Antifungal prophylaxis in HSCT Patients

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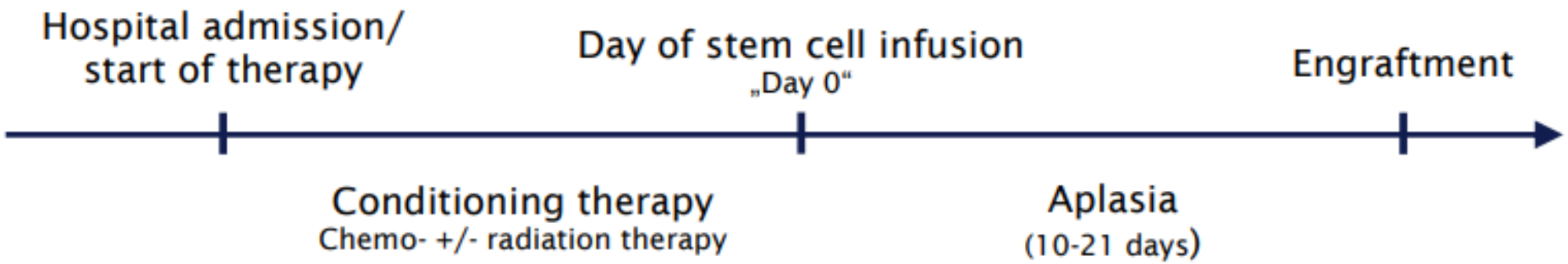
Hematopoietic stem cell transplantation (HSCT)



- **Autologous HSCT**

  Infusion of the patient‘s own hematopoietic stem cells after prior harvest and storage

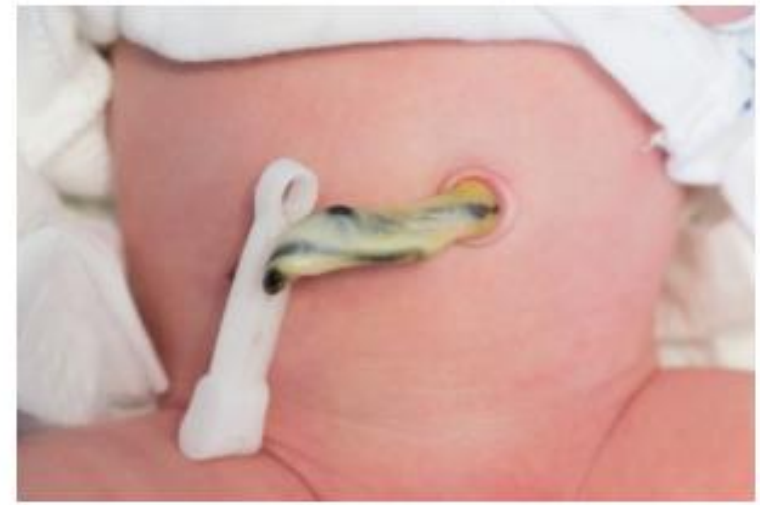
- **Allogeneic HSCT**

  Infusion of hematopoietic stem cells from a non-self related or unrelated donor according to genetic matching (HLA compatibility)

Stem Cell Source

Bone marrow

Peripheral blood



Cord blood

Specific Types of Allogeneic Donors

- **Matched related** or partially matched related donor, such as a sibling with the same or similar HLA type
- **Unrelated** donor or matched unrelated donor
- **Haploidentical**: parent, cousin, sibling, or childis the donor; one HLA haplotype matches. Although haploidentical or other HLA-mismatched transplants may lead to a high incidence of graft-versus-host disease(GVHD), administration of cyclophosphamide early posttransplant and T-cell depletion of the grafts may limit risks of GVHD.
- **Cord:** umbilical cord blood (UCB) usually partially HLA matched not matched for blood type; sometimes two cords used to provide blood with sufficient cells in adults
- **Haplocord**: haploidentical peripheral blood stem cells plus cord blood cells; haplocord engrafts rapidly but may not be sustained, yet provides neutrophil production until the cord engrafts

