Treatment of invasive fungal infections in cancer patients-Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

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REVIEW ARTICLE

Treatment of invasive fungal infections in cancer patients—Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

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Abstract Invasive fungal infections are a main cause of morbidity and mortality in cancer patients undergoing intensive chemotherapy regimens. Early antifungal treatment is mandatory to improve survival. Today, a number of effective and better-tolerated but more expensive antifungal agents compared to the former gold standard amphotericin B deoxycholate are available. Clinical decision-making must consider results from numerous studies and published

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guidelines, as well as licensing status and cost pressure. New developments in antifungal prophylaxis improving survival rates result in a continuous need for actualization. The treatment options for invasive *Candida* infections include fluconazole, voriconazole, and amphotericin B and its lipid formulations, as well as echinocandins. Voriconazole, amphotericin B, amphotericin B lipid formulations, caspofungin, itraconazole, and posaconazole are available for the treatment of invasive aspergillosis. Additional procedures, such as surgical interventions, immunoregulatory therapy, and granulocyte transfusions, have to be considered. The Infectious Diseases Working Party of the German Society of Hematology and Oncology here presents its 2008 recommendations discussing the dos and do-nots, as well as the problems and possible solutions, of evidence criteria selection.

Keywords Cancer · Invasive fungal infections · Antifungals

Introduction

Invasive fungal infections represent a primary cause of morbidity and mortality in cancer patients. In particular, invasive infections caused by *Aspergillus* species are increasing complications of intensive chemotherapy regimens. In Germany, the substances currently approved for use in the systemic therapy of invasive fungal infections are amphotericin B deoxycholate (D-AmB), liposomal AmB (L-AmB), amphotericin B lipid complex (ABLC), fluconazole, itraconazole, 5-flucytosin, caspofungin, anidulafungin, voriconazole, and posaconazole. The Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology actualized the recommendations from 2003 [7] based on EBM criteria proposed by the Infectious Diseases Society of America (IDSA) [42]. Special aspects of fungal septicemia or fungal infections in allogeneic bone marrow/stem cell transplantat recipients, which are published in separate manuscripts [22, 80], are not considered in this article.

Methods

Data Clinical studies and guidelines published in English were searched on Medline from 1990 up to June 2008. The data were selected by the first author and edited by the coauthors. Databases and randomized or well-designed nonrandomized controlled clinical trials for invasive *Candida* or *Aspergillus* infections that included more than 50 patients were considered. Studies of treatment for mixed invasive fungal infections involving a minimum of 25 patients with invasive *Candida* infections or aspergillosis were evaluated. Retrospective analyses in rare infection types, such as hepatosplenic candidosis or mucormycosis included at least 20 patients. Fungal infections in allogeneic stem cell transplant patients, which have special aspects of risk/prognostic factors and comedication problems, were not considered. *Pneumocystis jiroveci*, which affiliates to the fungal pathogens as well, has not been included since epidemiology and treatment options are completely different compared to other invasive mycoses.

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Evidence criteria Wherever possible, evidence categories of the IDSA were integrated (Table 1) [42]. Recommendations for treatment in neutropenic patients, however, are problematic for substances that are only or mainly studied in nonneutropenic patients but are already widely and successfully used in clinical practice. Evidence levels give only a reflection of study activities and are not always correlated with practice and experience. The IDSA guidelines for the treatment of invasive *Candida* infections published in 2004 avoid this dilemma, giving their recommendations without any rating [77]. The new guidelines, however, presented at Interscience Conference on Antimicrobial Agents and Chemotherapy 2007, decide on "down-grading" of recommendation levels for substances proved only or mainly in nonneutropenic patients. The first European Conference on Infections in Leukemia proceeded in a similar manner [35]. The AGIHO subgroup "Treatment of fungal infections" agreed on the following procedure: Study data are the basis for recommendation levels, since we assume an analog antifungal efficacy, but we added the mark "only" or "mainly proven for nonneutropenic patients." In contrast to other consensus groups, the AGIHO subgroup decided to assess not only the efficacy but also the tolerability of substances.

Assessment of license Principally, we do not consider the status of license for our recommendations and recommend the substances in accordance with study data. We urgently want to point out *that the state of license must not be mixed up with the degree of efficacy*. On the other hand, the availability of less expensive treatment modalities may put a high pressure on physicians to decide on off-label use. One should consider, however, that off-label use of medications given without necessity or without evidence for clear superiority compared to the licensed substances may cause legal problems in the case of severe complications or death by treatment failure.

