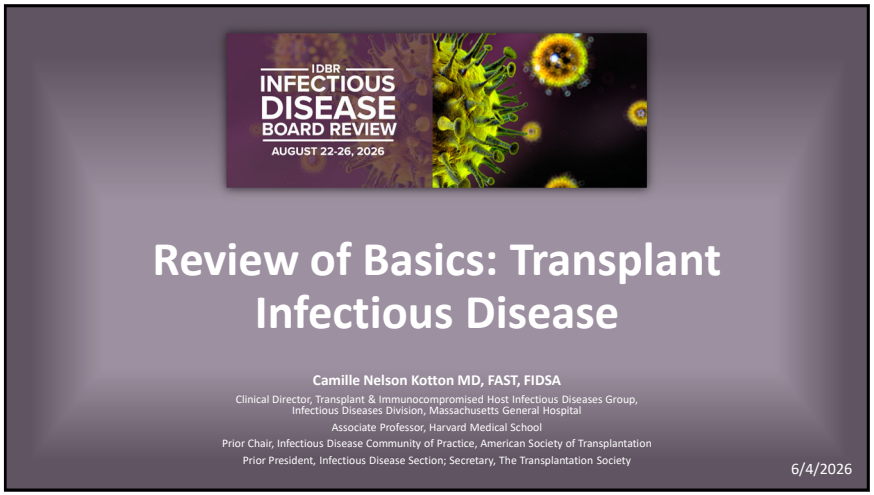


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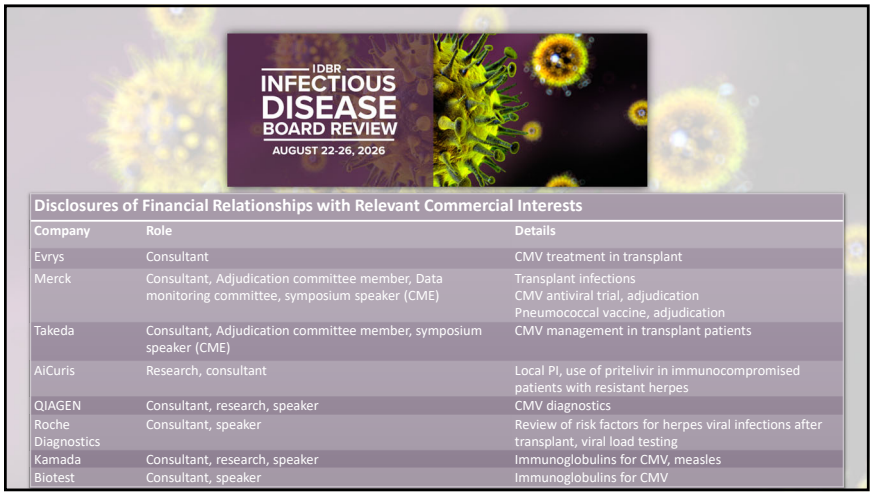



2

## Outline: What I Hope You Will Learn

- Type of immunosuppression seen with organ and stem cell transplant
- Timelines of infection
- Prevention is paramount
  - Gaps in prophylaxis help develop the differential diagnosis
- Syndromes
- Diagnostics
  - Differential diagnosis is broad, imperative to obtain diagnosis
- Treatment – including drug interactions
- Latest strategies for prevention, recognition, diagnosis, and treatment
  - Guidelines
  - Best practices for safety and practice improvement
- **Bootcamp: meant as an introduction/review to subsequent similar talks**

3

**Prevalence of Immunosuppression Among US Adults, Martinson & Lapham, JAMA Feb 2024**

CDC National Health Interview Survey

**6.6% are immunosuppressed**

- 4.4% reported immunosuppressive condition
- 3.9% take an immunosuppressive medication
- 1.8% report both immunosuppressive condition and medication

*This number has doubled in the past decade*

Table. Self-Reported Status of Immunosuppression for 2021

| | Unweighted data, No. (%) | | Weighted prevalence per 100 US population, % (95% CI) |
|---|---|---|---|
| | Total sample (N = 29 164) | Had immunosuppression (n = 2123) | |
| Had immunosuppression | | 2123 (7.2)[a] | 6.6 (6.2-6.9) |
| Sex | | | |
| Male | 13 246 (45.4) | 737 (35.3) | 5.2 (4.8-5.7) |
| Female | 15 918 (54.6) | 1351 (64.7) | 7.9 (7.4-8.4) |
| Race and ethnicity[b] | | | |
| Hispanic | 4044 (13.9) | 229 (11.0) | 5.0 (4.3-5.8) |
| Non-Hispanic | | | |
| African American or Black | 3126 (10.7) | 222 (10.6) | 6.1 (5.2-7.2) |
| American Indian or Alaska Native | 401 (1.4) | 43 (2.1) | 8.4 (6.0-11.7) |
| Asian | 1774 (6.1) | 70 (3.3) | 3.7 (2.8-4.8) |
| White | 19 458 (66.7) | 1508 (72.2) | 7.4 (6.9-7.8) |
| Other[c] | 361 (1.2) | 16 (0.8) | 4.2 (2.3-7.3) |
| Age group, y | | | |
| 18-29 | 3836 (13.2) | 141 (6.8) | 3.3 (2.8-4.0) |
| 30-39 | 4713 (16.2) | 224 (10.7) | 4.5 (3.8-5.2) |
| 40-49 | 4341 (14.9) | 300 (14.4) | 6.6 (5.8-7.4) |
| 50-59 | 4731 (16.2) | 422 (20.2) | 8.7 (7.8-9.6) |
| 60-69 | 5341 (18.3) | 514 (24.6) | 9.5 (8.6-10.5) |
| 70-79 | 4059 (13.9) | 355 (17.0) | 8.9 (7.9-10.0) |
| ≥80 | 2143 (7.3) | 132 (6.3) | 6.6 (5.4-8.1) |
| Health insurance status | | | |
| Insured | 27 210 (93.3) | 2018 (96.6) | 6.9 (6.6-7.3) |
| Uninsured | 1954 (6.7) | 70 (3.4) | 3.0 (2.2-3.9) |

4

## Defining: Moderate to Severe Immune Compromise
*honed during the COVID-19 pandemic (USA CDC)*

- **Active treatment for solid tumor and hematologic malignancies**
- **Receipt of solid-organ transplant and taking immunosuppressive therapy**
- **Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)**
- **Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)**
- **Advanced or untreated HIV infection**
- **Active treatment with:**
  - **high-dose corticosteroids (i.e., ≥20mg prednisone or equivalent per day)**
  - **alkylating agents, antimetabolites**
  - **transplant-related immunosuppressive drugs**
  - **cancer chemotherapeutic agents classified as severely immunosuppressive**
  - **tumor-necrosis (TNF) blockers and other biologic agents that are immunosuppressive or immunomodulatory.**

Factors to consider in assessing the general level of immune competence in a patient include disease severity, duration, clinical stability, complications, comorbidities, and any potentially immune-suppressing treatment.

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

5

## Broad Categorization of Examples of Immunocompromised Status Based on Medical Condition or Immunosuppressive Treatment

| Risk Category | Example Health Condition | Example Therapeutics |
|---|---|---|
| Higher risk immunocompromised patients | • Stem cell transplant <2 y<br>• Graft versus host disease, grade 3 or 4<br>• Hematological malignancy on therapy<br>• Lung transplant<br>• Fewer than 1% peripheral B-cells assessed in past 6 months | • B-cell depleting agents in past 12 months (eg, rituximab, ofatumumab, ocrelizumab, others)<br>• CAR-T therapy in past 12 months<br>• Abatacept |
| Moderate risk immunocompromised patients | • Solid organ transplant other than lung<br>• Solid tumor on treatment<br>• Congenital agammaglobulinemia<br>• Graft versus host disease, grade 1 or 2<br>• HIV infection with CD4 <200 cells/mm$^3$<br>• Other severe primary immunodeficiency | • Tyrosine kinase inhibitor (eg, ibrutinib, acalabrutinib, others)<br>• High-dose corticosteroids (>20 mg prednisone or equivalent for >4 wks)<br>• Anthracycline derivates |
| Lower risk immunocompromised patients | • HIV infection with CD4 >200 cells/mm$^3$<br>• Inflammatory bowel disease<br>• Cirrhosis<br>• ESRD<br>• Solid tumor (treatment >12 months prior) | • Anti-TNF<br>• Anti-IL-6<br>• Anti-IL-12 and -23<br>• Corticosteroids ≤10 mg long-term, or <20 mg for <4 wks<br>• Intra-articular steroids |

**2024 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Management of COVID-19: Anti-SARS-CoV-2 Neutralizing Antibody Pemivibart for Pre-exposure Prophylaxis**
*Clinical Infectious Diseases*, ciae435, https://doi.org/10.1093/cid/ciae435 **Published:** 29 October 2024

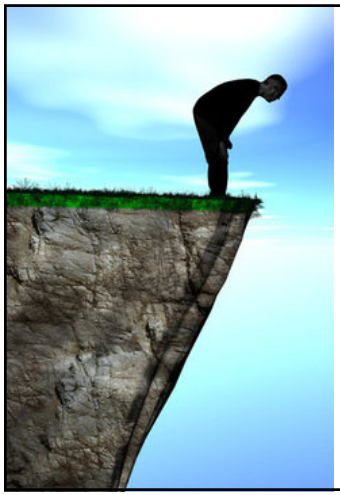
6

## The Less Immunocompromised Host

- **Stem cell transplant recipients > 2 years post-transplant, not on immunosuppressive drugs, no graft versus host disease**
- Chemotherapy for leukemia/lymphoma or cancer more than 3 months earlier with malignancy in remission
  - Those who have received immunotherapy with agents such as checkpoint inhibitors may need longer
- HIV patients with >500 CD4 lymphocytes
- Asplenia
- Nutritional deficiencies
- Steroid inhalers, topical steroids, intra-articular, bursal, or tendon injection of steroids, or on high-dose steroids over a month ago

https://www.cdc.gov/yellow-book/hcp/travelers-with-additional-considerations/immunocompromised-travelers.html (28 April 2026)

7



***"Net state of immunosuppression"***
**Dr. Robert Rubin, Massachusetts General Hospital**

**IMMUNOSUPPRESSION IS A COMPOSITE OF RISK FACTORS**

- **Disease state** may alter the immune system
  - Autoimmune diseases
  - Advanced organ failure
  - Other organ compromise: kidney, liver
- **Comorbidities/conditions**
  - Diabetes, obesity, malnutrition/weight loss
  - Hypogammaglobulinemia
  - Viral infections (HIV, CMV, EBV, HCV)
  - Altered microbiome
  - Advanced age
- **Exogenous immunosuppression**
  - Pre-transplant immunosuppression
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection

8

## Types of Stem Cell Transplants: a Spectrum

**Autologous stem cell transplant** (*lower* infection risk)

- The patient's **own stem cells** are collected before high-dose chemotherapy and then reintroduced after treatment. This allows for high doses of chemotherapy that would otherwise kill the patient's normal blood cells.

