Fred Hutch Cancer Center

Infectious Disease Complications

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15th Annual Comprehensive Hematology & Oncology Review Course

UW Medicine

Conflict of Interest Statement

- **I have no commercial associations or competing interests to disclose.**

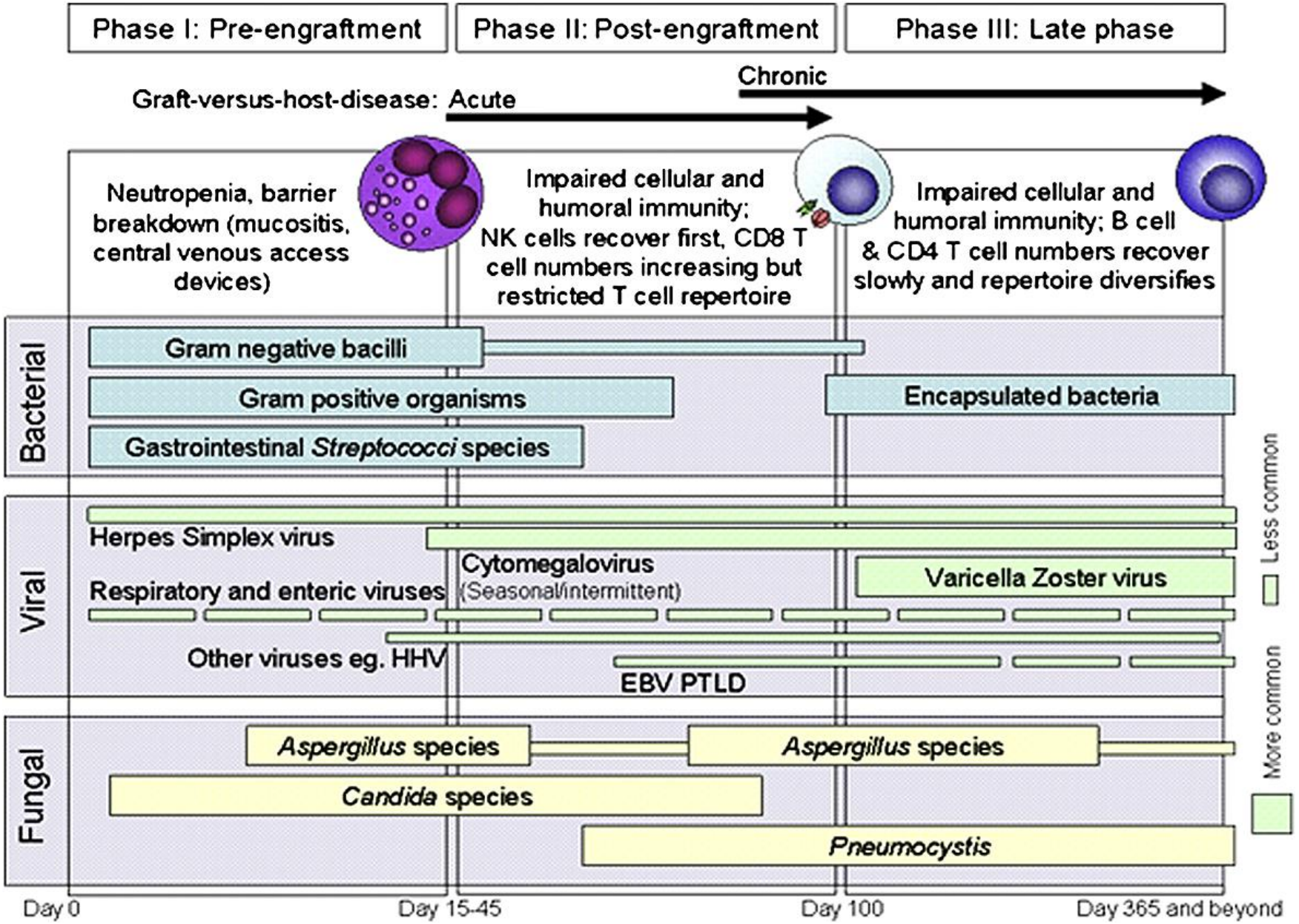
Outline

- Infections after hematopoietic cell transplantation (HCT).
  - Epidemiology and risk factors.
  - Changes in practice over time.
  - Case-based examples.
- Infections after novel cellular therapies.
  - Emphasis on CD19 and B-cell maturation antigen (BCMA)-targeted CAR-T Cell therapies.
- COVID-19.

Disclaimer: The field of Infectious Diseases after transplantation and cellular therapies is both large and constantly evolving!

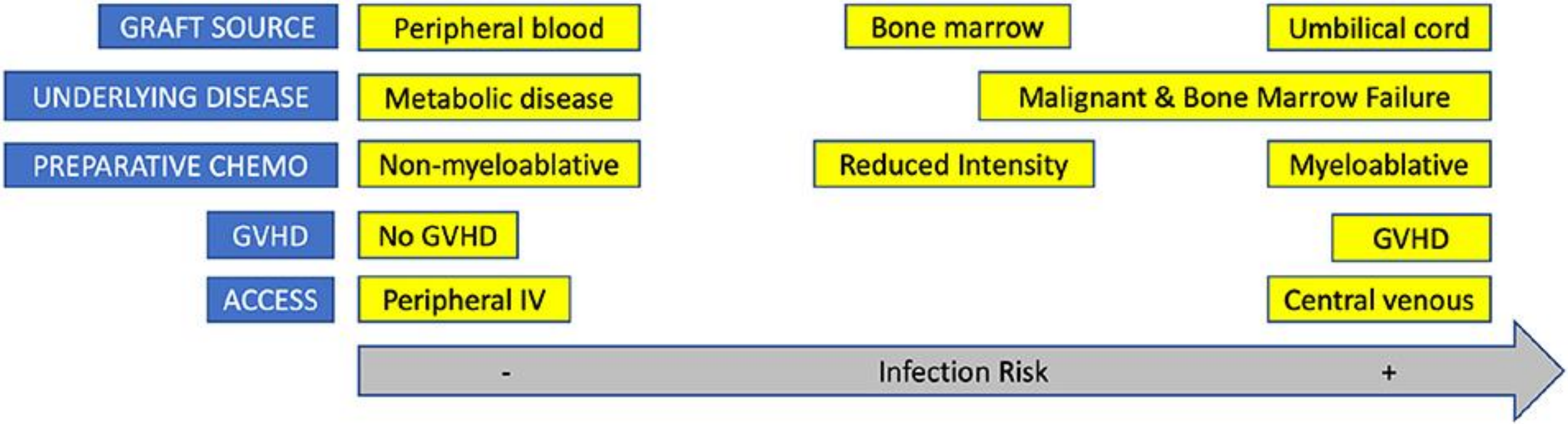
Infectious Disease Complications after HCT

“Phases” of Infection Risks after HCT



Tomblyn et al *BBMT* 2009

Clinical and Transplantation Risk Factors



Ferdjallah et al *Front Pediatr* 2021

42M Day +66 status post mismatched unrelated donor (mmURD) HCT for ALL with diarrhea

- **Conditioning:**
  - busulfan/cyclophosphamide
- **GVHD prophylaxis:**
  - tacrolimus/methotrexate
- Recipient HSV+, VZV+, CMV+; Donor CMV-
- **Infection prophylaxis:**
  - TMP-SMX
  - acyclovir
  - Fluconazole
- Fever x1 day, diarrhea x2 weeks
- Lower GI endoscopy with ulcerations, not typical for GVHD.

What is the most likely diagnosis?

