Ann Hematol (2014) 93:13–32
DOI 10.1007/s00277-013-1867-1

ORIGINAL ARTICLE

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

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Received: 14 May 2013 / Accepted: 29 July 2013 / Published online: 12 September 2013

Abstract The Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) here presents its updated recommendations for the treatment of documented fungal infections. Invasive fungal infections are a main cause of morbidity and mortality in cancer patients undergoing intensive chemotherapy regimens. In recent years, new antifungal agents have been licensed, and agents already approved have been studied in new indications. The choice of the most appropriate antifungal treatment depends on the fungal species suspected or identified, the patient's risk factors (e.g., length and depth of neutropenia), and the expected side effects. This guideline reviews the clinical studies that served as a basis for the following recommendations. All recommendations including the levels of evidence are summarized in tables to give the reader rapid access to the information.

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Keywords Mycoses · Antifungal agents · Aspergillosis · Invasive candidiasis · Hematologic malignancies

Introduction

In cancer patients, invasive fungal disease (IFD) remains an important complication causing considerable mortality and morbidity. Chemotherapy or transplantation procedures are often delayed or postponed in patients with IFD which might lead to impaired overall survival. In recent years, new antifungal agents have been licensed or agents already approved have been studied in new indications, which is why the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) here presents its updated recommendations.

The current version of the guideline focuses on patients with solid tumors or hematologic malignancies and includes treatment of acute invasive infections caused by the species *Aspergillus*, *Candida*, *Cryptococcus*, *Scedosporium*, *Fusarium*, *Zygomycetes*, and *Trichosporon*. Chronic or superficial fungal infections were excluded. We hereby give an overview of the treatment options for invasive fungal disease and classify the recommendations according to their evidence level.

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Methods

Data Clinical studies and guidelines published in English were searched via Medline from 1990 up to June 2012. Studies published in form of abstracts were only considered if their data lead to a change in the level of recommendation for a given treatment.

Evidence criteria Wherever possible, evidence categories of the "Infectious Diseases Society of America" (IDSA) were integrated (Table 1) [80]. Evidence levels for treatment in neutropenic patients were "downgraded" (e.g., from AII to BII) if available studies only included a small proportion of neutropenic patients or no neutropenic patients at all.

Assessment of license The status of license for the presented medications was not considered, and substances are solely recommended based on available clinical study data. Therefore, the responsibility for a selected therapy is exclusively that of the ordering physician. Currently used dosages of available fungal agents are listed in Table 6.

Finding consensus These recommendations were first prepared by a panel of experts in the field of infections in immunocompromised patients during two meetings and then circulated via e-mail. All recommendations and evidence levels were then voted first via e-mail and then during a meeting of the AGIHO consensus group general assembly.

Treatment of invasive *Aspergillus* infections

Acute invasive pulmonary aspergillosis (IPA) is the most frequent manifestation of systemic aspergillosis in

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. Criteria of the IDSA [80]

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

neutropenic patients [162] with a fatality rate that ranges from 30 to 60 % [11, 116, 123]. Early treatment at first signs of infection is mandatory and improves the chance of survival (BIII) [25].

Neutropenic patients Although data are limited, the response to liposomal amphotericin B is reduced by >20 % in the neutropenic host (43 %) as compared to non-neutropenic patients (67 %) with invasive aspergillosis as compared to voriconazole where response rates were similar in patients with and without neutropenia (50.8 vs. 54.3 %, respectively) [35, 65].

Antifungal therapy

Azoles

Voriconazole In an open, non-comparative study, voriconazole showed a response rate of 59 % in the primary treatment of invasive aspergillosis and a 38 % response rate when used for salvage treatment [41]. The randomized comparison between voriconazole and amphotericin B deoxycholate (D-AmB) (both followed by other licensed antifungal agents in the case of failure/intolerance) included patients with a malignant underlying disease or another immunocompromising condition. In this study, voriconazole had a significantly higher response and survival rate including less *Aspergillus*-related deaths and side effects than D-AmB. Since then, voriconazole has been established as the gold standard for treatment of invasive aspergillosis [65, 186]. Although the study design has some limitations (e.g., lack of details of administered antifungal agents in the comparator arm and inclusion of cases without sufficient evidence for IFD), we recommend voriconazole as the standard therapy for aspergillosis (AI). In case of a different first-line therapy, voriconazole is recommended for salvage treatment of invasive aspergillosis (BII). In an observational efficacy and safety analysis, clinical response with voriconazole as monotherapy was observed in 42/72 patients [76]. In addition, voriconazole is more active in vitro against *Aspergillus terreus* compared to D-AmB [59, 91].

After oral or intravenous administration, adequate concentrations of voriconazole were documented in many body sites including brain parenchyma [56]. However, a large variability in trough plasma levels has been observed [130]. A recent study demonstrated a positive correlation between plasma levels, clinical efficacy, and toxicity. Plasma concentrations of >1 mg/L were found to be correlated with response to therapy. However, plasma levels >5.5 mg/L were associated with neurotoxicity [131]. Therapeutic concentrations could only be achieved with a dose of 2×200 mg oral voriconazole in about 50 % of patients, increasing to about 70 % with 2×300 mg and nearly 100 % with 2×400 mg given [131] (see also "Therapeutic drug monitoring of antifungal agents" section).

Main side effects of voriconazole therapy are reversible visual disturbances in up to 40 % of patients. Primarily due to cytochrome P450 metabolism, voriconazole can interact with a large number of other drugs. Therefore, contraindications and co-medications (e.g., vinca alkaloids, statins, chinidin) have to be monitored closely.

