

Infection Prevention and Management in Solid Organ Transplant Patients

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Disclosure of Potential Conflicts of Interest

➤ **None to disclose**



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Learning Objectives

- Develop appropriate pre-transplant serologic testing recommendations and interpretation of these results.
- Identify risk factors associated with post-transplant infections and the epidemiology and timing of these infections.
- Design strategies to prevent post-transplant opportunistic infections, including prophylaxis regimens and monitoring parameters.
- Formulate treatment plans for bacterial, viral, and fungal infections in solid-organ transplant recipients.
- Develop monitoring plans for patients receiving antimicrobials, complete with management of adverse effects and intolerances.

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Pre-transplant Serologic Testing Recommendations

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Pre-transplant serologic testing recommendations

Recipient Screening Recommendations

- HIV fourth generation screening test
- Cytomegalovirus (CMV) IgG antibody
- Hepatitis B surface antigen, core antibody, surface antibody
- Hepatitis C antibody*
- Epstein-Barr virus (EBV) antibody
- *Toxoplasma gondii* IgG antibody
- *Strongyloides* IgG antibody**
- *Trypanosoma cruzi* serology**
- *Coccidioides* serology**
- Syphilis (treponemal antibody testing or rapid plasma reagin)
- Tuberculosis (interferon gamma release assay [IGRA] or purified protein derivative [PPD])

Additional recommendations exist to assess for immunity against vaccine preventable diseases – reference “Best Practices in Primary Care of the Transplant Patient” lecture

*+Nucleic acid amplification test (NAT) if recipient on dialysis, **if recipient from endemic areas

Clin Transplant. 2019 Sep;33(9):e13548.

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Pre-transplant serologic testing recommendations

Donor Screening Recommendations

- HIV fourth generation screening test, NAT*
- Cytomegalovirus (CMV) IgG antibody
- Hepatitis B surface antigen, core antibody, NAT*
- Hepatitis C antibody, NAT
- Epstein-Barr virus (EBV) antibody
- West Nile virus serology or NAT***
- *Toxoplasma gondii* IgG antibody
- *Strongyloides* IgG antibody**
- *Trypanosoma cruzi* serology**
- *Coccidioides* serology**
- Syphilis (treponemal antibody testing or rapid plasma regain [RPR])
- Tuberculosis (IGRA or PPD)***

*Covid-19 testing for all deceased donors via PCR; lower respiratory testing required for all potential lung donors

*HIV and HBV NAT now required for all living and deceased donors

**if donor from endemic areas
***if living donor

Clin Transplant. 2019 Sep;33(9):e13548.

MMWR Recomm Rep. 2020 Jun 26;69(4):1-16.

https://www.mayast.org/sites/default/files/Donor%20Testing%20Document_07.07.21.pdf

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Recommendations for Recipients Based on Serologic Testing

Hepatitis B Serologic Testing Interpretation

Serology result	Interpretation
HBsAg – / Anti-HBc – / Anti-Hbs –	Susceptible to infection – recommend vaccination
HBsAg – / Anti-HBc + / Anti-Hbs +	Immune due to natural infection
HBsAg – / Anti-HBc – / Anti-Hbs +	Immune due to vaccination
HBsAg + / Anti-HBc + / Anti-HBc IgM + / Anti-Hbs –	Acute infection
HBsAg + / Anti-HBc + / Anti-HBc IgM - / Anti-Hbs –	Chronic infection
HBsAg – / Anti-HBc + / Anti-Hbs –	Unclear (resolved infection vs. false positive vs. low level or resolving infection)

Adapted from: <https://www.cdc.gov/hepatitis/hbv/pdfs/SerologicChartv8.pdf>

Clin Transplant. 2019 Sep;33(9):e13548.
Am J Transplant. 2015 May;15(5):1162-72.

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Recommendations for Recipients Based on Serologic Testing

- Hepatitis B Infected Liver Transplant Recipients
 - Require prophylaxis against HBV recurrence
 - Antiviral therapy +/- Hepatitis B immune globulin (HBIG)
 - HIV co-infection may require longer uses of HBIG
 - Antiviral therapy
 - Entecavir 0.5-1 mg daily
 - Tenofovir disoproxil fumarate (TDF) 300 mg daily
 - Tenofovir alafenamide (TAF) 25 mg daily
 - Obtain HBV DNA PCR and hepatitis B surface antigen every 3-6 months

Clinical Transplantation. 2019;33:e13514.
Am J Transplant. 2015 May;15(5):1162-72.

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Recommendations for Recipients Based on Serologic Testing

- Liver Transplant with Donor Hepatitis B Core Antibody Positive
 - Long term antiviral prophylaxis for recipient: indefinite vs. 1 year
- Non Liver Transplant with Donor Hepatitis B Core Antibody Positive
 - Antiviral prophylaxis may be considered in recipients without immunity
 - Not recommended for those with natural OR vaccine immunity
- Antiviral agents
 - Lamivudine 100 mg daily
 - Entecavir 0.5-1 mg daily
 - Tenofovir disoproxil fumarate 300 mg daily
 - Tenofovir alafenamide 25 mg daily

Clinical Transplantation. 2019;33:e13514.
Am J Transplant. 2015 May;15(5):1162-72.

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Recommendations for Recipients Based on Serologic Testing

Bacteria	Recommendations
Syphilis (<i>Treponema pallidum</i>)	<ul style="list-style-type: none"> • Transplant not contraindicated • Recommend Treponemal Ab test with confirmatory RPR • Recommend treatment in recipient if donor or recipient + and not previously treated <ul style="list-style-type: none"> • Penicillin benzathine G 2.4 million units IM x 1 – 3 doses • Doxycycline 100 mg PO BID x 14 days (if penicillin allergic)
Tuberculosis (<i>Mycobacterium tuberculosis</i>)	<ul style="list-style-type: none"> • Avoid transplant if donor thought to have active TB • Recommend workup for active TB in those with + PPD or IGRA • Treat recipients found to have latent TB (prefer isoniazid 5 mg/kg daily x 9 months, maximum 300 mg daily, +vitamin B6/pyridoxine)

Clin Transplant. 2019 Sep;33(9):e13548.
MMWR Recomm Rep. 2021 Jul 23;70(4):1-187.

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Recommendations for Recipients Based on Serologic Testing

Parasite	Recommendations
<i>Toxoplasma gondii</i>	<ul style="list-style-type: none"> Prophylaxis if D+/R-, and R+ (D+/R- highest risk) <ul style="list-style-type: none"> Particularly for heart transplantation → Trimethoprim-sulfamethoxazole, atovaquone +/- pyrimethamine & leucovorin
<i>Strongyloides stercoralis</i>	<ul style="list-style-type: none"> Recommend recipient treatment even if asymptomatic and IgG+ → Ivermectin 200 mcg/kg daily x 2 doses, consider repeating at 2 weeks Risk of <i>Strongyloides</i> hyperinfection syndrome
Chagas disease (<i>Trypanosoma cruzi</i>)	<ul style="list-style-type: none"> Recommend avoidance of heart transplantation if donor serology + Abdominal transplantation may be considered with consent

Clin Transplant. 2019 Sep;33(9):e13548.

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Recommendations for Recipients Based on Serologic Testing

Fungi	Recommendations
Coccidioidomycosis (<i>Coccidioides immitis</i>)	<ul style="list-style-type: none"> Prophylaxis recommended for all recipients living in endemic areas regardless of serostatus <ul style="list-style-type: none"> Fluconazole 200 mg daily x at least 6-12 months If seropositive recommend azole prophylaxis at least 6-12 months, consider lifelong <ul style="list-style-type: none"> Fluconazole 400 mg daily x lifelong if lung transplant Fluconazole 400 mg daily x 6-12 months, option for lifelong fluconazole 200 mg daily vs. discontinuation

Clin Transplant. 2019 Sep;33(9):e13548.
Clin Transplant. 2019 Sep;33(9):e13553.