**Allogeneic stem cell transplant** (*higher* infection risk)

- **Stem cells from a donor**, who can be a blood relative or someone who is not related but is a close genetic match
- **Haploidentical:** stem cells from a "half-matched" donor
- **Cord blood:** stem cell found via an umbilical cord blood bank
- **Reduced-intensity** allogeneic stem cell transplantation (also called **mini-transplant** or **nonmyeloablative** transplant): conditioning treatment contains lower, less toxic doses of chemotherapy and radiation

9

## HCTs performed in United States, 2019-2023
## Center for International Blood and Marrow Transplant Research

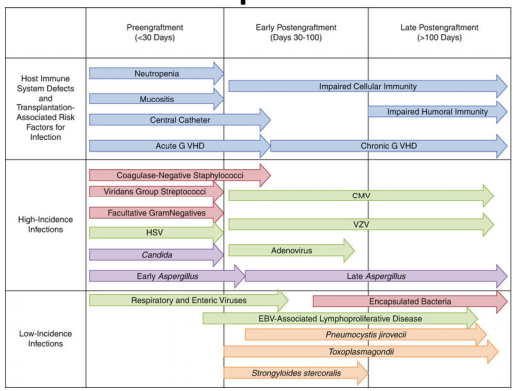
| Donor type | No. | % |
|---|---|---|
| Autologous stem cell | 66,418 | 58 |
| Allogenic stem cell | 47,499 | 42 |
| HLA-matched sibling | 9,319 | 8 |
| Other related donor | 11,535 | 10 |
| Unrelated | 26,645 | 23 |
| Grand Total | 113,917 | 100 |

https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report#summary accessed 22 March 2026

10

10

## Timeline of host immune defects and infections in allo-HSCT recipients




From Pereira MR, Pouch SM & Scully B, *Infections in Allogeneic Stem Cell Transplantation*, Principles and Practice of Transplant Infectious Diseases (2019)

11

## Common Immunosuppression after ***Allogeneic*** Stem Cell Transplant (not Autologous*)

- Chemotherapy
- Anti-graft versus host disease <u>prophylaxis</u>
  - Tacrolimus, cyclosporine
  - Methotrexate
  - Mycophenolate mofetil
  - Antithymocyte globulin (rabbit)
- Anti-graft versus host disease <u>treatment</u>
  - The first-line treatment of acute GVHD is methylprednisolone

* Immunosuppression generally not needed

12

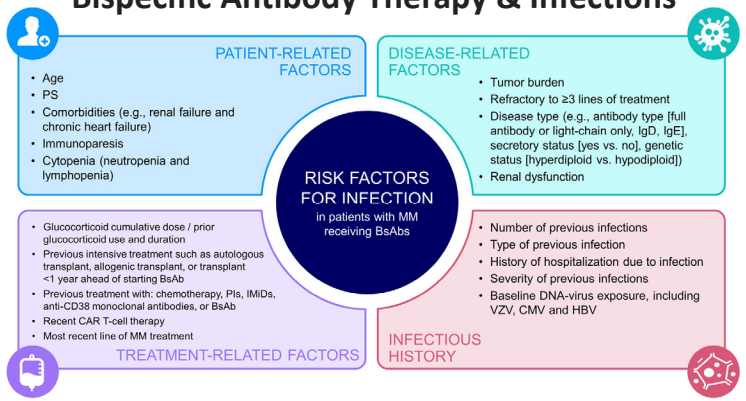
## CAR-T cell Therapy & Infectious Complications

- Chimeric antigen receptor (CAR) T-cell therapy involves lymphocyte engineering to produce CARs directed towards tumor cell antigens
- Can be profoundly immunosuppressed and often cytopenic, via a multitude of patient- and treatment-related factors.
  - ~1/3 patients will suffer a serious bacterial infection in the first 30 days
  - Viral respiratory tract infection (esp late phase) can be severe
    - CMV rare, seen w/in 6 weeks, 5/72 needed treatment*
  - Fungal infection is uncommon (<5%)
- Numerous off-target effects can cause toxicity-related adverse events
  - cytokine release syndrome
  - immune effector cell neurotoxicity syndrome

Stewart AG and Henden AS, Infectious complications of CAR T-cell therapy: a clinical update. Ther Adv Infect Dis. 2021.
*Kampouri E et al, CMV Reactivation and CMV-Specific Cell-Mediated Immunity after Chimeric Antigen Receptor T-Cell Therapy , CID 2023

13

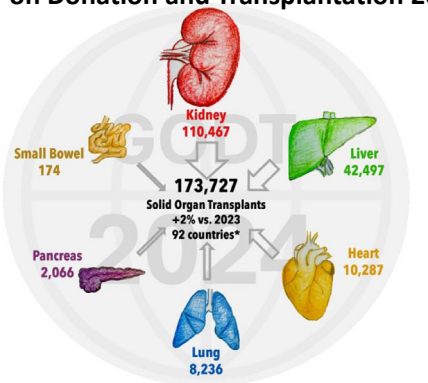
## Bispecific Antibody Therapy & Infections




Raje N et al, Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel, Blood Cancer Journal 2023 https://www.nature.com/articles/s41408-023-00879-7

14

## Organ Donation and Transplantation Worldwide: The Global Observatory on Donation and Transplantation 2024 Report




* Data submissions included until October 31, 2025.

Martin, Friederike; Carmona, Mar; Mahillo, Beatriz; Alvarez, Marina; Luengo, Amparo; Chatzixiros, Efstratios; López-Fraga, Marta; Dominguez-Gil, Beatriz; Tullius, Stefan G. Transplantation, March 2026,110(3):e655-e669

15

## National Organ Transplant Data – USA

> 1 million transplants done in USA since 1988

| | To Date | 2026 | 2025 | 2024 | 2023 | 2022 | 2021 | 2020 | 2019 |
|---|---|---|---|---|---|---|---|---|---|
| All Organs | 1,072,835 | 7,903 | 49,065 | 48,150 | 46,634 | 42,889 | 41,356 | 39,036 | 39,719 |
| Kidney | 629,830 | 4,416 | 27,574 | 27,760 | 27,332 | 25,500 | 24,670 | 22,817 | 23,401 |
| Liver | 237,334 | 2,133 | 12,344 | 11,458 | 10,659 | 9,528 | 9,236 | 8,906 | 8,896 |
| Pancreas | 9,614 | 11 | 107 | 114 | 102 | 108 | 143 | 135 | 143 |
| Kidney / Pancreas | 29,530 | 106 | 804 | 733 | 812 | 810 | 820 | 827 | 872 |
| Heart | 101,865 | 670 | 4,587 | 4,572 | 4,545 | 4,111 | 3,818 | 3,658 | 3,552 |
| Lung | 59,214 | 557 | 3,490 | 3,340 | 3,026 | 2,692 | 2,524 | 2,539 | 2,714 |
| Heart / Lung | 1,641 | 3 | 61 | 64 | 54 | 51 | 45 | 58 | 45 |
| Intestine | 3,651 | 3 | 88 | 97 | 95 | 82 | 96 | 91 | 81 |

*UNOS data downloaded 14 March 2026
https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/

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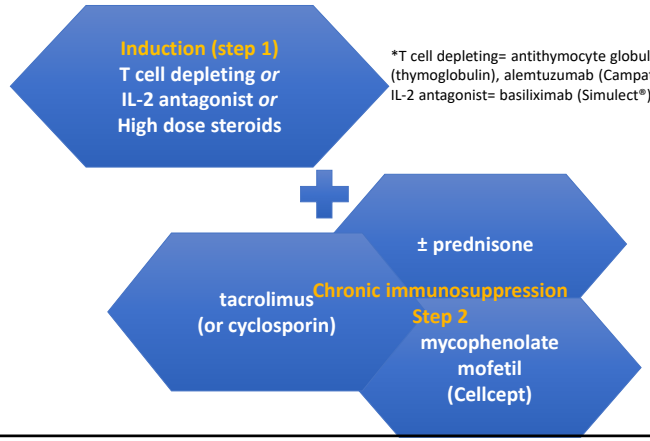
## Common Immunosuppression after Organ Transplant

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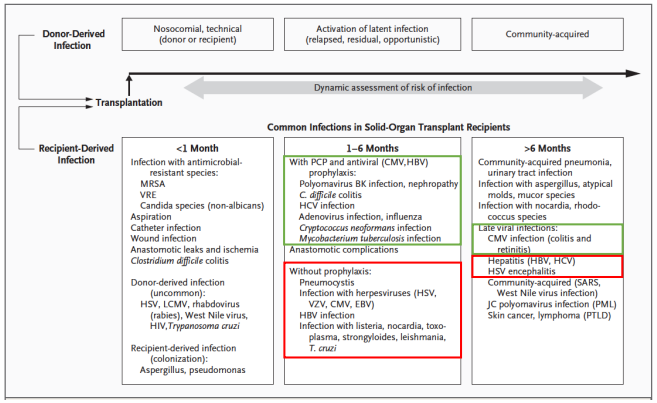
## Timeline of Infection after Organ Transplantation




Fishman, Infection in Solid-Organ Transplant Recipients, NEJM 2007

18

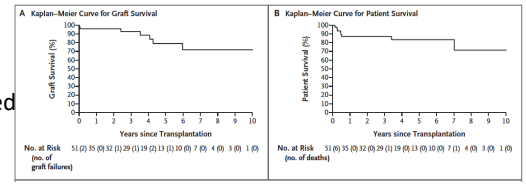
## What's Trendy? (Might be on boards?) Hepatitis C Donors and Organ Transplant

- Many programs are using hepatitis C positive donors into negative or positive recipients and treating after transplant
  - Yes, we are infecting people with hepatitis C
- Can be either HCV viral load and/or antibody positive
- For all organs, ~100% clearance
- Was often research protocol, now standard of care
- Need to have a good plan for medications (insurance)
- Trend towards shorter treatment protocols

19

## Longer-Term Outcomes of *HIV-Positive–to–HIV-Positive Renal Transplantation*, Selhorst, Muller et al, NEJM 2018

- n=51
- 8 patients (16%) died after transplantation from non–graft-related causes
- No transmission of drug resistant virus




- **5-year overall survival and graft survival similar to the 3-year overall survival and graft survival observed among HIV-positive patients who received an organ from an HIV-negative donor in the United States**