Posaconazole Posaconazole was licensed for second-line therapy of aspergillosis in 2005 by EMA. In a retrospective comparison of posaconazole versus standard treatment (e.g., AmB lipid formulations and itraconazole) in a historical control group, patients (including neutropenic patients) demonstrated a response rate of 42 versus 26 %, respectively [189]. The response to posaconazole correlated with plasma concentrations [189]. Additionally, in a retrospective not stratified investigation, the response rate of posaconazole compared favorably to high-dose AmB lipid formulations (≥7.5 mg/kg) or caspofungin plus high-dose lipid-AmB in salvage therapy for invasive aspergillosis. Response rates were 40 versus 8 versus 11 %, respectively, in 143 patients with hematological malignancies [140]. Thus, posaconazole is recommended as a salvage therapy in this patient group (BII). Posaconazole is generally well tolerated, also in long-term use [138]. The drug is a substrate of both uridine diphosphate glucuronosyltransferase and the transporter P-glycoprotein, but is not significantly metabolized by cytochrome P450, although the compound inhibits isoenzyme 3A4 [50, 192]. Therefore, different potential interactions have to be considered if co-medications are given. Posaconazole also demonstrates activity in mucormycosis, which is clinically difficult to distinguish from aspergillosis of the lungs, paranasal sinuses, or CNS [181]. Up to now, posaconazole is only available as an oral suspension and should be administered with food. The co-medication with a proton pump inhibitor might limit the posaconazole exposure.

Echinocandins

Caspofungin A phase II study of caspofungin as first-line therapy demonstrated survival rates of 66 % (6 weeks) and 53 % (12 weeks) in 61 patients with hematologic malignancies [184]. Most patients were not in remission of their underlying disease, 72 % presented with severe neutropenia for >10 days, and in contrast to other studies, aspergillosis had to be proven or probable strictly according to European Organization for Research and Treatment of Cancer (EORTC)-MSG criteria [10]. An EORTC study in allogeneic stem cell-transplanted patients was stopped due to inadequate recruitment with 42 patients enrolled. At week 6 and week 12, the survival rate was 79 and 50 %, respectively [68]. In a prospective observational registry, 12 out of 20 patients responded to caspofungin first-line treatment [98]. In summary, the AGIHO working group considers caspofungin as a therapeutic option in the first-line therapy (CII) (vote, 7:4, 3 abstentions).

When used for salvage treatment, caspofungin resulted in a response rate of 45–49 % in two non-comparative studies of patients with invasive aspergillosis and failure of or intolerability to standard antifungal therapy [100, 112]. A case collection of 118 patients demonstrated a response rate of 61 % [52]. In the CAN-DO study, 45/81 patients responded to caspofungin treatment [98]. As caspofungin is well tolerated, it is recommended for salvage therapy (BII).

Micafungin Micafungin has been investigated mostly in salvage therapy studies and retrospective analyses as mono- and particularly combination therapy which resulted in efficacy rates of about 25–36 % [40, 82]. Therefore, the role of micafungin in the treatment of acute invasive aspergillosis has not been clarified so far (CII).

Anidulafungin Data on anidulafungin as a monotherapy for the treatment of invasive aspergillosis are too limited to allow inclusion of this drug into therapy algorithms of invasive aspergillosis (see "Combination therapy" section).

Amphotericin B formulations

Amphotericin B lipid complex (ABLC) A retrospective analysis of a large company-based dataset (Collaborative Exchange of Antifungal Research) showed a 44 % efficacy in about 400 patients with IA (55 % response in 42 neutropenic patients) [31] and 31 % response rate in patients after allogeneic stem cell transplantation [74], mainly in patients with second-line therapy (BII). There are no sufficient data for first-line therapy (CIII).

Liposomal amphotericin B (L-AmB) Several non-comparative studies with L-AmB for second-line therapy exist which included only smaller numbers of patients and resulted in response rates of 50–70 % [108, 147]. In a pooled efficacy analysis, this resulted in a response rate of 47 % for the treatment of invasive aspergillosis [32]. In a randomized study, L-AmB was equally efficacious compared to D-AmB in the first-line therapy of invasive mycosis [92], but the study was not restricted to patients with IA. The efficacy of L-AmB versus ABLC in the first-line therapy has been compared in an analysis of eight open-label studies with more than 1,000 patients resulting in a response rate of 61 versus 46 % favoring L-AmB over ABLC [121]. A retrospective study in 158 consecutive patients with mainly acute leukemia or allogeneic stem cell transplantation receiving L-AmB or ABLC for invasive aspergillosis resulted in a poor outcome of both groups (12 %) [58]. ABLC was associated with significantly higher nephrotoxicity compared to L-AmB [58].

The studied dosages of L-AmB for treatment of invasive aspergillosis are 1–10 mg/kg/day (manufacturer recommendation, 1–3 mg/kg) [35, 43, 92]. A randomized study comparing L-AmB 4 versus 1 mg/kg resulted in similar efficacy rates, but survival at day 14 and response in patients with proven aspergillosis were higher in the 4-mg/kg arm [43]. A randomized comparison of L-AmB 3 versus 10 mg/kg (mainly cancer patients) in first-line therapy of invasive aspergillosis showed equal efficacy but an increased toxicity with the higher dosage [35]. The response rate was high and comparable to voriconazole.

In summary, we recommend L-AmB (3 mg/kg) for the first-line treatment with lesser strength than voriconazole (AII), since all available trials did not compare L-AmB with a standard treatment. L-AmB may be also used as second-line treatment (BII) [180].

Amphotericin B deoxycholate (D-AmB) Until 2002, intravenous therapy with D-AmB had been the therapeutic gold standard for IA with response rates of 30–50 %. Maximum tolerable daily dosages of up to 1.5 mg/kg have been recommended. Comparative clinical studies on dose regimens are, however, not available. Due to its high toxicity and inferiority compared to voriconazole in a randomized controlled study [65], we strongly recommend not to use D-AmB (EI).

Combination therapy

The benefit of combination of D-AmB plus 5-flucytosine has not been substantiated by appropriate clinical trials. There are limited data from uncontrolled trials with response rates of 42 % for combinations of L-AmB and caspofungin as primary or salvage therapy [81], 55 % for combinations of caspofungin and polyenes or triazoles in cancer patients [99], and a significantly reduced mortality rate for patients receiving caspofungin plus voriconazole versus voriconazole alone in refractory aspergillosis in a historically controlled trial among stem cell transplant recipients [102]. A randomized pilot study comparing the 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 number of patients included ($n=30$) was rather small [27]. A recent large prospective randomized trial comparing voriconazole monotherapy to voriconazole plus anidulafungin for first-line therapy did not show any superiority of the combination for the primary endpoint of overall survival at week 6. In a post hoc analysis for patients with galactomannan-positive aspergillosis, survival at week 6 was significantly better in the group with the combination treatment. These data have not been published in a peer-reviewed journal, and therefore, up to now final assessment cannot be made (Marr abstract ECCMID 2012, LB 2812) (CIII). In summary, data of combination treatment regimens are very limited, so that combinations cannot generally be recommended and may be considered for refractory disease and/or severely ill patients (CIII).

