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REVIEW ARTICLE

Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO)

Sibylle C. Mellinghoff[1,2] · Jens Panse[3] · Nael Alakel[4] · Gerhard Behre[5] · Dieter Buchheidt[6] · Maximilian Christopeit[7] · Justin Hasenkamp[8] · Michael Kiehl[9] · Michael Koldehoff[10] · Stefan W. Krause[11] · Nicola Lehners[12] · Marie von Lilienfeld-Toal[13] · Annika Y. Löhnert[2] · Georg Maschmeyer[14] · Daniel Teschner[15] · Andrew J. Ullmann[16] · Olaf Penack[17] · Markus Ruhnke[18] · Karin Mayer[19] · Helmut Ostermann[20] · Hans-H. Wolf[21] · Oliver A. Cornely[1,2,22]

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Abstract

Immunocompromised patients are at high risk of invasive fungal infections (IFI), in particular those with haematological malignancies undergoing remission-induction chemotherapy for acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) and recipients of allogeneic haematopoietic stem cell transplants (HSCT). Despite the development of new treatment options in the past decades, IFI remains a concern due to substantial morbidity and mortality in these patient populations. In addition, the increasing use of new immune modulating drugs in cancer therapy has opened an entirely new spectrum of at risk periods. Since the last edition of antifungal prophylaxis recommendations of the German Society for Haematology and Medical Oncology in 2014, seven clinical trials regarding antifungal prophylaxis in patients with haematological malignancies have been published, comprising 1227 patients. This update assesses the impact of this additional evidence and effective revisions. Our key recommendations are the following: prophylaxis should be performed with posaconazole delayed release tablets during remission induction chemotherapy for AML and MDS (AI). Posaconazole iv can be used when the oral route is contraindicated or not feasible. Intravenous liposomal amphotericin B did not significantly decrease IFI rates in acute lymphoblastic leukaemia (ALL) patients during induction chemotherapy, and there is poor evidence to recommend it for prophylaxis in these patients (CI). Despite substantial risk of IFI, we cannot provide a stronger recommendation for these patients. There is poor evidence regarding voriconazole prophylaxis in patients with neutropenia (CII). Therapeutic drug monitoring TDM should be performed within 2 to 5 days of initiating voriconazole prophylaxis and should be repeated in case of suspicious adverse events or of dose changes of interacting drugs (BIItu). General TDM during posaconazole prophylaxis is not recommended (CIItu), but may be helpful in cases of clinical failure such as breakthrough IFI for verification of compliance or absorption.

Keywords Invasive fungal infection · Antifungal prophylaxis · Itraconazole · Fluconazole · Posaconazole · Amphotericin B · Liposomal · Isavuconazole

Introduction

Invasive fungal infections (IFIs) cause substantial morbidity and mortality in patients with haematological malignancies, especially in those receiving remission-induction therapy for acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) and allogeneic haematopoietic stem cell transplantation (HSCT) [53, 97]. In addition, the increasing use of

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✉ Sibylle C. Mellinghoff
sibylle.mellinghoff@uk-koeln.de

Extended author information available on the last page of the article

new immune modulating drugs in cancer therapy has opened up an entirely new spectrum of patients at risk [57, 84]. Patients with haematological or oncological diseases without risk for prolonged neutropenia (< 500 cells/μL > 7 days) are not at increased risk for IFI and should therefore not receive routine prophylaxis (DI).

Epidemiology of IFI varies upon host and environmental factors [63]. *Aspergillus* spp. and *Candida* spp. cause most cases of IFI in haematological patients [65, 81]. However, the introduction of routine prophylaxis for patients at high risk for IFI plus local environmental factors have caused a shift in epidemiology, in particular to non-albicans *Candida* spp. such as *C. glabrata*, *C. krusei* and *C. Tropicalis* [28, 78, 99, 112]. Despite improvements in diagnosis and treatment, IFI-associated mortality remains high [54, 78], and thus, antifungal prophylaxis represents an important strategy in patients at high risk for IFI.

Since the 2014 edition of these recommendations [95], seven clinical trials regarding antifungal prophylaxis in patients with haematological malignancies have been published, comprising 1227 patients. This 2017 update intends to facilitate evidence-based decision making in daily clinical practice. Additional evidence from clinical trials and its impact on changes compared to our previous recommendations will be discussed.