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Pre-transplant serologic testing recommendations

2013 PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission

- Donors who have been exposed to HIV, HBV, HCV infection
 - 12 criteria (excluding drug use in the past 12 months)
- Additional testing required
 - HIV nucleic acid amplification testing (NAT)
 - HBV NAT
- Informed consent from recipient is required

NEW UPDATE 2020

Public Health Rep. 2013 Jul;128(4):247-343.
MMWR Recomm Rep. 2020 Jun 26;69(4):1-16.

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Pre-transplant serologic testing recommendations

The Guideline issued by the U.S. Public Health Service in 2020 that provides recommendations for organ transplantation related to Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) transmission

- Remove label of “Increased risk donor”
- Remove the following as donor risk criteria, now risk criteria within 30 days prior to procurement
 - Woman who has sex with a man who has had sex with another man
 - Newly diagnosed or treated syphilis, gonorrhea, chlamydia, or genital ulcers
 - Hemodialysis
 - Hemodiluted blood specimen used for donor HIV, HBV, and HCV testing
 - Child (aged ≤ 18 months) born to a mother **at increased risk** for HIV, HBV, or HCV infection
 - Child breastfed by a mother **at increased risk** for HIV infection

Public Health Rep. 2013 Jul;128(4):247-343.
MMWR Recomm Rep. 2020 Jun 26;69(4):1-16.

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Pre-transplant serologic testing recommendations

- HBV and HIV NAT testing now recommended for all living and deceased donors
 - Deceased donor testing must be collected within 96 hours of procurement
- Remove requirement to obtain specific informed consent
 - Require hospitals must inform recipients when the donor has any risk criteria
- Recommend universal post-transplant testing for ALL recipients
 - HIV, HBV, HCV NAT at 4-6 weeks post-transplant
 - HBV NAT testing at 11-13 months post-transplant for liver transplant recipients
- All candidates should receive hepatitis B vaccination

*Public Health Rep. 2013 Jul;128(4):247-343.
MMWR Recomm Rep. 2020 Jun 26;69(4):1-16.*

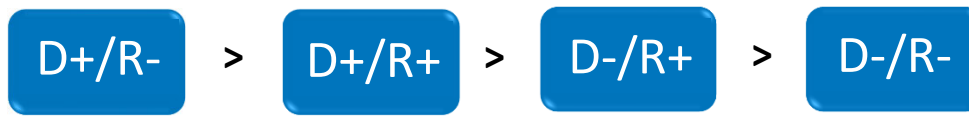
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Post-transplant Prophylaxis Against Opportunistic Infections

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Cytomegalovirus: Risk Factors

- Immunosuppression depletes the number and functioning of T cells → increases the risk for CMV
- Rejection is also a risk factor for CMV
- Lung and small bowel transplant recipients are at the highest risk



Transpl Infect Dis. 2020;e13483.
Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.

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Post-transplant CMV Prophylaxis

- CMV Universal Prophylaxis vs. Pre-emptive therapy
 - Pre-emptive monitoring
 - R+ → Pre-emptive therapy can be used in kidney, liver, pancreas, and heart transplants
 - D+/R- → Pre-emptive therapy can be used in liver, pancreas and kidney transplants with close follow-up
 - Not recommended for lung transplant and intestinal transplant recipients
 - Less preferred in heart transplant recipients
 - Suggest pre-emptive monitoring via CMV PCR once weekly x 12 weeks post-transplant
 - Optimal threshold for starting therapy is still unknown
 - Data more limited, difficult to coordinate

Ann Intern Med. 2005;143:870-880.
Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.

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Post-transplant CMV Prophylaxis

- First line for CMV prophylaxis (D+/R-, D+/R+, D-/R+):
 - Valganciclovir 900 mg daily, dose adjusted for renal dysfunction
 - Low dose valganciclovir not recommended
 - Caution for post-prophylaxis late-onset CMV disease
- First line for HSV prophylaxis (D-/R-):
 - Acyclovir 400-800 mg BID
 - Valacyclovir 500 mg BID
 - Famciclovir 500 mg BID

Clin Transplant. 2019 Sep;33(9):e13512.
Clinical Transplantation. 2019;e13526.
Transplantation. 2018 Jun;102(6):900-931.
Transpl Infect Dis. 2015;17:163-173.

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Post-transplant CMV Prophylaxis

Organ	Serostatus	Duration
Kidney	D+/R-	6 months
	R+	3 months
Kidney/pancreas, Liver	D+/R-	3-6 months
	R+	3 months
Heart	D+/R-	3-6 months
	R+	3 months
Lung	D+/R-	6-12 months
	R+	6-12 months
Intestinal	D+/R-	6 months (minimum)
	R+	3-6 months

Adapted from: Transplantation. 2018 Jun;102(6):900-931.
Clin Transplant. 2019 Sep;33(9):e13512.

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Post-transplant CMV Prophylaxis

- Alternate options for CMV prophylaxis:
 - Other antivirals such as foscarnet and cidofovir not recommended
 - Letermovir:
 - Phase III trial ongoing comparing to valganciclovir in D+/R- renal transplant recipients
 - Single center matched cohort study (n=31)
 - Similar rates of CMV breakthrough
 - Improved leukopenia with letermovir
 - Caution for interaction with tacrolimus, required dose reductions of ~40-50%
 - Thoracic transplant recipients (n=9)
 - 3/8 (37.5%) of patients developed CMV DNAemia while on letermovir prophylaxis
 - Minor side effects noted
 - Caution for breakthrough while on prophylaxis

Clin Transplant. 2019 Sep;33(9):e13512.
Transpl Infect Dis. 2021 Aug;23(4):e13570.
Transpl Infect Dis. 2021 Jun;23(3):e13515.
Transpl Infect Dis. 2019 Dec;21(6):e13166.

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Question 1: Which of the following agents is most appropriate for CMV prophylaxis in a CMV donor positive/recipient negative transplant?

- a) Valganciclovir
- b) Cidofovir
- c) Ganciclovir
- d) High-dose valacyclovir

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Question 1: Which of the following agents is most appropriate for CMV prophylaxis in a CMV donor positive/recipient negative transplant?

- a) Valganciclovir
- b) Cidofovir
- c) Ganciclovir
- d) High-dose valacyclovir

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Post-transplant Covid-19 Prophylaxis

- Covid-19 mRNA vaccination (see Best Practices in Primary Care of the Transplant Patient” lecture)
- Tixagevimab/cilgavimab (EVUSHELD™)
 - SARS-CoV-2 spike protein-directed attachment inhibitor, IgG1_k monoclonal antibody
 - EUA authorization for pre-exposure prophylaxis against SARS-CoV-2 with no recent exposure
 - Moderate-severe immune compromise OR
 - Severe adverse reaction/allergy to Covid-19 vaccine
 - Dosing: 300 mg tixagevimab / 300 mg cilgavimab IM as 2 separate consecutive injections
 - If initially 150 mg/150 mg and within 3 months: re-dose with 150/150 mg
 - If initially 150 mg/150 mg and greater than 3 months: re-dose with 300/300 mg
 - Frequency of re-dosing???

<https://www.fda.gov/media/154701/download>
<https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html>

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Post-transplant Covid-19 Prophylaxis

- Tixagevimab/cilgavimab (EVUSHELD™)
 - Efficacy: **PROVENT** trial
 - At least 60 years old or co-morbidity or increased risk of SARS-CoV-2, unvaccinated
 - Incidence of PCR-positive, symptomatic Covid-19 → Tixa/cilga 0.2% vs. placebo 1.0%
 - 77% (46, 90) relative risk reduction
 - Mean follow-up = 83 days
 - Safety:
 - Most common adverse events: headache, fatigue, cough
 - Any cardiac serious adverse event: 0.6% tixa/cilga vs. 0.2% placebo in PROVENT trial
 - Included myocardial infarctions, cardiac failure, arrhythmia
 - All patients with events had prior cardiac risk factors/disease

<https://www.fda.gov/media/154701/download>
<https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html>

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Peri-operative Antibacterial Prophylaxis

Organ type	IDSA/ASHP/SHEA	AST-ID COP	Duration
Kidney	Cefazolin	Cefazolin PCN allergy: Vancomycin or clindamycin + gentamicin	24 hours
Pancreas, kidney-pancreas	Cefazolin	Ampicillin-sulbactam + fluconazole or echinocandin PCN allergy: Vancomycin or clindamycin + gentamicin + fluconazole	24-48 hours Antifungal dependent on risk
Liver	Piperacillin-tazobactam OR third-generation cephalosporin + ampicillin	Ampicillin-sulbactam + fluconazole or echinocandin PCN allergy: Vancomycin + ciprofloxacin	24-48 hours Antifungal dependent on risk

PCN = penicillin

Adapted from: *Clin Transplant*. 2019 Sep;33(9):e13589.
 Adapted from: *Am J Health Syst Pharm*. 2013 Feb 1;70(3):195-283.