20

## HIV Organ Policy Equity (HOPE) Act: USA

- **Permits donated, HIV-positive organs to be used for transplantation in HIV-positive patients (only)**
  - Previously prohibited by federal law
- **An active program at multiple centers**
  - Previously research setting only, moving towards standard of care (kidney, liver)
  - Will remain research program for heart and lung transplant (for now)
- **+/- Half of organ donors have false positive HIV testing**
  - Screening test positive, confirmatory test (done later, takes time) negative
- Within 4.5 y, 70% HOPE candidates (n=324) underwent kidney transplant vs 43% non-HOPE*
- 22% of HOPE vs 39% of non-HOPE candidates died or were removed from the waitlist*
- Median transplant wait time: 10.3 months for HOPE vs 60.8 mo for non-HOPE ( P < 0.001)*
- HOPE candidates had a 3.30-fold higher kidney transplant rate*

*Motter et al, Transplantation 2024

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## Prevention & Prophylaxis: Solid Organ Transplant

- Pre-immunosuppression evaluation**
  - Vaccines
  - Screening for latent infections
  - Plan for chronic infections
  - Optimize diabetes, stop smoking/marijuana use, etc
  - Education to prevent illness
- Management: peritransplant/initiation of immunomodulatory tx
- Prophylaxis and/or screening after transplant/immunomodulatory therapy started

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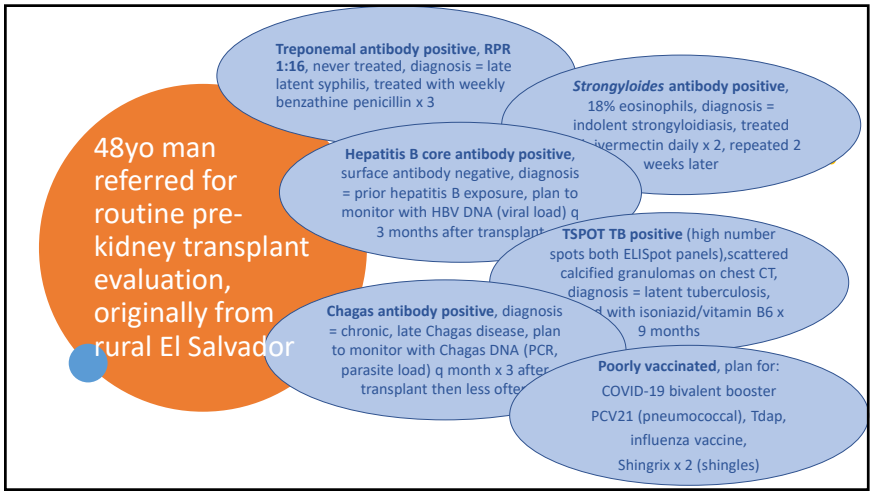
Pearl:
pre-immunosuppression vaccination optimizes vaccine immunogenicity

Best (only?) time to give MMR, varicella, yellow fever vaccines

23

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Review for Infectious Disease Exposures/Risk Factors *(my dot phrase)*

- Birth place: ***
- Have they lived outside of New England? ***
- Have they lived outside of the country for more than 3 months? ***
- Have they ever lived in the American Southwest, Arizona, New Mexico, California? *** (Coccidioides/Valley Fever risk)
- Any exotic travel history, outside of Europe, Canada, Australia (i.e. Asia, Africa, South or Central America)? Where/how long? ***
- Are they planning to travel to any exotic regions after transplant? If yes, where? ***
- Served in the military abroad? ***
- Who do they live with currently, or live alone? ***
- Wellwater - *** *(If yes, we discussed the recommendation to boil water or drink bottled water after transplant, filters not adequate)*
- Do they use a Nettie pot or other similar device to lavage to their sinuses; if so do they use untreated water? (chlorinated tap water should be fine) ***
- Do they eat any raw meat, raw milk/dairy, raw fish, raw seafood? ***
- Do they eat cold cuts? *** (Given the risk of Listeria and other pathogens we would discourage this after transplant)
- Employment/career: ***
- Any hobbies that involve exposure to outdoors/woods, gardening/farming, animals etc? ***
- Any pets at home or animal contacts? *** (*We discourage exposure to birds, reptiles, rodents after transplant due to zoonotic risk. Horses convey a risk of Rhodococcus equi. Dogs, cats, and fish are fine, although we discourage changing the kitty litter due to the risk of Toxoplasmosis, and discourage cleaning the fish tank due to the risk of mycobacterial and other infections)*
- Have they seen a dentist in the past year? *** Any dental issues? ***
- Have they ever been on a long course of antibiotics (>3 weeks) or intravenous antibiotics at home? ***

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## Pre-Solid Organ Transplant Evaluation (MGH)

| | Everyone | Vaccinate if neg | If risk factors |
|---|---|---|---|
| Hepatitis A | x | x | |
| Hepatitis B surface antigen | x | | |
| Hepatitis B core antibody (IgG not IgM) | x | | |
| Hepatitis B surface antibody | x | x | |
| Hepatitis C | x | | |
| HIV | x | | |
| Tuberculosis screening | x | | |
| Varicella | x | x | |
| Cytomegalovirus | x | | |
| Mumps-measles-rubella | x | x | |
| Syphilis antibody | x | | |
| Coccidioides antibody | | | x |
| Strongyloides serology | | | x |
| *Trypanosoma cruzi* (Chagas disease) | | | x |

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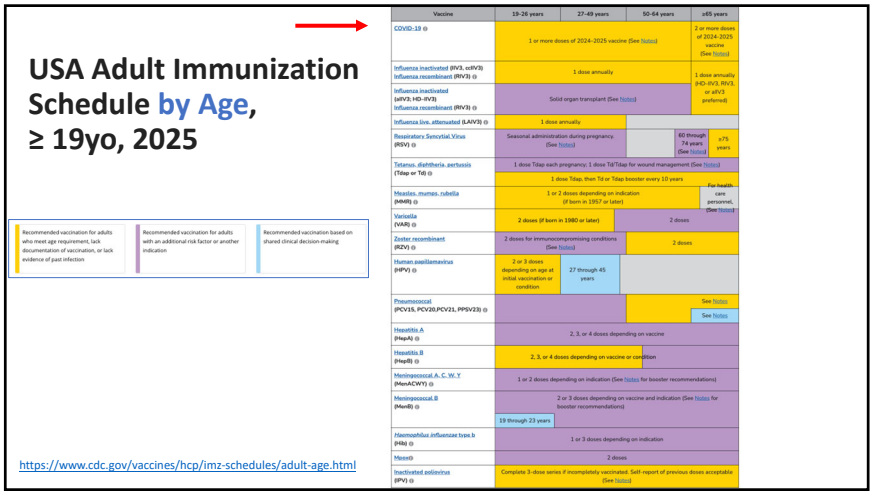
## USA Adult Immunization Schedule by Age, ≥ 19yo, 2025




https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html

27

## USA Adult Immunization Schedule by Condition, ≥19yo, 2025


https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-medical-condition.html

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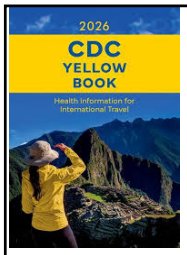
**OL6 Review of Basics: Transplant Infectious Disease**

*Speaker: Camille Kotton, MD, FAST, FIDSA*




CDC YELLOW BOOK

Immunocompromised Travelers

CDC Yellow Book 2026

Travelers with Additional Considerations

Author(s): Camille Kotton, Andrew Kroger, David Freedman

| Live vaccines | Severe immunosuppression |
|---|---|
| **Live vaccines** | |
| Bacillus Calmette Guérin (BCG) | Contraindicated |
| Chikungunya (Ixchiq) | Contraindicated |
| Cholera (Vaxchora) | No data, generally recommend against use |
| Ebola (Ervebo) | Consider |
| Influenza, live attenuated | Contraindicated |
| Measles-mumps-rubella (MMR/MMR-V) | Contraindicated |
| Smallpox/mpox (JYNNEOS) | Use as indicated |
| Smallpox/mpox (ACAM2000) | Contraindicated |
| Typhoid, Ty21a | Contraindicated |
| Varicella (adults) | Contraindicated |
| Yellow Fever | Contraindicated |

https://www.cdc.gov/yellow-book/hcp/travelers-with-additional-considerations/immunocompromised-travelers.html revised for 2026

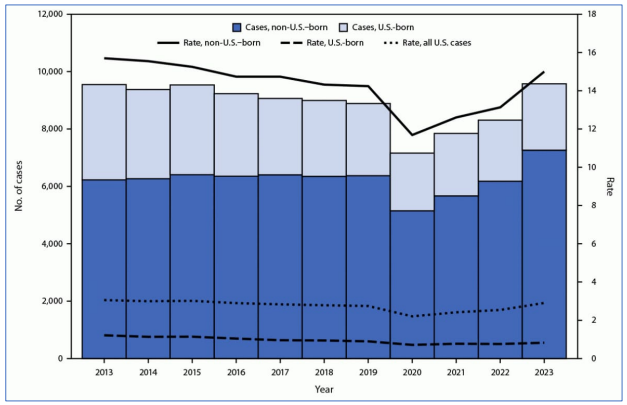
29

## CDC: Who Should Get Tested for TB

- TB tests are generally not needed for people with a low risk of infection
- Certain people should be tested for TB bacteria because they are more likely to get TB disease, including:
  - People who have spent time with someone who has TB disease
  - **People with HIV infection or another medical problem that weakens the immune system**
  - People who have symptoms of TB disease (fever, night sweats, cough, and weight loss)
  - People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
  - People who live or work somewhere in the US where TB disease is more common (homeless shelters, prison or jails, or some nursing homes)
  - People who use illegal drugs

www.cdc.gov/tb/topic/testing/

30




CDC March 2025:
- more than 10,300 tuberculosis (TB) cases were reported in 2024
- an 8% increase from 2023
- highest case count since 2011

Tuberculosis — United States, 2023, MMWR, March 28, 2024 / 73(12);265–270
https://www.cdc.gov/mmwr/volumes/73/wr/figures/mm7312a4-F_v2-large.gif?_=51657

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## Latent TB Screening

- Medical history
- Epidemiologic risk factors
- TB skin test (TST)
- Interferon gamma release assay (IGRA) (blood test) (sometimes preferentially vs TST, IDSA guidelines 2016)
  - T-SPOT.®*TB*
  - QuantiFERON®-TB Gold
- Radiographic findings
  - Old granulomatous disease, apical scarring
- *Clinical pearl: search for "granuloma" in the electronic medical record*

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## T-SPOT.®*TB* and QuantiFERON®-TB Gold

- Enumerates effector T-cell response to stimulation with a combination of peptides simulating ESAT-6 and CFP10 (+ TB7.7 for QFN) antigens
- Detects prior exposure to:
  - *M. tuberculosis* complex organisms (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti)*
  - *M. kansasii, M. szulgai,* and *M. marinum*
- Not + with prior BCG vaccine (bacille Calmette–Guérin)
- Interpret test correctly:
  - If either test or PPD positive, take as positive
  - Borderline results = partway b/w + and negative
  - **Indeterminate results = assay did not work**

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**Your patient has latent TB. Should and when should you start chemoprophylaxis? When can immunosuppressive medications be started?**

A. Start TB chemoprophylaxis ASAP as per guidelines. (Ensure no active TB, pulmonary or extrapulmonary.) Can start immunosuppression any time.