Finding consensus These recommendations were first prepared by a panel of experts in the field of infections in immunocompromised patients. In a second step, the manuscript was reviewed by the AGIHO subgroup "Treatment of fungal infections" and finalized by AGIHO Consensus Group. We point out that the responsibility for selected therapy is exclusively that of the ordering physician.

Invasive *Candida* infections

Invasive *Candida* infections in cancer patients are primarily caused by *Candida albicans*, although an increase of candidemia by non-albicans *Candida* spp. has partially been found in patients with hematological malignancies [30, 110]. Due to high mortality, especially in patients with delayed sufficient treatment [24], antifungal treatment should be started in neutropenic patients as soon as possible. Study data for neutropenic patients, however, are limited.

Azoles

Fluconazole In noncomparative trials, observational studies and larger randomized trials, including mainly nonneutropenic patients, fluconazole demonstrated a high efficacy rate [2, 66, 82, 90]. Compared to D-AmB, fluconazole was not inferior and showed significantly better tolerability (AI) [2, 82, 90], but lower efficacy compared to anidulafungin [89]. Additionally, the incidence of invasive *Candida* infections with primary fluconazole resistance like *Candida krusei* or reduced susceptibility like *Candida glabrata* is rising in hematological patients [30, 110]; therefore, an echinocandin should be preferred, even if mainly proven in nonneutropenic patients (AI). A switch to fluconazole is possible if a susceptible species has been confirmed and the patient is clinically stable and has no prior azole exposure. Initially, fluconazole 800 mg/day should be preferred and may be reduced to 400 mg/day if the patient is clinically stable and not neutropenic (AII) [26, 77, 91].

Table 1 Categories indicating the strength of each recommendation for or against its use, and grades indicating the quality of evidence on which recommendations are based

A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
I	Evidence from at least 1 properly randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time series, or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Criteria of the IDSA [1]

Itraconazole A study comparing itraconazole with fluconazole in invasive *Candida* infections of nonneutropenic patients has been stopped since only a few patients reached the endpoint (data published only in abstract format). Other data about itraconazole are very limited (CIII).

Voriconazole In nonneutropenic patients, voriconazole resulted in similar success and significantly better tolerability compared to D-AmB followed by fluconazole (AI) [46]. Voriconazole may be given safely to patients without neutropenia with refractory infections or resistant C*andida* spp. [70].

Posaconazole There are no sufficient data for posaconazole [CIII].

Echinocandins

Caspofungin In a large randomized study also including neutropenic patients, caspofungin demonstrated similar efficacy and significantly fewer side effects compared to D-AmB (AI) [63]. Due to its good efficacy against non-*C. albicans* spp., as well as its good safety profile, caspofungin may be regarded as the drug of choice in severely ill, clinically instable patients with organ dysfunction, especially in patients with neutropenia.

Micafungin A noncomparative trial of micafungin for 126 newly diagnosed and refractory candidemias resulted in an 85% success rate for adults [69]. A recently published study, including mainly nonneutropenic patients, demonstrated an equally high efficacy and a higher tolerability of micafungin compared to L-AmB in the first-line therapy of invasive *Candida* infections (AI) [47]. A large randomized study (also small numbers of neutropenic patients) resulted in equal efficacy of micafungin 150 vs 100 mg/day vs caspofungin [78].

Anidulafungin In a randomized study including less than 5% neutropenic patients, anidulafungin resulted in higher clinical efficacy and clearance of *Candida* bloodstream infection compared to fluconazole. The authors discussed a potential influence of a center effect but could not find an influence on the study endpoints. Anidulafungin fulfilled the criteria for noninferiority (AI) [89].

Amphotericin B formulations

Amphotericin B lipid complex (ABLC) ABLC is effective in the second-line therapy of invasive *Candida* infections shown in emergency use study and a large mycoses database (CLEAR) (AII) [41]. A randomized study comparing ABLC vs D-AmB, also including neutropenic patients, showed similar efficacy and better tolerability of ABLC, but the definite study results are not published.

Liposomal Amphotericin B (L-AmB) The above mentioned randomized study comparing L-AmB with micafungin for first-line treatment demonstrated a high efficacy but lower tolerability of L-AmB in invasive *Candida* infections, but mainly nonneutropenic patients had been included (AI) [47]. An analysis of eight open-label studies on D-AmB and AmB lipid formulations showed an efficacy rate of 75% in ABLC-treated and 80% in L-AmB-treated patients with candidiasis [71]. L-AmB may be given as second-line therapy (AII).