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Peri-operative Antibacterial Prophylaxis

Organ type	IDSA/ASHP/SHEA	AST-ID COP	Duration
Small bowel	N/A	Vancomycin + [piperacillin-tazobactam or cefepime/metronidazole] + [fluconazole or echinocandin] PCN allergy: Vancomycin + levofloxacin + metronidazole	72 hours – 7 days
Heart	Cefazolin	Vancomycin + ceftriaxone or cefepime (with prior VAD) Vancomycin + cefazolin (without prior VAD) PCN allergy: Vancomycin + levofloxacin	24-48 hours
Lung	Cefazolin	Vancomycin + anti-pseudomonal β -lactam PCN allergy: Vancomycin + levofloxacin	48-72 hours

Adapted from: *Clin Transplant*. 2019 Sep;33(9):e13589.
 Adapted from: *Am J Health Syst Pharm*. 2013 Feb 1;70(3):195-283.

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Post-transplant Antibacterial Prophylaxis

- Regimens vary widely across transplant centers due to lack of data
- Durations also vary widely – typically 24-72 hours, up to 7 days
- **Lung transplant:**
 - Modify based on donor pathogens isolated
 - Patients with cystic fibrosis (CF) should receive prophylaxis targeted against prior colonizing pathogens (suggest 7 day duration)
- **Delayed chest closure**
 - Significant infectious risk factor in heart and lung transplant recipients
 - Expert opinion commonly recommends antibacterial coverage against methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and fungi until chest is closed
 - Suggest extending duration of surgical prophylaxis for heart or lung transplant until chest closure

Clin Transplant. 2019 Sep;33(9):e13589.
Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283.
Am J Transplant. 2009 Dec;9 Suppl 4:S173-9.

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Post-transplant Fungal Prophylaxis

- **Candida prophylaxis**
 - **Small bowel transplant:** Fluconazole or echinocandin recommended for 4 weeks, or until anastomosis has healed (with no rejection)
 - **Liver transplant:** Fluconazole recommended for those at risk
 - Re-operation, re-transplantation, renal failure, choledochojejunostomy, *Candida* colonization, prolonged procedure time, >40 units blood products
 - Duration 2-4 weeks
 - **Pancreas, pancreas/kidney transplant:** Fluconazole recommended for those at risk
 - Enteric drainage, vascular thrombosis, post-perfusion pancreatitis
 - Duration dependent on risk factor mitigation
 - **Renal & heart transplant:** Not recommended routinely

Clin Transplant. 2019 Sep;33(9):e13623.
Am J Transplant. 2015 Jan;15(1):180-9.
Am J Transplant. 2014 Dec;14(12):2765-76.

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Post-transplant Fungal Prophylaxis

- **Mold prophylaxis**
 - **Lung transplant:**
 - Recipients at an increased risk of *Aspergillus* due to inhalation of pathogens
 - Universal vs. targeted vs. pre-emptive strategies exist
 - Duration: 4-6 months, 3-4 months for pre-emptive strategy
 - Regimens vary across centers
 - Voriconazole/itraconazole
 - » Can be used for universal prophylaxis or pre-emptive therapy
 - » Posaconazole/isavuconazole can be alternatives
 - Inhaled amphotericin B/lipid amphotericin
 - » Can be used for universal or targeted prophylaxis
 - » Not recommended for pre-emptive therapy

Clin Transplant. 2019 Sep;33(9):e13623.
Clin Transplant. 2019:e13544.

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Post-transplant Fungal Prophylaxis

- Mold prophylaxis
 - Heart transplant:
 - Targeted *Aspergillus* prophylaxis indicated in the following scenarios:
 - *Aspergillus* isolated in respiratory cultures
 - Presence of *Aspergillus* spores isolated in the ICU
 - Thoracic re-operation
 - CMV disease
 - Post-transplant hemodialysis
 - An episode of invasive aspergillosis in any patient in the heart transplant program 2 months before or after transplant
 - Voriconazole, itraconazole x 50-150 days
 - Echinocandin x 120 days

Clin Transplant. 2019 Sep;33(9):e13623.
Clin Transplant. 2019;e13544.

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Post-transplant Fungal Prophylaxis

- Mold prophylaxis
 - Liver transplant:
 - Targeted *Aspergillus* prophylaxis indicated in those with certain risk factors
 - Re-transplantation
 - Renal replacement therapy within 7 days of transplantation
 - Re-operation involving thoracic or intra-abdominal cavity
 - Voriconazole or echinocandin x 14-21 days

Clin Transplant. 2019 Sep;33(9):e13623.
Clin Transplant. 2019 Sep;33(9):e13544.

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Post-transplant Fungal Prophylaxis

- *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis
 - Trimethoprim/sulfamethoxazole
 - Preferred regimen
 - Single strength tablet QD or three times weekly (400/80 mg) or double strength tablet three times weekly (800/160 mg)
 - Dapsone 50-100 mg PO QD
 - Atovaquone 1500 mg PO QD with food
 - Aerosolized pentamidine 300 mg nebulized monthly
 - Clindamycin 300 mg PO QD + pyrimethamine 15 mg PO QD
- *If regimens other than trimethoprim/sulfamethoxazole are used, urinary tract infection prophylaxis should be added for renal transplant recipients
- *Recommended for at least 6-12 months post-transplant

Clinical Transplantation, 2019;33:e13587.

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Question 2: Which of the following is true?

- a) Lung transplant recipients typically require anti-mold prophylaxis post-operatively
- b) Renal transplant recipients typically require prophylaxis against *Candida* spp. infections
- c) Liver transplant recipients should only receive anti-bacterial peri-operative prophylaxis
- d) Post-operative prophylaxis should never be tailored to cultures isolated in the organ donor

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Question 2: Which of the following is true?

- a) Lung transplant recipients typically require anti-mold prophylaxis post-operatively
- b) Renal transplant recipients typically require prophylaxis against *Candida* spp. infections
- c) Liver transplant recipients should only receive anti-bacterial peri-operative prophylaxis
- d) Post-operative prophylaxis should never be tailored to cultures isolated in the organ donor

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Post-transplant Infectious Considerations

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Infections Post-Transplantation

- Epidemiology of Infections Post-Transplant
 - Majority of infections are bacterial in nature
 - Pathogens and source vary based on organ type
 - Herpesviruses are most common type of viral infection
 - *Candida* sp. infections most common type of fungal infection
 - Opportunistic infections (OI) remain rare, but are a possibility

Clin Infect Dis. 2020 Jan 9. pii: ciz1113.
N Engl J Med. 2007 Dec 20;357(25):2601-14.

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Infections Post-Transplantation

- Timing of infections
 - **Month 0-1:**
 - Nosocomial bacteria or *Candida* spp.
 - **Month 1-6:**
 - **With PJP and antiviral prophylaxis:** BK virus, *C. difficile*, HCV, adenovirus, influenza, *Cryptococcus*, *M. tuberculosis*
 - **Without standard prophylaxis:** PJP, herpesviruses, HBV, *Listeria*, *T. gondii*, *Nocardia*, *T. cruzi*, *Strongyloides*
 - **6 months +:** Dependent on immune status of patients
 - Community acquired pneumonia, urinary tract infections
 - OI's are rare in patients with uncomplicated course
 - Patients with rejection are at an increased risk to develop OI's: viral infections, PJP, *Cryptococcus*, *Nocardia* spp.

Clin Infect Dis. 2020 Jan 9. pii: ciz1113.
N Engl J Med. 2007 Dec 20;357(25):2601-14.

