Fred Hutch Cancer Center

Infectious disease complications

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COI disclosures

- Research funding from Pfizer, unrelated to the content of this presentation

1 Overview of infectious risks after HCT

2 Neutropenic fever

3 Invasive fungal infections

4 Viral infections

5 Prevention & prophylaxis

Overview of infectious risks after HCT & CAR-T

ID on the board exam

Medical Oncology

Clinical manifestations of advanced cancer and its treatment 4.5%

- Cutaneous and mucosal manifestations
- Endocrine manifestations
- Gastrointestinal manifestations
- Hematologic manifestations
- Musculoskeletal manifestations
- Neurologic manifestations
- Renal, metabolic, and nutritional manifestations
- Paraneoplastic syndromes
- Cardiothoracic manifestations
- Fatigue
- Psychiatric manifestations
- Infectious risks and complications
- Lymphedema

https://www.abim.org/media/ww2l2gw2/medical-oncology-cert.pdf

Hematology

Other complications after hematopoietic cell transplantation <2%

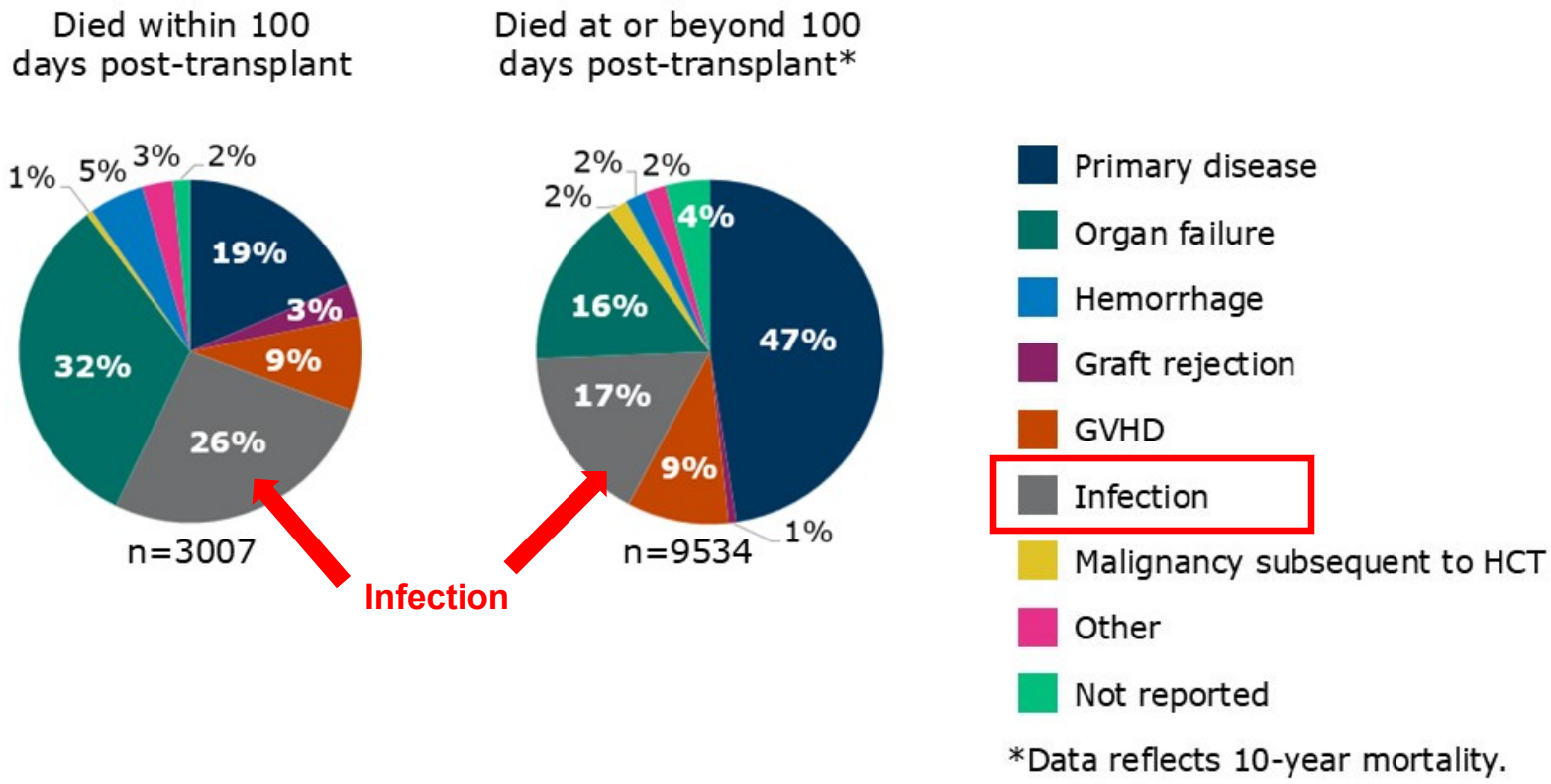
- Engraftment failure or rejection
- Infections
- Organ toxicity

Supportive care <2%

- Preventing infectious disease
- Transfusion support, including graft compatibility and blood product issues

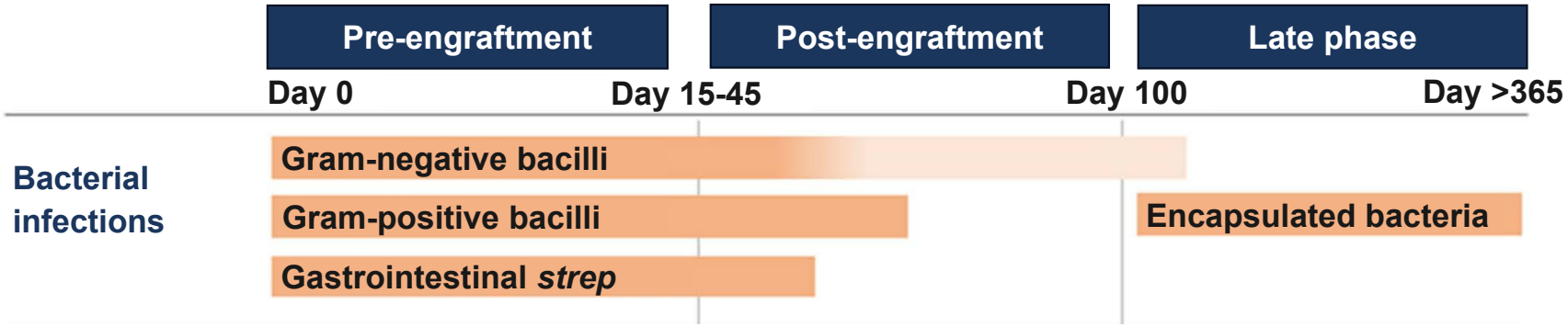
https://www.abim.org/media/qdydjg1v/hematology-cert.pdf

ID in clinical practice



Slide courtesy of Josh Hill, MD

Image adapted from: Zajac-Spychala et al. Frontiers in Pediatrics, 2022



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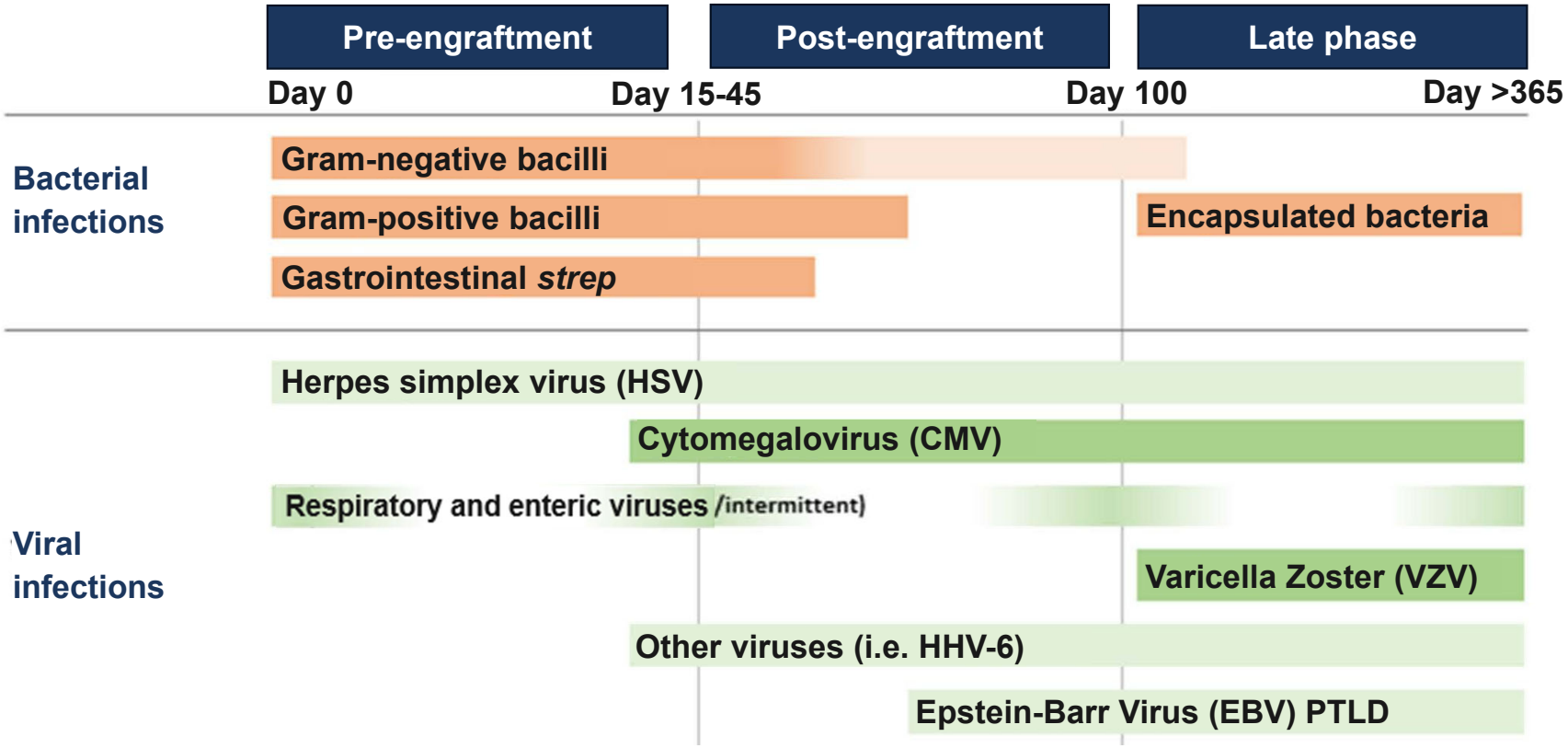

