onkopedia

onkopedia guidelines

Primary antifungal prophylaxis in patients with hematologic neoplasms

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

SSMO SSOM SGMO

SGH+SSH

Publisher

DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
Bauhofstr. 12
D-10117 Berlin

Executive chairwoman: Prof. Dr. med. Claudia Baldus

Phone: +49 (0)30 27 87 60 89 - 0

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

www.onkopedia-guidelines.info

Table of contents

Primary antifungal prophylaxis in patients with hematologic neoplasms

Date of document: October 2023

Compliance rules:

- Guideline
- Conflict of interests

Authors: Jannik Stemler, Sibylle Mellinghoff, Yascha Khodamoradi, Rosanne Sprute, Annika-Yanina Classen, Sonja Zapke, Martin Hoenigl, Robert Krause, Martin Schmidt-Hieber, Werner Heinz, Michael Klein, Philipp Köhler, Blasius Liss, Michael Koldehoff, Christoph Buhl, Olaf Penack, Georg Maschmeyer, Enrico Schalk, Cornelia Lass-Flörl, Meinolf Karthaus, Markus Ruhnke, Oliver A. Cornely, Daniel Teschner

on behalf of the Working Group on Infections in Hematology and Oncology (AGIHO)

Previous authors: Nael Alakel, Gerhard Behre, Dieter Buchheidt, Maximilian Christopeit, Nicola Giesen, Justin Hasenkamp, Michael Kiehl, Stefan Krause, Karin Mayer, Silke Neumann, Helmut Ostermann, Jens Panse, Christina Rieger, Michael Sandherr, Katharina Schweer, Daniela Tacke, Andrew J. Ullmann, Marie von Lilienfeld-Toal, Hans-Heinrich Wolf

1 Summary

Immunosuppressed patients are at high risk for invasive fungal infections, especially after intensive chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and after allogeneic stem cell transplantation. Despite advances in the treatment of invasive fungal infections in recent decades, they are still associated with substantial morbidity and mortality. Thus, for certain patient populations and clinical situations, there is a proven benefit of antifungal prophylaxis through clinical trials. More recent data lead to periodic changes in previous recommendations.

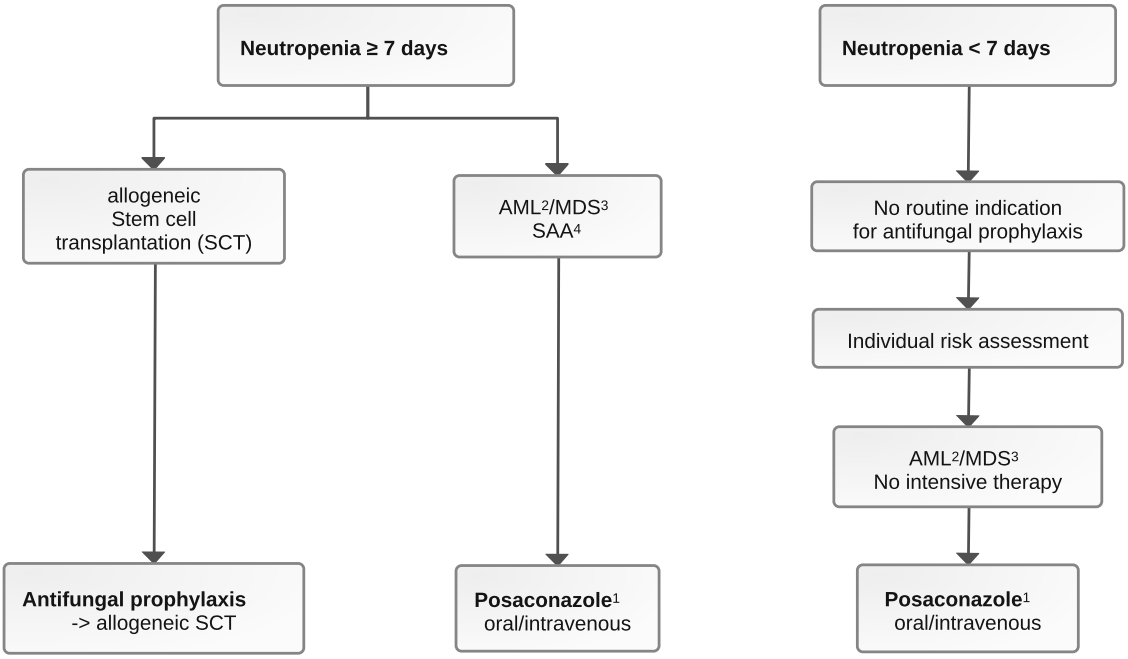
The guideline 'Antifungal primary prophylaxis in patients with hematologic neoplasms' was prepared by the Working Group on Infections of the DGHO (AGIHO) for the diagnosis and therapy of these patients [1]. It is based on a systematic literature search, a uniform assessment of the strength of evidence [2] and a consensus-building process. This is the summary of these recommendations.