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Question 3: Which of the following statements is true?

- a) The most common infections among solid-organ transplant recipients are fungal due to immunosuppression
- b) Patients in the American Midwest are most at risk for *Coccidioides* infection
- c) Patients who test positive for *Strongyloides* IgG should only be treated if they are symptomatic
- d) All potential transplant recipients should be screened for HIV and syphilis

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Question 3: Which of the following statements is true?

- a) The most common infections among solid-organ transplant recipients are fungal due to immunosuppression
- b) Patients in the American Midwest are most at risk for *Coccidioides* infection
- c) Patients who test positive for *Strongyloides* IgG should only be treated if they are symptomatic
- d) **All potential transplant recipients should be screened for HIV and syphilis**

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Donor infections at the time of transplant

- Donors with bacteremia
 - Organs can typically be utilized
 - Donor should receive active antibiotic therapy for 24-48 hours
 - Recipient should be treated for 7-14 days with antibiotics targeted against the pathogen
- Donors with meningitis
 - Organs can typically be utilized; dependent on the causative organism
 - Donor should receive active antibiotic therapy for 24-48 hours
 - Recipient should be treated for 7-14 days with antibiotics targeted against the pathogen
 - Encephalitis typically should be avoided

*Clin Transplant. 2019 Sep;33(9):e13547.
J Heart Lung Transplant. 2010;29:914-56.*

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Donor infections at the time of transplant

- Suggest treating recipients for donors with infections and/or positive cultures in the transplanted organ
 - Donors with respiratory infections in lung transplant
 - Perioperative prophylaxis often continued until donor cultures result
 - Donors with urinary tract infections in kidney transplant
 - Donors with perfusion fluid cultures positive in kidney transplant
- Duration of therapy
 - 7-14 days is typical, dependent on virulence of organisms
 - Ex) *Staphylococcus aureus* vs. coagulase-negative *Staphylococci* (CONS)

Clin Transplant. 2019 Sep;33(9):e13547.

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HIV in Solid-Organ Transplant

- Becoming more common to offer transplants to recipients living with HIV
 - Kidney and liver most common currently
- Outcomes similar to non-HIV patients
- Data limited with other organs
- May be associated with increase in rejection and/or infection
- Recommended that recipient have:
 - Undetectable HIV viral load
 - CD4 > 200 (or >100 if no prior OI's)
- Optimal immunosuppression
 - Recommend induction given high rejection rates
 - Optimal maintenance regimen unclear

*Clinical Transplantation. 2019;e13499.
J Heart Lung Transplant. 2019;38:1296-1305.*

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HIV in Solid-Organ Transplant

1. Nucleoside reverse transcriptase inhibitors (NRTIs):

- Abacavir, lamivudine, emtricitabine, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF)

Drug-drug Interactions

- Tenofovir-DF may minimally increase levels of cyclosporine via mild P-gp inhibition

Relevant adverse effects

- Tenofovir can cause concomitant renal dysfunction (less with TAF)

*Clinical Transplantation. 2019;e13499.
<https://www.hiv-druginteractions.org/checker>
<http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>*

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HIV in Solid-Organ Transplant

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- Efavirenz, etravirine, rilpivirine, doravirine, delavirdine

Drug-drug interactions

- Doravirine may decrease tacrolimus and sirolimus levels due to CYP3A4 induction
- Efavirenz may decrease CNI and mTORi levels due to CYP3A4 induction (moderate)
- Etravirine and nevirapine may decrease CNI and mTORi levels due to CYP3A4 induction (minor)
- Delavirdine may increase CNI and mTORi levels due to CYP3A4 inhibition (minor)

Relevant adverse effects

- Efavirenz can increase lipid function tests

Clinical Transplantation. 2019;e13499.
<https://www.hiv-druginteractions.org/checker>
<http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

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HIV in Solid-Organ Transplant

3. Protease inhibitors (PI)

- Darunavir, atazanavir, lopinavir, fosamprenavir
 - Combined with either ritonavir (PI) or cobicistat (pharmacokinetic booster)

Drug-drug interactions

- All will severely increase mTORi, CNI, steroid levels via CYP3A4 inhibition – avoid if possible
 - Suggest cyclosporine 25-50 mg daily, tacrolimus 0.5-1 mg once weekly, sirolimus 1 mg once-twice weekly

Relevant adverse effects

- May increase lipid function tests
- May worsen diabetes/glucose management
- Cobicistat may increase SCr (without change in GFR)

Clinical Transplantation. 2019;e13499.
<https://www.hiv-druginteractions.org/checker>
<http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

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HIV in Solid-Organ Transplant

4. Integrase inhibitors

- Raltegravir, dolutegravir, bictegravir, elvitegravir, cabotegravir

Drug-drug interactions

- Cyclosporine may increase bictegravir concentrations – unlikely to be clinically significant

Relevant adverse effects

- Dolutegravir can increase SCr (without change in GFR)

University of Liverpool Drug-Drug interaction checker:
<https://www.hiv-druginteractions.org/checker>

Clinical Transplantation. 2019;e13499.
<https://www.hiv-druginteractions.org/checker>
<http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

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HIV in Solid-Organ Transplant

5. Miscellaneous

- Maraviroc, enfuvirtide, ibalizumab

Drug-drug interactions

- Cyclosporine may increase maraviroc concentrations via CYP3A4 and OATP inhibition

*Be aware of many new co-formulations of HIV medications and one pill once daily regimens

- Bictegravir/emtricitabine/tenofovir alafenamide
- Darunavir/cobicistat/emtricitabine/tenofovir alafenamide
- Dolutegravir/abacavir/lamivudine
- Dolutegravir/rilpivirine
- Dolutegravir/lamivudine

Clinical Transplantation. 2019;e13499.
<https://www.hiv-druginteractions.org/checker>
<http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

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HCV in Solid-Organ Transplant

- Associated with worse outcomes prior to use of direct-acting antivirals
- Treatment of recipient's HCV can take place pre- or post-transplant
 - HCV+ patients with MELD scores > 27 often treated POST-transplant
 - Unlikely to avoid transplant
 - Can receive HCV NAT + organs
 - Caution for HBV reactivation and graft dysfunction after HCV treatment post-transplant

*Clinical Transplantation. 2019;e13499.
Clinical Transplantation. 2019;33:e13514.*

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HCV in Solid-Organ Transplant

- HCV Antibody Positive/HCV NAT negative AND HCV Antibody Positive/HCV NAT positive donor organs
 - Increasingly being utilized for use in HCV Antibody Negative/HCV NAT negative recipients
 - Must have an established plan to treat recipient post-transplant
- Liver transplant recipients
 - Treatment can be pre-emptive or early post-transplant after detection of HCV viremia
 - Pan-genotypic regimens such as glecaprevir/pibrentasvir or sofosbuvir/velpatasvir commonly utilized x 12 weeks
- Non-liver transplant recipients
 - Shorter durations with early initiation may be used
 - AASLD/IDSA recommends glecaprevir/pibrentasvir x 8 weeks or sofosbuvir/velpatasvir x 12 weeks
 - Sofosbuvir/velpatasvir x 4 weeks in heart or lung transplant recipients has also been studied

*Clinical Transplantation. 2019;e13499.
Clinical Transplantation. 2019;33:e13514.
Hepatology. 2020;71:686-721.
N Engl J Med. 2019 Apr 25;380(17):1606-1617.
J Am Soc Nephrol. 2020 Nov;31(11):2678-2687.*

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HCV in Solid-Organ Transplant

- Drug-drug interactions
 1. **Ledipasvir/sofosbuvir**
 - Minimal drug-drug interactions with immunosuppressants
 - Potential to increase mTORi levels due to mild P-gp inhibition
 2. **Sofosbuvir/velpatasvir**
 - Minimal drug-drug interactions with immunosuppressants
 - Potential to increase mTORi levels due to mild P-gp inhibition
 3. **Daclatasvir**
 - Minimal drug-drug interactions with immunosuppressants
 - Potential to increase mTORi levels due to mild P-gp inhibition

Clinical Transplantation. 2019;33:e13514.
<https://www.hep-druginteractions.org/checker>

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HCV in Solid-Organ Transplant

- Drug-drug interactions
 4. **Ombitasvir/paritaprevir/ritonavir**
 - Increases tacrolimus levels due to CYP3A4 inhibition – contraindicated
 - Increases cyclosporine levels due to CYP3A4 inhibition – administer 1/5th total daily dose of cyclosporine once daily
 - Increases mTORi levels - contraindicated
 5. **Elbasvir/grazoprevir**
 - Increases tacrolimus levels due to weak inhibition of CYP3A4
 - Cyclosporine increases grazoprevir levels due to inhibition of OATP1B – contraindicated
 - May increase levels of mTORi
 6. **Glecaprevir/pibrentasvir**
 - Increases tacrolimus levels due to inhibition of CYP3A4/P-gp
 - Cyclosporine increases glecaprevir levels due to inhibition of OATP1B
 - **Not recommended in patients requiring stable cyclosporine doses >100 mg/day**
 - May increase levels of mTORi

Clinical Transplantation. 2019;33:e13514.
<https://www.hep-druginteractions.org/checker>

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Question 4: Which of the following pairs of drugs are most likely to interact?