Design and methods

The guideline was prepared by German clinical experts in haematology, oncology, stem cell transplantation and infectious diseases in a stepwise consensus process. Systematic literature search was conducted by OAC and SCM as previously described [15, 95]. Data were extracted and tabulated; preliminary recommendations for each patient group were proposed for discussion and sent to the committee, i.e. all authors. Tables were revised after email-based discussion and put up for final discussion at a telephone conference on June 20th, 2017. If no unanimous consensus was reached, majority vote of the conference was adopted. The final version of this guideline was approved by the AGIHO plenary session on September 30th, 2017.

A major change to the 2014 edition of this guideline is the elimination of the recommendations for allogeneic HSCT recipients in order to avoid duplication. Instead, we refer to the guidelines for infectious complications after allogeneic HSCT provided by the Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology [104] and specifically developed for this patient group. For prophylaxis of *Pneumocystis jirovecii* pneumonia, please refer to the guidelines for primary prophylaxis of bacterial infections and *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and solid tumours provided by the AGIHO [75].

In contrast to the last edition, we used grading for strength of recommendation and quality of evidence (Table 1) established by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) [17]. When propositions did not change since 2014, the reader may refer to that previous publication [95]. The synopsis of our recommendations is given in Tables 2, 3 and 4.

In order to provide a complete overview, this paper includes tables of the trials on antifungal prophylaxis published to date by compound and comprising information about author, publishing year, trial design, medication/daily dose per treatment group, number of patients, risk factors, percentage of proven, probable and possible IFI and attributable and overall mortality (Supplementary Tables 5 to 11, updating previous information published here[15, 95]). Two authors (SCM and AYL) double-checked the detailed information provided.

Recommendations apply for adult patients only, and clinical trials evaluating antifungal prophylaxis exclusively in

Table 1 ESCMID-ECMM Grading 2017

Category, grade		Definition
Strength of recommendation	A	Strongly supports a recommendation for use
	B	Moderate evidence to support a recommendation for use
	C	Poor evidence to support a recommendation
	D	Supports a recommendation against use
Quality of evidence—level	I	Evidence from ≥ 1 properly randomised controlled trial
	II	Evidence from ≥ 1 well-designed clinical trial, without randomisation; from cohort or case-controlled analytic studies (preferably from > 1 centre); from multiple time series; or from dramatic results from uncontrolled experiments
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees
Quality of evidence—index (for level II)	r	Meta-analysis or systematic review of randomised controlled trials
	t	Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation
	h	Comparator group is a historical control
	u	Uncontrolled trial
	a	Published abstract (presented at an international symposium or meeting)

Table 2 Recommended antifungal prophylaxis in patients with neutropenia (< 500 cells/μL > 7 days)

Intention	Intervention	SoR	QoE
Prevent IFI in patients with neutropenia (< 500 cells/μL > 7 days), excluding alloSCT[a]	Posaconazole	A	I[b]
		B	III[c]
	Amphotericin B, liposomal, inhalation	B	II[d]
	Amphotericin B, liposomal, iv	C	I
	Caspofungin	C	I
	Fluconazole	C	I
	Itraconazole	C	I
	Itraconazole, iv	C	I
	Voriconazole	C	II
	Amphotericin B deoxycholate	D	I
	Micafungin	C	IIh
	Isavuconazole	C	IIu

[a] Currently, no recommendations for ALL patients applicable

[b] Strong recommendation in AML/MDS remission induction chemotherapy only

[c] Other settings, e.g. very severe aplastic anaemia and palliative treatment of MDS

[d] All patients received fluconazole—dose and route were not reported

paediatric patients are beyond the scope of our review. Status of approval of drugs in national health care systems was not taken into account.

These recommendations are evidence-based, but not necessarily follow approved indications or the respective labelling of antifungal compounds as they may differ substantially between countries and over time.

