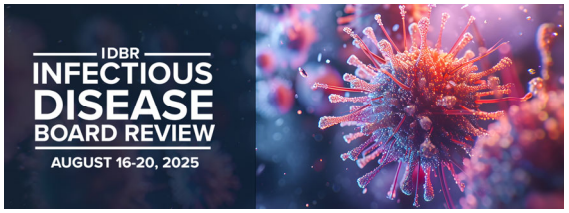
OL-3 Bootcamp: Transplant

Speaker: Camille Kotton, MD



Solid Organ and Stem Cell Transplant ID Bootcamp

Camille Nelson Kotton MD, FAST, FIDSA

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Associate Professor, Harvard Medical School
Prior Chair, Infectious Disease Community of Practice, American Society of Transplantation
Prior President, Infectious Disease Section, The Transplantation Society

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Disclosures of Financial Relationships with Relevant Commercial Interests

Camille Nelson Kotton, Disclosures		
Company	Role	Details
Evrys	Consultant	CMV treatment in transplant
Merck	Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME)	Transplant infections CMV antiviral trial, adjudication Pneumococcal vaccine, adjudication
Shire/Takeda	Consultant, Adjudication committee member, symposium speaker (CME)	CMV management in transplant patients
AiCuris	Research, consultant	Local PI, use of pritelivir in immunocompromised patients with resistant herpes
QIAGEN	Consultant, research, speaker	CMV diagnostics
Roche Diagnostics	Consultant, speaker	Review of risk factors for herpes viral infections after transplant, viral load testing
Kamada	Consultant, research, speaker	Immunoglobulins for CMV, measles
Biotest	Consultant, speaker	Immunoglobulins for CMV

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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 to subsequent similar talks**

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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)

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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

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

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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://wwwnc.cdc.gov/travel/yellowbook/2024/travelers-with-additional-considerations/immunocompromised-travelers, Kotton, Kroger, Freedman

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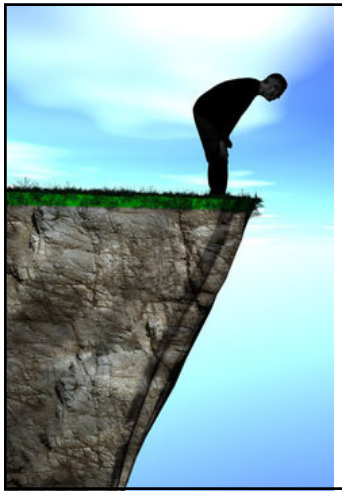

"Net state of immunosuppression"

Dr. Robert Rubin,
Massachusetts General Hospital

IMMUNOSUPPRESSION IS ADDITIVE/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 (i.e., autoimmune hepatitis)
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection

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National Organ Transplant Data – USA

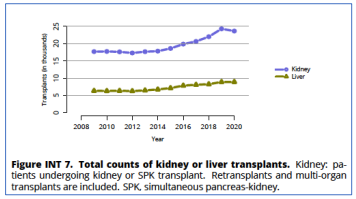

Figure INT 7. Total counts of kidney or liver transplants. Kidney: patients undergoing kidney or SPK transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

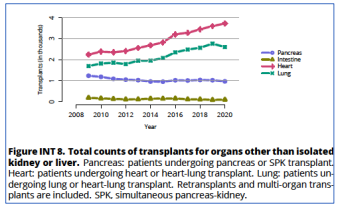

Figure INT 8. Total counts of transplants for organs other than isolated kidney or liver. Pancreas: patients undergoing pancreas or SPK transplant. Heart: patients undergoing heart or heart-lung transplant. Lung: patients undergoing lung or heart-lung transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

>850,000 transplants done in USA since 1988

OPTN/SRTR 2020 Annual Data Report: Introduction, AJT Feb 2022

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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

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Total Number of HCTs Performed in the United States
Center for International Blood and Marrow Transplant Research, 2016-2020

Donor Type	Number	%
Autologous:	*66,458*	*59%*
Allogeneic:		
HLA-Matched Sibling	10,792	10%
Other Related Donor	10,037	9%
Unrelated	24,697	22%
Total	**111,984**	**100**

https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report#summary
accessed 18 March 2025

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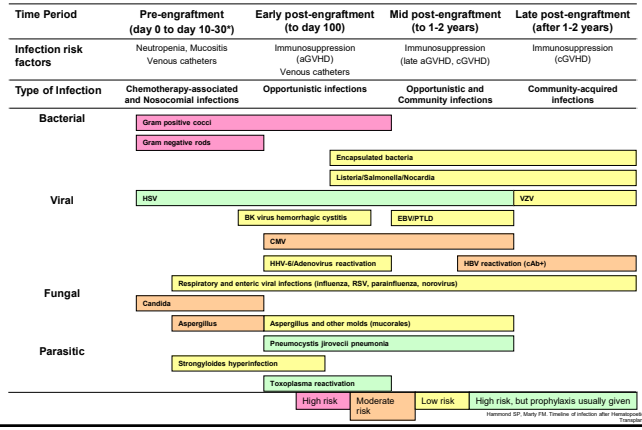
Timeline of Infection after HSCT