B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.

C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

34

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C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

35

Excellent Prophylaxis is Paramount…
*and provides important clues for boards questions*

- Antivirals
- Pneumocystis/Toxoplasmosis
- Antifungals

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## Cytomegalovirus Prevention
### Prophylaxis vs. Preemptive Therapy

**Antiviral Prophylaxis**
*Valganciclovir or Letermovir*

MORE COMMON

Typically 3-6 months

0 4 8 12 16 20 24

**Preemptive Monitoring**
*Once weekly for 12-16 weeks*

Monitor weekly (PCR or pp65 Ag) – *If CMV detected, treat until cleared*

0 4 8 12 16

*Weeks Post-Transplant*

*Humar A, Snydman D; AST Infectious Diseases Community of Practice. Am J Transplant. 2009;9 (Suppl 4):S78-S86.*

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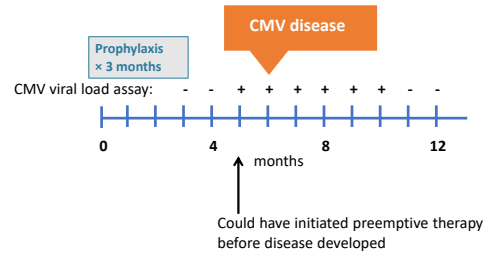
## Hybrid Strategy for SOT:
## CMV Surveillance After Prophylaxis

Consider "net state of immunosuppression"

- Weekly monitoring after end of prophylaxis, for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression)
- Guidelines experts use approach, not strongly evidence-based




Kotton CN et al,The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation, Transplantation 2025

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JAMA | Original Investigation

## Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients
### A Randomized Clinical Trial

June 2023

Ajit P. Limaye, MD; Klemens Budde, MD; Atul Humar, MD, MSc; Flavio Vincenti, MD; Dirk R. J. Kuypers, MD, PhD; Robert P. Carroll, BM, BCh, DM; Nicole Stauffer, BS; Yoshihiko Murata, MD, PhD; Julie M. Strizki, PhD; Valerie L. Teal, MS; Christopher L. Gilbert, BS; Barbara A. Haber, MD

- D+R- kidney transplants
- Compared letermovir 480mg, orally daily (with acyclovir) or valganciclovir 900mg, orally daily (adjusted for kidney function) for up to 200 days after transplant
- **Confirmed CMV disease: 10.4% on letermovir vs 11.8% on valganciclovir = SAME (17% each, per PI)**
- **Leukopenia (11% vs 37%) or neutropenia (3% vs 17%)** by week 28 lower w/ letermovir vs valganciclovir
- **Quantifiable CMV DNAemia** detected in 2.1% on letermovir vs 8.8% on valganciclovir by week 28
  - Of participants evaluated for suspected CMV disease or CMV DNAemia, none (0/52) who received letermovir and 12.1% (8/66) who received valganciclovir had resistance-associated substitutions.
- Fewer participants in the letermovir group than the valganciclovir group **discontinued prophylaxis** due to adverse events (4.1% vs 13.5%) or drug-related adverse events (2.7% vs 8.8%)
- Valganciclovir dosing adjusted to renal function, details N/A - could explain neutropenia & breakthrough infections
- IMPACT trial comparing 100 versus 200 days of valganciclovir prophylaxis reported **neutropenia** rate of 3% after 100 days and **5% after 200 days (19% leukopenia)**, 15% at some point in trial (Humar et al, 2010)

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MERCK

Media > News releases > News release

June 6, 2023

U.S. FDA Approves New Indication for Merck's PREVYMIS® (letermovir) for Prevention of Cytomegalovirus (CMV) Disease in High-Risk Adult Kidney Transplant Recipients

**important drug interactions**
Tacrolimus
Cyclosporine
Azoles

**US$277** letermovir 480 mg/day vs **US$4** valganciclovir 900 mg/day per goodrx.com (April 2026)

**PREVYMIS® (letermovir) tablets, for oral use**
**PREVYMIS® (letermovir) injection, for intravenous use**
**Initial U.S. Approval: 2017**

**----------RECENT MAJOR CHANGES----------**
Indications and Usage, CMV Prophylaxis in Kidney Transplant Recipients (1.2) 06/2023
Dosage and Administration, Recommended Dosage for Adult Patients (2.2) 06/2023

**----------INDICATIONS AND USAGE----------**
PREVYMIS is a CMV DNA terminase complex inhibitor indicated for:
- Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (1.1)
- Prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]). (1.2)

**---------- DOSAGE AND ADMINISTRATION ----------**
- HSCT: 480 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour through 100 days post-transplant. (2.1, 2.2)
- Kidney Transplant: 480 mg administered once daily orally or as an IV infusion over 1 hour through 200 days post-transplant. (2.1, 2.2)

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**TABLE 3.**
**Recommended approaches for CMV prevention in different organs for adult solid organ transplant recipients**

| Organ | Serostatus | Risk level | Recommended[a] | Alternate |
|---|---|---|---|---|
| All | D-/R- | Low | Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections | Preemptive therapy (if higher risk, ie, significant transfusions) |
| Kidney | D+/R- | High | 6 mo of (V)GCV or 6 mo of LET or preemptive therapy | High-dose VALACY |
| | R+ | Intermediate | 3 mo of VGCV or preemptive therapy | High-dose VALACY. If on mTOR-based immunosuppression, preemptive therapy or close clinical monitoring recommended |
| Liver | D+/R- | High | 3–6 mo of VGCV or preemptive therapy | |
| | R+ | Intermediate | 3 mo of VGCV or preemptive therapy | |
| Pancreas | D+/R- | High | 3–6 mo of VGCV | Preemptive therapy |
| | R+ | Intermediate | 3 mo of VGCV or preemptive therapy | |
| Islet | D+/R- | Intermediate | 3 mo of VGCV | Preemptive therapy |
| | R+ | Intermediate | 3 mo of VGCV or preemptive therapy | |
| Heart | D+/R- | High | 3–6 mo of (V)GCV | -Preemptive therapy<br>-Some experts add CMVIG to prophylaxis |
| | R+ | Intermediate | 3 mo of (V)GCV or preemptive therapy | |
| Lung | D+/R- | High | 12 mo of (V)GCV | -Preemptive therapy |
| | R+ | Intermediate | 6–12 mo of (V)GCV | -Some experts add CMVIG to prophylaxis |
| Intestinal, composite tissue | D+/R- | High | Minimum 6 mo (V)GCV | -Preemptive therapy |
| | R+ | High | 3–6 mo (V)GCV | -Some experts add CMVIG to prophylaxis |

Kotton CN et al, The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation, Transplantation 2025

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## Antiviral Prophylaxis: Stem Cell Transplant

- Acyclovir/valacyclovir/famvir for everyone
  - Prevents herpes, varicella/zoster
  - Duration varies a lot across programs, 6-12+ months is common
- **Letermovir** x 100 days if higher CMV risk
  - if recipient is CMV positive – opposite of solid organ (D-R+ is high risk after HSCT)
  - Prevents CMV, NOT herpes, varicella/zoster
  - Decreased mortality
  - **If small viral load "blips", carry on and retest a week later – only stop therapy if high blips (>1,000 IU/ml)**
  - Main side effect is cost

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## Antiviral Prophylaxis/Treatment Agents

| Antiviral agent | CMV | HSV | Varicella | BK | Adeno-virus | EBV |
|---|---|---|---|---|---|---|
| **Commercially available** | | | | | | |
| ganciclovir IV/valganciclovir PO | x | x | x | | | |
| acyclovir/valacyclovir/famciclovir* | high dose +/- | x | x | | | |
| letermovir | x | | | | | |
| maribavir | x | | | | | *in vitro* |
| foscarnet** | x | x | x | | | |
| cidofovir** | x | x | x | poor | +/- (IC50) | |
| **Novel/investigational antiviral agents (SOT)** | | | | | | |
| *brincidofovir (not available)* | *x* | *x* | *x* | *x* | *x* | *x* |

*acyclovir/valacyclovir/famciclovir and letermovir for prophylaxis only
**foscarnet, cidofovir not usually used for prophylaxis

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## When should we use letermovir prophylaxis? My opinion

Stem cell transplant recipients at high to moderate risk

In SOT recipients who truly cannot tolerate valganciclovir

As secondary prophylaxis after treatment of resistant CMV

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## Pneumocystis/Toxoplasmosis Prophylaxis

- First line:
  - Bactrim SS daily or DS three times a week
- Second line (only if real Bactrim allergy or intolerance) alternatives:
  - Atovaquone (Mepron) 1500 mg QD
  - Dapsone 100 mg QD
    - √ G6PD
    - watch for methemoglobinemia, low white blood cell count
  - Pentamidine IV q month (does not cover Toxoplasmosis)
- Duration variable, usually until end of PPx

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## Antifungal Prophylaxis: Solid Organ Transplant

| Organ | Common Practice | Comments |
|---|---|---|
| Kidney, liver, heart | None for most; some programs give fluconazole/echinocandins peri-liver | Some Nystatin swish and swallow |
| Pancreas | Fluconazole post-op for variable time, < 1 month | |
| **Lung** | **Voriconazole, posaconazole, itraconazole for variable times after transplant** | Voriconazole and augmented skin cancer, osteitis risks a major concern |
| Intestinal transplant, Composite tissue | Often longer courses of fluconazole/echinocandins | |

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## Antifungal Prophylaxis: Hematopoietic Stem Cell Transplant

- Fluconazole often used in first 100 days after HSCT
  - Generally for higher risk receipts
  - Classic population for *C. krusei,* R to fluconazole
- Posaconazole generally reserved for higher risk patients
  - Only FDA approved agent for this indication
- Voriconazole – higher risk of mucormycosis reported
- Isavuconazole – not approved for prophylaxis, but often used, less drug interactions and no QT interval prolongation

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## Pearls on Antifungal Therapy