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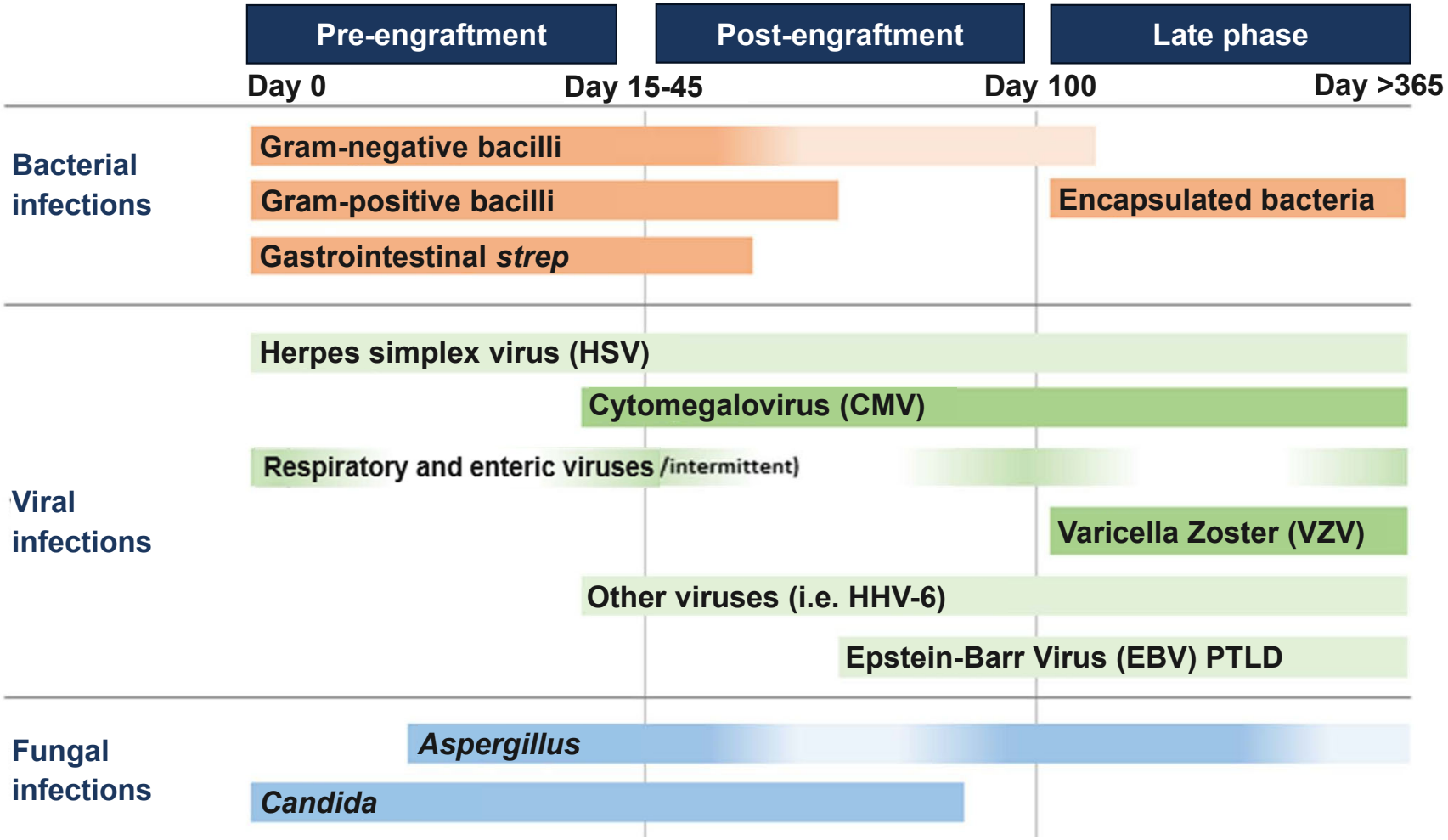

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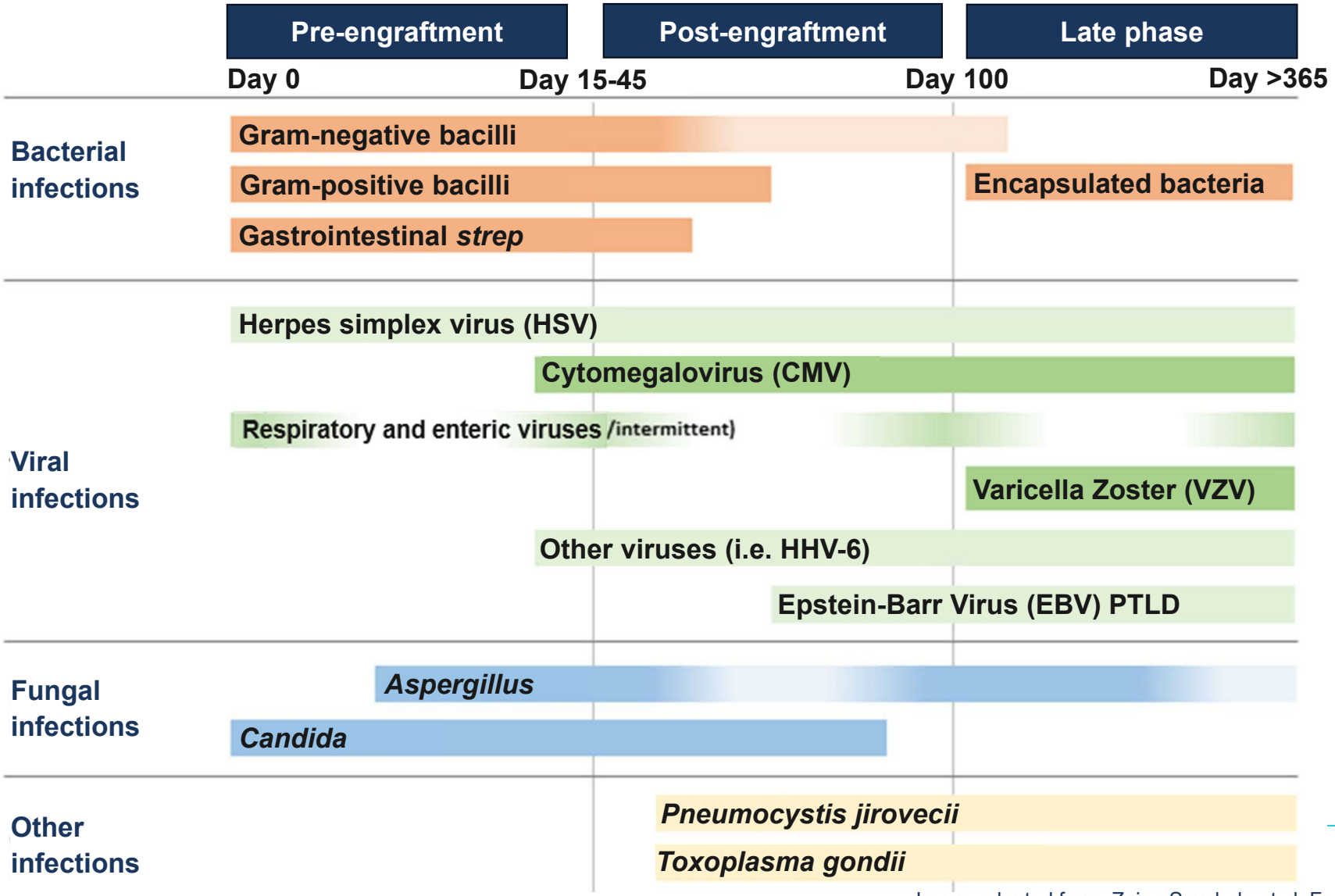
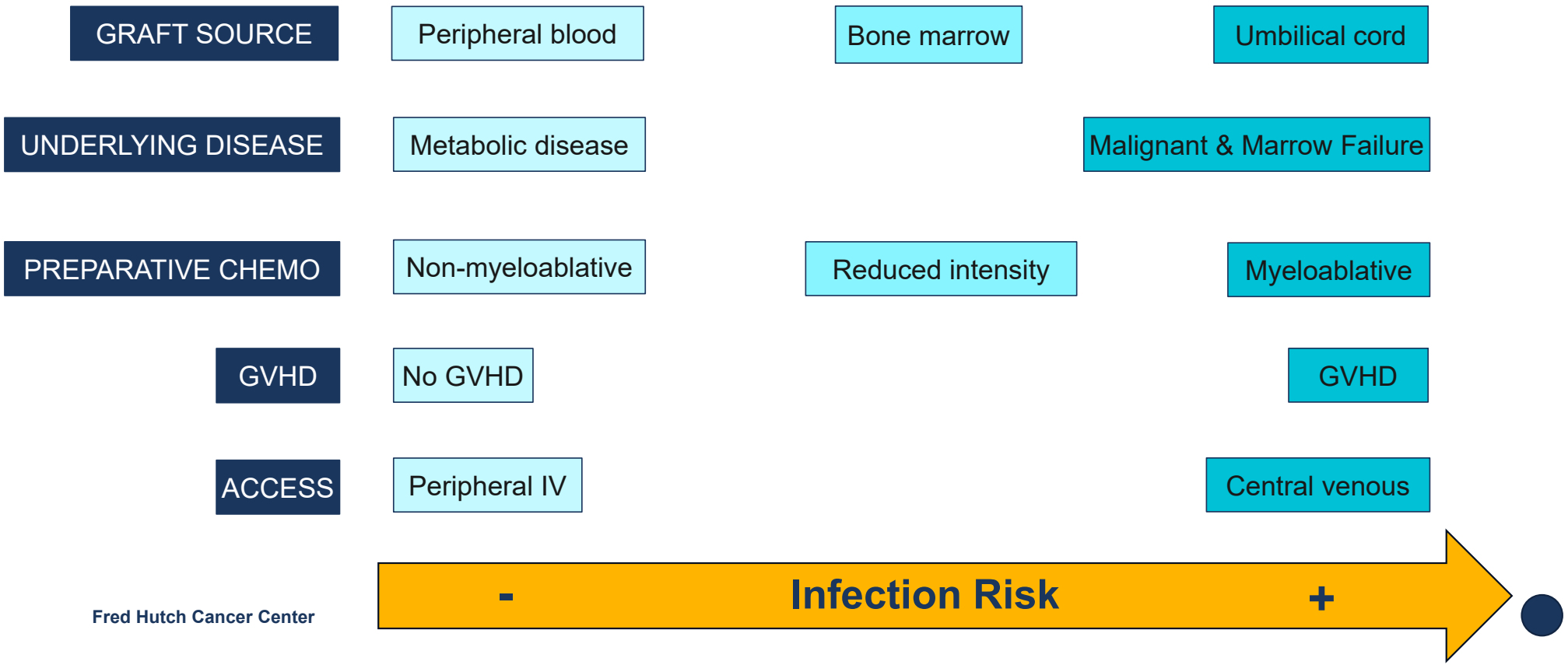