Salvage therapy

It is important to differentiate between a replacement of first-line therapy with another substance because of toxicity from change of substance due to refractory infection. Generally, given a stable clinical situation, a minimum of 14 days of full-dose treatment is recommended before a reliable first clinical response assessment can be done.

Apart from evident failure due to intrinsic resistance of the pathogen (e.g., *A. terreus* to AmB), lack of adequate drug levels (see "Therapeutic drug monitoring of antifungal agents"), intolerance, or severe organ toxicity, non-response of IA to an established antifungal therapy should be stated with caution [104, 163]. A temporary increase in the volume of pulmonary lesions during the first week of treatment or neutrophil recovery must not be misinterpreted as antifungal treatment failure [26]. Since most available studies for salvage therapy included patients who failed to respond to D-AmB as a first-line treatment, no general conclusion can be drawn to salvage treatment after failure of newer antifungal agents (e.g., triazoles and echinocandins) (CIII).

Invasive aspergillosis occurring during posaconazole or voriconazole prophylaxis Recommendations for the treatment of invasive mycoses have to consider the prophylactic regimens, but so far, studies in this field are lacking. Therefore, the expert group recommends the switch to another class of antifungal agent, but to take into account an inadequate exposition to the prophylactic agent (CIII).

Duration of antifungal treatment

Generally, the antifungal therapy should be continued during the period of neutropenia and until the manifestations of IA have been completely resolved or are reduced to residual scarring, up to 12 weeks [65] (BIII).

Other manifestations

Invasive sinus aspergillosis Severe *Aspergillus* sinusitis most often occurs in allogeneic stem cell transplant recipients (2–3 %) and is primarily caused by *Aspergillus fumigatus* or *Aspergillus flavus* [42, 182]. Frequently, additional surgical debridement is required (BII) (see "Interventional strategies"). Overall, *Aspergillus* sinusitis has been associated with a mortality rate of 26.1 % while treated with AmB formulations [95]. Therapy recommendations do not differ from pulmonary manifestations (see Table 2).

Aspergillosis of the CNS Aspergillus spp. rarely cause meningitis or micro-abscesses of the brain, but macro-abscesses—especially in severe immunosuppressed patients—are most often caused by *A. fumigatus* or *A. flavus*. Patients with aspergillosis within the CNS typically present with focal neurological signs such as pareses or seizures. Comparable studies regarding drug treatment of CNS aspergillosis do not exist, but it is clear that the prior standard therapy with D-AmB is not effective [161]. Due to its good permeability into the cerebrospinal fluid, voriconazole is recommended for primary treatment [152] and has shown a survival rate of 30–40 % [41, 159, 160] (AII). Successful therapy with L-AmB has also been reported in case reports [77, 161] and might be administered in case of contraindication, intolerance, or poor response to voriconazole (BIII). A retrospective study of 81 patients with CNS aspergillosis resulted in significantly better survival in patients undergoing surgery [160]. Therefore, surgical resection of singular lesions is recommended together with systemic antifungal treatment (AII).

Table 2 Treatment of invasive *Aspergillus* infections in hemato-oncological patients

First-line treatment of invasive pulmonary aspergillosis	
Voriconazole	AI
Liposomal AmB	AII
Caspofungin	CII
Micafungin	CII
ABLC	CIII
Anidulafungin + voriconazole	CIII
D-AmB	EI
Second-line treatment of invasive pulmonary aspergillosis	
Voriconazole	BII
Caspofungin	BII
Posaconazole	BII
Liposomal AmB	BII
ABLC	BII
Micafungin	CIII
Voriconazole + caspofungin	CIII
CNS infection	
Voriconazole	AII
Liposomal AmB (≥5 mg/kg)	BIII
Surgical intervention	AII
Sinusitis	
Antifungals: see invasive pulmonary aspergillosis	
Surgical intervention	BII

Treatment of invasive *Candida* infections

The most common causes of IFD in cancer patients are yeast pathogens, in particular *Candida albicans*, followed by non-*Candida albicans* species (e.g., *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*) [122, 151, 183]. In patients with hematological malignancies primarily

non-*Candida albicans* species (e.g., *C. tropicalis*, *C. glabrata*) have been identified in most studies [83, 174, 183]. The proper identification of the infecting *Candida spp.* is crucial for the choice of antifungal therapy (e.g., fluconazole-resistant *Candida spp.*) [178]. Due to frequent colonization with *Candida* species in hospitalized patients, detection of yeasts in non-sterile material is not sufficient to confirm invasive *Candida* infection. Colonization index and *Candida* scores have been developed to predict invasive *Candida* infections for non-neutropenic patients in the ICU [94], but are not validated for patients with hematological malignancies. In patients with acute leukemia, the degree of mucosal damage and profound neutropenia are the most important risk factors for invasive *Candida* infection in contrast to other patient groups at risk for IFD with other "classical" risk factors (e.g., central venous catheters) [23, 141]. The high pathogen-related mortality, which may approach 50 %, should prompt immediate initiation of therapy in all patients with suspected yeasts in the blood culture, as delays in treatment result in an increased mortality [48, 111].

Neutropenic patients Although data are limited, the response rate as shown for therapy with echinocandins or amphotericin B formulations is reduced by approximately 15–20 % in neutropenic host as compared to other (non-neutropenic) patients with candidemia [86, 110, 128]. According to data from a large cohort study in patients treated with ABLC, a favorable clinical response was observed in 61 % of all patients infected with *Candida* species, but was as low as 20 % in patients who were neutropenic at the time of diagnosis or became neutropenic during antifungal treatment [75].

Antifungal therapy

Azoles

A randomized clinical trial [5] and a cohort study [7] did not show a significant difference in antifungal efficacy between fluconazole (400 mg daily) and D-AmB (25–50 mg daily; 0.67 mg/kg daily) in neutropenic patients with systemic *Candida* infection. There was a trend to a lower response to antifungal treatment in patients with neutrophil counts ≥1,000/μl at enrolment treated with fluconazole (58 %) as compared to D-AmB (74 %). However, in the small subset of patients with neutrophil counts <1,000/μl, fluconazole appeared to be superior to D-AmB (response rate 77 % for fluconazole vs. 48 % for D-AmB).