A. Typhlitis

B. CMV colitis

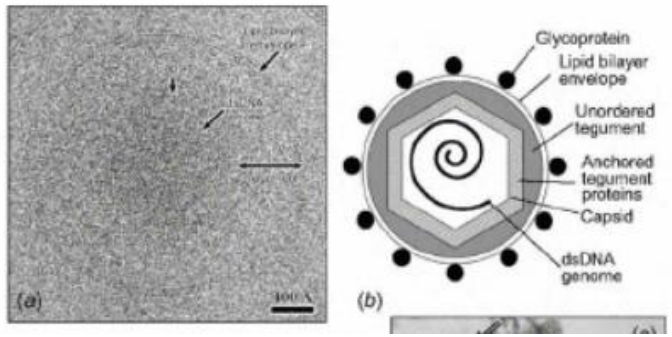
C. Adenovirus colitis

D. Invasive fungal disease

E. Acute GVHD

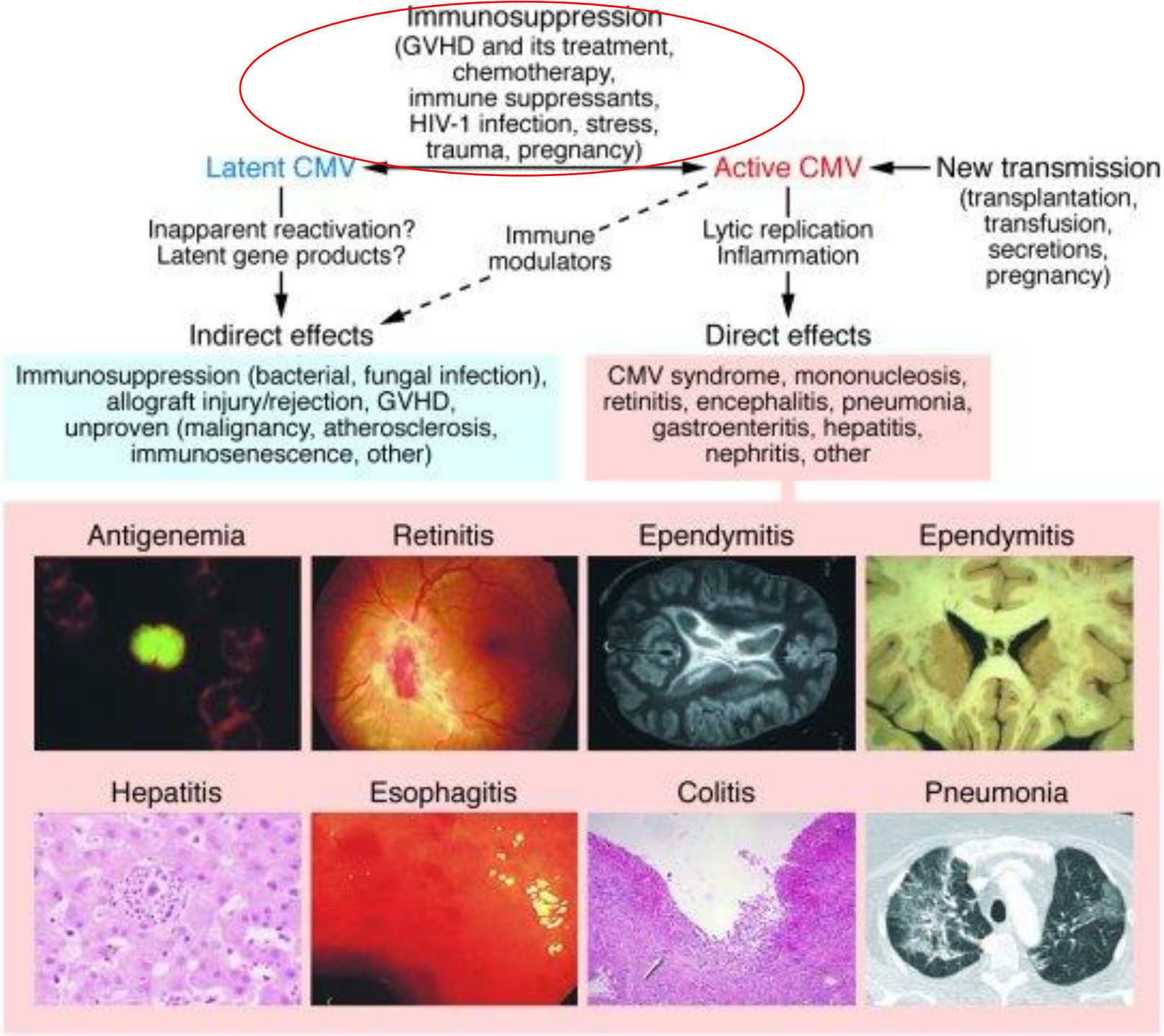
CMV Epidemiology and Clinical Manifestations

- Human betaherpesvirus
- ~50% all adults in US infected by adulthood.
- Multiple clinical manifestations:
  - Asymptomatic (most common)
  - “Flu-like”
  - End-organ disease (e.g. GI disease, CNS disease, pneumonitis, nephritis)
- Immunocompromised (e.g. HCT recipients) at highest risk for end-organ disease.
  - Highest risk in CMV D-R+ HCT.



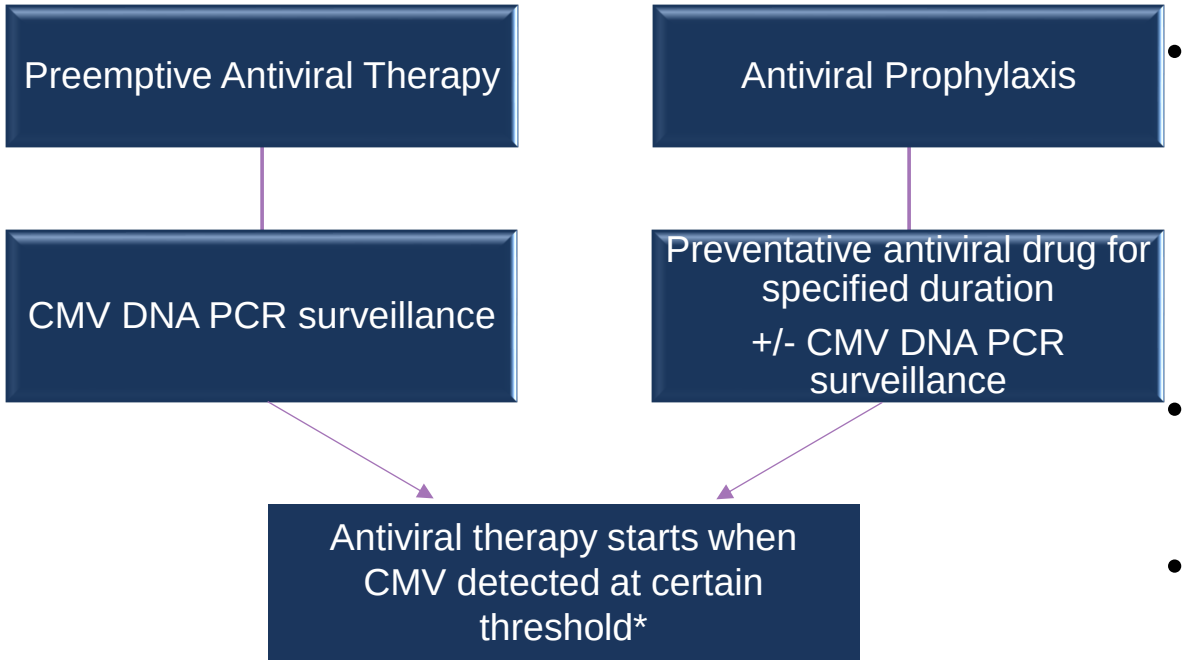
Source	Infectious fluid	Mode of transmission
Pregnant women	Blood; genital secretions	Blood-borne transmission to Fetus; intrapartum ingestion of infected genital secretions
Lactating women	Breast milk	Ingestion of cell free virus by breast feeding infants
Young children	Saliva; urine	Ingestion

Arvin et al. *Human herpesviruses:Biology, therapy, and immunoprophylaxis.* 2007.



Boeckh et al. *JCI*. 2011

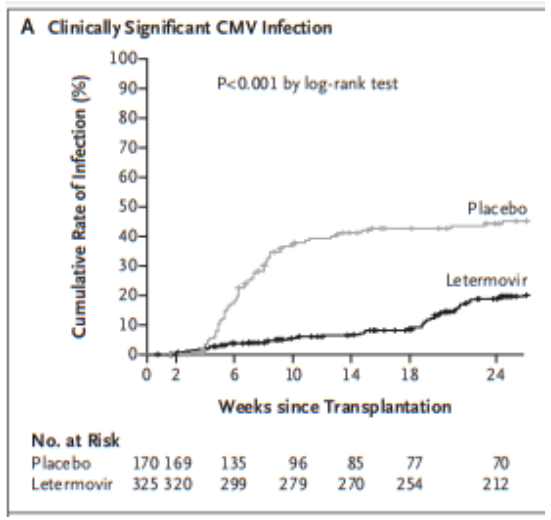
Post-HCT CMV Management Strategies



- Two strategies: Preemptive therapy vs. Prophylaxis
- First line therapy with ganciclovir or valganciclovir (prodrug)
  - Second line therapies: foscarnet, cidofovir.
  - Use as prophylaxis limited by hematologic toxicity and nephrotoxicity.
- 1-2 weeks induction dosing followed by maintenance dosing (can use PCR to guide).
- End-organ disease may require longer duration of therapy.