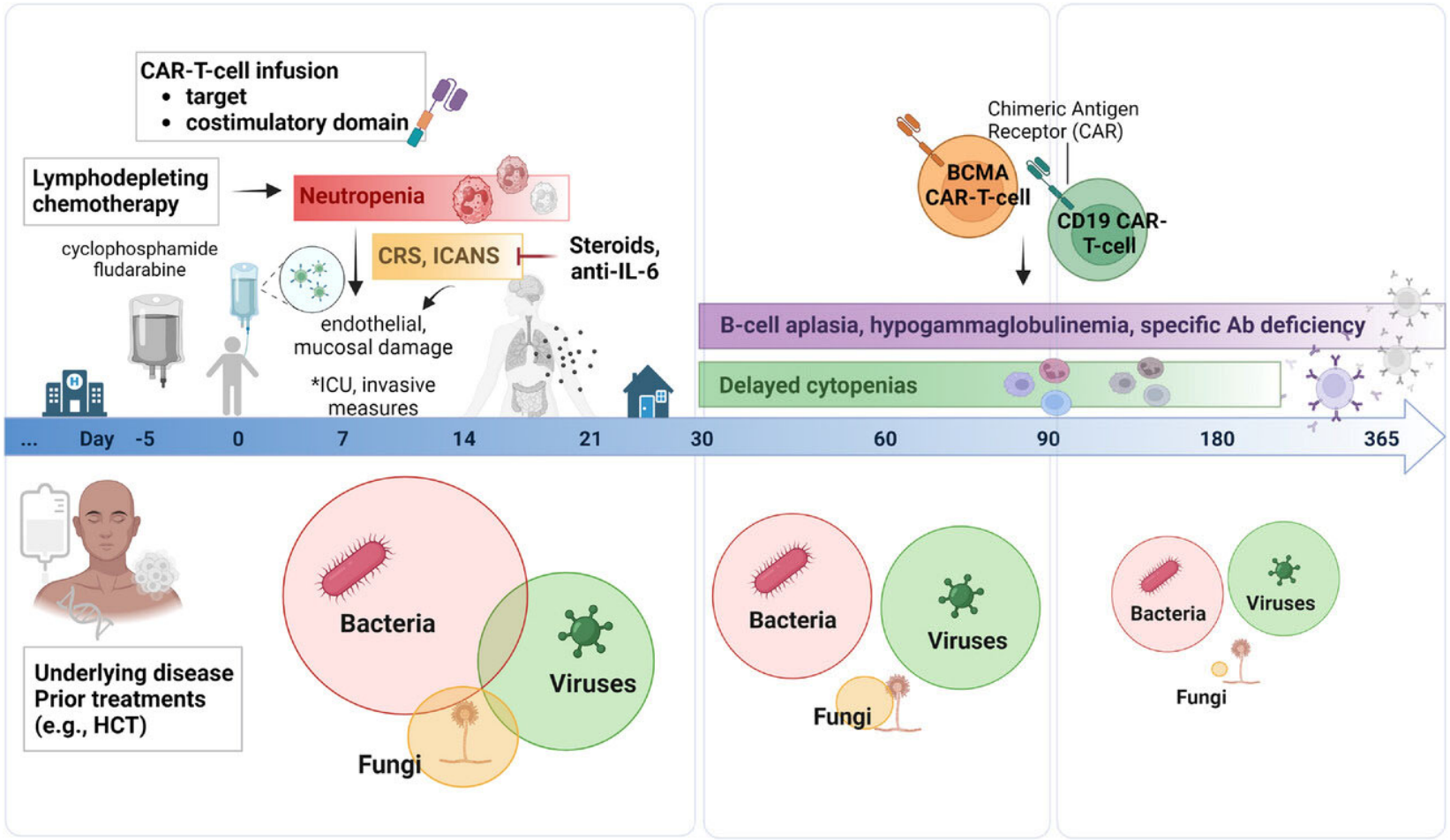
Image adapted from: Zajac-Spychala et al. Frontiers in Pediatrics, 2022

Clinical and Transplantation Risk Factors



Ferdjallah et al *Front Pediatr* 2021

“Phases” of Infection Risk Following CAR-T Cell Therapy



Kampouri et al. *TID*. 2023

Neutropenic fever

Infection Risk in patients with cancer

LOW	INTERMEDIATE	HIGH

NCCN Guidelines Version 1.2024. Prevention and Treatment of Cancer-Related Infections

Infection Risk in patients with cancer

LOW	INTERMEDIATE	HIGH
• **Anticipated neutropenia <7 days** • Standard chemotherapy regimens for most solid tumors		

NCCN Guidelines Version 1.2024. Prevention and Treatment of Cancer-Related Infections

Infection Risk in patients with cancer

LOW	INTERMEDIATE	HIGH
• **Anticipated neutropenia <7 days** • Standard chemotherapy regimens for most solid tumors	• **Anticipated neutropenia 7–10 days** • Autologous HCT • Lymphoma • Multiple myeloma • CLL • Purine analog therapy (fludarabine, cladribine) • CAR T-cell therapy	

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Infection Risk in patients with cancer

LOW	INTERMEDIATE	HIGH
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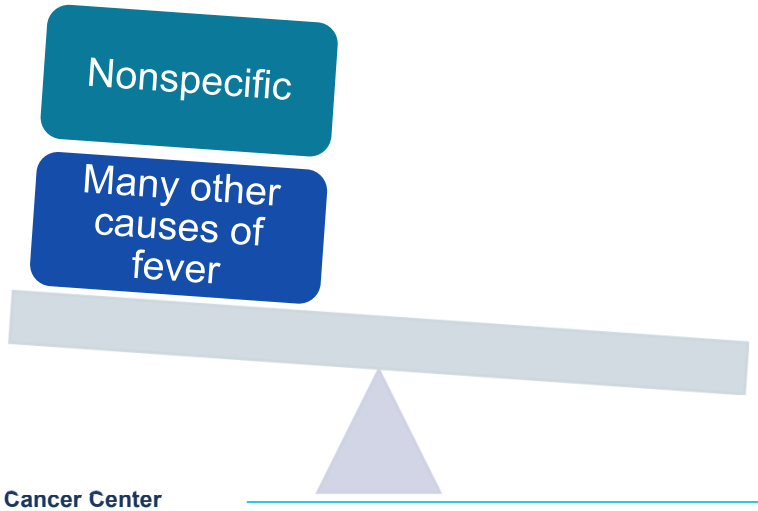
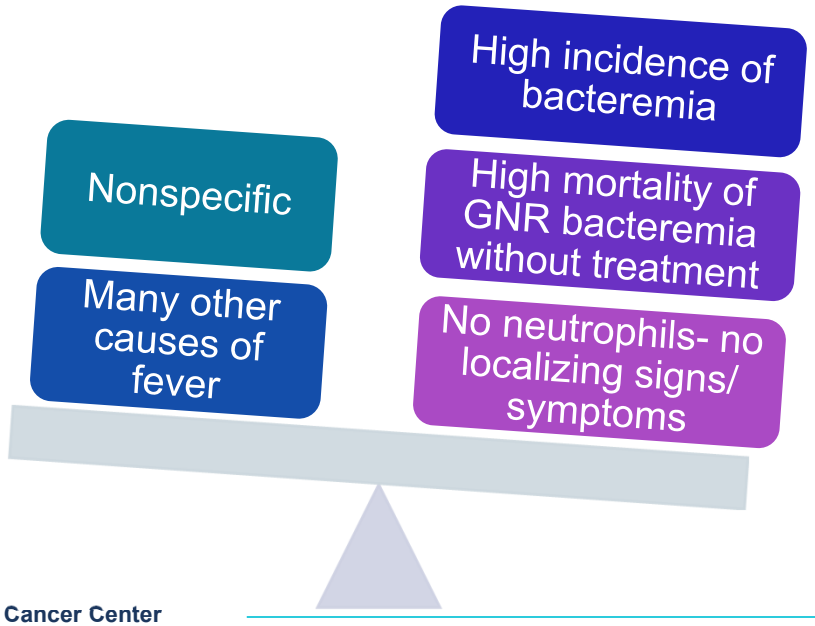
NCCN Guidelines Version 1.2024. Prevention and Treatment of Cancer-Related Infections

