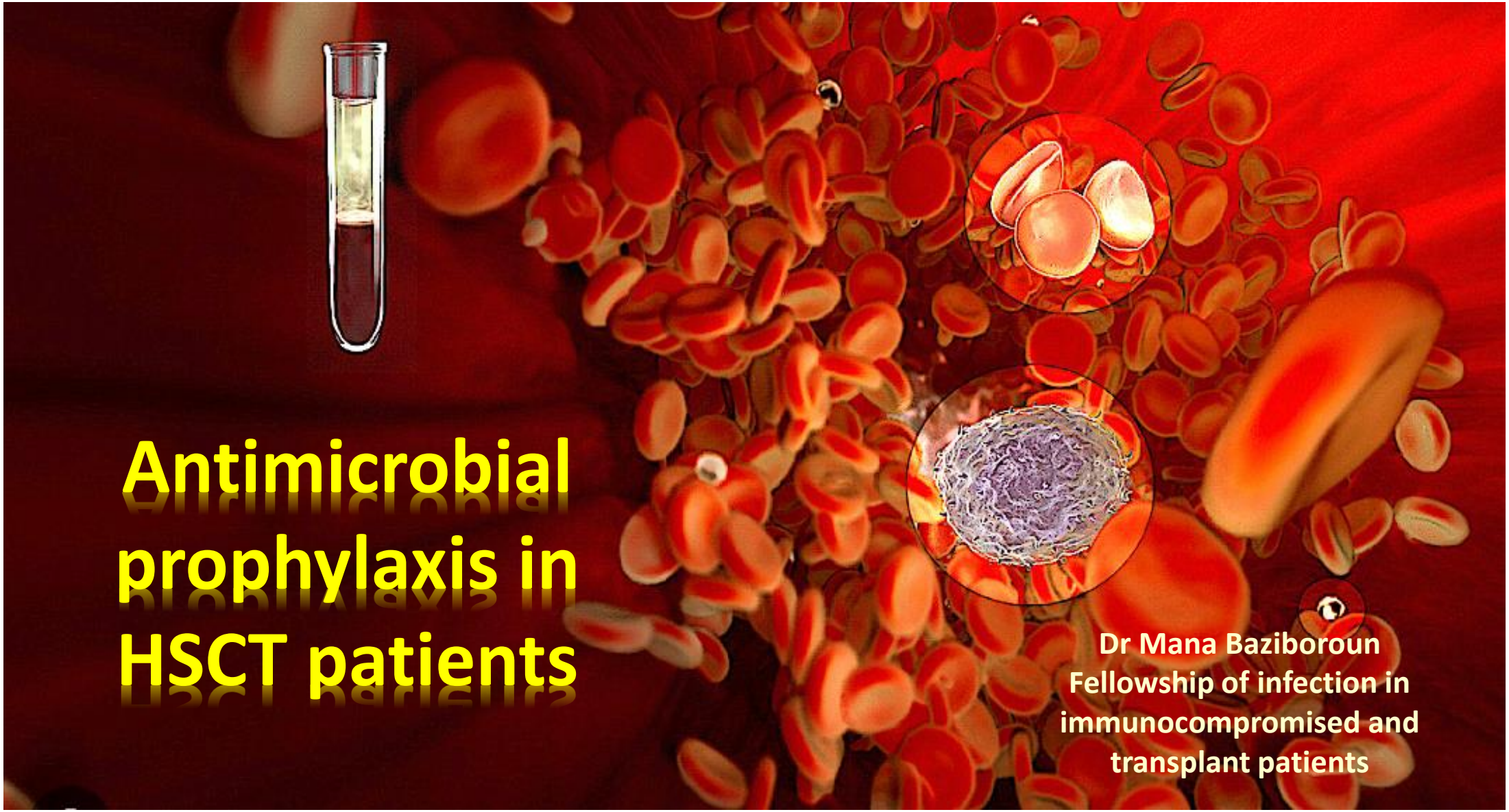

Antimicrobial prophylaxis in HSCT patients

Dr Mana Baziboroun
Fellowship of infection in immunocompromised and transplant patients

Case presentation

- A 54-year-old man was diagnosed with high-risk **myelodysplastic syndrome**. Following 2 cycles of induction therapy he entered a complete remission and was a candidate for allo-HCT.
- He was scheduled to receiving **myeloablative conditioning** and a transplant from a **fully matched unrelated donor**, as well as GVHD prophylaxis included **ATG and cyclosporine/methotrexate**.

- **On his screening tests before transplantation:**
  - ✓ Both donor & recipient were **Seropositive** for HSV1&2,VZV EBV and CMV
  - ✓ **Negative** for HBV,HCV,HIV,HTLV1 and Syphilis
  - ✓ **IGRA+ , PPD-**

- **In your opinion does this patient need any prophylactic antimicrobial regimen?**

Antimicrobial px based on overall infection risk

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what prophylactic anti-HSV regimen do you recommend?

Start & stop time?

Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 days	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologo • Lympho • Multiple • CLL[c] • Purine a clofarab • Anticipated neutropenia 7–10 days	sider fluoroquinolone prophylaxis enia[e] der prophylaxis during neutropenia ted mucositis (See INF-2); consider s (See INF-6) eutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation/maintenance • Alemtuzumab therapy • Moderate to severe GVHD • Anticipated neutropenia greater than 10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PJP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

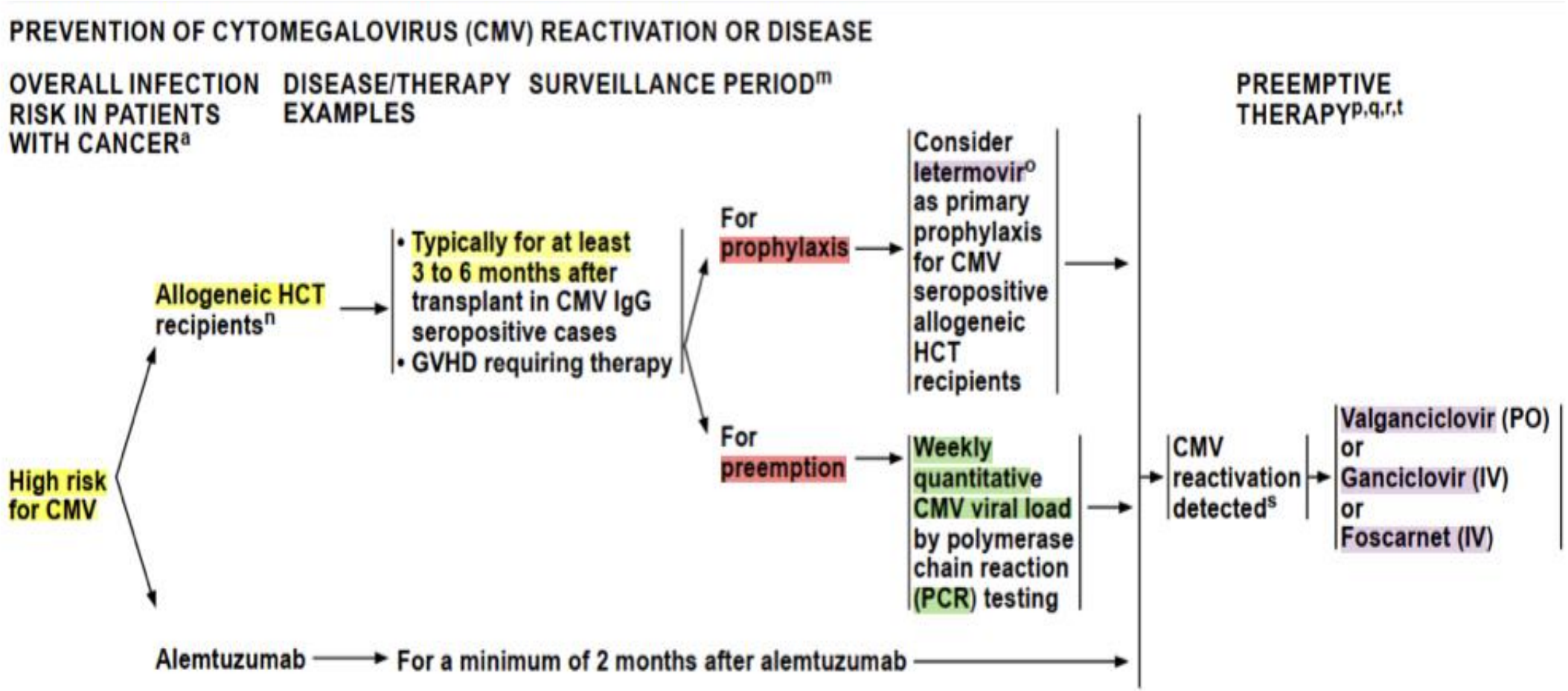
Viral PX in BMT patients

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy F…	…l Prophylaxis
Low		…t during active
High	• … of immunosuppression.	…2200 cells/mcL …considered for at least 1 year after allogeneic HCT

- **HSV Prophylaxis: with acyclovir 400 mg/BID**
- **VZV Prophylaxis: with acyclovir 800 mg/BID**

what `s your opinion about CMV prevention?

