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Primary prophylaxis of invasive fungal diseases in patients with haematological malignancies: 2022 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO)

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Patients with haematological malignancies (HM) are at high risk of developing invasive fungal disease (IFD) with high morbidity and attributable mortality. We reviewed data published until September 2021 to update the 2017 antifungal prophylaxis recommendations of the German Society of Haematology and Medical Oncology (DGHO). The strong recommendation to administer antifungal prophylaxis in patients with HM with long-lasting neutropenia, i.e. <500 cells/μL for >7 days remains unchanged. Posaconazole remains the drug of choice for mould-active prophylaxis in these patients. Novel treatment options in HM, such as CAR-T-cell treatment or novel targeted therapies for acute myeloid leukaemia (AML) were considered, however, data are insufficient to give general recommendations for routine antifungal prophylaxis in these patients. Major changes regarding specific recommendations compared to the 2017 edition are the now moderate instead of mild support for the recommendations of isavuconazole and voriconazole. Furthermore, published evidence on micafungin allows

recommending it at moderate strength for its use in HM. For the first time we included recommendations for non-pharmaceutical measures regarding IFD, comprising the use of high-efficiency particulate air (HEPA) filters, smoking, measures during construction work and neutropenic diets.
We reviewed the impact of antifungal prophylaxis with triazoles on drug–drug interactions with novel targeted therapies that are metabolized via cytochrome p450 where triazoles inhibit CYP3A4/5. The working group recommends reducing the dose of venetoclax when used concomitantly with strong CYP3A4 inhibiting antifungals. Furthermore, we reviewed data on the prophylactic use of novel antifungal agents. Currently there is no evidence to support their use in a prophylactic setting in clinical practice.

Introduction

Invasive fungal disease (IFD) remains an important cause of severe morbidity and high mortality in patients with haematological malignancies (HM). Patients with long-lasting neutropenia (≤500/μL for ≥7 days), such as patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) during remission-induction chemotherapy (RIC) or patients with severe aplastic anaemia, continue to represent the population at highest risk of developing IFD.[1,2]

The most frequently identified fungal pathogens are *Aspergillus* spp. and *Candida* spp., significantly contributing to mortality in these patients.[3,4] Therefore, mould-active antifungal prophylaxis has been established as a standard-of-care in these patients while those with shorter duration of expected neutropenia (≤500/μL for <7 days) are not considered to be at increased risk of IFD.[5] Other strategies, such as pre-emptive or empiric treatment for IFD are widely implemented, however, these are not discussed in this guideline.[6]

The fungal epidemiology has changed since implementation of routine antifungal prophylaxis with the emergence of resistant fungal pathogens and identification of novel species causing breakthrough IFD (bIFD).[7]

New aspects, such as increased use of targeted drugs and immunomodulating treatment approaches (e.g. chimeric antigen receptor (CAR)-T cells) in many haematological entities fuel the discussion on implementation of antifungal prophylaxis.[8–10] Patients and physician face unknown effects on immune response to fungal pathogens, and in addition, cytochrome p450-mediated potential drug–drug interactions (DDI) between established antifungals and new antineoplastic approaches.[9,11]

Design and methods

An expert group of clinical experts in haematology, oncology, infectious diseases and stem cell transplantation of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO) prepared this guideline document in an established consensus process from August 2021 to January 2022.

This guideline focuses on adult patients and primary antifungal prophylaxis only and excludes autologous and allogeneic HSCT patients. These patient populations as well as treatment of IFD and recommendations regarding antibiotic prophylaxis and prophylaxis of *Pneumocystis jirovecii* pneumonia (PJP) are discussed in separate AGIHO guidelines.[5,12–14]

Topics were distributed among the authors and systematic literature research in PubMed in English language journals was conducted by all authors including the search terms as previously described from August to September 2021. Full texts for all included studies were obtained. Data were extracted and tabulated. Preliminary recommendations for each antifungal agent and patient group were discussed in three online meetings between October and December 2021. Tabulated data were accessible at any time to all authors. If consensus for a recommendation could not be reached by discussion, a majority vote was adopted. The final version of this manuscript was again discussed and finally approved in the present version by the full author panel.