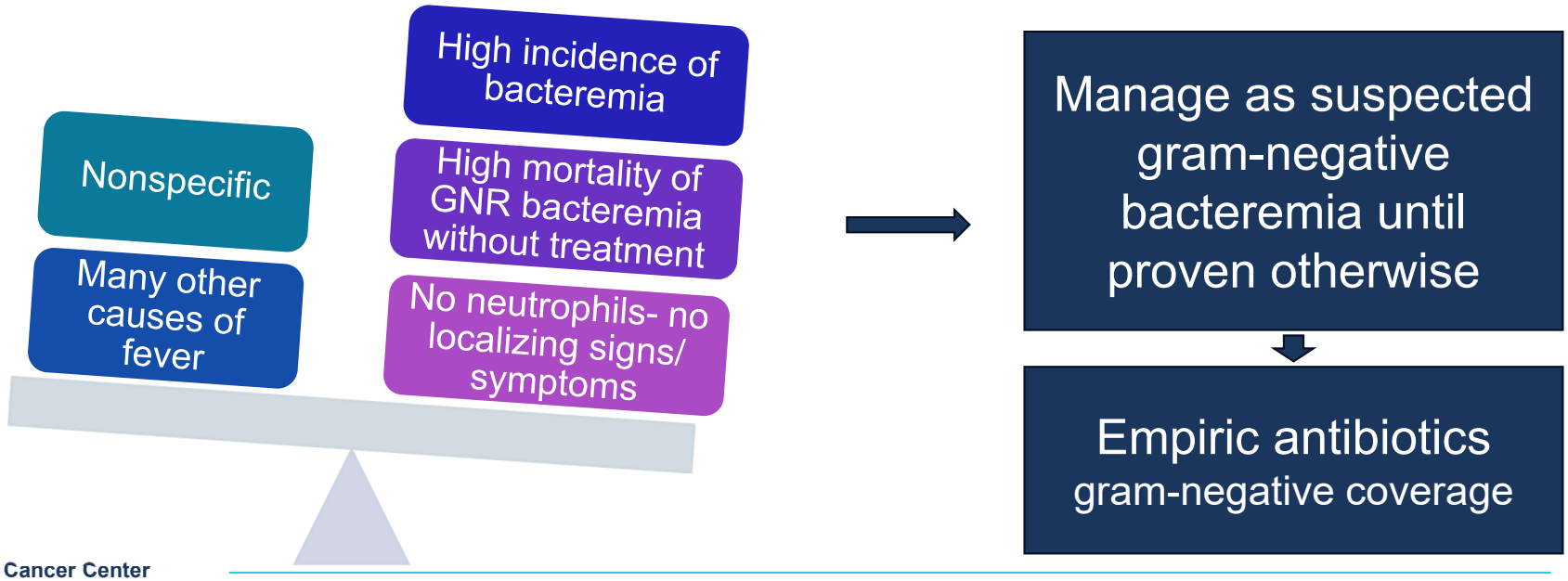
Neutropenic fever: general principles



Neutropenic fever: general principles

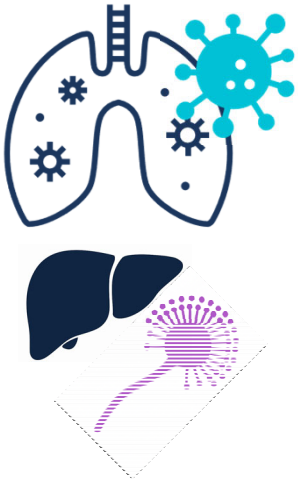


Neutropenic fever: general principles

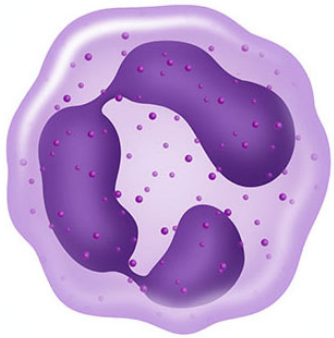


General Principles – neutropenic patients may…

≥ 1 infectious process



Lack classic signs & symptoms



Present with unusual manifestations

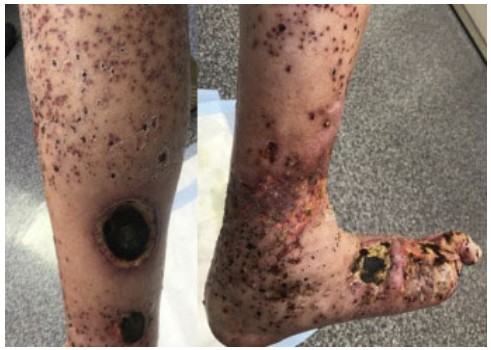
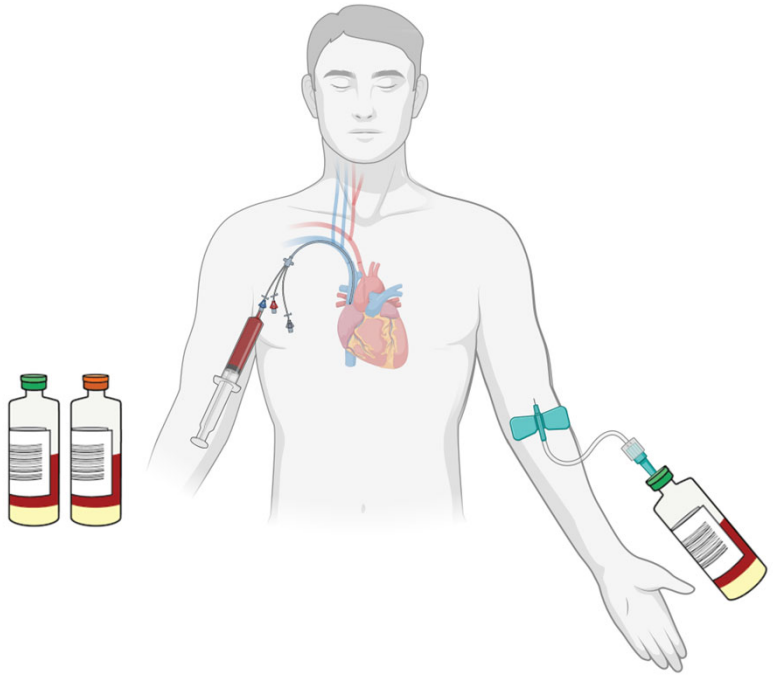


Image: Massoud, Cathy M. et al. Journal of The American Academy of Dermatology(JAAD) Case Reports, 2021

Diagnostic work-up of Fever and Neutropenia

- **All patients:** obtain **2 sets of blood cultures**
- (1 set = 1 aerobic / 1 anaerobic bottle) **PRIOR** to antibiotics
  - If CVC: 1 peripheral + 1 central OR 2 central cultures



Diagnostic work-up of Fever and Neutropenia

Headache/AMS: CT, LP?

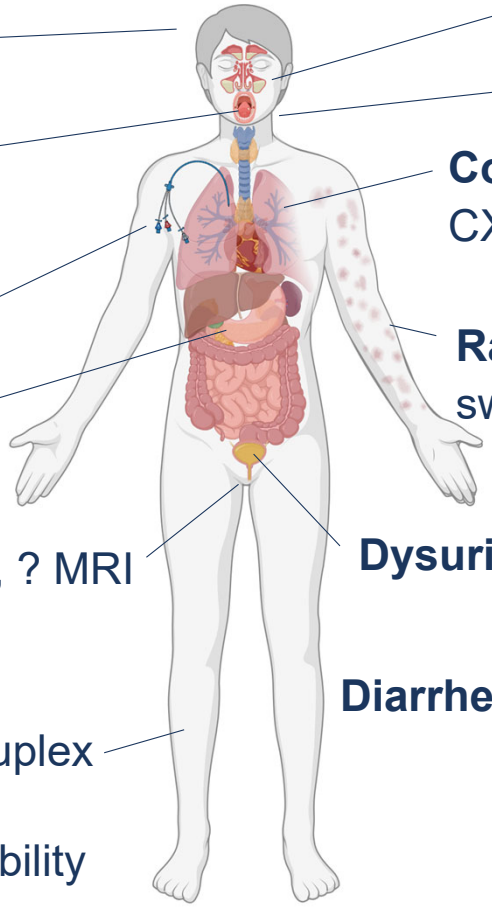
Mouth pain/oral lesions:
Swab for viral PCR, biopsy?, thrush?

Lines

Abdominal pain: CT abdomen

Rectal pain: physical exam, CT pelvis, ? MRI

Micro: review prior cultures & susceptibility



Edema: duplex

Nasal/sinus pain: Sinus CT/MRI, Oto

Rhinorrhea, sore throat: Viral PCR

Cough or hypoxemia:
CXR, CT chest, bronchoscopy

Rash: Derm consult,
swab for viral PCR, biopsy, Rx history

Dysuria, urgency, frequency: UA/UCx

Diarrhea: review meds, C diff, enteric pathogens

Neutropenic fever case

- 63 yo M with AML s/p induction chemotherapy presents with fever during platelet transfusion. No other associated symptoms.

- VS: 38.6˚C 110/78 92 22 98% RA
- Exam: Severe mucositis
- Line: Hickman catheter site w/o erythema

- Prophylaxis: levofloxacin, fluconazole, acyclovir
- ANC < 100 (x 10 days)

After drawing blood cultures, what agent(s) would you choose as empiric therapy?

A. Vancomycin alone

B. Cefepime alone

C. Vancomycin and piperacillin-tazobactam

D. Meropenem + amikacin

E. Ceftazidime-avibactam + vancomycin

After drawing blood cultures, what agent(s) would you choose as empiric therapy?

A. Vancomycin alone

B. **Cefepime alone**

C. Vancomycin and piperacillin-tazobactam

D. Meropenem + amikacin

E. Ceftazidime-avibactam + vancomycin

Vancomycin for Febrile Neutropenia?