Table 3 Dosage of recommended drugs (please refer to Table 2)

Drug	Dosage
Posaconazole, oral suspension	200 mg tid po
Posaconazole, tablet	300 mg qd po (bid on day 1)
Posaconazole, iv	300 mg/day iv (bid on day 1)
Amphotericin B, liposomal, inhalation	12.5 mg biw
Amphotericin B, liposomal, iv	50 mg q 48 h or 5 mg/kg biw (CI) 15 mg/kg single infusion (CIII)
Caspofungin	50 mg qd iv
Fluconazole	400 mg qd po
Itraconazole, capsules	Any dose
Itraconazole, oral solution	2.5–7.5 mg/kg/day or 200 mg
Itraconazole, iv	200 mg qd iv
Voriconazole	200 mg bid iv
Amphotericin B deoxycholate	Any dose
Micafungin	50 mg iv
Isavuconazole	200 mg/d iv (tid on days 1–2)

Table 4 Recommendations on therapeutic drug monitoring during antifungal prophylaxis

Intention	Intervention		SoR	QoE
	Drug	Target level		
Achieve exposure effective for antifungal prophylaxis and reduce toxicity	Voriconazole	1–2 mg/L	B	IItu
	Posaconazole	> 500 ng/ml	C	IItu

Results

Triazoles

Triazoles represent an important class of antifungal drugs for both prevention and treatment of *Aspergillus* spp. and certain yeasts including many *Candida* spp. However, *A. fumigatus* being resistant to triazoles has emerged within the past decade [9, 45]. The SEPIA study assessed the epidemiology of invasive aspergillosis (IA) and azole resistant *Aspergillus* spp. in patients with acute leukaemia in 19 haematology centres in Germany. The authors found resistance in two in 179 (1.1%) cases [53]. A European expert group recently published a statement proposing that local resistance rates of < 5% should not trigger changes in national or international management recommendations [108]. Therefore, a modification of antifungal prophylaxis in Germany does not appear to be warranted. The 5% cut-off was not reached in any of the SEPIA study sites [53].

Fluconazole

Since 2014, one prospective study on fluconazole prophylaxis was conducted. This small prospective study compared posaconazole with fluconazole for prophylaxis in 37 AML patients during induction and consolidation chemotherapy. IFI rates did not differ significantly (10 and 7 cases), but posaconazole direct costs exceeded fluconazole considerably (24€ and 2400€, respectively) [6]. However, posaconazole was demonstrated to have a survival benefit in prospective randomised controlled clinical trials (RCTs) when given for fungal prophylaxis treatment and decreased indirect and overall costs [22, 86]. Fluconazole is a weaker CYP3A4 inhibitor than other azoles and, specifically, fluconazole prophylaxis has been used in acute lymphoblastic leukaemia (ALL) induction chemotherapy, but there are no reliable data to support a recommendation for prophylaxis in this setting. Thus, our recommendation (CI) regarding fluconazole prophylaxis in patients with neutropenia remains unchanged.

Itraconazole

A non-comparative prospective trial evaluated the administration of itraconazole prophylaxis in AML patients [52]. Eighty-four patients received 200-mg oral solution twice daily during induction, re-induction and consolidation chemotherapy. IFI occurred in 3.4%, adverse events occurred in 7%, none leading to discontinuation. The study added only little more information to the already vast body of evidence on the prophylactic use of the itraconazole oral solution; therefore, the recommendation with poor evidence to support the prophylactic use of itraconazole (CI) did not change.

Isavuconazole

Isavuconazole is a novel antifungal approved in 2015. An open-label dose escalation study in 23 patients with AML was conducted (ClinicalTrials.gov identifier NCT00413439): 11 patients received 200 mg and 12 received 400 mg isavuconazole intravenously as antifungal prophylaxis [16]. Two patients developed possible IFI; most adverse events were mild or moderate, leading to discontinuation in four cases. In this small, phase II study, isavuconazole appeared safe and tolerable as prophylaxis in immunosuppressed high-risk patients. Only a well-designed RCT could provide solid evidence of prophylactic efficacy of isavuconazole. Currently, there is poor evidence to recommend prophylactic isavuconazole (CIIu).

Posaconazole

We strongly recommend antifungal prophylaxis with posaconazole (AI) in patients with neutropenia. Posaconazole is available in different formulations: oral suspension, tablet and iv formulation. Strong recommendation for posaconazole use bases on a large RCT with the oral suspension [22].

