates tested to be resistant to one azole should be considered pan-azole resistant, unless otherwise proven (30,31). In selected cases, an elevated MIC to posaconazole may still be amenable to high-dose posaconazole therapy under strict TDM (trough >1.5 mg/l) (28).
Patients may have mixed infections caused by susceptible and resistant *Aspergillus* strains. In 2015, azole-susceptible and azole-resistant colonies in culture were found in 13 of 50 patients (26%) with azole-resistant cultures from three centers in the Netherlands (26,32).

Screening and detection of resistance
Controlled studies of the clinical implications of azole resistance have not been published, but case series have demonstrated a mortality rate of azole-resistant invasive aspergillosis between 50% and 100% (33,34), which is higher than the mortality rate of <30% in azole-susceptible infection. Therefore, it is important to identify patients infected by azole-resistant *A. fumigatus*, and to adapt the choice of empirical therapy to potential azole-resistant strains.

Detection of resistance requires culture of the infecting strains; however, *Aspergillus* cultures are negative in the majority of patients. Even when cultures are positive, resistance may be missed due to concomitant presence of azole-susceptible and azole-resistant colonies. As routine MIC testing of multiple *A. fumigatus* colonies is not feasible, an agar-based screening method has been developed (30). Growth of *A. fumigatus* on azole-containing agar is highly suggestive of resistance, and these colonies should then undergo MIC testing. As the screening agar is not 100% sensitive, clinically relevant isolates may be tested for MIC irrespective of screening results.
It is recommended to test ≥5 separate colonies if present in the primary culture. If MIC testing is not available, selected isolates should be referred to a reference laobratory for MIC testing and/or sequence-based analysis of the cyp51A gene. For details, laboratories are referred to the NVMy Technical Note on fungal culture and susceptibility testing (www.nvmy.nl).

Biomarkers such as galactomannan are unable to detect azole resistance. However, an increasing galactomannan index during azole therapy may indicate treatment failure.

Cyp51 resistance PCR
Unfortunately, *Aspergillus* cultures are negative in the majority of patients with an invasive aspergillosis. Therefore, non-culture based methods could help in the detection of infections with an azole resistant Aspergillus fumigatus strain. Both in-house and commercial PCRs have been developed to detect markers for the TR34/L98H and TR46/Y121F/T289A resistance mechanisms, in the absence of positive cultures (27,35–37).
In a recent multicenter study such Cyp51 resistance PCR was used on 202 BAL samples from hematology patients with invasive aspergillosis (34). In patients with PCR-positive TR34/L98H or TR46/ Y121F/T289A resistance mechanisms, azole treatment failed in 6 of 8 patients, compared to 12 of 45 patients without the presence of resistance (P = 0.01). Mortality was 2.7 times higher in patients with resistance (50.0% versus 18.6%; P = 0.07) (34).
It should be noted that these PCRs detect only 2 of at least 15 known *Cyp51A* resistance mutations. In the Netherlands, these 2 mutation patterns are currently by far the most frequently observed mutations. Also, the sensitivity of the PCR is far from optimal. Future studies are therefore needed to better define the role of these non-culture based resistance tests.

Conclusions 2.1. – Antifungal susceptibility	
Conclusion 7	Resistance of *Aspergillus* species to azole antifungals has been rapidly rising in the Netherlands
Level 1	SWAB NethMap, 2016 (A1)
Conclusion 8	Azole resistant *Aspergillus* species in azole-naïve patients originate from environmental sources
Level 1	Van der Linden, 2013 (A2); Verweij, 2015 (A2)
Conclusion 9	Patients may have mixed infections caused by susceptible and resistant *Aspergillus* strains, requiring multiple colonies to be tested for susceptibility
Level 2	SWAB NethMap, 2016 (A2); Kolwijck, 2016 (B); Schauwvlieghe, 2017 (C)

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Conclusion 10	Azole resistant *Aspergillus* species is diagnosed by screening clinical isolates on 4-well agar screening plates, followed by MIC and/or sequencing, or cyp51 resistance gene PCR on direct materials
Level 3	Van der Linden, 2015 (B); Verweij, 2016 (C)
Conclusion 11	Most environmentally azole-resistant *Aspergillus* isolates are resistant to all azoles
Level 3	Van der Linden, 2015 (B); Verweij, 2016 (C)

Recommendation 4	For all patients with suspected invasive aspergillosis, maximal efforts should be made to obtain samples for mycology culture and susceptibility testing.[1]

Recommendation 5	From patients with suspected invasive aspergillosis, clinical isolates should be tested for antifungal susceptibility.[1]

Recommendation 6	Resistance to azoles should be tested by MIC or 4-well screening agar screening followed by MIC testing.[1]

Recommendation 7	*Aspergillus* isolates tested to be resistant to one mould-active azole should be considered pan-azole resistant, unless otherwise proven

Recommendation 8	In case of negative fungal cultures in patients with invasive aspergillosis, Cyp51 PCR for resistance-associated genes on BAL fluid is strongly recommended

[1]See: Technical Note on fungal culture and susceptibility testing (www.nvmy.nl)

2.2. Treatment of acute invasive pulmonary aspergillosis with proven susceptibility to azoles

The present guideline provides separate treatment recommendations for isolates with known or with (yet) unknown azole susceptibility.
The mortality associated with invasive aspergillosis remains substantial despite treatment, i.e., 28.5% in a recent population-based study (38). This prompts early initiation of antifungal therapy in patients with probable or proven invasive aspergillosis. This chapter addresses treatment principles of azole-susceptible aspergillosis. The approach to aspergillosis with unknown susceptibility is discussed in Chapter 2.3; empiric and preemptive therapy are described in chapter 2.5.
To select appropriate therapy, infection due to *Aspergillus* species should be distinguished from other molds (e.g., mucormycosis, see chapter 5), as voriconazole is not active against mucorales. Thus, a specific microbiological diagnosis followed by in-vitro susceptibility testing is critical to guiding therapy (see chapter 2.1). In the absence of positive mycology cultures, Cyp51 PCR for the TR34/L98H and TR46/Y121F/T289A resistance-associated genes on BAL fluid is strongly recommended. The TR34/L98H and TR46/Y121F/T289A mutations are the most prevalent resistance mechanisms in the Netherlands, accounting for >80% of resistant isolates. Therefore, culture-negative invasive aspergillosis cases with a wild-type for these genes in the Cyp51 resistance PCR are considered to have a low risk of bearing azole-resistance. The committee considers these patients eligible for treatment with regimens as recommended for cases with proven susceptibility to azoles, as described in this chapter.

Treatment of acute invasive aspergillosis with proven susceptibility to azoles
Importantly, all randomized studies of invasive aspergillosis have been conducted before the emergence of azole resistance, and the results should be viewed in the light of current resistance epidemiology in the Netherlands. Therefore, the conclusions and recommendations in this paragraph are limited to patients with an *A. fumigatus* isolate that has been cultured and has confirmed susceptibility to azoles.

Voriconazole
In a pivotal randomized study (15), voriconazole was superior to c-AmB (1.0-1.5 mg/kg/d) for the treatment of invasive aspergillosis. Voriconazole success rate was 53% vs. 32% with c-AmB, 12-weeks survival was 71% vs. 58% (p=0.02) (15). Recently, subjects entered into this trial were recategorized according to the 2008 EORTC/MSG criteria, including baseline serum galactomannan levels obtained from frozen samples (39). Overall voriconazole success rate was 55% vs. 30% with c-AmB (p<0.0001). Survival in probable/proven aspergillosis cases was 70% with voriconazole and 55% with AmB (p=0.01). In patients classified as possible invasive aspergillosis, success rates with voriconazole were also significantly higher (66% vs 39%, p<0.02) (39). This suggests that patients classified as possible invasive aspergillosis in that study actually did have aspergillosis and required antifungal therapy. This also supports the more recent recommendations that BAL for culture and galactomannan testing is strongly recommended to diagnose invasive aspergillosis in this patient group, especially in the current setting with azole-resistant aspergillosis.

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Isavuconazole
In a recent randomized trial, voriconazole was compared with isavuconazole (40). All-cause mortality was 19% with isavuconazole vs. 20% with voriconazole (difference -1%, 95% CI –8 to 6). Thus, the trial showed noninferiority in terms of clinical efficacy in patients with possible, probable, and proven invasive mold infections. There were fewer drug-related adverse effects in patients with isavuconazole (42%) than with voriconazole (60%; p<0·001). Specifically, isavuconazole-treated patients had fewer hepatic disorders (9% vs. 16%; p=0·016), ocular adverse events (15% vs. 27%; p=0·002), and skin adverse events (33% vs. 42%; p=0·037). While interactions of isavuconazole with substrates and inducers of the CYP3A4 enzyme do occur, current data suggest that these are less severe than with voriconazole. Based on these data, isavuconazole has been approved for first-line therapy of invasive aspergillosis.

Other azoles
Itraconazole and posaconazole have not been studied as primary therapy for invasive aspergillosis in randomized trials. The efficacy of itraconazole has not been well established, and its use is limited by its poor bioavailability and restricted availability of the i.v. formulation. Likewise, the bioavailability of posaconazole as suspension has been variable. The new delayed-release tablet formulation has improved bioavailability and is dosed once daily, as is the new intravenous formulation in β-cyclodextrin (41). Pending data from primary treatment trials, posaconazole is considered an option for patients who do not tolerate voriconazole or isavuconazole.

Amphotericin B
Based on the significantly greater mortality and lower success rates associated with c-AmB in the randomized trial compared to voriconazole (15), c-AmB is not considered appropriate therapy for invasive aspergillosis.

Liposomal AmB (L-AmB) has not been compared to voriconazole or c-AmB in randomized trials. In a large retrospective cohort study on 289 patients fulfilling EORTC/MSG criteria in France, survival associated with L-AmB initial therapy was 47%, vs. 69% with voriconazole (p<0.02) (42). In a randomized double-blind study of L-AmB at 3 mg/kg/d (L-AmB3) compared with 10 mg/kg/d (L-AmB10), there was no difference in response (L-AmB3, 50% vs. L-AmB10, 46%; p>0.05) and no difference in survival at 12 weeks (72% vs. 59%; p=0.09) (43). Retrospectively, subjects entered into this trial have been recategorized according to the 2008 EORTC/MSG criteria. Survival at 12 weeks for probable/proven cases was 58% with L-AmB3, vs. 50% with L-AmB10 (44). Greater toxicity was observed in the 10mg/kg/d group, specifically nephrotoxicity (L-AmB3 14% vs. LAmB10 31%; p<0.01) (43).

AmB lipid complex (ABLC) has not been studied in randomized trials for invasive aspergillosis, and published data are merely observational (45). A retrospective case series on limited numbers of patients with EORTC/ MSG proven/probable invasive aspergillosis has suggested outcomes similar to those with L-AmB, but a higher rate of nephrotoxicity (21% vs. 3%, P<0.01) (46). In a retrospective cohort study, frequency of severe nephrotoxicity was 11.5% for c-AmB, 7.2% for ABLC, and 2.4% for L-AmB (P<0.05) (47). In a multivariate analysis, L-AmB, but not ABLC, was suggested to be a protective factor for mortality (OR vs c-AmB, P=0.047) (47).

Echinocandins
All three echinocandins (caspofungin, anidulafungin, micafungin) have fungistatic activity against *Aspergillus* species. Caspofungin and micafungin have been approved for salvage treatment of invasive aspergillosis based on cohort studies (48–50). Subsequent small trials on primary treatment with caspofungin have yielded less favorable outcomes. In a prospective, nonrandomized EORTC trial including 61 hematology patients with EORTC/MSG probable/proven invasive aspergillosis, success rate with caspofungin was 33%, and 12-week mortality was 47% (51). In the companion EORTC study including 24 allogeneic HSCT recipients, success rate was 43%, and mortality 50% (52). Based on these limited data, echinocandin monotherapy is not recommended as primary treatment for invasive aspergillosis.

Combination therapy
Combination therapy of an azole with an echinocandin of invasive aspergillosis has initially been supported by historically controlled cohorts, suggesting a survival benefit in primary or salvage therapy (53–55). A recent randomized trial compared outcomes of voriconazole monotherapy to combination therapy with voriconazole and anidulafungin, in 454 hematology patients with EORTC/ MSG probable/proven invasive aspergillosis (56). Mortality (6 weeks) was 20% for voriconazole+anidulafungin vs. 28% for voriconazole monotherapy (p=0.087; 95%CI, -19 to 1.5). Thus, the primary superiority endpoint was not met. In a post-hoc exploratory analysis of the largest subgroup of 218 patients with positive serum galactomannan (EORTC/MSG probable aspergillosis), mortality was 16% for voriconazole + anidulafungin vs. 28% for voriconazole (p<0.05; 95%CI, -23 to -0.4). It should be noted that the combination therapy study randomized patients for initial combination therapy vs. monotherapy, regardless of severity of illness (56). Thus, there is no information whether later addition of combination therapy in deteriorating patients would be associated with similar outcomes.

Primary therapy of invasive aspergillosis with proven susceptibility to azoles in children
The majority of studies on treatment of invasive aspergillosis have been conducted in adults or children >12 years. Therefore, treatment recommendations for children are based on efficacy data derived from adult studies in combination

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with pharmacokinetic and safety data in children, as well as supportive pediatric clinical data. The pharmacokinetics and dosing regimens of various antifungals differ substantially in children. Specific dosing recommendations for children are given in the national Children's Formulary, based on the following observations.

Voriconazole pharmacokinetics are substantially different in children. In a pooled data analysis of 138 immuno-compromized children and adolescents, a loading dose of 9 mg/kg bid, followed by 8 mg/kg bid maintenance led to similar AUCs as did 4 mg/kg bid iv or 200 mg bid orally in adults (57). In adolescents <50 kg, body weight-based dosing was required to achieve appropriate AUC, while adolescents >50 kg could be dosed as adults. Another cohort study reported similar results, and found that bioavailability of oral voriconazole was lower in children than in adults (approximately 60% vs. 95%), requiring dedicated dosing and TDM after iv-to-oral switch (58).

For posaconazole and isavuconazole, no dose regimens have been formally established for children yet. In mycology expertise centers, experience with dosing for children has been obtained, based on TDM. Treatment of children with these drugs is not recommended, unless after consultation with an expert center.

Caspofungin at a weight-based loading dose of 70mg/m^2, followed by 50mg/m^2 maintenance (maximum 70 mg/d) in 39 children and adolescents led to a similar exposure as that in adults had after standard dosing in a prospective study (59). Micafungin was found to have a nonlinear relationship to bodyweight in a population pharmacokinetics study in children aged 2–17 years (60). For children <40 kg, a dose of 2-4 mg/kg (maximum 100 mg/d) was established (60). In a prospective study of anidulafungin in neutropenic pediatric patients aged 2–17 years, a loading dose of 3 mg/kg and a maintenance of 1.5 mg/kg/d were found to be equivalent to a maintenance of 100 mg/d in adults (61). However, anidulafungin is not licensed for use in children, and its use is not recommended.

Conclusions 2.2 – First-line therapy for acute invasive aspergillosis with proven voriconazole susceptibility	
Conclusion 12	Voriconazole is superior to c-AmB in the treatment of invasive aspergillosis.
Level 2	Herbrecht, 2002 (A2); Herbrecht, 2015 (B); Nivoix, 2008 (B); Lortholary, 2011 (B), Perkhofer, 2010 (B)
Conclusion 13	Isavuconazole is as effective as voriconazole in the treatment of invasive aspergillosis and associated with fewer side effects but is substantially more expensive
Level 2	Maertens, 2016 (A2)
Conclusion 14	Combination therapy with voriconazole and anidulafungin was suggested to be associated with lower mortality rates in galactomannan positive patients with invasive aspergillosis compared to voriconazole monotherapy in a post-hoc analysis
Level 2	Marr, 2015 (A2); Singh, 2006 (B)
Conclusion 15	L-AmB at a dose of 3 mg/kg/d is as effective as L-AmB at 10 mg/kg/d in the treatment of invasive aspergillosis, and is associated with fewer side effects
Level 2	Cornely, 2005 (A2); Cornely, 2011 (B)
Conclusion 16	Caspofungin therapy of invasive aspergillosis leads to lower success rates than those that have been achieved with voriconazole
Level 2	Viscoli, 2009 (B); Herbrecht, 2010 (B)
Conclusion 17	Therapy of invasive aspergillosis with voriconazole or with voriconazole plus echinocandin is associated with higher survival rates than primary therapy with L-AmB or caspofungin
Level 2	Herbrecht, 2002 (A2); Herbrecht, 2015 (B); Nivoix, 2008 (B); Lortholary, 2011 (B), Perkhofer, 2010 (B); Viscoli, 2009 (B); Herbrecht, 2010 (B)
Conclusion 18	Treatment of invasive aspergillosis in children is comparable to that in adults. However, pharmacokinetics of azoles and echinocandins differs substantially from those in adults and require dedicated dosing regimens. Isavuconazole and anidulafungin have not been licensed for use in children.
Level 3	Walsh, 2005 (C), Benjamin, 2006 (C); Hope, 2007 (C); Walsh, 2010 (C); Friberg, 2012 (C)
Conclusion 19	In the absence of an *Aspergillus* isolate suitable for susceptibility testing, the committee considers a wild-type result of the Cyp51 resistance PCR on BAL material as a reasonable surrogate marker for azole-susceptibility
Level 4	Expert opinion

Recommendations

For the primary treatment of invasive aspergillosis with confirmed susceptibility to azoles, the committee considers voriconazole and isavuconazole equally effective. The safety benefit of isavuconazole as suggested by the comparative trial (40) and its better predictable pharmacokinetics (62,63) may counterbalance the limited clinical experience with the drug in the coming years.

Initial azole-echinocandin combination therapy for patients with presumably mostly azole-susceptible strains did not meet the primary superiority endpoint in a recent comparative trial (mortality 20%, vs. 28% for azole monotherapy (p=0.087) (56). In a secondary analysis of patients with EORTC/MSG probable aspergillosis based on serum galactomannan positivity, mortality was significantly reduced in the combination arm (16% vs. 28%, p<0.05). While these subgroup data suggest a survival benefit with primary combination therapy in patients with serum galactomannan-positive invasive aspergillosis, no

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definite conclusions can be drawn from this post-hoc analysis. Based on these findings, the committee does not recommend initial azole+echinocandin combination as a first choice therapy for patients with confirmed azole-susceptible isolates.

There is accumulating evidence that the individual variations in the pharmacokinetics of voriconazole, posaconazole and itraconazole have a major influence on treatment outcome. Recommendations on therapeutic drug monitoring (TDM) are provided in chapter 2.5. Likewise, TDM should be considered for isavuconazole, pending more data.

Recommendation 9	Primary treatment with voriconazole or isavuconazole is recommended for patients with acute invasive aspergillosis caused by isolates with confirmed susceptibility to azoles.

Recommendation 10	The committee recommends against the use of itraconazole or c-AmB for primary treatment of invasive aspergillosis

Recommendation 11	In case of contraindications to voriconazole or isavuconazole, L-AmB (3mg/kg/d) or posaconazole are suitable alternatives for patients with acute invasive aspergillosis with confirmed susceptibility to azoles.

For recommended drugs and standard doses for treatment of invasive aspergillosis see Table 2.1

2.3. Treatment of acute invasive pulmonary aspergillosis with resistance or unknown susceptibility to azoles

While no specific randomized studies have been conducted among patients with invasive aspergillosis due to azole-resistant *Aspergillus* species, case series have reported a mortality rate between 50% and 100% for azole-resistant invasive aspergillosis (33,34). As of the release of the present guidelines, resistance of *Aspergillus* species to azole antifungals had increased to 12.9% in the Netherlands, with local prevalences up to 35% in specific ICU and hematology departments. Updates on the prevalence of azole resistance can be found in the yearly NethMap reports (26).
As expected resistance rates now generally are >10%, treatment of patients with (suspected or proven) invasive aspergillosis of unknown susceptibility should include coverage for azole-resistant strains (28).

Unknown azole susceptibility
Cohort studies have suggested an approximately 15% improved survival at 12 weeks with voriconazole or voriconazole-echinocandin combination treatment, compared with other intravenous therapies such as L-AmB or echinocandin monotherapy (15,42,44,51,52,64–66). Based on these data, modeling suggests that combination therapy with voriconazole and either an echinocandin or L-AmB is associated with highest survival rates in patients with unknown azole susceptibility, combining the superior efficacy of voriconazole against susceptible isolates with a second agent active against voriconazole-resistant strains. In view of the recent trial comparing voriconazole monotherapy to voriconazole plus anidulafungin for azole-susceptible isolates (56), combination of voriconazole with an echinocandin is a reasonable choice for patients with unknown azole susceptibility (28). No published outcome data are available on the combination of voriconazole with L-AmB. Assuming that the combination causes no clinically relevant antagonism or synergism, modeling suggests similar benefits as those with the voriconazole-echinocandin combination in settings with >5% voriconazole resistance.
The voriconazole-echinocandin and voriconazole-L-AmB combinations are expected to be equally effective at prevalence rates for azole resistance of 5 to 50%. With very high (≥50%) resistance rates, the voriconazole-L-AmB combination is expected to be more effective, in view of the limited effectiveness of echinocandins monotherapy.
Monotherapy with L-AmB would be an acceptable alternative, although less effective than an azole in the majority of patients who will still be infected by azole-susceptible strains. Therefore, expected survival rates with L-AmB monotherapy in a setting with 5% to 50% azole resistance are predicted to be less favorable than with either combination therapy. Caspofungin monotherapy is expected to be associated with a higher mortality compared to azole-echinocandin combination or L-AmB monotherapy, in view of the less favorable outcomes of the two prospective caspofungin studies (51,52).