IDSA and NCCN Guidelines:

- **Do not** recommend initial vancomycin w/ exception of selected situations
- Recommend **discontinuation after 48-72 hours** if cultures are negative for resistant gram-positive organism

Freifeld CID 2011;52 (4): e56-393; NCCN Guidelines Prevention and Treatment of Cancer Related Infections 2024

Indications for Empiric Use of Vancomycin

	IDSA (2010)	ECIL (2011)	NCCN (2020)
Clinically apparent serious catheter related infection	✓	✓	✓
Hemodynamic instability	✓	✓	✓
MRSA colonization	✓	✓	✓
Skin or soft tissue infection	✓	✓	✓
Positive blood cultures for gram + bacteria (before ID & susceptibilities)	✓		✓
Pneumonia	✓	✓	
Severe mucositis **(if FQ prophylaxis AND ceftazidime used empirically)**	✓		

Averbuch et al, Hematologica, 2013.

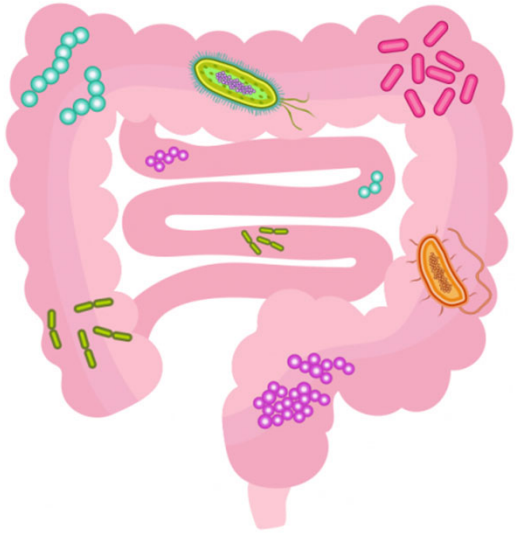
What is the optimal empiric gram-negative coverage?

It depends

- Local epidemiology – prevalence of resistant organisms
- Patient's history – infection or colonization with ESBL or MDR bacteria
- Severity of infection – protocols for septic shock, etc.

Broader isn't always better

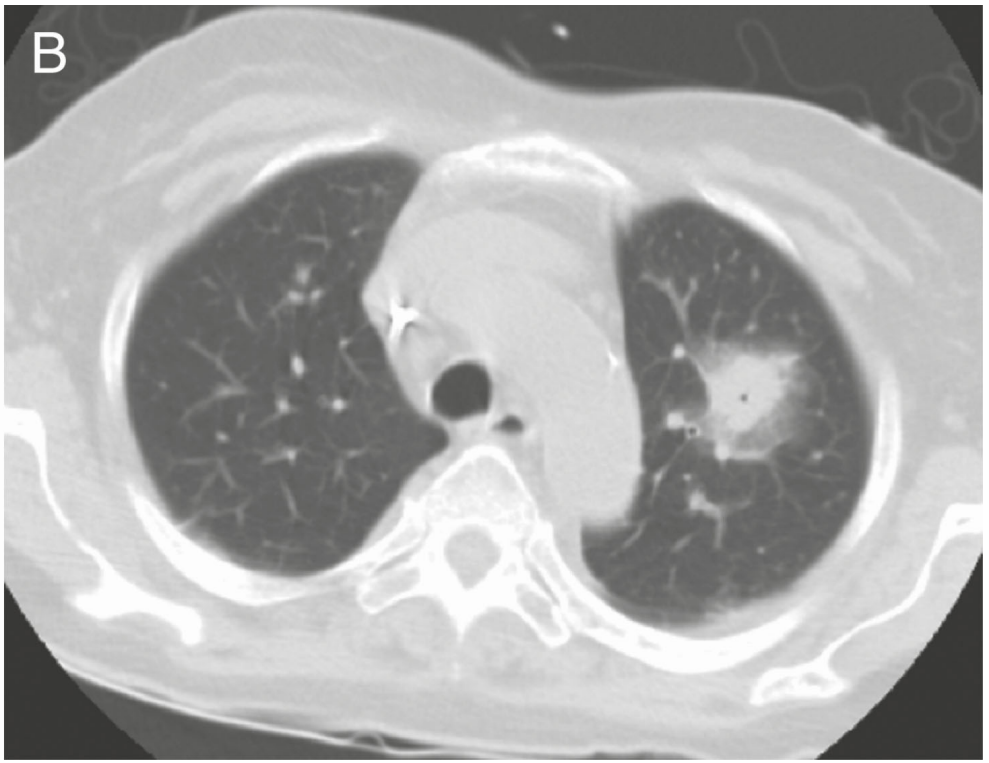
- ↓ microbiota diversity
  - ↑ GVHD
  - Worse survival



Invasive fungal infections

55 F day +12 s/p Umbilical Cord Transplantation for AML

- **Conditioning**: busulfan/fludarabine
- **GVHD ppx**: cyclosporine/methotrexate
- **Serology:**
  - Recipient HSV+, VZV+, CMV+
  - Donor CMV-
- **Prophylaxis**
  - letermovir
  - acyclovir
  - Fluconazole
- **Fever x 2 days → cefepime**



Alexander et al *CID* 2021

What is the most likely etiology?

A. Aspergillus

B. Mucormycosis

C. Candida

D. Nocardia

E. All of the above

What is the most likely etiology?

A. Aspergillus

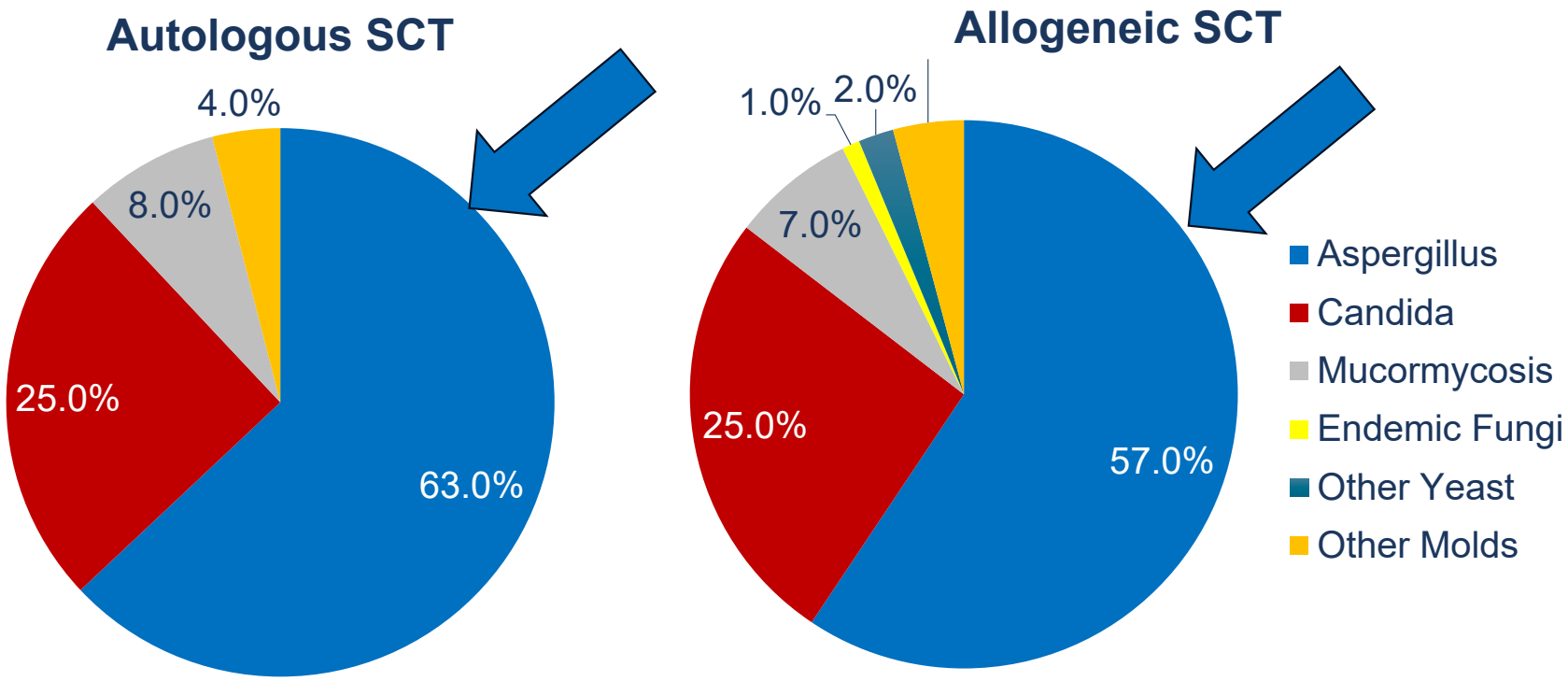
B. Mucormycosis

C. Candida

D. Nocardia

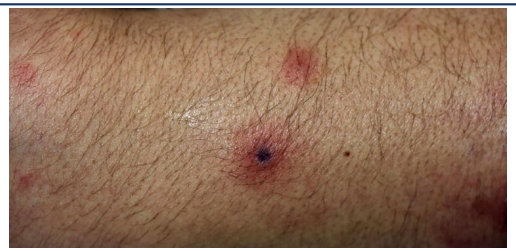
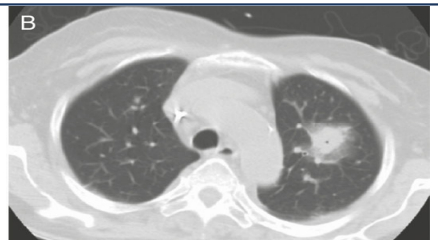
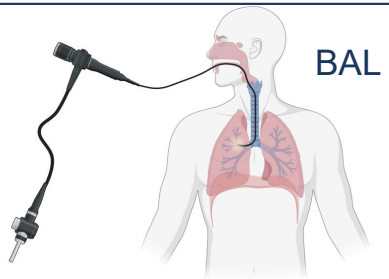
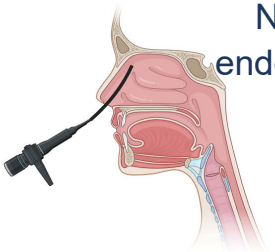
E. All of the above

Epidemiology of Invasive Fungal Infection in HSCT Recipients



PATH Alliance Registry: 16 centers, 2004-2007
N=234 HSCT pts

Diagnostic Evaluation for Invasive Fungal Infection

History & Physical	• Review of sinus symptoms • Exposure & travel history	Careful skin exam 
Studies	Chest CT 	*Consider:* • Aspergillus galactomannan • Beta-D-Glucan • Microbial cell-free DNA
Consults & procedures	 BAL  Biopsy  Nasal endoscopy	

Skin photo: Nucci M, Anaissie E. 2023. Invasive fusariosis. Clin Microbiol Rev 36:e00159-22. Illustrations: BioRender

What is the next best step in management?