Posaconazole oral suspension was used in a single-centre, retrospective cohort study since 2014. This study compared clinical effectiveness of posaconazole with fluconazole in 130 patients receiving prophylaxis during first induction or first re-induction chemotherapy for AML or MDS. The primary endpoint was possible, probable or definite breakthrough IFI. Efficacy of posaconazole was superior to fluconazole, probable/definite breakthrough IFI occurred in 9.2 and 27.0%, respectively. High differences of IFI in different studies can be explained by incomplete data sets due to retrospective acquisition and varying definitions of IFI despite wide spread use of EORCT criteria. Additionally, centre effects driven by differences in rigour of diagnostic strategies may contribute to discrepancy. These results support our previous strong recommendation for antifungal prophylaxis with posaconazole in patients at high risk for IFI (AI). In 2015, a retrospective analysis of 70 AML patients after induction chemotherapy found the frequent necessity of systemic antifungal treatment for probable or proven IFI despite prophylaxis with posaconazole oral suspension [92].

No data are available for populations with persisting neutropenia, e.g. very severe aplastic anaemia or MDS treated with hypomethylating agents. Thus, one must extrapolate from findings of other high-risk neutropenic patient studies [22]. The group recommends posaconazole prophylaxis in such clinical settings (BIIt), unless such prophylaxis is contraindicated because of drug-drug interactions, e.g. ALL patients [5, 20].

No evidence-based recommendations can be made on the duration of prophylaxis in patients with persisting neutropenia. There is poor evidence regarding posaconazole prophylaxis during AML consolidation therapy (CIIt). Further prospective trials on antifungal prophylaxis in patients with ALL, aplastic anaemia or MDS are required to give evidence-based recommendations in future.

Posaconazole oral suspension has limited bioavailability underlining the need for better absorbable formulations [24, 92]. Since 2014, two studies have been published on prophylaxis with posaconazole delayed release (DR) tablets. One study compared 200 and 300 mg tablets in 54 patients to evaluate pharmacokinetics and safety profile (NCT01777763). The exposure target of a steady-state average concentration of > 500 ng/mL was reached in 15 of 19 patients receiving 200 mg once daily and in 31 of 32 on 300 mg once daily. Tablets were well tolerated [27]. The second study characterised posaconazole tablet pharmacokinetic and safety in 210 patients with neutropenia following chemotherapy for haematological malignancy or recipients of allogeneic HSCT. Patients took posaconazole 300 mg DR tablets once daily independent of food intake. Pre-specified exposure targets were achieved in almost all patients. The drug was well tolerated and safe, similar to posaconazole oral suspension [18]. The tablet formulation of posaconazole is safe, effective and provides predictable absorption. We thus recommend posaconazole tablets as drug of choice for IFI prevention in AML and MDS patients (AI).

One study evaluated pharmacokinetics and safety of intravenous posaconazole in antifungal prophylaxis of neutropenic patients with AML, MDS or in the context of allogeneic HSCT [20]. In total, 237 received 300 mg posaconazole iv twice daily on day 1 and thereafter 300 mg iv once daily for up to 28 days. Average concentrations were reached in 94% of patients between 500 and 2500 ng/mL. The most common treatment-related adverse events were diarrhoea, nausea and rash (8, 5 and 5%, respectively). We recommend posaconazole iv in patients when oral formulations are not appropriate, but emphasise the need for further randomised trials.

Voriconazole

Voriconazole has been shown to be efficacious in the treatment of IA [44], but—apart from haematopoietic stem cell recipients—data on prophylaxis in patients at risk for IFI is still scarce [62, 111]. One retrospective study compared safety and efficacy of voriconazole and oral suspension posaconazole prophylaxis in patients with haematological malignancies ($n = 200$) [39]. IFI occurred in 0 and 3%, respectively; symptomatic adverse events were more frequent in the voriconazole group (6 and 0%). Our CII recommendation for voriconazole remains therefore unchanged.

Clotrimazole, miconazole and ketoconazole

No additional literature has been published since 2014. There is poor evidence to support the prophylactic use of clotrimazole, miconazole or ketoconazole (DII).