- Voriconazole: when used longer term
  - Higher risk of skin cancers
  - Osteitis
  - Pseudoporphyria in sunlight
  - Best pick for *Scedosporium sp* (as part of initial therapy)
  - Does not cover mucormycosis
  - Levels variable
- Isavuconazole
  - Reduce drug interactions
  - Reduced QT prolongation
  - Breakthrough candidiasis
- Posaconazole
  - Usually covers mucormycosis (lower MICs than isavuconazole)

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## Sources of Infection after Transplant

- Community-acquired
- Nosocomial
- Prior colonization
  - + Intraoperative *Aspergillus* culture w/ cystic fibrosis & lung transplant → OR 4.36 invasive aspergillosis (Luong *et al*, Transplantation 2014)
- Emerging
- Donor-derived infection
  - Organ graft, blood products

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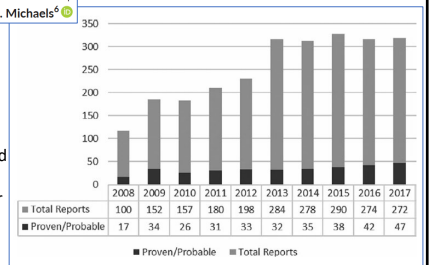
**Ten years of donor-derived disease: A report of the disease transmission advisory committee**

*Am J Transplant.* 2021;21:689–702

Daniel R. Kaul[1] | Gabe Vece[2] | Emily Blumberg[3] | Ricardo M. La Hoz[4] | Michael G. Ison[5] | Michael Green[6] | Timothy Pruett[7] | Michael A. Nalesnik[8] | Susan M. Tlusty[2] | Amber R. Wilk[2] | Cameron R. Wolfe[9] | Marian G. Michaels[6]

- The Organ Procurement and Transplantation Network (OPTN) created The Disease Transmission Advisory Committee (DTAC) to review and classify reports of potential disease transmission to inform national policy and improve patient safety.
- January 1, 2008 to December 31, 2017, DTAC received 2185 reports
  - 335 (15%) classified as a proven/ probable donor transmission event
- ~2/3 infection, ~1/3 malignancy
- **Overall risk 17.8/10,000 or 0.178%**
- **All types of infections (!)**
- **Note: initial trigger is transplant center reporting to local organ bank (you!)**




| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total Reports | 100 | 152 | 157 | 180 | 198 | 284 | 278 | 290 | 274 | 272 |
| Proven/Probable | 17 | 34 | 26 | 31 | 33 | 32 | 35 | 38 | 42 | 47 |

FIGURE 2 Total reports of potential donor transmission events by year

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## Examples of severe transfusion-transmitted infections in solid organ transplant recipients

| Infectious agent | Organ transplant | Total blood units given | Infected blood component | Timing of transfusion | Incubation | Recipient outcomes | Reference | Year |
|---|---|---|---|---|---|---|---|---|
| WNV | Heart | 174 | Apheresis platelets | Perioperative period | 2 weeks | Severe neurological impairment | Murtagh et al [33] | 2002 |
| Yellow fever vaccine virus | Kidney (2)<br>Heart<br>Liver | N/A | Blood transfusion (received by donor) | 27 days prior to organ donation (received by donor) | 4 weeks<br>17 days<br>15 days | Dead (1)<br>Dead<br>Recovered | Gould et al [36] | 2021 |
| HIV | Kidney | Unspecified | Fresh frozen plasma | Unspecified | Recipient asymptomatic | Commenced on antiretroviral therapy | CDC [58] | 2008 |
| Trypanosoma cruzi | Kidney | 1 | Apheresis platelets | 4 months prior to transplantation | >2 years | Dead | Ries et al [70] | 2008 |

From Stewart AG & Kotton CN, Impact of Blood Donation Biovigilance and Transfusion Transmitted Infections on Organ Transplantation, accepted for publication, Transplant ID, 2024

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## Syndromes

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## CMV: the most common pathogen after transplant, one of the "*great masqueraders*"

- Asymptomatic viremia**
- CMV syndrome
- End organ disease:
  - Colitis
  - Pneumonitis
  - Retinitis

- Best diagnosed by CMV viral load
- Best treated with valganciclovir or ganciclovir IV
- Treat to resolution of infection and/or viral load – check weekly
- If low absolute lymphocyte count at end, consider secondary prophylaxis or monitoring

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## Treatment of CMV: Massachusetts General Hospital

Determine severity of infection

**Mild to moderate** CMV infection → Valganciclovir (oral) 900mg po q12 hours, renally adjusted

**Severe** (clinically), ophthalmologic, colitis with severe malabsorption, refractory/resistant, or life-threatening → Intravenous ganciclovir 5mg/kg q12, renally adjusted
Convert to oral treatment when clinically improving

Consider lowering immunosuppression
If total IgG < 400, consider giving either CMV Ig 150mg/kg or IVIG

Check weekly CMV DNAemia (i.e. CMV viral load) on plasma (vs whole blood).
**Trend weekly until there are one-two negative/very low (<200 IU/ml) results, then stop therapy.**

If CMV DNA level does not fall after 2-3 weeks, consider sending CMV resistance testing.
(This does not need to be sent after 1 week of treatment where we commonly see a small increase in the CMV viral load.)

Consider weekly monitoring after the end of treatment for 8-12 weeks so as to capture early recurrent disease vs restarting prophylaxis (especially in high risk D+R- patients, or with higher immunosuppression).

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## What to do with very low viral load cases? (<500-1000 IU/ml plasma or whole blood)

- *Treatment not always indicated*
- *With very low viral loads, I think about:*
  - *Risk factors for severe viral infection (D+R- versus R+)*
  - *Net state of immunosuppression*
  - *Absolute lymphocyte count*
  - *Likelihood of major disease flare with waiting*
  - *Ability to reliably repeat testing*
- *Important to understand issues with diagnostics at very low results*
- ***Retesting in a week** is key so you know which trend of infection*
- *Approaches vary widely among clinicians; need to formalize guidance*

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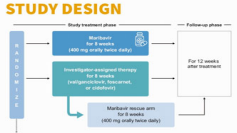
## Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

Robin K. Avery, Sophie Alain, Barbara D. Alexander, Emily A. Blumberg, Roy F. Chemaly, Catherine Cordonnier, Rafael F. Duarte, Diana F. Florescu, Nassim Kamar, Deepali Kumar, Johan Maertens, Francisco M. Marty, Genovefa A. Papanicolaou, Fernanda P. Silveira, Oliver Witzke, Jingyang Wu, Aimee K. Sundberg, and Martha Fournier, for the SOLSTICE Trial Investigators

### INTRODUCTION

This was a phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared with IAT in HCT and SOT recipients with CMV infections refractory to most recent treatment, with or without resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

### STUDY DESIGN




### STUDY ENDPOINTS

The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of Week 8, maintained through Week 16 after receiving exclusively study-assigned treatment.

### RESULTS

352 patients were randomized (maribavir, n=235; IAT, n=117)

40.1% HCT | 59.9% SOT

**PRIMARY ENDPOINT (WEEK 8)**

| | Maribavir | IAT | n/N |
|---|---|---|---|
| | 55.7% | 23.9% | 131/235 / 28/117 |

p<.001

**Adjusted difference (95% CI): 32.8 (22.80–42.74)**

A significantly higher proportion of patients treated with maribavir achieved the primary endpoint of confirmed CMV viremia clearance at Week 8 compared with IAT.

**KEY SECONDARY ENDPOINT (WEEK 16)**

| | Maribavir | IAT | n/N |
|---|---|---|---|
| | 18.7% | 10.3% | 44/235 / 12/117 |

p=.013

**Adjusted difference (95% CI): 9.5 (2.02–16.88)**

A greater proportion of patients treated with maribavir achieved the composite key secondary endpoint of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16 compared with IAT.

### SAFETY

Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT.

Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%).

Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%).

Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%).

One patient per treatment group had fatal treatment-related TEAEs.

### CONCLUSIONS

Maribavir was superior to IAT for cytomegalovirus viremia clearance, and viremia clearance plus symptom control, with maintenance of these effects post-therapy in transplant recipients with refractory cytomegalovirus infections with or without resistance.

Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir *than IAT.*

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

*Clin Infect Dis* 2022, ciab988, https://doi.org/10.1093/cid/ciab988

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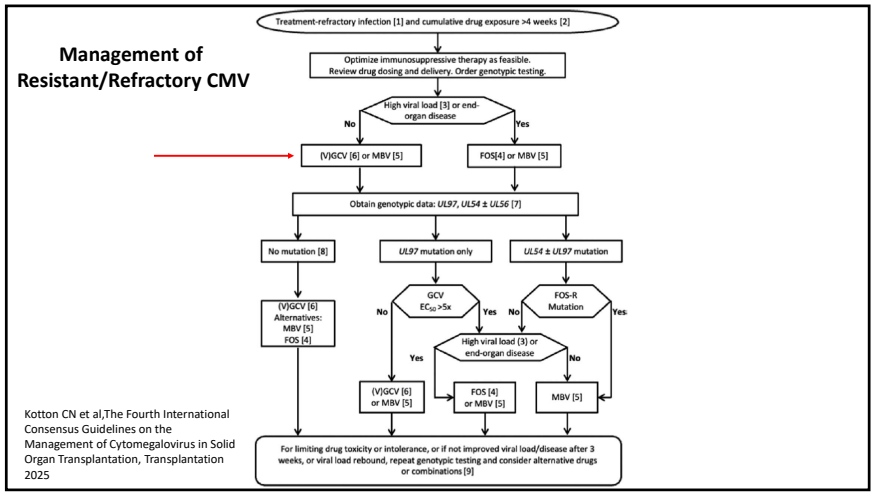


Kotton CN et al,The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation, Transplantation 2025

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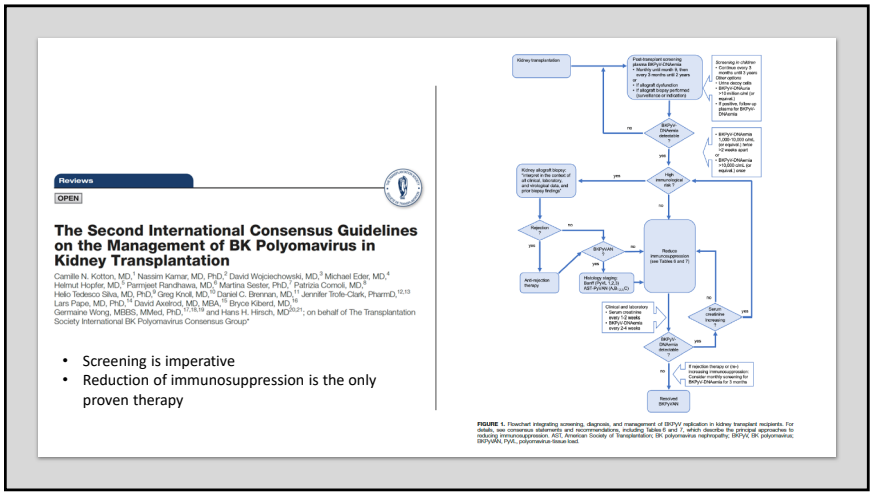