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Conclusions 2.3 – First-line therapy for aspergillosis with unknown susceptibility to voriconazole or isavuconazole	
Conclusion 20	Based on modeling, an antifungal combination regimen containing voriconazole and either L-AmB or an echinocandin is associated with the lowest mortality rates in a setting with 5–50% prevalence of azole resistant *Aspergillus*
Level 4	(D)
Conclusion 21	In settings with >50% azole resistance, a combination of voriconazole with L-AmB is associated with lower expected mortality than echinocandin monotherapy or voriconazole plus echinocandin combination therapy
Level 4	(D)

Recommendations

Given the high prevalence of azole-resistance in the Netherlands, maximum efforts should be made to obtain clinical specimens to perform in vitro susceptibility testing from all patients with suspected invasive aspergillosis (see chapter 2.1). Direct detection of resistance mutations by PCR on clinical specimens may help the identification of resistance in the mycology reference laboratory.

In view of the high mortality rates associated with invasive aspergillosis, the committee recommends that azole monotherapy should not be prescribed as standard therapy in patients with proven, probable or possible invasive aspergillosis of unknown azole resistance.

The majority of these patients will still be infected by a voriconazole-susceptible *Aspergillus* strain. Therefore, combination regimens combining voriconazole with a non-azole antifungal (L-AmB or echinocandin) will retain the efficacy benefit in those patients with azole-susceptible isolates, while covering azole-resistant strains by the companion drug. Based on this modeling, the committee favors an azole-echinocandin or azole-L-AmB combination for cases with unknown azole susceptibility.

The choice between azole-echinocandin or azole-L-AmB combination therapy may be individualized, e.g., a preference for azole-echinocandin in case of potential renal toxicity, for azole-L-AmB in settings with a higher than average prevalence of azole resistance, or if mixed infections caused by azole-susceptible and azole-resistant isolates are present, or for suspected mucormycosis (e.g., reversed halo sign, negative galactomannan in BAL).

For hematology patients in settings where BAL is performed for resistance gene PCR, the committee considers initial azole monotherapy a reasonable alternative for the first few days, pending susceptibility testing or resistance gene PCR results. Susceptibility or PCR results should subsequently guide escalation to L-AmB in case of resistance detection, and to combination therapy if susceptibility results are unavailable. In view of the higher mortality rate among ICU patients with invasive aspergillosis, the committee recommends that those patients receive initial combination therapy, even when resistance gene PCR results are pending.

In addition, close clinical follow-up, with therapeutic drug monitoring (TDM), sequential galactomannan assays, and imaging to monitor progress, is required for patients infected by strains of unknown susceptibility.

Recommendation 12	For patients with invasive aspergillosis caused by isolates with unknown susceptibility to azoles, initial combination therapy with voriconazole/isavuconazole plus L-AmB, or voriconazole/isavuconazole plus an echinocandin is recommended. Monotherapy with L-AmB is considered as a second choice in these patients. In case of mixed azole-resistant and azole-susceptible mold infections, or suspected co-infection with mucorales, voriconazole/isavuconazole plus L-AmB is recommended.

Recommendation 13	If susceptibility or BAL Cyp51 resistance PCR results are expected shortly, initial monotherapy with voriconazole may be prescribed to patients with invasive aspergillosis of unknown azole susceptibility. Subsequent PCR results should guide escalation to L-AmB in case of resistance, and to combination therapy if susceptibility results are unavailable. Severely ill patients and patients in the ICU should receive initial combination therapy pending susceptibility results.

Proven azole resistance

In patients infected by isolates that underwent susceptibility testing and were confirmed to be resistant to all azoles, including voriconazole, or patients with positive Cyp51 resistance PCR results, treatment with combination therapy containing voriconazole is irrational. In these cases, L-AmB monotherapy is associated with higher expected survival rates than echinocandin monotherapy (42,44,51,52,64–66), and echinocandins are not recommended as primary treatment for invasive aspergillosis.

ABLC has not been studied in randomized trials for invasive aspergillosis, and published observational data are equivocal about both its relative effectiveness and its safety compared to L-AmB. Therefore, the committee does not make any recommendations for the use of ABLC.

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In exceptional situations, and only if the posaconazole MIC has been documented to be <2, a step down from L-AmB to posaconazole in combination may be considered, provided that therapeutic drug monitoring is performed to maintain high serum levels. Consultation with an expert center before a step-down to posaconazole is required.

Recommendation 14	For patients with invasive aspergillosis caused by isolates with confirmed resistance to azoles, L-AmB is recommended. Echinocandin monotherapy is recommended as a second choice in these patients.

Table 2.1. Recommended drug and standard adult dose for treatment of invasive aspergillosis[†]

A. Therapy for isolates with *unknown susceptibility* to azoles		
Antifungal agent	**Loading dose**	**Maintenance dose**
1st choice*		
Azole+Echinocandin combination:		
Voriconazole OR	bid 6 mg/kg iv or bid 400 mg po	4 mg/kg bid iv[#] or 200-300 mg bid po[#]
Isavuconazole	tid 200 mg iv or po on days 1 +2	200 mg qd iv or po
AND		
Caspofungin OR	70 mg	50 mg qd, (>80kg: 70 mg qd)
Micafungin OR	-	100 mg qd
Anidulafungin	200 mg	100 mg qd
OR		
Azole + L-AmB combination:		
Voriconazole	bid 6 mg/kg iv or bid 400 mg po	4 mg/kg bid iv[#] or 200-300 mg bid po[#]
OR		200 mg qd iv or po
Isavuconazole	tid 200 mg iv or po on days 1 +2	
AND		3 mg/kg/d
L-AmB	-	
2nd choice*		
Liposomal AmB	-	3 mg/kg/d
3rd choice*		
Caspofungin	70 mg	50 mg qd, (>80kg: 70 mg qd)
Micafungin	-	100 mg qd
Anidulafungin	200 mg	100 mg qd

B. Therapy for isolates with *confirmed susceptibility* to azoles		
Antifungal agent	**Loading dose**	**Maintenance dose**
1st choice*		
Voriconazole	bid 6 mg/kg iv or bid 400 mg po	4 mg/kg bid iv[#] or 200 mg bid po[#]
Isavuconazole	tid 200 mg iv or po on days 1 +2	200 mg qd iv or po
2nd choice*		
Liposomal AmB	-	3 mg/kg/d
3rd choice*		
Voriconazole+Echinocandin combination:		
Voriconazole		
AND	bid 6 mg/kg iv or bid 400 mg po	4 mg/kg bid iv[#] or 200-300 mg bid po[#]
Caspofungin OR		50 mg qd, (>80kg: 70 mg qd)
Micafungin OR	70 mg	100 mg qd
Anidulafungin	-	100 mg qd
	200 mg	

C. Therapy for isolates with *confirmed resistance* to azoles		
Antifungal agent	**Loading dose**	**Maintenance dose**
1st choice*		
Liposomal AmB	-	3 mg/kg/d
2nd choice*		
Caspofungin	70 mg	50 mg qd, (>80kg: 70 mg qd)
Micafungin	-	100 mg qd
Anidulafungin	200 mg	100 mg qd

* For specific recommendations, exceptions, and contra-indications, see text.
† The dosages in this table are specific for invasive aspergillosis; for other mycoses, different dosages may apply.
# Individual dose based on therapeutic drug monitoring

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2.4. Invasive aspergillosis in special populations

Aspergillosis in ICU patients

Invasive aspergillosis has been increasingly diagnosed in patients in the intensive care unit without traditional risk factors. In retrospective analyses in Europe and the USA, corticosteroid use either before or during ICU admission, COPD or other structural lung diseases, sepsis and post-sepsis immunoparalysis, and H1N1 influenza were identified as the major risk factors (67–69). The 2008 EORTC/MSG criteria perform poorly in ICU patients without classical risk factors (1,70).
In ICU patients with respiratory samples growing *Aspergillus* species, discrimination between colonization and invasive aspergillosis is difficult, while lung biopsy to demonstrate invasive infection is frequently contraindicated. In a case series of 172 culture-positive ICU patients, 52% had confirmed colonization without infection, 10% had histologically proven invasive aspergillosis, and 38% had probable aspergillosis based on ICU-specific risk factors and radiology (71). A recent international prospective study in Europe among 563 ICU patients found that 47% were colonized, 17% had proven and 36% had putative invasive aspergillosis (72).
In a prospective ICU study, the sensitivity of serum galactomannan was limited to 42% in ICU patients with invasive aspergillosis (18). Galactomannan in BAL fluid had a specificity of 87% and sensitivity of 88% which significantly exceeds the sensitivity of cultures (58%) (see Chapter 2.1) (18).
Based on these data, it is recommended that ICU patients with clinically relevant unexplained chest radiology abnormalities who have a positive *Aspergillus* colonization culture in respiratory samples and risk factors for ICU-related aspergillosis (corticosteroids, COPD, sepsis, or classical EORTC/MSG risk factors for aspergillosis) are tested for serum galactomannan and undergo BAL for galactomannan (70). A positive galactomannan index in either sample indicates probable invasive aspergillosis. Likewise, ICU patients with unexplained chest radiology abnormalities and risk factors for ICU-related aspergillosis who are not *Aspergillus* culture positive should undergo serum and BAL galactomannan testing. A positive BAL galactomannan (specificity 87%) should prompt for antifungal therapy, if false-positivity and alternative etiology are considered unlikely.
Influenza-related invasive aspergillosis is discussed separately in the next paragraph.

In view of the severity of illness of patients admitted to the ICU, it is recommended that initial therapy for ICU patients covers azole-resistant *Aspergillus* isolates, until susceptibility has been confirmed. For specific treatment choices, see Chapter 2.3 and Table 2.1. Patients who have clinically improved after 2 weeks, are stable and have unknown azole-resistance may be stepped down to azole monotherapy under strict follow-up.

Aspergillosis in patients with influenza

Recently, high rates of secondary invasive pulmonary aspergillosis complicating influenza pneumonia have been reported, in apparently immunocompetent patients (73–75). A case series from Belgium included 9 cases of invasive aspergillosis among 40 critically ill patients with H1N1 viral infection (23%). Corticosteroid use was the major independent risk factor for influenza-related invasive aspergillosis (73).
In the Netherlands, 25 patients with post-influenza invasive aspergillosis were identified among 110 ICU patients with influenza (23%) in a 4 months' period in 2016 (76). Mortality was 56%. Five of 16 isolates (31%) were azole-resistant. BAL culture was positive in 84%, BAL galactomannan in 89%, and serum galactomannan in 67%. Two patients had *Aspergillus* tracheobronchitis at autopsy (76).
In view of the recent data, diagnostic recommendations cannot be based on prospective studies yet. Based on a series of consensus conferences in 2016, the committee has made the following recommendations for ICU patients.
During the influenza season, patients admitted to the ICU with a respiratory infection should be tested by nasopharynx swab influenza PCR. All ICU patients with PCR-confirmed influenza should undergo sampling for serum galactomannan, bronchoscopy to rule out tracheobronchitis, and BAL for galactomannan and culture. In case of tracheobronchitis, a positive serum galactomannan or a positive BAL galactomannan (index ≥0.8), patients should be treated as a probable invasive aspergillosis with combination azole+echinocandin therapy (or alternatives) as outlined in Chapter 2.3.
If tracheal aspirate and BAL cultures reveal no Aspergillus growth but galactomannan is positive, Aspergillus PCR as well as Cyp51 PCR for the presence of mutations associated with azole resistance should be performed on BAL.

Influenza-confirmed ICU patients for whom all three diagnostic criteria (bronchoscopy, serum galactomannan and BAL galactomannan) are negative should be followed by standard tracheal aspirate screening cultures. Once screening cultures yield *Aspergillus* colonization or new respiratory complications occur, the diagnostic workup (bronchoscopy, serum galactomannan and BAL galactomannan) should be repeated.
If BAL cannot be performed, positive *Aspergillus* colonization cultures should guide antifungal treatment, in addition to serum galactomannan and bronchoscopy to macro-/microscopically rule out tracheobronchitis.

Administration of corticosteroids should be avoided in patients with proven/probable influenza-related invasive aspergillosis. Combination azole+echinocandin therapy for probable influenza-related invasive aspergillosis of unknown azole susceptibility should be continued for a minimum of 2 weeks. Patients who have clinically improved after 2 weeks, are

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stable and have wild-type cyp51 PCR results may be stepped down to azole monotherapy under strict follow-up. In case of azole resistance detected by agar screening, MIC or cyp51 resistance PCR, therapy should be changed to L-AmB as outlined in Chapter 2.3.
For patients with confirmed influenza not admitted to the ICU, new respiratory complications, clinical worsening, or a sputum culture positive for *Aspergillus* spp should prompt a diagnostic workup as described for ICU patients. Physicians should consider starting antifungal therapy pending diagnostic results, depending on the clinical status of the patient.

Aspergillosis in patients with chronic granulomatous disease (CGD)

Patients with chronic granulomatous disease have mutations in the NADPH-oxidase complex, rendering patients highly susceptible to invasive fungal infections (77,78). In a cohort study of 268 CGD patients over 4 decades, invasive aspergillosis occurred in 125 (44%), and was the major determinant for mortality (79). Of these patients, 70% were on antifungal prophylaxis, mostly itraconazole. Antifungal prophylaxis with itraconazole in CGD patients has decreased the incidence of IFD in CGD patients (80). Posaconazole has been suggested to be a favorable alternative (81).
The sensitivity of serum galactomannan in CGD patients with invasive aspergillosis is very low (<20%) (3,10). Due to the fact that patients with CGD are at risk to develop invasive fungal disease caused by a wide range of different molds, every attempt should be made to make a causative diagnosis.
Recombinant IFN-γ (rIFN-γ) prophylaxis in patients with chronic granulomatous disease (CGD) reduced the incidence of fungal and bacterial infections by approximately 70% (82) (See Chapter 2.5).

Conclusions 2.4 – Invasive aspergillosis in ICU patients, patients with influenza, and patients with CGD	
Conclusion 22	Invasive aspergillosis in ICU patients occurs in subjects without classical risk factors for aspergillosis; corticosteroid administration, COPD, sepsis, post-sepsis immunoparalysis are the major determinants.
Level 2	Meersseman, 2004 (C); Vandewoude, 2006 (B); Meersseman, 2007 (C); Blot, 2012 (C); Baddley, 2013 (B); Taccone, 2015 (B)
Conclusion 23	BAL galactomannan has predictive value to diagnose probable invasive aspergillosis in ICU patients
Level 3	Meersseman, 2008 (C); Blot, 2012 (C)
Conclusion 24	Invasive aspergillosis is a frequent early complication of influenza pneumonia in the ICU; 31% of cases in the Netherlands were caused by azole-resistant isolates
Level 3	Wauters, 2012 (C); Van de Veerdonk, 2016 (C)
Conclusion 25	The sensitivity of serum galactomannan testing in CGD patients is <20%
Level 3	Verweij, 2000 (C); Mortensen, 2011 (C)

Recommendation 15	ICU patients with a positive *Aspergillus* culture from respiratory samples, who have chest radiology abnormalities and risk factors for ICU-related aspergillosis should undergo BAL and serum galactomannan testing. A positive galactomannan index in either sample prompts for antifungal therapy, covering azole-resistant *Aspergillus*, unless the isolate has been proven susceptible.

Recommendation 16	ICU patients with clinically relevant unexplained chest radiology abnormalities and risk factors for ICU-related aspergillosis who are not *Aspergillus* culture-positive should undergo serum and BAL galactomannan testing. A positive galactomannan index in either sample in the absence of other explanations prompts for antifungal therapy, covering azole-resistant *Aspergillus*. Patients who have clinically improved after 2 weeks, are stable and have unknown azole resistance may be stepped down to azole monotherapy under strict follow-up.

Recommendation 17	ICU patients with confirmed influenza should undergo sampling for serum galactomannan. It is recommended that ICU patients with confirmed influenza and radiologic abnormalities on chest X-ray should undergo bronchoscopy and BAL for galactomannan and culture. In case of tracheobronchitis, a positive serum galactomannan or a positive BAL galactomannan (index ≥0.8), patients should be treated with combination azole+echinocandin or azole+L-AmB therapy. Monotherapy with L-AmB is considered as a second choice in these patients. If cultures reveal no *Aspergillus* growth, galactomannan-positive BAL material should be tested by PCR for the presence of Cyp51 mutations. ICU patients with influenza and negative *Aspergillus* serum and bronchoscopy/BAL screening, and non-ICU influenza patients should undergo (repeat) serum and bronchoscopy/BAL diagnostics if new respiratory complications or clinical worsening occur, or if sputum/tracheal *Aspergillus* colonization cultures are positive.

Recommendation 18	Serum galactomannan should not be used to screen for or rule out invasive aspergillosis in CGD patients

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2.5. Management of patients treated for invasive aspergillosis

Therapeutic drug monitoring (TDM)

Accumulating evidence has identified therapeutic drug monitoring (TDM) of itraconazole, posaconazole and voriconazole as required to optimize the efficacy and safety of these drugs (83,84). Both interindividual variation in pharmacokinetics and the specific concentrations required for the MIC established for the infecting strain require individual dosing and monitoring (85).

Itraconazole
Itraconazole is available as both tablets and suspension for oral administration, as well as in iv formulation. For oral use, the suspension has superior bioavailability and is more effective in prophylaxis than tablets (86). For antifungal prophylaxis, a cumulative plasma trough level of 1mg/l for both itraconazole and its metabolite hydroxy-itraconazole was found effective (87,88). For antifungal therapy, higher trough levels were shown to correlate with successful outcomes (89,90). As a result, trough levels of 2 to 4 mg/l (itraconazole + hydroxy-itraconazole) are recommended, to be assessed within 3-5 days after start of therapy.

Voriconazole
Voriconazole is available as tablets, suspension and iv formulation. The tablets and suspension have similar bioavailability. The kinetics of voriconazole are nonlinear. In addition, concentrations are variable, not only between patients but also intra-individually over time. In a randomized trial, voriconazole TDM resulted in similar incidence of adverse events but significantly better success rates among patients with invasive aspergillosis (91).
Clinical failure was associated with trough voriconazole concentrations <1 mg/l in adults and children (83,92). In several large cohort studies using trough concentration cutoffs of 1.5, 1.7 or 2.0 mg/l, levels above the cutoff were significantly associated with greater probability of response (84,92,93). In a retrospective analysis of >1000 patients enrolled in trials for invasive aspergillosis, a trough/MIC ratio of 2 to 5 was associated with near-maximal chance of successful outcomes (94).
A step-down from 4 mg/kg bid iv to a standard dose of 200mg/bid (i.e., 2.5 to 3 mg/kg bid in most patients) resulted in insufficient trough levels in a large proportion of patients (84). Initial 200–300 mg iv bid and 300–400 mg oral bid were best-suited to achieve initial therapeutic concentrations of 1.5 to 4.5 mg/l (84).
Neurotoxicity, was found to be associated with concentrations >4–6 mg/L, whereas a strict correlation of hepatotoxicity with high concentration was not established (83,84,93). However, in the Asian population, an association of concentrations >4 mg/l with hepatotoxicity was established (95).
Concentrations are to be assessed 2-3 days after first administration, and to be repeated once or twice weekly during therapy regardless of previous concentrations, in view of the high intra-individual variation.

Posaconazole
Posaconazole is available as both tablets and suspension for oral administration, as well as in an iv formulation. For oral use, the suspension has an inferior and highly variable bioavailability as compared to tablets (96), and recommended dosing is different for tablets and suspension. For prophylactic use of posaconazole, failures were significantly associated with low trough concentrations (Dolton et al. 2012; Jang et al. 2010). Hence, for antifungal prophylaxis, a steady state plasma trough level of >0.7 mg/l is recommended (99). An association of higher mean steady state plasma concentrations with successful outcomes was found in a prospective study of posaconazole salvage therapy for invasive aspergillosis (100). Hence, a trough level of >1.0 mg/l is recommended for antifungal therapy of azole-susceptible *A. fumigatus*. In selected cases, an elevated MIC to posaconazole may still be amenable to posaconazole therapy at trough concentrations >1.5 mg/l under strict TDM (28).
Posaconazole iv formulation and tablets are dosed using a loading dose to achieve early steady state concentrations (96,101), and TDM should be initiated around day 3 of therapy. As the intra-individual variation is less than with voriconazole, repeat TDM should be performed no more than once weekly once target concentrations have been reached.