Risk for infection after HSCT

Allogeneic HSCT  **Autologous HSCT**

- Type of conditioning therapy
- *In vivo* T-cell depletion (anti-thymocyte globulin [ATG])
- More extensive mucosal injury during conditioning
- Immunosuppressive therapy (CNIs, MMF, MTX, ***corticosteroids [!]***)
- Immunodisparity (increased risk of infection with HLA mismatches)
- Graft-versus-host disease (GVHD)

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Risk for infection after HSCT

- Age
- Comorbidities
- Diagnosis *(previous therapies [!])*
- Prior infections of the donor and/or the recipient
- Pre-transplant specific immunity to *cytomegalovirus* (CMV), *herpes simplex virus* (HSV), *varicella-zoster virus* (VZV), and/or *Epstein-Barr virus* (EBV)

Patient-related risk factors

General measures to reduce the risk of infection

- Environmental measures

Neutropenic diet, no plants, wearing of masks, isolated patient rooms, laminar air flow etc.

- Donor selection

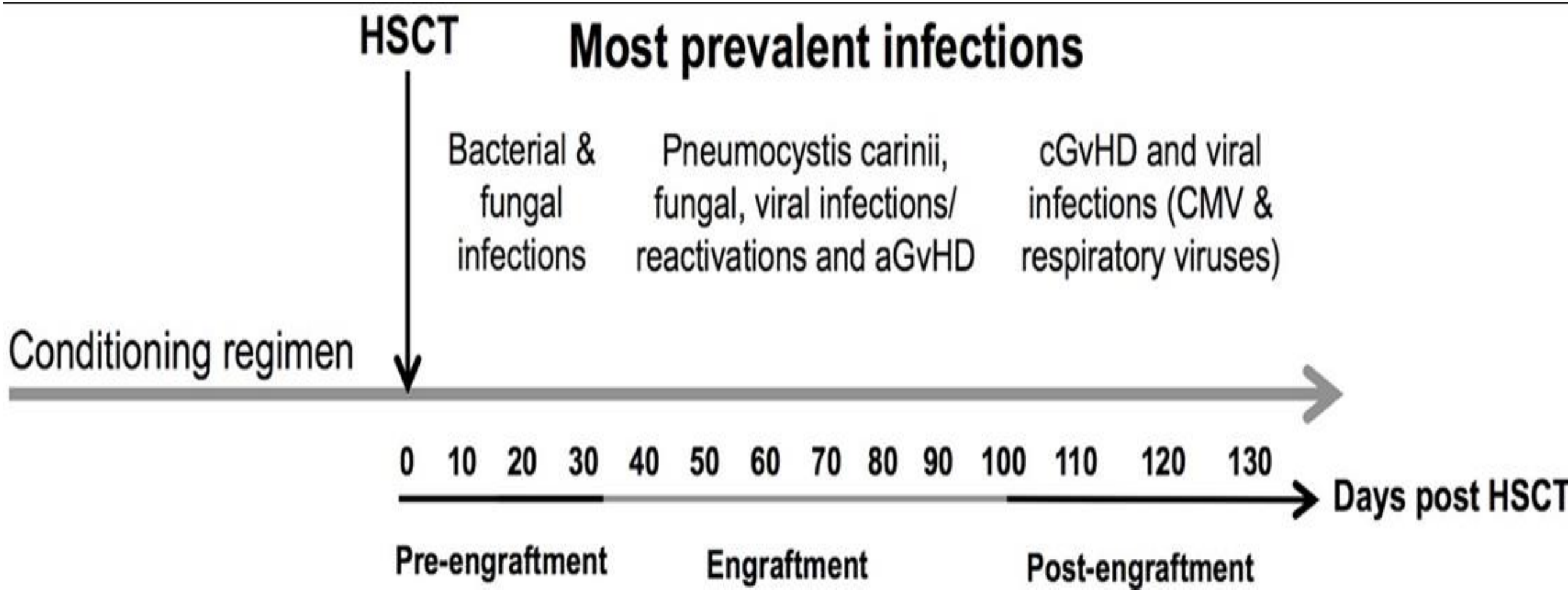
HLA matching, Donor/recipient CMV serostatus, Donor/recipient hepatitis B virus serostatus, pre-HSCT testing