Due to the better in vitro susceptibility of voriconazole in non-*Candida albicans* species, this agent may provide an alternative to fluconazole, but only data from salvage therapy studies are available [135]. Neutropenic patients were not included in a randomized trial comparing voriconazole to the regimen of D-AmB followed by fluconazole in the primary treatment of candidemia [85]. Data on the effect of itraconazole and posaconazole in candidemia are lacking.

Amphotericin B formulations

The major disadvantages of D-AmB are nephrotoxicity, hypokalemia, and acute infusion-related side effects. Increasing number of publications report long-term nephrotoxicity with D-AmB resulting in inferior survival especially in stem cell transplant patients [16, 61, 107, 180, 196].

A recent study comparing L-AmB with micafungin for first-line treatment of invasive *Candida* infections demonstrated a high efficacy of L-AmB [86]. Overall success at the end of therapy was 89.6 % for micafungin and 89.5 % for L-AmB, respectively. Efficacy was independent of the *Candida* spp. and primary site of infection, as well as neutropenia status, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and central venous catheter removal.

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 invasive *Candida* infections [121]. Amphotericin B colloidal dispersion (ABCD) is unavailable in Germany, and tolerability is less favorable when compared to ABLC or L-AmB.

Echinocandins

The results of a study comparing fluconazole (800 mg on day 1 and then 400 mg daily) versus anidulafungin (200 mg on day 1 and then 100 mg daily) demonstrated superiority of anidulafungin (response rate 75 vs. 60 %) in the treatment of candidemia and invasive *Candida* infections in a general population with only few neutropenic patients (3 %) [143]. Anidulafungin fulfilled the criteria for non-inferiority in non-neutropenic patients (AI). A subgroup analysis demonstrated the superiority of anidulafungin compared to fluconazole in patients diagnosed with *C. albicans* infections (95 vs. 81 %).

In general, echinocandins (anidulafungin, caspofungin, and micafungin) have been tested for the treatment of candidemia in various controlled clinical trials [86, 110, 143], but the number of neutropenic patients in these trials was limited (max. 10 %).

A direct comparison of caspofungin and micafungin showed similar efficacy and safety. In addition, no difference in safety or efficacy was seen in patients treated with two different dosages of micafungin (100 or 150 mg/day) [128]. Further studies comparing one echinocandin to another echinocandin are lacking.

Higher dosages of caspofungin (150 vs. 70/50 mg/day) and micafungin (150 vs. 100 mg/day) showed a trend towards improved efficacy in subgroups of patients (APACHE II score >20, neutropenia) and might be used in selected patients [19, 36, 128].

A reduced sensitivity to fluconazole ("susceptible dose dependent") is frequently seen in *Candida* species such as *C. glabrata* and *C. tropicalis*. Non-*Candida albicans* infections

are more common in patients with hematologic malignancies than in those with solid tumors, which favors initial broad-spectrum antifungal therapy with an echinocandin (e.g., anidulafungin, caspofungin, or micafungin) in this patient group (BI) [66].

A switch to (oral) fluconazole (800 mg/day as loading dose, followed by 400 mg/day) or voriconazole (6 mg/kg bid as loading dose, followed by 4 mg/kg bid) is optional. If a susceptible species has been confirmed, the patient is clinically stable and has no prior azole exposure (BII) [127].

In summary, due to its good efficacy especially against non-*Candida albicans* spp. as well as its good safety profile and the importance of a fungicidal mode of action, echinocandins or L-AmB may be regarded as the drug of choice in severely ill, clinically instable patients with organ dysfunction, especially in patients with neutropenia (BI). For non-neutropenic patients, data on echinocandins, liposomal AmB, and voriconazole allow a recommendation level of AI (see Table 3). In non-neutropenic patients with no prior azole exposure, fluconazole is an alternative for the treatment of yeasts in the blood culture while awaiting susceptibility tests (AI; vote, 8:4; abstentions, 2) (see Table 3).

Combination therapy

In non-neutropenic patients, the combination of fluconazole (800 mg per day) plus placebo with fluconazole plus D-AmB (0.7 mg/kg per day, with the placebo/D-AmB component given only for the first 5–6 days) did not show antagonism, a similar mortality but improved clinical outcome (69 % for Flu/D-AmB vs. 56 % for Flu/Placebo) and more rapid eradication of yeasts from bloodstream compared to fluconazole alone [146]. However, in patients with cancer or hematological malignancies, there are no data about combination therapies for invasive *Candida* infections.

Table 3 Treatment of invasive *Candida* infections in hemato-oncological patients

Candidemia	
Neutropenic patients	
Echinocandins	BI
Liposomal AmB	BI
Non-neutropenic patients	
Echinocandins	AI
Liposomal AmB	AI
Voriconazole	AI
Fluconazole	AI
Hepatosplenic candidosis	
Neutropenic patients	
Liposomal AmB/ABLC	BIII
Echinocandins	BIII
Voriconazole	CIII
Non-neutropenic patients	
Fluconazole[a]	BIII
Steroids	CIII

[a] If no prior azole exposure

Salvage therapy

Data on second-line therapy in cancer patients, in particular during neutropenia, are limited to case reports and specific recommendations cannot be given.

Duration of antifungal therapy

Duration of treatment in non-neutropenic patients is recommended for at least 14 days after the first negative blood culture and resolution of signs and symptoms of candidemia (BIII) [127, 153, 178], but should be adapted in case of organ manifestations.

Acute disseminated candidosis

Acute disseminated candidosis is the most severe form of systemic *Candida* infection in neutropenic patients. It is characterized by hemodynamic instability, persistent positive blood cultures, and deep organ and/or skin involvement. Patients present with sepsis, spiking fever, shaking chills, and disseminated lesions of the skin and sometimes other organ infections such as endophthalmitis or osteomyelitis [18, 109]. Echinocandins and L-AmB are recommended as initial antifungal treatment (BIII).

In addition to fundoscopy, an abdominal ultrasound (liver, spleen, kidneys) should be performed in neutropenic patients with candidemia after bone marrow recovery to exclude chronic disseminated infection/hepatosplenic candidosis that may not be associated with clinical symptoms other than fever (BIII).