Amphotericin B colloidal dispersion (ABCD) ABCD is unavailable in Germany. The tolerability is lower compared to that of ABLC or L-AmB.

Amphotericin B deoxycholate (D-AmB) Randomized studies did not demonstrate an advantage of D-AmB compared to fluconazole, caspofungin, voriconazole, or AmB lipid formulations [2, 46, 63, 66, 71, 82, 90]. The main disadvantages of D-AmB are nephrotoxicity, hypokalemia, and infusion-related adverse events. An increasing number of publications reported long-term nephrotoxicity with D-AmB interfering with nephrotoxic medications especially in stem cell-transplanted patients [33, 46, 61], partially resulting in inferior survival [33, 61]. In a recently published prospective study of 418 patients, treatment with D-AmB vs L-AmB vs ABLC or ABCD resulted in a deterioriation of kidney function in 66% vs 30% vs 55% [108]. So, in contrast to other authors, we clearly recommend avoidance of D-AmB for routine use (EI).

Combinations

In nonneutropenic patients, the combination of D-AmB for 5–6 days and fluconazole 800 mg/day showed no antagonism, a similar mortality, but improved clinical outcome and more rapid eradication of yeasts from bloodstream compared to fluconazole alone (AI) [91]. In cancer patients, there are no data about combination therapies in patients with invasive *Candida* infections.

Central venous catheter

Central venous catheters should be removed if presumed to be causative for *Candida* infection (BII) [77, 87, 114]. In vitro data suggest that echinocandins or L-AmB are more effective against biofilms [13]. This would support the idea to avoid a removal, but clinical data are lacking to support this approach. One recent paper hypothesizes that candidemias

in neutropenic patients derives from colonization in the gastrointestinal tract and less from central venous catheters [87].

Duration of treatment and maintenance therapy

Duration of treatment in nonneutropenic patients is recommended for at least 14 days after the first negative blood culture and resolution of signs and symptoms of candidemia (BIII) [77] but should be adapted to possible organ manifestations. In the case of a proven (fluconazole sensitive) invasive *Candida* infection, an initial therapy with an i.v. antifungal agent followed by oral fluconazole or voriconazole has been shown to be feasible.

Hepatosplenic candidosis

If fever persists after neutrophil recovery, hepatosplenic candidosis should be considered in hematological patients. Treatment experience is mainly available for D-AmB and fluconazole, showing response rates of more than 50% of cases [1, 3, 15, 21, 74, 98], but caspofungin is today accepted as alternative therapy when the Candida species is not identified [77, 105]. If *Candida* spp. are susceptible, fluconazole is recommended for primary therapy in clinically stable patients who are no longer neutropenic (BIII). For neutropenic patients, AmB lipid formulations or caspofungin may be given (BIII); less data exist for voriconazole (CIII). Due to the high risk of relapse in cancer patients, antifungal therapy should be given until there is a calcification or complete remission of the lesions, frequently several months are necessary (BIII). In stable patients, intravenous therapy may be switched to oral medication. However, this has not been studied so far.

Other manifestations

Candida infections of the central nervous system, usually caused by hematogenic dissemination, are infrequent in adults. Based on studies in children, the most recommended treatment for Candida meningitis is D-AmB in combination with 5-flucytosine. Case reports of patients treated with L-AmB and fluconazole are available in small numbers. Animal studies show a better penetration of L-AmB into the brain tissue as compared to ABLC [29]. Due to its good permeability into the cerebrospinal fluid, voriconazole may be a potential alternative. Treatment should be continued for an additional 4 weeks following the resolution of manifestations (BIII) [73, 77]. In brain abscess cases, additional drainage or, if possible, surgical resection is recommended. Renal *Candida* infections (infiltrations) are usually caused by blood stream infection and should be treated in the same manner. For urinary *Candida* infection, fluconazole has been proven in mainly nonneutropenic patients and is the drug of choice, if a susceptible *Candida* spp. is cultured (AI) [52, 104]. If a urine catheter is in place, it should be removed whenever possible (BII) [77]. The treatment options for invasive candidosis are summarized in Table 2.

Infections by *Aspergillus* species

In neutropenic patients, invasive pulmonary aspergillosis (IPA) is the most frequent manifestation (80–90%). The fatality rate is 30–60% [34, 58, 72]. Early treatment at first signs of infection is mandatory and can improve the chance of survival (BIII) [11, 43]. For primary and secondary treatment of invasive aspergillosis, voriconazole, D-AmB, AmB lipid formulations, caspofungin, itraconazole, and posaconazole have been proven to be effective.