6 Therapy

6.1 Therapy structure

The recommendations for antifungal prophylaxis in relation to the underlying disease and treatment are summarized in Figure 1.

Figure 1: Antifungal prophylaxis in patients with hematologic neoplasms.



Legend:

[1] alternative antifungal agents with lower strength of evidence see Table 1,
[2] acute myeloid leukemia,
[3] myelodysplastic syndrome,
[4] severe aplastic anemia

6.1.1 Prolonged neutropenia (<500 neutrophils/µl for ≥ 7 days) after therapy of hematologic neoplasms

Prolonged neutropenia was defined as <500 neutrophils/µl for ≥7 days. Data and recommendations are summarized in Table 1. Patients after allogeneic stem cell transplantation were excluded [2].

Table 1: Recommendations for primary antifungal prophylaxis in patients with hematologic neoplasms with neutropenia ≥ 7 days.[1]

Drug	Recommendation and evidence[1] [2]
Posaconazole	**A-I**[2] **B-III**[3]
Amphotericin B, liposomal, inhalation	**B-II**
Amphotericin B, liposomal, iv	**C-I**
Caspofungin	**C-I**
Fluconazole	**C-I**
Itraconazole, p.o. + iv	**C-I**
SUBA itraconazole	**C-II$_{t,h}$**
Isavuconazole	**B-II$_{t}$**
Micafungin	**B-II$_{u,\ t}$**
Voriconazole	B-II$_{u}$
Amphotericin B, deoxycholate	**D-I**

Legend:
:
[1] *Recommendations are not applicable to patients with ALL.*
[2] *strong recommendation for induction therapy of patients with AML/MDS.*
[3] *vSAA, non-intensive therapy of MDS.*

Table 2: Dosages of antifungal primary prophylaxis

Drug	Dosages	Drug monitoring (target mirror)	Recommendation and evidence [2]
Amphotericin B liposomal, inhalation	1. mg 2 times/week		
Amphotericin B liposomal, infusion solution	Recommended dose is not defined		
Anidulafungin	100 mg q24h i.v. (200 mg on day 1).		
Caspofungin, iv	50 mg q24h i.v. (70 mg on day 1, 70 mg also from day 2 if > 80 kg).		
Fluconazole, capsules	400 mg q24h p.o.		
Isavuconazole, iv	200 mg q24h (on day 1-2 q8h)		
Itraconazole, capsules	200 mg q24h p.o.		
Itraconazole, oral suspension	1. - 7.5 mg/kg or 200 mg q24h		
Itraconazole, iv	200 mg q24h i.v.		
SUBA - Itraconazole	200 mg q24h p.o.		
Micafungin, iv	50 mg q24h i.v.		
Posaconazole, oral suspension	200 mg q8h p.o. (2 times/day on day 1)	> 700 ng/ml	**B-II$_{t,u}$**
Posaconazole, tablets	300 mg q24h p.o. (2 times/day on day 1)	> 500 ng/ml	**B-II$_{t,u}$**
Posaconazole, iv	300 mg q24h i.v. (2 times/day on day 1)	> 500 ng/ml	**B-II$_{t,u}$**
Voriconazole	4 mg/kg q12h i.v./p.o.		**B-II$_{t,u}$**