Echinocandins

Resistance to drugs of the echinocandin class remains low for most *Candida* spp., e.g. *C. albicans* at < 3% [10]. In contrast, *C. glabrata* shows increasing in vitro resistance to this drug class [1, 80]. Expanding use of echinocandins for prophylaxis in patients with high risk of invasive candidiasis has some potential to contribute to emergence of resistance. We hence recommend to consider antifungal prophylaxis with echinocandins on the basis of local epidemiology (BIII) [35].

Anidulafungin and caspofungin

No additional relevant data have been published since 2014; our recommendation in patients with neutropenia remains unchanged (CI).

Micafungin

No prospective clinical trial on micafungin prophylaxis in the non-transplant setting was published since 2014. Results from a retrospective single-centre observational study comparing micafungin 50 mg iv with posaconazole 200 mg orally (historical control) in the prevention of IFI in neutropenic patients with haematological malignancies ($n = 302$) showed that there was no statistically significant difference in IFI rates (6.0 versus 5.4%) [73]. The authors propose micafungin as a good alternative for antifungal prophylaxis in patients with neutropenia while posaconazole and liposomal amphotericin B should remain first-line therapy. Our recommendation in patients with neutropenia remains unchanged (CIIh).

Polyenes

Liposomal amphotericin B Prophylactic aerosolized liposomal amphotericin B in severely neutropenic patients significantly reduced invasive pulmonary aspergillosis (IPA) rates, resulting in a BII recommendation in 2014 [87]. A recently published cohort study confirmed that prophylactic liposomal amphotericin B inhalation resulted in a substantial decrease in IPA incidence [12]; 235 AML patients inhaled 12.5 mg twice weekly from initiation of remission induction chemotherapy until recovery of their neutrophils. The primary endpoint was incidence of proven or probable IPA until 28 days after neutrophil recovery. IPA rates were 9.5% in the liposomal amphotericin B and 23.4% in the historical no-prophylaxis control group. Liposomal amphotericin B inhalation appeared cost saving. Considering increasing azole resistance, non-azoles may become an option for future strategies in antifungal prophylaxis. Our recommendation to BII recommendation remains unchanged.

A prospective non-comparative trial has demonstrated feasibility and safety of prophylaxis with a single 15-mg/kg intravenous L-AmB dose in 48 AML patients undergoing induction chemotherapy [2]. Apart from six patients with hypokalaemia, no grade 3–4 adverse events were reported. This approach needs validation by further clinical trials and can only be recommended with poor evidence at this time (CIIu).

Liposomal amphotericin B prophylaxis was also evaluated in adult patients with ALL receiving remission-induction chemotherapy (NCT01259713). Currently, there is no approved standard of care for this group of patients regarding antifungal prophylaxis. Azole antifungal drugs are problematic because of drug-drug interactions with vin-caalkaloids, an integral component of ALL induction chemotherapy regimens [5, 19]. The authors hypothesised that liposomal amphotericin B is an alternative due to its broad spectrum of activity [14, 21, 56]. Yet, IFI rates in the liposomal amphotericin B group (7.9%) did not significantly differ from the placebo group (11.7%). Given the high IFI rate in the placebo group, further clinical trials are needed to define an adequate antifungal prophylaxis strategy in ALL patients during remission-induction. Until then, there is poor evidence to recommend intravenous liposomal amphotericin B for prophylaxis in ALL (CI).

Amphotericin B deoxycholate has been shown to be too toxic and therefore is not recommended for prophylactic use (DI).

Nystatin

The use of nystatin mouthwash was compared to placebo in patients with haematological malignancies ($n = 158$) and

was—surprisingly—found effective for prophylaxis of pulmonary IFI (IFI rates 1.6 and 27.7%, respectively) [46]. Due to the missing mechanistic explanation of the result and the uncertain attribution of colonisation and IFI, the study did not impact our recommendations on antifungal prophylaxis in neutropenic patients (DII).

Risk factors for IFI

Novel targeted cancer therapy

New drug classes for haematological and oncologic diseases such as tyrosine kinase inhibitors (TKI) and other immunomodulatory drugs put a broader spectrum of patients at risk for IFI [84].