Azoles

Voriconazole In an open, noncomparative study, voriconazole showed a response rate of 59% in the primary treatment of invasive aspergillosis and a 38% rate when used for salvage treatment [20]. In a large, randomized study including mainly cancer patients, the therapy with

Table 2 Therapy of main invasive *Candida* infections in patients with hematooncological malignancies

Primary treatment for candidemia
Echinocandins[a]: AI
Liposomal AmB: AI
Voriconazole[b]: AI
If the patient is stable and not neutropenic + susceptible *Candida* spp +no prior azole exposure: fluconazole 800 mg/day (dose reduction to 400 mg in responders): AI
Itraconazole and posaconazole: CIII
Conventional AmB: EI[c]
Secondary treatment:
Liposomal AmB or amphotericin B Lipid complex: AII
Voriconazole, echinocandins: BIII
Hepatosplenic candidiasis:
Clinically stable patients with normal neutrophils, without prior azole exposure: fluconazole 800 mg/day: BIII
In responders: reduction to 400 mg/day: BIII
Neutropenic or unstable patients:
Liposomal AmB/AmB lipid complex: BIII
Echinocandins: BIII
Voriconazole: CIII

AmB amphotericin B

[a] Proven mainly for nonneutropenic patients

[b] Proven only for nonneutropenic patients

[c] Conventional AmB is no longer recommended as first-line antifungal agent due to significant higher toxicity with equal clinical efficacy as compared to all other compounds studied in randomized trials.

voriconazole compared to D-AmB (both followed by other licensed antifungal therapy in the case of failure/intolerance) demonstrated a significantly higher response and survival rate with fewer *Aspergillus*-related deaths and side effects, which resulted in the establishment of voriconazole as new gold standard [34] (AI). Although the study design has been questioned and improvements have been suggested, we recommend voriconazole as standard therapy for aspergillosis [AI]. In addition, compared to AmB, voriconazole is more active in vitro against *Aspergillus terreus* [32, 49]. After oral or intravenous administration, voriconazole concentrations are adequate in all body sites, including brain parenchyma [28], but a large variability in trough plasma levels has been observed [79]. Main complications are reversible visual disturbances in up to 40% of patients. Primarily due to cytochrome P450 metabolism, voriconazole may interact with a large number of other drugs. Therefore, contraindications and comedications (e.g., vinca alkaloids, statins, chinidins) have to be closely monitored. Oral and intravenous formulations are available.

Posaconazole Posaconazole was licensed in Germany for second-line therapy of aspergillosis in 2005. In a retrospective comparison of posaconazole vs standard treatments in a historical control group, patients (also including neutropenic) demonstrated a response of 42% vs 26%, respectively; the response to posaconazole was associated with plasma concentrations [113]. The response rate of posaconazole compared to high-dose AmB lipid formulations (≥7.5 mg/kg) or caspofungin plus high-dose lipid-AmB in salvage therapy for invasive aspergillosis was 40% vs 8% vs 11%, respectively, in a total of 143 patients with hematological malignancies [88]. Thus, posaconazole is recommended as salvage therapy (AII). While posaconazole was generally well tolerated, also in long-term use [86], its metabolism via cytochrome P450-system, however, has to be considered if comedications are necessary. Posaconazole is also efficacous in zygomycosis, which is frequently not distinguishable from aspergillosis in imaging procedures of lungs, paranasal sinuses, or brain. Posaconazole is only available as an oral suspension.

Itraconazole No appropriate studies with sufficient patient numbers have been conducted. For therapy of IPA in patients with persistent immunosuppression, the administration of an intravenous formulation is preferable, as this ensures a more rapid response (BIII) [106]. In a noncomparative study involving a limited number of patients, intravenous itraconazole followed by oral administration showed a response rate of 48% but had to be discontinued due to intolerability in one third of the patients [10]. Randomized studies comparing intravenous itraconazole with polyenes or other azoles in patients with IPA are not available. Since more potent and adequately investigated substances are available, itraconazole may only play a role if none of these other substances are tolerated (BIII).

Echinocandins

Caspofungin Therapy with caspofungin resulted in a response rate of 45%–49% in noncomparative salvage therapy studies of patients with invasive aspergillosis and failure of or intolerability to standard antifungal therapy [55, 64]. A case collection of 118 patients demonstrated a response rate of 61% [25]. Limited experiences in first-line treatment are available. Additionally, this therapy is proved to be very well tolerated and is recommended as salvage therapy (AII).