Isavuconazole
Isavuconazole is available as tablets and iv formulation. Optimal target concentrations have not yet been established, but based on modeling studies, aimed troughs are assumed to be 2 to 4 mg/l (62,63). In view of the clear relationship between plasma concentrations and clinical outcomes established for the other azoles, the committee recommends TDM for all patients receiving isavuconazole (e.g., once weekly until target has been reached), pending more study results.

Intravenous to oral stepdown

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Little prospective data are available to support recommendations on the step-down from intravenous to oral azoles in patients with acute invasive pulmonary aspergillosis. Based on pharmacokinetic data, azoles may be switched to oral in patients who tolerate oral therapy, provided that specific efforts are made to monitor therapeutic drug levels, as outlined above.

Conclusions 2.5 – Therapeutic drug monitoring (TDM) and oral stepdown	
Conclusion 26	Itraconazole oral suspension has superior bioavailability compared to tablets. Itraconazole trough concentrations correlate with successful outcomes.
Level 2	Glasmacher, 2003 (B); Glasmacher 1999 (B); Boogaerts, 1989 (B); Denning 1994, (A2); Lestner, 2009 (B)
Conclusion 27	Voriconazole concentrations show high inter- and intra-individual variation. Utilization of TDM and maintaining trough concentrations >1.5 to 2 mg/l trough concentrations correlate with successful outcomes.
Level 2	Park, 2012 (A2); Pascual, 2008 (B); Pascual, 2008 (B); Troke, 2011 (B); Dolton, 2012a (B); Pascual, 2012 (B); Lee, 2013 (B)
Conclusion 28	Posaconazole tablets has superior bioavailability compared to oral suspension. Posaconazole trough concentrations correlate with successful outcomes.
Level 2	Kersemaekers, 2015 (C); Walsh, 2007 (B); Jang, 2010 (B); Dolton, 2012b (B); Dolton, 2012c (B)
Conclusion 29	Isavuconazole trough concentrations >2–4 mg/l are assumed to be required for successful outcome
Level 3	Kovanda, 2016 (C); Desai, 2016 (C)

Recommendation 19	TDM is strongly recommended for patients using itraconazole. For prophylaxis, trough levels of >1 mg/l (itraconazole + hydroxy-itraconazole) should be achieved; for therapy, trough levels should be 2 to 4 mg/l. For oral administration, itraconazole suspension is preferred over tablets.
Recommendation 20	TDM is recommended for patients using voriconazole. Trough levels should be 1.5-2 to 6 mg/l. Concentrations should be assessed 2–3 days after first administration, and repeated during therapy, regardless of previous concentrations.
Recommendation 21	TDM should be considered for patients using posaconazole tablets or iv. For patients using posaconazole suspension, TDM is required. Posaconazole suspension should only be used if tablets are contraindicated. For prophylaxis, trough levels of >0.7 mg/l should be achieved; for therapy, trough levels should be >1 mg/l. Concentrations should be assessed 3 days after first administration using a loading dose, and repeated during therapy.
Recommendation 22	Pending further evidence, TDM should be considered for patients using isavuconazole. Trough levels of 2 to 4 mg/l should be achieved for therapy. Using a loading dose, concentrations should be assessed 3 days after first administration.
Recommendation 23	For children, TDM is strongly recommended for all mould-active azoles.
Recommendation 24	Patients may be stepped down from an iv to oral azole, provided that they can tolerate oral therapy, and with TDM where appropriate.

Streamlining and Duration of therapy

In general, primary treatment of invasive pulmonary aspergillosis is continued for 6 to 12 weeks. Patients should be monitored serially by clinical evaluation, radiographic imaging, and course of serum galactomannan index (if positive at baseline).

The course of serum galactomannan has been found to be a measure of response to therapy in an earlier review of studies (102), as well as in more recent prospective cohort studies (103–105). In patients enrolled in a large prospective trial (15), a galactomannan increase between baseline and week 1 was significantly associated with failure, and a reduction of >35% predicted a probability of a favorable clinical response (16,106). However, resolution of serum galactomannan is not a sole criterion for discontinuation of antifungal therapy, and the decision to discontinue primary therapy is taken on the basis of the clinical response, the status of underlying disease, course of biomarkers, and the evolution of CT-scan findings. In

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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 (107).

For patients receiving initial combination therapy for pulmonary aspergillosis of unknown azole susceptibility, no data exist to recommend a specific streamlining strategy.
Patients receiving combination therapy may be stepped down to azole monotherapy as soon as azole susceptibility (culture) or absence of Cyp51 mutations (BAL Cyp51 PCR) has been documented.

In case of azole resistance detected by agar screening, MIC or Cyp51 resistance PCR, therapy should be changed to L-AmB as outlined in Chapter 2.3.

In the absence of Cyp51 results and unknown azole susceptibility, continuation of initial combination therapy is rational but difficult to maintain if prolonged treatment is required.
In the absence of evidence, some experts consider streamling in clinically improved patients after 2 weeks. Depending on the underlying disease and immune status, step-down regimens covering potentially azole-resistant strains have been considered by some experts, e.g., voriconazole plus thrice weekly echinocandin, or high-dose posaconazole monotherapy based on TDM (trough concentrations >1.5 mg/l), despite the absence of published evidence. Alternatively, stepping down to voriconazole monotherapy despite unknown susceptibility had been considered in selected clinically stable and immunologically improved patients.
All streamlining should be done under strict follow-up of serum galactomannan (twice weekly) and repeated CT-scan of the lesions (e.g., every 3 weeks), until further resolution has been documented. None of these policies have been supported by current evidence, and no formal recommendation can be made.

Secondary prophylaxis

After discontinuation of primary treatment in patients with persistent immunosuppression or those undergoing HSCT, maintenance therapy or resumption of antifungal therapy at the time of subsequent courses of immunosuppression may be considered. In 2 prospective open-label trials, patients undergoing allo-HSCT after invasive aspergillosis received secondary prophylaxis with voriconazole or other antifungals, leading to a protective effect of >90% in both studies (108,109).
In case of proven/probable aspergillosis, the susceptibility pattern should guide the choice of secondary prophylaxis. In case of unknown susceptibility, high-dose posaconazole, L-AmB, or echinocandins have been used.

Conclusions 2.5 – Duration of therapy and secondary prophylaxis for acute invasive aspergillosis	
Conclusion 30	The duration of antifungal therapy has not been investigated. In general, treatment is continued for 6 to 12 weeks, and at least 2 weeks after the resolution of neutropenia.
Level 4	Singh, 2003 (D)
Conclusion 31	The course of serum galactomannan is an indicator of response to therapy.
Level 2	Micelli, 2008 (C); Park, 2011 (B); Chai, 2012(B); Fisher, 2013 (B); Chai, 2014 (C); Neofytos, 2015 (B)
Conclusion 32	Secondary prophylaxis is effective in preventing a relapse of invasive aspergillosis in patients undergoing allo-HSCT
Level 3	Cordonnier, 2010 (B); Liu, 2014 (C)

Recommendation 25	The duration of therapy for patients with acute invasive pulmonary aspergillosis depends on the clinical course of the disease and the evolution of serum galactomannan index and CT-scan findings. Duration of therapy is at least 6 to 12 weeks and, in neutropenic patients, not less than 2 weeks after resolution of neutropenia.

Recommendation 26	Secondary prophylaxis is recommended after recent invasive aspergillosis in patients undergoing new immunosuppressive treatment (e.g., HSCT) or patients with a specific primary immune deficiency (e.g., CGD). In case of proven/probable aspergillosis, the susceptibility pattern should guide the choice of prophylaxis. Voriconazole or posaconazole are eligible as oral prophylaxis for azole-susceptible isolates, with appropriate TDM.

Adjunctive immunotherapy

While the role of prophylactic colony-stimulating factors (mainly G-CSF) to reduce the duration of neutropenia has been established, their adjunctive role for the treatment of fungal infections in neutropenic patients is unclear. Whereas

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preclinical studies have demonstrated a beneficial effect of G-CSF and GM-CSF on antifungal host defense mechanisms, no clinical data are available, and no specific recommendations can be made for patients with invasive fungal infections.
Granulocyte transfusions have been used as adjunctive treatment in persistently neutropenic patients with neutropenia. A recent randomized multicenter trial compared adjunctive G-CSF-elicited granulocyte transfusions with standard therapy in 97 neutropenic patients with severe bacterial or fungal infections (including 28 cases with proven/probable aspergillosis) (110). Overall success rate was 42% for the granulocyte transfusion group and 43% for the controls, and survival curves were similar for both treatment groups. Whereas the trial formally was underpowered to detect small treatment differences, there was no trend towards improved outcomes in the total study group, nor was there in the subgroup with proven or presumed fungal infections (110).

Interferon-γ is a crucial mediator of antifungal host defense. Recombinant IFN-γ (rIFN-γ) prophylaxis in patients with chronic granulomatous disease (CGD) reduced the incidence of fungal and bacterial infections by approximately 70% (82). No controlled trials have been conducted to investigate adjunctive therapy with rIFN-γ as a treatment of invasive aspergillosis in patients with CGD. However, based on theoretical considerations, many experts advocate adjunctive rIFN-γ treatment for CGD patients with invasive aspergillosis.

Recent studies have reported defective IFN-γ in patients with chronic pulmonary aspergillosis (111), as well as in patients with severe acute invasive candidiasis or aspergillosis (112). Patients without known immunodeficiency and invasive skull base aspergillosis were found to have a normal IFN-γ response but an impaired Th17 response, which is also known to be important for fungal host defense (113). Adjunctive therapy with rIFN-γ was shown to have beneficial effects on the immune status including IL-17 and IL-22 responses in a case series of patients with invasive fungal infections, including 3 patients with proven/probable invasive aspergillosis (112). Functional testing of IFN-γ production capacity during invasive aspergillosis may be used to guide the decision to start immunotherapy with rIFN-γ in fulminant or refractory cases with invasive aspergillosis.

Conclusions 2.5 – Immunotherapy for acute invasive aspergillosis	
Conclusion 33	Adjunctive therapy with granulocyte transfusions or colony-stimulating factors for patients with invasive aspergillosis has no proven benefit.
Level 3	Price, 2015 (B); expert opinion 9D)
Conclusion 34	Patients with invasive aspergillosis may have defects in the Th1/IFN-γ or Th17 antifungal host defense pathways
Level 3	Smith, 2014 (C); Delsing, 2014 (C)
Conclusion 35	Prophylaxis with IFN-γ protects against invasive aspergillosis in CGD patients
Level 2	International CGD Study Group, 1991 (A2)
Conclusion 36	Adjunctive therapy with IFN-γ may have beneficial effects in patients with invasive aspergillosis
Level 3	Safdar, 2005 (C); Delsing, 2015 (C)

Recommendation 27	Testing for IFN-γ production defects by a reference lab should be considered, to guide the decision to start rIFN-γ immunotherapy in non-neutropenic patients with invasive aspergillosis with fulminant or refractory disease. Adjunctive IFN-γ therapy should be considered in all CGD patients, and in other patients with proven or suspected Th1/Th17 host defense pathway defects and invasive aspergillosis.

Salvage therapy

Salvage therapy is defined as treatment given in the event of failure of first-line therapy, or undue toxicity of first-line therapy. No double-blind controlled studies have been conducted in this category of patients.
Following failure of primary antifungal therapy for invasive aspergillosis, a number of causes should be taken into consideration. Firstly, drug exposure may have been suboptimal, in particular to azoles that require intensive TDM. Secondly, the infection may have been caused by mucorales, alone or in combination with *Aspergillus* species. Thirdly, the infection may stem from an *Aspergillus* species that is intrinsically less susceptible to certain antifungal agents (such as A. *terreus*, which is less susceptible to AmB compounds) or is azole-resistant. For these reasons, the *Aspergillus* species and the susceptibility should be determined in the event of therapy failure.
Lipid formulations of AmB, voriconazole, posaconazole, itraconazole, caspofungin and micafungin have all been described as salvage treatments. Comparison of studies is difficult, since patient populations and definitions of outcome considerably differ between studies. In addition, the indication for salvage therapy may be a major confounder, since patients intolerant for a first-line agent have better outcomes than those with efficacy failures on primary treatment.
In patients who fail initial voriconazole or isavuconazole therapy, a change of antifungal class is recommended. L-AmB (114,115), ABLC (116), caspofungin (48,49,117) and micafungin (50) have been described as salvage options, as has the

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combination of voriconazole plus caspofungin (54). The value of adding a second antifungal to the failing therapy rather than discontinuing the first agent has not been investigated.

Conclusions 2.5 – Salvage therapy for acute invasive aspergillosis	
Conclusion 37	No comparative studies have assessed the relative efficacy of antifungals for salvage treatment of invasive aspergillosis. L-AmB, ABLC, caspofungin, micafungin, and voriconazole plus caspofungin have been described for salvage regimens
Level 3	Ng, 1995 (C); Walsh, 1998 (C); Marr, 2004 (C); Maertens, 2004 (C); Betts, 2006 (C); Denning, 2006 (C); Hiemenz, 2010 (C)

Recommendation 28	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 (co)-infection with mucorales should be taken into consideration.

Recommendation 29	On failure of voriconazole or isavuconazole, the committee considers it to be of primary importance that azole resistance and a co-infection with mucorales be excluded. In view of this differential diagnosis, L-AmB is recommended. An echinocandin may be considered as the second choice if mucormycosis has been excluded and there is no evidence of cerebral aspergillosis.

2.6. Preemptive (Diagnostic-driven) and empirical therapy for invasive aspergillosis

Preemptive or diagnostic-driven 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. In contrast, the classical concept of empirical antifungal therapy is defined as initiating antifungal therapy in patients in specific risk groups (e.g., neutropenia) with fever, where there is no specific evidence of fungal infection.

Diagnostic-driven therapy

Several studies have supported the value of diagnostic-driven (preemptive) strategies as compared to classical fever-driven (empirical) therapy. Recommended diagnostic techniques, including galactomannan antigen index and HRCT chest scan, are described in chapter 2.1. In a feasibility study, diagnostic-driven therapy based on galactomannan screening and HRCT was compared to empirical therapy in 117 patients with leukemia (17). Diagnostic-driven therapy led to a 78% reduction of antifungal use, and no cases of invasive aspergillosis were missed.

Several randomized studies have compared diagnostic-driven strategies based on serum galactomannan. In a large multicenter randomized study from France, survival was similar in the diagnostic-driven and empirical therapy groups (118). Probable or proven invasive aspergillosis was more commonly detected in the diagnostic-driven group, but costs of antifungal therapy were 35% lower. A small study from Singapore yielded comparable results (119). In a large trial from Australia, 240 leukemia/alloHSCT patients were randomized between a standard empirical strategy and a diagnostic-driven strategy based on serum galactomannan and PCR screening followed by HRCT (11). Antifungal use was lower in the diagnostic-driven group (15% vs. 32%, p=0.002). Notably, 55% of probable/possible invasive aspergillosis cases in the diagnostic-driven group were diagnosed in the absence of fever. No cases of invasive aspergillosis were missed in that group. The diagnosis of probable/possible aspergillosis was established a median of 4-7 days earlier with the galacto-mannan/PRC-driven strategy. Mortality did not differ significantly between the groups (11). In a recent randomized trial from Spain, 219 leukemia/alloHSCT patients underwent a diagnostic-driven antifungal strategy based on galactomannan screening vs. galactomannan plus serum PCR (120). Patients in the galactomannan-PCR group had a shorter median interval to the diagnosis of (probable) invasive aspergillosis (13 vs 20 days; P<0.05).

Empiric therapy

Empiric antifungal therapy in neutropenic patients with fever despite broad spectrum antibiotics has been studied in several large randomized trials. L-AmB was as effective as c-AmB but associated with significantly fewer proven breakthrough infections (121). In a randomized trial using a composite endpoint, voriconazole (overall success rate 26%) was slightly worse than L-AmB (success rate 31%). However, significantly fewer breakthrough infections occurred with voriconazole (p=0.02) (122). In a large randomized study, caspofungin was as effective as L-AmB but L-AmB caused

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significantly more nephrotoxicity and more infusion-related adverse event and was more frequently discontinued early. Survival 7 days after discontinuation appeared to be better in the caspofungin group (93% vs. 89%, p=0.05) (123).

Conclusions 2.6 – Diagnostic-driven (preemptive) and empirical antifungal therapy in leukemia/HSCT patients	
Conclusion 38	Diagnostic-driven antifungal therapy based on serum galactomannan and/or PCR screening and HRCT results in similar mortality rates, earlier diagnosis of aspergillosis, more patients identified with probable/proven aspergillosis, and less antifungal use compared to a fever-driven empirical therapy strategy.
Level 2	Maertens, 2005 (B); Cordonnier, 2009 (A2); Tan, 2011 (B); Morrissey, 2013 (A2);
Conclusion 39	L-AmB, voriconazole and caspofungin have been assessed as empirical treatment for neutropenic patients with fever; caspofungin was associated with fewer side effects and better survival than L-AmB.
Level 2	Walsh, 1999 (A2); Walsh, 2002 (A2); Walsh, 2004 (A2)

Recommendations
Based on the proven safety, the higher diagnostic yield, and the reduction in unnecessary antifungal use of diagnostic-driven compared to empirical therapy, a diagnostic-driven therapy based on a minimum of twice weekly serum galactomannan screening, followed by HRCT when positive, should be used in all neutropenic patients with hematological malignancies and HSCT recipients.

If a diagnosis of possible, probable or proven diagnosis is established, antifungal therapy should be started, following the recommendations given in Chapters 2.2 and 2.3. The use of blood-based PCR for screening cannot be recommended for routine use in clinical practice at present, due to the lack of standardization and validation for commercially available assays.
Classical fever-driven empiric therapy is not recommended, and it should be noted that voriconazole or other azoles are not suitable for empiric therapy at present, given the present azole resistance rate of 5 to 35% in the Netherlands. Whenever it would be necessary to use an empiric rather than diagnostic-driven therapy, e.g., in situations were timely galactomannan screening or HRCT are (temporarily) not available, caspofungin or L-AmB would be appropriate choices.

Recommendation 30	In neutropenic patients with hematological malignancies or HSCT, a diagnostic-driven antifungal strategy is recommended, based on screening serum *Aspergillus* galactomannan at least twice weekly.

Recommendation 31	In neutropenic patients with hematological malignancies or HSCT and a positive serum *Aspergillus* galactomannan index (≥0.5) or persistent unexplained fever, an HRCT lung scan should be carried out. Preemptive therapy against *Aspergillus* should be given in the event of 2 x a positive GM >0.5 or findings consistent with invasive fungal infection on the HRCT scan.

Recommendation 32	The committee recommends the use of a diagnostic-driven antifungal strategy as opposed to symptom-driven empiric strategy. If circumstances require an empiric strategy in patients with persistent fever and neutropenia, L-AmB or caspofungin may be used.

2.7 Aspergillus sinusitis and otitis, cerebral aspergillosis, chronic pulmonary aspergillosis and aspergilloma

Aspergillus sinusitis and otitis

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, pain, and headache.
Non-invasive *Aspergillus* sinusitis manifests as a sinusitis nonresponsive to antibiotics in immunocompetent patients (124). In these cases, endoscopic removal of a fungal ball is usually curative. Local or systemic antifungals have no role in the treatment of a maxillary fungal ball.
In acute as well as chronic or granulomatous *Aspergillus* sinusitis in immunocompetent patients, surgical debridement and systemic antifungal therapy is recommended. The choice of antifungal agents has not been specifically studied in this patient group. For *Aspergillus* sinusitis, there is no reason to deviate from the general recommendations as outlined in Chapters 2.2 and 2.3.

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Invasive *Aspergillus* otitis is rare and occurs in immunocompromized patients, in contrast to *Aspergillus* colonization (otomycosis), which is common in healthy persons and noninvasive. Malignant otitis externa cause by *Aspergillus* is usually treated with local antimycotic agents when confined to the external auditory canal. Tissue-invasive *Aspergillus* otitis should be treated with surgical debridement and prolonged systemic antifungals as outlined in chapters 2.2 and 2.3. A series of patients with invasive skull base aspergillosis were found to have an impaired Th17 lymphocyte response, leading to a specific host defense defect for fungal. Skull base aspergillosis is a severe complication of progressive *Aspergillus* otitis or sinusitis, and usually requires repeated surgical debridements and prolonged antifungal therapy (113). A series of these patients were found to have a specific host defense defect for *Aspergillus*, requiring adjunctive immunotherapy (113).

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. In a study of 81 patients with cerebral aspergillosis treated with voriconazole, the response was 35%, and aspergillosis-related mortality was 46% (125). Multivariate analysis showed neurosurgical intervention to be associated with improved survival (p=0.02). Case reports also have described favorable responses in patients with CNS aspergillosis treated with lipid formulations of AmB (126). Itraconazole, posaconazole and the echinocandins do not reach appropriate levels in CSF, although brain tissue concentrations may be acceptable, if systematic exposure is in the accepted range (127). Animal models have indicated that L-AmB reached substantially higher concentrations in the brain were significantly higher compared to c-AmB and ABLC (128). When indicated, neurosurgical intervention may also improve prognosis (126).

Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis (CPA) is a generic term for a variety of diseases. The most common form of CPA is chronic cavitary pulmonary aspergillosis (CCPA), defined as one or more pulmonary cavities, with a positive *Aspergillus* IgG antibody test or microbiological evidence implicating *Aspergillus* spp with significant pulmonary or systemic symptoms and overt radiographic progression (new cavities, increasing pericavitary infiltrates, or increasing pleural thickening) over at least 3 months (129,130). When untreated, CCPA may progress to chronic fibrosing pulmonary aspergillosis. Less common manifestations of CPA include *Aspergillus* nodule or single aspergilloma. CPA usually develops in apparently non-immuno-compromized patients with underlying lung disease.

Subacute invasive pulmonary aspergillosis (formerly called chronic necrotizing pulmonary aspergillosis) is a more rapidly progressive infection, usually found in moderately immunocompromized patients, which should be managed as invasive aspergillosis (130).

The diagnosis of CPA requires CT abnormalities (fungal ball, multiple empty cavities, with of without associated pleural thickening, and pericavitary infiltrates) present for >3 months, and evidence of *Aspergillus* infection by culture, galactomannan, PCR, or serum *Aspergillus* IgG (130,131). Approximately half of patients with CPA have an increased total and *Aspergillus*-specific IgE titer and/or eosinophilia.

Patients with CPA often have underlying genetic defect in antifungal host defense, and long-term suppressive antifungal therapy is often warranted. Except for single uncomplicated aspergilloma (see below), azole treatment for CPA is now considered standard of care, leading to substantial health improvement in the majority of patients (132). In a randomized trial, CCPA patients treated with itraconazole (400 mg/d) for 6 months had significantly better overall, clinical and radiological responses than patients receiving supportive care (133). In two open, prospective trials, oral voriconazole for 6-12 months) was effective in approximately 60% of patients (134). Initial azole therapy usually is 6-9 month; nonresponders are switched to an alternative regimen, while responders usually require indefinite suppressive treatment (130).

In a randomized trial, micafungin was as effective as i.v. voriconazole for 4 weeks in 107 patients with CPA (success rates 60.0 vs. 53.2%; CI, -12.9, 26.5) (135). In a subsequent small randomized study, caspofungin was as effective as micafungin (136). Case series have described successful treatment of CPA with repeated short courses of L-AmB or caspofungin (137,138).

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 pulmonary aspergillosis (130).

For a single uncomplicated aspergilloma, defined as a single pulmonary cavity containing a fungal ball in a nonimmuno-compromized patient with minimal clinical symptoms and no radiographic progression over at least 3 months, the optimal treatment is unknown (130). Surgical resection is indicated in case of severe bleeding (139). Peri-operative antifungal therapy may be considered if risk of spillage of *Aspergillus* during surgery exists, and discontinued postoperatively if no spillage has occurred. In patients who are not eligible for surgery, prolonged antifungal therapy to minimize recurrent hemoptysis has been described, and bronchial artery embolization may be required in case of hemoptysis (130).

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Recommendations

Deeply invasive cranial and chronic pulmonary aspergillosis are difficult to manage, and may be associated with azole resistance and with subtle host defense defects that require specific diagnostic expertise or adjuvant immunotherapy. For these patients, consultation with the National Mycology Expertise Center is strongly recommended.

Conclusions 2.7 – Therapy of other forms of invasive aspergillosis	
Conclusion 40	Invasive *Aspergillus* sinusitis or otitis should be distinguished from non-invasive forms of otomycosis or fungal balls. For invasive *Aspergillus* sinusitis or otitis, combination of surgical debridement and systemic antifungal therapy is favored.
Level 3	DeShazo, 1997 (C)
Conclusion 41	Voriconazole has favorable pharmacokinetics and efficacy in treatment of cerebral aspergillosis. Of the other antifungals, L-AmB is assumed to have the most favorable penetration into the brain.
Level 3	Schwartz, 2005 (C); Coleman, 1995 (C); Felton, 2014 (C)
Conclusion 42	The diagnosis of chronic pulmonary aspergillosis (CPA) requires CT abnormalities (fungal ball or cavities, with of without associated pleural thickening, and pericavitary infiltrates) present for >3 months, and evidence of *Aspergillus* infection by positive culture, galactomannan, PCR, or serum Aspergillus IgG.
Level 3	Page, 2015 (C); Denning, 2016 (C)
Conclusion 43	Prolonged azole antifungal therapy improves the outcome of CPA. Initial echinocandin therapy had similar effects as had voriconazole in CPA patients.
Level 2	Cadranel, 2012 (B); Agarwal, 2013 (B); Al-Shair, 2013 (C); Kohno, 2010 (B); Kohno, 2013 (C); Keir, 2014 (C); Denning, 2016 (C); Newton, 2016 (C)
Conclusion 44	For single aspergilloma with bleeding, surgical resection is considered to be the treatment of choice. In patients not eligible for surgery, prolonged antifungal therapy and/or bronchial artery embolization have been suggested to reduce the chance of bleeding.
Level 3	Muniappan, 2014 (C); Denning, 2016 (C)

Recommendation 33	For the treatment of invasive *Aspergillus* sinusitis, the combination of surgery and systemic antifungal therapy are recommended, except for a non-invasive fungal ball, which can be removed surgically without systemic antifungals.
Recommendation 34	For cerebral aspergillosis, combination antifungal therapy with voriconazole and L-AmB is recommended pending confirmation of voriconazole susceptibility, and, if feasible, surgical debridement.
Recommendation 35	Uncomplicated *Aspergillus* otitis externa should be treated with topical antifungals or boric acid. For invasive aspergillosis of the ear, the combination of surgery and prolonged systemic antifungal therapy are recommended.
Recommendation 36	For chronic pulmonary aspergillosis (CPA), prolonged azole therapy is recommended. Echinocandins are an acceptable alternative if azoles are not suitable.
Recommendation 37	Surgical resection is recommended for both symptomatic single aspergilloma with bleeding. In patients not eligible for surgical therapy, prolonged antifungal therapy and bronchial arterial embolization should be considered in case of bleeding.
Recommendation 38	For patients with complicated cranial or pulmonary aspergillosis, consultation with the National Mycology Expertise Center should be considered.

2.8. Antifungal prophylaxis in patients with hematological malignancies or stem cell recipients

Several meta-analyses have evaluated antifungal prophylaxis studies in neutropenic patients with hematological malignancies or allogeneic hematopoietic cell transplant recipients. In patients undergoing myeloablative allogeneic HSCT, the incidence of invasive mycoses is considerably higher than among patients undergoing autologous HSCT or chemotherapy (140). For this reason, antifungal prophylaxis in patients with alloHSCT is described separately in these guidelines.

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In an older meta-analysis, antifungal prophylaxis decreased all-cause mortality compared with placebo in alloHSCT recipients (RR, 0.62; 95% CI, 0.45 to 0.85), but not in acute leukemia patients (RR, 0.88; 95% CI, 0.74 to 1.06) (141). In a more recent systematic review, comparisons between drugs yielded nonsignificant differences in mortality, and there were no consistent differences in incidence of proven/ probable invasive aspergillosis between various prophylaxis regimens in alloHSCT recipients (142).
Itraconazole prophylaxis compared with fluconazole in patients undergoing alloHSCT led to a significant reduction in invasive aspergillosis (fluconazole 12%; vs. itraconazole 5%; p=0.03) at the costs of more adverse events (16% vs. 36%; p<0.001) but no difference in mortality in one study (Marr et al. 2004). In another trial, there was no significant reduction of invasive aspergillosis, fungal infection-related mortality, or overall mortality (144).
Voriconazole prophylaxis was compared with fluconazole (145) or itraconazole (146) in patients undergoing alloHSCT. Compared to fluconazole, there was a trend towards fewer probable/proven aspergillosis with voriconazole (3% vs. 6%, p=0.09), but the fungal-free survival and overall survival were not different (145). Compared to itraconazole, there was no difference in probable/proven aspergillosis (0.4% vs. 2%, p=0.12) or survival, but voriconazole was better tolerated (146).
Posaconazole (suspension) was randomized to fluconazole in alloHSCT patients with a severe graft-versus-host disease (GVHD) (147). There was no difference for the primary endpoint, incidence of all invasive fungal infections, but posaconazole led to fewer proven/probable aspergillosis (2.3% vs. 7.0%; 95%CI 0.13-0.75; p=0.006) (147). In the second trial, posaconazole was compared with fluconazole or itraconazole oral solution in a randomized, non-blinded study during consecutive neutropenic episodes in patients with AML or MDS (148). Proven/probable invasive aspergillosis developed in 1% vs. 7% (p<0.001), and 100-days mortality was 14% vs. 21% in the control arm (p=0.04), at the costs of more serious adverse events (p=0.01) (148).
In a double-blind study comparing micafungin with fluconazole prophylaxis in neutropenic HSCT recipients, there was no significant difference in the numbers of invasive fungal infections 1.6% vs. 2.4%; p=0.48), invasive aspergillosis (0.2% vs. 1.5%; p=0.07) or mortality (149).

Children
Only 2 RCTs on antifungal prophylaxis have included children (145,149) but there are no specific studies available to guide pediatric recommendations (150). For children undergoing allogeneic HSCT, prophylaxis until engraftment has been recommended. Options include fluconazole (if local incidence of aspergillosis is low), itraconazole or voriconazole. Alternatively, micafungin, L-AmB B or posaconazole (in children >13y) have been used. In the presence of GvHD, prophylaxis has been recommended with posaconazole (>13y), voriconazole, or itraconazole. Alternatively, micafungin or L-AmB have been used. In children with acute leukemia, itraconazole, posaconazole (>13y), L-AmB or fluconazole are among the options mostly favored (150).

Conclusions 2.8. – Antifungal prophylaxis in patients with hematological malignancies or HSCT	
Conclusion 45	Antifungal prophylaxis has been shown to decrease mortality compared with placebo in alloHSCT recipients, but not convincingly in acute leukemia patients
Level 1	Robenshtok, 2007 (A1); Ziakas, 2014 (A1)
Conclusion 46	Itraconazole and voriconazole are superior to fluconazole for the prevention of invasive aspergillosis in alloHSCT patients
Level 1	Marr, 2004 (A2); Winston, 2003 [A2); Wingard, 2010 (A2); Marks, 2011 (A2)
Conclusion 47	Posaconazole is superior to fluconazole in the prevention of invasive aspergillosis in patients with severe graft-versus-host disease and in neutropenic patients
Level 2	Ullmann, 2007 (A2); Cornely, 2007 (A2)

Recommendations
The incidence of invasive mycoses in patients undergoing chemotherapy for hematological malignancies or autologous HSCT is relatively low. In patients undergoing myeloablative allogeneic HSCT, or AML remission-induction therapy, the incidence of invasive mycoses is considerably higher, particularly in the group with severe GVHD and/or undergoing immunosuppressive therapy. Meta-analyses suggest that itraconazole is more effective than fluconazole in preventing invasive aspergillosis, as are voriconazole and posaconazole. Whether or not their use as prophylaxis is also efficient, depends on the incidence in the specific patient group, the costs, adverse effects and interactions. It should be noted that all published analyses have been based on settings without azole resistance. Given the present azole resistance rate of 5 to 35% in the Netherlands, the actual benefit of azole prophylaxis may be lower. Nevertheless, the committee considers azole prophylaxis potentially useful, but the indication is strongly dependent upon the local incidence of invasive aspergillosis and patient population.

Recommendation 39	In patients with neutropenia following chemotherapy for AML/MDS or HSCT, posaconazole (until resolution of the neutropenia, or during treatment of severe GVHD, and monitored by TDM where appropriate) may be considered for antifungal prophylaxis, depending on the local incidence of invasive mycoses.

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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 (151). Positive blood cultures taken via an intravascular catheter are also associated with a high mortality (152,153). Patients with a positive blood culture growing *Candida,* therefore, must always be treated with antifungal agents. In contrast, there is no evidence supporting the relevance of catheter tip cultures growing *Candida* in the absence of positive blood cultures.

3.1. Treatment of candidemia and acute disseminated candidiasis

Prospective randomized studies

In earlier studies, fluconazole, voriconazole, and caspofungin were as effective as conventional amphotericin B (c-AmB) but associated with significantly lower toxicity and therapy discontinuations (154–156). These results have indicated that c-AmB is no longer appropriate for treatment of invasive candidiasis (157). In two subsequent comparative trials, micafungin was as effective as liposomal amphotericin B (L-AmB) and as caspofungin (158,159).

In a pivotal study, anidulafungin was compared with fluconazole in patients with candidemia and invasive candidiasis (160). The overall response rates were significantly higher with anidulafungin (76%) than fluconazole (60%; difference 15.4%, 95%CI: 3.85-26.99, p=0.009). 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 susceptible to fluconazole in vitro. Inferior outcomes with fluconazole were also present in patients with low APACHE II scores, and therefore not related to disease severity (160). In post-hoc multivariate analyses, these outcome differences could not be related to other, confounding factors (161).
In a similar randomized trial, isavuconazole was compared with caspofungin in 400 patients with candidemia and invasive candidiasis (162). The primary endpoint of successful overall response significantly better with caspofungin (71.1%) than with isavuconazole (60.3%; adjusted difference -10.8, 95%CI: -19.9, -1.8).

In separate publications, the subgroups of patients who were in the ICU at time of randomization into the echinocandin trials have been described. The success rate (MITT) among ICU patients was 68% for caspofungin vs 56% for c-AmB (163), 63% for micafungin vs. 66% for L-AmB (164), and 69% for anidulafungin vs. 46% for fluconazole (p=0.076) (165).

Meta-analysis

Andes et al. conducted an individual patient-level quantitative review of randomized trials (166). A patient-level database was built on 1915 patients from 7 trials, who had been randomized to c-AmB, fluconazole, c-AmB plus fluconazole, c-AmB followed by fluconazole, voriconazole, caspofungin, micafungin, or anidulafungin (154–156,158–160,167). Mortality was chosen as the primary endpoint. Overall 30-day mortality among patients in the entire data set was 31%, and the rate of treatment success was 67 %. Across the trials, logistic regression analysis identified two interventions as independent determinants of reduced mortality: removal of a central venous catheter (Odds ratio, 0.50; 95% CI, 0.35–0.72; P=0.0001), and randomization to an echinocandin antifungal (OR, 0.65; 95% CI, 0.45–0.94; P=0.02). This was also the case for patients infected by *C. albicans* (OR, 0.55; 95% CI, 0.32–0.95; P=0.03). Similar findings were observed for the clinical success end point: in multivariate analysis, randomization to an echinocandin was associated with increased chance of resolution of candidiasis in all patients (OR, 2.33; 95% CI, 1.27–4.35; P=0.01), and in patients infected by *C. albicans* (OR, 3.70; 95% CI, 1.49–9.09; P=0.005) (166).

Non-randomized studies

The efficacy of anidulafungin in patients in the ICU and those with additional risk factors (renal or hepatic impairment, recent abdominal surgery, elderly, solid tumors, solid organ transplant, or neutropenia,) in Europe was studied in a prospective, non-comparative multicenter trial (168). The MITT success rate was between 68% and 76% in all groups of ICU patients with additional risk factors, except for those with neutropenia (6/12, 50%) or solid organ transplant (3/8, 38%) (168). In a retrospective cohort study of 224 patients with septic shock due to candidemia, multivariate logistic regression analysis showed that early appropriate antifungal therapy, source control (intravascular catheter removal), and treatment with an echinocandin all were independently associated with improved survival (P<0.001) (169).

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Whereas the various *Candida* species slightly differ in their susceptibility to echinocandins, additional data have provided reasonable support for the efficacy of echinocandins as initial therapy in patients infected by other species than *C. albicans,* reported success rates ranging from 67% to 85% for all major *Candida* species (170,171).

Initial therapy in neutropenic patients

No randomized trials have been specifically 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 judgment on the treatment of invasive candidiasis in neutropenic patients. In those trials, the response of patients who were neutropenic at start of treatment was between 50% and 64% for caspofungin, micafungin, anidulafungin and fluconazole, and 40% for c-AmB (155,158,159,171). On the basis of these data, the outcomes of treatment in neutropenic patients appear not to be much different from those in non-neutropenic patients.

Step down

Little data are available to support recommendations on the total duration of therapy or the step-down from echinocandins to intravenous or oral azoles (172). In general, candidemia trials have required a minimum 10 days of parenteral echinocandin therapy, before allowing a step down to oral azoles (155,158–160). A recent Phase 4 study has demonstrated feasibility of a step-down strategy to an oral azole as early as 5 days after start of iv treatment, provided the *Candida* has been cleared from the bloodstream, likely is azole-susceptible, and the patient is clinically stable and capable of taking oral therapy (173). Such studies were, however, not randomized to compare early step-down therapy to prolonged echinocandin therapy, and patients transitioned to azoles were less severely ill. In order to assess the time point of blood culture negativity, as required for making decisions on oral step down or total duration of therapy, blood culture samples should be obtained daily until negative.

Conclusions 3.1 – Treatment of candidemia due to unidentified *Candida* species of unknown susceptibility	
Conclusion 1	Initial treatment with an echinocandin is more effective than treatment with fluconazole, voriconazole, isavuconazole, or c-AmB in patients with invasive candidiasis, irrespective of severity of illness.
Level 1	Andes, 2012 (A1); Reboli, 2007 (A2); Kullberg, 2016 (A2); Kollef, 2013 (B)
Conclusion 2	L-AmB, caspofungin, micafungin, and anidulafungin have similar response rates in non-neutropenic patients with invasive candidiasis
Level 2	Mora-Duarte, 2002 (A2); Kuse, 2007 (A2); Reboli, 2007 (A2); Pappas, 2007 (A2)
Conclusion 3	There are no significant differences in outcomes of initial echinocandin therapy for invasive candidiasis infected by distinct *Candida albicans* or non-albicans species
Level 3	Colombo, 2010 (B); Kullberg, 2017 (B)
Conclusion 4	Step-down from initial echinocandin therapy to an oral azole after ≥5 days is safe in patients with negative follow-up blood cultures, clinical stabilization, and azole-susceptible invasive candidiasis
Level 3	Vazquez, 2014 (B)

Recommendations

Recent studies have significantly changed the insights into the optimal initial therapy of (culture-proven) candidemia and invasive candidiasis. A randomized, double-blind trial demonstrated that anidulafungin was more effective than fluconazole (160). In the 2008 edition of these guidelines, the committee recommended an echinocandin in seriously ill or hemodynamically unstable patients.

At present, support for the superiority of echinocandins over fluconazole has accumulated for *all* patient groups with candidemia. In the second randomized trial comparing an echinocandin with an azole, i.e., caspofungin with isavuconazole, the success rates were highly similar to those from the first study: caspofungin outcomes were superior to those with isavuconazole (162). In a large individual patient-level quantitative analysis of randomized trials (166), using 30-day mortality as a solid primary endpoint, randomization to an echinocandin was an independently associated with reduced mortality (OR, 0.65; P=0.02). In agreement with the earlier randomized trial (160), the superiority of echinocandins was also significant in the group of patients infected by *C. albicans* (166). The association of echinocandins with reduced mortality was also significant in the lower two APACHE II quartiles. The committee considers these data providing level 1 evidence to support the notion that initial therapy with an echinocandin (as opposed to azoles or AmB) is associated with a reduction of mortality, regardless of severity of illness.

Further support for the relative benefit of echinocandins was derived from the cohort study in severely-ill candidemia patients with septic shock, identifying prescription of an echinocandin as an independent determinant of reduced mortality in multivariate analysis (169), and from subgroup analyses and non-randomized prospective studies suggesting favorable success rates of initial echinocandin therapy in ICU patients with candidemia or invasive candidiasis, irrespective of *Candida* species (163–165,168,170,171,173–176). The committee considers the three echinocandins anidulafungin, caspofungin and micafungin to be equally effective.

Exceptions to the preferential use of echinocandins as initial therapy for candidemia or invasive candidiasis are meningitis, endophthalmitis, and urinary tract candidiasis, as in these conditions, echinocandins are limited by their pharmacokinetics.

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Likewise, echinocandins are not the preferred agents in patients pre-exposed to echinocandins for prolonged periods of time (151).
Conventional amphotericin B has no place in the treatment of candidemia in adults, since, based on comparative studies and meta-analyses, the drug is less effective and significantly more toxic than the echinocandins (155,166,169). L-AmB is considered as effective as the echinocandins, but has a less favorable safety profile (158).