- Conditioning regimen and dose of hematopoietic stem cells

Avoidance of T-cell depletion, shorter duration of aplasia

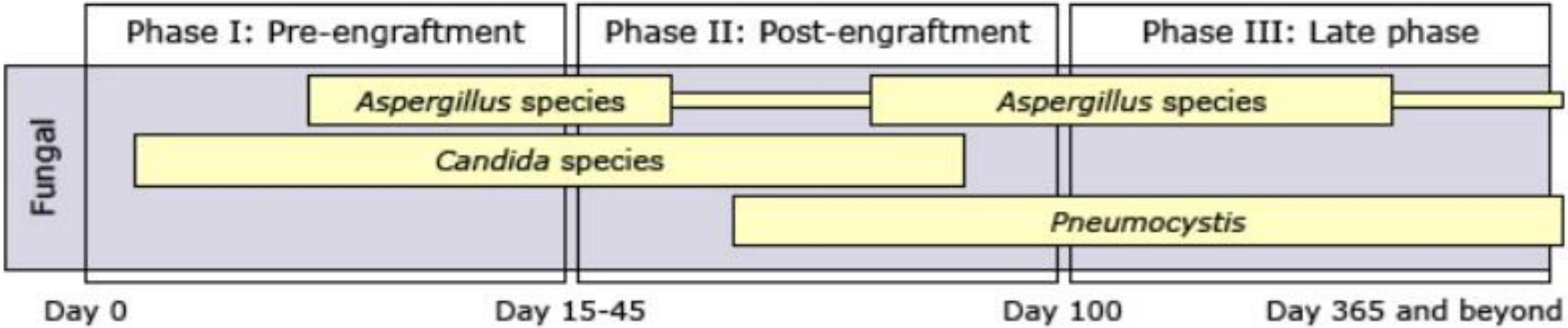
- Avoidance of excessive immunosuppression and myelosupression