Among TKI, in particular inhibitors of bruton tyrosine kinase (BTK) [77, 84], mammalian target of rapamycin (mTOR) [31, 72, 88], janus kinase (JAK) [41, 70, 113] and phosphatidylinositol 3 kinase (PI3K) delta [58] showed attributable increase of risk of IFI. Targeting critical components of the immune system, they impair diverse features of immune cells (e.g. dendritic cells, T cells) [42, 91, 114]. However, underlying haematological disease, recent treatment, as well as neutropenia put these patients at an increased baseline risk for IFI. Currently, it remains unclear, if antifungal prophylaxis is indicated in these cases.

Inhibition of immune checkpoints, e.g. programmed cell death protein 1 (PD1) or cytotoxic T lymphocyte-associated protein 4 (CTLA4), shows wide-ranging, mostly immune-related adverse events [7, 59, 98]. Subsequent immunosuppression, primarily including corticosteroids, may result in opportunistic infections including fungi [32, 57, 110]. Prospective clinical trials may help optimizing management of immune-related adverse events.

Hypomethylating agents such as azacitidine put patients with AML or MDS at risk of IFI (probable/proven IFI 1.6%, $n = 121$, to 8.3%, $n = 64$) [30, 82]. Further, independent risk factors are low neutrophil and platelet counts [68], as well as prior intensive chemotherapy [30, 68]. Evaluation of risk factors should precede prescription of hypomethylating agents and antifungal prophylaxis could be considered accordingly.

Targeting CD20 leads to prolonged B cell depletion and in rare cases to late-onset neutropenia [29, 106, 109]. One retrospective case-control study reported that a significantly higher IFI rate was reported in patients treated with rituximab regimens compared to chemotherapy alone (41.7 vs. 17.1% among all infections, $n = 69$) [61]. Large randomised trials evaluating efficacy and safety of adding rituximab to standard chemotherapy did not find increased IFI rates [13, 38]. Antifungal prophylaxis should only be considered in case of additional risk factors.

Further antibodies target CD19, CD33 or interleukin-2 (IL-2). Low evidence on risk of IFI makes it difficult to give specific recommendations and guidelines on empiric or pre-emptive therapy should be followed [43, 74]. In rare occasions where CD52 antibody is part of the antineoplastic strategy, mould directed prophylaxis should be considered [51, 71]. Bispecific antibodies frequently cause neutropenic fever and infections, but direct causal relationship with these drugs is difficult to attribute being used in patients with advanced lymphoma at high risk for infection anyhow [85]. An increased risk for IFI has not been reported to date.

Given the high attributable mortality of IFI, the individual risk of patients treated with the drug classes above should be evaluated, and antifungal prophylaxis prescribed on case by case basis. Guidance that is more precise needs prospective trials focussed on infections.

Infection control for prevention of IFI

Infection-control measures in the haematological and oncologic setting are heterogeneous and contentious, particularly about transmission of fungi. The *Robert Koch-Institute* in Germany published recommendations on hygiene requirements for the medical care of immunocompromised patients [3]. However, most recommendations are based on expert opinion rather than actual published evidence. We reviewed recent trials on infection-control measures intending to prevent or reduce the rate of IFI.

Most studies focusing on the role of protective isolation are non-randomised and biased by renovation and reconstruction [67]. Available studies suggested clinical benefit of air filters and positive pressure environments, but mainly evaluated fungal conidia air concentration instead of patient outcome [55, 76]. None was randomised. One meta-analysis confirmed the low level of available evidence. No data showing a reduction of mould infections are available [90].

Surgical masks are used for protection of immunocompromised high-risk patients, but a clinical benefit has not been demonstrated [64]. One RCT compared 80 adult patients treated for acute leukaemia or HSCT regarding standard hospital hygiene procedures with or without wearing masks. A reduction of IFI was not seen (proven/probable IFI in 19.5 and 20.5%) [66]. In contrast, one study compared neutropenic patients wearing surgical masks during hospital construction with a historical control and found a reduction in *Aspergillus* spp. infections [83]. Specific settings may justify the use of well-fitting face masks; routine use seems inappropriate.

The value of germ-reduced diet including so-called "neutropenic diet" is unproven. No RCT proved a benefit for prevention of infection and related outcomes. All studies had

limitations regarding confounding interventions, outcome definitions, intervention and control diets [25, 33, 69, 105, 107].