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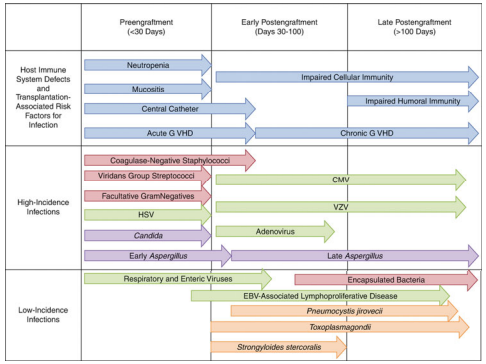
Timeline of Host Immune Defects and Infections in Allo-HSCT Recipients



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

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

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

* Immunosuppression generally not needed

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Infectious Complications from CAR-T Cell Therapy

Reference	CAR T-cell therapy	*N*	Underlying malignancy	Severity grade	Timepoint	Bacterial infection incidence (n, %)	Viral infection incidence (n, %)	Fungal infection incidence (n, %)
Abramson et al.[18]	Lisocabtagene maraleucel	269	R/R B-cell lymphoma	≥3	12 months	27/269 (10)	4/269 (1)	2/269 (1)
Locke et al.[20]	Axicabtagene ciloleucel	108	Refractory B- cell lymphoma	All	12 months	44/108 (40)	11/108 (10)	7/108 (6)
Logue et al.[21]	Axicabtagene ciloleucel	85	R/R B-cell lymphoma	All	≤30 days	26/85 (31)	12/85 (14)	2/85 (2)
					>30 days	13/85 (15)	19/85 (22)	0/85 (0)
Wittmann Dayagi et al.[16]	CD28-based CAR T cells	88	R/R B-cell lymphoma	All	≤30 days	22/85 (25)	14/85 (16)	0/85 (0)
					30–60 days	8/85 (9)	2/85 (2)	1/85 (1)
Baird et al.[22]	Axicabtagene ciloleucel	41	R/R B-cell lymphoma	All	≤28 days	7/41 (17.1)	8/41 (19.5)	4/41 (9.8)
					>28 days	10/41 (24.4)	10/41 (24.4)	9/41 (22)
Wudhikarn et al.[23]	Axicabtagene ciloleucel OR tisagenlecleucel	60	R/R DLBCL	All	≤30 days	20/60 (33)	10/60 (17)	1/60 (2)
					>30 days	14/60 (24)	17/60 (28)	3/60 (5)
Hill et al.[24]	Anti-CD19 CAR autologous T cells	133	ALL, CLL, NHL	All	≤28 days	22/133 (16.5)	11/133 (8.3)	4/133 (3)
					>28 days	7/119 (5.9)	11/119 (9.2)	2/119 (1.7)
Munshi et al.[51]	Idecabtagene vicleucel	54	R/R multiple myeloma	All	12 months	13/54 (24)	15/54 (28)	4/54 (7)

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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

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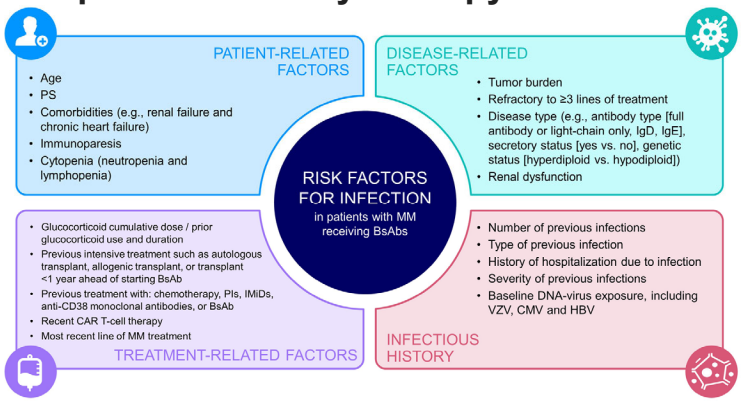
Bispecific Antibody Therapy & Infections



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

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National Organ Transplant Data – USA

> 1 Million Transplants Done in USA Since 1988

	To Date	2025	2024	2023	2022	2021	2020	2019	2018	2017	2016	2015	2014	2013	2012	2011
All Organs	1,023,665	7,816	48,137	46,629	42,889	41,356	39,036	39,719	36,530	34,770	33,610	30,974	29,540	28,956	28,059	28,553
Kidney	602,288	4,449	27,759	27,332	25,500	24,670	22,817	23,401	21,167	19,849	19,060	17,878	17,108	16,896	16,487	16,816
Liver	224,798	1,941	11,458	10,659	9,528	9,236	8,906	8,896	8,250	8,082	7,841	7,127	6,730	6,455	6,256	6,342
Pancreas	9,514	18	114	102	108	143	135	143	192	213	215	228	245	256	242	287
Kidney / Pancreas	28,748	128	733	812	810	820	827	872	835	789	798	719	709	762	801	795
Heart	97,320	712	4,572	4,545	4,111	3,818	3,658	3,552	3,408	3,244	3,191	2,804	2,655	2,531	2,378	2,322
Lung	55,707	540	3,340	3,026	2,692	2,524	2,539	2,714	2,530	2,449	2,327	2,057	1,925	1,923	1,754	1,822
Heart / Lung	1,588	11	64	54	51	45	58	45	32	29	18	15	24	23	29	27
Intestine	3,577	17	97	95	82	96	91	81	104	109	147	141	139	109	106	129

*UNOS data downloaded 8 April 2025
https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/