For the grading of quality of evidence (QoE) and strength of recommendations (SoR), established methodology by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) was implemented (Table 1).[15]

We discuss changes of QoE and SoR wherever applicable compared to the previous editions of this guideline.[5,16,17]

The reader is also referred to an updated summary of trials on antifungal prophylaxis published to date by antifungal drug with tabulated information on authors, publishing year, trial design, medication and daily dose per treatment group, number of patients, population characteristics/risk factors, share of proven, probable and possible IFD, and mortality (Tables S1–S8, available as Supplementary data at *JAC* Online).

The recommendations are evidence- and consensus-based, but do not necessarily follow approved indications or the respective labelling of antifungal compounds in different countries or regions.

Results

Since the 2017 edition of this guideline, 38 novel studies comprising 5083 patients receiving primary antifungal prophylaxis have been identified and analysed.

An overview of our recommendations separated by antifungal compounds is tabulated synoptically in Tables 2 and 3.

Antifungal prophylaxis is recommended in patients with long-lasting neutropenia (<500 cells/μL for >7 days) independent from the underlying disease. This typically includes patients with AML or MDS during RIC but also patients with AML/MDS during consolidation chemotherapy, patients with ALL, aplastic anaemia or with relapsed/refractory AML/MDS having curative treatment options.[18,19]

In contrast, patients with shorter expected duration of neutropenia (i.e. <500 cells/μL for ≤7 days) are not at significantly increased risk to develop IFD and should not receive routine antifungal prophylaxis (DI). This comprises patients treated with CAR-T cells and after high-dose chemotherapy with autologous HSCT as well as patients with lymphoma or multiple myeloma.[20]

Azoles

The orally available azoles are the drugs of choice for antifungal prophylaxis. However, there are substantial differences between the various azoles in terms of antifungal spectrum, absorption and DDI. Due to its efficacy and readily absorbable oral tablet

Table 1. ESCMID grading

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 randomized controlled trial
	II	Evidence from ≥1 well-designed clinical trial, without randomization; 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 RCT
	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. Strength of recommendation and QoE for antifungal prophylaxis in patients with high-risk neutropenia (<500 cells/μL ≥ 7 days)

Intention	Intervention	SoR	QoE
Prevent IFD in patients with neutropenia (<500 cells/μL >7 days), excluding allogeneic HSCT	Posaconazole	A	I[a]
		B	III[b]
	Amphotericin B, liposomal, inhalation	B	II
	Isavuconazole	B	IIt
	Voriconazole	B	IIu
	Micafungin	B	II u,t
	Amphotericin B, liposomal, i.v.	C	I
	Caspofungin	C	I
	Fluconazole	C	I
	Itraconazole, p.o. and i.v.	C	I
	SUBA-Itraconazole	C	IIt,h
	Amphotericin B deoxycholate	D	I

[a]Strong recommendation in AML/MDS RIC only.
[b]Other settings, e.g. VSAA and palliative treatment of MDS.
HSCT, haematopoietic stem cell transplantation; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; SUBA, SuperBioAvailability.

formulation the mould-active posaconazole remains the drug of choice for antifungal prophylaxis (AI).

In a network meta-analysis and pharmacoeconomic evaluation of triazole prophylaxis on 5505 participants in 21 randomized controlled trials (RCT) with HM or HSCT, excluding itraconazole capsules, all triazole antifungals were effective in reducing IFD. However, the antifungal efficacy of fluconazole was lower compared to posaconazole or voriconazole.[21]

Posaconazole

Evidence

In patients undergoing RIC for AML or MDS in a well-designed phase 3 RCT, posaconazole significantly reduced incidence of proven and probable IFD and all-cause mortality.[19] In this trial, posaconazole oral suspension was compared to the former standards of fluconazole or itraconazole solution.[19] With the development of posaconazole delayed release tablets and intravenous formulations, non-comparative phase 1b/3 studies found favourable pharmacokinetic results, i.e. drug exposure sufficient for prophylactic efficacy in most patients. No new safety signal was found, including in patients with high plasma concentrations.[22–25] Of note, the intravenous formulation has a very low pH and should be administered via central venous line.[24,25]

Since the 2017 edition of this guideline, three large retrospective cohort studies have reported results in line with the prospective studies mentioned before. A US study compared oral suspension and delayed release tablet formulations in 547 consecutive patients with AML (69%), graft-versus-host disease (GvHD) (18%) or MDS (3%). The incidence of proven or probable bIFD was 1.6% and did not differ significantly between

Table 3. Dosage of recommended drugs (also refer to Table 2)