Prevention of CMV disease



Prevention of CMV disease

Preemptive therapy

- Start from 2 weeks after HSCT

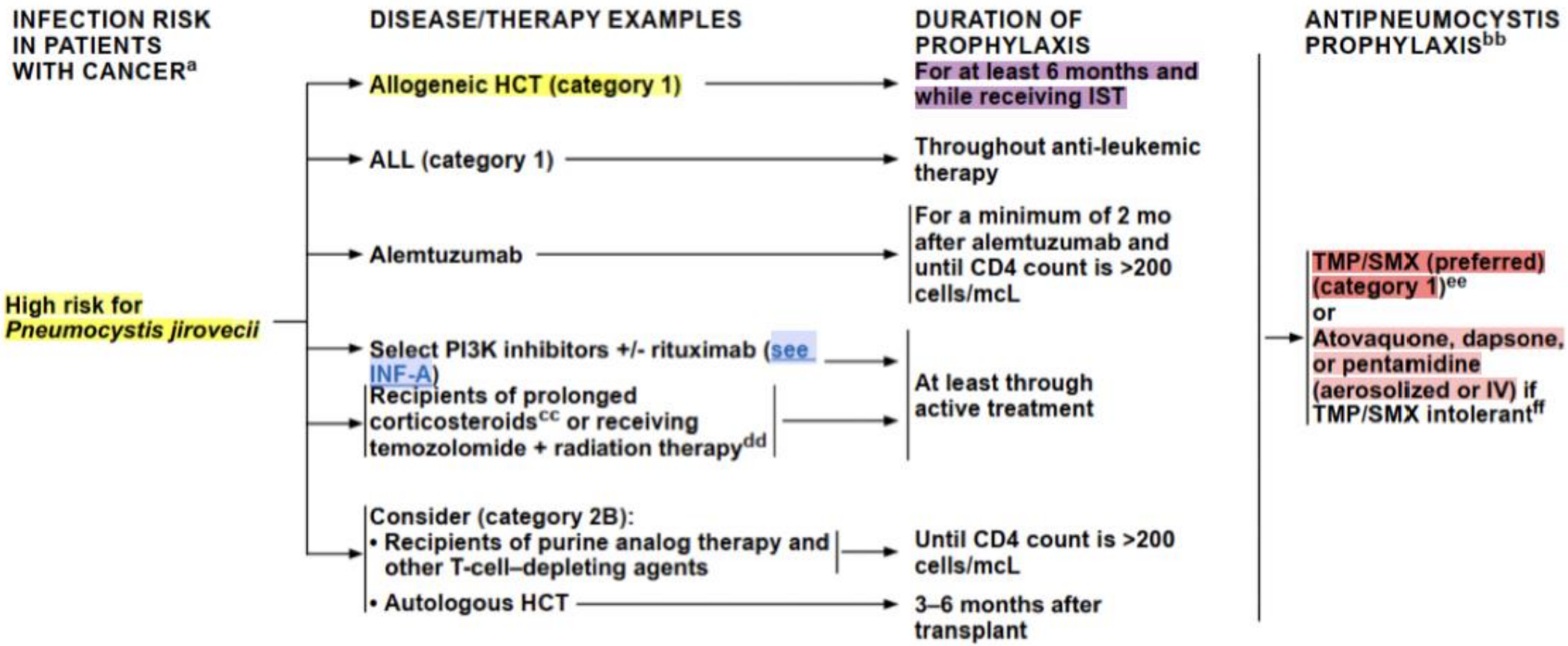
Weekly monitoring

- CMV PCR or PP65 Ag

At least for the first 100 days

what should we do for PCP prophylaxis?

Prophylaxis for PCP



Antifungal PX

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PREVENTION OF FUNGAL INFECTIONS

See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Consider antifungal Prophylaxis Based on Patient- and Center-Specific Risk Factors See Antipneumocystis Prophylaxis (INF-6)	Duration
Intermediate to High	ALL	• Fluconazole[g] or an echinocandin[h] • Amphotericin B products[i] (category 2B)	Typically until resolution of neutropenia
	MDS (neutropenic)	• Posaconazole[g] (category 1) • Voriconazole,[g] fluconazole,[g] an echinocandin,[h] or amphotericin B products[i] (all category 2B)	
	AML (neutropenic)		
	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

J Antimicrob Chemother 2018; **73**: 3221–3230
doi:10.1093/jac/dky286 Advance Access publication 1 August 2018

Journal of Antimicrobial Chemotherapy

European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

Johan A. Maertens[1]*, Corrado Girmenia[2], Roger J. Brüggemann[3], Rafael F. Duarte[4], Christopher C. Kibbler[5], Per Ljungman[6], Zdeněk Racil[7], Patricia Ribaud[8], Monica A. Slavin[9,10], Oliver A. Cornely[11–13], J. Peter Donnelly[14] and Catherine Cordonnier[15,16] on behalf of the European Conference on Infections in Leukaemia (ECIL)†, a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and the European LeukemiaNet (ELN)

Table 4. ECIL recommendations on primary antifungal prophylaxis in adult allogeneic HSCT recipients: pre-engraftment period

	Pre-engraftment risk of mould infections	
Antifungal agent	low	high
Fluconazole 400 mg q24h	A-I	
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	B-II	B-II
Itraconazole oral solution 2.5 mg/kg q12h	B-I	B-I
Voriconazole 200 mg q12h	B-I	B-I
Micafungin 50 mg q24h	B-I	C-I
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h	C-III	B-II
Fluconazole 400 mg q24h		A-III against