Micafungin Micafungin has been investigated in a mostly salvage therapy study as monotherapy and, particularly, combination therapy, which resulted in efficacy rates of about 36% [19]. The relevance of micafungin for the treatment of IA cannot be assessed as of yet (CIII).

Anidulafungin Data on anidulafungin in the treatment of invasive aspergillosis are very limited.

Amphotericin B formulations

Amphotericin B lipid complex (ABLC) A large database (CLEAR/Collaborative Exchange of Antifungal Research) showed a 44% efficacy in about 400 patients with aspergillosis (55% response in 42 neutropenic patients) [14], and 31% response in patients after allogeneic stem cell transplantation [40], mainly in patients with second-line therapy (AII).

Liposomal amphotericin B (L-AmB) In several noncomparative studies with L-AmB for second-line therapy, which, however, included only smaller patient numbers, each resulted in response rates of 50–70% [62, 92]. A pooled efficacy analysis resulted in a response rate of 47% in invasive aspergillosis [16]. In a randomized study, L-AmB was equally effective compared to D-AmB in the first-line therapy of invasive mycosis [50], but the study was not restricted to aspergillosis as well as the second-line use studies. The efficacy of L-AmB vs ABLC in the first-line therapy has been compared by an analysis of eight open label studies with more than 1,000 patients, resulting in a response of 61% vs 46% [71]. Most studies show that ABLC is more toxic. A retrospective study in 158 consecutive patients with mainly acute leukemia or alloge-

neic stem cell transplantation receiving L-AmB or ABLC for invasive aspergillosis resulted in a very poor outcome of both drug groups (12%), but about 25% of patients had a persistent neutropenia, 40% a history of transplantation and about 85% a use of corticosteroids. ABLC was associated with significantly higher nephrotoxicity compared to L-AmB [31]. The studied dosages of L-AmB for treatment of invasive aspergillosis are 1–10 mg/kg/day (manufacturer recommendation: 1–3 mg/kg) [17, 23, 50]. A randomized study comparing L-AmB 4 vs 1 mg/kg resulted in similar efficacy rates, but survival at day 14 and response in patients with proven aspergillosis was higher in the 4-mg/kg arm [23]. A randomized comparison of L-AmB 3 vs 10 mg/kg (mainly cancer patients) in primary therapy of aspergillosis showed equal efficacy and higher toxicity of the higher dosage [17], the response rate is comparable to voriconazole. We recommend L-AmB as primary therapy with less strength (AII), since the trial did not compare L-AmB with a standard treatment. Dosages higher than 3 mg/kg are not necessary (AI). L-AmB may be also used as second-line treatment (AII).

Amphotericin B deoxycholate (D-AmB) Until 2002, intravenous therapy with D-AmB had been the therapeutic gold standard with response rates of 30–50%. Maximum tolerable daily dosages of up to 1.5 mg/kg have been recommended [106]. Comparative clinical studies on dose regimens are, however, not available. In the case of a good partial response, the therapy had been frequently switched to oral itraconazole in order to facilitate outpatient treatment; however, there are no formal studies confirming this approach (CIII). Due to its high toxicity (see the chapter "invasive candidosis") and without any clinical evidence for superiority compared to the newer highly-potent antifungals, we strongly recommend avoiding D-AmB (EI) [34].

Combinations

The benefit of a combination of D-AmB plus 5-flucytosine has not been substantiated by appropriate clinical trials. There are limited data, which show a response rate of 42% for combinations of L-AmB and caspofungin as primary or salvage therapy [44], 55% for combinations with caspofungin + polyenes or triazoles in cancer patients [54], and a significantly reduced mortality rate for patients receiving caspofungin plus voriconazole vs voriconazole alone in refractory aspergillosis among stem cell transplant recipients [56]. A recently published randomized pilot-study comparing combination of L-AmB plus caspofungin (standard dosages) to high-dose L-AmB in patients with hematological malignancies resulted in a better response with the combination at the end of treatment but similar overall survival after 12 weeks, and the patient number (30) was very small [12]. The data are very limited, so combinations should be restricted to controlled clinical trials and may be considered for refractory disease and severely ill patients (CIII).

Duration of treatment

Generally, the antifungal therapy should be continued until the manifestations of IPA have been completely resolved or are reduced to residual scarring (BIII). Before the first clinical response assessment, a minimum of 14 days of full-dose treatment is recommended. Apart from clearly evident failure due in resistance of the pathogen (e.g., *A. terreus* to AmB), lack of adequate drug levels at the site of infection, intolerance, or severe organ toxicity, nonresponse of IA to an established antifungal therapy during this period should be stated with caution [57]. A temporary increase in the volume of pulmonary lesions during the first week of treatment or neutrophil recovery should not be misinterpreted as antifungal treatment failure.