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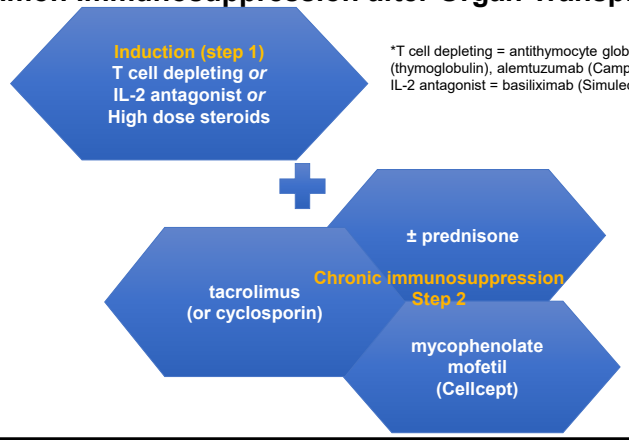
Common Immunosuppression after Organ Transplant



*T cell depleting = antithymocyte globulin (thymoglobulin), alemtuzumab (Campath®)
IL-2 antagonist = basiliximab (Simulect®)

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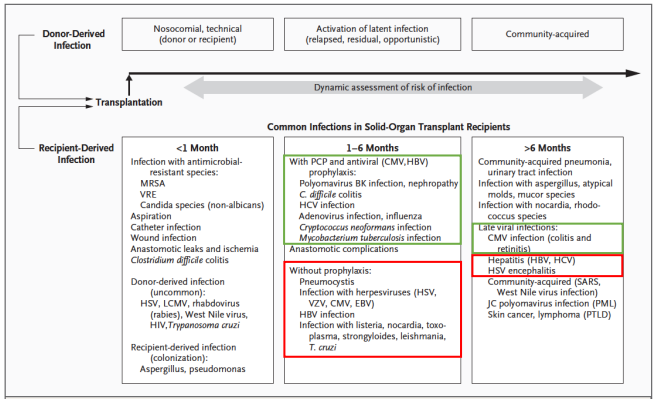
Timeline of Infection after Organ Transplantation



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

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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 moving towards standard of care
- Need to have a good plan for medications (insurance)
- Trend towards shorter treatment protocols

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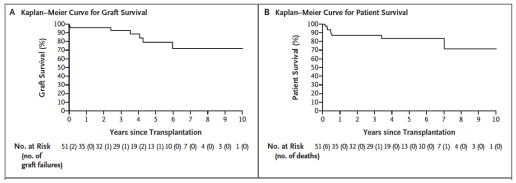
Longer-Term Outcomes of *HIV-Positive-to-HIV-Positive Renal Transplantation*, Selhorst, Muller et al, NEJM 2018

- 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**



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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
- Management: peritransplant/initiation of immunomodulatory tx
- Prophylaxis and/or screening after transplant/immunomodulatory therapy started

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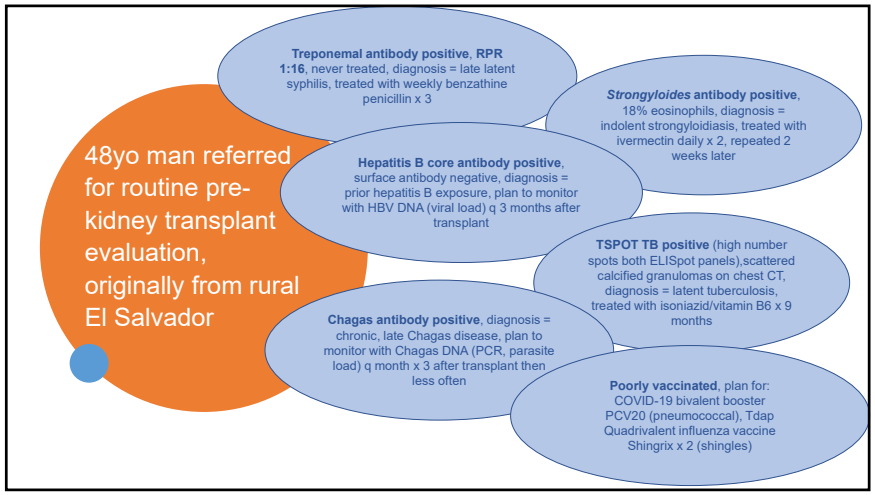

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Pre-Immunosuppression Evaluation (MGH)

	Everyone	If risk factors
Hepatitis B surface antigen	x	
Hepatitis B core antibody (IgG not IgM)	x	
Hepatitis B surface antibody	x	
Hepatitis C	x	
HIV	x	
Tuberculosis screening	x	
Coccidioides serology		x
Strongyloides serology		x
Trypanosoma cruzi (Chagas disease)		x

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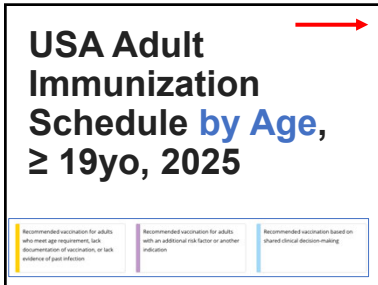
USA Adult Immunization Schedule by Age, ≥ 19yo, 2025