Although randomized studies of step down from echinocandin to oral azole therapy are lacking, accumulating data supports the safety of step down as early as after ≥5 days (173). Patients with *Candida* infection of cardiac valves, thrombi, or prosthetic material should not be switched to azole therapy, in view of the limited activity of azoles in biofilms (177). Based on the superiority of initial echinocandin therapy in preventing mortality, the committee stresses that the transition to azoles should not primarily be based on the species identification and azole susceptibility, but rather on the clinical stability of the patient and negative follow-up blood cultures, obtained during the first days of echinocandin therapy. Thus, transition to an azole is reasonable around day 5 of therapy, provided that follow-up blood cultures obtained at day 1–2 of therapy are still negative, the patient has been clinically stabilized, has no intravascular infection or unchanged iv catheter, and the isolate has been proven susceptible to azoles.

Additional therapy choices based on known identification and susceptibility of *Candida* species and susceptibility are discussed below in 3.2.

Recommendation 1	For adult patients with candidemia or invasive candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is the preferred initial therapy. This recommendation applies to all non-neutropenic and neutropenic patients, except those with *Candida* meningitis, endophthalmitis, or invasive urinary tract candidiasis, and neonates.
Recommendation 2	For patients who have *Candida* endophthalmitis, or invasive urinary tract candidiasis, fluconazole is recommended as initial therapy.
Recommendation 3	A follow-up blood culture sample should be obtained daily from patients with candidemia, until negative.
Recommendation 4	Initial echinocandin therapy should be continued until the patient has stabilized, regardless of *Candida* species.
Recommendation 5	Stable patients may be stepped down from an echinocandin to fluconazole after ≥5 days, provided that follow-up blood cultures during therapy are still negative, the patient is clinically improving, the isolate has been confirmed fluconazole-susceptible, and the patient has no *Candida* endocarditis, intravascular candidiasis, unchanged vascular catheters, or prosthesis-associated candidiasis.

Table 3.1. Recommended drug and standard adult dose of antifungal agents used for candidemia[†]

Antifungal agent	Loading dose	Maintenance dose
1st choice*		
Anidulafungin	200 mg	100 mg qd
Caspofungin	70 mg	50 mg qd, > 80kg: 70 mg qd
Micafungin	-	100 mg qd
2nd choice*		
Liposomal AmB	-	3 mg/kg/d
Voriconazole	bid 6 mg/kg iv or bid 400 mg po	4 mg/kg bid iv[#] or 200 mg bid po[#]
Isavuconazole	tid 200 mg iv or po on days 1 +2	200 mg qd iv or po
3rd choice*		
Fluconazole	800 mg iv/po	400mg /d iv/po

* For specific recommendations, exceptions, and contra-indications, see text.
[†] The dosages in this table are specific for invasive candidiasis and candidemia; for other mycoses, different dosages may apply.
[#] Individual dose based on therapeutic drug monitoring

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3.2. Treatment of candidemia and acute disseminated candidiasis of known species and susceptibility

Candida albicans

Based on the meta-analysis and studies discussed in the previous paragraph (161,162,166,169), the committee considers initial therapy with an echinocandin in patients with candidemia or invasive candidiasis superior to that with fluconazole or other azoles. As noted above, early step-down from an echinocandin to i.v. or oral fluconazole is suggested to be safe, once the patient has clinically improved and follow-up blood cultures are negative. This implies that – even for *C. albicans* known to be susceptible to fluconazole – initial therapy with an echinocandin should not be changed to fluconazole on the basis of species identification or susceptibility results per se, but only after favorable clinical and microbiological follow-up, as described in 3.1.

Candida parapsilosis

C. parapsilosis is generally less susceptible to echinocandins than the other *Candida* strains (178). Outcomes of a full course of i.v. echinocandin therapy in patients with *C. parapsilosis* candidemia or invasive candidiasis have been less optimal in some studies (155,160), whereas other studies reported outcomes similar to those for other *Candida* species (158,159,171). A retrospective cohort study including 307 patients with *C. parapsilosis* candidemia did not demonstrate a difference in 30-days' mortality between patients receiving echinocandins (9.9%) or fluconazole (9.5%; risk-adjusted OR, 0.82, 95% CI 0.33–2.07) (179). Based on these data, the committee gives preference to therapy with fluconazole for *C. parapsilosis* infections, but does not advise against therapy with an echinocandin.

Candida krusei and Candida glabrata

C. krusei is inherently resistant to fluconazole (180). *C. glabrata* has a variable susceptibility to fluconazole (181). Although the in-vitro activity of voriconazole against *C. glabrata* is usually greater than that of fluconazole, *C. glabrata* may be resistant to voriconazole, and fluconazole and voriconazole are considered less appropriate for treating infections by *C. glabrata* (181,182). Thus, the committee gives preference to an echinocandin for the treatment of *C. glabrata* and *C. krusei*, even in the case of in-vitro azole-susceptible strains. If oral azole treatment is deemed possible, voriconazole is preferred to fluconazole. In individual patients, fluconazole may be considered based on MIC data, if strict clinical and microbiological monitoring is carried out.
Candida isolates with acquired echinocandin resistance have been reported with increasing frequency. *C. glabrata* is overrepresented among echinocandin-resistant isolates (178,183). However, in the two largest prospective collections of patients treated with an echinocandin, the success rate was 78–85% for patients with *C. glabrata*, vs. 77% for patients with *C. albicans* (170,171). Thus, the committee considers an echinocandin as the first choice for candidemia or invasive candidiasis by *C. glabrata*.

Duration of therapy

For candidemia without proven metastatic foci, treatment lasting 14 days after the last positive blood culture is appropriate in non-neutropenic patients who have responded well to therapy (151,172). In patients with acute disseminated candidiasis, the treatment depends upon the resolution of the metastatic foci. In general, a duration of treatment from 4 to 8 weeks is necessary in those cases. FDG PET-CT imaging may guide the resolution of foci and duration of therapy (184,185).

Conclusions 3.2. Therapy of candidemia with identified *Candida* species of known susceptibility	
Conclusion 5	*C. krusei* is usually resistant to fluconazole. *C. glabrata* is generally less susceptible to fluconazole and voriconazole than the other *Candida* species.
Level 2	Pfaller, 2010 (B); Pfaller, 2011 (B); Arendrup, 2014 (C)
Conclusion 6	Increasing echinocandin resistance of *C. parapsilosis* and *C. glabrata* has been reported
Level 3	Alexander, 2013 (C); Arendrup, 2014 (C); Kullberg & Arendrup, 2015 (D)
Conclusion 7	Clinical experience has established a treatment duration of 14 days after the last positive blood culture, unless there are proven metastatic foci.
Level 4	Rex, 1994 (C); Mora-Duarte, 2002 (C); Oude Lashof, 2003 (C); Kullberg, 2005 (C); Reboli, 2007 (C); Pappas, 2007 (C)

Recommendation 6	For *Candida albicans* or *C. parapsilosis* candidemia/invasive candidiasis in stabilized patients, step-down to fluconazole is preferred after initial echinocandin treatment, provided that follow-up blood cultures during therapy are negative, the patient is clinically improving, the isolate has been confirmed fluconazole-susceptible, and the patient has no *Candida* endocarditis, intravascular candidiasis, unchanged vascular catheters, or prosthesis-associated candidiasis.

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Recommendation 7	For *Candida krusei* candidemia/invasive candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is preferred. Voriconazole or L-AmB may be used as an alternative.

Recommendation 8	For *Candida glabrata* candidemia/invasive candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is preferred. L-AmB may be used as an alternative.

Recommendation 9	Patients with an uncomplicated candidemia should be treated for 14 days after the last positive blood culture. Treatment of acute disseminated candidiasis depends on clinical and radiological findings. In case of proven metastatic foci, the duration of therapy is at least 4 to 8 weeks.

3.3. Management of intravascular catheters

The gut is the major portal of entry for *Candida,* rather than the skin or intravascular catheters being the primary source of candidemia. Even if an intravascular catheter is not the portal of entry, it may be secondarily infected, and subsequently lead to persistent candidemia and the formation of metastatic foci (151). This is supported by the observation that candidemia may persist until catheters have been exchanged. Recent studies found catheter removal at any time point to be associated with lower mortality and better clinical success rates (169,186,187). In a pooled patient-level analysis of 7 randomized treatment trials, treatment with an echinocandin and catheter removal were identified as the two modifiable management strategies associated with better survival rates (166). A new catheter should be inserted at a different site; catheter exchange at the original site using a guidewire is inadequate (188).

Based on the identification of catheter retention as an independent risk factor for mortality in a recent meta-analysis (166), the committee considers the evidence to be so compelling that it recommends removal or replacement of all intravascular catheters (central, peripheral and arterial) whenever logistically feasible.
No studies have been conducted as to the optimal interval between removal of an intravascular catheter and the insertion of a new catheter. In the studies cited, no minimal interval was specified, and usually, a new catheter is inserted without catheter-free interval (166). 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, there are insufficient grounds for observing a minimum interval before inserting a new catheter (166).

Conclusions 3.3. – Catheter management	
Conclusion 8	Exchange of intravascular catheters in patients with candidemia is associated with reduced mortality.
Level 1	Andes, 2012 (A); Kollef, 2012 (B)
Conclusion 9	Replacement of an intravascular catheter at the same site and using a guidewire has no favorable effect on the duration of candidemia
Level 3	Rex, 1995 (B)
Conclusion 10	There are no grounds for delaying the insertion of a new catheter following the removal of an intravascular catheter.
Level 3	Andes, 2012 (C)

Recommendation 10	In patients with candidemia, all intravascular catheters (central, peripheral and arterial) should be removed or replaced.

3.4. Disseminated candidiasis and secondary metastatic foci

Candida species relatively frequently cause hematogenous dissemination (acute disseminated candidiasis). The most common metastatic foci are endophthalmitis and chorioretinitis. In a prospective study in 370 patients with candidemia who were followed ophthalmologically, abnormal fundoscopic findings were noted in 16%; in 11% the anomalies were probably *Candida* related: chorioretinitis in 14.5% and endophthalmitis in 1.5% (189). Retinal *Candida* lesions sometimes only develop in the course of 1-2 weeks during therapy (189).
For patients with ocular candidiasis (chorioretinitis or endophthalmitis), a longer duration of therapy may be required than the standard (14 days) treatment of uncomplicated candidemia, and fundoscopic examination of is desirable before the duration of therapy is decided upon. While echinocandins penetrate poorly into the eye, comparative studies have not

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reported increased risk of developing ocular candidiasis in patients treated with echinocandins (160,162). Since the incidence of endophthalmitis among patients treated for candidemia is as low as 1.5% (189), the committee no longer makes a strong recommendation to perform routine ophthalmoscopies in every patient. Clinical vigilance is warranted to detect signs of ocular involvement or any other metastatic foci in individual patients. In ICU patients or patients otherwise not able to communicate about visual symptoms, ophthalmoscopy is recommended. In view of the poor ocular penetration of echinocandins, the timing of ophthalmoscopy should be early during echinocandin therapy.
Treatment of ocular candidiasis is described in chapter 3.7.

Candida meningitis and central nervous system candidiasis are rare manifestations in adults and mostly related to neurosurgical procedures. Initial treatment with L-AmB combined with flucytosine is most commonly used, with fluconazole as step-down treatment. Voriconazole does achieve excellent levels in CSF and may be used for fluconazole-resistant isolates. Posaconazole and echinocandins do not reach adequate CSF concentrations and are not recommended.

Frequently occurring manifestations of dissemination are spondylodiscitis, osteomyelitis, pulmonary metastatic foci and renal abscesses (151). Intravascular foci, such as endocarditis, an infected thrombus, or a mycotic aneurysm may develop. In patients with candidemia, there is a clear association between persistently positive blood cultures and the presence of an infected intravascular catheter or other intravascular foci. Thus, exchange of all indwelling (arterial, central and peripheral) intravascular lines is a prerequisite to prevent hematogenous dissemination of *Candida* and associated mortality.
A recent prospective single-center study from Spain has suggested that up to 6% of patients with candidemia develop *Candida* endocarditis (190). This risk was highest among patients with a valvular prosthesis or prolonged candidemia.
Specific diagnostic approaches to metastatic foci include echography, CT, MRI or FDG PET-CT. The FDG PET-CT scan is the most sensitive for this purpose (184,185).

The committee is of the opinion that persistently positive blood cultures despite antifungal therapy, or the presence of cardiac valve disease, valve prosthesis, or an intravascular device, prosthesis, or thrombus should initiate examination targeted at intravascular and metastatic foci. Likewise, proven dissemination (e.g., spondylodiscitis) should prompt search for other foci. Whereas no solid data are available to define a cut off for persistently positive blood cultures, ≥72h after initiation of antifungal therapy is considered a strong indicator of dissemination and increased mortality. Diagnostic procedures include ophthalmoscopy, transesophageal echocardiography (unless a diagnosis of endocarditis has already been established by transthoracic echocardiography), and FDG PET-CT.

Severe disseminated candidiasis may be difficult to manage, and may be associated with host defense defects that are require specific diagnostic expertise or adjuvant immunotherapy. For these patients, consultation with the National Mycology Expertise Center is strongly recommended.

Chronic disseminated candidiasis

Chronic disseminated (or hepatosplenic) candidiasis is a specific syndrome in hemato-oncology patients after the recovery of neutrophils due to prior chemotherapy. Chronic disseminated candidiasis is diagnosed by imaging (CT or MRI). The role of PET-CT may be helpful but has not been fully defined yet (185,191). Confirmation of the diagnosis by biopsy remains troublesome as the sensitivity histology and culture are low (192). Data on optimal treatment are mostly based on case series. Mortality with c-AmB has been very high (74%) (193). Initial therapy with L-AmB or an echinocandin is associated with better outcomes and lower mortality rates (20-25%) (192). Therapy may be continued with fluconazole or voriconazole, and should be given until all lesions have disappeared on repeated imaging, which is usually for several months. Premature discontinuation of antifungal therapy often leads to relapse. If chemotherapy or HSCT is required, it should not be delayed because of the presence of chronic disseminated candidiasis, and antifungal therapy should be continued throughout the period of high risk to prevent relapse. Increasing evidence suggests that chronic disseminated candidiasis is a form of immune reconstitution inflammatory syndrome (194). A retrospective multicenter study of patients with symptomatic chronic disseminated candidiasis with fever unresponsive to antifungal therapy suggested that systemic corticosteroids (0.5 to 0.8 mg/kg prednisone for 2-3 weeks, followed by tapering after deferescence) can result in rapid clinical improvement. The duration of antifungal therapy and corticosteroids in symptomatic chronic disseminated candidiasis patients has been reported to be as long as several months (194).

Conclusions 3.4. – Secondary metastatic foci in candidemia	
Conclusion 11	In patients with prolonged candidemia, a persistent intravascular focus is often present.
Level 4	(D)
Conclusion 12	*Candida* endocarditis as a complication of candidemia is most frequent in patients with valvular prostheses or prolonged candidemia.
Level 3	Fernandez-Cruz, 2015 (B)
Conclusion 13	Chronic disseminated candidiasis in hemato-oncology patients is diagnosed by CT, MRI or PET-CT, and

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	usually requires antifungal therapy for several months. Persistent inflammation and fever in these patients may be based in an immune reconstitution inflammatory syndrome, responsive to combined antifungal and systemic corticosteroid therapy.
Level 3	Anttila, 1997 (C); Legrand, 2008 (C); De Castro, 2012(C)

Recommendation 11	Fundoscopy should be considered for patients with candidemia, and is strongly recommended for patients with signs of disseminated infection, ocular symptoms, or patients unable to communicate about visual symptoms.

Recommendation 12	A search for intravascular and metastatic foci, using ophthalmoscopy, echocardiography (TEE) and FDG PET-CT, should be considered for all patients with candidemia who have persistently (≥96h) positive blood cultures during therapy, or signs of disseminated candidiasis, ocular symptoms, or cardiac valve disease, a valve prosthesis, or an intravascular device, prosthesis, or thrombus.

Recommendation 13	For patients with chronic disseminated candidiasis, prolonged therapy with either L-AmB or an echinocandin is recommended, followed by fluconazole or voriconazole, until radiographic resolution of all lesions. In patients with signs of immune reconstitution inflammatory syndrome (IRIS), corticosteroids may be considered.

Recommendation 14	For patients with complicated disseminated candidiasis, *Candida meningitis, endocarditis or osteomyelitis,* consultation with the National Mycology Expertise Center should be considered.

3.5. Therapy of candidemia and acute disseminated candidiasis in children

Neonates

Candidemia and invasive candidiasis occur relatively frequently in premature neonates. A specific syndrome in neonates is hematogenous *Candida* meningoencephalitis, with invasion of the central nervous system, associated with high mortality and long-term sequelae. Neonates with a smaller gestational age and low birth weight have a higher incidence of invasive candidiasis (Reviewed in Hope et al. 2012; Roilides 2011).

A neonate with candidemia or invasive candidiasis should be considered to have acute disseminated candidiasis, and therapy should potentially include the central nervous system (197).

For candidemia and hematogenous *Candida* meningoencephalitis in neonates, both c-AmB and lipid amphotericin B formulations have been used, specifically L-AmB (3-7 mg/kg/d) and ABLC (5 mg/kg/d). Fluconazole has been used at 12 mg/kg/d, with a loading dose up to 25 mg/kg/d (Reviewed in Hope et al. 2012). Echinocandins, in particular micafungin (4 mg/kg/d), have been used for neonatal candidiasis. In view of the limited penetration of micafungin into the CNS, a dose of 10 mg/kg/d is used when hematogenous *Candida* meningoencephalitis is thought to be likely (Reviewed in Hope et al. 2012). Clinical efficacy of caspofungin (25 mg/kg/d) has been described in case reports, while little documented experience exists with anidulafungin for this indication.

Based on this information, the committee considers L-AmB, ABLC and fluconazole appropriate choices for neonatal candidemia and invasive candidiasis, with micafungin or c-AmB as potential alternatives if *Candida* meningoencephalitis is not suspected. Dosage recommendations are listed in the national Children's Formulary.

Infants and older children

In older children, candidemia and invasive candidiasis closely resemble the disease in adults. The recommendations for children are based on established efficacy of the antifungal drugs in adults, pharmacokinetic data in children, documented safety, and a pediatric label from the EMA. Only one prospective randomized study has been performed In children with invasive candidiasis or candidemia, comparing micafungin (2 mg/kg/d) to L-AmB (3 mg/kg/d) in 98 children <16 years old (198). Whereas the trial was not formally powered for noninferiority, the response rates at end of therapy were comparable: 73% in the micafungin arm vs. 76% (p=0.73) in the L-AmB arm. There were significantly more treatment discontinuations due to adverse events in the L-AmB arm (198).

In line with the recommendations for adults, the committee considers echinocandins the first-line therapy for candidemia and invasive candidiasis in children. Pharmacokinetic studies in children have established dosing regimens for caspofungin (70 mg/m2 loading dose followed by 50 mg/m2/day i.v.) (59,199), and micafungin (2–4 mg/ kg/day i.v.) (60)

L-AmB (3 mg/kg/d) is an alternative choice for candidemia and invasive candidiasis in children (198). Clinical experience with ABLC in children has been published, but pharmacokinetic studies on ABLC in children are absent. Whereas the toxicity

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of c-AmB in children may be somewhat less than in adults, the committee considers c-AmB no longer appropriate for therapy of candidemia and invasive candidiasis in infants and older children because of its significant toxicity.

For fluconazole (8–12 mg/ kg/day), extensive pharmacokinetic and safety data in children exist (200,201). In view of the recent data on the relative superiority of echinocandins for candidemia and invasive candidiasis (obtained in adults), the committee considers fluconazole no longer the first choice in children, and strongly favors an echinocandin. Exceptions where fluconazole is still the first choice for invasive candidiasis are meningitis, endophthalmitis, and urinary tract candidiasis, in which echinocandins are limited by their pharmacokinetics, and for invasive candidiasis caused *by C. parapsilosis*.
Voriconazole can be used for candidemia and invasive candidiasis in children. Especially in children <4y of age, drug levels ar highly variable, and TDM is indispensable for all age groups (202). Dosage recommendations are listed in the national Children's Formulary, and have been based on several pharmacokinetic studies (58,203,204). Whereas voriconazole has a broader spectrum than fluconazole against *C. krusei* and some strains of *C. glabrata*, the committee does not consider voriconazole first-line therapy for candidiasis, in view of the relative superiority of echinocandins.