Management of intravenous lines

Intravenous lines should be removed at initiation of antifungal therapy whenever feasible (AII). If the central venous lines are retained, the duration of candidemia increases (from 3 to 6 days) as does the mortality of patients [22, 87, 145, 193]. The role of central venous catheter removal in neutropenic patients is controversial as the gastrointestinal mucosa, damaged by cytotoxic chemotherapy, is thought to be the main port of entry for yeasts [6, 142, 198]. However, as the central venous line might be colonized, it is recommended that it should be removed also in neutropenic patients (AII). If the catheter has to be kept in place, patients should be treated with an echinocandin or L-AmB (CII) as these agents have a better minimal inhibitory concentration in biofilms [84].

Chronic disseminated candidosis (CDC)

If fever persists after neutrophil recovery, hepatosplenic candidosis should be considered in hematological patients. CDC is usually not an acute life-threatening condition but may require systemic antifungal therapy for months. After stabilization of signs and symptoms, CDC is not a contraindication for the continuation of chemotherapy or hematopoietic stem cell transplantation [78, 125].

Data on antifungal treatment in patients with CDC are limited to case series with D-AmB given as a single therapy or in combination with flucytosine [172, 191], lipid formulations of amphotericin B [190], fluconazole [3, 79], or caspofungin [34]. Due to the need for prolonged antifungal therapy, oral agents such as fluconazole (400–800 mg/day) are recommended if the *Candida* strain was isolated and proven to be susceptible (BIII). Echinocandins or L-AmB should be used as initial therapy in unstable or refractory patients (BIII). Voriconazole is an alternative option (CIII). The duration of antifungal therapy in patients with CDC should be individualized and may be continued until the resolution of all radiographic signs or calcification of the lesions. In contrast, newer data suggest that hepatosplenic candidosis may represent an immune reconstitution syndrome as steroids (in addition to antifungal treatment) can lead to a rapid resolution of clinical signs [93] (CIII). In stable patients, intravenous therapy may be switched to oral medication (step down strategy). This strategy has not been studied in CDC so far, but is regarded as safe and effective in patients with candidemia (see above).

Other manifestations

CNS CNS infections caused by *Candida* spp. might be treated with L-Amb (BIII) or voriconazole (BIII) [70, 115, 157]. Animal studies show a better penetration of L-AmB into the brain tissue as compared to ABLC [57]. Fluconazole might be a treatment option for CNS *Candida* infection if the patient is clinically stable, without prior azole exposure, not neutropenic, and if sensitivity to this agent has been documented by in vitro resistance testing (CIII). Preclinical data further suggest that echinocandins (e.g., caspofungin) may be useful to treat *Candida* infections of the CNS albeit the poor CNS penetration of these agents have to be taken in account—at least if the blood–brain barrier is intact [45].

Treatment should be continued for an additional 4 weeks following the resolution of manifestations (BIII) [124, 127]. In case of a brain abscess, additional drainage or surgical resection is recommended.

Urinary tract For urinary tract *Candida* infection, fluconazole has been proven in mainly non-neutropenic patients and is the drug of choice, if a susceptible *Candida* spp. is cultured (AI). If a urine catheter is in place, it should be removed (BII) [127, 153].

Treatment of mucormycosis

Mucormycosis is an emerging invasive fungal infection in patients with hematological malignancies and allogeneic stem cell transplantation. In neutropenic patients, it usually involves the lung and causes high mortality rates. The clinical presentation is difficult to distinguish from invasive pulmonary aspergillosis [126, 148]. A reverse halo or atoll sign has been described on computed tomography scans, but is not specific for mucormycosis. Such ring-shaped consolidation surrounding a central infiltrate should prompt a diagnostic work-up including bronchoalveolar lavage and biopsy [30, 49, 185].

Treatment combines surgical debridement and antifungal treatment (AII). Surgery is often necessary to confirm diagnosis and may be used to decrease the fungal burden [29, 54, 148, 167, 171].

For first-line antifungal treatment, options include a lipid-based amphotericin B formulation or posaconazole. D-AmB yielded inferior results and is nephrotoxic [29, 126, 148, 167, 180, [187]. ABLC treatment was published in small series only [90, 148, 167, 188], while there are a larger number of reports including one series of L-AmB treatment for mucormycosis [35, 126, 148, 154, 166, 167]. Posaconazole first-line treatment has been reported in two small series [154, 167]. In a single series, lipid-based amphotericin B has been combined with caspofungin for rhino-orbital-cerebral diseases (CIII), a pattern not typical for hematologic but rather for diabetic patients [144].

In second-line treatment, the same drugs were used either for refractory disease or because of intolerance of the patient, i.e., ABLC [90, 188], L-AmB [126], ABCD [67], or posaconazole [54, 167, 181].

Voriconazole is inactive in mucormycosis, and breakthrough infections during voriconazole exposure have been reported from retrospective evaluations and various case reports [103]. However, prospective clinical trials on voriconazole prophylaxis did not confirm an increased incidence [101, 195].

Taken together, most data, including results of multivariate prognostic factor analyses, support the use of L-AmB 5 mg/kg/day (AII) and doses >5 up to 10 mg/kg/day (AIII), while ABLC and posaconazole 4×200 mg/day are recommended with lesser strength (BII) in the first-line treatment. Second-line treatment with posaconazole is recommended (AII), while all three lipid-based amphotericin B formulations are alternatives (BII) (see Table 4). Use of D-AmB is strongly discouraged in any indication and at any dose (EI).

Treatment of cryptococcosis

The vast majority of clinical studies on treatment of cryptococcosis have been performed in patients with AIDS, albeit patients with hemato-oncological malignancies might also be affected [15, 24, 62]. Infections by *Cryptococcus* spp.—mainly

Cryptococcus neoformans or *Cryptococcus gattii*—commonly involve the CNS, but fungemia or disseminated infections might also occur. Diagnosis is usually based on fungal cultures, India ink smear examination, latex-antigen test, and PCR studies using cerebrospinal fluid. Treatment of CNS cryptococcosis in hematological patients should comprise L-AmB together with flucytosine (5-FC) (AIII), usually followed by maintenance therapy with fluconazole [21, 24, 134] (see Table 5).