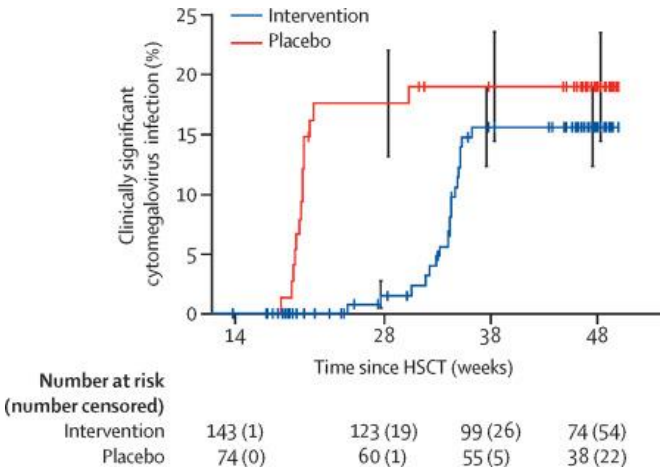
Letermovir

- ↓ clinically significant CMV infection in first 100 days in phase 3, randomized, controlled trial.
  - Favorable side-effect profile (no neutropenia or renal injury).
- Recent phase 3 data on extension of from 100 to 200 days post-HCT.
  - ↓ clinically significant CMV infection through 200 days post-HCT.
- High-risk patients may benefit more.
  - HLA-mistmatched
  - Cord blood donor
  - Ex-vivo T-cell depletion
  - GVHD requiring ≥1 mg/kg steroids



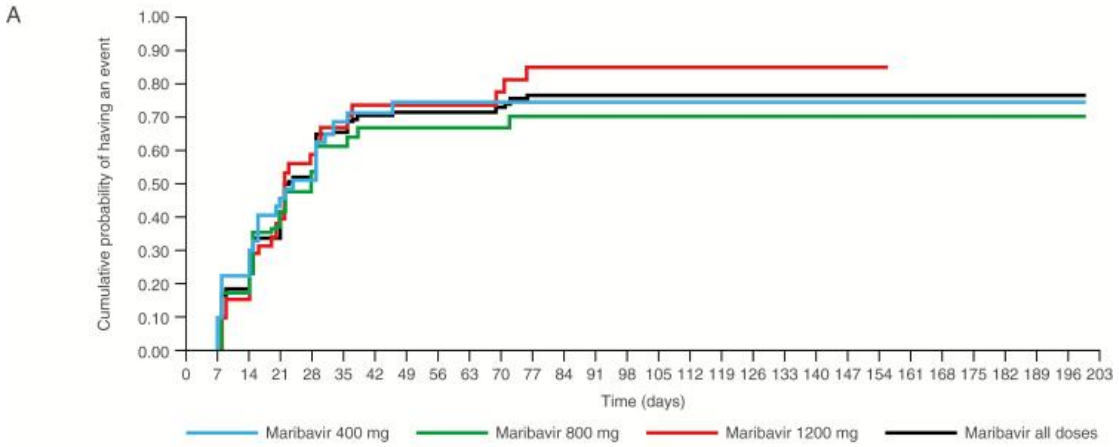
Russo et al. *Lancet Haematol.* 2024

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

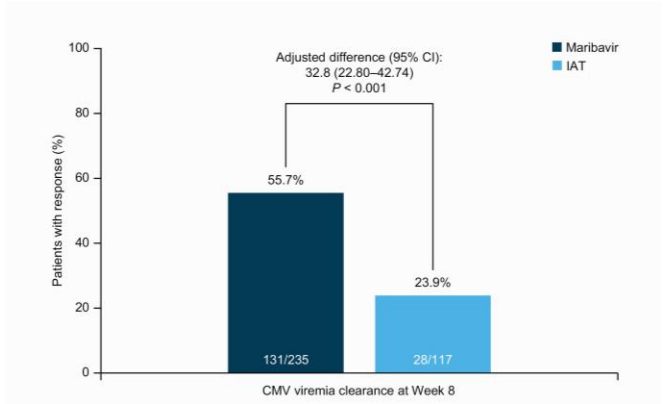


Maribavir for Refractory or Resistant CMV

- 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

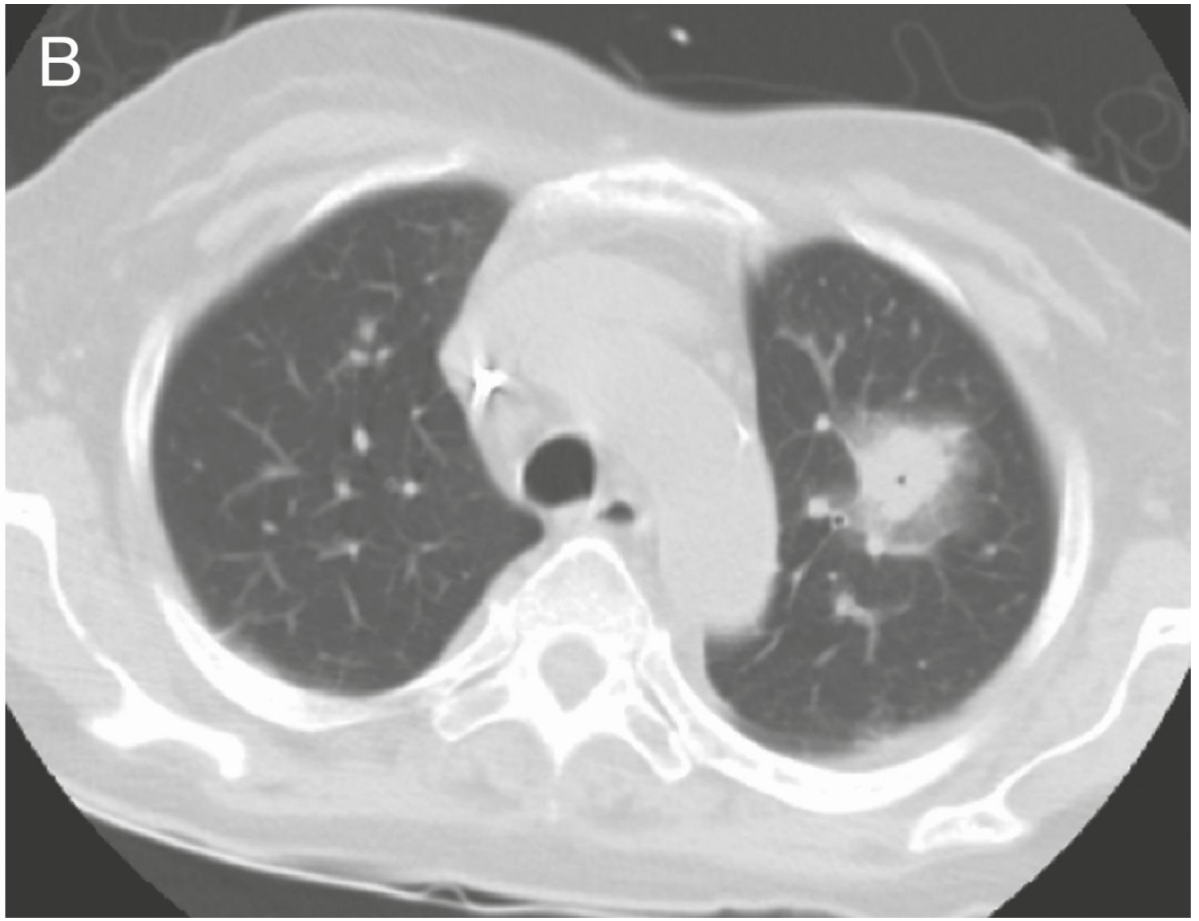
Per Ljungman,[1,2] Roy F. Chemaly,[3] Fareed Khawaya,[3] Sophie Alain,[4] Robin Avery,[5] Cyrus Badshah,[6] Michael Boeckh,[7,8] Martha Fournier,[9] Aimee Hodowanec,[10] Takashi Komatsu,[10] Ajit P. Limaye,[11] Oriol Manuel,[12] Yoichiro Natori,[13] David Navarro,[14,15] Andreas Pikis,[10] Raymund R. 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.

55F Day +12 status post Umbilical Cord Transplantation (UCT) for AML now with Fever

- **Conditioning:**
  - busulfan/fludarabine
- **GVHD prophylaxis:**
  - cyclosporine/methotrexate
- Recipient HSV+, VZV+, CMV+; Donor CMV-
- **Infection prophylaxis:**
  - letermovir
  - acyclovir
  - fluconazole
- Fever x2 days.
- Started on Cefepime.
- CT Chest shows…