Risk level	Risk groups	Recommended prophylaxis†	SoR	QoE
High risk >10% incidence of IFD	Neutrophil <0.1 × 10^9/L for >3 weeks or <0.5 × 10^9/L for >5 weeks (e.g. allogeneic HSCT) Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × 10^9/L for >1 week Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks Unrelated, mismatched or cord blood allogeneic HSCT GVHD – extensive or severe AML – induction/reinduction ALL – induction/[illegible]	First line: Posaconazole Alternate agents: Voriconazole Itraconazole Micafungin Liposomal amphotericin Isavuconazole	A	I
Low risk Less than 5% incidence of [illegible]				
Very low [illegible] incidence of [illegible] No mucositis				
	Other myeloproliferative [illegible] Treatment for solid organ tumours			

SUPPLEMENT ARTICLE

Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021

Benjamin W. Teh,[1,2,3] Daniel K. Yeoh,[2,3,4] Gabrielle M. Haeusler,[1,2,3,5,6] Costas K. Yannakou,[7] Shaun Fleming,[8] Julian Lindsay[2,3,9] and Monica A. Slavin,[1,2,3,10] Australasian Antifungal Guidelines Steering Committee*

[1]Department of Infectious Diseases, and [3]National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, [2]Sir Peter MacCallum Department of Oncology, University of Melbourne, [5]Department of Infectious Diseases, Royal Children's Hospital, [7]Department of Molecular Oncology and Cancer Immunology, Epworth Freemasons Hospital, Epworth HealthCare, [8]Malignant Haematology and Stem Cell Transplantation Service, Alfred Health, and [10]Immunocompromised Host Infection Service, Royal Melbourne Hospital, Melbourne, [6]Murdoch Children's Research Institute, Parkville, Victoria, [4]Department of Infectious Diseases, Perth Children's Hospital, Perth, Western Australia, and [9]Department of Haematology, Royal North Shore Hospital, Sydney, New South Wales, Australia

Established risk groups for IFD and recommended antifungal prophylaxis

Anti-mold prophylaxis in allo-HSCT:

- **Prolonged neutropenia before transplantation (AL,AA,MDS)**
- **MUD, CBT**
- **Previous mold infection**

(within 6-9 m before transplant)

JAMA Network | Open

Original Investigation | Infectious Diseases

Comparison of Antifungal Prophylaxis Drugs in Patients With Hematological Disease or Undergoing Hematopoietic Stem Cell Transplantation

A Systematic Review and Network Meta-analysis

Jing Wang, MD, PhD; Min Zhou, MD, PhD; Jing-Yan Xu, MD, PhD; Rong-Fu Zhou, MD, PhD; Bing Chen, MD, PhD; Yuan Wan, PhD

200 mg twice daily

What do you think about latent tuberculosis screening test?

(IGRA+, PPD-)

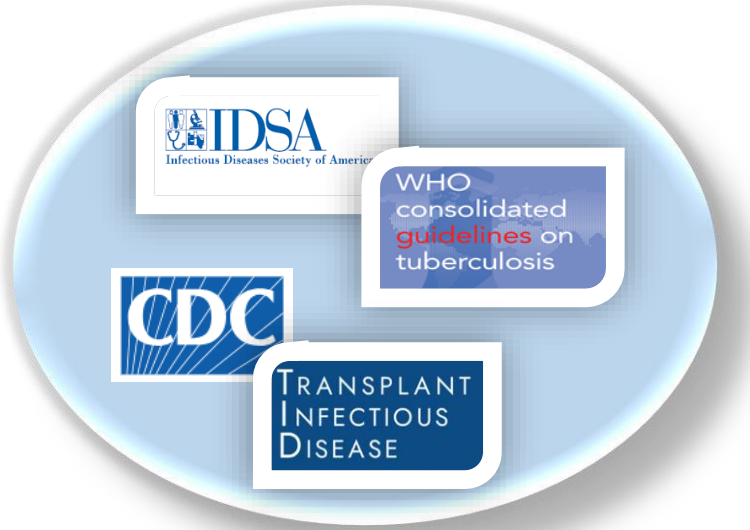
Recommendations for choice and dose of antifungal prophylaxis agents