Conclusions 3.5. – Treatment of candidemia and acute disseminated candidiasis in children	
Conclusion 14	Candidemia or invasive candidiasis in neonates is often associated with hematogenous *Candida* meningo-encephalitis, and therapy should include potential central nervous system infection.
Level 2	Benjamin, 2010 (B); Roilides, 2011 (B)
Conclusion 15	Fluconazole, c-AmB, L-AmB, ABLC, micafungin and caspofungin have been reported effective in case series of candidemia and invasive candidiasis in neonates.
Level 3	Reviewed in Hope, 2012 (C)
Conclusion 16	Micafungin is as effective as L-AmB in the treatment of invasive candidiasis in children.
Level 3	Queiroz-Telles, 2008 (B)
Conclusion 17	The treatment of children with candidemia or invasive candidiasis is not different from that in adults, based on established efficacy of the antifungal drugs in adults, and pharmacokinetic and safety data in children.
Level 3	Walsh, 2005 (C); Zaoutis, 2009 (C); Hope, 2007 (C); Lee, 1992 (C); Novelli, 1998 (C); Walsh, 2010 (C); Driscoll, 2011 (C); Neely, 2010 (C);

Recommendation 15	In neonates, treatment of candidemia or invasive candidiasis should be targeted at potential hematogenous *Candida* meningoencephalitis. Fluconazole or L-AmB is the preferred initial therapy for candidemia or invasive candidiasis in neonates.
Recommendation 16	For treatment of children with candidemia or invasive candidiasis, caspofungin or micafungin is the preferred initial therapy. L-AmB, fluconazole or voriconazole are second-line alternatives.
Recommendation 17	For children who have *Candida* meningitis, endophthalmitis, or invasive urinary tract candidiasis, fluconazole is recommended as initial therapy.
Recommendation 18	Recommendations for children to step down from echinocandin to fluconazole, for catheter management, treatment duration, follow-up, and management of complications are similar to those for adults (sections 3.1 and 3.2).

3.6. Empirical or pre-emptive therapy against invasive candidiasis

In view of the high mortality of candidemia, 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 signs (e.g., a positive ß-D-glucan test) in the absence of a proven invasive infection.

Empirical therapy

Retrospective observational studies and recent multivariate analyses have consistently identified early appropriate antifungal therapy and infection source control as major determinants of survival (166,169,186). Thus, although it is

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plausible that early, presumptive treatment of patients with invasive candidiasis is beneficial, only 2 randomized studies of empirical therapy has been conducted, which did not demonstrate a survival benefit (205,206). In a randomized study of micafungin vs. placebo in 260 ICU patients with sepsis, *Candida* colonization and organ failure, there was no significant difference in 28-days survival between micafungin-treated (87/128, 68%) and placebo-treated (74/123, 60.2%) groups (206). Likewise, an older placebo-controlled study of fluconazole in 270 ICU patients did not show any beneficial outcomes (205).

Pre-emptive therapy

Pre-emptive (or diagnostic-driven) therapy is initiated on the basis of positive markers that may indicate an invasive *Candida* infection. Prediction rules have been based on clinical risk factors, *Candida* colonization, or serum ß-D-glucan screening (207,208). However, to date, such strategies have not been demonstrated to reduce mortality or length of stay in prospective studies.
In addition, published prediction rules have been shown not to be generally applicable in other regions or settings (209,210). Application of the *Candida score* prediction rule developed in Spain (207,211) to an Australian cohort of ICU patients reduced the PPV to only 2% (210). These regional differences are mainly driven by the low prevalence of invasive candidiasis. In typical ICU settings where the pretest likelihood of candidiasis is 0.5–10%, both individual non-culture tests and risk factor-based rules, having a specificity of 50–80%, will merely lead to a positive predictive value (PPV) of 1–30% (reviewed in 148).

Biomarkers

β-D-glucan and *Candida* mannan/anti-mannan are the surrogate markers available for invasive candidiasis (212–214). β-D-glucan is a circulating fungal polysaccharide that is not specific for *Candida*. Positive test result requires confirmation and identification of the infecting organism (*Aspergillus, Pneumocystis jirovecii* or *Candida*) (212,214). Its specificity is limited by many potential sources for contamination: cellulose hemodialysis membranes, human blood products (immunoglobulins or albumin), amoxicillin-clavulanate or piperacillin-tazobactam, surgical sponges & gauzes containing glucan, and severe mucositis (213,215). The performance of the β-D-glucan test depends on the cut off value and number of positive samples required. The sensitivity ranges from 65% to 91%, and the specificity is 31% to 79% (216,217). In uninfected or colonized children, circulating β-D-glucan may be higher, and the test performance may be less favorable than in adults (218).
The negative predictive value (NPV) of β-D-glucan was high in several studies (217). This has led to the general assumption that the main diagnostic benefit of β-D-glucan lies in excluding invasive candidiasis. However, this applies only to published series with a low prevalence of candidemia (i.e., screening strategies), where the NPV is mainly driven by the low prevalence. The limited sensitivity of β-D-glucan in other studies implies that the NPV will be insufficient in selected high-prevalence groups, such as ICU patients selected by diagnostic rules, where the limited sensitivity becomes the major driver of the NPV (208,214,216).

The *Candida* mannan and anti-mannan test is a combined antigen/antibody test that is specific for *Candida* species. Its sensitivity ranges from 55% to 87%, and its specificity from 82% to 98% (213,219). The test has also been applied for detection of blood culture-negative hepatosplenic candidiasis and CNS candidiasis (reviewed in 213). For clinical use, the same limitations apply as described for the β-D-glucan test.

Candida PCR

Recently, two *Candida* PCR tests have been marketed, the SeptiFast and, in 2015, the fully automated multiplex T2*Candida* (220,221). Based on a meta-analysis of published data, the SeptiFast sensitivity is 48% to 72%, and its specificity 99% (220). Until now, the T2*Candida* test has been tested in a single clinical trial (221). Its reported sensitivity was 91%, and specificity 99%. Its use is limited by the availability of the T2*Candida* equipment required.

Conclusions 3.6. – Empirical or pre-emptive therapy against invasive candidiasis	
Conclusion 18	While early appropriate antifungal therapy for candidemia is associated with reduced mortality, controlled trials showing benefit of empirical therapy are lacking.
Level 2	Schuster, 2008 (A2); Timsit, 2016 (A2), Kollef, 2013 (B)
Conclusion 19	Prediction rules based on *Candida* colonization or risk scores have limited reproducibility, and a very low positive predictive value in countries with low incidence of candidemia.
Level 3	Playford, 2009 (B); Reviewed in Kullberg & Arendrup, 2015 (D).
Conclusion 20	Biomarkers such as β-D-glucan and mannan/anti-mannan have limited sensitivity and specificity, and a low predictive value in high-risk groups.
Level 3	Karageorgopoulos, 2011 (A1); Lamoth, 2012 (A1); Tissot, 2013 (B); Reviewed in Kullberg & Arendrup, 2015 (D).

Recommendations

Early appropriate treatment of candidemia or invasive candidiasis has been consistently identified as a major determinant of survival. However, to date, strategies based on empiric or pre-emptive therapy have not been demonstrated to reduce mortality or length of stay in prospective studies. Clinical prediction rules that have been developed in regions with a high

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prevalence of invasive candidiasis perform poorly in settings such as in the Netherlands, with a low prevalence of invasive candidiasis.
Even in typical ICU settings, the predictive value of prediction rules or *Candida* biomarkers is low. As an example, based on data collected in the US (217), the positive predictive value of ß-D-glucan will only be 6% in an ICU population with an incidence of candidemia of 1%. 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. Conversely, the limited specificity of ß-D-glucan precludes its use to rule out invasive candidiasis in selected patients with a high clinical likelihood of *Candida* infection. Thus, rather than be viewed as definitive diagnostics, prediction rules or nonculture tests might be best viewed as markers that help assess a patient's risk of having invasive candidiasis.

In selected cases, initiation of empirical therapy 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, 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. Appropriate culture samples should always be obtained prior to the initiation of treatment and that empirical therapy is discontinued if blood cultures or nonculture diagnostic tests prove negative.

Recommendation 19	The predictive value of nonculture diagnostic tests is not sufficiently validated for use in the diagnosis of invasive candidiasis.

Recommendation 20	The indication of empirical therapy on suspicion of candidemia in non-neutropenic patients is controversial. Empirical therapy may be considered in selected individual cases, such as patients >7 days in the ICU and unexplained sepsis, with a combination of the following factors: (1) significant colonization with *Candida* and (2) clinical risk factors (e.g., abdominal surgery, anastomotic leakage, broadspectrum antibiotics, central venous line).

3.7. Ocular candidiasis

Candida chorioretinitis is an infection of the choroid and the retina; *Candida* endophthalmitis is a more advanced infection extending into the vitreous body, associated with poor visual outcome. *Candida* chorioretinitis occurs in around 10% of patients with candidemia (189,222). Epidemiology and screening recommendations for ocular candidiasis are described in chapter 3.4.
The treatment of ocular candidiasis is limited by the poor penetration of systemic amphotericin B and echinocandins into the vitreous body (223). These drugs are therefore not a first choice in the treatment of *Candida* endophthalmitis or chorioretinitis. While *Candida* chorioretinitis (without vitreous involvement) usually responds to standard antifungal therapy (189), treatment of *Candida* endophthalmitis with involvement of the vitreous body usually comprises three components: administration of systemic antifungal therapy, intravitreal injection of antifungal agents, and early vitrectomy (224). While Amphotericin B deoxycholate (5–10µg) has been used as intravitreous injection, intravitreal voriconazole (25 mg/l; total dose 100µg) was found to be safe and effective as part of a combined approach (225).

Conclusions 3.7 – Treatment of *Candida* endophthalmitis and chorioretinitis	
Conclusion 21	Echinocandins do not reach adequate concentrations in the vitreous body. Fluconazole, voriconazole or the combination of AmB + flucytosine do reach therapeutic concentrations in the vitreous body
Level 3	Rodriguez-Adrian, 2003 (C); Oude Lashof, 2005 (C); Gauthier, 2005 (C)
Conclusion 22	The treatment of *Candida* endophthalmitis is based on a combination of systemic antifungal therapy, intravitreal injection of amphotericin B or voriconazole, and vitrectomy. Early vitrectomy, within 1 week after the occurrence of *Candida* endophthalmitis, appears to improve the prognosis.
Level 3	Martinez-Vazquez, 1998 (C); Rodriguez-Adrian, 2003 (C); Riddell, 2011 (C)

Recommendations
Whereas the pharmacokinetics of echinocandins limits their activity in the eye, initial therapy of candidemia and acute disseminated candidiasis with echinocandins has not lead to increased incidence of ocular complications. Thus, standard echinocandin therapy of candidemia is assumed to prevent progression of ocular foci in most cases. Nevertheless, the committee favors systemic therapy with an azole whenever chorioretinitis or endophthalmitis with an azole-susceptible *Candida* strain are diagnosed. In patients who require systemic echinocandin therapy for disseminated candidiasis, an azole

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should be added in case of ocular involvement, until clinical stability allows step-down to azole monotherapy. In patients with candidiasis with unknown azole-susceptibility, initial therapy with liposomal AmB and flucytosine is recommended.
Depending on the clinical course of the infection, a treatment duration of 4 to 12 weeks is usually required in endophthalmitis, as determined by repeat fundoscopies.

Recommendation 21	*Candida* chorioretinitis or endophthalmitis should be treated systemically with an azole (fluconazole or voriconazole i.v.) in case of proven or presumed azole susceptibility. For proven or potentially azole-resistant cases, liposomal AmB combined with flucytosine is recommended. In the event of invasion into the vitreous body, vitrectomy should be performed in combination with intravitreal voriconazole or c-AmB. Treatment duration is generally lengthy and depends on the clinical course of the infection.

3.8. Urinary tract candidiasis

Candida-positive urine cultures may be an expression of *Candida* colonization, of *Candida* cystitis, of *Candida* pyelonephritis, or, incidentally, candidemia/disseminated candidiasis. During a prospective surveillance study in 530 patients with *Candida*-positive urine cultures, candiduria resolved in 76% of the untreated patients, vs. 35% following catheter removal, vs. 50% following antifungal therapy. Candidemia developed in only 1% of patients (226).

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 (227). Removal of the urinary catheter alone led to clearance of the *Candida* in 20% of the cases. At two weeks after end of treatment, candiduria rates were similar between fluconazole and placebo groups (68% vs. 65%) There was no difference in mortality and none of the patients developed candidemia.

Symptomatic candiduria and invasive renal candidiasis

No studies have specifically addressed symptomatic *Candida* cystitis and pyelonephritis (228). In a large randomized candidemia study, 5 patients (1.4%) presented with a proven *Candida* pyelonephritis as source of the candidemia, mostly related to urinary tract obstruction (156).
Echinocandins do not achieve high urine concentrations and are thus not suitable for urinary tract candidiasis. Some cases though have successfully been treated with caspofungin (229). Bladder irrigation with c-AmB (50-200 µg/ml) has been used with success (230).

Conclusions 3.8 – Treatment of candiduria	
Conclusion 23	In patients with asymptomatic candiduria, initiation of antifungal therapy has no measurable effect on the resolution of candiduria or the clinical outcomes.
Level 3	Sobel, 2000 (A2); Kauffman, 2000 (C)
Conclusion 24	Symptomatic candiduria or invasive renal candidiasis, especially in the presence of a urinary tract obstruction, can lead to complications and should be treated.
Level 3	Kullberg, 2005 (C).
Conclusion 25	Systemic fluconazole and c-AmB bladder irrigation are suitable for treatment of symptomatic urinary tract candidiasis. Echinocandins may be effective in infections with parenchymal kidney involvement.
Level 2	Tuon, 2009 (A1); Sobel, 2000 (A2); Sobel, 2007 (C); Fisher, 2011 (C).

Recommendations
Asymptomatic candiduria is common, but not associated with clinical consequences. Prospective studies show that asymptomatic candiduria almost never leads to invasive candidiasis, and that antifungal treatment does not lead to eradication any more frequently than does catheter removal or replacement. Treatment of asymptomatic candiduria may be considered in patients with severe neutropenia, with a kidney transplant, 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. Echinocandins are not excreted in the urine and have barely been investigated for this indication. It is recommended that symptomatic, invasive renal candidiasis be treated with fluconazole if susceptible. In case of fluconazole-resistance, local irrigation with c-AmB is a suitable alternative; lipid formulations of AmB do not achieve appreciable levels in the kidneys

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(228). A duration of treatment of 2 weeks following removal of the urinary tract obstruction seems adequate; where there are stones or other foreign bodies or persistent obstructions, more prolonged treatment is required. Fungal balls should be surgically removed.

Recommendation 22	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, kidney transplant, in low birth weight neonates, and prior to renal surgery.

Recommendation 23	Symptomatic candiduria or invasive renal candidiasis should be treated with fluconazole (loading dose 800mg, followed by 400 mg qd for 2-4 weeks). In case of fluconazole-resistance, local irrigation with c-AmB is a suitable alternative for lower urinary tract candidiasis. Fungal balls or persistent obstructions require surgical intervention.

3.9. Abdominal candidiasis

Candida peritonitis usually occurs following abdominal surgery, perforation of the gut or anastomotic leakage, or in conjunction with necrotizing pancreatitis. Deep-seated infections may remain localized or lead to secondary candidemia. The limited published data suggest that invasive abdominal candidiasis may be significantly more common than recognized (231,232). Cultures from nonsterile sites, such as wounds or surgical drains, are frequently positive, but lack specificity for differentiating infection from colonization. The gold standard for deep-seated candidiasis are sterilely collected cultures obtained by surgery, puncture or drain insertion (232–235). *Candida* obtained from indwelling surgical drains (in place for >24h) are not sufficient for diagnosis of deep-seated candidiasis, and should be considered as a colonization (235). The role of biomarkers such as β-D-glucan and *Candida* mannan/anti-mannan has not been sufficiently established. In a Swiss prospective cohort study among patients with recurrent GI tract perforation, anastomotic leakage, or necrotizing pancreatitis, and thus, at very high risk for abdominal candidiasis, the sensitivity of 2 consecutive positive β- D-glucan results was 65%, and the specificity 78% (208).

No randomized trials have been conducted specifically on treatment of *Candida* peritonitis. The choice of the appropriate antifungal agent for invasive abdominal candidiasis is mainly supported by indirect evidence from studies on invasive candidiasis (155,158–160). Fluconazole and isavuconazole have been associated with higher failure rates compared with echinocandins (160,162,166). Besides antifungal therapy, early source control is mandatory to reduce mortality (169).

Conclusions 3.9 – Management of abdominal candidiasis	
Conclusion 26	*Candida* cultured from surgically collected deep sites or from recently (<24h) inserted drains are indicative of invasive candidiasis. Samples obtained from drainage tubes or wound swabs are not valuable for diagnosing deep-seated infection
Level 3	Calandra, 1989 (B); Sandven, 2002 (B); Bassetti, 2013 (C)
Conclusion 27	β-D-glucan may have additional diagnostic value in high-risk patients with anastomotic leakage or acute necrotizing pancreatitis
Level 3	Tissot, 2013 (B); Reviewed in Kullberg & Arendrup, 2015 (D)
Conclusion 28	Successful treatment of intraabdominal candidiasis has been described using caspofungin, micafungin, anidulafungin, and L-AmB. Success rates with fluconazole and isavuconazole tended to be lower.
Level 3	Andes, 2012 (A1); Mora-Duarte, 2002, (C); Kuse, 2007 (C); Pappas, 2007 (C); Reboli, 2007 (C); Kullberg, 2016 (C)

Recommendations

On the basis of published trials and clinical experience, the committee's recommendations for treatment of abdominal candidiasis follow those for candidemia and disseminated candidiasis. Echinocandins are considered the first choice, except for *C. parapsilosis* infection, for which fluconazole is favored. Based on susceptibility patters, L-AmB may be an appropriate alternative. Appropriate source control, including surgical debridement and drainage is crucial in treatment of abdominal candidiasis.

Step-down to fluconazole should be considered after initial echinocandin treatment, provided that infected foci have been drained, the patient is clinically improving, the isolate has been confirmed fluconazole-susceptible, and the patient has no

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vascular or prosthesis-associated candidiasis. The total duration of treatment depends primarily on surgical and radiological resolution of infected foci, and should usually be 2 to 4 weeks but may be prolonged in case of undrained abscesses or vascular involvement.
The role β-D-glucan as a biomarker for abdominal candidiasis has not been sufficiently established. In a single cohort study, 2 consecutive β-D-glucan results had a reasonable positive and negative predictive value around 70% among very high risk patients with recurrent GI tract perforation, anastomotic leakage, or necrotizing pancreatitis (208). While this approach may be helpful in settings where β-D-glucan testing is available on a regular basis, the committee does not consider these data sufficient for a general recommendation on β-D-glucan use for these patient groups.

Recommendation 24	For patients with invasive abdominal candidiasis, an echinocandin (anidulafungin, caspofungin, or micafungin) is the preferred initial therapy. L-AmB is an appropriate alternative in case of echinocandin resistance. Appropriate source control, including surgical debridement and drainage is crucial in treatment of abdominal candidiasis. The duration of treatment depends primarily on surgical and radiological resolution of infected foci. Stable patients may be stepped down from an echinocandin to fluconazole after ≥5 days, provided that all infected foci have been drained, the patient is clinically improving, the isolate has been confirmed fluconazole-susceptible, and the patient has no vascular or prosthesis-associated candidiasis.

3.10. Esophageal candidiasis

The treatment of *Candida* esophagitis has been investigated in various double-blind randomized studies, in particular in HIV-positive patients (236–240). In these studies, response rates with fluconazole, voriconazole, or isavuconazole were >95%. Conventional AmB was inferior to echinocandins (238). Responses with voriconazole, isavuconazole, caspofungin, micafungin, or anidulafungin were not significantly different from the fluconazole comparator at or shortly after end of treatment (236–240). However, the relapse rate 2 to 4 weeks after end of treatment was higher in the echinocandin groups. 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). Posaconazole has not been investigated for esophageal candidiasis in randomized studies. Two open-label studies suggested reasonable efficacy op posaconazole suspension, but the tablet formulation has not been investigated (241,242).
The optimal dose and duration of treatment in *Candida* esophagitis have not been investigated. Treatment with a minimum fluconazole dose of 200 mg qd (loading dose, 400 mg) for at least 2 weeks is recommended. This duration can be prolonged on the basis of the clinical and endoscopic course (where available).

Conclusions 3.10 – Treatment of esophageal candidiasis	
Conclusion 29	Echinocandins are more effective than c-AmB, and as effective as fluconazole for the treatment of *Candida* esophagitis in immunocompromized patients, but more often lead to relapse
Level 2	Villanueva, 2001 (B); Villanueva, 2002 (A2); De Wet, 2004 (A2); Ally, 2001 (A2); Krause, 2004 (A2); Viljoen, 2015 (A2)

Recommendation 25	For esophageal candidiasis, fluconazole (loading dose 400mg, followed by 200 mg qd) for 2 weeks is the preferred treatment. In case of fluconazole resistance, voriconazole (based on the susceptibility spectrum) is eligible, or, as a second choice, an echinocandin.