- a) Darunavir/ritonavir/emtricitabine/tenofovir disoproxil AND tacrolimus
- b) Abacavir/lamivudine/dolutegravir AND sirolimus
- c) Bictegravir/emtricitabine/tenofovir alafenamide AND cyclosporine
- d) Ledipasvir/sofosbuvir AND mycophenolate mofetil

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Question 4: Which of the following pairs of drugs are most likely to interact?

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- d) Ledipasvir/sofosbuvir AND mycophenolate mofetil

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Management of Bacterial Infections in Solid-Organ Transplant Recipients



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Urinary Tract Infections (UTIs)

- Most common infection type in renal transplant recipients
- Occurs most often in first 3-6 months post-transplant
- Transplant specific risk factors:
 - Ureteral stents, urological abnormalities, rejection, deceased donor, duration of hemodialysis, antithymocyte globulin (ATG) induction, UTIs prior to transplant
- Common microorganisms:
 - *E. coli* >> Enterobacterales, Enterococci, *Pseudomonas* sp, *S. saprophyticus*
- Treatment of asymptomatic bacteriuria not recommended when > 1 month post-transplant

Clin Transplant. 2019 Sep;33(9):e13507.
Clin Infect Dis. 2019 May 2;68(10):1611-1615.

56

Urinary Tract Infections (UTIs)

- Simple cystitis
 - Oral therapy
 - 3rd generation cephalosporin, amoxicillin-clavulanate, ciprofloxacin/levofloxacin
 - TMP-SMX often resistant if on prophylaxis
 - Fosfomycin for multi-drug resistant *E. coli*
 - Nitrofurantoin if CrCl > 40 mL/min
 - 5-10 days of therapy
- Complicated UTI or pyelonephritis
 - Mild: Ceftriaxone, ampicillin-sulbactam, fluoroquinolone
 - Severe: Cefepime, piperacillin-tazobactam, carbapenem
 - 14-21 days of therapy

Clin Transplant. 2019 Sep;33(9):e13507.
Clin Infect Dis. 2011 Mar 1;52(5):e103-20.
Clin Infect Dis. 2019 May 2;68(10):1611-1615.

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Bacterial Pneumonia

- Special consideration in lung transplant recipients for donor derived pathogens and prior colonization
- Empiric therapy should be based on local antibiogram and risk factors for multidrug-resistant organisms (MDROs)
 - Common community-acquired pathogens:
 - *S. pneumoniae*, *H. influenzae*, *M. cattarhalis*
 - Common healthcare-associated pathogens:
 - *P. aeruginosa*, *S. aureus*, Enterobacterales, *A. baumannii*, *S. maltophilia*

Clin Transplant. 2019 Sep;33(9):e13545.
Clin Infect Dis. 2016 Sep 1;63(5):e61-e111.

58

Intra-abdominal Infections

- Empiric coverage should be tailored to the specific site of infection, local antibiogram, patient risk-factors for MDROs
- *Enterococcus* coverage recommended; vancomycin-resistant *Enterococci* (VRE) is common in liver transplant recipients
- Empiric antifungal therapy should be considered in those with risk factors or clinical instability
- Example empiric regimens
 - Piperacillin-tazobactam
 - Vancomycin, cefepime, metronidazole
 - Carbapenem
- Duration highly variable and case-by-case

Clin Transplant. 2019 Sep;33(9):e13595.

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Intra-abdominal infections: *C. difficile*

- Preferred regimens for CDI treatment:
 - 1. Fidaxomicin 200 mg PO BID x 10 days (2021 update)
 - More narrow spectrum compared to vancomycin
 - Fewer recurrence rates following initial CDI episode
 - May be beneficial to elderly population, immunocompromised
 - Can be quite costly
 - 2. Vancomycin 125 mg PO QID x 10-14 days
 - Still an acceptable alternative to fidaxomicin
 - Similar initial clinical response
- Fulminant: vancomycin 500 mg PO QID + IV metronidazole + vancomycin enema

Clin Infect Dis. 2021 Sep 7;73(5):755-757.
Clin Transplant. 2019 Sep;33(9):e13564.

60

Surgical Site Infections

- Occur within 30 days of the procedure (90 days if prosthetic implant is utilized)
- Incidence and common pathogens vary based on organ type
 - Highest rates overall in small bowel, liver, and pancreas recipients
 - Gram-positive organisms predominate in heart, kidney, and pancreas-kidney
 - Gram-negative organisms predominate in liver, small bowel, and lung
- Empiric regimens should be based on type of transplant, patient risk factors for MDROs, and normal flora
 - Recommend coverage for MSSA and MRSA (depending on risk factors)
 - Recommend broad gram-negative coverage depending on patient risk factors and type of transplant

Clin Transplant. 2019 Sep;33(9):e13589.

61

Ventricular-assist Device Infections

- VAD-specific infections
 - Involve the device
 - Ex) Pocket infections, driveline infections, pump infections
- VAD-related infections
 - Complication of the procedure or a VAD-specific infection
 - Ex) Endocarditis, bloodstream infections, mediastinitis
- Pathogens
 - Varies depending on type of VAD infection
 - Most common: *S. aureus*, CONS, *P. aeruginosa*, Enterobacterales, *Candida sp.*

*Clin Transplant. 2019 Sep;33(9):e13552.
J Heart Lung Transplant. 2017 Oct;36(10):1137-1153.*

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Ventricular-assist Device Infections

- VAD specific infections
 - Superficial driveline infections commonly treated with oral antibiotics, all other types typically IV
 - Empiric therapy typically includes MRSA and *Pseudomonas* sp. coverage
 - Typical duration length: Pump/cannula > Pump pocket > deep driveline > superficial driveline
 - 2 weeks – 8 weeks depending on infection type
- VAD-related infections
 - Empiric therapy typically includes MRSA and *Pseudomonas* sp. coverage
 - Bloodstream infections typically at least 2 week duration
 - Endocarditis, mediastinitis typically prolonged courses
 - Oral suppressive antibiotic therapy is common

Clin Transplant. 2019 Sep;33(9):e13552.
J Heart Lung Transplant. 2017 Oct;36(10):1137-1153.

63

Post-transplant *Nocardia* infections

- Gram-positive bacteria, filamentous branching rods
 - *N. nova*, *N. abscessus*, *N. farcinica*, *N. cyriacigeorgica* most common
- Inhalation, ingestion, injury are points of entry
 - Respiratory infection most common
 - Predilection for CNS infection
- Prevalence ~3.5% in lung transplant, 2.5% in heart transplant, and less in other organs
- Risk mainly related to deficiencies in T-cell function

Clin Transplant. 2019 Sep;33(9):e13509.