IGRA and TST

- **in high-income and upper-middle-income countries**

two-step strategy

- **in low income countries**



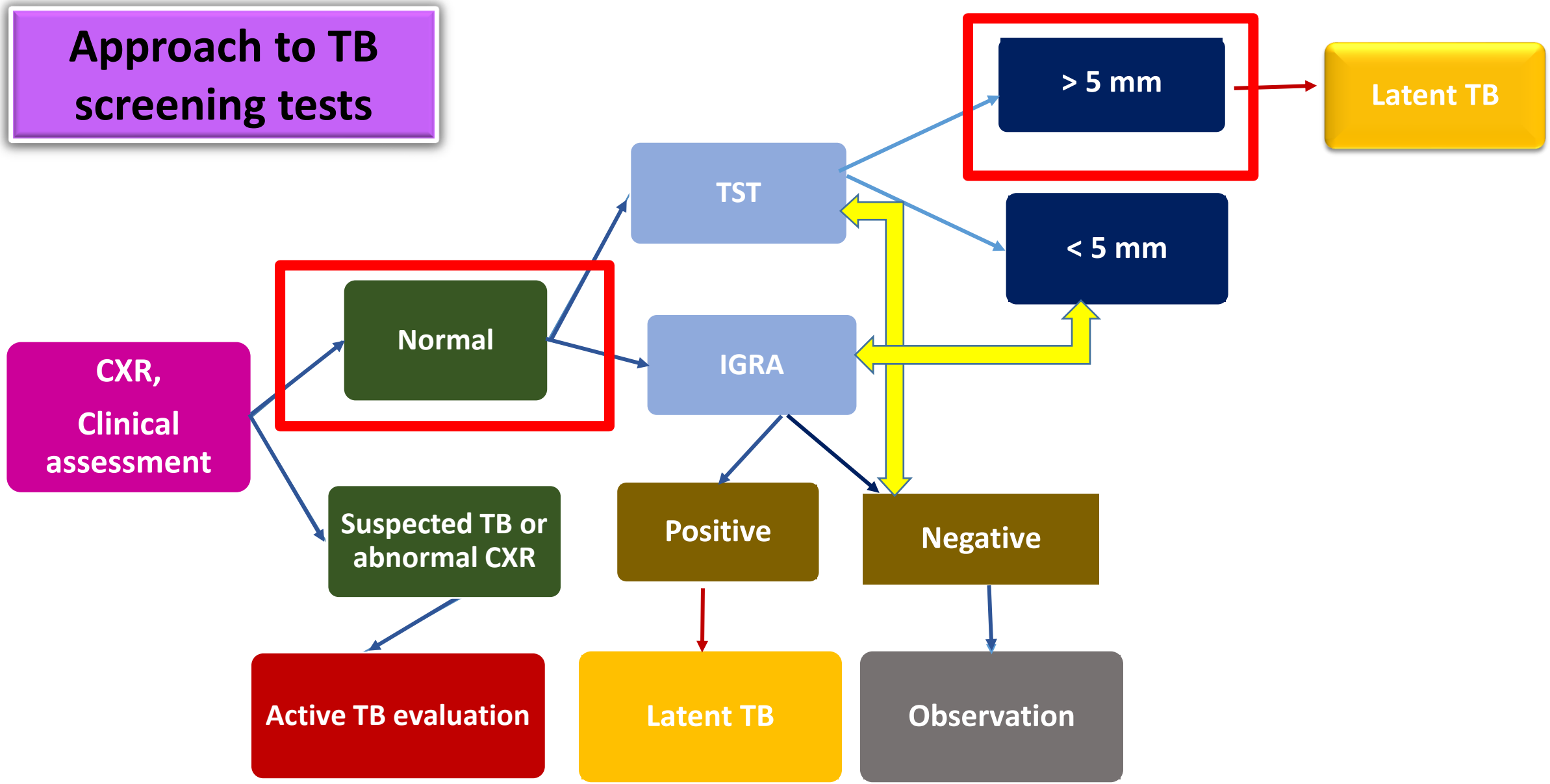
Both tests

For screening of LTB in transplant recipients

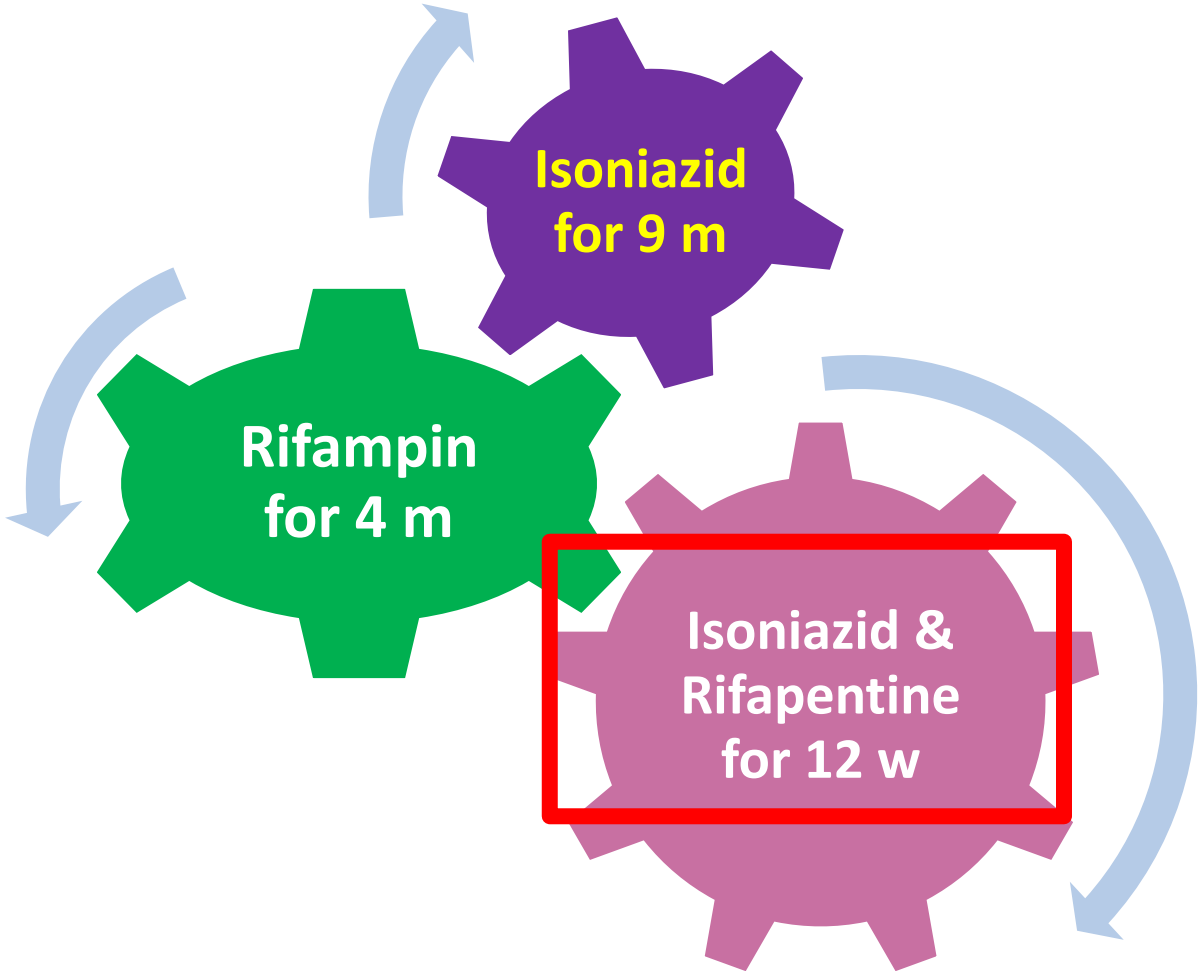
IGRA over TST

because of the higher sensitivity of IGRA in immucompromised patients. interpretation with caution, due to falsely negative or indeterminate results.

Approach to TB screening tests



Regimens used for treatment of LTBI



❖However, if HSCT is life-threatening, earlier institution of immunosuppressive agents was accepted, even in a same day.

Recommendation of most guidelines

Delaying transplantation for 1month after commencement of LTBI treatment

The optimal time

Complete treatment of LTBI before transplantation

❖ He was prescribed with :

✓ **Levofloxacin**

✓ **Acyclovir**

✓ **Voriconazole**

✓ **Co-trimoxazole**