Specific manifestations

Aspergillus sinusitis predominantly occurs in allogeneic stem cell transplant recipients (2–3%) and is primarily caused by *Aspergillus fumigatus* or *Aspergillus flavus* [102, 109]. Frequently, additional surgical intervention is required (BIII) [106], resulting in a higher survival rate. Overall, aspergillus sinusitis has been associated with a relatively low mortality rate of 26.1% [53]. For therapy recommendations, see IPA. While meningitis is rarely caused by *Aspergillus* spp., brain abscesses after allogeneic stem cell transplantation are most often caused by *A. fumigatus* or *A. flavus*. Comparable studies regarding drug treatment do not exist. The prior standard therapy with D-AmB is not effective [18]. The combination with 5-flucytosine (suggested due to its good blood–brain barrier penetration), has not been studied in controlled clinical trials (CIII). Due to its good permeability into the cerebrospinal fluid, voriconazole is recommended for primary treatment [94] and has shown a survival of 8 in 19 patients [20]. Single case reports describe an additional intrathecal and intracavitary administration of AmB; however, this therapy is presently not approved and the efficacy has not been appropriately validated. Successful therapy with L-AmB has also been reported in clinical trials. In animal models, L-AmB demonstrated superior penetration into brain tissue when compared to D-AmB, especially when given in higher doses. A retrospective study of 81 patients with CNS aspergillosis resulted in significantly better survival in patients undergoing surgery [99]. So, if feasible, surgical resection of singular lesions is recommended (AII). Drainage of epidural abscesses is also suggested (BIII) [106]. Cutaneous aspergillosis is a rare variant of invasive

Aspergillus infection [111]. *Aspergillus flavus* and *A. fumigatus* are the most frequent causative agents. Therapy should be initiated early and, due to missing specific trials, recommendations have to be deduced from those for IPA. In case of necrosis, surgical wound debridement should be considered (BIII) [106].

Aspergilloses occurring under posaconazole or voriconazole prophylaxis Recommendations for the treatment of invasive mycoses have to consider the prophylactic regimens, but so far, experiences or studies in this field are lacking. Therefore, the expert group recommends the switch to another class of antifungal agents (BIII).

Therapy recommendations for invasive aspergillosis are summarized in Table 3.

Most recently published updated IDSA guidelines for aspergillosis recommended voriconazole, but in contrast to our grading, L-AmB has also been recommended for first-line therapy of IPA with the level AI [112]. For salvage therapy, we agree to level AII for L-AmB but explicitly favor posaconazole (AII) and caspofungin (AII) to micafungin (insufficient data; CIII) or itraconazole (less well studied and tolerated than posaconazole; BIII). The IDSA assessed all these compounds with the level BII.

Cryptococcus neoformans infections

Cryptococcosis is rare in cancer patients [45, 60]. However, an infection may occur along with T-cell defects or following a CD4-lymphocyte-depleting therapy. D-AmB (0.7–1 mg/kg) plus 5-flucytosine (100 mg/kg) for 2 weeks followed by maintenance therapy with fluconazole 400 mg/day for 10 weeks is the recommended antifungal treatment of cryptococcal meningitis in HIV-infected patients (see Table 4) (AI) [5, 8, 38, 84, 95]. Data about AmB lipid formulations are limited. Initial treatment with L-AmB (4 mg/kg/day) compared to D-AmB (0.7 mg/kg/s), both followed by fluconazole, showed a more rapid eradication of *Cryptococcus* from the cerebrospinal fluid within the first 14 treatment days (AI) [51]. ABLC demonstrated a total response of 66% in 101 patients, 75% in 44 cases of first-line therapy (BII) [4]. Posaconazole was effective in 14 from 29 patients [83]; voriconazole data are very limited (CIII). In isolated pulmonary cryptococcosis, fluconazole 200–400 mg for 6–12 months may be sufficient (AIII) [45, 95]; alternatively, itraconazole 200–400 mg may be used (BIII). Treatment should be continued for at least 12 weeks and prolonged in case of delayed response (positive culture of cerebrospinal fluid after 2 weeks of therapy) (CIII). The duration of maintenance therapy should consider the individual immune status of the patient.