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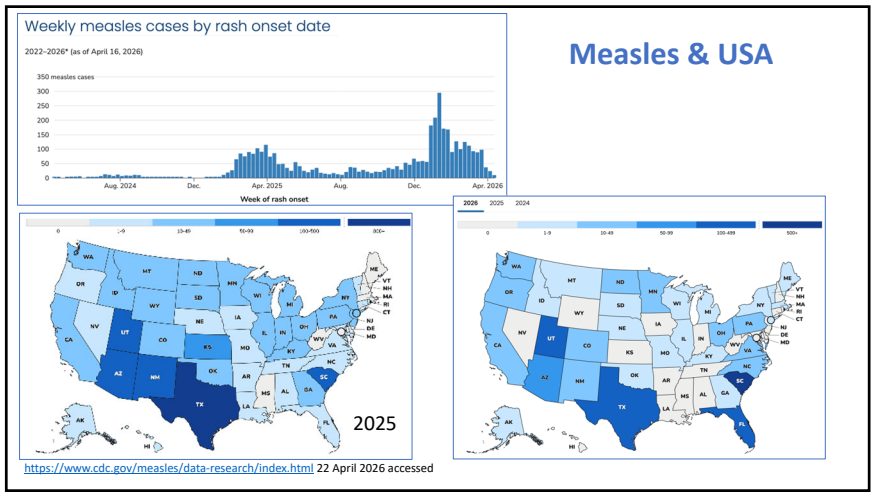


https://www.cdc.gov/measles/data-research/index.html 22 April 2026 accessed

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## CDC: Post Measles Exposure Prophylaxis in Severely Immunocompromised Patients (2013)

- Unvaccinated/seronegative, within 6 days of exposure:
  - < 30 kg give gamma globulin IM 0.5 mL/kg max 15 mL
  - > 30 kg give IVIG 400mg/kg
- US, CDC (2013)[2]: "Immunocompromised patients. **Severely immunocompromised patients who are exposed to measles should receive IGIV prophylaxis regardless of immunologic or vaccination status** because they might not be protected by the vaccine."
- "Severely immunocompromised patients include **patients with severe primary immunodeficiency; patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer in patients who have developed graft-versus-host disease; patients on treatment for ALL within and until at least 6 months after completion of immunosuppressive chemotherapy; and patients with a diagnosis of AIDS or HIV-infected persons with severe immuno-suppression."**

[2]McLean et al, Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013. Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR Recomm Rep . 2013 Jun 14;62(RR-04):1-34, https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm

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Mass General Brigham

MGB Antimicrobial Stewardship Program

## Measles Post-Exposure Prophylaxis

This document provides current guidance for evaluation and management of asymptomatic individuals with exposure to measles and indications for measles post-exposure prophylaxis (PEP).

| | | |
|---|---|---|
| **Moderate to Severely Immunocompromised (any age)** | **Non-immune** (regardless of vaccine or measles IgG status) | < 12 months: IMIG 0.5 ml/kg (max dose = 15 mL) if no contraindications to IMIG[a]<br>≥ 12 months - IVIG 400 mg/kg if no contraindications to IVIG[a] |

https://partnershealthcare.sharepoint.com/:w:/r/sites/MGBAntimicrobialInfectiousDiseasesQualityCollaborativeASIDQC/_layouts/15/Doc.aspx?sourcedoc=%7B24AE2760-1707-477F-9D28-44A6C056001C%7D&file=MGB%20ASP%20-%20Measles%20PEP%20V.2.0.docx&action=default&mobileredirect=true

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## Measles Post Exposure Prophylaxis: Challenges

- IVIG 400 mg/kg takes hours to infuse
- Strict respiratory infection control needed
  - Measles highly contagious
  - Might not want many immunocompromised in same infusion suite?
- Requires infusion suite or hospital level care
- Cost likely starts at several thousand dollars ($2500-10,000)
- Local IVIG supplies may not be robust enough in outbreak
- Duration of protection not known, concerning in ongoing outbreak
  - PKPD studies lacking

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## The Dreaded Pulmonary Nodule

For the boards (and clinical medicine), consider the prophylaxis and what's not covered

Let the prophylaxis and epidemiology drive your differential diagnosis

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## Who gets fungal infections?

- Post-solid organ transplant: Incidence of invasive fungal infections in the first year has been reported to be 3%[1]
  - Candidiasis (sterile space), esp liver transplant*surgery
  - Cryptococcal disease
    - Among most common causes of meningitis
  - Invasive aspergillosis in 1-15%[2]
    - Accounts for significant % of deaths in first year
    - Mortality dropping in recent times, however
  - Mucormycosis less common, higher mortality
- Stem cell transplant: similar, longer risk if graft-vs-host disease
- Non-transplant immunocompromised hosts: less frequent/"net state of immunosuppression"

1 Shoham S, Marr K. Invasive fungal infections in solid organ transplant recipients. Future Microbio 2012; 7(5): 639-655
2 Singh N, Husain S, Aspergillosis in Solid Organ Transplantation, AJT, 2013

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# Diagnostics

- Culture
  - Fungal stain and culture
  - Notify lab not to mince specimen if suspicion of mucormycosis
  - Fungal isolators (blood) very rarely +
    - *Candida* will grow in routine cultures
    - *Histoplasma* better; lysis centrifugation isolators is best
- Pathology: Morphology
  - Septate (*Aspergillus*) vs non-septate (*Mucor/Zygomycetes*) hyphae
  - Grocott-Gomori's (or Gömöri) methenamine silver stain
  - Periodic acid-Schiff (PAS)

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# Diagnostics: Fungal Markers

| Diagnostic Assay | Specimen | Comments |
|---|---|---|
| Cryptococcal antigen | Blood, CSF | High sensitivity/specificity |
| 1,3 beta – D - glucan | Blood | Primarily for yeast;<br>Low sensitivity/moderate specificity<br>*Excellent for Pneumocystis* |
| Galactomannan | Blood, BAL, other body fluids | Primarily for Aspergillus;<br>Low sensitivity/high specificity on blood, higher sensitivity on body fluids |
| Aspergillus PCR | Blood, BAL, other body fluids | |
| *Karius Spectrum, a cell-free DNA (cfDNA) test to identify and quantify fungal pathogens* | *Blood* | *Uses shotgun metagenomic sequencing*<br>*Higher sensitivity with proven vs probable disease (60% vs 37% Sim BZ et al CID 2025)* |

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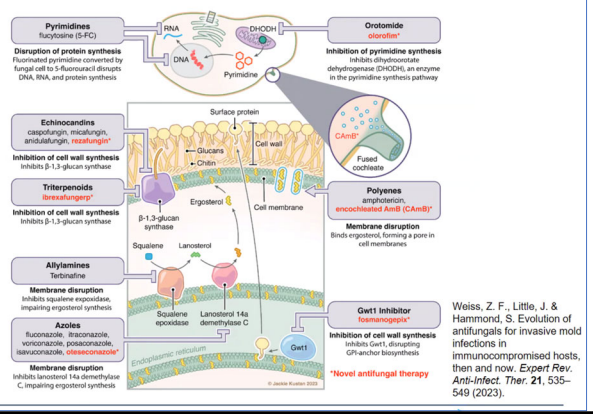
# Antifungal Mechanisms of Action




Weiss, Z. F., Little, J. & Hammond, S. Evolution of antifungals for invasive mold infections in immunocompromised hosts, then and now. *Expert Rev. Anti-Infect. Ther.* **21**, 535–549 (2023).

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# Clinical Vignette

- 54 yo woman with history of primary systemic AL amyloidosis, complicated by cardiac amyloidosis, treated cytoxan/bortezomib/dexamethasone initially, followed by lenalidomide/dexamethasone
- Orthotopic cardiac transplant Feb 2016
- Autologous stem cell transplant, Day 0=7/11/16.
- CMV DNA VL on Day 0 was 29,800 IU/ml.
- Neutropenic sepsis with a blood culture on Day 5 with *Strep salivarius*.
- Ongoing fevers, new 2 cm pulmonary nodule by CT on Day 18

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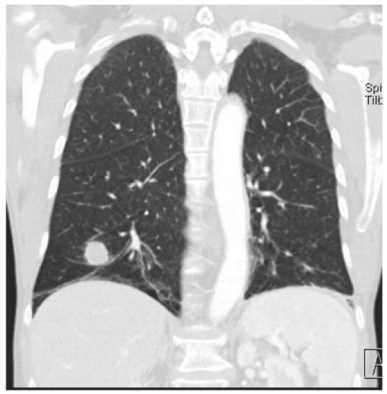

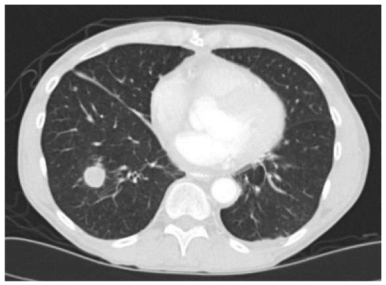

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After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

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After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

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- "She has had a dry cough but denies any sputum production, chest pain, SOB or headache. She has felt very well, and was quite determined to be discharged in the next few days."
- Voriconazole started
- She was underwent bronchoscopy, radial EBUS, washings, brushings and transbronchial biopsy → nonseptate hyphae seen
- Diagnosis: likely Zygomycetes
- She was switched from voriconazole to dual antifungal therapy with loading of isavuconazole and Ambisome.
- Repeat CT scan performed 2 days later showed significant increase in size of the nodule with new satellite lesions. She proceeded to RLL resection that evening by the cardiothoracic surgeons.