64

Management of Post-transplant *Nocardia* infections

- Antibiotics with activity:

- Trimethoprim-sulfamethoxazole
- Imipenem-cilastatin
- Amikacin
- Minocycline
- Ceftriaxone
- Ciprofloxacin, moxifloxacin
- Amoxicillin-clavulanate
- Linezolid
- Azithromycin, clarithromycin
- Tigecycline

Suggested Empiric Treatment

- Pulmonary disease
 - Trimethoprim-sulfamethoxazole (TMP-SMX)*
 - Imipenem + TMP-SMX or amikacin*
- CNS disease
 - Imipenem + TMP-SMX or amikacin*
- Disseminated
 - Imipenem + TMP-SMX or amikacin*

*Requires renal dose adjustment

Clin Transplant. 2019 Sep;33(9):e13509.

65

Management of Post-transplant *Nocardia* infections

- Doses of antimicrobials should be maximized, especially in CNS/disseminated disease
 - Ex) Ceftriaxone 2g IV Q12H, minocycline 200 mg PO/IV Q12H
- Susceptibilities vary widely depending on species of *Nocardia*
 - Tailor therapy based on species identification
- Typical duration of therapy between 6-12 months
 - Can consider the use of secondary prophylaxis

Clin Transplant. 2019 Sep;33(9):e13509.

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Question 5: Which of the following is a reasonable empiric treatment choice for a severe *Nocardia* spp. Infection?

- a) Imipenem-cilastatin 500 mg Q6h + metronidazole 500 mg Q8h
- b) Amikacin 15 mg/kg/day
- c) Ceftriaxone 2g Q12h + gentamicin 5 mg/kg/day
- d) Trimethoprim-sulfamethoxazole 15 mg/kg/day trimethoprim + imipenem-cilastatin 500 mg Q6h

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Question 5: Which of the following is a reasonable empiric treatment choice for a severe *Nocardia* spp. Infection?

- a) Imipenem-cilastatin 500 mg Q6h + metronidazole 500 mg Q8h
- b) Amikacin 15 mg/kg/day
- c) Ceftriaxone 2g Q12h + gentamicin 5 mg/kg/day
- d) **Trimethoprim-sulfamethoxazole 15 mg/kg/day**
trimethoprim + imipenem-cilastatin 500 mg Q6h

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Post-transplant *Mycobacterium tuberculosis*

- Prevalence in SOT ranges from 1.2% to 12% depending on area
 - Lung transplant highest risk
- Reactivation vs. donor transmission
- **Latent TB treatment**
 - Isoniazid x 9 months
 - Rifampin x 4 months
 - Isoniazid and rifapentine weekly x 12 weeks
- **Active TB treatment**
 - RIPE therapy first line
 - Duration ranges from at least 6 to 12 months dependent on site of infection

Clin Transplant. 2019 Sep;33(9):e13513.
Clin Infect Dis. 2017 Jan 15;64(2):111-115.

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Management of Post-transplant *Mycobacterium tuberculosis*

- | | |
|--|---|
| <ul style="list-style-type: none"> - RIPE Therapy <ul style="list-style-type: none"> - Rifampin 10 mg/kg daily (max 600 mg) - Isoniazid 5 mg/kg daily (max 300 mg) - Pyrazinamide <ul style="list-style-type: none"> - 40-55 kg: 1000 mg - 56-75 kg: 1500 mg - 76-90 kg: 2000 mg - Ethambutol 15-20 mg/kg daily (max 1600 mg) | <ul style="list-style-type: none"> - Alternatives to rifampin: <ul style="list-style-type: none"> - Rifabutin 5 mg/kg daily (max 300 mg) - Rifapentine 10-20 mg/kg once weekly |
|--|---|

In transplant recipients: rifabutin is typically substituted for rifampin due to drug-drug interactions and less CYP 3A4 induction compared to rifampin

Clin Transplant. 2019 Sep;33(9):e13513.
Clin Infect Dis. 2017 Jan 15;64(2):111-115.

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Management of Post-transplant *Mycobacterium tuberculosis*

Rifampin/rifabutin/rifapentine

- Discoloration of bodily fluids, hepatotoxicity, rash, interstitial nephritis, cytopenias
- Rifabutin similar, also uveitis

Isoniazid

- Hepatotoxicity, neurotoxicity, cytopenias
- Administer with pyridoxine (vitamin B6) 25-50 mg daily

Pyrazinamide

- Hepatotoxicity, interstitial nephritis, cytopenias

Ethambutol

- Hepatotoxicity, neurotoxicity, vision loss, optic neuritis, cytopenias

Clin Transplant. 2019 Sep;33(9):e13513.
Clin Infect Dis. 2017 Jan 15;64(2):111-115.

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Management of Post-transplant *Mycobacterium tuberculosis*

Drug-drug interactions

Rifampin/rifabutin/rifapentine

- Less drug-drug-interactions with rifabutin, rifapentine compared to rifampin
- Will **severely** decrease CNI, mTORi levels via CYP3A4 induction
- Will **moderately** decrease prednisone levels via CYP3A4 induction
- Will **mildly** decrease MMF and MPA levels due to induction of UGT/OATP
 - Recommend 2-fold dose increase of CNI dose initially, close monitoring of levels

Isoniazid, Pyrazinamide, Ethambutol

- Little to no interactions expected

Increased risk of rejection in
transplant patients due to rapid
metabolism of immunosuppression

Clin Transplant. 2019 Sep;33(9):e13513.
Clin Infect Dis. 2017 Jan 15;64(2):111-115.
Clin Transplant. 2019;33:e13510.

72

Post-transplant Non-tuberculous *Mycobacteria* (NTM)

- Incidence varies from 0.16%-8% among SOT recipients
 - Highest incidence occurs in lung transplant recipients
 - CF patients predisposed
 - Acute cellular rejection, NTM pre-transplant, African-American race, high-risk CMV mismatch, rabbit ATG are also risk factors
- Donor derived infections are rare but a possibility
- Mean time to infection is 48 months, with a wide range of variability
- Most common site of infection in lung transplant recipients is pulmonary
- Non-lung recipient infections commonly consist of disseminated disease, including cutaneous lesions and visceral organs
- Antimicrobial therapy varies according to species

Clin Transplant. 2019;33:e13588.

73

Post-transplant Non-tuberculous *Mycobacteria* (NTM)

- Treatment recommendations based on limited data
- Combination therapy including 2-3 drugs is common, duration is months to years

Species	Recommended treatment regimen
<i>M. avium complex</i>	Azithromycin, rifabutin, ethambutol
<i>M. kansasii</i>	Rifabutin, ethambutol, isoniazid OR azithromycin
<i>M. marinum</i>	Azithromycin, ethambutol +/- rifabutin
<i>M. haemophilum</i>	Azithromycin, rifabutin, ciprofloxacin
<i>M. xenopi</i>	Azithromycin OR moxifloxacin, rifabutin, ethambutol +/- isoniazid or other unused agent

Clin Transplant. 2019;33:e13588.
Clin Infect Dis. 2020;71:905-13.

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Post-transplant Non-tuberculous *Mycobacteria* (NTM)

Species	Recommended treatment regimen
<i>M. abscessus</i>	Azithromycin + two of: amikacin, imipenem, tigecycline, ceftazidime
<i>M. chelonae</i>	Azithromycin + one of: amikacin, tobramycin, linezolid, tigecycline, imipenem
<i>M. fortuitum</i>	Two of: amikacin, ciprofloxacin or fluoroquinolone, sulfonamide

- Treatment recommendations in SOT population differ from non-SOT population due to significant drug-drug interactions with immunosuppressive regimens
 - Rifampin, clarithromycin

Clin Transplant. 2019;33:e13588.
Clin Infect Dis. 2020;71:905-13.

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Management of Viral Infections in Solid-Organ Transplant Recipients

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Post-transplant Cytomegalovirus (CMV)

- Herpesvirus: prevalence ~50% of the US population
- Viral replication is possible during periods of acute illness
- **CMV Infection**
 - Isolation of the virus or viral proteins or nucleic acid in any body fluid or specimen
 - DNAemia regardless of symptoms
- **CMV Disease**
 - CMV infection with associated symptoms
 - CMV syndrome: fever, fatigue, bone marrow suppression, liver function test abnormalities
 - End-organ CMV disease:
 - Colitis, pneumonitis, hepatitis, nephritis, retinitis, etc.
- Overall associated with immune modulatory effects
 - Associated with other infections, rejection, decreased survival

Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.
Clin Infect Dis. 2017;64:97-91.