Table 3 Therapy of aspergillus infections in hematooncological patients

Primary treatment of IPA
Voriconazole: AI, switch to oral therapy if clinically justified
Liposomal AmB: AII, dosage 3 mg/kg: AI
Conventional AmB: EI
Secondary treatment:
Generally: switch to another class of substance
Caspofungin: AII
Posaconazole: AII
ABLC: BII
Itraconazole: only if no other *aspergillus*-effective substance may be tolerated: BIII
Micafungin: CIII
Sinusitis: see IPA, + surgical intervention, if indicated: BIII[a]
CNS: voriconazole (see IPA), alternatively high dose L-AmB(at least 5 mg/kg), surgical intervention if feasible (AII)[a]

IPA invasive pulmonary aspergillosis, *AmB* amphotericin B, *ABLC* amphotericin B lipid complex

[a] Downgrading compared to IPA (lower patient numbers published)

Zygomycosis

Zygomycosis is a rare disease with a fatality rate up to 90% in neutopenic patients [75], who have mainly pulmonary manifestations [93]. Recently, reports on breakthrough zygomycoses in patients with voriconazole therapy have been published. In a retrospective survey of 59 cases, L-AmB was found to be a favorable prognostic factor [75]. Attempts to achieve high concentrations of AmB at the site of infection might be beneficial, but there is a lack of solid data on daily dosages required for effective therapy. Experts recommended L-AmB with doses of at least 5 mg/kg (BIII). ABLC showed a response of 72% in 64 immunosuppressed patients [48]. Additional surgical intervention resulted in a lower fatality rate as compared with antifungal therapy alone (11% vs. 60%) (BIII) [75, 107]. Twelve of 20 patients using ABCD had a favorable outcome [36]. The benefit of combination is unclear. In salvage treatment, posaconazole is effective with response rates of about 50–80% [9, 27].

Table 4 Treatment of *Cryptococcus neoformans* infections in patients with malignancies

Central nervous system:
Very limited data; analogs to HIV-infected patients:
cAmB plus 5-flucytosin or AmB-lipidformulation followed by maintenance therapy with fluconazole: BIII
Voriconazole or posaconazole: CIII
Pulmonary infection:
Fluconazole: AIII
Itraconazole BIII

AmB amphotericin

The recommendations for treatment of zygomycosis are listed in Table 5. An overview of the recommended dosages of antifungal substances is given in Table 6.

Interventional strategies

Surgical intervention

The following may be potential indications for a possible surgical intervention in pulmonary fungal infection: (1) acute hemoptysis, (2) histological diagnostics, (3) removal of residuals prior to the next chemotherapy cycle, and (4) prevention of bleeding in the case of fungal lesions with vessel involvement. Hemoptysis occurs in pulmonary aspergillosis or mucormycosis in up to 30% of cases, frequently during the phase of neutrophil recovery. The fatality rate is approximately 10%. A successful procedure in 18 of 19 patients and a reduction of the mortality from 41% to 14% after introduction of systemic computed tomography (CT)-examinations combined with frequent use of surgical resections has been noted compared to a historical control in a monocenter study [6, 11]. In 41 patients with hematologic diseases undergoing surgical intervention of IPA, the mortality within 30 days was about 10%, fungal relapse occurred in 10%, and the overall survival at 6 months was 65%. Perioperative complications did not influence the outcome [59]. If a patient is considered at high risk for bleeding, i.e., contact of the lesion with the pulmonary artery in the CT scan, a lung resection should follow immediately. The resection of residual infiltrations, combined with antifungal therapy, may result in a local control of the fungal infection in patients requiring further intensive chemotherapy or transplantation [67]. Experience in surgical treatment of IPA, however, are based on the cAmB era; with the new antifungal agents, surgical intervention has less importance. Therefore, we recommend surgical resections for special circumstances, analog to IDSA guidelines (BIII).

Resection recommendations for CNS or sinus mold infections are described elsewhere. In sinonasal aspergillosis, additional surgical intervention may be necessary in individual cases (BIII) [106, 112]. A retrospective study of 81 patients with CNS aspergillosis resulted in significantly better survival in patients undergoing surgery [99]. So, if feasible, surgical resection of singular lesions is recommended (AII).