- **Antimicrobial prophylaxis or pre-emptive therapy**

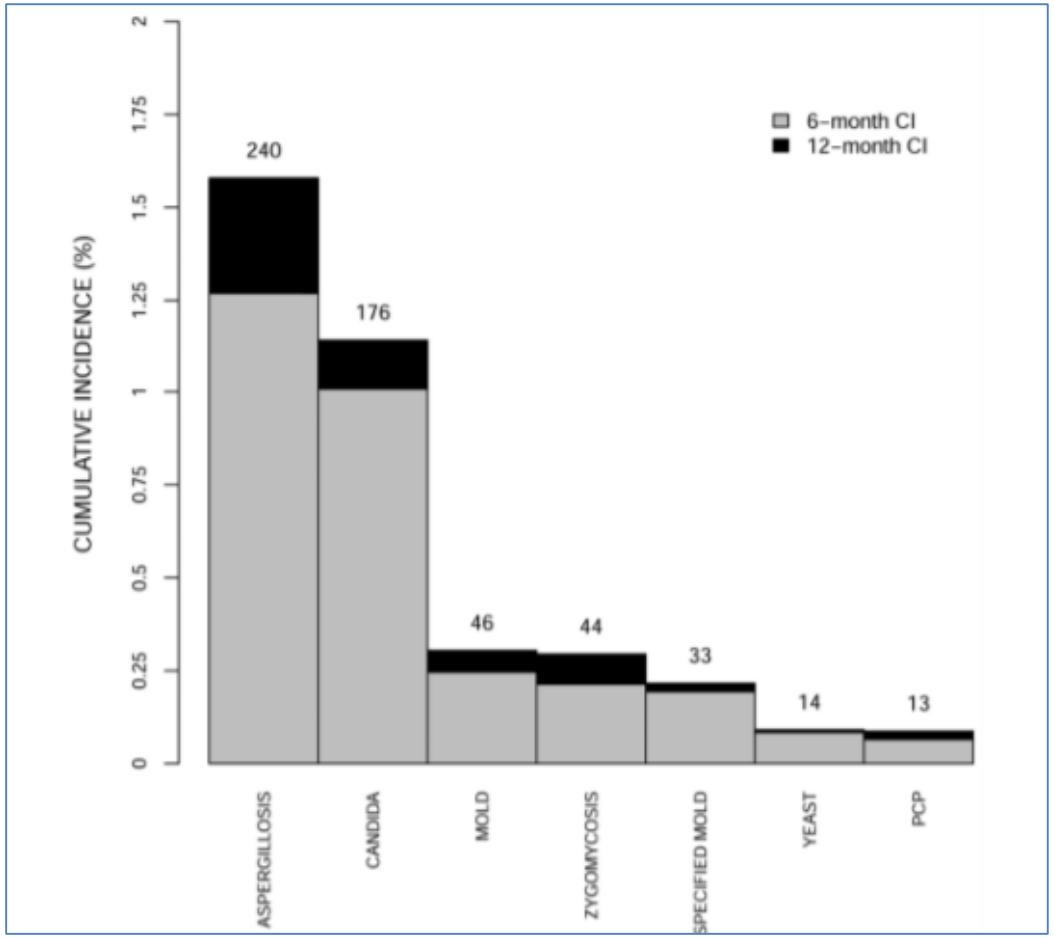

HSCT
Most prevalent infections
Bacterial & fungal infections
Pneumocystis carinii, fungal, viral infections/ reactivations and aGvHD
cGvHD and viral infections (CMV & respiratory viruses)
Conditioning regimen
0 10 20 30 40 50 60 70 80 90 100 110 120 130
Days post HSCT
Pre-engraftment
Engraftment
Post-engraftment

Three separate “at risk” periods:

- First peak around **peri-engraftment** associated with neutropenia,
- Second peak **between 40 and 70 days** associated with acute GVHD,
- Late peak late after transplant with **cGVHD**.


Phase I: Pre-engraftment
Phase II: Post-engraftment
Phase III: Late phase
Fungal
Aspergillus species
Aspergillus species
Candida species
Pneumocystis
Day 0
Day 15-45
Day 100
Day 365 and beyond

- **Invasive aspergillosis** is the most common invasive fungal infection HSCT recipients.



Risk factors for IFD in allogeneic HSCT

High risk-conditions during engraftment	High-risk conditions after engraftment*
Active acute leukaemia at transplant	Grade III-IV acute GVHD
Cord-blood transplant	Grade II acute GVHD in transplant from alternative donors, or unresponsive to standard steroid therapy
MMRD or UD and ≥ 1 additional risk factor: Iron overload, Early or recurrent CMV infection, acute GVHD ≥ grade 2, Delayed engraftment(> 3weeks neutropenia),	Secondary neutropenia cGVHD+ high dose streiod therapy
Prior fungal infection (secondary prophylaxis) Age>40+acute GvHD receiving steroids	Multiple factors: alternative donor, early CMV infection, steroid therapy for more than 1 week

		Yeasts						Molds	
		Candida albicans	Candida glabrata	Candida parapsilosis	Candida tropicalis	Candida krusei	Candida lusitaniae	Aspergillus fumigatus	Mucorales
Yeast-active	Fluconazole	++	+/-	++	++	-	++	-	-
	Echinocandins	++	+	++	++	++	++	+/-	-
Mold-active	Amphotericin B	++	++	++	++	++	-	++	++
	Itraconazole	++	+/-	++	++	+/-	++	++	-
	Voriconazole	++	++	++	++	++	++	++	-
	Posaconazole	++	++	++	++	++	++	++	++
	Isavuconazole	++	++	++	++	++	++	++	++