3.11. Antifungal prophylaxis in the intensive care unit

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 patients with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages, fluconazole prophylaxis (400mg qd) was effective in a placebo-controlled study, in a setting with a

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very high incidence of *Candida* peritonitis in the control group (35%) (243). In other selected patient groups in the ICU, e.g. high-risk surgical patients with an estimated ICU stay >3 days, randomized, placebo-controlled studies have shown a reduction of the incidence of invasive candidiasis by at least 50%, but the strategy did not improve survival in any of the studies (244,245).
Two meta-analyses suggest that prophylaxis with azoles is associated with a reduction of invasive candidiasis (fluconazole, RR 0.21, 95%CI 0.06-0.72, p=0.01), but not of mortality (246,247). The value of these meta-analyses is limited by the fact that the studies included are heterogeneous (aimed at patients with a prolonged ICU stay, patients with anastomotic leakage, patients with gut perforation or patients with pancreatitis). Also, the dosage and duration of administration of fluconazole (single dose or 100 – 400 mg qd) varied widely.
A recent randomized study utilized targeted caspofungin prophylaxis in high-risk ICU patients, selected by a clinical prediction rule (248). In this study, both serum ß-glucan and cultures were used to define invasive candidiasis. Overall, there were no significant differences in incidence of candidemia, all cause mortality, antifungal drug use, or length of stay between the two study arms (248).

Clinical prediction rules for prophylaxis

Defining a subgroup of ICU patients with a high risk of invasive candidiasis, for whom antifungal prophylaxis may be efficient, has failed to date. In the US, prediction rules for patients with a high risk of candidemia identified a subgroup with a 10.1% incidence of invasive candidiasis (249,250). However, the rule identified only 50% of all patients with candidemia after day 4. Applying the prediction rule, therefore, will fail to identify the majority of the patients who develop candidemia. Moreover, the clinical utility of prediction rules is shaped by the low prevalence of invasive candidiasis (151). In typical ICU settings in the Netherlands, where the pretest likelihood of candidiasis is 0.5–1%, risk factor-based rules with a specificity of around 80% will merely lead to a positive predictive value (PPV) of 1.5 to 3%, and a number needed to treat of 70 to 140.

Conclusions 3.11 – Antifungal prophylaxis in patients in the intensive care setting	
Conclusion 30	Fluconazole prophylaxis (400 mg qd) is effective in preventing intra-abdominal candidiasis in patients undergoing relaparotomy for anastomotic intestinal leakage in circumstances characterized by a high incidence of candidiasis, and reduces the incidence of invasive candidiasis in a predefined category of high-risk ICU patients. Caspofungin prophylaxis has not been shown to reduce the incidence of invasive candidiasis in the ICU.
Level 1	Eggimann, 1999 (B); Pelz, 2001 (A2); Garbino, 2002 (A2); Ostrosky-Zeichner, 2014 (A2)
Conclusion 31	The use of clinical prediction rules to select patients for antifungal prophylaxis in the intensive care has not lead to improved clinical outcomes or survival in published studies.
Level 2	Ostrosky-Zeichner, 2011 (C); ; Ostrosky-Zeichner, 2014 (A2)

Recommendations
Antifungal prophylaxis in ICU patients is not supported by clinical studies, from which results have been negative, or at most modest. The major challenge is to select individual patients or subgroups who will benefit most from prophylaxis, in order to limit the number needed to treat. In the Netherlands, where the incidence of invasive candidiasis has traditionally been <1% in the ICU, trial results and algorithms published from high-incidence settings do not apply. In addition, the use of selective decontamination (SD), containing non-resorbable c-AmB or nystatin, has been suggested to be associated with a further declining incidence of candidemia. The committee considers prophylaxis with fluconazole to be effective in very selected high-risk situations, such as those involving patients undergoing relaparotomy following anastomotic intestinal leakage in units with a very high incidence of invasive candidiasis, as well as for pancreas, small bowel, and selected high-risk liver transplant recipients (see chapter 3.13).

Recommendation 26	Prophylaxis with fluconazole in intensive care is not recommended, except in specific situations, such as relaparotomy following anastomotic intestinal leakage in units with an unacceptably high local incidence of invasive candidiasis.

3.12. Antifungal prophylaxis in patients with hematological malignancies or solid organ transplant recipients

Hemato-oncology patients

Gastrointestinal tract colonization with *Candida* spp. is recognized as a risk factor for disseminated candidiasis in neutropenic hematology patients, especially HSCT recipients. In the 1990s, two randomized studies have demonstrated the

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benefit of oral fluconazole (400 mg/d up to 75 days post transplant) as antifungal prophylaxis after HSCT (251,252). Moreover, long-term follow-up has shown an improved long-term survival benefit of prophylaxis (253,254). However, recent changes in transplantation practices, including the use of peripheral blood stem cells (PBSC), reduced intensity conditioning (RIC) regimens with better preservation of the intestinal barrier and fewer oral mucositis might challenge the value of fluconazole prophylaxis. In general, autologous HSCT is not considered a high-risk situation for invasive candidiasis, because of the short neutropenic phase. Anti-*Candida* prophylaxis has remained recommended for allogeneic HSCT during the neutropenic phase after myeloablative regimens, and is usually continued until 100 days post-HSCT.

Conclusions 3.12 – Anti-Candida prophylaxis in hemato-oncology patients	
Conclusion 32	Fluconazole protects against invasive candidiasis in patients undergoing allogeneic HSCT.
Level 1	Goodman, 1992 (B); Slavin, 1995 (B); Marr, 2000 (B)

Recommendation 27	Fluconazole (400 mg qd) anti-*Candida* prophylaxis is recommended for allogeneic HSCT recipients during the neutropenic phase who do not receive anti-mold prophylaxis. Prolonged prophylaxis up to 100 days post transplant may be considered

Lung transplants

Several studies have assessed the use of fluconazole, voriconazole, or aerosolized conventional or lipid AmB as primary prophylaxis in lung transplant recipients (255–259). Studies of antifungal prophylaxis with anti-mold azoles or inhaled AmB formulations overall demonstrated decreased rates of invasive fungal infection as compared with historical controls, but as most studies were not prospectively designed and randomized, no conclusion can be drawn about the optimal choice.

Liver transplants

Prophylaxis against invasive mycoses in liver transplant patients has been studied using L-AmB (260–262), ABLC (263), fluconazole (264), anidulafungin (265), or micafungin (266). In the latter study, 344 high-risk patients received micafungin or center-specific standard care post transplant. Clinical success was 96.5% for micafungin and 93.6% for standard care (Δ -2.9% [-8.0% to 1.9%]).
In an earlier meta-analysis of antifungal prophylaxis in liver transplant patients (267), fluconazole resulted in a significant reduction of invasive mycoses, but without effect on mortality. In a recent meta-analysis including 14 randomized studies (268), antifungal prophylaxis reduced the rate of proven invasive fungal infections (OR 0.37, 95%CI 0.19–0.72, p=0.003), and mortality due to fungal infections (OR 0.32, 95%CI 0.10–0.83, p=0.02) when compared to placebo. An equivalent reduction in the rate of fungal infections was seen specifically with fluconazole (OR 0.21, CI 0.06–0.57) and L-AmB (OR 0.21, CI 0.05–0.71) (268).
Factors associated with an increased risk of invasive mycoses in liver transplant patients include renal insufficiency, re-transplantation, choledochojejunostomy, perioperative massive blood transfusion, or fungal colonization around the day of transplantation, and in absence of these risk factors, the risk of invasive fungal infection is very low (267,269).

Other solid organ transplants

The incidence of invasive mycoses in patients undergoing kidney, kidney-pancreas, or heart transplantation is low (270), and studies of the possible effect of antifungal prophylaxis have not been conducted in these patient groups.

Conclusions 3.12 – Antifungal prophylaxis in solid organ transplantation	
Conclusion 33	In liver transplant patients without specific risk factors, the incidence of invasive mycoses is very low. Fluconazole, L-AmB, anidulafungin, and micafungin are effective in the prevention of invasive mycoses in high-risk liver transplant patients.
Level 1	Playford, 2006 (A1); Evans, 2014 (A1); Pappas, 2006 (B); Winston, 2014 (B)
Conclusion 34	The incidence of invasive mycoses in patients undergoing kidney, kidney-pancreas, or heart transplantation is low, and a favorable effect of antifungal prophylaxis has not been demonstrated in these groups.
Level 3	Pappas, 2010 (B)

Recommendation 28	Fluconazole (400 mg qd) is only recommended for patients undergoing liver transplantation who have an elevated risk of invasive mycoses, i.e., those with renal insufficiency, re-transplantation, choledochojejunostomy, perioperative massive blood transfusion, or proven perioperative colonization with *Candida*.

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3.13. Antifungal prophylaxis in neonates

Prophylaxis with fluconazole was investigated in ten placebo-controlled studies in premature neonates with very low birth weight (defined as <1500, <1000, or <750g) (271). In a Cochrane meta-analysis (272), fluconazole significantly reduced the incidence of invasive candidiasis, but not the risk of death prior to hospital discharge. In the most recent study among 362 infants <750g, the primary composite endpoint of death or invasive candidiasis was not significantly different between the study arms (273). Fluconazole had no effect on neurodevelopmental outcomes at 18-22 months. The incidence of invasive candidiasis among neonates has been decreasing, and it is questionable whether prophylaxis of invasive candidiasis translates into substantial improvements in the outcomes of prematurity (273).

Conclusions 3.14 – Antifungal prophylaxis in premature neonates	
Conclusion 35	Fluconazole prophylaxis reduces the incidence of invasive candidiasis in premature neonates with a very low birth weight, but is not associated with an improved survival or neurodevelopmental outcomes.
Level 2	Cleminson, 2015 (A1); Benjamin, 2014 (A2)

Recommendation 29	In premature neonates with a very low birth weight, fluconazole prophylaxis (3 mg/kg twice weekly) should only be considered in settings in which there is a proven high incidence of invasive candidiasis.

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Chapter 4 Cryptococcosis

4.1. Cryptococcal meningitis

Immunocompromized patients, e.g., HIV/AIDS patients or organ transplant recipients, have an increased risk of cryptococcal infection. The majority of patients present with subacute meningitis or meningoencephalitis. The principle of rapid fungicidal activity should be the primary focus of any induction strategy (274), and sterilization of the CSF within 2 weeks is significantly associated with favorable outcome (275). This was underlined in a recent study (276), where fluconazole-based induction treatment and slow clearance of CSF infection were independently associated with increased mortality. Other determinants of mortality were: altered mental status (OR, 3.1), high cerebrospinal fluid (CSF) fungal burden (OR, 1.4 per log10 cfu/mL increase), older age (>50 years; OR, 3.9), and high peripheral white blood cell count (>10 × 10^9/L; OR, 8.7) (276).
In a variety of randomized trials, a fungicidal induction strategy using combination therapy of c-AmB with flucytosine (5-FC) yielded better outcomes than c-AmB monotherapy (274,275,277–279). Fluconazole monotherapy has been associated with higher mortality and poorer outcomes in comparative trials (276,280,281). Combination therapy consisting of fluconazole+5-FC was more fungicidal than fluconazole monotherapy, and associated with significantly fewer deaths (282).

Several trials have further defined the importance of rapid fungicidal activity. In a randomized study among patients with cryptococcal meningitis in Thailand, four treatment strategies were compared: c-AmB, c-AmB+5-FC, c-AmB/fluconazole, or c-AmB+5-FC+fluconazole, all for 2 weeks (274). The primary end point was the rate of reduction in CSF cryptococcal colony-forming units (CFUs) from repeated CSF cultures. Combination therapy with c-AmB and 5-FC was the most effective in sterilizing 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). In a subsequent, large, randomized trial in Vietnam, c-AmB monotherapy was compared to c-AmB+5-FC and c-AmB+fluconazole (at a dose of 400mg twice daily) (279). Mortality was lower among patients receiving c-AmB+5-FC compared to c-AmB alone (HR, 0.61; 95%CI, 0.39, 0.97; P = 0.04). Combination therapy with c-AmB+fluconazole yielded intermediate results (compared with c-AmB monotherapy, HR 0.71; 95%CI, 0.45, 1.11; P=0.13). In a smaller 4-arm trial (278), c-AmB+5-FC, c-AmB+fluconazole (800 mg daily), AmB+fluconazole (600 mg daily), and AmB+voriconazole were compared. There were no statistically significant differences in mortality or the rate of CFS clearance of cryptococcal CFU among the 4 treatment groups, suggesting that AmB plus fluconazole or voriconazole is an effective alternative combination to c-AmB+5-FC, if the latter is unavailable (278).

Different dosages of c-AmB (0.7 vs 1.0 mg/ kg per day) plus flucytosine have been compared, and the higher dosage was more fungicidal, although no difference in mortality was observed (283). Several trials have compared c-AmB to L-AmB for the treatment of cryptococcal meningitis. In two small pilot studies, monotherapy with L-AmB yielded similar outcomes as c-AmB monotherapy (284,285). Monotherapy with c-AmB was compared to L-AmB (3mg/kg/d) and L-AmB (6mg/kg/d) (286). Efficacy was similar among all 3 treatment groups. The 2-week mycological success of L-AmB 3 mg/kg (64%) and 6 mg/kg (54%) was similar. The lower dose of L-AmB was accompanied by significantly fewer adverse effects, in particular nephrotoxicity (286).

Adjunctive therapy

There is ample evidence that endogenous interferon-γ (IFN-γ) production is associated with the rate of clearance of cryptococci from CSF (287,288). In a double-blind, placebo-controlled pilot study (289), adjuvant immunotherapy with recombinant IFN-γ (100µg vs. 200µg 3 x per week) was compared to placebo in patients with cryptococcal meningitis receiving standard therapy (c-AmB+5-FC). CSF sterilization after 2 weeks tended to be greater with rIFN-γ (p=0.064), compared to standard therapy (289). In a larger controlled trial (290), patients receiving standard therapy (c-AmB+5-FC) were randomized to receive no adjunctive therapy, rIFN-γ (100µg) on days 1 and 3 (rIFN-γ two doses), or on days 1, 3, 5, 8, 10 and 12 (rIFN-γ six doses). Primary outcome was rate of clearance of *Cryptococcus* from the CSF (early fungicidal activity, EFA), previously shown to be independently associated with survival. Rate of fungal clearance was significantly faster in the rIFN-γ groups than with standard treatment. Mean EFA [log colony forming unit (CFU)/ml per day] was -0.49 with standard treatment, -0.64 with rIFN-γ two doses, and -0.64 with rIFN-γ six doses (P<0.02). Mortality was 16% at 2 weeks and 31% at 10 weeks, with no significant difference between groups. All treatments were well tolerated (290).

The use of adjuvant corticosteroids in patients with cryptococcal meningitis has been supported by preclinical and observational data. However, dexamethasone was shown to be deleterious in a recent randomized trial (291). In this study, in patients with cryptococcal meningitis were randomized to receive either dexamethasone or placebo for 6 weeks, along with combination antifungal therapy with AmB and fluconazole. The trial was stopped for safety reasons after enrollment of 451 patients. Fungal clearance in CSF was significantly slower in the dexamethasone group. The endpoint of death or disability at 10 weeks was higher in the dexamethasone group (OR for good outcome, 0.42; 95%CI, 0.25 to 0.69; P<0.001).

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Adverse events were more common in the dexamethasone group (P=0.01), with significantly more patients in having secondary infection, renal events, or cardiac events. In addition, there was no reduction in paradoxical IRIS (immune reconstitution) reactions with dexamethasone.

Auto-antibodies against GM-CSF have been reported in apparently immunocompetent patients infected by *Cryptococcus gattii*. These autoantibodies can be functionally tested and also determined in serum. The presence of these auto-antibodies may guide initiation of immunotherapy with high-dose rGM-CSF, in addition to antifungal therapy (292).

Elevation of intracranial pressure in cryptococcal meningitis

Elevated intracranial pressure in patients with cryptococcal meningitis is associated with a less favorable prognosis (275,293). However, earlier studies have not clearly demonstrated an association between baseline opening pressure and 2-week mortality. In a recent study (294), patients underwent an LP to diagnose cryptococcal meningitis, and subsequent therapeutic LPs were recommended for elevated intracranial pressure (>25 cmH_2O) or new symptoms. All patients were treated with combination antifungal therapy with AmB and fluconazole. Therapeutic LPs were associated with a 69% relative improvement in survival, regardless of initial intracranial pressure. The adjusted relative risk of mortality was 0.31 (95%CI, 0.12 to 0.82) (294).

Antiretroviral therapy

Early start of combination antiretroviral therapy (cART) has been associated with better outcomes of several AIDS-defining infectious diseases. In a small randomized study, early cART was associated with a trend towards higher mortality (295). In a large, sufficiently powered trial (296), HIV-infected patients with cryptococcal meningitis and no previous cART were randomized to initiate early cART (1-2 weeks after diagnosis) or deferred cART (after 5 weeks). All patients received combination antifungal therapy with c-AmB and fluconazole. The 26-week mortality with earlier cART initiation was significantly higher than with deferred cART initiation (45% vs. 30%; HR for death, 1.73; 95%CI, 1.06 to 2.82; P=0.03). The excess deaths associated with earlier cART initiation occurred 2 to 5 weeks after diagnosis (P=0.007), particularly in patients with low CSF leukocyte counts (<5/mm^3) at baseline. The incidence of cryptococcal IRIS did not differ significantly between the groups (296).

Conclusions 4.1 – Treatment of cryptococcal meningitis	
Conclusion 1	Combination therapy with AmB plus 5-FC leads to more rapid sterilization of CSF and better survival than monotherapy with AmB.
Level 1	Bennett, 1979 (A2); van der Horst, 1997 (A2); Brouwer, 2004 (A2); Loyse, 2012 (A2); Day, 2013 (A2)
Conclusion 2	Fluconazole induction therapy results in slower clearance of CSF infection and increased mortality compared to AmB of AmB plus 5-FC.
Level 1	Saag, 1992 (A2); Brouwer, 2004 (A2); Larsen, 1990 (B); Jarvis, 2014 (B)
Conclusion 3	The combination of AmB plus fluconazole (800mg/d) results in a reasonable rate of CSF clearance.
Level 1	Brouwer, 2004 (A2); Loyse, 2012 (A2); Day, 2013 (A2)
Conclusion 4	L-AmB (3 mg/kg/d) has similar efficacy as c-AmB in cryptococcal meningitis and is associated with significantly less nephrotoxicity and other side effects.
Level 2	Hamill, 2010 (A2)
Conclusion 5	Adjunctive therapy with rIFN-γ (100µg) on days 1 and 3 of antifungal therapy leads to more rapid clearance of CSF infection.
Level 1	Pappas, 2004 (A2); Jarvis, 2012 (A2)
Conclusion 6	Adjunctive therapy with dexamethasone is associated with more adverse events and disability, and higher mortality in patients with HIV-associated cryptococcal meningitis.
Level 2	Beardsley, 2016 (A2)
Conclusion 7	Auto-antibodies against GM-CSF may be associated with cryptococcosis in apparently immunocompetent patients.
Level 3	Saijo, 2014 (C)
Conclusion 8	In patients with elevated (>25 cm H_2O) intracranial pressure or new events, repeated therapeutic lumbar punctures are associated improvement in survival, regardless of initial intracranial pressure.
Level 3	Rolfes, 2014 (B)
Conclusion 9	Deferring cART for 5 weeks after the diagnosis of cryptococcal meningitis is associated with significantly improved survival, as compared with initiating cART at 1 to 2 weeks
Level 2	Bisson, 2013 (B); Boulware, 2014 (A2)

Recommendations

Recent randomized trials have demonstrated the importance of rapid sterilization of the CSF as a major determinant of patient survival in the treatment cryptococcal meningitis (274,276,278,279). Induction therapy with the combination of

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AmB and 5-FC is associated with rapid CSF clearance and better survival compared to other induction regimens. In view of the severe toxicity of c-AmB and the extensive clinical experience with L-AmB for treatment of cryptococcal meningitis, the committee considers c-AmB no longer indicated. This policy is in agreement with the treatment recommendations for aspergillosis, candidiasis and mucormycosis in this guideline, as well as with international expert opinion on cryptococcosis (297). Therefore, L-AmB (3 mg/kg/d) combined with 5-FC (100 mg/kg/d; with therapeutic drug monitoring) for at least 2 weeks is the preferred induction therapy for all patients with cryptococcal meningitis.

It must be emphasized that control of CSF pressure is a critical determinant of outcome, and antifungal therapy should be combined with optimal pressure management. Repeated therapeutic lumbar punctures may be required for patients with elevated intracranial pressure or clinical deterioration (294).

If 5-FC is contraindicated, the combination of L-AmB plus fluconazole (800 mg/d) is a reasonable alternative, although the CSF clearance and survival rate with this regimen were less favorable than those with AmB + 5FC in the largest trial (279).

In patients who have responded favorably, induction therapy should be followed by fluconazole (loading dose 800mg, followed by 400 mg qd) for a total of at least 10 weeks (298). Subsequently, fluconazole maintenance therapy (or secondary prophylaxis) should be prescribed (see paragraph 4.3).

Adjunctive therapy with dexamethasone has been demonstrated deleterious in patients with cryptococcal meningitis and should not be given (291). In contrast, rIFN-γ administration was associated with a significantly greater rate of clearance of Cryptococcus from the CSF (early fungicidal activity, EFA) in two randomized trials (289,290). While these trials were not powered to demonstrate a survival benefit, the EFA is known to be an important determinant of outcome and survival (274,276). As two doses of rIFN-γ (100µg) on days 1 and 3 were as effective as six doses in the comparative trial (290), it is suggested that 2 doses suffice in responding patients, while rIFN-γ may be continued twice weekly in patients with a less favorable clinical response. As the trials were not designed to demonstrate a survival benefit of adjunctive therapy with rIFN-γ, the committee considers the present data not strong enough to recommend rIFN-γ as standard adjunctive therapy in all patients with severe cryptococcosis.