Further clinical implications include appropriate hand hygiene. This aspect has recently been pointed out within the context of *Candida auris* transmission considering that hands can be key vectors in the transmission of yeasts [89]. Housing of patients as well as limitation of environmental exposure to air-borne conidia are matters of infection control and may outweigh impact of chemoprophylaxis. Because of difficulties in randomisation evidence remains low.

Due to lack of evidence, we do not provide recommendations for clinical practice.

Role of therapeutic drug monitoring

Therapeutic drug monitoring (TDM) of serum samples may improve efficacy and safety of antifungal prophylaxis. Two variables influence the potential utility of TDM: variable pharmacokinetics and a clear correlation between plasma drug concentration and efficacy or toxicity [47, 94].

Voriconazole meets both criteria: pharmacokinetics are variable while exhibiting difficulty to predict drug dose-exposure relationship [8, 50, 100, 101], and serum concentration was linked to efficacy [79, 102] and toxicity [26, 48, 79, 96, 100, 102, 115]. Voriconazole serum levels were often out of target range at the initiation of antifungal prophylaxis, 18% were sub-therapeutic (< 1 mg/L) and 11% too high (> 5.5 mg/L) ($n = 107$) [37]. Based on current literature, we recommend a concentration of 1–2 mg/L for prophylactic efficacy [79, 102]. In addition, concentrations > 5–6 mg/L should be avoided to prevent central nervous system and liver toxicity [26, 79, 102, 115]. TDM should be done within 2 to 5 days of treatment initiation, and repeatedly in case of suspicious adverse events, or initiation or termination of interacting drugs (BIItu).

There is no well-defined minimum serum concentration for posaconazole prophylaxis. Neither did serum concentrations of posaconazole correlate with efficacy nor with toxicity in the two large RCT [22, 103]. A level of 500 mg/L has been proposed, but was merely extrapolated from itraconazole data [34]. Despite lack of evidence [23, 49] to support a specific reference range, there is a general consensus of 500 to 700 mg/L being a desirable lower bound [4, 11, 40, 60, 93]. A retrospective study analysing posaconazole serum levels of 31 patients described lower serum levels in 43% of patients associated with advanced age and mucositis [36]. Routine TDM is not recommended (CIItu). Yet, in cases of clinical failure such as breakthrough IFI, it may be helpful for verification of compliance or absorption. An important parameter influencing usefulness of TDM is the turnaround time from sampling to result.

Conclusion

There is good evidence to recommend antifungal prophylaxis with posaconazole as oral suspension or—preferably—tablet in patients with remission induction chemotherapy for AML and MDS (AI). Posaconazole iv administration can be considered in those cases unable to take or absorb oral formulation. Liposomal amphotericin B did not significantly decrease IFI rates in ALL induction chemotherapy patients (CI). Since the IFI rate in ALL patients is considerable, further clinical trials are needed to find effective antifungal prophylaxis.

TDM should be performed within 2 to 5 days of voriconazole prophylaxis initiation and should be repeated in case of suspicious adverse events or dose changes of interacting drugs (BIItu). TDM is not generally necessary during posaconazole prophylaxis (CIItu), although in individual cases, for example potential breakthrough infection, it may be helpful to evaluate compliance, absorption and likelihood of IF.

Compared to the 2014 edition of this guideline, a further change is the elimination of the recommendations for allogeneic HSCT recipients regarding antifungal prophylaxis. We moved them to our guidelines specifically developed for this group of patients [104].