as his preventive regimen, as well as **Isoniazid** with **vit.B6** for anti-TB prophylaxis.

- **neutrophil engraftment** was achieved on day 17 after BMT.

On day 28 after BMT, **complete hematological remission** was achieved in the BM examination.

Levofloxacin and voriconazole were discontinued.

- On day +38, **acute GVHD** of the **skin (grade II)** and abnormal liver function tests, indicating an elevation of aminotransferases and bilirubin was developed .

✓ The patient received The **topical steroid** and high-dose systemic corticosteroid (methylprednisolone, 2 mg/kg) and additional **ruxolitinib** for insufficient control of GvHD following tapering of the steroids.

Do you recommend any modification in his prophylaxis regimen?

Antimicrobial px based on overall infection risk in GVHD

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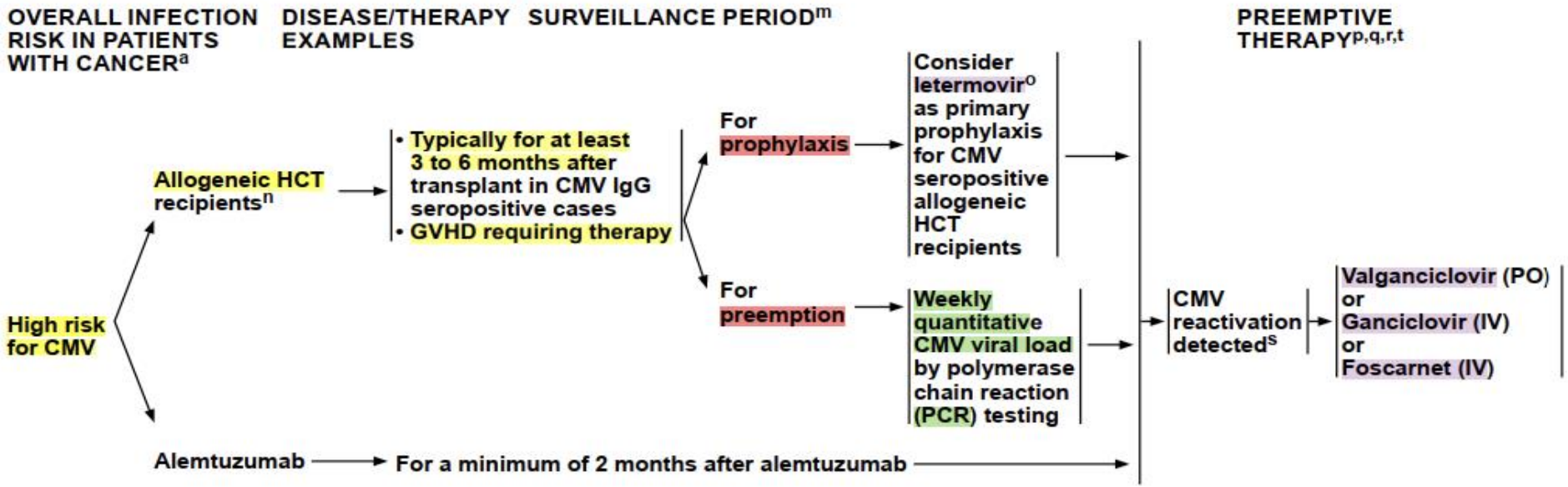
ANTIMICROBIAL PROPHYLAXIS BASED ON OVERALL INFECTION RISK IN PATIENTS WITH CANCER