Drug	Dosage
Posaconazole, oral suspension	200 mg q8h p.o.
Posaconazole, tablet	300 mg q24h p.o. (q12h on day 1)
Posaconazole, i.v.	300 mg q24h i.v. (q12h on day 1)
Amphotericin B, liposomal, inhalation	12.5 mg twice weekly
Amphotericin B, liposomal, i.v.	Dosage not defined; variable dosages and dosing intervals
Caspofungin	50 mg q24h i.v. (70 mg on day 1, 70 mg q24h if patient weighs >80 kg)
Micafungin	50 mg q24h i.v.
Anidulafungin	100 mg q24h i.v. (200 mg on day 1)
Fluconazole	400 mg q24h p.o.
Itraconazole, capsules or i.v. formulation	200 mg q24h p.o./i.v.
Itraconazole, oral solution	2.5–7.5 mg/kg/d or 200 mg q24h
SUBA-itraconazole	200 mg q24h p.o.
Voriconazole	4 mg/kg q12h i.v./p.o.
Isavuconazole	200 mg q24h i.v. (q8h on days 1–2)

i.v., intravenous; p.o., per os; SUBA, SuperBioAvailability.

posaconazole formulations. In eight of these 14 bIFD serum concentrations were determined, and in 7 of 8 they were ≥0.7 µg/mL.[26] A retrospective study from Spain compared prophylaxis with posaconazole oral suspension with intravenous itraconazole in 174 consecutive patients treated for AML or MDS. Rates of proven or probable bIFD were 1.7% and 5.3%.[27] A study from South Korea compared posaconazole prophylaxis with no prophylaxis in 247 patients with AML. Incidence rates of proven or probable IFD were 2.5% and 9.4%.[28]

Recommendation

AGIHO strongly recommends posaconazole prophylaxis for patients undergoing RIC for AML or MDS (AI). The previous recommendation for very severe aplastic anaemia (VSAA) and less intensive treatment settings for AML/MDS remains unchanged (B III) due to a lack of well-designed prospective studies in this specific population and treatment setting.

The formulations appear interchangeable and can be chosen according to the individual patient situation and preference. Posaconazole infusion should be considered in patients who are unable to swallow an oral drug.

Fluconazole

Evidence

Since 2018, one prospective study on fluconazole prophylaxis was conducted. In this multi-centre, randomized, open-label trial caspofungin versus fluconazole was compared for prophylaxis in children, adolescents and young adults with newly diagnosed *de novo*, relapsed or secondary AML during neutropenia. The 5-month cumulative incidence of IFD was 3.1% in the caspofungin group versus 7.2% in the fluconazole group, and 0.5% versus 3.1% for invasive aspergillosis. In this population, prophylaxis with caspofungin compared with fluconazole resulted in significantly lower incidence of IFD, although limited due to the paediatric setting.[29]

Recommendation

Our recommendation regarding fluconazole prophylaxis in long-term neutropenic haematology patients remains low (CI).

Isavuconazole

Evidence

Isavuconazole has been evaluated for primary or secondary antifungal prophylaxis in several retrospective and prospective studies. Hereby, most studies were focused on patients after HSCT[30,31] or solid organ transplantation.[32] More limited data are available on isavuconazole antifungal prophylaxis in non-transplant patients with haematological diseases.[33–35] Efficacy and tolerability of prophylactic isavuconazole in comparison to other antifungal agents such as posaconazole or voriconazole still remains controversial. Bogler *et al.* performed a propensity score matched cohort analysis including allogeneic HSCT recipients of whom 210 received voriconazole and 95 isavuconazole antifungal prophylaxis. While efficacy did not differ significantly between both study groups (incidences of bIFD at day 180 were 2.9% and 3.2%, respectively), isavuconazole was better tolerated than voriconazole.[30] By contrast, another retrospective study including 145 patients with haematological diseases with or without previous HSCT who received 197 courses of isavuconazole prophylaxis found that isavuconazole prophylaxis was associated with a higher percentage of bIFD compared to either posaconazole or voriconazole.[34] Here, bIFD occurred in 10.2% of isavuconazole, 4.1% of posaconazole and 1.1% of voriconazole courses among patients with *de novo* or relapsed/refractory AML.

Recommendation

Isavuconazole might be considered as primary or secondary antifungal prophylaxis in long-term neutropenic haematology patients (BIIt).