77

Management of Post-transplant CMV

- Quantitative CMV nucleic acid amplification test (QNAT) preferred lab test
 - Higher viral load typically associated with CMV disease, exceptions exist
 - Viral load values can vary from lab to lab despite World Health Organization international standard
 - Threshold for when to start treatment when patients asymptomatic is still unclear
- Histopathology
 - Gold standard for diagnosis of end-organ CMV disease

Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.
Clin Infect Dis. 2013;56:367-73.

78

Management of Post-transplant CMV

- First line treatment
 - Ganciclovir/valganciclovir
- CMV resistance
 - Should be suspected with persistent CMV viremia or symptoms after 2 weeks of appropriate therapy and total exposure > 6 weeks
 - UL97 mutation
 - Affects drug phosphorylation, confers resistance to ganciclovir in varying amounts
 - High dose ganciclovir may be effective in certain circumstances
 - Switch for foscarnet recommended if high level ganciclovir resistance conferred
 - UL54 mutation
 - Confers ganciclovir resistance and likely cross-resistance to cidofovir and/or foscarnet

Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.
Clin Infect Dis. 2019;68:1420-26.
Clin Microbiol Rev. 2010;23:689-712.

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Management of Post-transplant CMV

- Ganciclovir/Valganciclovir
 - Ganciclovir preferred in severe disease or unclear GI absorption
 - Dosing:
 - **Induction:** Ganciclovir 5 mg/kg q12h / Valganciclovir 900 mg BID
 - 10 mg/kg q12h may be used in UL97 mutations with lower levels of ganciclovir resistance
 - **Maintenance:** Ganciclovir 5 mg/kg daily / Valganciclovir 900 mg daily
 - Must be dose adjusted for renal dysfunction
 - Major toxicities: neutropenia, thrombocytopenia
 - Do not decrease dose to mitigate bone marrow suppression, recommend evaluation of concomitant medications, granulocyte colony stimulating factor supplementation, platelet transfusion if necessary

Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.
 Ganciclovir [package insert]. Lenoir, NC: Exela Pharma Sciences; 2017.
 Valganciclovir [package insert]. San Francisco, CA: Genentech USA, Inc; 2017.

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Management of Post-transplant CMV

- Foscarnet
 - Should be reserved for suspected or confirmed resistance to ganciclovir and severe CMV disease
 - Dosing:
 - **Induction:** 60 mg/kg IV q8h or 90 mg/kg q12h, **Maintenance:** 90-120 mg/kg IV daily
 - Recommend 750–1000 mL of fluids prior to the first infusion, then 750–1000 mL with 90-120 mg/kg dosing and 500 mL with 40–60 mg/kg dosing
 - Must be renally dose adjusted
 - Dose using modified Cockcroft-Gault equation $(140 - \text{age}) / (\text{SCr} \times 72) \times 0.85$ for females = mL/min/kg
 - Major toxicities: nephrotoxicity, electrolyte imbalances (hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia) – can result in paresthesias, seizures

Clin Transplant. 2019 Sep;33(9):e13512.
 Transplantation. 2018 Jun;102(6):900-931.
 Foscavir [package insert]. Lake Forest, IL: Hospira Inc; 2017.

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Management of Post-transplant CMV

- Cidofovir
 - Reserve for UL54 and/or UL97 mutation with foscarnet resistance and cidofovir susceptibility
 - Dosing:
 - **Induction:** 5 mg/kg once weekly x 2 weeks
 - **Maintenance:** 5 mg/kg once every other week
 - Must be renally dose adjusted, can also decrease to 3 mg/kg for increases in SCr
 - Pre-medicate each dose with normal saline and oral probenecid (2g 3 hr prior to cidofovir and 1g at 2 and 8 hrs post-dose)
 - Major toxicities:
 - Nephrotoxicity, proteinuria, Fanconi syndrome, neutropenia
 - Not recommended to initiate when baseline serum creatinine > 1.5 mg/dL, creatinine clearance ≤ 55 mL/min, or a urine protein ≥ 100 mg/dL

Clin Transplant. 2019 Sep;33(9):e13512.
 Transplantation. 2018 Jun;102(6):900-931.
 Cidofovir [package insert]. Rockford, IL: Mylan Institutional LLC; 2012.

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Management of Post-transplant CMV

- Maribavir
 - Newly approved for treatment of refractory/resistant CMV
 - UL97 kinase inhibitor
 - Dosing:
 - 400 mg BID with or without food
 - Major toxicities:
 - Dysgeusia, nausea, vomiting, diarrhea
 - CYP3A4 substrate, weak CYP3A4 inhibitor caution with drug-drug-interactions
 - Efficacy:
 - Maribavir vs. investigator assigned treatment for up to 8 weeks in SOT & HSCT patients
 - Primary endpoint: CMV DNA <137 IU/mL at week 8 → 56% maribavir vs. 24% IAT (p<0.001)

Maribavir [package insert]. Lexington, MA: Takeda Pharmaceuticals America, Inc.; 2021.
Clin Infect Dis. 2021 Dec 2;ciab988.

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Management of Post-transplant CMV

- Other treatments
 - Leflunomide
 - Data limited to case reports/series, caution in severe disease
 - Monitoring for teriflunomide levels and liver toxicity is recommended
 - Letermovir
 - UL56 terminase inhibitor, currently indicated for prophylaxis in stem cell transplant patients
 - Efficacy in treatment of CMV disease is unclear; data limited to case reports/series
 - Low barrier to resistance development
 - Managing immunosuppression
 - mTOR inhibitors may have activity, consider changing antimetabolite
 - CMV immune globulin/intravenous immunoglobulin
 - Insufficient evidence, may improve immune response

Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.
Transplantation. 2020;104:404-09.
Case Rep Nephrol Dial. 2015;5:96-105.

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Management of Post-transplant CMV

- Duration of treatment:
 - Induction treatment should continue for at least 2 weeks, until CMV DNAemia is documented to be undetectable and resolution of clinical symptoms
 - Maintenance treatment/secondary prophylaxis may be considered after completion of induction (1-3 months), not routinely recommended unless high risk scenarios
- Monitoring treatment:
 - Monitoring of CMV PCR should be done weekly during treatment to assess response
 - Consider CMV resistance if viral load fails to decline (by 1 log or more) or if increases after 2 weeks of adequate dose antiviral therapy
 - Consider reduction in immunosuppression for severe CMV disease

*Clin Transplant. 2019 Sep;33(9):e13512.
Transplantation. 2018 Jun;102(6):900-931.*

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Post-transplant Epstein-Barr Virus (EBV)

- Common cause of post-transplant lymphoproliferative disorders (PTLD)
 - Important risk factor is EBV IgG Donor + / Recipient – transplants
 - Especially for early-onset PTLD
- Universal antiviral prophylaxis for EBV mismatched patients not recommended
 - Controversial because acyclovir and ganciclovir have activity in-vitro
- EBV DNA PCR monitoring in high risk patients (D+/R-) recommended weekly or biweekly in the first year post transplant
 - If EBV DNA detected, monitoring should occur weekly until stable
- Reduction in immunosuppression is best intervention for EBV viremia
- Histopathology is the gold standard for diagnosis of PTLD
 - PTLD necessitates treatment with rituximab +/- cytotoxic chemotherapy

Clin Transplant. 2019 Sep;33(9):e13652.

86

Post-transplant Herpes Simplex Virus (HSV)

- HSV-1 typically oral lesions; HSV-2 typically genital lesions
- Prevalence up to ~60% and 21%, respectively
- Disseminated disease can occur: fever, hepatitis, leukopenia
 - Pneumonitis, esophagitis, hepatitis, keratitis
- HSV DNA PCR most sensitive diagnostic method
- Consider immunosuppression reductions for severe/life-threatening HSV

Clin Transplant. 2019 Sep;33(9):e13526.