Souza, Front Microbiol 2017

Intervention	**Fluconazole/Itraconazole/Posaconazole**		**Fluconazole**	**Voriconazole**
Comparator	**No systemic antifungal**		**Anti-mold agent**	**Fluconazole**
Patients	All patients	Allogeneic HSCT	All patients	Allogeneic HSCT
Documented IFI	↓ (RR 0.50; 95%CI: 0.41-0.61)	↓ (RR 0.33; 95%CI: 0.18-0.63)	= (RR 1.40; 95%CI: 0.91-2.14)	=/↓ (7.3% vs. 11.2%; p=0.12)
IFI-related mortality	↓ (RR 0.55; 95%CI: 0.41-0.57)	↓ (RR 0.52; 95%CI: 0.27-0.99)	↑ (RR 1.58; 95%CI: 1.00-2.50)	
All-cause Mortality	↓ (RR 0.84; 95%CI: 0.74-0.95)	↓ (RR 0.62; 95%CI: 0.45-0.85)	= (RR 1.14; 95%CI: 0.95-1.37)	= (81% vs. 72%; p=0.32)
Drug discontinuation			↓ (RR 0.40; 95%CI: 0.30-0.52)*	= (44% vs. 40%; p=n.s.)

* for itraconazole vs. fluconazole; confirmed for other triazoles in Ethier, Br J Cancer 2012

Comparison of Antifungal Prophylaxis Drugs in Patients With Hematological Disease or Undergoing Hematopoietic Stem Cell Transplantation A Systematic Review and Network Meta-analysis

JAMA Network Open. 2020;3(10):e2017652.

- Of 39 709 studies identified, **69 studies** met the criteria for inclusion.

- Regarding **IFIs**, **posaconazole** was the approach with the highest ranking (SUCRA, 86.7%) was associated with a significant reduction in IFIs (RR, 0.57; 95% CI, 0.42-0.79) and **invasive aspergillosis** infections (RR, 0.36; 95% CI, 0.15-0.85).

- **Caspofungin** (SUCRA, 84.9%) treatment ranked the highest for **reducing fungal infections**.

JAMA Network Open. 2020;3(10):e2017652.

- Findings suggest that, in terms of **the prevention of IFIs and tolerance**, **voriconazole** may be the best prophylactic option for patients undergoing HSCT, and posaconazole may be the best prophylactic option for patients with AML or MDS.

- JAMA Network Open. 2020;3(10):e2017652.

2020 by American Society of Clinical Oncology

- Administer systemic antifungal prophylaxis to **children and adolescents** undergoing allogeneic HSCT pre-engraftment and to those receiving systemic immunosuppression for the treatment of graft-versus host disease

- The panel recognized that these two phases of therapy are associated with different epidemiology of IFD

- We suggest that systemic antifungal prophylaxis not be used routinely in children and adolescents undergoing autologous HSCT.
- In **allogenic HSCT**, If systemic antifungal prophylaxis is warranted, administer a **mold-active agent**
- This **strong recommendation** was based on the comparison of different systemic antifungal prophylaxis agents where mold-active agent versus fluconazole significantly reduced proven or probable IFD, mold infection, and IA, and reduced fungal infection–related mortality.

NCCN Clinical Practice Guidelines in Oncology

Version 2.2022 — August 19, 2022

Autologous HCT with mucositis[f]	• Fluconazole[g] or an echinocandin[h] (both category 1)	
Autologous HCT without mucositis	No prophylaxis (category 2B)	N/A
Allogeneic HCT (neutropenic)	• Fluconazole[g] or an echinocandin[h] (both category 1) • Voriconazole,[g] posaconazole,[g] isavuconazole,[g] or amphotericin B products[i] (all category 2B)	Continue during neutropenia[j]
Significant GVHD receiving immunosuppressive therapy	• Posaconazole[g] (category 1) • Voriconazole,[g] echinocandin, or amphotericin B products[i] (all category 2B)	Until resolution of significant GVHD