Compliance with ethical standards

Conflict of interest Author JP received honoraria, travel support by MSD Sharp & Dohme, Gilead Sciences, Pfizer, Astellas Pharma. Author DB has received honoraria and research grants by Astellas, Basilea, Gilead Sciences, Merck Sharp & Dohme/Merck (MSD), and Pfizer. Author MC has received fees by Basilea, Gilead, and MSD. Author MKi is a consultant and on the speakers' bureaus of MSD, and he is a consultant for Gilead and on the speakers' bureau of Astellas. Author MvLT is supported by the German Federal Ministry of Research and Education (BMBF grants 01EO1002 and 13GW0096D); has received research grants from Pfizer and MSD, is a consultant to Merck/MSD; and received honoraria or travel grants from Basilea, Gilead, Merck/MSD, and Astellas. Author GM has been a consultant to Gilead and F2G and received honoraria for lectures from Gilead, Pfizer, Basilea, and Astellas. Author DT received honoraria and travel grant from Gilead and MSD. Travel grant from Astellas and Jazz. Consultant of advisory board for MSD and Pfizer. Author AJU has received support for travel to meetings from Astellas and Basilea. He is a consultant and on the speakers' bureaus of Astellas, Gilead, MSD, and Pfizer. He has also received support for travel and accommodation from Astellas, Boehringer Ingelheim, Gilead, MSD, and Pfizer for activities unrelated to the current study. His institution has received grants from Astellas, Gilead, MSD, and Pfizer. Author OP received research grants from Bio-Rad and Gilead; is consultant to Merck/MSD and Gilead; and received lecture honoraria and travel grants from Astellas, Gilead, Pfizer, and Merck/MSD. Author MR is commercially sponsored by Basilea. Author HO received research grants from Gilead and MSD; is consultant to Astellas and MSD; and received lecture honoraria and travel grants from Astellas, Basilea, Gilead, Pfizer, and Merck/MSD. Author OAC is supported by the German Federal Ministry of Research and Education and the European Commission and has received research grants from, is an advisor to, or

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Affiliations

Sibylle C. Mellinghoff[1,2] · Jens Panse[3] · Nael Alakel[4] · Gerhard Behre[5] · Dieter Buchheidt[6] · Maximilian Christopeit[7] · Justin Hasenkamp[8] · Michael Kiehl[9] · Michael Koldehoff[10] · Stefan W. Krause[11] · Nicola Lehners[12] · Marie von Lilienfeld-Toal[13] · Annika Y. Löhnert[2] · Georg Maschmeyer[14] · Daniel Teschner[15] · Andrew J. Ullmann[16] · Olaf Penack[17] · Markus Ruhnke[18] · Karin Mayer[19] · Helmut Ostermann[20] · Hans-H. Wolf[21] · Oliver A. Cornely[1,2,22]

1 Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

2 Department I of Internal Medicine, German Centre for Infection Research (DZIF), University Hospital of Cologne, University of Cologne, Cologne, Germany

3 Department of Oncology, Haematology, Haemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen, Germany

4 Department I of Internal Medicine, Haematology and Oncology, University Hospital Dresden, Dresden, Germany

5 Division of Haematology and Oncology, Leipzig University Hospital, Leipzig, Germany

6 Department of Internal Medicine–Haematology and Oncology, Mannheim University Hospital, Heidelberg University, Mannheim, Germany

7 Department of Stem Cell Transplantation, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

8 Clinic for Haematology and Medical Oncology with Department for Stem Cell Transplantation, University Medicine Göttingen, Göttingen, Germany

9 Department I for Internal Medicine, Klinikum Frankfurt (Oder), Frankfurt (Oder), Germany

10 Department of Bone Marrow Transplantation, West German Cancer Centre, University Hospital of Essen, University of Duisburg-Essen, Duisburg, Germany

11 Department V for Internal Medicine, University Hospital Erlangen, Erlangen, Germany

12 Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany

13 Department of Haematology and Oncology, University Hospital of Jena, Jena, Germany

14 Department of Haematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann, Potsdam, Germany

15 Department of Haematology, Medical Oncology, and Pneumology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

16 Department II of Internal Medicine, University Hospital Wuerzburg, Wuerzburg, Germany

17 Department for Haematology, Oncology and Tumour immunology, Charité Universitätsmedizin Berlin, Berlin, Germany

18 Department of Haematology and Oncology, Paracelsus-Kliniken Osnabrück, Osnabrück, Germany

19 Department III of Internal Medicine, University Hospital Bonn, Bonn, Germany

20 Department of Haematology and Oncology, University of Munich, Munich, Germany

21 Department IV of Internal Medicine, University Hospital Halle, Halle, Germany

22 Clinical Trials Centre Cologne (ZKS Köln), University of Cologne, Cologne, Germany