Second-line or salvage treatment options for CNS cryptococcosis include L-Amb as single agent (BI), ABLC (5 mg/kg) (BIII), voriconazole (BIII), posaconazole (CIII), D-AmB combined with voriconazole or fluconazole (BII), and voriconazole combined with 5-FC (BII) [12, 60, 97, 120, 165]. Severe cryptococcosis of the lungs or of other organ systems should be treated like CNS cryptococcosis (CIII). Very few and mainly preclinical data are available concerning treatment of cryptococcosis by other agents such as caspofungin or posaconazole. Therefore, these agents should not be used in the clinical routine setting to treat cryptococcosis (Table 6).

Treatment of fusariosis

Invasive fusariosis is a severe sporadic mold infection affecting mainly neutropenic patients. It is associated with a very high mortality rate of 50–80 % [28, 118, 119]. The skin and the lungs are the most frequent sites of infection, albeit involvement of the sinus, soft tissues, and fungemia or disseminated infections occurs frequently [28]. Systematic prospective analyses on the treatment of *Fusarium* infections are still lacking. Retrospective case series suggest that L-AmB might be preferable in hematological patients who often receive other nephrotoxic drugs (BII). Voriconazole has been used within the last years with success to treat invasive fusariosis (BII) ([96], Nucci et al. M-1234 ICAAC 2012). Posaconazole (BIII) or ABLC (BIII) might be used as alternative treatment options [28, 96, 118, 133, 135, 139] (see Table 5). Surgical resection of necrotic tissues (e.g., skin), central venous line removal, or in vitro resistance testing might be further measures to improve the outcome of patients with invasive fusariosis (CIII).

Table 4 Treatment of mucormycosis in hemato-oncological patients

First-line treatment	
Liposomal AmB (≥5 mg/kg)	AII
ABLC	BII
Posaconazole	BII
Lipid-based amphotericin B plus caspofungin	CIII
Second-line treatment	
Posaconazole	AII
Liposomal AmB (≥5 mg/kg)	BII
ABLC	BII
Additional surgical debridement	AII

Treatment of *Trichosporon* infections

Trichosporon species underwent different taxonomies and are genetically heterogeneous. Apart from colonization of skin or mucosal membranes, these yeast-like pathogens may cause deep-seated infections, mostly in immunocompromised patients, specifically those with hematologic malignancies.

Regarding treatment, there are no data from randomized trials in cancer patients, and we recommend guiding therapy by susceptibility tests. Conclusions are restricted by the fact that the majority of studies are examining sensitivity with *Trichosporon asahii*/*beigelii*; other *Trichosporon* species were less present and may differ in results.

Clinical data confirm that azoles improve response rates (CIII) [4, 150, 169] and markedly voriconazole (B III) has been used in patients with hematological malignancies [8, 9, 44, 46, 51, 150] (see Table 5). As high MIC values correspond to low response rates in hematological patients receiving amphotericin B [51] or an echinocandin [17, 53, 105], these agents cannot be recommended as monotherapy (DIII). Clinical data to recommend these agents in combination therapy with each other or with an azole are too scarce to establish any recommendation [14, 51, 71].

Treatment of *Scedosporium* infections

Pseudallescheria/*Scedosporium* species are opportunistic fungal species causing life-threatening disseminated infections in immunocompromised patients [55, 88, 149, 173]. The most common pathogens are *Scedosporium prolificans* and *Scedosporium apiospermum* (teleomorph *Pseudallescheria boydii*). Systemic infections with *Scedosporium*/*Pseudallescheria* species are often refractory to treatment as these pathogens are highly resistant to available antifungal agents [37]. No treatment data from randomized trials exist for any patient group, and available information about treatment outcome only stems from case reports and case collections.

S. prolificans Grenouillet and coworkers describe 119 patients with systemic *Scedosporium* infections. Only 11/119 patients survived, resulting in a death rate of >90 % [55]. Reviewing the cases of the surviving patients, treatment of systemic scedosporiosis should include a multimodal approach using surgery, if possible, antifungal combination therapy, and supportive measures of immune reconstitution (e.g., growth factor support). Tintelnot and coworkers reported on nine patients with an underlying hematologic malignancy, and all nine died [173]. Taken together, voriconazole plus terbinafine

seems to give the most promising results (CIII) [20, 55, 72, 114, 173, 194]. Another alternative is L-AmB in a dosage of at least 5 mg/kg (CIII) (see Table 5).

S. apiospermum Reports about *S. apiospermum* infections are even scarcer. Besides single case reports [13, 38], 21 patients with an underlying hematologic malignancy were reported from MD Anderson Cancer Center, TX [89]. Mortality rate in patients with disseminated *S. apiospermum* infection was 79 %. Most survivors received a combination therapy consisting of L-AmB and a triazole (voriconazole, posaconazole). Given these data, the treatment recommendation for *S. apiospermum* infection is L-AmB in a dosage of 5 mg/kg (BIII) or an azole such as voriconazole or posaconazole (BIII) (see Table 5).

Therapeutic drug monitoring of antifungal agents

Bioavailability might have an impact on clinical efficacy, and pharmacokinetic properties of antifungal agents vary substantially. For flucytosine with its known association of plasma concentration and toxicity, therapeutic drug monitoring has broadly been established [47]. Meanwhile, several studies investigated triazole concentrations in plasma or serum and correlations with clinical efficacy or toxicity. Most of these analyses are limited to retrospective investigations and nearly all of them focus on *Aspergillus* infections. In contrast to current triazoles, plasma levels of echinocandins and systemic polyenes are comparatively stable, and sufficient concentrations are supported by obligatory intravenous application. For these classes of antifungal agents, monitoring of drug concentration is not required in general. For fluconazole, efficacy seems also to be associated with dosage and achieved blood concentrations.

Voriconazole plasma concentrations show a broad range of intra- and interindividual variation. This triazole is metabolized at least by the isoenzymes 2C19, 2C9, and 3A4 of the cytochrome P450 system, which can cause many potential drug interactions [64, 168]. In addition, genetic variations of isoenzyme 2C19 alter biodegradation of voriconazole significantly, and other factors including food and absorption may change its bioavailability. Therefore, voriconazole plasma concentrations cannot be predicted by dosage [132].