A. Start Ambisome 3 mg/kg/d

B. Start Ambisome 10 mg/kg/d

C. Start posaconazole 300mg BID x 1 then 300mg daily

D. Start micafungin 150 mg IV qd

E. Start voriconazole + micafungin

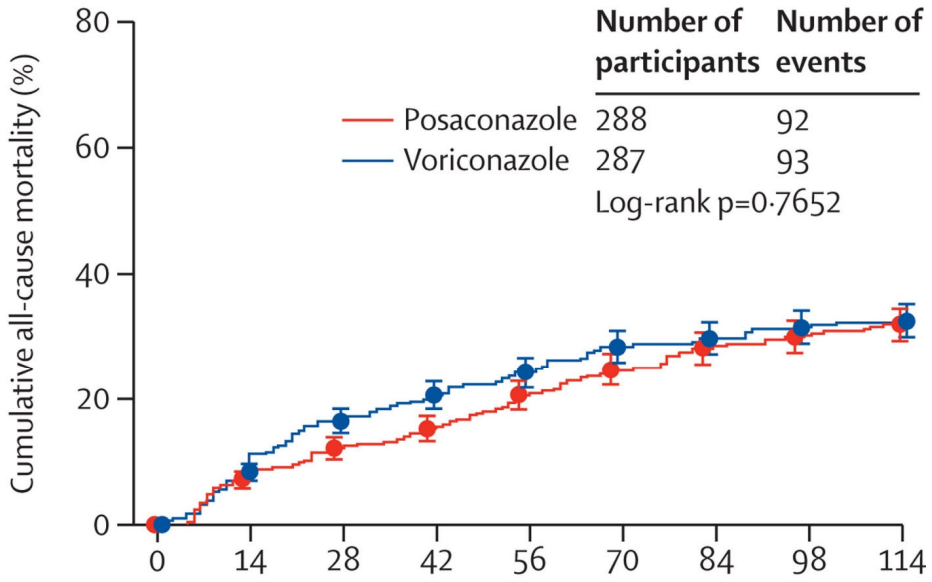
Why not voriconazole?

Lancet 2021; 397: 499–509

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial

*Johan A Maertens, Galia Rahav, Dong-Gun Lee, Alfredo Ponce-de-León, Isabel Cristina Ramírez Sánchez, Nikolay Klimko, Anne Sonet, Shariq Haider, Juan Diego Vélez, Issam Raad, Liang-Piu Koh, Meinolf Karthaus, Jianying Zhou, Ronen Ben-Ami, Mary R Motyl, Seongah Han, Anjana Grandhi, Hetty Waskin, on behalf of the study investigators**

Posaconazole Non-Inferior to Voriconazole



Number at risk

Posaconazole	288	268	254	244	230	219	207	202	196
Voriconazole	287	267	240	230	215	204	199	195	192

Maertens JA, et al. *Lancet*. 2021.

Viral infections

42M day +66 s/p mismatched unrelated donor HCT for ALL

- **Conditioning**: busulfan + cyclophosphamide
- **GVHD prophylaxis**: tacrolimus + methotrexate
- **Serology:**
  - Recipient HSV+, VZV+, CMV+
  - Donor CMV-
- **Antimicrobial prophylaxis:**
  - TMP-SMX
  - acyclovir
  - Fluconazole

42M day +66 s/p mismatched unrelated donor HCT for ALL

- Fever x 1 day, diarrhea x 2 weeks
- Lower GI endoscopy with ulcerations, not typical for GVHD.

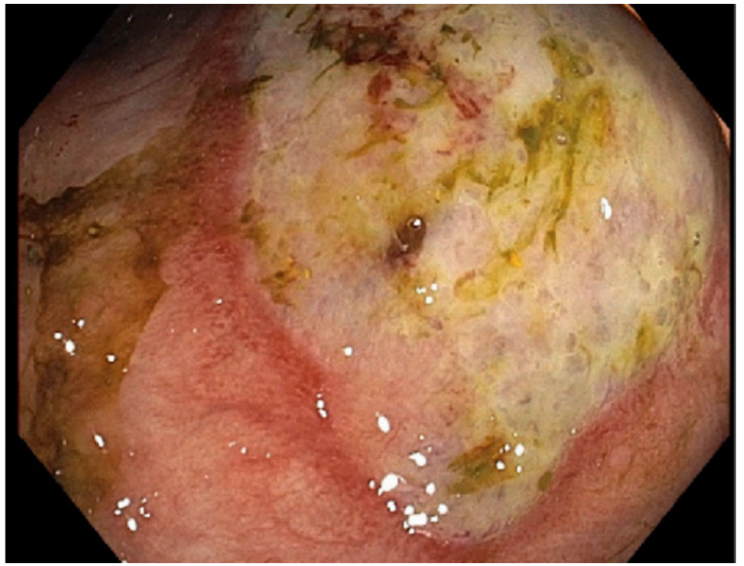


Image: Case R Jr, et al. Solitary ascending colon ulcer diagnosed as gastrointestinal CMV disease. BMJ Case Rep. 2019

What is the most likely diagnosis?

A. Typhlitis
B. CMV colitis
C. Adenovirus colitis
D. Invasive fungal disease
E. Acute GVHD

The troll of transplantation

CMV epidemiology and clinical presentation

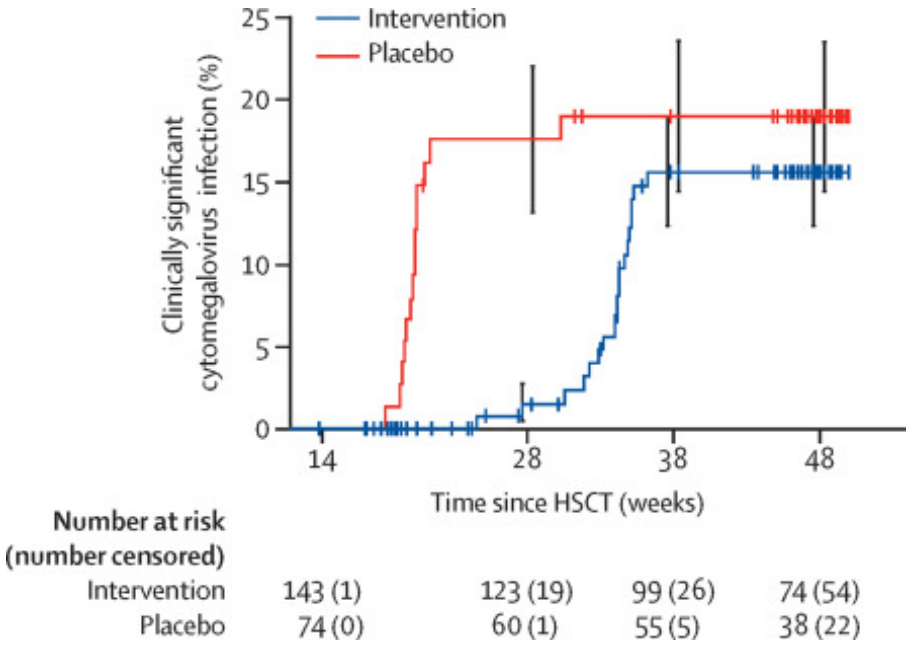
Risk factors for CMV after HCT

- T-cell dysfunction or deficiency; lymphopenia
- Allo HCT - especially cord, haplo, HLA-mismatched, T-cell depleted
- GVHD and high-dose steroids
- Seropositive (recipient CMV +)

CMV reactivation after HCT

- Weekly monitoring with CMV PCR
- Increases all-cause mortality even with pre-emptive therapy
- CMV antivirals are toxic: ganciclovir, foscarnet

CMV prophylaxis with letermovir:



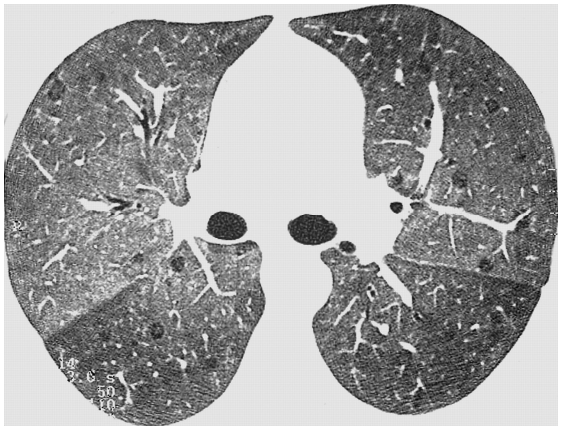
↓ clinically significant CMV infection

↓ all-cause mortality at 24 weeks

Favorable safety profile

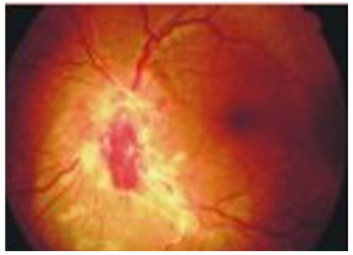
Marty et al. *N Engl J Med*. 2017.