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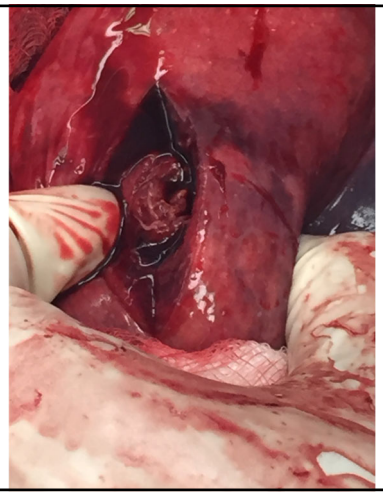

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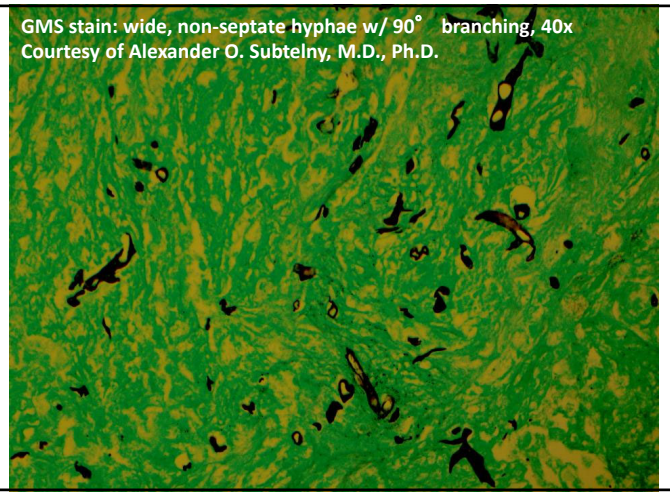


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Very Rare RHIZOPUS SPECIES

SUSCEPTIBILITY Performed at UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, Dept of Pathology, San Antonio, TX

MIC DILUTION METHOD

No CLSI interpretive guidelines available

| | |
|---|---|
| Amphotericin B | MIC=1 |
| Isavuconazole | MIC=1 |
| Miconazole | MIC=2 |
| Posaconazole | MIC=0.5 |

***In view of this, Ambisome was stopped on POD #9 and isavuconazole converted to 372mg daily for months/indefinite, plan is for radiographic resolution, immune reconstitution (heart transplant immunosuppression is for life).***

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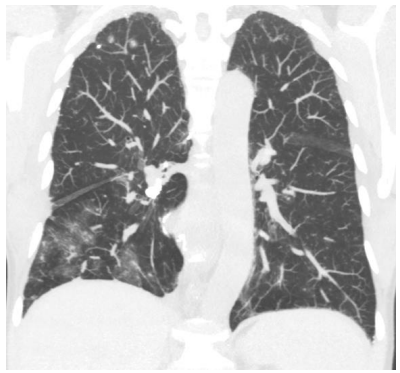

A year after transplant, she presented with disseminated zoster, new patchy infiltrates. Responded well to IV acyclovir.

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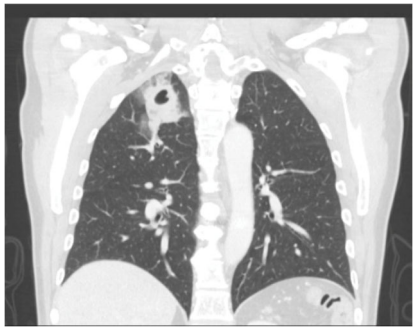
## What's This?

- Man in 50s diagnosed with multiple myeloma in 2011 → autologous stem cell transplant in March 2019.
- Due to disease progression in June 2020, he was treated with daratumumab and pomalidomide. He received radiation therapy to the thoracic and cervical spine.
- He consented to participate in a clinical trial protocol and underwent CAR infusion in January 2021. On fluconazole and acyclovir prophylaxis.
- Routine screening PET 4 months later "new thick walled multiloculated cavitary lesion in the right upper lobe with surrounding groundglass and clustered nodularity is concerning for infection, including bacterial as well as atypical and fungal infections in an immunocompromised patient". No symptoms at all



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## Epidemiology (ID fellow note)

- Living situation - lives with wife, 3 kids
- Outdoor exposures - rare, walks outside with dog in rode, has stopped dirt biking/hiking with thrombocytopenia
- Occupational exposures - Denies, works as a contractor for DoD, currently working at home
- Hobbies - mostly spending time at home right now
- Travel - Frequent travel pre-pandemic for work, has been to Australia, multiple countries in Asia and Europe, never to Africa or South America
- TB – no history of TB or known TB exposures; homeless or incarcerated? Denies
- Animals - Dog
- Food - raw or unpasteurized foods? Denies
- Dental work - None recent, does have a wisdom tooth pressing on a facial nerve
- Smoking - Denies
- Alcohol - Denies
- Recreational drugs - Denies
- Sex and prior STIs- Denies

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## What would you do next?

A. Start voriconazole, loading dose then maintenance based on weight
B. Start "vancopime" (cefepime plus vancomycin)
C. Start azithromycin
D. A-C (all of the above)
E. Bronchoscopy

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## Pseudomonas!

All other studies negative:

- BAL mycobacterial, fungal stains/cultures
- Cryptococcal antigen (blood)
- 1,3 beta D glucan (blood)
- Galactomannan (BAL and blood)
- Pathology: Bronchial epithelium with rare scattered neutrophils. Alveolated lung with fibroinflammatory changes and chronic inflammation. There is no evidence of malignancy. No microorganisms are seen on Brown-Hopps, GMS, Steiner, PAS-D, FITE, and AFB stains. Immunohistochemical stains for CMV, HSV, VZV, and adenovirus are negative. Trichrome and elastic stains were examined. The histologic findings are compatible with acute infection.

04/19/2021 1657 | 04/29/2021 1323 | Wound culture/smear [818905205] (Abnormal)
Other from Biopsy
RUL LUNG TBBX

Susceptibility

| | Pseudomonas aeruginosa MIC METHOD | |
|---|---|---|
| Amikacin | <=2 | Susceptible |
| Cefepime | 2 | Susceptible |
| Ceftazidime | 2 | Susceptible |
| Ciprofloxacin | <=0.25 | Susceptible |
| Levofloxacin | 1 | Susceptible |
| Meropenem | <=0.25 | Susceptible |
| Piperacillin-tazobactam | <=4 | Susceptible |
| Tobramycin | <=1 | Susceptible |

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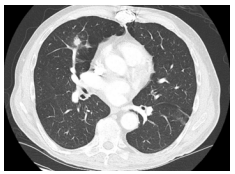
**A 73-year-old heart transplant recipient admitted with fevers, weight loss, diarrhea, cough and a pulmonary mass**

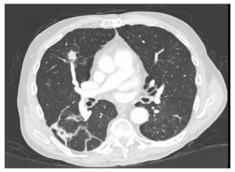
Adam Stewart, MBBS, MPH and Carlos Portales, MD, Massachusetts General Hospital Transplant ID fellows

- 15 months PTA → DBD OHT (CMV D+R-, EBV D-/R+) for left ventricular non compaction cardiomyopathy
- 1 month PTA → cough, fevers, diarrhea.
- 25 days PTA CT chest → 1.6 cm nodule, attributed to pneumonia – Rx IV cefepime → Augmentin.
- Despite Rx, ongoing cough, malaise. Immunosuppression maintained
- Follow up CT scan done 9 days PTA → Stable 1.6 cm nodule
- Due to ongoing symptoms, presents for admission, admission CT → worsening 5.5 cm nodule!

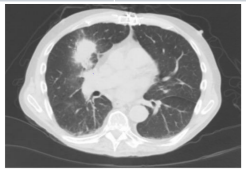
| Workup | |
|---|---|
| Respiratory Viral Panel | Negative |
| Stool culture | Neg Salmonella, Shigella, Campylobacter (no PCR) |
| Serum GM | 0.05 |
| 1-3-BDG | Negative |
| EBV PCR | 1,270 (H) |
| CMV DNA | Negative |
| Respiratory culture | Yersinia enterocolitica |



*25 days PTA*



*9 days PTA*



*On day of admission*

**IV cefepime and amphotericin B were started. IS decreased. A lung biopsy was performed...**

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**A 73-year-old heart transplant recipient admitted with fevers, weight loss, diarrhea, cough and a pulmonary mass**

- **Lung biopsy pathology:** Scattered EBV positive B cells in a background of organizing fibrosis, chronic inflammation, hemosiderin deposits and necrosis. Purulent necrosis seen. *Although the finding of EBV+ B cells raises the possibility of an EBV-associated PTLD, the tissue sample is scant and precludes definitive histologic subtyping. In addition, the unusual presence of purulent necrosis may reflect a concurrent bacterial infection, and an associated reactive process with increased EBV+ immunoblasts cannot be excluded*
- **No organisms seen on AFB, GMS or Steiner stains. CMV stain negative**
- **Lung biopsy culture: Moderate Yersinia enterocolitica**, no fungal or AFB growth.

| PTLD+ | PTLD- |
|---|---|
| Compatible syndrome | Low EBV PCR |
| Suggestive path | Recurrent growth of Yersinia in sputum |
| EBV D/R mismatch | Path suggestive of reactive EBV cells |

**EBV:1270**

IS decreased

Heme-Onc: Low likelihood PTLD - favor reactive EBV

**EBV 671**

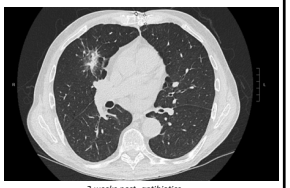
14 days IV ceftriaxone → PO ciprofloxacin

Resolution of symptoms

Discharged

**EBV 36**

**EBV <35 x 3**



*2 weeks post- antibiotics*

**Diagnosis to date: Yersinia enterocolitica pneumonia in ICH**

Yersinia enterocolitica Pneumonia in a Heart Transplant Recipient Transpl Infect Dis. 2025 Jan-Feb;27(1):e14422.

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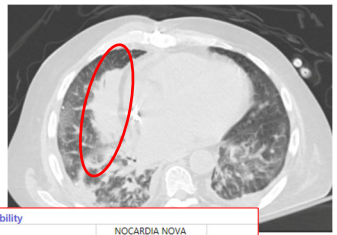
# Pneumonia

- 45yo s/p heart transplant 3 months earlier on posaconazole, atovaquone prophylaxis (not on TMP-SMX due to renal failure)
- New pneumonia, right middle lobe
- What is the cause?



Susceptibility

| | NOCARDIA NOVA COMPLEX MIC METHOD |
|---|---|
| Comment | SEE NOTES Note[1] |
| Amikacin | Susceptible |
| Amoxicillin + Clavulanate | Resistant |
| Ceftriaxone | Susceptible |
| Ciprofloxacin | Resistant |
| Clarithromycin | Susceptible |
| Doxycycline | Intermediate |
| Imipenem | Susceptible |
| Linezolid | Susceptible |
| Minocycline | Susceptible |
| Moxifloxacin | Resistant |
| Tobramycin | Resistant |
| Trimethoprim/sulfamethoxazole | Susceptible |

[1] SUSCEPTIBILITY TESTING Performed at the University of Texas Health Center at Tyler, Tyler TX

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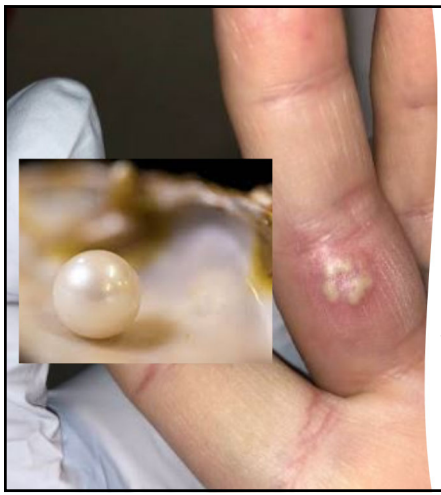

A 42-year-old woman underwent liver transplant.