NCCN Clinical Practice Guidelines in Oncology

- **Fluconazole** prophylaxis has been shown to effectively decrease fungal colonization, invasive infection, and fungal infection-related mortality in nontransplant patients with leukemia and in **autologous HCT** recipients in a placebo-controlled trial

- In neutropenic allogeneic HCT recipients, prophylactic fluconazole controlled yeast colonization and also decreased the rate of mucosal candidiasis and invasive Candida infections

- Fluconazole conferred significant long-term improvement in survival, possibly by **decreasing Candida antigen-induced GI tract GVHD**

NCCN Clinical Practice Guidelines in Oncology

- **No difference** was noted in the primary endpoint (invasive fungal infection-free survival rate at 180 days) between the fluconazole and voriconazole prophylaxis arms (75% vs. 78%, respectively),

- but a trend for reduced incidence of Aspergillus infections (17% vs. 9%), reduced incidence of invasive fungal infections (11% vs. 7%), and less frequent use of empiric antifungal treatment (30% vs. 24%) was noted in the voriconazole arm, although the differences were not statistically significant

- Data from a prospective, randomized study showed that **posaconazole** was as effective as prophylaxis in allogeneic HCT recipients with **severe GVHD** and reported reduced incidence of invasive aspergillosis and overall invasive fungal infections compared to patients receiving fluconazole

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GUIDELINES/EXPERT CONSENSUS

VIA MEDICA

Antimicrobial prophylaxis in adults and children undergoing hematopoietic cell transplantation: 2021 Polish recommendations

Jan Styczyński[1#*], Agnieszka Piekarska[2#], Agnieszka Zaucha-Prażmo[3], Jan Maciej Zaucha[2], Olga Zając-Spychała[4], Tomasz Wróbel[5], Agnieszka Wierzbowska[6], Adam Walter-Croneck[7], Jacek Wachowiak[4], Marek Ussowicz[8], Tomasz Szczepański[9], Agnieszka Sobkowiak-Sobierajska[4], Małgorzata Sobczyk-Kruszelnicka[10], Katarzyna Smalisz[11], Mariola Sędzimirska[12], Piotr Rzepecki[13], Beata Piątkowska-Jakubas[14], Anna Łojko[15], Ewa Lutwin[16], Ewa Lech-Marańda[17], Bogusław Machaliński[18], Aleksandra Krasowska-Kwiecień[19], Krzysztof Kałwak[8], Marek Hus[7], Iwona Hus[17], Grzegorz Helbig[20], Dorota Hawrylecka[21], Kazimierz Hałaburda[17], Jolanta Goździk[19], Sebastian Giebel[10], Adam Fronczak[6], Jarosław Dybko[12], Agnieszka Druzd-Sitek[22], Katarzyna Drabko[3], Krzysztof Czyżewski[1], Anna Czyż[5], Edyta Cichocka[23], Piotr Boguradzki[24], Maria Bieniaszewska[2], Bartłomiej Baumert[18], Grzegorz Basak[24], Lidia Gil[15##]

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[2]Department of Hematology and Transplantology, Medical University of Gdańsk, Gdańsk, Poland

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[5]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Medical University, Wrocław, Poland

[6]Department of Hematology, Medical University, Łódź, Poland

- The experts **contraindicate fluconazole** in patients with GvHD and high-risk factors , while oral posaconazole continues to be the drug of choice

Recommendations for allogeneic HSCT recipients

Antifungal prophylaxis*	**Pre-engraftment Low risk for molds**	**Pre-engraftment High risk for molds**	**GvHD**
Fluconazole	**A-I**	A-III – against	A-III against
Itraconazole	B-I	B-I	B-I
Voriconazole	B-I	B-I	B-I
Posaconazole OS/tablet	B-II	B-II	**A-I**
Micafungin	B-I	C-I	C-II
Caspofungin /anidulafungin	No data	No data	No data
Liposomal amphotericin B	C-II	C-II	C-II
Aerosolised amphotericin B plus fluconazole	C-III	B-II	No data

Recommendations for PAP in Allogeneic HSCT Patients (**mandell2020**)