Voriconazole

Evidence

Voriconazole remains a cornerstone in the treatment of aspergillosis and some other invasive mould infections.[36,37] Results for voriconazole in the prophylaxis setting had been less convincing, with the largest studies conducted in the early phase after allogeneic HSCT[38]. Several retrospective studies have recently evaluated voriconazole in patients with acute leukaemia receiving chemotherapy.[34,39–45] One retrospective study ($n=175$) found an incidence of bIFD of 3.3% in the voriconazole arm versus 7.2% in the fluconazole arm.[39] In another study in 241 AML patients receiving (re)induction chemotherapy, bIFD rate was 1.1% in the voriconazole arm, slightly lower than observed with either isavuconazole or posaconazole prophylaxis.[34] A study in

AML/MDS patients found that a switch to intravenous antifungals was significantly less common in those 471 patients receiving voriconazole prophylaxis (20.6%) versus those receiving fluconazole or itraconazole (30.1%).[43]

Recommendation

Our recommendation for antifungal prophylaxis with voriconazole in neutropenic haematology patients was upgraded to BIIu.

Itraconazole

Evidence

No prospective clinical trials investigating itraconazole for antifungal prophylaxis in HM have been published since 2018. One retrospective, single-centre, observational study comparing posaconazole ($n=179$) with itraconazole in the prevention of IFD in AML/MDS patients during intensive chemotherapy showed statistically significant differences in the rates of proven or probable IFD (1.4% versus 5.3%).[27] Another retrospective, single-centre, observational study comparing posaconazole ($n=45$) with itraconazole ($n=90$) in the prevention of IFD during AML RIC yielded similar results (bIFD rate 2.2% versus 5.5%).[46]

One single-centre prospective cohort study compared the use of Super BioAvailability (SUBA®)-itraconazole ($n=27$) versus a historical control group of conventional liquid itraconazole ($n=30$) for prophylaxis in patients with HM or undergoing allogeneic HSCT, achieving faster and more stable serum through concentrations.[47]

One non-comparative retrospective study ($n=74$) evaluated safety and tolerability of SUBA-itraconazole, showing moderate rates of breakthrough proven/probable IFD (6%).[48] Another single-centre, retrospective study in lung transplant patients ($n=150$) compared triazoles ($n=78$) with SUBA-itraconazole ($n=88$), with equal incidence rates of IFD (two per group, respectively). However, this study was not designed to assess the efficacy of antifungal prophylaxis.[49]

Recommendation

The AGIHO recommendation for itraconazole or SUBA®-itraconazole prophylaxis for neutropenic haematology patients remains low (CI and CIIt, h, respectively).

Other azoles

Evidence

For other azoles, no relevant literature regarding prophylaxis in HM has been published since 2017. One meta-analysis to assess prevention of oral candidiasis showed the lowest rates for oral candidiasis in patients with clotrimazole treatment, however, it had no comparative studies and did not assess systemic IFD.[50] There is no evidence to support the prophylactic use of clotrimazole, miconazole or ketoconazole (DII).

Recommendation

There is a recommendation against the use of other than the previously listed azole antifungals for systemic antifungal prophylaxis (DII).

Echinocandins

Echinocandins are mostly used for treatment of candidemia reducing overall attributable mortality.[51] However, the use of echinocandins as first-line antifungal prophylaxis is not recommended due to limited evidence from RCTs in this setting.

Anidulafungin

Since 2017, no additional studies have been published for anidulafungin or caspofungin as antifungal prophylaxis in adults.

Caspofungin

Since 2017, one multi-centre, randomized, open-label trial compared caspofungin versus fluconazole for prophylaxis in children, adolescents and young adults with newly diagnosed *de novo*, relapsed or secondary AML during neutropenia following induction and consolidation chemotherapy. Among the 517 randomized participants, 22 in the caspofungin arm and 18 in the fluconazole arm were 18 years or older (median age 9 years). Twenty-three proven or probable IFD events (six in the caspofungin group versus 17 in the fluconazole group) including 14 moulds, seven yeasts and two fungi not further speciated were detected. The 5-month cumulative incidence of IFD was 3.1% in the caspofungin group versus 7.2% in the fluconazole group, and for invasive aspergillosis, it was 0.5% with caspofungin versus 3.1% with fluconazole. In this study, prophylaxis with caspofungin resulted in a significantly lower incidence of IFD; however, the reduction in the very small adult population ($n=40$, 7.7%) in this trial was not determined and is therefore not fully considered in this guideline.[29] The prophylactic use of caspofungin has also been shown to be non-inferior to triazole prophylaxis in another RCT in the paediatric allogeneic HSCT population.[52]