Table 3: Recommendations for therapeutic drug monitoring

Substance	Rationale	Destination	SoR	QoE	Comment
All triazoles: In the event of a possible breakthrough IFI	description of therapeutic options	variable	A	III	
Oral itraconazole	Monitoring for efficacy and toxicity	>0.5 mg/L	B	IIt	
Isavuconazole	Monitoring in case of toxicity	2 - 5 mg/L	C	IIt	Higher concentrations are associated with increased toxicity
Posaconazole Oral suspension	Optimization of efficacy (even in case of reduced absorption)	>0.7 mg/L (prophylaxis) >1 mg/L (therapy)	B	IIt	Reduced plasma levels in GI-GvHD, diarrhea, PPI simultaneous.
Posaconazole p.o./i.v.	Optimization of efficacy		B	III	
Voriconazole	Optimization of efficacy	>1 mg/L	B	IIt	
Voriconazole	To avoid toxicity	<4.5 mg/L	A	II	Recommended in case of suspected toxicity

Table 4: Oral tumor therapy for AML/MDS and potential interactions with antifungals.

Therapy	Intention	Intervention	SoR	QoE
Venetoclax	Prophylaxis of invasive mycoses	Triazoles	A	$II_{u,t}$
	Reduction of interactions / toxicity	Dose reduction of venetoclax by at least 75% in combination with posaconazole or voriconazole and by 50% in combination with fluconazole or isavuconazole.	A	$II_{u,t}$
Gilteritinib	Prophylaxis of invasive mycoses	Triazoles, no dose adjustment necessary	A	II_{u}
Midostaurin	Prophylaxis of invasive mycoses	Triazoles, no dose adjustment necessary	A	$II_{u,a}$
Quizartinib	Prophylaxis of invasive mycoses	Triazoles, no dose adjustment necessary	A	$II_{u,t}$
	Reduction of interactions / toxicity	Dose reduction of quizartinib (60 to 30 mg or 30 mg to 20 mg) in combination with posaconazole or voriconazole.	B	III
Ivosidenib	Prophylaxis of invasive mycoses	Triazoles, no dose adjustment necessary	A	III
	Reduction of interactions / toxicity	Dose reduction ivosidenib to 250 mg/d in combination with posaconazole or voriconazole.	B	III

9 References

1. Stemler, J, Mellinghoff, SC, Khodamoradi Y et al: 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). J Antimicrob Chemother. 2023 Aug 2;78(8):1813-1826. DOI:10.1093/jac/dkad143
2. Ullmann AJ, Schmidt-Hieber M, Bertz H et al: Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. Ann Hematol 95:1435-1455, 2016. DOI:10.1007/s00277-016-2711-1

15 Authors' Affiliations

Dr. med. Christoph Buhl
Klinikum Leverkusen
Medizinische Klinik 3
Am Gesundheitspark 11
51375 Leverkusen
christoph.buhl@klinikum-lev.de

Dr. med. Annika-Yanina Classen
Universitätsklinikum Köln
Klinik I für Innere Medizin
Klinische Infektiologie
Kerpener Str. 62
50937 Köln
annika.classen@uk-koeln.de

Prof. Dr. med. Oliver A. Cornely
Uniklinik Köln, Klinik I für Innere Med.
Zentrum für Klinische Studien
Infektiologie-Hämatologie-Onkologie
Kerpener Str. 62
50937 Köln
oliver.cornely@uk-koeln.de

Prof. Dr. med. Werner Heinz
Caritas-Krankenhaus Bad Mergentheim
Med. Klinik 2
Uhlandstr. 7
97980 Bad Mergentheim
Werner.Heinz@ckbm.de

Ass.-Prof. Dr. med. univ. Martin Hoenigl
University of California
Division of Infetctious Diseases
UCSD
200 W. Arbor Drive #8208
San Diego, CA 92103
mhoenigl@ucsd.edu