Recommendation 1	Cryptococcal meningitis should be treated with L-AmB (3 mg/kg/d) plus 5-FC (100 mg/kg/d) for at least 2 weeks. Thereafter, the treatment of stable and favorably responding patients may be continued with fluconazole (loading dose 800mg, followed by 400 mg qd), for a total of at least 10 weeks, followed by chronic maintenance therapy.
Recommendation 2	For patients with contraindications to 5-FC, induction therapy with L-AmB (3 mg/kg/d) plus fluconazole (400 mg twice daily) for at least 2 weeks is an acceptable second choice.
Recommendation 3	Adjunctive therapy with rIFN-γ (100µg) on days 1 and 3 may be considered for patients with cryptococcal meningitis. In patients with a slow clinical response, rIFN-γ may be continued twice weekly.
Recommendation 4	Control of CSF pressure is a critical determinant of outcome, and repeated therapeutic lumbar punctures are required for patients with elevated intracranial pressure or clinical deterioration.
Recommendation 5	Dexamethasone adjunctive therapy is contraindicated in patients with cryptococcal meningitis.
Recommendation 6	In cART-naïve HIV-infected in patients with cryptococcal meningitis, the initiation of cART should be deferred until 5 weeks after start of antifungal therapy.
Recommendation 7	In apparently immunocompetent patients with *C. gattii* infection auto-antibodies against GM-CSF should be tested, to guide initiation of rGM-CSF immunotherapy.

4.2. Treatment of nonmeningeal cryptococcosis

Extrameningeal cryptococcal infection occurs mainly in patients not infected with HIV. Pulmonary cryptococcosis includes clinical presentations ranging from asymptomatic pneumonia to diffuse interstitial pneumonia ands severe ARDS. There are no prospective studies that specifically address the management of pulmonary cryptococcosis or any other nonmeningeal manifestations. Case series have described treatment of such patients mostly with L-AmB with or without 5-FC, while c-AmB and fluconazole were alternative regimens. (299–302). In a large case series including 208 HIV-positive and HIV-negative patients presenting with or without meningitis, combination therapy for ≥14 days of AmB plus 5-FC was independently associated with improved outcomes in a multivariate analysis (302). Non-HIV patients with cryptococcosis as a complication of T-cell deficits reportedly benefit from adjunctive immunotherapy with rIFN-γ (112,303).

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Conclusion 4.2 – Treatment of nonmeningeal cryptococcosis	
Conclusion 10	Although randomized studies specifically addressing patients with nonmeningeal cryptococcosis are lacking, cohort studies suggest that combination therapy with AmB plus 5-FC leads to more rapid sterilization of CSF and better survival than alternative induction regimens.
Level 3	Dromer, 2009 (B).
Conclusion 11	Adjunctive therapy with rIFN-γ (100µg twice weekly) restores anti-cryptococcal host defenses in patients with functional T-cell defects and invasive cryptococcosis.
Level 3	Netea, 2004 (C); Delsing, 2014 (C)

Recommendations

No studies of sufficient quality have been conducted in patients with extrameningeal cryptococcosis. The available data suggest that the early fungicidal activity (EFA) associated with combination therapy with AmB plus 5-FC is also important in nonmeningeal cryptococcosis, especially in immunocompromized patients (300–302). Therefore, the committee considers L-AmB plus 5-FC the therapy of choice for all patients with cryptococcosis. Fluconazole may be a reasonable alternative for patients with mild, localized, nonmeningeal infection, and less severe immunosuppression. When considering this option, it is important to exclude cryptococcal meningitis, disseminated disease and cryptococcemia. This requires that a lumbar puncture and blood cultures should be performed.

Based on the functional T-cell defects generally underlying invasive or disseminated cryptococcosis (112,303), adjunctive immunotherapy with rIFN-γ may be considered for all patients with severe meningeal, pulmonary or disseminated cryptococcosis, and those in whom T-cell immunity cannot be restored by cART or withdrawal of immunosuppressive therapy.

The duration of antifungal therapy in non-meningeal cryptococcosis has not been investigated, but lengthy treatment (usually ≥ 6 months) is assumed to be necessary.

Recommendation 8	Nonmeningeal or disseminated cryptococcosis should be treated with L-AmB (3 mg/kg/d) plus 5-FC (100 mg/kg/d) for at least 2 weeks. Consolidation therapy of stable and favorably responding patients should follow with fluconazole (loading dose 800mg, followed by 400 mg qd, for 6 to 12 months).
Recommendation 9	Fluconazole (loading dose 800mg, followed by 400 mg qd, for 6 to 12 months) may be a reasonable alternative for patients with mild, localized, nonmeningeal infection, and less severe immunosuppression. Before considering this option, a lumbar puncture and blood cultures are required in all patients, to rule out cryptococcal meningitis, disseminated disease and cryptococcemia.
Recommendation 10	Adjunctive therapy with rIFN-γ (100µg twice weekly) may be considered for all patients with severe meningeal, pulmonary or disseminated cryptococcosis, and for patients in whom T-cell immunity cannot be restored by cART or withdrawal of immunosuppressive therapy.

4.3. Secondary prophylaxis of cryptococcosis

With the introduction of early cART for all HIV-infected patients with low CD4+ cell counts, primary antifungal prophylaxis for cryptococcosis is no longer required for HIV-infected patients in the United States and Europe.

Despite existing evidence suggesting that most cryptococcal disease in transplant recipients likely results from reactivation of a subclinical infection, there are no data suggesting that routine primary prophylaxis for cryptococcosis in transplant recipients would be beneficial.

Secondary prophylaxis is required for patients who have suffered from invasive cryptococcosis, in view of their underlying immune defect. For the prevention of cryptococcal meningitis relapse in HIV-infected patients, several randomized trials have demonstrated the superiority of fluconazole over placebo, c-AmB, or itraconazole (304–306).

Several studies have demonstrated that discontinuation of secondary cryptococcal prophylaxis (fluconazole 200mg qd) in patients with a CD4 count of >100/µl and an undetectable HIV RNA during cART is safe and does not lead to relapses (307,308). Therefore, it is recommended to discontinue antifungal maintenance therapy for cryptococcosis in patients whose CD4 cell counts are ≥100 cells/µL, who have undetectable viral loads on cART for >3 months, and who have received a minimum of 1 year of maintenance therapy after successful treatment of cryptococcosis (309).

In solid organ transplant recipients who receive long-term immunosuppressive medication and did not receive secondary prophylaxis, relapses of cryptococcosis frequently occurred within 6 months, and in all cases within 1 year after cessation of antifungal therapy (300,301). Thus, continuation of maintenance antifungal therapy with fluconazole 200-400mg/day in solid-organ transplant recipients for at least 6 and up to 12 months is rational.

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Conclusions 4.3 – Secondary prophylaxis of cryptococcosis	
Conclusion 12	Fluconazole (200 mg qd) is effective in the prevention of cryptococcosis relapse patients with persistent host defense deficits.
Level 1	Bozzette, 1991 (A2); Powderly, 1992 (A2); Saag, 1999 (A2); Singh, 2005 (C)
Conclusion 13	Secondary antifungal prophylaxis in patients having had cryptococcal meningitis can be discontinued in HIV-positive patients who have a favorable immunological and virological response to cART (CD4 >100 cells/µl and HIV load < 50 copies/ml, for > 3 months), and after 6 to 12 months after resolution of cryptococcosis in solid organ transplant recipients.
Level 2	Vibhagool, 2003 (A2); Mussini, 2004 (B); Singh, 2005 (C); Singh, 2009 (D).

Recommendation 11	Chronic maintenance therapy with fluconazole (200mg qd) is required for patients who have suffered from invasive cryptococcosis and continue to have an underlying immune defect. In solid organ transplant recipients, maintenance therapy with fluconazole (200-400mg qd) for 6-12 months is recommended.

Recommendation 12	After a minimum of 1 year after successful treatment of cryptococcosis, chronic maintenance therapy can be discontinued in solid organ transplant recipients, and in HIV-positive patients with CD4 counts ≥100 cells/µL, who have undetectable viral loads on cART for >3 months.

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Chapter 5 Mucormycosis

Introduction

Mucormycosis, also known as Zygomycosis, is an infection caused by fungi belonging to the order Mucorales. The genera of mucorales causing disease are *Rhizopus*, *Mucor*, *Lichtheimia*, *Cuninghamella, Rhizomucor*, *Saksenaea* and *Apophysomyces*. *Rhizopus arrhizus (Rhizopus oryzae)* is the most frequently isolated pathogen in mucormycosis (310–312). Mucormycosis is often a severe and fatal infection and the most common sites of mucormycosis are the paranasal sinuses and adjacent areas (rhinocerebral, sino-orbital and sinopulmonary mucormycosis), the lungs, the skin, and the brain (311). In children, mucormycosis may occur in the gastro-intestinal tract (313).
The incidence of invasive mucormycosis appears to be rising (from 0.09% to 0.17%) in recent years, especially in hematological patients (314), which has been related to the increasing use of voriconazole (315). The conduct of prospective, randomized studies of the treatment of mucormycosis is difficult due to its low incidence. Data on the treatment of mucormycosis are therefore predominantly based on clinical experience and retrospective analyses.

5.1. Diagnosis of mucormycosis

Similar to aspergillosis, mucormycosis is diagnosed as proven, probable or possible according to EORTC/MSG criteria. Direct microscopy can be useful in distinguishing Mucorales from more common filamentous fungi such as *Aspergillus* or *Fusarium*, since Mucorales have broad non-septate hyphae with irregular ribbon-like appearance (316). Histology from patients with mucormycosis predominantly shows neutrophilic inflammatory responses and invasive disease was characterized by infarction and angioinvasion; angioinvasion is more prominent in neutropenic patients (316,317). Since Mucorales do not contain significant galactomannan and β-glucan in their cell wall, diagnostic tests such as galactomannan and β-D-glucan assays are not helpful (318). Thus, a negative GM index in BAL in the clinical context of suspected pulmonary invasive fungal disease should raise suspicion for mucormycosis (17,319). Radiological signs are not very specific, although a reversed halo sign, which is a rim of consolidation surrounding a center of groundglass opacity on CT, might indicate pulmonary mucormycosis (320,321). In a study investigating radiologic imaging in 189 patients with proven or probable pulmonary invasive fungal infection a reverse halo sign was present in 19% of patients diagnosed with mucormycosis compared to <1% for other fungal infections (321). Mucorales grow rapidly, however negative cultures of mucorales have been associated with aggressive handling of the specimen before plating, such as grinding (322).

Conclusions 5.1. – Diagnosis of mucormycosis	
Conclusion 1	Direct microscopy is useful in distinguishing mucormycosis from other invasive fungal infections and septation, width, branching angle and morphology should be evaluated. Aggressive processing of the specimens is associated with negative cultures.
Level 3	Ribes, 2000 (C); Frater, 2001 (C)
Conclusion 2	A negative GM index in serum and BAL in the clinical context of suspected pulmonary invasive fungal disease increase the likelihood of mucormycosis.
Level 3	Maertens, 2005 (C); Pang, 2012 (C)
Conclusion 3	A reverse halo sign on CT is an indicator of mucormycosis.
Level 3	Wahba, 2008 (C); Juan, 2014 (C)

Recommendation 1	Direct microscopy of clinical specimens followed by culture is strongly recommended for the diagnosis of mucormycosis.

5.2 Treatment of invasive mucormycosis

Most experience in the treatment of invasive mucormycosis has been gained with c-AmB (323). Retrospective analyses of primary and salvage therapy with ABLC (116,324) and ABCD (325) have suggested response rates of 50 to 75%. In a retrospective study in 58 patients with hematological malignancies and mucormycosis, multivariate analysis showed that the only factor associated with cure was treatment with liposomal amphotericin B (326). Similarly, L-AmB (average dose, 5mg/kg) was associated with a better clinical outcome and survival in an international registry (327).
A phase II study investigated the efficacy and toxicity of high-dose L-AmB (10 mg/kg) as first-line therapy for mucormycosis. Response rate at 12 weeks was 45% and renal toxicity was frequently observed (40%) (328). Anecdotal reports have

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suggested a benefit of the combination of ABLC and caspofungin (329). However, a recent retrospective study among 101 patients with mucormycosis did not find a survival benefit after introduction of L-AmB-echinocandin combination therapy (330).
Isavuconazole was evaluated as first-line therapy in an open-label non-comparative trial in 37 patients with proven and probable mucormycosis (VITAL study)(331). The most common sites of infection were the lung (59%) and sinuses (43%). By day 42, 11% had a partial response, 43% had stable disease, 3% had progression, and 35% had died. In a matched cohort comparison, patients from the VITAL study were compared with patients who received primary AmB-based treatment from the international FungiScope registry. At day 42 all-cause mortality (isavuconazole study 33%; AmB registry 32%) was similar in both groups (331). Although isavuconazole has not been investigated in a randomized, comparative trial for this indication, and comparison of a prospective open-label study with a retrospective observational cohort has serious limitations (332), the FDA has approved the drug for first line therapy in the treatment of mucormycosis; the EMA has approved isavuconazole as treatment option in mucormycosis when amphotericin B is clinically inappropriate.
Posaconazole suspension (800mg qd) as salvage therapy has been investigated retrospectively in three cohorts, with 60 to 79% response rates, mostly partial responses (327,333,334). Primary therapy with posaconazole has been sporadically documented, with disappointing outcomes (327,335).

Adjunctive treatment regimens
Surgical debridement was associated with better outcomes and increased survival in two retrospective analyses (312,336) and in a multivariate analysis based on a ECMM registry (335). Particularly for rhino-cerebral mucormycosis, survival with surgery (100%) was suggested to be superior to conservative therapy (25%) (336).

Iron chelators have been investigated in the setting of mucormycosis, since iron overload is a risk factor for mucormycosis (337). A phase II trial with 8 patients with mucormycosis demonstrated that deferasirox was safe in patients with proven mucormycosis (338). However, in a randomized prospective double blind placebo controlled trial (DEFEAT study) including 20 patients with probable and proven mucormycosis, 82% of 11 patients with deferasirox had died at 3 months, compared to 22% of 9 patients without deferasirox (339).

Recommendations
The absence of randomized comparative studies on the treatment of invasive mucormycosis has resulted in the choice of therapy being based on retrospective analyses and expert opinion. Results with c-AmB have been very poor, and L-AmB in a daily dosage of at least 5 mg/kg has been associated with best clinical outcomes and survival rates in observational cohort studies. The experience with posaconazole is still limited; this drug has only been investigated as second line therapy in patients with refractory infections and appears to have reasonable efficacy in these circumstances. Whereas isavuconazole was associated with reasonable response rates in 37 patients undergoing primary treatment of invasive mucormycosis, the committee considers the evidence not sufficient to recommend isavuconazole as primary choice for this indication.
In view of the poor prognosis of invasive mucormycosis despite antifungal treatment, surgical debridement and correction of underlying risk factors (e.g. immunosuppression, ketoacidosis) is of great importance.

Conclusions 5.2 – Treatment of invasive mucormycosis	
Conclusion 4	L-AmB is effective for the treatment of invasive mucormycosis
Level 3	Pagano, 2004 (C); Rüping, 2010 (C); Skiada, 2011 (C); Lanternier, 2015 (C)
Conclusion 5	Antifungal treatment of invasive mucormycosis combined with surgical debridement leads to a better response than antifungal therapy only.
Level 3	Skiada, 2011 (C); Vironneau, 2014 (C); Lanternier, 2015 (C)
Conclusion 6	Adjunctive therapy of mucormycosis with deferasirox was not demonstrated to be beneficial
Level 2	Spellberg, 2012 (B)
Conclusion 7	Posaconazole appears to be effective as a salvage therapy in refractory invasive mucormycosis
Level 3	Van Burik, 2006 (C); Greenberg, 2006 (C)
Conclusion 8	Isavuconazole appears to be effective in invasive mucormycosis
Level 3	Marty, 2016 (C)

Recommendation 2	Invasive mucormycosis should be treated with L-AmB in a dosage of at least 5 mg/kg/day.

Recommendation 3	Where possible, the antifungal treatment of invasive mucormycosis should be combined with surgical debridement and correction of underlying risk factors.

Recommendation 4	For salvage treatment of invasive mucormycosis on failure or intolerance of L-AmB, posaconazole or isavuconazole may be considered.

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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:
Prof. Dr. N.M.A. Blijlevens: she or her department received contributions for scientific research or education from Novartis, BMS, Pfizer, Ariad, MSD, Astellas, Xenikos, Celgene, Janssen Cilag.
Dr. R. Brüggemann: his department received contributions for scientific research and consultancy services from Astellas, F2G, Gilead, MSD, and Pfizer.
Dr J.J.W.M. Janssen: participated in CME with support from Pfizer and Ariad; he receivend contributions for scientific research from Novartis and BMS, and for consultancy services from Novartis and Pfizer.
Prof Dr B.J. Kullberg: participated in CME with support from Pfizer and Gilead; he or his department received contributions for consultancy services for Amplyx, Astellas, Basilea, Cidara, and Scynexis.
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Dr T. Wolfs: participated in CME with support from Abbvie; received support for conference attendance from Gilead.
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Appendix

Specific considerations for dosing of antifungals in children

Table S1. Recommended doses of antifungal agents for children[†]

Antifungal agent	Loading dose	Maintenance dose
Azoles		
Voriconazole	2-14 years and <50kg: bid 9 mg/kg 12-14 years and >50kg; and 15-17 years: bid 6 mg/kg iv or bid 400 mg po ≥ 18 years refer to adult recommendations	8 mg/kg bid iv[#] or 9 mg/kg bid po[#] 4 mg/kg bid iv[#] or 200 mg bid po[#]
Isavuconazole	*	
Posaconazole	*	
Echinocandins		
Anidulafungin	not licensed for children	
Caspofungin	12 months to 17 years: 70 mg/m^2/d (maximum 70 mg) 3 to 11 months: 50 mg/m^2/d Neonates / < 3 months: 25 mg/m^2/d	12 months to 17 years: 50 mg/m^2/d (maximum 70 mg) 3 to 11 months: 50 mg/m^2/d Neonates / < 3 months: 25 mg/m^2/d
Micafungin	-	4 months – 16 years and <40 kg: 2 mg/kg/d (maximum 4 mg/kg/d) 4 months – 16 years and ≥40 kg: 100 mg/d (maximum 200 mg/d) Neonates / < 4 months 4 mg/kg/d (maximum 10 mg/kg/d)
Amphotericin B		
Liposomal AmB	3 mg/kg/d	3 mg/kg/d

[†] The dosages in this table are specific for invasive aspergillosis. For other mycoses, different dosages may apply.
For specific recommendations, exceptions, and contra-indications, see text and Table 2.1.
* For dosing, consult with experts
[#] Individual dose based on therapeutic drug monitoring

Table S2. Recommended doses of antifungal agents for treatment of invasive candidiasis in neonates

Antifungal agent	Loading dose	Maintenance dose
Azoles		
Fluconazole	Consider 25 mg/kg	12 mg/kg/d
Echinocandins		
Caspofungin		25 mg/m^2/d
Micafungin		4–10 mg/kg/d
Amphotericin B		
Amphotericin B deoxycholate		1 mg/kg/d
Liposomal AmB		3 mg/kg/d

[†] The dosages in this table are specific for invasive candidiasis. For other mycoses, different dosages may apply.
For specific recommendations, exceptions, and contra-indications, see text.

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Table S3. Recommended doses of antifungal agents for treatment of invasive candidiasis in children

Antifungal agent	Loading dose	Maintenance dose
Azoles		
Fluconazole		8-12 mg/kg/d
Voriconazole	2-14 years and <50kg: bid 9 mg/kg 12-14 years and >50kg; and 15-17 years: bid 6 mg/kg iv or bid 400 mg po	8 mg/kg bid iv[#] or 9 mg/kg bid po[#] 4 mg/kg bid iv[#] or 200 mg bid po[#]
Echinocandins		
Caspofungin	12 months to 17 years: 70 mg/m^2/d (maximum 70 mg) 3 to 11 months: 50 mg/m^2/d	12 months to 17 years: 50 mg/m^2/d (maximum 70 mg) 3 to 11 months: 50 mg/m^2/d
Micafungin	-	4 months – 16 years and <40 kg: 2 mg/kg/d (maximum 4 mg/kg/d) 4 months – 16 years and ≥40 kg: 100 mg/d (maximum 200 mg/d)
Amphotericin B		
Liposomal AmB		3 mg/kg/d

[†] The dosages in this table are specific for invasive candidiasis. For other mycoses, different dosages may apply.
For specific recommendations, exceptions, and contra-indications, see text.
[#] Individual dose based on therapeutic drug monitoring

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