Micafungin

Evidence

Several retrospective studies[53–58] in the transplant setting (allogeneic HSCT and SOT) as well as one prospective clinical trial[59] assessing micafungin prophylaxis in the non-transplant setting have been published since the last update of the guideline. The prospective trial included patients undergoing RIC for AML who received micafungin once daily from the first day of induction therapy until the end of neutropenia.[59] None of the 41 patients developed bIFD. Further retrospective studies in the transplant setting confirmed these findings in larger sample sizes (ranging from 69 to 216 included patients).

Recommendation

Considering the small sample size of the prospective study as well as retrospective data from allogeneic HSCT and SOT patients, our recommendation for micafungin in neutropenic HM changes from CIIh to BIIt, u and the recommendation for caspofungin remains unchanged (CI) due to very limited data in the adult population whereas anidulafungin does not receive a recommendation due to lack of evidence.

Polyenes

Evidence

Regarding the emerging threat of increasingly detected azole-resistant isolates, non-azole antifungal drugs may be of importance for future prophylactic strategies. Comparable to posaconazole, liposomal amphotericin B (L-AmB) exhibits broad-spectrum activity and thus may be helpful in a prophylactic setting. The use of polyenes has been studied in different populations and several clinical trials. Intravenous (IV) L-AmB prophylaxis has been evaluated in adult ALL patients during RIC.[18] The choice of L-AmB in this specific setting arises from CYP3A4-mediated DDI of azoles with vinca-alkaloids that prohibit the concomitant use of azoles during chemotherapy. However, there was no significant difference in IFD incidence comparing L-AmB 5 mg/kg per week and placebo recipients (7.9% versus 11.7%).[18] There is poor evidence to recommend IV L-AmB prophylaxis in ALL (CI). Several other dosing regimens have been used in clinical studies, e.g. a standard dose of 50 mg/q48h[60] or, in the most recent studies, weight-adapted regimens such as 1 mg/kg three times weekly, 3 mg/kg weekly up to 7.5 mg/kg weekly.[18,61–63] Safety and efficacy of these dosing regimens have not been compared systematically, therefore we refrain from recommending a specific dose.

The prophylactic use of aerosolized L-AmB in severely neutropenic patients was graded with BII in the previous versions of this guideline[5,16] as it significantly reduced invasive pulmonary aspergillosis rates and was cost efficient.[64,65]

Recommendation

Our recommendation for the prophylactic use of IV L-AmB with any dose in neutropenic HM remains unchanged (CI). The recommendation for aerosolized L-AmB remains BII; note that this should be administered concomitantly to systematic fluconazole for prophylaxis of candidemia. L-AmB prophylaxis may play an important role in centres with higher rates of azole-resistant fungal isolates. However, the group recommends against the use of amphotericin B deoxycholate due to its toxicity (DI).

Other antifungals (nystatin, terbinafine)

A comprehensive literature review from 2014 identified a meta-analysis from 11 historic trials in cancer patients where nystatin was used as antifungal prophylaxis.[66] No benefit compared to a placebo was found and nystatin is not recommended in this indication (DIIr).

Otherwise, no additional literature has been published since 2017. There is no evidence to support the prophylactic use of terbinafine (DII).

Therapeutic drug monitoring and metabolism

Evidence

Therapeutic drug monitoring (TDM) of antifungals may be useful as toxicity depends on plasma drug levels and inter- and intraindividual pharmacokinetics may vary. However, the association of triazole plasma concentration and efficacy has primarily been shown in the setting of IFD treatment and for itraconazole.[67] Prospective studies proving a plasma concentration-dependent effect on clinical outcome or adverse events in the setting of prophylaxis are scarce.[68] However, the results of some retrospective analyses indicate which azole levels may be required to protect against IFD and avoid toxicity.