Prof. Dr. med. Meinolf Karthaus
MVZ Perlach
Schmidbauerstr. 44
81737 München
studien.karthaus@gmx.de

Dr. med. Yascha Khodamoradi

Dr. med. Michael Klein
Klinikum Vest, Knappschaftskrankenhaus Recklinghausen
Akademisches Lehrkrankenhaus der
Ruhr-Universität Bochum
Medizinische Klinik III
Dorstener Str. 151
45657 Recklinghausen
michael.klein@knappschaft-kliniken.de

PD Dr. med. Philipp Köhler
Universitätsklinikum Köln
Klinik I für Innere Medizin
Kerpener Str. 62
50937 Köln
philipp.koehler@uk-koeln.de

Prof. Dr. med. Dipl.-Biol. Michael Koldehoff
MVZ ZotzKlimas Düsseldorf
Immermannstr. 65D
40210 Düsseldorf

Univ. Prof. Dr. med. Robert Krause
Klinische Abteilung für Infektiologie
Universitätsklinik für Innere Medizin (UKIM)
Medizinische Universität Graz
Auenbruggerplatz 15
A-8036 Graz
robert.krause@medunigraz.at

Univ.-Prof. Dr. Cornelia Lass-Flörl
Medizinische Universität Innsbruck
Institut für Hygiene und
Med. Mikrobiologie
Schöpfstr. 41
A-6020 Innsbruck
cornelia.lass-floerl@i-med.ac.at

Dr. med. Blasius Liss
HELIOS Universitätsklinikum Wuppertal
Med. Klinik 1 für Hämatologie,
Onkologie und Palliativmedizin,
Nephrologie, Rheumatologie
Heusnerstr. 40
42283 Wuppertal
blasius.liss@helios-gesundheit.de

Prof. Dr. med. Georg Maschmeyer
Deutsche Gesellschaft für Hämatologie
und Medizinische Onkologie (DGHO)
Onkopedia-Koordinator
Bauhofstr. 12
10117 Berlin
maschmeyer@dgho.de

PD Dr. med. Sibylle Mellinghoff
Universitätsklinikum Köln
Klinik I für Innere Medizin
Kerpener Str. 62
50937 Köln
Sibylle.mellinghoff@uk-koeln.de

Prof. Dr. med. Olaf Penack
Charité - Universitätsmedizin Berlin
CVK: Campus Virchow-Klinikum
CC 14: Tumormedizin
Augustenburger Platz 1
13353 Berlin
olaf.penack@charite.de

Prof. Dr. med. Markus Ruhnke
Helios Klinikum Aue
Klinik für Hämatologie/Onkologie
und Palliativmedizin
Gartenstr. 6
08280 Aue
Markus.Ruhnke@helios-gesundheit.de

PD Dr. med. habil. Enrico Schalk
Universitätsklinikum Magdeburg
Klinik für Hämatologie, Onkologie und Zelltherapie
Leipziger Str. 44
39120 Magdeburg
enrico.schalk@med.ovgu.de

Prof. Dr. med. Martin Schmidt-Hieber
Medizinische Universität Lausitz - Carl Thiem
2. Med. Klinik
Klinik für Hämatologie und Onkologie
Thiemstr. 111
03048 Cottbus
M.Schmidt_Hieber@mul-ct.de

Rosanne Sprute
Uniklinik Köln
Klinik I für Innere Medizin
Klinische Infektiologie
50931 Köln
rosanne.sprute@uk-koeln.de

Dr. Jannik Stemler
Universitätsklinikum Köln
Klinik I für Innere Medizin
CECAD Institut für Translationale Forschung
Kerpener Str. 62
50937 Köln
jannik.stemler@uk-koeln.de

PD Dr. med. habil. Daniel Teschner
Universitätsklinikum Würzburg
Medizinische Klinik II
Oberdürrbacher Str. 6
97080 Würzburg
teschner_d@ukw.de

Dr. med. Sonja Zapke
Helios Universitätsklinikum Wuppertal
Medizinische Klinik I
Heusnerstr. 40
42283 Wuppertal
sonja.zapke@helios-gesundheit.de

16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.