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Antimicrobial Prophylaxis[d]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 days	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PJP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ‣ Induction ‣ Consolidation/maintenance • Alemtuzumab therapy • Moderate to severe GVHD • Anticipated neutropenia greater than 10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PJP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Minimum Duration of Antiviral Prophylaxis
Low	• Standard chemotherapy regimens for solid tumors	No prophylaxis unless prior HSV episode; if needed, treat during active therapy including periods of neutropenia.
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (eg, fludarabine)	HSV prophylaxis[k] • Consider during active therapy and possibly longer depending on degree of immunosuppression VZV prophylaxis[l] • Consider for at least 6–12 months after autologous HCT
High	• Acute leukemia	HSV prophylaxis during active therapy including periods of neutropenia[k]
	• Proteasome inhibitors	VZV prophylaxis during active therapy including periods of neutropenia[l]
	• Alemtuzumab therapy • Allogeneic HCT • GVHD requiring significant escalation of immunosuppression	HSV prophylaxis[k] • Minimum of 2 months after alemtuzumab and until CD4 ≥200 cells/mcL VZV prophylaxis[l] • Prophylaxis should be considered for at least 1 year after allogeneic HCT

KEY: CLL = chronic lymphocytic leukemia; GVHD = graft versus host disease; HCT = hematopoietic cell transplant; HSV = herpes simplex virus; VZV = varicella zoster virus

PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE



Antifungal PX

PREVENTION OF FUNGAL INFECTIONS

See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Consider Antifungal Prophylaxis Based on Patient- and Center-Specific Risk Factors See Antipneumocystis Prophylaxis (INF-6)	Duration
Intermediate to High	ALL	• Fluconazole[g] or an echinocandin[h] • Amphotericin B products[i] (category 2B)	Typically until resolution of neutropenia
	MDS (neutropenic)	• Posaconazole[g] (category 1) • Voriconazole,[g] isavuconazole,[g] an echinocandin,[h] amphotericin B products[i], or fluconazole (if mold activity not needed)[g] (all category 2B)	
	AML (neutropenic)		
	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)[a]	• 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 acute GVHD (especially grade 3/4) receiving IST	• Posaconazole[g] (category 1) • Voriconazole,[g] echinocandin,[h] amphotericin B products,[i] or isavuconazole,[g] (all category 2B)	Until resolution of significant GVHD

Recommendation for allogenic HSCT

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

In post-engraftment phase for GVHD:

- **Ruxolitinib:** Increase in viral reactivation TB , PCP, IFD

Anti mold In H.R patients:

- Acute GVHD grade III,IV ,steroid dependent/ refractory
- Acute GVHD grade II in unrelated or mismatched donor, persistent or late onset, recurrent CMV, Extensive chronic GVHD

Anti yeast in L.R patients:

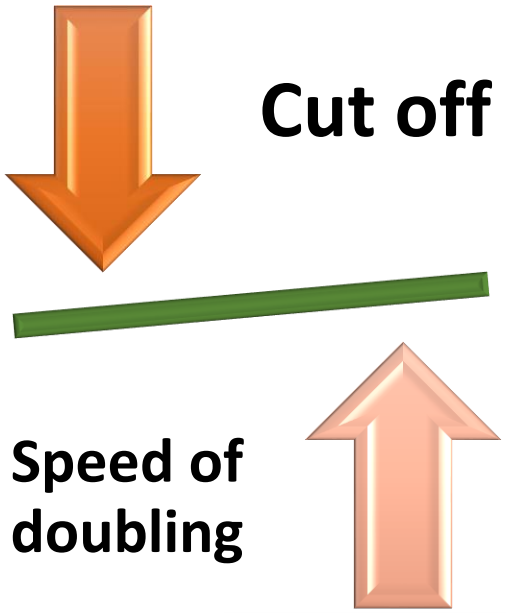
- Acute GVHD grade II respondent to treatment
- New onset chronic GVHD without steroid therapy

- **voriconazole** was restarted.
- Acyclovir, co-trimoxazole, isoniazid and monitoring of CMV continued.

- On day **+52**, the patient showed a **CMV** plasma viral load of **240 IU/mL**.

What do you recommend for the management of this patient?

NOTABLE POINT



Is the increase in CMV viral load due to infection or disease?