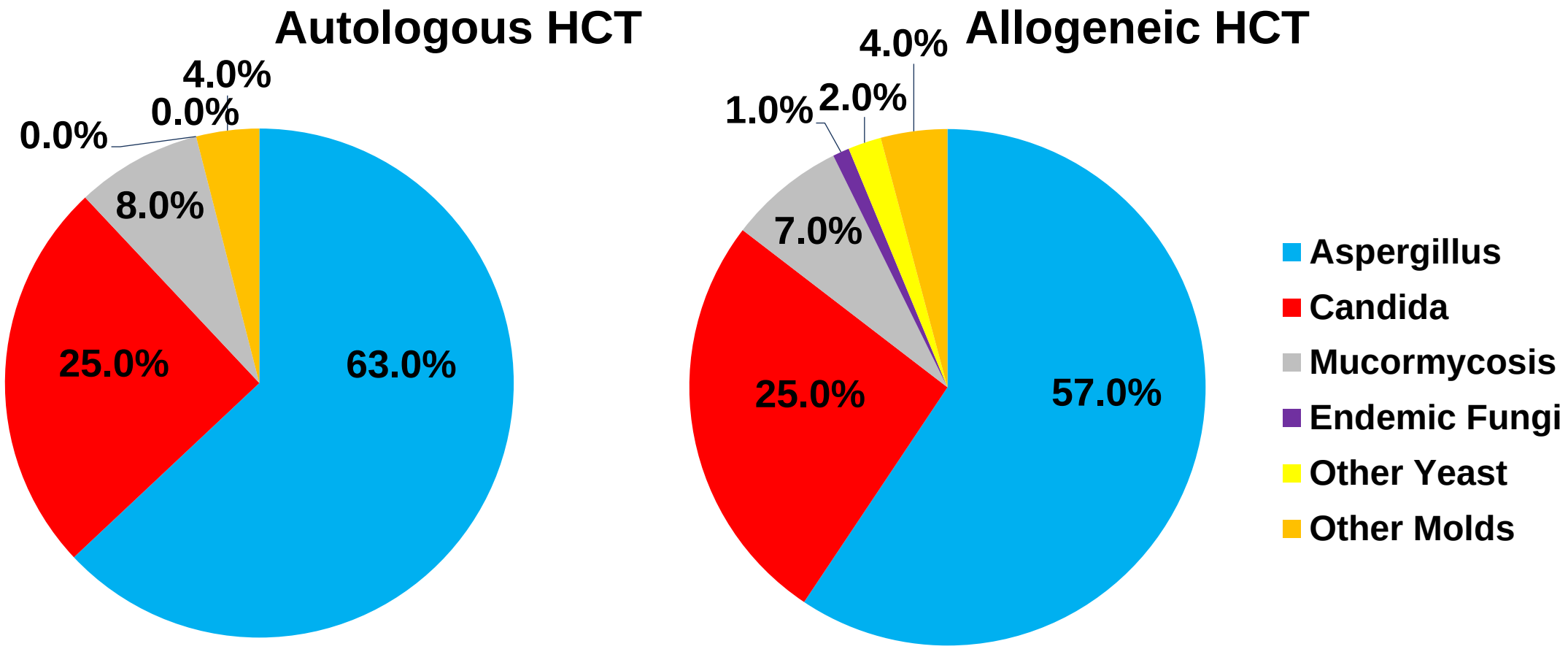


Alexander et al *CID* 2021

What is the next best step in management?

A. Start Ambisome 3 mg/kg/d
B. Start Ambisome 10 mg/kg/d
C. Start voriconazole (6 → 4 mg/kg BID)
D. Start micafungin 150 mg IV qd
E. Start voriconazole + anidulafungin

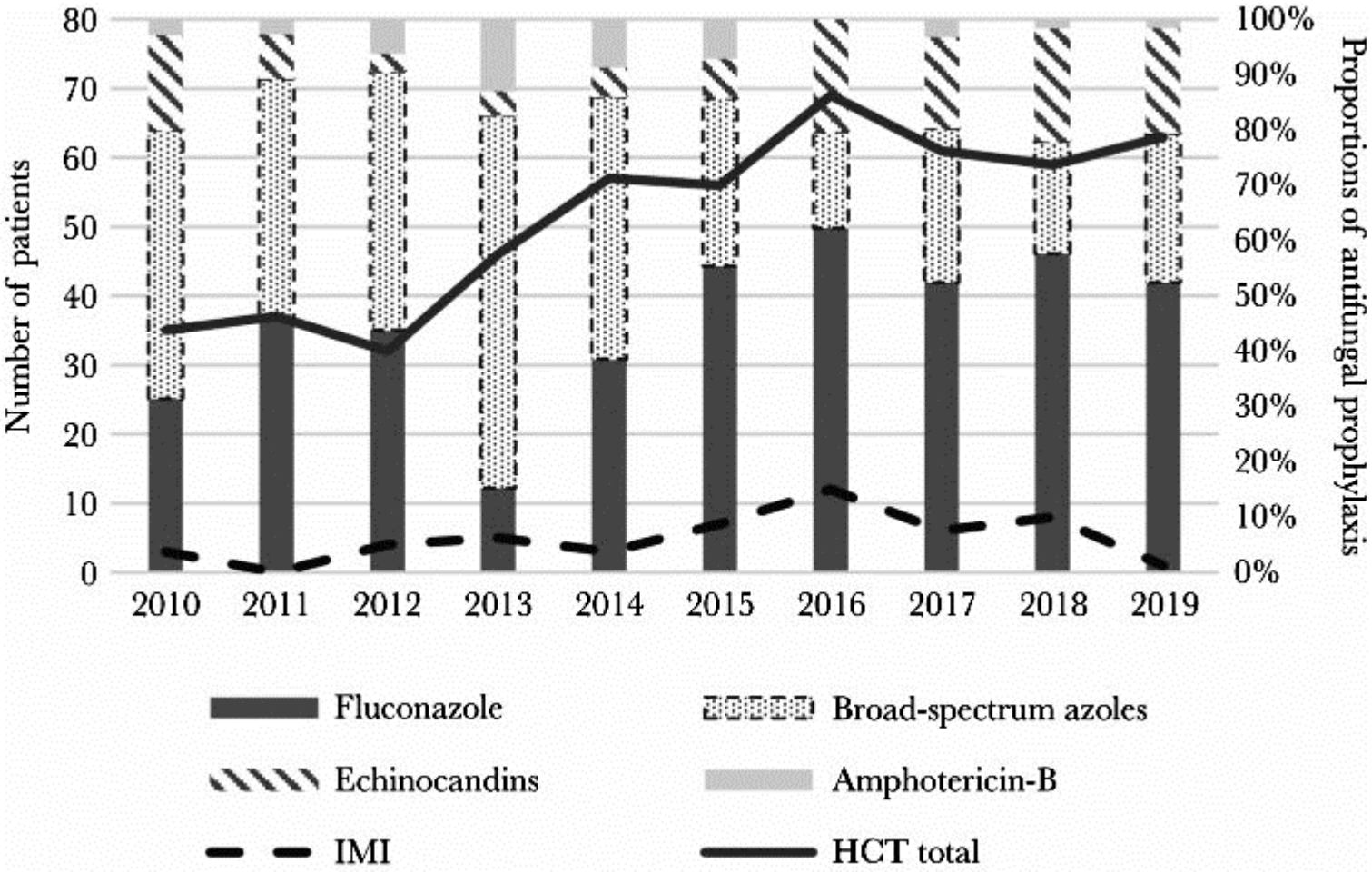
Epidemiology of Invasive Fungal Infection in HCT



Prospective Antifungal Therapy (PATH) Alliance Registry: 16 centers, 2004-2007 (N=234 HCT pts)

Neofytos et al *CID* 2009

Evolution of Primary Antifungal Prophylaxis

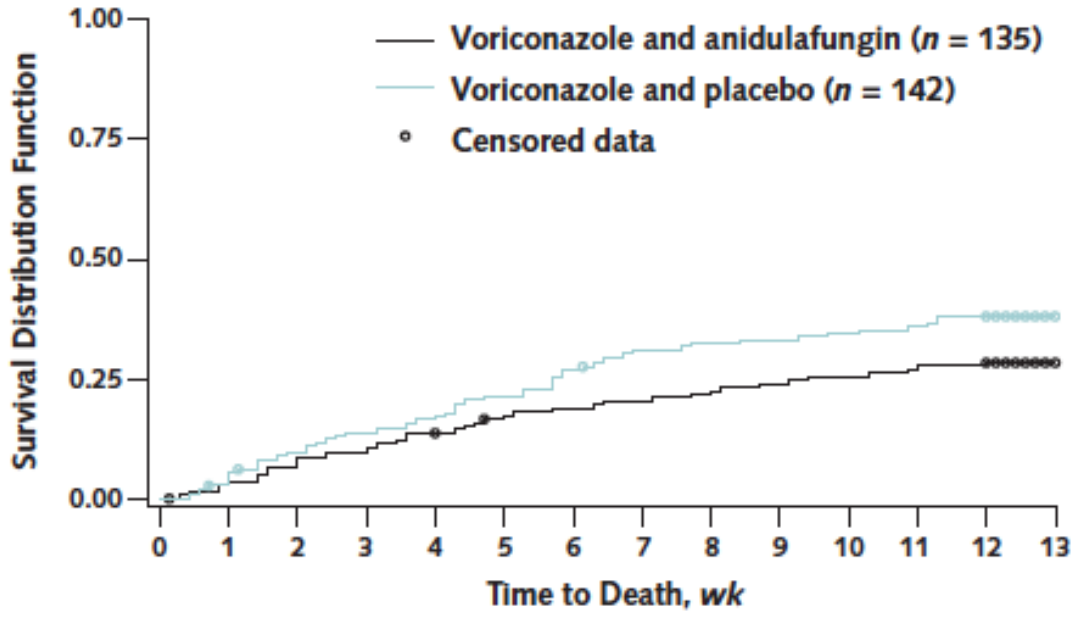


Roth et al *OFID* 2021.