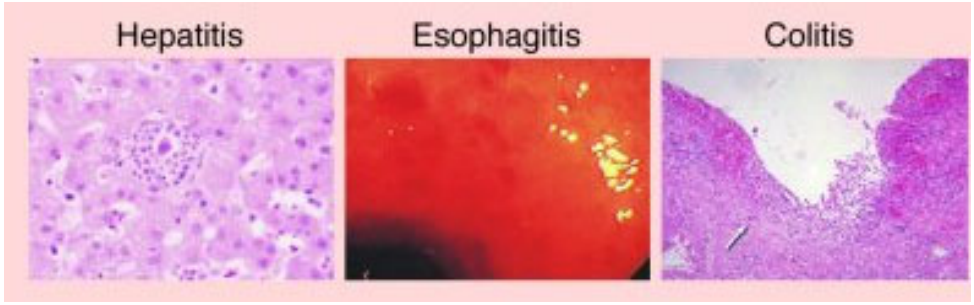
CMV end-organ disease



Pneumonia

Retinitis





Diagnosis of CMV <u>disease</u>:

- Signs & symptoms

  PLUS

- CMV in affected tissue
  - Histopathology
  - Immunohistochemistry

Exception – retinitis with characteristic findings on ophthalmologic exam

Boeckh et al. *JCI*. 2011

Prophylaxis

"I'll have an ounce of prevention."

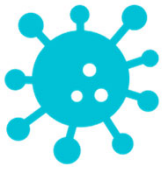
Prophylaxis - HCT

Bacteria

- Strep
- Enteric gram negatives

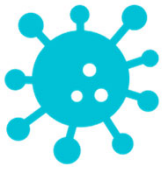
- Levofloxacin
- Moxifloxacin
- Cefpodoxime

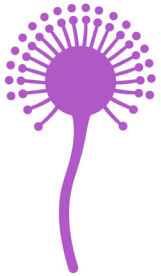
Prophylaxis - HCT



Bacteria	Viruses
• Strep • Enteric gram negatives	• HSV • VZV • CMV
• Levofloxacin • Moxifloxacin • Cefpodoxime	• Acyclovir • Valacyclovir • Letermovir

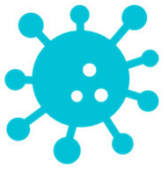
Prophylaxis - HCT

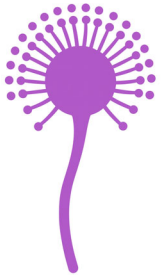


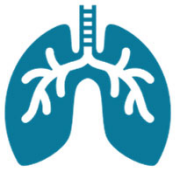


Bacteria	Viruses	Fungus
• Strep • Enteric gram negatives	• HSV • VZV • CMV	• Candida • Aspergillus
• Levofloxacin • Moxifloxacin • Cefpodoxime	• Acyclovir • Valacyclovir • Letermovir	• Fluconazole • Micafungin • Posaconazole

Prophylaxis - HCT

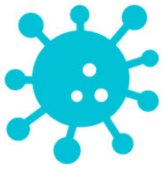


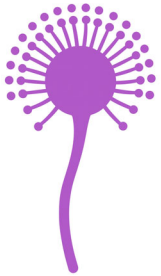


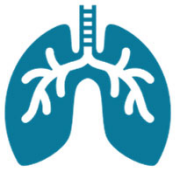


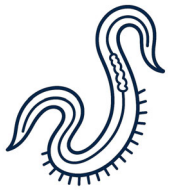
Bacteria	Viruses	Fungus	PJP / PCP
• Strep • Enteric gram negatives	• HSV • VZV • CMV	• Candida • Aspergillus	• Pneumocystis jirovecii
• Levofloxacin • Moxifloxacin • Cefpodoxime	• Acyclovir • Valacyclovir • Letermovir	• Fluconazole • Micafungin • Posaconazole	• TMP/SMX • Atovaquone • Dapsone

Prophylaxis - HCT



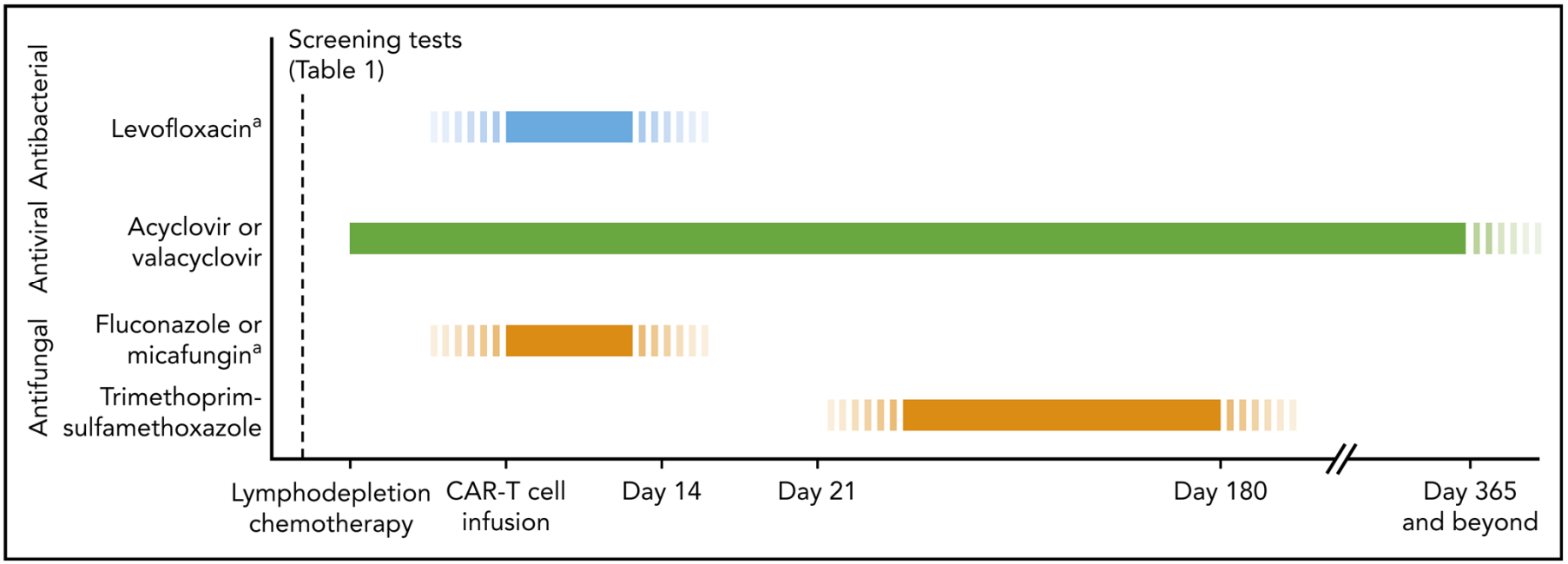






Bacteria	Viruses	Fungus	PJP / PCP	Parasites
• Strep • Enteric gram negatives	• HSV • VZV • CMV	• Candida • Aspergillus	• Pneumocystis jirovecii	• Toxoplasma • Strongyloides • [Trypanosoma]
• Levofloxacin • Moxifloxacin • Cefpodoxime	• Acyclovir • Valacyclovir • Letermovir	• Fluconazole • Micafungin • Posaconazole	• TMP/SMX • Atovaquone • Dapsone	• TMP/SMX • Ivermectin