Small retrospective analyses showed an association between plasma concentrations and clinical response in the treatment of invasive aspergillosis, but also an increased rate of adverse events for high plasma concentrations (usually above 5.0 or 5.5 mg/l) [41, 130, 175, 177]. A retrospective analysis of nine clinical phase I to III trials revealed an association between plasma concentration and clinical response for all invasive fungal infection [176]. This could be demonstrated separately for both *Candida* and *Aspergillus* infections. On the basis of these studies, an improved rate of global response can be expected in case of plasma concentrations between 1 and 5.5 mg/l [176]. The retrospective design and the incomplete documented timing for the drawing of blood samples are major limitations of these investigations. In a small prospective study comparing weight-adjusted voriconazole therapy with drug monitoring-guided voriconazole application for first-line or salvage therapy could not demonstrate a significant difference in the primary endpoint of adverse events [129]. However, although only a rather small number of patients were enrolled, the clinical response was significantly better when voriconazole dosage was adjusted to the determined plasma concentrations. Voriconazole concentrations were determined on day 3 after the start of therapy and always 3 days after change of dosage. When interpreting these results, it has to be kept in mind that the study population consisted of Asians, and azole metabolism enzyme patterns differ in Asians and Caucasians [129].

Posaconazole is currently available as oral solution only. Absorption is limited and doses above 800 mg daily did not increase plasma concentration [179]. Drug interaction, fasting condition, and increased gastric pH, e.g., due to proton pump inhibitor usage, may impair bioavailability [64, 156]. The initial study of posaconazole for salvage therapy of IA already included a post hoc analysis on the impact of plasma concentration. Patients were divided in quartiles of rising drug concentration, which paralleled global response [189].

In summary, therapeutic drug monitoring for triazoles can be used to improve clinical response (BII). Determination of plasma/serum concentrations of voriconazole and posaconazole should be considered at least in case of suspected breakthrough infection, (suspected) lack of response despite sufficient

Table 5 Treatment of rare fungal infections in hemato-oncological patients

Cryptococcus neoformans infections	
Liposomal AmB (3–4 mg/kg) + 5-FC	AIII
Fusariosis	
Voriconazole	BII
Liposomal AmB (≥5 mg/kg)	BII
ABLC	BIII
Scedosporium spp. infections	
S. apiospermum (=*Pseudallescheria boydii*)	
Liposomal AmB (≥5 mg/kg)	BIII
Voriconazole	BIII
Posaconazole	BIII
S. prolificans	
Voriconazole + terbinafin	CIII
Liposomal AmB (≥5 mg/kg)	CIII
Trichosporon spp. infections	
Voriconazole	BIII
Posaconazole	CIII

Table 6 Daily doses of antifungal agents for the treatment of IFD

	Daily dose	Loading dose day 1	Dose adjustments
Caspofungin	weight ≤80 kg; 50 mg weight >80 kg: 70 mg	70 mg	Liver cirrhosis: Child–Pugh score B: 35 mg/day; C: no data
Micafungin	100 mg		
Anidulafungin	100 mg	200 mg	
Liposomal AmB	3 mg/kg		CNS 3–5 mg/kg; mucormycosis ≥5 mg/kg
ABLC	5 mg/kg		
Voriconazole i.v.	2×4 mg/kg	2×6 mg/kg	Creatinine clearance <50 ml/min: preferably oral administration; liver cirrhosis: see below
Voriconazole p.o.	2×200 mg	2×400 mg	Consider 2×300 mg to obtain plasma levels comparable with 4 mg/kg i.v.; liver cirrhosis: Child–Pugh score A–B: 50 % dose reduction; C: no data
Posaconazole	2×400 mg		4×200 mg in case of insufficient enteral nutrition
Fluconazole i.v./p.o.	400–800 mg	800 mg	Creatinine clearance 11–50 ml/min: 50 % dose reduction
5-Flucytosine	150 mg/kg divided into 4 doses		

antifungal chemotherapy (adequate dosage, duration ≥2 weeks), suspected drug-related toxicity, switch from intravenous to oral therapy, oral therapy, and limited resorption because of nausea or diarrhea or specific co-medications (e.g., proton pump inhibitor in case of posaconazole). For voriconazole, a plasma concentration between 1 and 5 mg/ml and for posaconazole above 0.7 mg/ml should be targeted for therapy of invasive fungal infection (BII). Although optimal timing and quantity of determined plasma concentrations have not been sufficiently investigated, trough concentrations in steady state might be appropriate (CIII). For flucytosine, a plasma concentration of 30 to 80 mg/ml 2 h after application is recommended (BII).

Empirical versus preemptive antifungal therapy

In recent years, there has been controversy about the optimal therapeutic regimen for the initiation of antifungal therapy in the setting of persistent fever in patients with prolonged neutropenia.

Current guidelines recommend the implementation of antifungal therapy in neutropenic patients as soon as there is no defervescence after 3–5 days of treatment with broad-spectrum antibiotic chemotherapy. This so-called empirical antifungal strategy has drawbacks such as potential side effects and costs.

Preemptive treatment is commonly described as a diagnostic-driven therapy (i.e., the diagnostic work-up shows suspicious findings before initiation of antifungal treatment), whereas empirical therapy is often referred to as fever-driven therapy.

Several recent studies compare the diagnostic-driven approach with fever-driven antifungal therapy [2, 33, 63, 158, 170]: So far, the routine use of the diagnostic-driven approach cannot be recommended as long as the current diagnostic tools lack sensitivity and/or specificity and treatment triggers are not clearly defined. Furthermore, treatment delay might enhance mortality in this patient population.

Some of these studies used microbiological tools for the monitoring of fungal disease, e.g., fungal PCR techniques, serum galactomannan, or β-D-glucan testing; some studies asked for specific radiological signs such as a halo sign as trigger for initiating preemptive antifungal therapy. The polymerase chain reaction based-preemptive antifungal therapy creates a major difficulty, as this method is not yet established as a standard diagnostic for fungal infections. The assessment of outcomes was different and shows the difficulty in dealing with therapeutic strategies: some studies used survival of the invasive fungal infection as the information of choice, whereas others investigated the consumption and costs of antifungal treatment.