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

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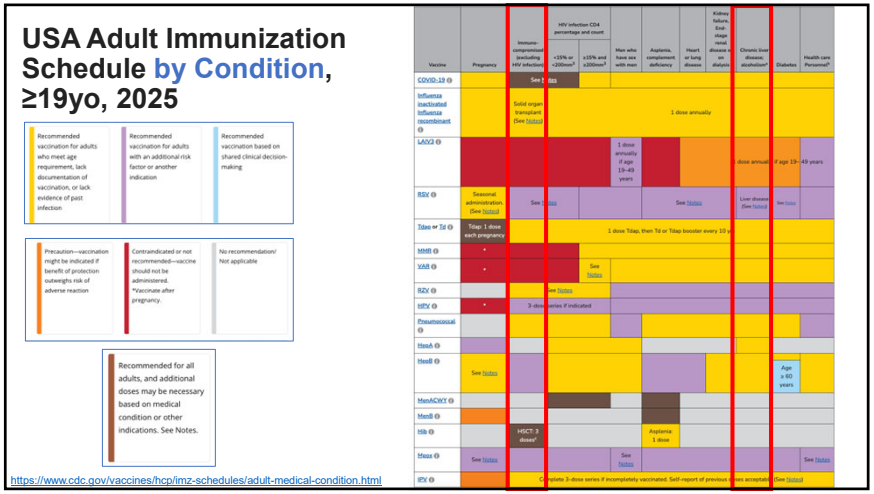
USA Adult Immunization Schedule by Condition, ≥19yo, 2025



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

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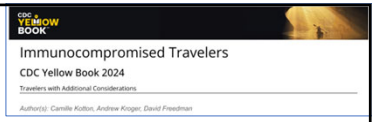

Live vaccines	Severe immunosuppression
Live vaccines	
Bacillus Calmette Guérin (BCG)	Contraindicated
Chikungunya (Ixchiq)	Contraindicated
Cholera (Vaxchora)	No data, generally recommend against use
Ebola (Ervebo)	Consider
Influenza, live attenuated	Contraindicated
Measles-mumps-rubella (MMR/MMR-V)	Contraindicated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

https://wwwnc.cdc.gov/travel/yellowbook/2024/additional-considerations/immunocompromised-travelers revised for 2026

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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/

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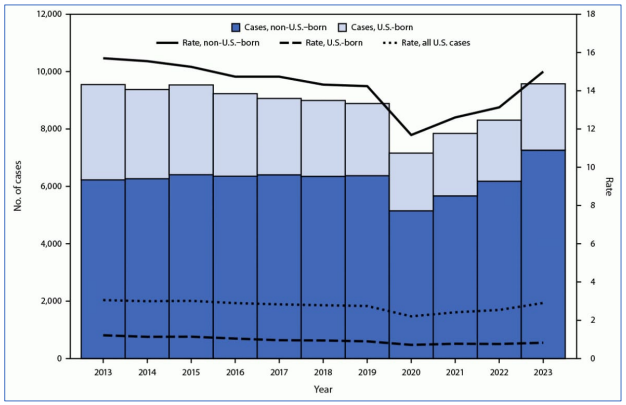
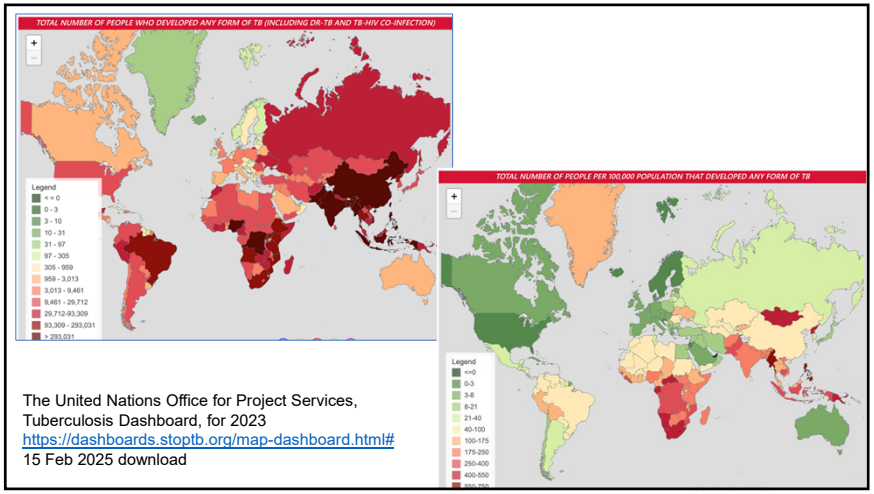


CDC March 2025:
- More than 10,300 tuberculosis (TB) cases were reported in 2024
- An 8% increase from 2023
- Highest case count since 2011

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

32



The United Nations Office for Project Services, Tuberculosis Dashboard, for 2023
https://dashboards.stoptb.org/map-dashboard.html#
15 Feb 2025 download

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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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Question #1

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.

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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.

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Excellent Prophylaxis is Paramount…

and provides important clues on boards questions

- Antivirals
- Pneumocystis/Toxoplasmosis
- Antifungals

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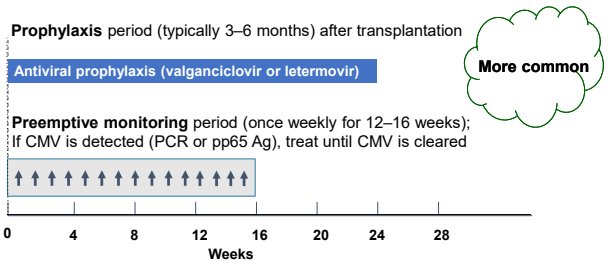
CYTOMEGALOVIRUS PREVENTION: Prophylaxis vs. Preemptive Therapy