Combination Therapy for Invasive Aspergillosis

- Randomized, double-blind, placebo-controlled multicenter trial (n=277).
- Voriconazole + anidulafungin vs voriconazole + placebo
- 1° endpoint: 6wk mortality
  - Combo 19.5% vs monotherapy 27.8% (p=.086)
- **Post-hoc: 6wk mortality in serum Aspergillus galactomannan (+) subgroup**
  - **Positive 15.7% vs negative 27.3 % (p=.037)**

Figure 2. Cumulative incidence of death in the modified intention-to-treat population.

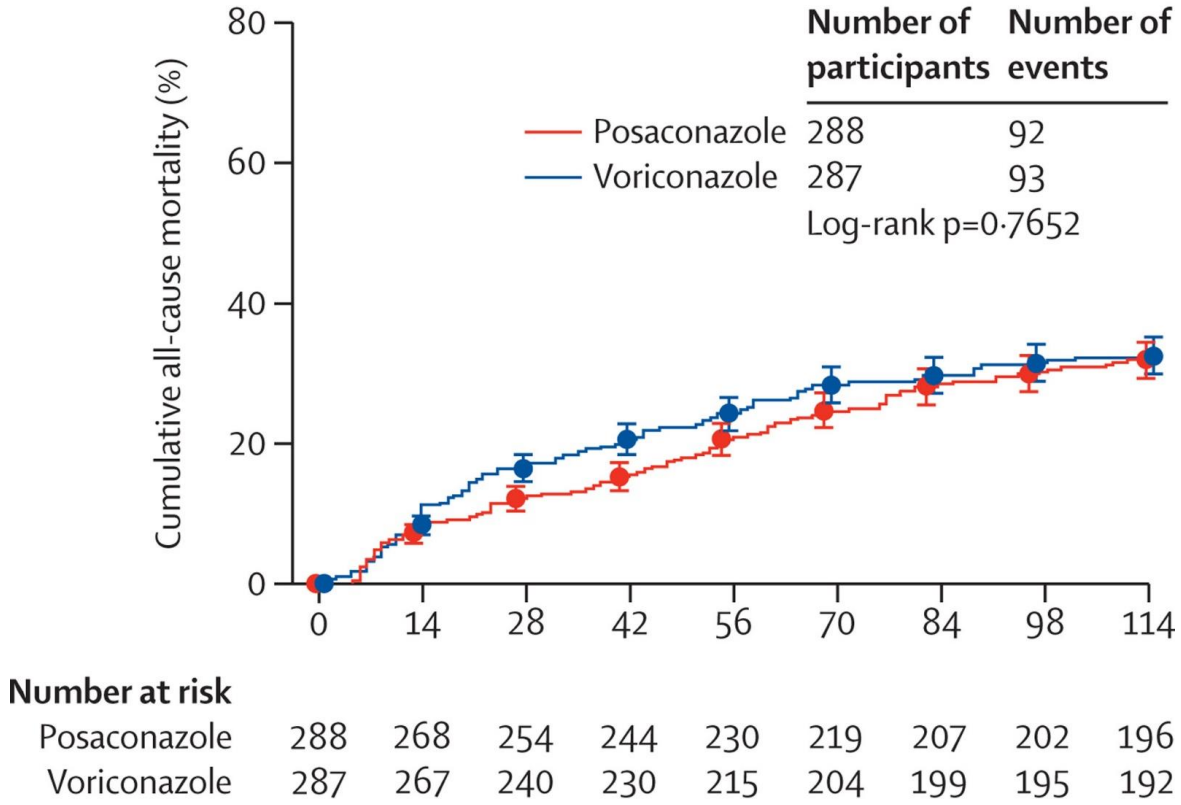


Log-rank, $P = 0.086$.

Marr K. *Ann Intern Med.* 2015

Posaconazole Non-Inferior to Voriconazole for Treatment of Invasive Aspergillosis

- Multi-center, double-blind, double-dummy randomized controlled trial.
- Posaconazole vs voriconazole for primary treatment of invasive aspergillosis.
- 1° endpoint: cumulative all-cause mortality until d42 42 in intention-to-treat (ITT) population with 10% non-inferiority margin.
  - Posaconazole 15% vs voriconazole 21% (treatment difference -5·3% [95% CI -11·6 to 1·0]; p<0·0001).



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

55F Day +12 status post UCT for AML with Fever (cont.)

- ~1 week into voriconazole therapy, the patient becomes lethargic.
- On exam oriented only to person, no focal deficits.

What is/are the next step(s) in management?

A. Obtain brain MRI
B. Check voriconazole level
C. Add micafungin
D. A and B
E. A, B, and C

The Art of Azole Dosing

Azole	Treatment	Prophylaxis	Trough timing
Voriconazole	1-5.5 mcg/mL	1-5.5 mcg/mL	≥ 5-7 days
Posaconazole	≥ 1 mcg/mL	≥ 0.7 mcg/mL	≥ 7 days
Isavuconazole	No recommendations for monitoring. Could consider on case-by-case basis		

- Switch to oral therapy as soon as possible.
- Identify drug-drug interactions early.
  - If on letermovir (for CMV), ↑ monitoring frequency.
  - Check ~1 week after letermovir discontinuation to guide voriconazole dose reduction.
- Evaluate for side effects (Tolerable?)
  - QTc prolongation (“class effect”)
  - Skin cancer and fluoride toxicity (voriconazole),
  - Mineralocorticoid excess (posaconazole).
- Monitor liver function tests.
  - Weekly in 1st month of voriconazole, twice monthly thereafter.
  - Twice monthly all other azoles.
- Weight-based dosing: adjusted body weight (obesity) vs actual body weight.
- Genotypic variability in drug metabolism (i.e., CYP2C19 loss/gain of function).

Chau et al. *Int Med J* 2014; Laverdiere et al *Can J Inf Dis Med Micro* 2014; Ashbee *JAC* 2014; Duong et al *J Antimicrob Chemother* 2020.

63M status post-induction chemotherapy for Acute Myelogenous Leukemia (AML) now with Fever

- Tmax 38.6 °C during platelet transfusion.
- No other symptoms.
- Post-chemo course complicated by severe mucositis.
- Infection prophylaxis: levofloxacin, fluconazole, acyclovir.
- Hickman catheter site without erythema.
- Labs: **Absolute Neutrophil Count (ANC) < 100 x10^3/uL x10 days.**

What empiric antibiotic therapy should you begin?

A. Vancomycin alone
B. Cefepime alone
C. Vancomycin and cefepime
D. No antibiotics should be initiated and await blood culture results; fever likely due to transfusion

Temporal Trends in Bacterial Pathogens in Neutropenic Patients

1960s-1970s → **1980s-2000s** → **2000-present**

Gram - >> Gram +

- *E. coli*
- *Klebsiella* spp.
- *Enterobacter* spp.
- *Pseudomonas* spp.
- *Stenotrophomonas*
- Anaerobes

Gram + >> Gram -

- Coagulase neg *Staphylococcus*
- *Staphylococcus aureus*
- Enterococcus
- Viridans group *Streptococci*

Gram + ≳ Gram -

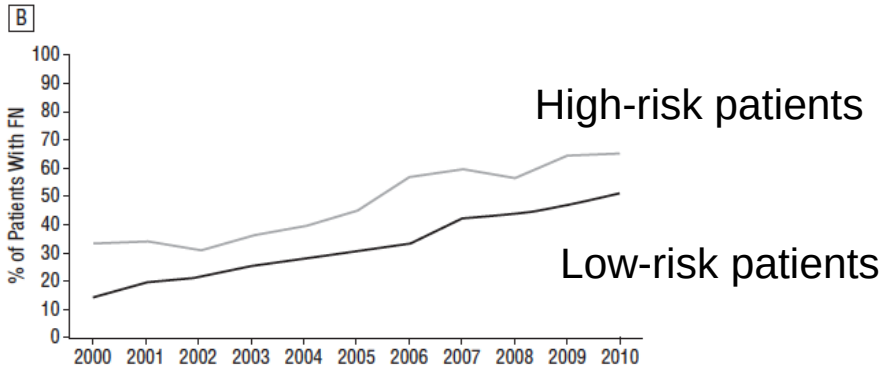
- Fluoroquinolone (FQ)-resistant and multi-drug resistant Gram negatives (Extended spectrum beta lactamase [ESBL], carbapenem resistant *Enterobacteriaceae* [CRE])
- Penicillin-and FQ-resistant viridans group *Streptococci*
- Vancomycin resistant *enterococcus* [VRE], methicillin resistant *Staphylococcus aureus* [MRSA]

Freifeld et al *CID* 2011; Freifeld A Poster#1016 IDWeek 2018; Zimmer A Poster#1585 IDWeek 2018

Excess Empiric Vancomycin Use in Febrile Neutropenia

- In a retrospective cohort of cancer patients with febrile neutropenia, **62%** (41/66) and **73%** (48/66) had an *inappropriate* **indication** or **duration,** respectively.
- In a large study of solid tumor patients admitted with febrile neutropenia from 2000-2010, **37%** (9,311/25,231) had an *inappropriate* **indication**.