In order to use a diagnostic-driven therapeutic approach, a stringent assessment of clinical signs and symptoms and microbiological and radiological diagnostics must be warranted (BIII), e.g., monitoring of galactomannan at least twice weekly, performance of high-resolution computed tomography of the chest and the paranasal sinuses in persistent fever despite adequate antibacterial antibiotic chemotherapy, and regular clinical examination of the patient.

Interventional strategies

Surgical intervention

Potential indications for a surgical intervention in pulmonary fungal infection might be (1) acute hemoptysis, (2) need of

histological diagnostics, (3) removal of residual infiltrates prior to the next chemotherapy cycle, (4) prevention of bleeding in the case of fungal lesions with vessel involvement, and (5) reduction of fungal burden (e.g., in mucormycosis).

Hemoptysis occurs in pulmonary aspergillosis or mucormycosis in up to 30 % of the cases, frequently during the phase of neutrophil recovery. 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 [117]. A monocenter study found a reduction in mortality from 41 to 14 % after introduction of systemic computed tomography (CT) examinations followed by frequent use of surgical resections when compared to a historical control [25]. In another study comprising 41 patients with hematologic diseases undergoing surgical intervention of their IPA, the mortality within 30 days was about 10 %, fungal relapse occurred in 10 %, and the overall survival at 6 months was 65 % [106]. Danner et al. reviewed 198 patients having undergone surgery for IPA. They found a day-30 mortality of 12 % and a 6-month survival of 50 % [39].

However, experience in surgical treatment of IPA is based on data from the era of D-AmB. With the newer antifungal agents, surgical intervention seems to have less importance. Therefore, we recommend surgical resections for the above-listed circumstances in accordance to other guidelines [186] (BII).

In sinu-nasal aspergillosis, additional surgical intervention may be necessary in individual cases (BII) [186]. In aspergillosis of the CNS, surgical resection should be considered (AII) as it seems to improve outcome [160].

Drug instillation

For treatment of refractory abscesses or caverns (e.g., in the lung or brain) in which surgical intervention is not feasible, a drainage as well as a local drug instillation may be considered. Here, antifungal preparations (commonly containing AmB) or disinfecting substances such as sodium iodide or potassium iodide can be administered (CIII) [197].

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 embolized (CIII) [69].

Immunotherapy and granulocyte transfusion

Colony-stimulating factors The application of hematopoietic growth factor should be considered on an individual case-by-case basis, according to the recommendations of the EORTC (B III) [1].

T cell therapy 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 haplo-identical stem cell transplantation, when receiving T cells raised against fungal pathogens [136]. 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. So far, this kind of therapeutic option is still considered experimental.

Granulocyte transfusions Compared to the 1980s, granulocyte harvest and granulocyte function have clearly improved by stimulating donors with G-CSF [137]. 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 [73]. 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 [155]. In 31 patients with invasive fungal infection (17 possible infections) undergoing granulocyte transfusions, 78 % survived [113].

A randomized study with prophylactic granulocyte transfusion thrice a week in patients with neutropenic fever and pulmonary infiltrates or a history of proven IFD failed to confirm the benefit of this procedure [164]. Currently, clear benefit of granulocyte transfusions in invasive mycoses has not been doubtlessly clarified [137]. However, it might be considered as a treatment option in selected patients (CIII).

Conflict of interest SM was a consultant to MSD; served at the speakers' bureau of MSD and Pfizer; and received travel grants from MSD, Astellas, Gilead Sciences, and Pfizer.

DB is consultant to Gilead Sciences; received research grants from Gilead Sciences and Pfizer; served on the speakers' bureau of Astellas, Gilead Sciences, Merck Sharp & Dohme/Merck, and Pfizer; and received travel grants from Astellas, Merck Sharp & Dohme/Merck, and Pfizer.

WH has received research grants from Astellas, Basilea, Gilead, MSD/Merck (previously Essex/Schering-Plough), and Pfizer and has served as a speaker for Cephalon, Gilead, MSD/Merck, and Pfizer.

MR has received research grants from Deutsche Krebshilfe/German Cancer Aid, Pfizer, and Merck/MSD; is a consultant to Astellas, Basilea, Essex/Schering-Plough, Gilead Sciences, Janssen, Merck/MSD, Novartis, Pfizer, and Pliva; and served at the speakers' bureau of Gilead Sciences, Merck/MSD, and Pfizer.

OAC is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN1106) and has received research grants from, is an advisor to, or received lecture honoraria from 3M, Actelion, Astellas, Basilea, Bayer, Celgene, Cubist, F2G, Genzyme, Gilead, GSK, Merck/MSD, Miltenyi, Optimer, Pfizer, Quintiles, Sanofi Pasteur, and Viropharma.

GE was a consultant to MSD, served at the speakers' bureau of MSD and Pfizer, and received travel grants from MSD.

SN was a consultant to MSD and served at the speakers' bureau of MSD and Gilead Sciences.

HO received research grants from MSD and Gilead Sciences; served on the speakers' bureau of Gilead, Pfizer, and MSD; and was a consultant to MSD, Gilead, and Astellas.

JP is consultant to MSD; served at the speakers' bureau of MSD and Gilead; and received travel grants from MSD, Astellas, Gilead, and Pfizer.

OP received research support from Fresenius Biotech, Bio Rad, Pierre Fabre Pharma GmbH, and Gilead; served at the speakers' bureau of MSD, Astellas, Gilead; and has been an advisory board of MSD.

CR served for the speakers' bureau of Gilead Sciences, Pfizer International, and MSD.

MSH served at the speaker's bureau of Gilead Sciences.

GS was a consultant to MSD, served at the speakers' bureau of MSD and Pfizer, and received travel grants from MSD, Astellas, Essex/Schering-Plough, Gilead Sciences, Janssen, and Pfizer.

AJU received research grants from MSD, Pfizer, and Schering-Plough and has served as a consultant to and has been on the speaker's bureau of Astellas, Basilea, Gilead, MSD, Pfizer, and Schering-Plough.

GM has served as a consultant and has been on the speakers' bureau for Gilead Sciences, MSD, and Pfizer.

AB has received research grant from Basilea, Astellas, Pfizer, and Essex/MSD; is a consultant to MSD and Gilead Sciences; and served at the speaker's bureau of MSD.

WK, HL, TS, and HHW have no conflicts of interest.

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