Table 5 Therapy of zygomycosis in hematooncologic patients

Lungs:
Liposomal AmB: AII, dosage at least 5 mg/kg: BIII
ABLC: AIII
Posaconazole: AIII
Posaconazole as maintenance therapy in patients with a partial response: CIII
CNS or sinus involvement
Additional surgical intervention, if feasible: BIII

Table 6 Daily dosages of recommended antifungals for treatment of invasive mycosis

Caspofungin: 50 mg, body weight >80 kg: 70 mg
Liver cirrhosis Child–Pugh-Score 7–9: 35 mg, >9: no data
Loading dose day 1: 70 mg
Micafungin: 100 mg
Anidulafungin: 100 mg (loading day 1: 200 mg)
Liposomal AmB: 3 mg/kg
Zygomycosis: at least 5 mg/kg
CNS manifestations: >3 mg/kg
AmB lipid complex: 5 mg/kg
Voriconazole: iv: 2×4 mg/kg; if not tolerable: 2×3 mg/kg; liver cirrhosis: see below
Creatinine-clearance <50 ml/min: preferably only oral therapy
Loading day 1: 2×6 mg/kg
po: 2×200 mg; body weight <40 kg: 2×100 mg; liver cirrhosis: see below
Loading: 2×400 mg; body weight <40 kg: 2×200 mg
Liver cirrhosis Child–PughA–B: 50% dosage.
Child–Pugh C: no data
Posaconazole: 2×400 mg; 4×200 mg in case of insufficient enteral nutrition
Fluconazole: iv/po: 800 mg, switch to 400 mg, if clinically justified; therapy start preferably with iv-formulation; creatinin clearance 11–50: 48 h-interval or 50% dosage
Itraconazole: iv: 200 mg, po: 2×200 mg
Loading dose: iv: day 1–2: 2×200 mg;
po: day 1-(3)-5: 3–4×200 mg
5-flucytosine: 150 mg/kg divided into 4 doses

Drug instillation

For treatment of refractory abscesses or caverns (e.g., in the lungs or brain) in which surgical intervention is not feasible, a drainage, as well as a local drug instillation, can be considered. Here, antifungal preparations (commonly containing AmB) or disinfecting substances such as sodium- or potassium-iodide are administered (CIII).

Embolization

Embolization may be considered in the case of large pulmonary infiltrates where the occurrence of hemoptysis due to vessel erosion is likely, including the development of aneurysms. The vessel involvement of fungal lesions should be diagnosed by a spiral CT. If confirmed, the bronchial and pulmonary vessels can be radiologically embolized (CIII) [37].

Immunotherapy and granulocyte transfusion

Studies investigating the prophylactic use of granulocyte (-macrophage) colony stimulating factor in hematological patients have shown a definite reduction of the number and severity of bacterial and fungal infections. A benefit from interventional use is not substantiated [68]. The application of hematopoietic growth factor should be considered on an individual case-by-case basis, according to the recommendations of the American Society of Oncology (B III) [103]. Interferon-γ showed a trend to more rapid sterilization of cerebrospinal fluid in cryptococcus meningitis of AIDS patients [76], and the benefit in invasive mycoses after stem cell transplantation is doubtful [97]. Due to the very limited patient numbers, the benefit is not clarified so far (C III). Studies with ligands to toll-like receptors, mycograb (recombinant antibody against Candida heat shock protein 90), or adoptive immunotherapy are ongoing [100]. A study from the Perugia Group showed a more rapid reduction in the galactomannan antigen titer and a better outcome in patients with IPA after haploidentical stem cell transplantation (when receiving T cells raised against fungal pathogens) [81]. Further studies with the transfer of immune-effector cells and better tools to determine the numbers of fungus-specific T cells prior and after cellular immunotherapy are urgently required.

Granulocyte transfusions In comparison to the 1980s, the granulocyte harvest and granulocyte function have clearly improved by stimulating the donor with G-CSF. Presently, interventional granulocyte transfusions are being studied in clinical trials. In a retrospective case controlled study on 74 stem cell transplant patients, there was a tendency toward worse outcome in the transfused patients [39]. Another case-controlled study in patients with candidemia showed an equal short-term survival rate, but the group with granulocyte transfusions had higher risk factors, which may be interpreted as a benefit of this option [96]. In 31 patients with invasive fungal infection (17 possible) undergoing granulocyte transfusions, 78% survived [65].

A randomized study with granulocyte transfusion in patients with invasive fungal infections including probable and proven invasive fungal infections during neutropenia after stem cell transplantation or antileukemic therapy had to be closed prematurely due to a dropping recruiting rate after the availability of several new and less toxic antifungal agents. A randomized study with granulocyte transfusion thrice a week in patients with neutropenic fever and pulmonary infiltrates or a history of proven invasive fungal infection (most included episodes were definite or probable invasive fungal infections) failed to confirm the benefit of this procedure [101]. By now, the real benefit of granulocyte transfusion in invasive mycoses is not doubtlessly clarified [85], but this option may be considered in very severe refractory infection courses (BIII).

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