Recommended Antimicrobial Prophylaxis after CAR-T Cell Therapy



Hill JA et al *Blood* 2020

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Mentors

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- Michael Boeckh, MD

Fred Hutch Cancer Center

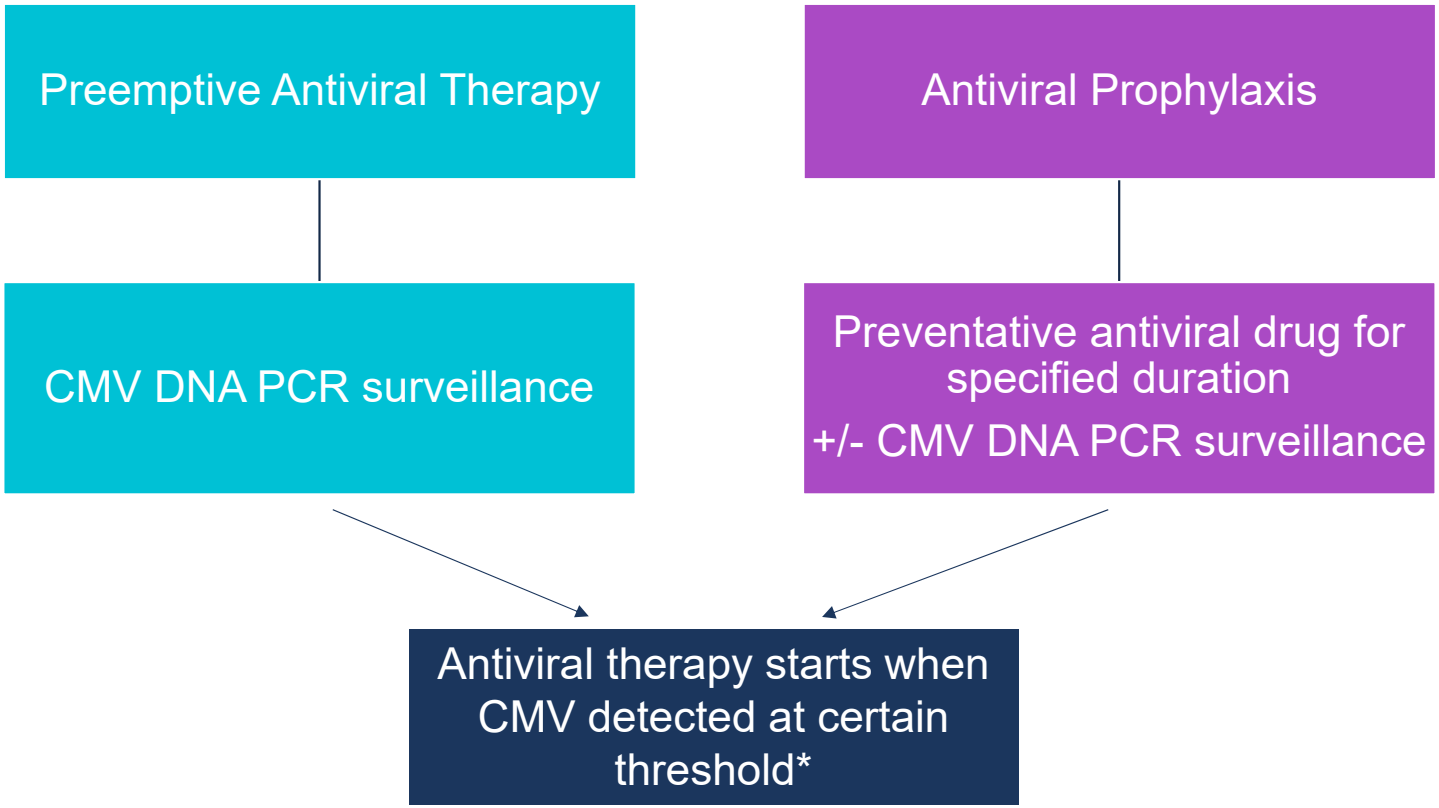
UNIVERSITY of WASHINGTON

Fred Hutch
Cancer Center

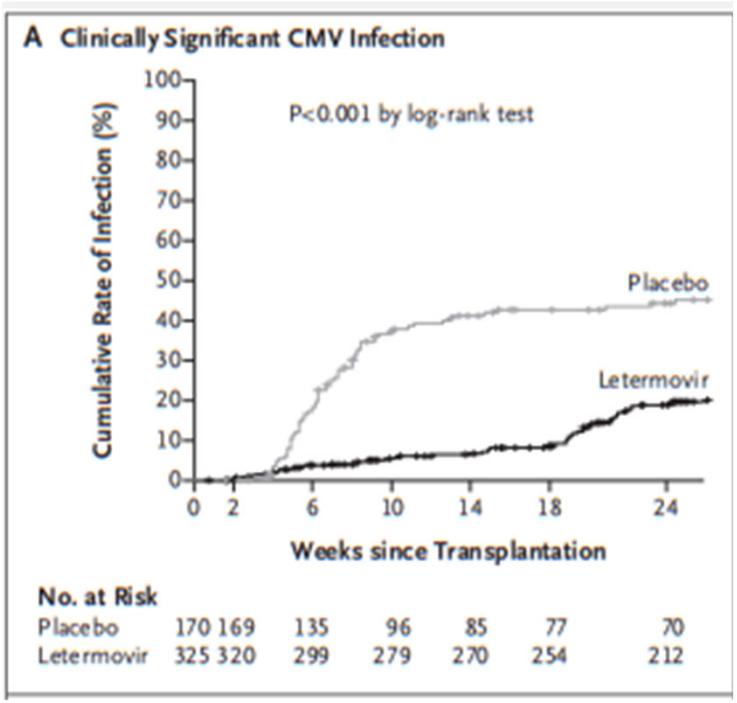
Thank you

Extra / reference slides

Post-HCT CMV Management Strategies

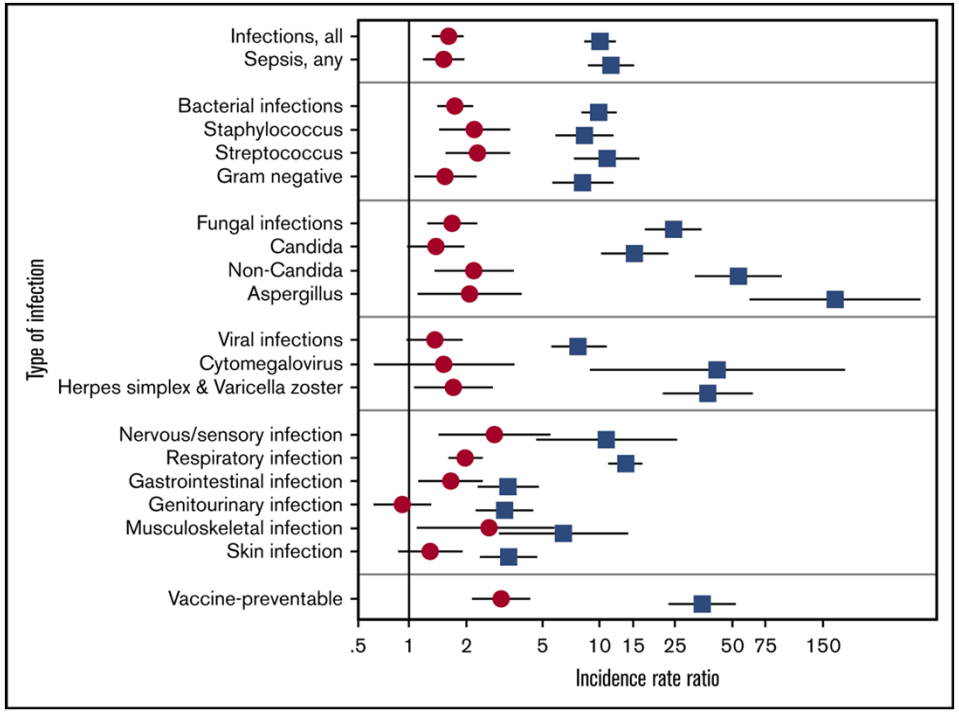


CMV ppx up to day 200



Russo et al. *Lancet Haematol.* 2024

Infections are significantly higher in individuals with a history of cancer or hematopoietic cell transplant



Red circles: ≥2-year HCT survivors vs non-HCT cancer survivors

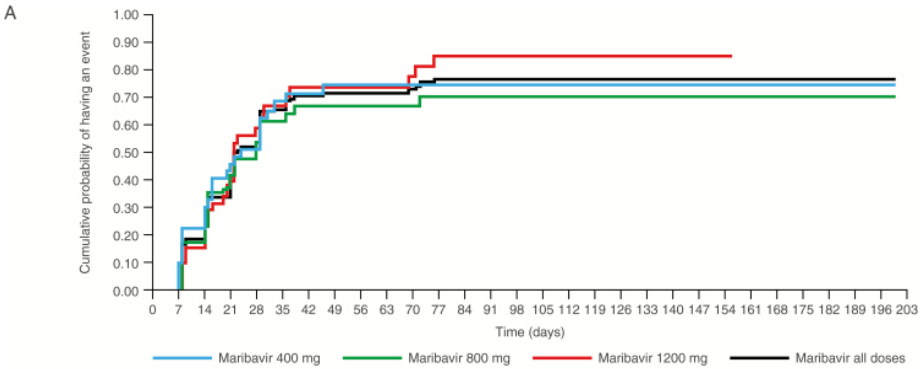
Blue squares: ≥2-year HCT survivors vs the general population

Foord et al, Blood Adv 2020

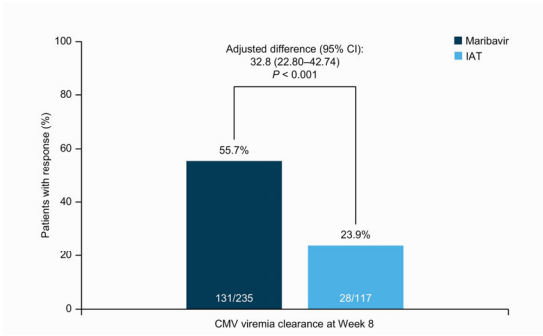
Slide courtesy of Josh Hill, MD

Maribavir for Refractory or Resistant CMV

- Phase 2 study of Maribavir for refractory or resistant CMV in HCT/SOT recipients.
  - Randomized to maribavir 400, 800, or 1200 mg BID for 24 weeks.
  - Comparable rates undetectable CMV DNA within 6 weeks.
  - **No new adverse safety signals identified**.
- Phase 3 study of Maribavir for refractory or resistant CMV in HCT/SOT recipients.
  - Maribavir vs. investigator assigned therapy including 1 or 2: ganciclovir, valganciclovir, foscarnet, cidofovir.
  - 1° endpoint: CMV DNA clearance at 8 weeks.
- FDA approved for adult and pediatric resistant or refractory CMV in HCT/SOT.



Papanicolaou et al. *Clin Infect Dis*. 2019



Avery RK et al. *Clin Infect Dis*. 2021

Clinical Infectious Diseases
MAJOR ARTICLE

Consensus Definitions of Cytomegalovirus (CMV) Infection and Disease in Transplant Patients Including Resistant and Refractory CMV for Use in Clinical Trials: 2024 Update From the Transplant Associated Virus Infections Forum

Per Ljungman,[1,2] Roy F. Chemaly,[3] Fareed Khawaya,[3] Sophie Alain,[4] Robin Avery,[5] Cyrus Badshah,[6] Michael Boeckh,[7,8] Martha Fournier,[9] Aimee Hodowanec,[10] Takashi Komatsu,[10] Ajit P. Limaye,[11] Oriol Manuel,[12] Yoichiro Natori,[13] David Navarro,[14,15] Andreas Pikis,[10] Raymund R. Razonable,[16,17] Gabriel Westman,[18,19] Veronica Miller,[20] Paul D. Griffiths,[21] and Camille N. Kotton[22]; for the CMV Definitions Working Group of the Transplant Associated Virus Infections Forum

- **Refractory CMV infection:** Defined as CMV viremia (DNAemia or antigenemia) that increases (ie, >1 log10 increase in CMV DNA levels in the same blood compartment from the peak viral load as measured in the same laboratory and/or with the same commercial assay) OR persists (≤1 log10 increase or decrease in CMV DNA levels) after at least 2 weeks of appropriate antiviral therapy.
- **Refractory CMV end-organ disease:** Defined by a worsening in signs and symptoms or progression to end-organ disease (for a patient not previously diagnosed with CMV end-organ disease) OR lack of improvement in signs and symptoms after at least 2 weeks of appropriately dosed antiviral therapy.

- For clinical purposes, **resistant CMV infection** is defined as refractory CMV infection as defined above in addition to viral genetic alteration that decreases susceptibility to 1 or more antiviral drugs. Drug resistance is defined by the occurrence of viral genetic alteration that affects in vitro susceptibility and/or clinical response, typically involving genes implicated in antiviral drug anabolism (eg, UL97-mediated phosphorylation of ganciclovir [26], the antiviral drug target (eg, UL54, UL97, UL56/89/51), ATP binding (maribavir resistance mediated by UL97 mutations [27]), or compensation for antiviral inhibition of biological function (eg, UL27 [28]). There are no changes in the definitions of decreased susceptibility and viral genetic alterations that decrease drug susceptibility.