-She was given three months of antiviral prophylaxis with valganciclovir, as both the donor and recipient were CMV IgG positive, and six months of trimethoprim-sulfamethoxazole.

-Two months later, she noticed this painful rash on her finger, as shown in the picture, with red streaking up her arm. What treatment would you initiate?

**Choices**

**tecovirimat (Mpox)**

**linezolid**

**fluconazole**

**valacyclovir**

**voriconazole**

This lesion was unroofed for sampling. Bacterial cultures grew *Staphylococcus epidermidis*. A serum cryptococcal antigen was negative. Fungal cultures were negative. Several days later, HSV-2 PCR of the lesion was positive, while HSV-1 and VZV were negative. **This is herpetic whitlow, which we usually associated with HSV-1 but can be from HSV-2.**

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## Let's Switch to Parasites

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## Toxoplasmosis

Epidemiology:

- 1988–1994 (NHANES III): ~22.5% of individuals in USA aged 12–49 years were seropositive
- 1999–2000: seroprevalence decreased to 14.3%
- 2009–2010: Further decline to 10.1%

Syndromes seen after Transplant:

- Toxoplasma encephalitis
  - Headache, confusion to coma, seizures, focal neurologic deficits
- Pneumonitis (lung inflammation)
- Myocarditis (heart inflammation)
- Chorioretinitis

Diagnostics

- Serology is useful for risk assessment, not for diagnosing active disease
- **Toxoplasma PCR** on blood, CSF, BAL (bronchoalveolar lavage), or tissue
- Highly sensitive and specific for detecting T. gondii DNA

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## Clinical Vignette

64yo man from Dominican Republic with end-stage liver disease, chronic abdominal pain, listed for liver transplant

- Eosinophilia (up to 70%) x 6 months
- Recurrent enteric Gram negative bacteremias
- Fluffy pulmonary infiltrates
- What does he have?

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## Test Results

Strongyloides Antibody by ELISA: 100.00

INTERPRETATION: POSITIVE

- All reactions of <=1.7 units/ml should be considered NEGATIVE.
- All reactions >1.7 units/ml should be considered POSITIVE, indicative of infection with *Strongyloides stercoralis* at some indeterminate time.
- Sensitivity of the test is 93% and specificity is 98%.

Centers for Disease Control testing

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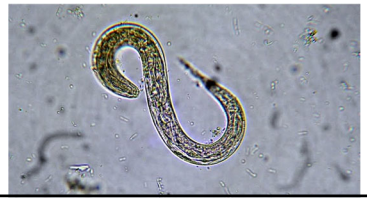
## Strongyloides

- Nematode “roundworm”
- 100-200 million people worldwide are infected
- Autoinfection*
- >50% mortality immunocompromised patients with disseminated disease



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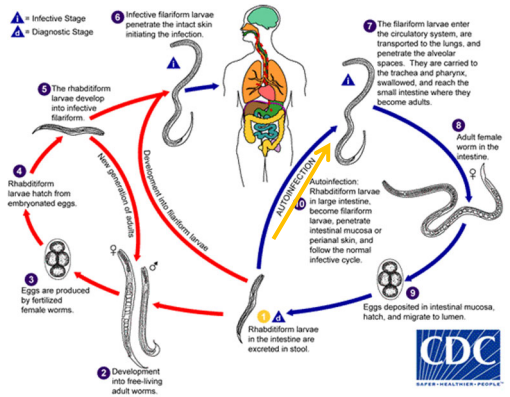
## *Strongyloides stercoralis* lifecycle




http://www.cdc.gov/dpdx/strongyloidiasis/

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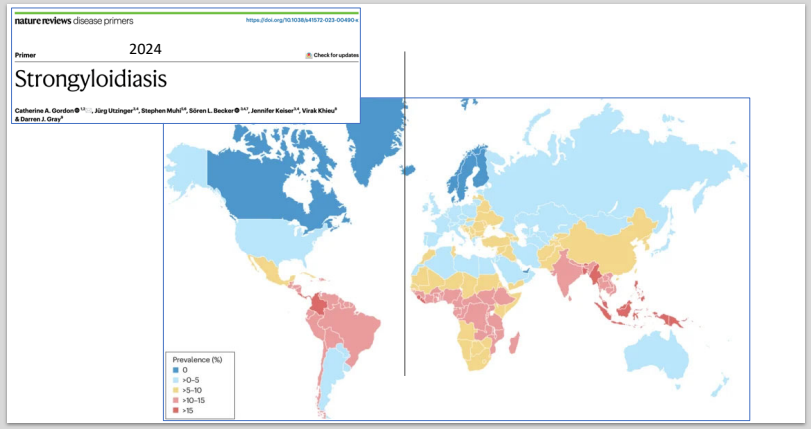


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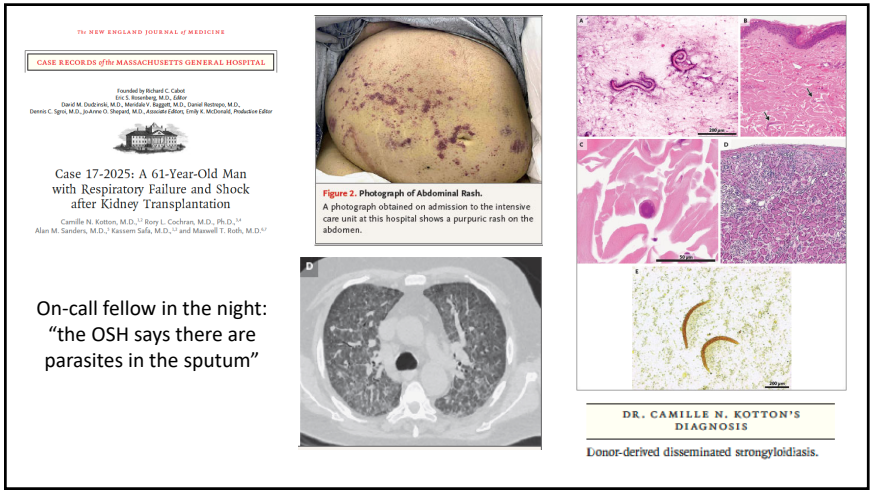


On-call fellow in the night: “the OSH says there are parasites in the sputum”

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## Diagnostics stewardship

MASSACHUSETTS GENERAL HOSPITAL TRANSPLANT CENTER

Consider best methods to achieve most likely diagnosis; Hickam's dictum* vs Occam's razor

The initial work up can be protocol driven; we have syndromic evaluations in the emergency room

Molecular diagnostics are superior but require us to be specific in our requests

- Multiplex (i.e. Biofire) helps

Non-invasive fungal diagnostics have been disappointing

- 1,3 beta D glucan, galactomannan (still love cryptococcal antigen!)
- serum *Mucorales* polymerase chain reaction is emerging

Toxoplasma PCR excellent example of sensitive and specific non-invasive test (rare diagnosis)

New technologies (i.e. cell free DNA testing) are emerging/interesting

***The sooner we achieve a diagnosis, the sooner we can stop broad-spectrum antimicrobials & better outcomes for the patient***

* Hickam's dictum is usually stated as "patients can have as many diseases as they damn (or darn) well please". This aphorism has been attributed to John Hickam (1914-1970) an American physician, who was Chair of the Department of Medicine at the University of Indiana [93]

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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**Rapid Diagnosis of Disseminated Tuberculosis Using Cell-Free DNA Sequencing in a Kidney Transplant Recipient, Transplantation 2023**
**Anna Apostolopoulou & Camille Nelson Kotton**

- Middle aged kidney transplant recipient presented with fevers
- Extensive workup done
- "**On hospital day 13, while she remained febrile and without a definitive diagnosis, we sent a quantitative cfDNA test (Karius, Inc., Redwood City, CA). On HD 15, the Karius cfDNA test returned positive for M tuberculosis.**
- Subsequently, the mycobacterial blood, urine, and bronchoalveolar lavage cultures grew M tuberculosis on hospital days 17, 17, and 21, respectively). Bone cultures grew M tuberculosis 34 days after biopsy (after discharged from the hospital)."

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## Drug Interactions: Transplant & Antimicrobials

- Azoles
  - Voriconazole, posaconazole > fluconazole
  - Isavuconazole – much less interaction
  - Increase tacrolimus (or cyclosporine, rapamycin)
- Rifamycins
  - Rifabutin < rifampin (=rifampicin)
  - Decrease tacrolimus (or cyclosporine, rapamycin)
  - Increase prednisone
- QT prolongation
  - Combination effect
  - May be present with liver disease
- Recommended: Use of on-line drug interaction calculator

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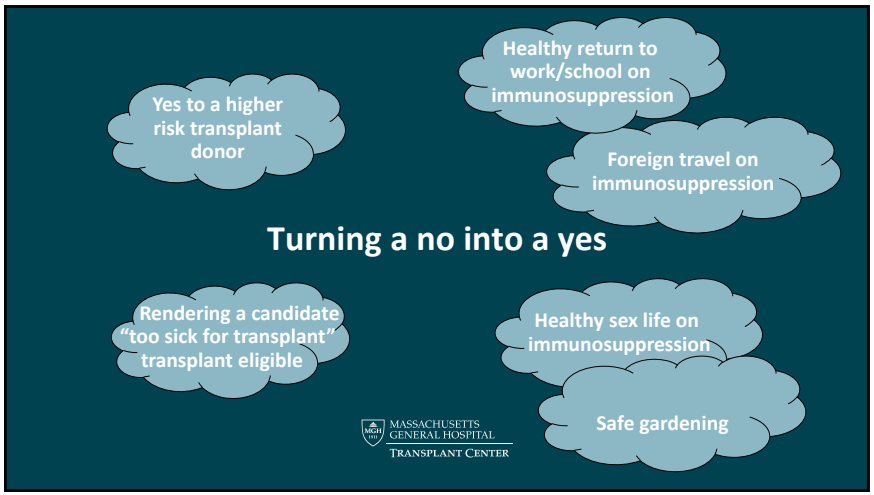


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## Cardinal Rules 2026: Immunosuppression and Infection

1. Immunosuppression and infections not always straightforward
2. Be prepared to be surprised – think broadly
3. Prepare patient before immunosuppression – role for ID specialists
4. Prophylaxis & vaccines alter the risk equation
   - Primary and secondary prevention
5. Consider the source of infection: donor, recipient, blood products, geographic, more antibiotic resistance

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