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

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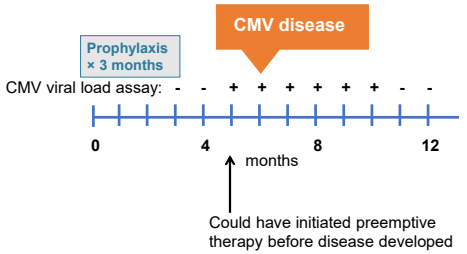
Hybrid Strategy for SOT: CMV Surveillance After Prophylaxis

- 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

Consider "net state of immunosuppression"



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

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Prophylaxis: Solid Organ Transplant Massachusetts General Hospital

CMV/Herpes Antiviral Prophylaxis

- Valganciclovir if any CMV risk (if either donor and/or recipient are CMV positive)
  - Prevents CMV, herpes, varicella/zoster
- Acyclovir/valacyclovir/famvir **if no CMV risk**
  - Prevents herpes, varicella/zoster
- Duration varies, 3-6 months is common (longer for lung transplant)
- Main side effect is leukopenia and cost with valganciclovir

Donor CMV Antibody	Recipient CMV Antibody	Prophylaxis	Duration
+	+	Valganciclovir	Antithymocyte globulin and D+R- → 6 months All others 3 months
-	+		
+	-		
-	-	ACV/Famvir/ValACV	

Anti-*Pneumocystis*/anti-bacterial

- Trimethoprim-sulfamethoxazole x 6-12 months (longer for heart/lung transplants)
- *or* dapsone or atovaquone if true allergy

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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$271 letermovir 480mg/d vs US$117 VGCV 900mg/d per goodrx.com (March 2025)

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 -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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Lung	D+/R-	High	12 months of GCV/VGCV	-Preemptive therapy
	R+	Intermediate	6-12 months of GCV/VGCV	-Some experts add CMVIG to prophylaxis

4th International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation
Confidential, accepted for publication

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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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Approach to Toxoplasmosis Prophylaxis

- Toxoplasmosis risk highest in Donor +/Recipient seronegative = 50-75% risk of symptomatic infection without prophylaxis within 3 months of heart transplant (much lower with other organs)
- ~7% of Americans age 12-49y are seropositive (https://www.ncbi.nlm.nih.gov/pubmed/25012250)
- Infection more common in patients from endemic regions (e.g., France, Caribbean)
- Can present in any organ system (CNS abscess, pneumonia, myocarditis, disseminated disease)
- Very rare with good prophylaxis

Duration of prophylaxis based on serologic combinations (MGH)			Prophylaxis
Serologies	Risk group	Duration of therapy	
D+/R-	Highest risk	Lifetime, if possible (otherwise discuss with infectious disease)	First line: FIRST YEAR: -Bactrim DS 1 tab QD x 1 year (for D+/R-) -Can dose reduce the DS to SS if CrCl<30 -Bactrim SS 1 tab QD (for all other serology; no need to dose reduce this dosage with renal failure/HD) AFTER FIRST YEAR: Bactrim SS 1 tab QD (see columns to left) Second line (only if real Bactrim allergy): Atovaquone (mepron) 1500 mg QD Third line (both Bactrim and mepron allergy): Dapsone 100 mg QD √ G6PD and watch for MetHgb
R+ (regardless of donor status)	Moderate risk	Can stop at one year, or when on low-dose prednisone 5 mg a day, whichever is later/longer.	
D-/R-	Lowest risk		

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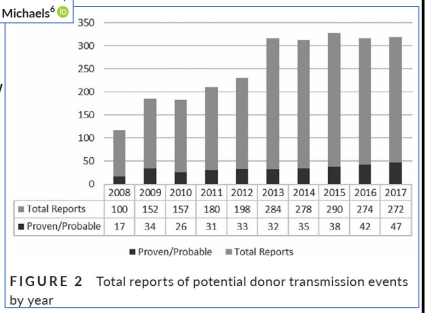
Ten years of donor-derived disease: A report of the disease transmission advisory committee

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[5]

- 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) Heart Liver	N/A	Blood transfusion (received by donor)	27 days prior to organ donation (received by donor)	4 weeks 17 days 15 days	Dead (1) Dead 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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TABLE 1 Proven and probable infection transmissions by type (by number of pathogens/syndromes in proven/probable donors) 2008-2017

Category of Infection	Pathogen		Total p/p: (percent of p/p by category)	Comment
Viral	Cytomegalovirus	Fungal (2)	*Aspergillus*	7 (13)	
	Hepatitis B virus		Mucorales	2 (4)	(one cotransmission with *Aspergillus*)
	Hepatitis C virus		*Candida*	13 (24)	
	Lymphocytic chori		Coccidioidomycosis	10 (19)	
	Community respira		Histoplasmosis	7 (13)	
	Parvovirus		*Cryptococcus*	11 (20)	
	West Nile virus		Other	4 (7)	*Scopulariopsis* (1), *Trichosporon* (1), *Geotrichum* (1), *Microsporidia* (2)
	Other		**Total Fungal**	54 pathogens (22) from 53 donors	
	Total Viral	Mycobacterial	Tuberculosis	9 (4)	
Bacterial (1)	***Gram-positive***				
	Staphylococcus aure	Parasitic	*Strongyloides*	13 (42)	
	Enterococcus		Toxoplasmosis	11 (35)	
	Other		Trypanosomiasis	3 (10)	
	Gram-negative		*Balamuthia*	2 (6)	
	Enterobacteriaceae		Other	2 (6)	Amoebic encephalitis (1), Schistosomiasis (1)
	Pseudomonas		**Total Parasite**	31 (12)	
	Other		Total Infectious Agents/Syndromes	250 pathogens from 244 donors	
	Mycoplasma spp.				
	Other				
	Total Bacterial				