Recommendation

In general, assessment of plasma concentration is recommended for triazoles in case of a (suspected) bIFD (AIII) to understand potential reasons for IFD and scope treatment options. In addition, TDM of specific azoles may be useful in specific clinical situations where resorption or metabolism might be affected, e.g. in obesity, renal/organ replacement therapy, gastrointestinal GvHD or intensive care (CIIt).[69] Recommendations for specific triazoles are listed in Table 4. To establish TDM, blood samples should be drawn 3 days (for posaconazole and voriconazole) or 7 days (for itraconazole) after initiation and dose adjustment of antifungal triazole prophylaxis or change of interfering medication.[70] TDM is not well established for fluconazole, echinocandins and polyenes and is therefore not recommended.

Antifungal prophylaxis, targeted therapies and potential drug–drug interactions

Evidence

Targeted antineoplastic therapy for AML is fraught with uncertainties regarding pharmacokinetic compatibility with antifungal prophylaxis, especially strong CYP3A4 inhibitors, with *in vitro* data suggesting potential DDI, however, clinical data on the impact of potential DDI remain sparse (Table S9).[71]

The quantitatively most important and well-studied DDI exists for triazole antifungals and the bcl-2 inhibitor venetoclax. A PK study of 12 patients with AML determined the need to reduce venetoclax dose by at least 75% in combination with posaconazole to achieve equivalent serum levels compared to venetoclax monotherapy.[72] The determination of the exact dose of venetoclax is an ongoing debate and clinical trials are continuing.[73] A retrospective cohort study analysed 121 AML patients treated with venetoclax and hypomethylating agents, 89 of theese concomitantly received an azole.[74,75] The combination resulted in prolonged cytopenia without increased rates of febrile neutropenia, infections or duration of hospitalization. Omission of venetoclax dose reduction was associated with numerically higher rates of these complications. The duration of antifungal prophylaxis in patients receiving venetoclax should be guided by neutropenia; note that the venetoclax dose must be increased on termination of moderate and strong CYP3A4 inhibitors.[71] Bose *et al.* reported no increase of isavuconazole serum levels or associated toxicities in a cohort of 65 AML patients receiving primary isavuconazole prophylaxis during RIC, 27 of which concomitantly received venetoclax alone or in combination with an *FLT3*-inhibitor.[33]

A retrospective analysis of midostaurin with concomitant strong CYP3A4 inhibitors, including posaconazole and voriconazole, from the phase III RATIFY trial demonstrated an earlier onset of but no overall increase in adverse events.[76]

For the second generation *FLT3*-inhibitor gilteritinib, no significant difference in toxicities, need for dose reduction or clinical

Table 4. Recommendations on TDM

Drug	Rationale	Target	SoR	QoE	Comment	Reference
Any triazole: in case of suspected breakthrough IFD	To clarify treatment options	Variable (see below)	A	III		
Oral itraconazole	To monitor for efficacy and toxicity	>0.5 mg/L	B	IIt		104–107
Isavuconazole	To monitor in case of toxicity	2–5 mg/L	C	IIt	Higher concentrations have been associated with an increased risk of adverse events	33,68,108–113
Posaconazole oral suspension	To support efficacy; in case of suspected impaired resorption	>0.7 mg/L (prophylaxis) >1 mg/L	B	IIt	Reduced plasma levels have been demonstrated e.g. in case of GI-GvHD, diarrhoea, concomitant PPI	19,114–125
Posaconazole oral or i.v.	To support efficacy	(treatment)	B	III		
Voriconazole	To support efficacy	>1 mg/L	B	IIt		126,127
Voriconazole	To avoid toxicity	<4.5 mg/L	A	II	Recommendation in case of clinically attributed toxicity	

Comment: recommendations are not generally applicable for a prophylactic setting and refer to specific situation, see section 'Therapeutic drug monitoring and metabolism'.
GI-GvHD, gastrointestinal graft-versus-host-disease; IFD, invasive fungal infection; PPI, proton pump inhibitors

Table 5. Targeted tumour therapies and potential drug–drug interactions

Population	Intention	Intervention	SoR	QoE	Reference
AML/MDS patients treated with					
Venetoclax	Prevent IFD	use triazole antifungal prophylaxis	A[a]	IIu,t	33, 72, 74, 75, 78
	Prevent toxicity	Reduce dose of venetoclax by at least 75% in combination with posaconazole or voriconazole and by 50% in combination with fluconazole or isavuconazole	A	IIu,t	
Gilteritinib	Prevent IFD	Use triazole antifungal prophylaxis without dose adjustment	A[a]	IIu	77
Midostaurin	Prevent IFD	If indicated, use triazole antifungal prophylaxis without dose adjustment	A	IIu	76
Quizartinib	Prevent IFD	If indicated, use triazole antifungal prophylaxis without dose adjustment	A[a]	IIu,t	79
	Prevent toxicity	Reduce quizartinib dose (60 to 30 mg *or* 30 to 20 mg) in combination with posaconazole or voriconazole	B	III	
Ivosidenib	Prevent IFD	If indicated, use triazole antifungal prophylaxis without dose adjustment	A[a]	III	80
	Prevent toxicity	Reduce ivosidenib dose to 250 mg/day in combination with posaconazole or voriconazole	B	III	