Empiric Vancomycin Use



Empiric vancomycin use (2000-2010): 17% ➔ 55%, p<.001

Libuit et al *OFID* 2014; Wright *JAMA IM* 2013

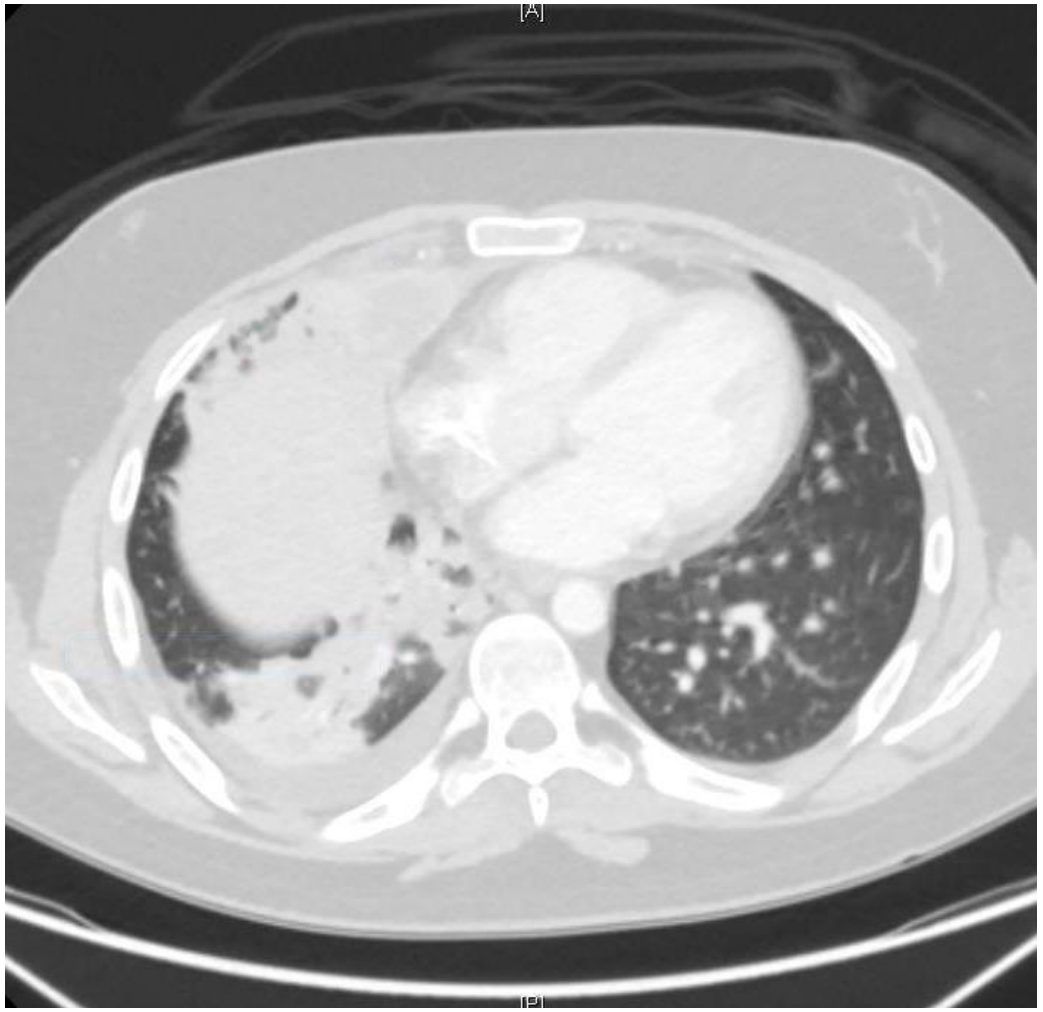
Indications for Empiric Use of Vancomycin

	Infectious Diseases Society of America (2010)	European Conference on Infections in Leukemia (2011)	National Comprehensive Cancer Network (2020)
Clinically apparent serious catheter related infection	✓	✓	✓
Hemodynamic instability	✓	✓	✓
MRSA colonization	✓	✓	✓
Skin or soft tissue infection	✓	✓	✓
Positive blood cultures for gram + bacteria (before identification & susceptibilities)	✓		✓
Pneumonia	✓	✓	
Severe mucositis **(if fluoroquinolone prophylaxis <u>AND</u> ceftazidime used empirically)**	✓		

Table used courtesy of Dr. Catherine Liu at Fred Hutch.

Infectious Disease Complications after CAR-T Cell Therapy

26M day +68 status post CD-19 CAR T-Cell Therapy for ALL now with Chest Pain and fever



- Fever x1 day. Right-sided chest pain x1-2 weeks.
- Exam notable for fever 38.1 °C.
- Started empirically on vancomycin/cefepime.
- CT imaging (**left**) with ride-sided pneumonia with evidence of cavitation.
- **Labs:**
  - ANC >500 x1 mo.
  - serum *Aspergillus* galactomannan (-),
  - *Legionella* urine Ag (-),
  - *Streptococcus pneumoniae* urine Ag (-).

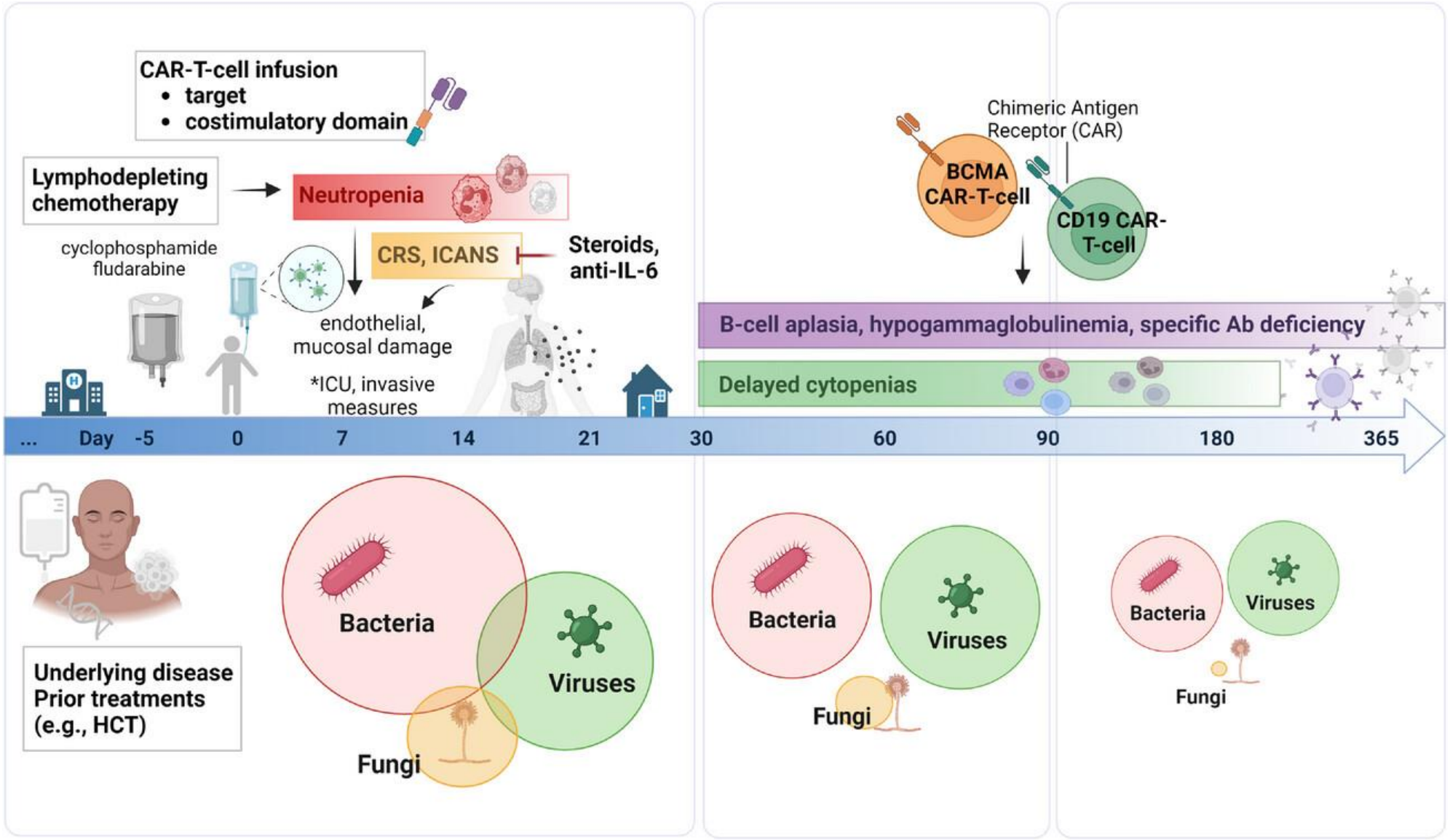
Which of the following is the next best step in management?

A. Add empiric voriconazole.
B. Consult pulmonology for consideration of bronchoscopic alveolar lavage (BAL).
C. Order non-invasive pathogen blood test.
D. Combination of A,B, and C.
E. None of the above.