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TABLE 7 Time to presentation of donor-derived infection

	Median (Range)	0-30 days	31-90 days	91-180 days	> 180 days
Viral	48 days (11-776)	LCM WNV (4) RSV	CMV (3) Parvovirus WNV	Hepatitis C	Hepatitis B
Bacterial	14 days (2-45)	Assorted (23)	*Klebsiella*		
Fungal	18 days (5-256)	*Candida* (3) *Coccidioides* (6) *Aspergillus* *Cryptococcus* (4) *Scopulariopsis* Zygomycetes (2)	*Aspergillus* *Coccidioides* (3) Histoplasmosis		*Aspergillus*
Mycobacterial	67 days (8-148)	M. tuberculosis (2)	M. tuberculosis (2)	M. tuberculosis (2)	
Parasitic	50 days (70-145)	*Toxoplasma* *Balamuthia* (5)	*Strongyloides* *Toxoplasma* *Encephalitozoon* (2)	*Strongyloides* (2) *Toxoplasma* *Encephalitozoon* *Balamuthia*	

Abbreviations: CMV, cytomegalovirus; LCMV, lymphocytic choriomeningitis; RSV, respiratory syncytial virus; WNV, West Nile virus.

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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

TABLE 8 Summary of key lessons learned

Recognition of donor-derived disease	**Trends requiring future confirmation**
Two thirds of DDI develop symptoms within 30 days of transplantation	Breast cancer and thyroid cancer were not transmitted using current screening protocols
Endemic fungal, parasitic, mycobacterial may be manifest after 30 days	Respiratory viruses, mycoplasma, tuberculosis, aspergillus primarily transmitted to lung recipients
Consider donor exposures in cases of unexpected recipient illness	Bacterial and candida DDI rarely noted later than 30 days posttransplant
Although infections predominate, one third of DDD is noninfectious	D + R- toxoplasma non-heart recipients are at high enough risk to merit prophylaxis
DDD from living donors may occur but is less common than from deceased donors	Peanut allergy rarely transmitted to kidney recipients
	No proven/probable transmissions of atypical mycobacteria or prion disease
	DDD from malignancy (other than renal cell carcinoma) has highest mortality
	MDRO organisms are a common cause of bacterial DDI
Donor evaluation	**System improvements**
Critical evaluation to determine accuracy of listed cause of death	Improve early warning systems and global harmonization to recognize and address emerging trends
Consideration of universal or targeted donor testing (even if results learned posttransplant as early interventions effectively prevent development of disease)	Lengthen and improve follow-up to better attribute death, graft loss
Strongyloides	Active tracking of recipients of donors with findings that suggest risk
Coccidioides	Rapid ability to scale up testing as new pathogens emerge
Cryptococcus	
Improved mechanism for development and evaluation of donor tests	
Reporting	
Critical as profound impact on other recipients because involvement of multiple recipients common allowing for interventions; graft or death loss occurred in about one third of recipients with DDD	
Culture of safety: reporting does not result in penalties unless significant policy violations	
DTAC information benefits all in transplant community	
Morbidity and mortality of DDI significant and attention to OPO or UNOS DDI communications necessary	

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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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Pathogens Contribute to Infection Risk: Indirect Effects of CMV

General indirect effects– elevated risks

- Bacterial, fungal, viral infections
- Post-transplant lymphoma (PTLD)
- Cardiovascular events
- New-onset diabetes mellitus after transplantation
- Immunosenescence
- Acute rejection
- Mortality

Transplant-specific indirect effects

- Chronic allograft nephropathy and/or allograft loss after renal transplant
- Accelerated hepatitis C recurrence after liver transplant
- Hepatic artery thrombosis after liver transplant
- Allograft vasculopathy after cardiac transplant
- Bronchiolitis obliterans after lung transplant

Kotton, CMV: Prevention, Diagnosis and Therapy, AJT 2013

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Management of Mild to Moderate CMV Infection-I

Who to treat

If Donor positive/recipient seronegative (highest risk group), likely need to treat if CMV viral load > 500 IU/ml (start at lower level if very low lymphocyte count or potent immunosuppression)

If recipient seropositive, likely need to treat if CMV viral load > 1500 - 2000 IU/ml (start at lower level if very low lymphocyte count or potent immunosuppression)

If not starting treatment, recheck all a week later – follow closely to see if better or worse

Diagnostically

Check weekly CMV DNAemia (i.e. CMV viral load) on plasma (not whole blood); **trend until there are two negative/very low (<300 IU/ml) results**, then stop therapy; consider weekly monitoring after the end of treatment for 8-12 weeks so as to capture early recurrent disease (especially in high-risk D+R- patients, or with higher immunosuppression).

Best to check CMV DNAemia with same specimen type, on same testing platform and at same lab, as whole blood can be +/- 10x higher (extremely variable) result c/w plasma and test results can vary significantly across different labs and testing platforms; best to pick one lab and use that for comparison.

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 some increase in the CMV viral load.

Consider checking total IgG level at the time of initiation of treatment. We would replete if the total IgG level was less than 400 with either CMV immunoglobulin or IVIG.

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Management of Mild to Moderate CMV Infection-II

Therapeutically

Start **valganciclovir** 900mg po q12 hours, renally adjusted as needed

Note: would use intravenous therapy if severe, ophthalmologic, refractory/resistant, or life-threatening disease. Consider using intravenous therapy with significant colitis with concern for malabsorption, or if viral load >100,000 IU/ml.