AML, acute myeloid leukaemia; IFD, invasive fungal disease; MDS, myelodysplastic syndrome.
[a]Strong recommendation for antifungal prophylaxis, if neutropenia ≥7 days is expected or present.

outcomes was reported between patients with AML receiving or not receiving concomitant triazole prophylaxis.[77]

Recommendation

The guideline group strongly recommends reducing the dose of venetoclax by at least 75% when administered concomitantly to strong CYP3A4 inhibitors (AI). For all other novel targeted therapies, well-designed studies with combined clinical and pharmacokinetic endpoints are currently lacking (Table 5).

Novel antifungals

Several new antifungal classes in late-stage clinical development have the potential for prophylactic use (Table 6).[81] Opelconazole is a novel triazole that is optimized for inhalation to maximize local efficacy while avoiding systemic toxicity.[82] A phase IIb trial will investigate the prophylactic use in lung transplant recipients. Rezafungin, an echinocandin with an extended half-life and once-weekly intravenous administration is currently being evaluated in a phase 3 trial for its potential to prevent IFD by *Candida* spp.,

Table 6. Novel antifungals

Antifungal	Mechanism of action	Future areas of use	Future use in prophylaxis	Clinical trials evaluating prophylactic use
Fosmanogepix/ Manogepix	Inhibition of Gwt1, targets GPI-anchored protein maturation	Invasive infections with *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., Mucorales, *Cryptococcus* spp., *Candida* spp. (except *C. krusei*) Endemic mycoses, including coccidioidomycoses	unclear	
Ibrexafungerp	Glucan synthase inhibitor with alternative binding site	Invasive candidiasis including *C. auris* and *C. glabrata*, resistant invasive pulmonary aspergillosis, other invasive fungal infections	PJP prophylaxis	Preclinical data
Olorofim	Inhibition of dihydroorotate dehydrogenase, targets pyrimidine synthesis	Invasive infections with multi-resistant moulds, including resistant *Aspergillus* spp. and *L. prolificans* Endemic mycoses, including coccidioidomycoses	Mould prophylaxis	NCT02856178
Opelconazole	Triazole with inhaled administration, targets lanosterol-14alpha-demethylase	Infections with *Aspergillus* spp.	Prophylaxis in lung transplants, ICU setting	NCT05037851
Rezafungin	Echinocandin with prolonged half-life, targets glucan synthase	Invasive infections with *Candida* spp., *Aspergillus* spp., *Pneumocystis jirovecii*	Prophylaxis in HSCT and SOT	NCT04368559

GPI, Glycosylphosphatidylinositol; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; PjP, Pneumocystis jirovecii pneumonia; SOT, solid organ transplantation.

Table 7. Recommendations for non-pharmaceutical interventions for prophylaxis of invasive fungal infections

Intention	Intervention	SoR	QoE	Reference
To prevent IFD	Neutropenic diet	D	IIr,u	84–86
To prevent invasive aspergillosis	Wearing well-fitting (FFP2) masks	C	IIt	87
To prevent IFD	HEPA filters	A	IIu	88–91
	LAF systems	B	IIu	
To prevent CVC-related fungal bloodstream infections	Chlorhexidine-coated CVC dressings	C	I	92
To prevent IFD	romyelocel-L*	B	I	93–95
	granulocyte transfusions	B	IIr	
	G-CSF	B	IIu	
To prevent IFD	Quit smoking	A	IIu	96–98

CVC, central venous catheter; FFP2, filtering face piece 2; G-CSF, granulocyte-colony-stimulating factor; HEPA, high efficiency particulate air; IFD, invasive fungal disease; LAF, laminar air flow.
*Cryopreserved human allogeneic myeloid progenitor cells.