Pre-engraftment risk period

(from start of conditioning therapy until 20-40 days after Tx)

Anti mold :

1- Those with extended pre-HSCT neutropenia such as:
AL who have undergone serial CT before Tx

2- MDS

3- AA

4- Fanconi Anemia

All remaining patients should receive anti-yeast Px (ie:1-4wk post Tx)

Recommendations for PAP in Allogeneic HSCT Patients (mandell2020)

Post-engraftment R. P. (4-26 wk post Tx) :

HR patients for mold inf.:

- those with continuing GVHD,
- those receiving HD corticosteroids,
- those with poor graft function

- Fungal infection that occurred within 6-9 mo before

  Tx may not be cured and could reactivate.
- **Patients with more remote fungal infections can receive a standard regimen of fungal prophylaxis.**

- If patients have a Hx of Aspergillosis within 4 mo of Tx or have suspect pulmonary nodules without a specific diagnosis, should :

  A-receive secondary fungal Px(i.e., ongoing maintenance antifungal therapy) and

  B-undergo rescanning before and after Tx

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkad143

Journal of Antimicrobial Chemotherapy

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)

Jannik Stemler [1,2,3], Sibylle C. Mellinghoff [1,2,3], Yascha Khodamoradi [4], Rosanne Sprute [1,2,3], Annika Y. Classen [1,3], Sonja E. Zapke[5], Martin Hoenigl [6], Robert Krause [6], Martin Schmidt-Hieber [7], Werner J. Heinz [8], Michael Klein[9], Philipp Koehler [1,2], Blasius Liss [5,10], Michael Koldehoff [11,12], Christoph Buhl[13], Olaf Penack [14,15], Georg Maschmeyer [16], Enrico Schalk [17], Cornelia Lass-Flörl [18], Meinolf Karthaus [19], Markus Ruhnke[20], Oliver A. Cornely [1,3,21,22] and Daniel Teschner [23,24]*

[1]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany; [2]University of Cologne, Faculty of Medicine and University Hospital Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; [3]German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany; [4]Department of Internal Medicine, Infectious Diseases, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt am Main, Germany; [5]Department Hematology, Oncology, Infectious disease and Palliatve Care, Helios University Hospital Wuppertal, Wuppertal, Germany; [6]Division of Infectious Diseases, Department of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Medical University of Graz, Graz, Austria and BioTechMed, Graz, Austria; [7]2nd Medical Clinic (Hematology, Oncology, Pneumology, Nephrology), Carl-Thiem Clinic Cottbus, Cottbus, Germany; [8]Medical Clinic II, Caritas Hospital, Bad Mergentheim, Germany; [9]Department of Hematology and Medical Oncology, Klinikum Vest, Knappschaftskrankenhaus, Recklinghausen, Germany; [10]School of Medicine, Faculty of Health, Witten/Herdecke University, Witten, Germany; [11]Department of Bone Marrow Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-

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)

Therapeutic drug monitioring (TDM) is recommended for itraconazole, voriconazole and posaconazole (ECIL)

- Posaconazole tablets or iv. formulation are preferred over oral solution (ECIL)
- Do not give azoles during conditioning phase!
- Be aware of drug interactions!

Triazole	Recommended plasma range	Strength of recommendation	Timing of first trough sample
Voriconazole	Prophylaxis and treatment: Acceptable : 1-6 mg/L; Optimal: 2-5 mg/L	AII (efficacy) AII (toxicity)	After 2-5 days; (repeat sampling recommended)
Posaconazole	Prophylaxis: >0.7 mg/L Treatment: >1.0 mg/L	BII (efficacy) AII (efficacy)	Tablet/IV: after 3 days Suspension: 5-7 days
Itraconazole	Prophylaxis: 0.5-4 mg/L Treatment: 1-4 mg/L	AII (efficacy) BII (toxicity)	7-15 days

Take Home Message

Risk factors for IFD in allogeneic HSCT

High risk-conditions during engraftment	High-risk conditions after engraftment*
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Thank you
&
Enjoy Summer