Consider lowering immunosuppression

If total IgG < 400, consider giving either CMV Ig 150mg/kg or IVIG (especially if severe or resistant disease)

References

Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, Humar A; The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation. Transplantation Society International CMV Consensus Group*.Transplantation. 2018 Mar 29.

Are We There Yet? Impact of the First International Standard for Cytomegalovirus DNA on the Harmonization of Results Reported on Plasma Samples. Preiksaitis JK et al, Clin Infect Dis. 2016 Sep 1;63(5):583-9. doi: 10.1093/cid/ciw370.

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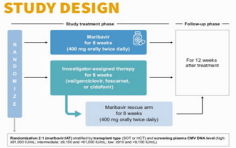
Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

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)

PRIMARY ENDPOINT (WEEK 8)

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)

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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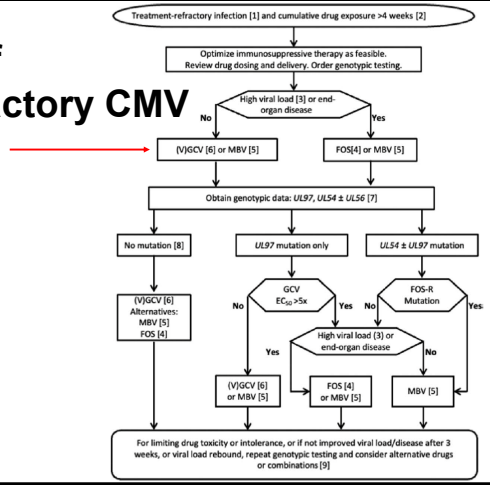
Management of Resistant/Refractory CMV



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

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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; Low sensitivity/moderate specificity *Excellent for Pneumocystis*
Galactomannan	Blood, BAL, other body fluids	Primarily for Aspergillus; 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* *Higher sensitivity with proven vs probable disease (60% vs 37% Sim BZ et al CID 2025)*

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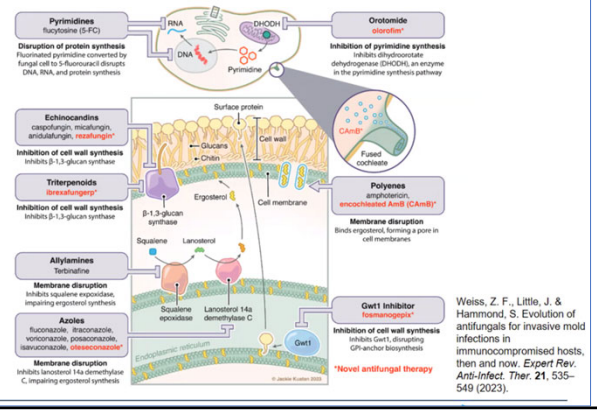
Antifungal Mechanisms of Action



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-year-old 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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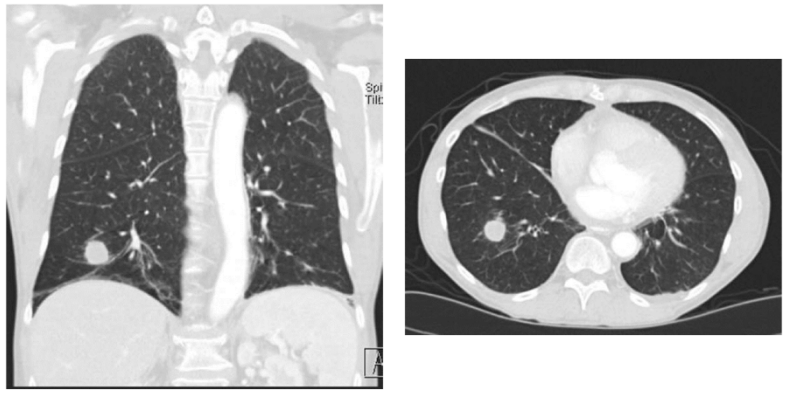

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Question #2

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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Question #2

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 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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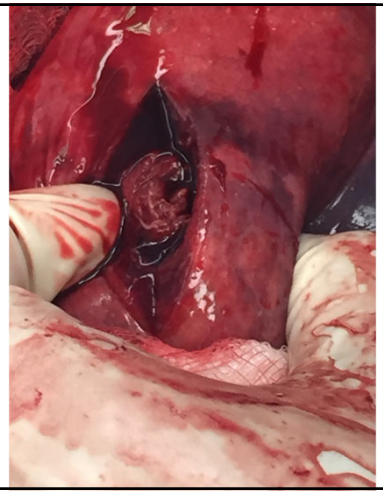

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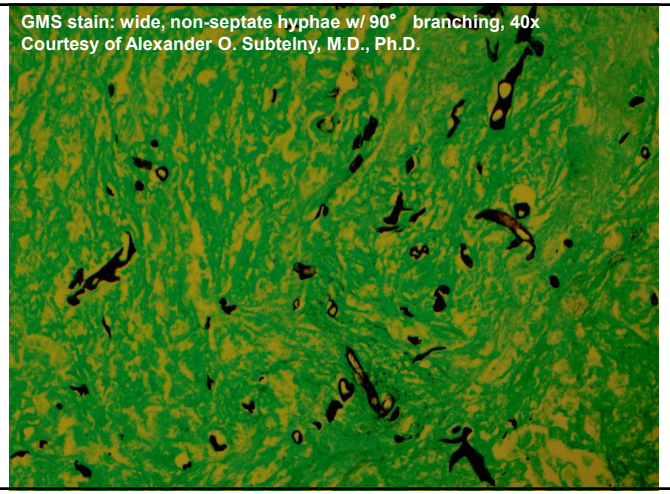