Aspergillus spp. and *P. jirovecii* in allogeneic HSCT recipients (NCT04368559).[83] Its prophylactic use could overcome current multidrug regimens. However, to date, clinical trial data on prophylaxis are not available for these promising novel antifungals.

Non-pharmaceutical interventions

Non-pharmaceutical interventions were not extensively reviewed in previous versions of this guideline, thus, in this update, we decided to include it for reasons of completeness and relevance, but only included the most recent studies on this topic (Table 7).

Evidence

Filamentous fungi are ubiquitous environmental organisms, and the risk of exposure depends on various conditions, for example geography, occupation and weather, including humidity, temperature and wind. Inhalation is the most common route, but

fungal uptake may occur following consumption of contaminated products or direct inoculation, too.[99] Regardless of scientific evidence, recommendations of regulatory authorities should be considered, especially for patients with HSCT.[100]

Recommendation

In high-risk neutropenic patients, germ-free diet to minimize pathogen exposure is not beneficial for the prevention of IFD (DIIr, u), but is associated with a higher incidence of nausea, diarrhoea and weight loss.[84–86]

In patients with chemotherapy or HSCT for acute leukaemia, a multicentric RCT failed to prevent the occurrence of IA by wearing well-fitting face masks (CIIt).[87]

HEPA filters—permanent, or portable in case of construction work—(AIIu) and/or laminar air flow (LAF) systems (BIIu) are effective to prevent IFD in patients with chemotherapy for acute leukaemia.[88–91]

In neutropenic patients, chlorhexidine-coated CVC dressings are not recommended for prevention of CVC-related bloodstream infections, including fungemia (CI).[92]

Application of romyelocel-L (cryopreserved human allogeneic myeloid progenitor cells) (BI), granulocyte transfusions (BIIr) or G-CSF (BIIu) may be effective for prevention of fungal infections, but did not show survival benefits.[93–95]

Smoking is a risk factor for invasive pulmonary aspergillosis, independent of antifungal prophylaxis.[96–98] Giving up smoking can be a patient's personal preventive measure (AIIu).

Measuring airborne fungal concentrations, mechanical preventive measures (air lock chambers, sealed windows, surgical masks for neutropenic patients) during hospital constructions and outbreaks are important measures. However, published and unpublished evidence is contradictory, which is why the group decided to not give a graded recommendation.[101,102]

Discussion and conclusion

In this updated guideline, the evidenced-based recommendation for antifungal prophylaxis in patients with AML and MDS after RIC is still valid (AI).

Major changes regarding specific recommendations are an upgrade for the prophylactic use of voriconazole in neutropenic haematology patients from C to B, as more studies showing lower bIFD rates compared to other triazoles. Isavuconazole was also upgraded from C to B with more evidence from retrospective studies published in the recent years. However, with still higher bIFD rates compared to posaconazole and voriconazole. Micafungin at a dose of 50 mg per day is now recommended at a moderate strength with more evidence transferred from the allogeneic HSCT population.

Prophylaxis should be administered preferably with mould-active azoles or an echinocandin, whereby posaconazole remains the drug of choice due to its efficacy and readily absorbable oral tablet formulation (AI). In a network meta-analysis and pharmacoeconomic evaluation of triazole prophylaxis on 5505 participants in 21 RCTs with HM or HSCT, other than itraconazole capsule, all triazole antifungals were effective in reducing IFD. However, the antifungal efficacy of fluconazole was lower compared to posaconazole or voriconazole.[21] In addition to the respective licensing status and the increased interaction potential, it is important to note that TDM may help monitoring potential toxicity, especially during prophylaxis with voriconazole (AIIt). Safety of voriconazole was inferior when compared to posaconazole in retrospective studies.[40,45] Patients with persistent neutropenia due to active underlying malignant disease and thus an increased risk of IFD may also benefit from antifungal prophylaxis (BIII). In individual cases, the specific cellular immune status must be considered, which, in addition to new antineoplastic compounds, is the primary driver of the IFD risk.[71,103] Under certain circumstances, non-pharmaceutical measures may help to prevent IFD in neutropenic haematological patients. With IFD rates remaining low in patients after high-dose chemotherapy with autologous HSCT or CAR-T-cell therapy, no general prophylaxis is recommended. For patients during or after allogeneic HSCT, we refer to the specific guideline of our society.[13]

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Supplementary data

Tables S1 to S9 are available as Supplementary data at *JAC* Online.

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