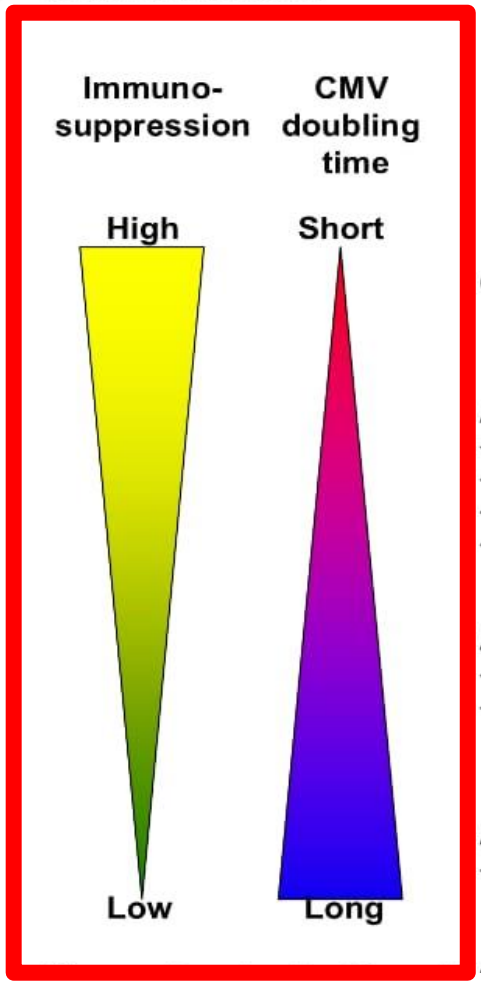
- The patient was afebrile with stable vital signs while his cutaneous and liver GVHD were improving and his corticosteroid dose was tapering.
- There was no significant finding in physical exam.

CBC:
WBC:8300 (PMN: 67%), Hb:10.3
PLT:110000

Risk of CMV doubling time depends on:

- **Graft source** → Umbilical cord blood>BM/ Peripheral blood stem cell
- **Serological status of D/R** → $D^-R^+ > D^+R^+ > D^+R^- > D^-R^-$
- **Conditioning regimen** → myloablative>RIC> Nonmyeloablative
- **Early or late CMV** → Early > Late (>100 d after transplantation)
- **Donor** → Mismatch unrelated donor > Match unrelated donor > Haploidentical
- **Present of GVHD or not** → Significant GVHD

- CMV cut off is different center by center.



Risk Groups	CMV Plasma DNA Level to Start PET at FHCRC*	CMV Whole Blood DNA Level to Start PET at Karolinska Institute**
Cord blood	Any level	1000 copies
Allograft - High-dose steroids† - T cell depletion - Anti-T cell antibodies - CD34 selection	> 100 copies/mL	1000 copies
Allograft - Low dose steroids - No T cell depletion or anti T cell antibodies	> 500 copies/mL > or 5-fold ⇑ †	1000 copies
Allograft - after day 100	> 1000 copies/mL > or 5-fold ⇑ †	1000 copies if GVHD Other individual assessment based on ⇑

CMV cut off for beginning preemptive therapy

Without R.F & <3m from transplant	Cut off > 500
Without R.F &>3m from transplant	Cut off > 1000
UCB, Seronegative	With any detectable load
GVHD	Cut off > 100

❖ **He was prescribed with Valganciclovir 900 mg BID.**

How long should the anti CMV therapy be continued? And what do you recommend for the management of this patient?

- ✓CMV treatment should be continued until the CMV viral load becomes **undetectable.**
- ✓The first CMV PCR should be done **2 weeks** after starting the treatment
- ✓As long as the CMV viral load is detectable, the **full dose of treatment** should be continued.

- After 2 weeks of starting valganciclovir, quantitative CMV PCR was repeated with **undetectable PCR** result.

What will be your next act?

❖ CMV induction therapy can be **stopped completely** or continued as **maintenance therapy** for a period of **2-3 weeks**, meanwhile weekly CMV monitoring needs to be continued.

Case presentation 2

- A 60-year-old female patient presented with a painless subcutaneous mass in the lower right limb. The mass was confirmed as a **plasmacytoma**
- The patient was diagnosed with **MM** λ type by BM aspiration and protein electrophoresis.

- The patient received three cycles of **bortezomib and dexamethasone** and achieved complete remission.
- Fourteen months later, the patient received a high-dose therapy (**melphalan 200 mg/m^2 and bortezomib)** to be ready for **auto-HCT.**

- **In your opinion does this patient need any prophylactic antimicrobial regimen?**
  - ✓ **If your answer is no, (Why)?**

And if your answer is yes, what prophylactic antimicrobial regimen?

For prophylaxis in autologous HSCT:

Antibacterial PX → • During neutropenia

Anti viral PX →
- Anti HSV: During neutropenia
- Anti VZV: at least 6-12 m

Prevention of CMV
- Monitoring CMV → 2-5 w in seronegative or seropositive patients

Anti fungal PX
- If mucositis exist → Anti-yeast PX during neutropenia or (until 75 d?)
  Unless patient with history of IFD

Anti PCP PX → • 3-6 months

Thanks for your attention!