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Very Rare RHIZOPUS SPECIES

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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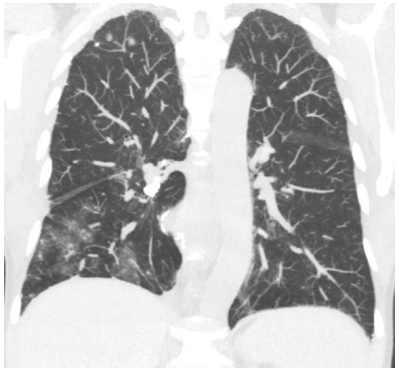

A year after transplant, she presented with disseminated zoster, new patchy infiltrates. Responded well to IV acyclovir.

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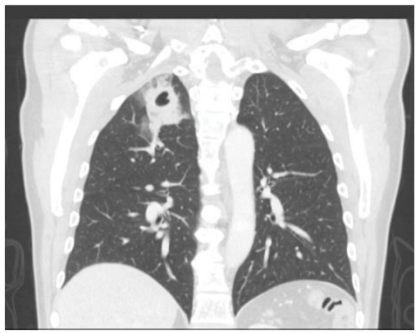
What's This?

- 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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Question #3

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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Question #3

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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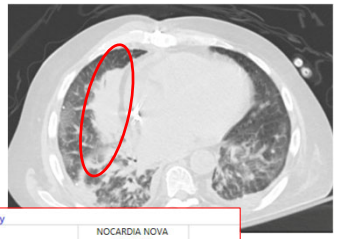
Pneumonia

- 45-year-old 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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Let's Switch to Parasites

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Toxoplasmosis

Epidemiology:
- 1988–1994 (NHANES III): ~22.5% of individuals 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

64-year-old 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 rod 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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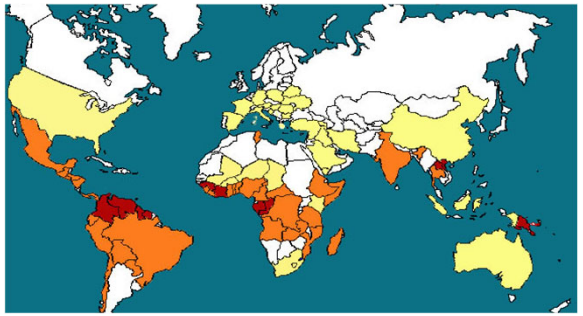

The countries highlighted in **yellow** have sporadic endemicity, on the range of 1-3%. Those that are **orange** are endemic, while those that are **red** are generally hyperendemic, with the highest frequency of *Strongyloides* infection.

http://web.stanford.edu/group/parasites/ParaSites2006/Strongylodiasis/epidemiology.html

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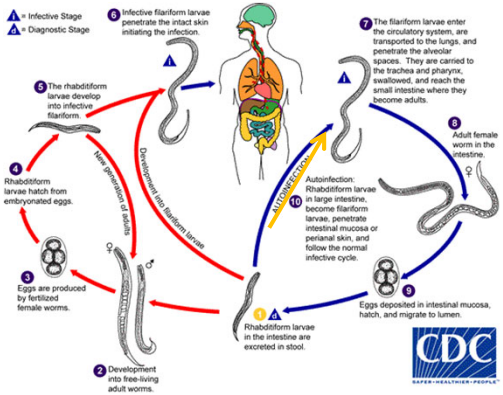
Strongyloides stercoralis Lifecycle



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

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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

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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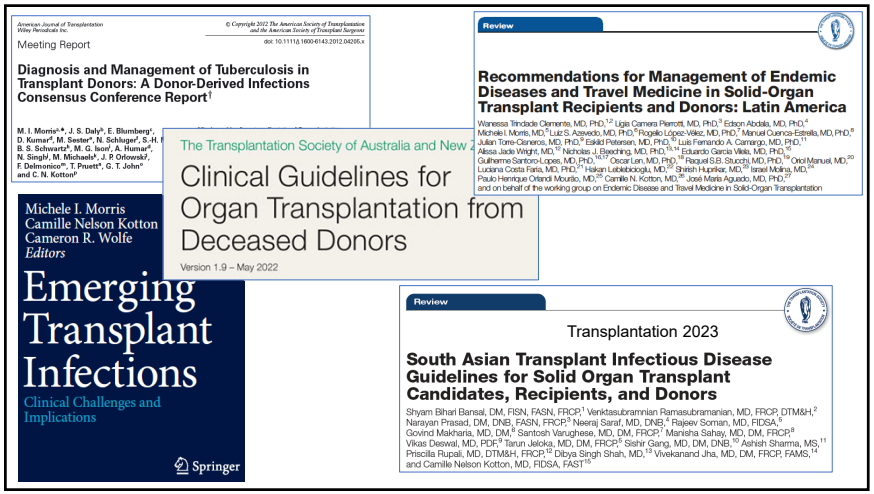

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Cardinal Rules 2025: Immunosuppression and Infection

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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Questions? ckotton@mgh.harvard.edu

@KottonNelson (Twitter)

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