Non-*pneumophila Legionella* spp. (*L. micdadei, bozemanni*, etc.)

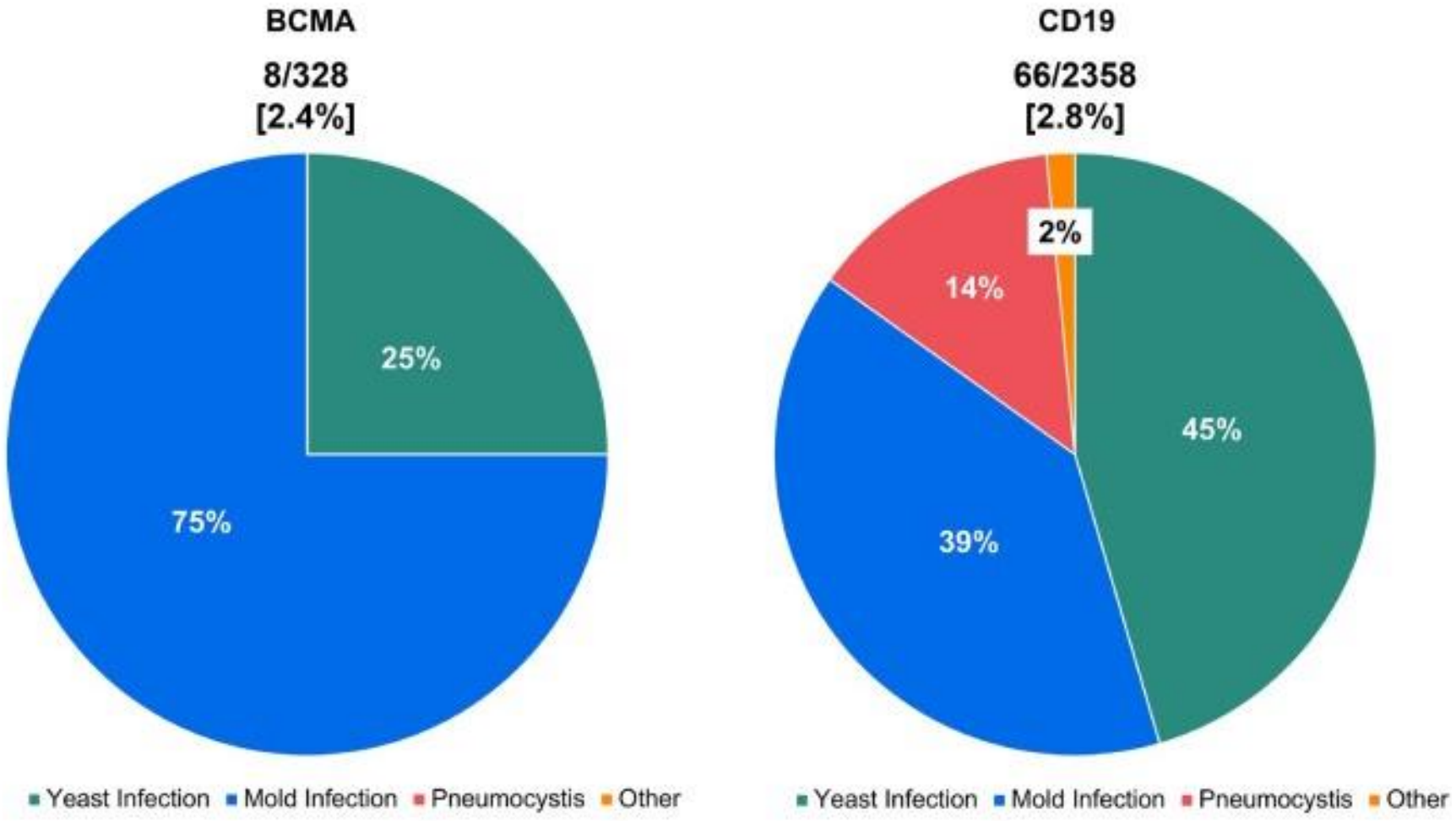
- *L. micdadei* 2nd most common *Legionella* spp. after *pneumophila*.
- Presentation variable including fever, shortness of breath, pleuritic chest pain, lethargy, and altered mental status.
- Immunocompromised at higher risk for abscess/cavitary pneumonia.
- *Legionella* urine antigen test does not detect all *Legionella* spp.
- Fluoroquinolones treatment of choice.

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



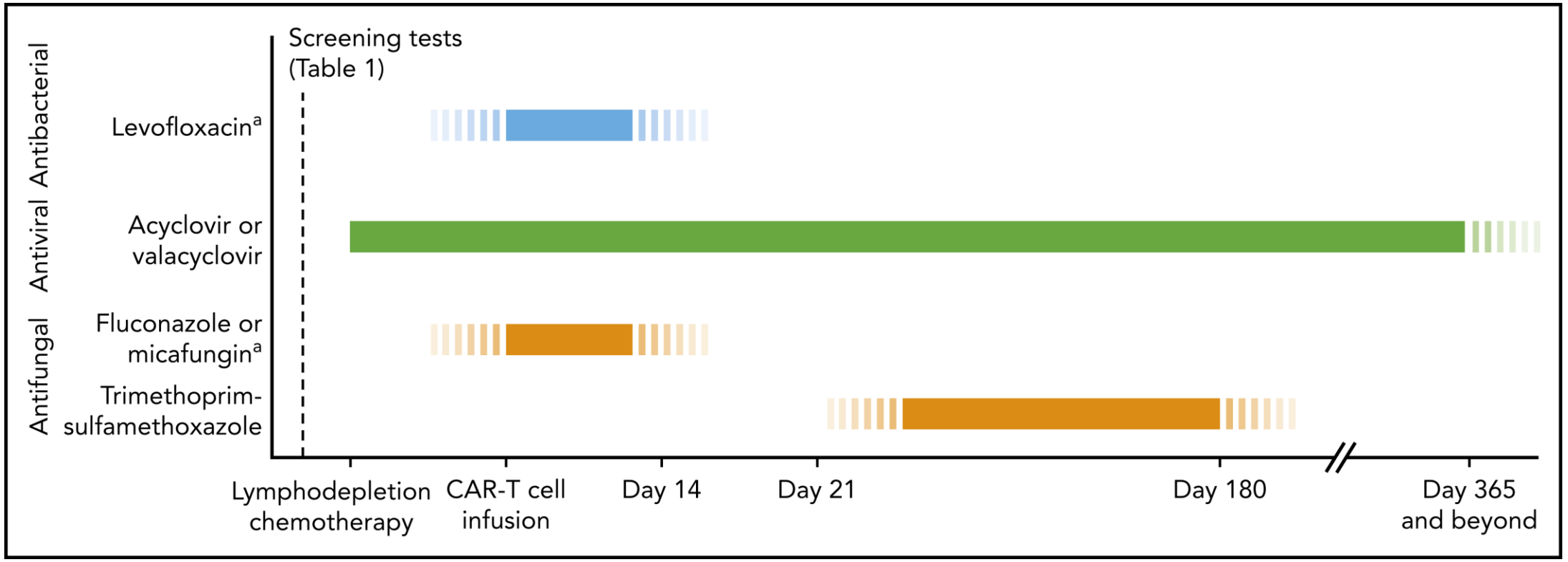
Kampouri et al. *TID.* 2023

Epidemiology of Fungal Infections after CAR-T Cell Therapy after ~1 Year



Little et al. Open Forum Infect Dis. 2024

Recommended Antimicrobial Prophylaxis after CAR-T Cell Therapy



Hill JA et al *Blood* 2020

COVID-19

54M Day +160 status post-HCT for AML with Cough

- **Conditioning:**
  - busulfan/cyclophosphamide
- **GVHD prophylaxis:**
  - tacrolimus/methotrexate
- Recipient HSV+, VZV+, CMV+; Donor CMV-
- **Infection prophylaxis:**
  - Valaciclovir
- Cough x2 days, recent positive COVID-19 rapid antigen test yesterday.
- On exam: O2 saturation 95%. Lungs with basilar crackles.
- Now SARS-CoV2 (+) by PCR.

What is the next best step in management?

A. Admit and start on IV remdesivir (Veklury).
B. Send prescription for oral remdesivir (Veklury) to local pharmacy.
C. Send prescription for molnupiravir to local pharmacy.
D. Send prescription for nirmatrelvir/ritonavir (Paxlovid) to local pharmacy.
E. Consult with pharmacy regarding drug-drug interactions with nirmatrelvir/ritonavir (Paxlovid) prior to sending prescription.

Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19

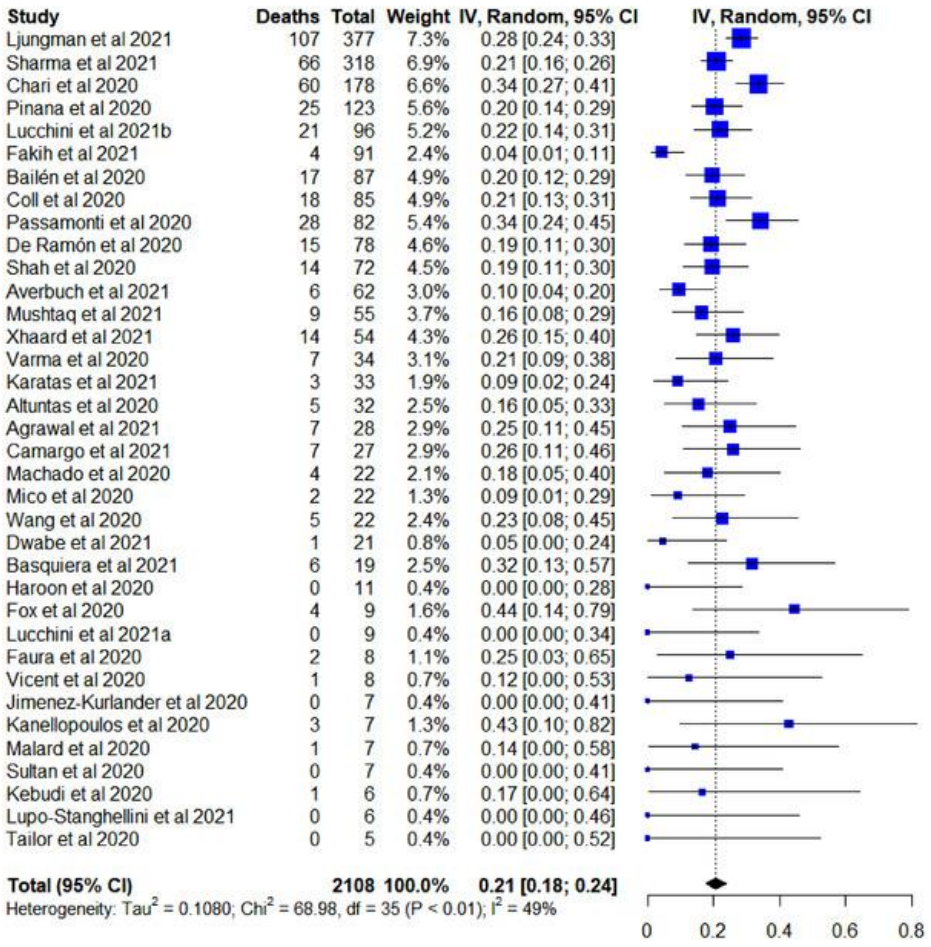
- **Higher risk** - an underlying medical condition or risk factor that has a published meta-analysis or systematic review or underwent the CDC systematic review process.

Condition	Evidence of Impact on COVID-19 Severity
Cancer •Hematologic Malignancies	CDC Systematic Review [O] Meta-Analysis/ Systematic Review [18-22] Cohort Study [23-25] Case Series [26-28] Case Control Study [29]
Solid organ or blood stem cell transplantation	Meta-Analysis [108] Case Series [136-147] Cohort [148-151]
Use of corticosteroids or other immunosuppressive medications	Meta-Analysis/ Systematic Review [152] Cohort Study [153] Cross-Sectional [154] Case Series [155-157]

https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html

Mortality from COVID-19 after HCT and CAR-T

- Meta-analysis of 26 studies (N=2141 HCT recipients)
  - Incidence of ICU admission and mechanical ventilation 18% and 14%, respectively
  - COVID-19-related death occurred in 21% (95% CI 18%–24%)
- No difference in outcomes including mortality between auto- and allo-HCT (Ljungman et al. *Leukemia* 2021).
- ICU admission ~40% and mortality between 33–41% after CAR-T early in pandemic (Kampouri et al. *TID*. 2023).

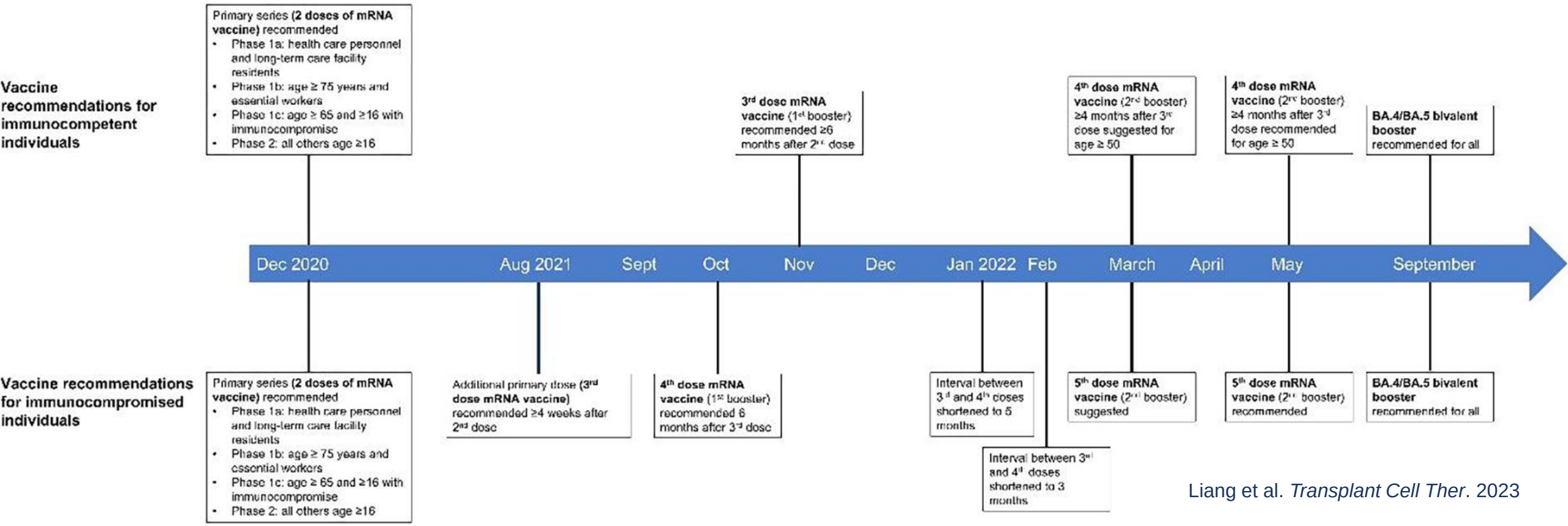


Lim et al. *EJHaem*. 2022

COVID-19 Treatment Options

Treatment	IDSA Level of Evidence	When	How	Special Considerations
Nirmatrelvir with Ritonavir (Paxlovid)	Conditional recommendation†, Low certainty of evidence	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally)	CYP3A4 inhibitor, requires DDI review, renal dose adjustment, side effects
Remdesivir (Veklury)	Conditional recommendation†, Low certainty of evidence	Start as soon as possible; must begin within 7 days of when symptoms start	Intravenous (IV) infusions at a healthcare facility for 3 consecutive days	Logistics of outpt admin, extended duration in IC hosts?
Molnupiravir (Lagevrio)	Conditional recommendation†, Low certainty of evidence	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally)	SARS CoV-2 mutagenic potential?

COVID-19 Prevention



Liang et al. *Transplant Cell Ther*. 2023

Currently guidance to administer SARS-CoV-2 vaccine ~3 months days after HCT or CAR-T cell therapy

Fred Hutch Cancer Center

Hosted by the
Infectious Disease Sciences Program

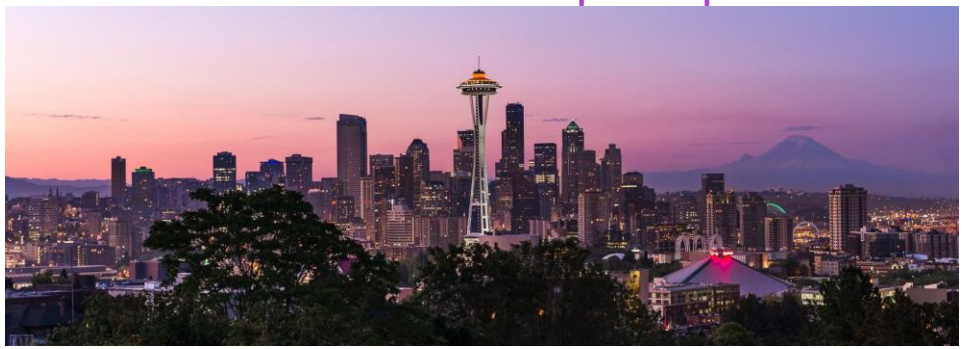
5th Symposium on Infectious Diseases in the Immunocompromised Host

Sunday, May 11th – Wednesday, May 14th, 2025

Grand Hyatt Seattle

Website **Program Agenda**

Trainee Travel Stipend Applications and Abstract Proposals open in Fall 2024!



Dr. Michael Boeckh

Scientific Topics Covered

Adenovirus & BK Virus
Cytomegalovirus Cellular Therapy
Respiratory Viruses
COVID-19
Pulmonary Complications
Bacterial Resistance - Microbiome Fungal Disease

Questions? Contact: IDSymposium@fredhutch.org

UW Medicine

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Questions?

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