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Post-transplant Herpes Simplex Virus (HSV)

Mucocutaneous Treatment

- Acyclovir 400 mg TID*
 - Valacyclovir 1000 mg BID*
 - Famciclovir 500 mg BID*
 - Acyclovir 5 mg/kg IV q8h*
- } Treat until lesions healed or at least 5-7 days

Severe/Disseminated/CNS Disease Treatment

- Acyclovir 10 mg/kg IV Q8H x 14-21 days*

***Requires renal dose adjustment**

Clin Transplant. 2019 Sep;33(9):e13526.

88

Post-transplant Varicella Zoster Virus (VZV)

- AKA 'Chickenpox'
- Majority of adults seropositive (97-98%)
- Primary infection (varicella) - rare
- Virus establishes latency in ganglia and can reactivate as herpes zoster (shingles)
- Can manifest as VZV encephalitis, visceral infection or disseminated
- PCR testing is standard in diagnosis of infection

Clin Transplant. 2019 Sep;33(9):e13622.

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Management of Post-transplant Varicella Zoster Virus (VZV)

Type of Infection	Treatment Options	Treatment Duration
Localized herpes zoster	<ul style="list-style-type: none"> ➤ Acyclovir 800 mg po five times daily ➤ Valacyclovir 1g po TID ➤ Famciclovir 500 mg po TID 	Treat until lesions healed or at least 7 days
Acute varicella	<ul style="list-style-type: none"> ➤ Acyclovir 10 mg/kg IV q8h ➤ Change to oral therapy once clinically improved 	Treat for at least 7 days until lesions healed
Disseminated herpes zoster or ophthalmicus	<ul style="list-style-type: none"> ➤ Acyclovir 10 mg/kg IV q8h ➤ Change to oral therapy once clinically improved 	Treat for at least 7 days, consider longer courses

*All require renal dose adjustment

Adapted from: Clin Transplant. 2019 Sep;33(9):e13622.

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Post-transplant BK Polyomavirus

- Highly prevalent in general population
- Can result in BK-virus associated nephropathy (BKVAN)
 - Rare outside of kidney transplant recipients
- Kidney transplant recipients should be screened monthly until month 9, and every 3 months until year 2, and if allograft dysfunction and biopsy
- **Diagnosis**
 - Probable nephropathy when plasma levels >1000 copies/mL
 - Presumptive nephropathy when plasma levels >10,000 copies/mL
 - Proven via kidney biopsy
 - In those without increased risk of acute rejection and baseline renal function, renal allograft biopsy is not required prior to reducing immunosuppression, but should be done in other cases

Clin Transplant. 2019 Sep;33(9):e13528.

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Management of Post-transplant BK Polyomavirus

- Mainstay of treatment is reduction in immunosuppression by one of two strategies:
 1. Reduction in CNI by 25-50%, followed by reduction in antiproliferative by 50% followed by discontinuation of antiproliferative
 2. Reduction in antiproliferative by 50%, followed by reduction in CNI by 25-50%, followed by discontinuation of antiproliferative
- Other strategies
 - Steroid taper to prednisone 10 mg daily or less
 - Tacrolimus trough levels targeted to <6 ng/mL
 - Cyclosporine trough levels targeted to <150 ng/mL
 - Sirolimus trough levels targeted to <6 ng/mL
 - Mycophenolate mofetil daily dose equivalents ≤ half of the daily maintenance dose

*Clin Transplant. 2019 Sep;33(9):e13528.
Transplantation. 2010 May 15;89(9):1057-70.*

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Management of Post-transplant BK Polyomavirus

- Other strategies
 - CNI → mTORi
 - Tacrolimus → cyclosporine
 - Mycophenolate → mTORi
 - Mycophenolate → leflunomide
 - IVIG as adjunctive therapy
- No randomized controlled trials exist to support the evidence of adjunctive therapies (e.g. IVIG, leflunomide, cidofovir, fluoroquinolones)

*Clin Transplant. 2019 Sep;33(9):e13528.
Transplantation. 2010 May 15;89(9):1057-70.*

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Post-transplant Respiratory Viruses

- Many respiratory viruses do not require treatment other than supportive care (e.g. rhinovirus, coronavirus, etc.)
- Viral infections in transplant recipients can result in increased complications and prolonged viral shedding
 - Can result in more severe pneumonias
- Transplant patients should be vaccinated against viruses and offered prophylaxis when indicated
 - Ex) Influenza vaccination should be offered to SOT patients. If contraindicated antiviral prophylaxis may be offered in select scenarios

Clin Transplant. 2019 Sep;33(9):e13511.

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Management of Post-transplant Respiratory Viruses

Virus	Treatment
Rhinovirus, coronavirus	Supportive care
Influenza	Supportive care, oseltamivir
Respiratory syncytial virus	Supportive care, consider ribavirin +/- IVIG
Parainfluenza virus	Supportive care, consider ribavirin +/- IVIG
Human metapneumovirus	Supportive care, consider ribavirin +/- IVIG
Adenovirus	Supportive care, consider cidofovir

Adapted from: *Clin Transplant*. 2019 Sep;33(9):e13511.

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Management of Post-transplant RSV

- Ribavirin: nucleoside analog
 - Inhaled ribavirin
 - FDA approved for lower respiratory tract disease in high-risk populations
 - Continuous inhalation x 12-18 hours daily x 3-7 days
 - Extremely expensive
 - Must be administered in an oxygen tent in negative pressure room
 - Oral ribavirin
 - Dosing: 15-20 mg/kg/day divided three times daily x 7-10 days
 - Requires renal dose adjustment
- Adverse effects:
 - Hemolytic anemia, rash, GI side effects
 - May increase concentration of active metabolites of azathioprine

Antimicrob Agents Chemother. 2013 Dec;57(12):6097-105.
Clin Infect Dis. 2013 Jan;56(2):258-66.
 Virazole [package insert]. McPherson, KS: Hospira Inc; 2019.

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Management of Post-transplant Covid-19

- Survival outcomes in transplant patients similar to non-transplant patients
- Concern for superinfection with bacterial, fungal pathogens
- Immunosuppression management still unclear, some studies suggest no benefit in changing immunosuppression
- Prevention is key; reference “Best Practices in Primary Care of the Transplant Patient” lecture
- Monoclonal antibody therapies are rapidly changing due to development of novel variants
 - <https://www.covid19treatmentguidelines.nih.gov/>

Clin Microbiol Infect. 2022 Feb 18:S1198-743X(22)00078-7.

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Management of Post-transplant Covid-19

Treatment	Evidence	Caution
Remdesivir	Shortens time to recovery in mild Covid-19	No benefit noted in those in high-flow O2 or greater
Dexamethasone	Decreased 28-day all-cause mortality (23% vs. 26%)	Additive immunosuppression, known steroid-related adverse effects
Tocilizumab	Decreased in-hospital mortality (28% vs. 35.8%)	Additive immunosuppression, GI perforation/bleeding
Baricitinib	Decreased 28-day all-cause mortality in those on high flow/non-invasive ventilation (17.5% vs. 29.4%)	Additive immunosuppression, VTE treatment, thrombotic CVA
Nirmatrelvir-ritonavir	Decreased hospitalizations/deaths compared to placebo (0.8% vs. 7%) in mild-moderate Covid-19	Caution with drug-drug interactions with immunosuppression (see next slide), unclear safety in pregnancy
Molnupiravir	Decreased mortality vs. placebo (0.1% vs. 1.3%) in mild-moderate Covid-19	Do not administer to pregnant patients

See reference summary slides.

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Management of Post-transplant Covid-19

AST Statement on Oral Antiviral Therapy for COVID-19 for Organ Transplant Recipients

Outpatient Treatment of Covid-19

- Consider MAB therapy or remdesivir x 3 days
- If using nirmatrelvir-ritonavir (Paxlovid®):
 - Reduce cyclosporine to 20% of current dose
 - Reduce tacrolimus and sirolimus dose substantially or hold
- Molnupiravir is less efficacious compared to other options

<https://www.myast.org/sites/default/files/AST%20Statement%20on%20Oral%20Antiviral%20Therapy%20for%20COVID%20Jan%204%20%28%29.pdf>

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Management of Fungal Infections in Solid-Organ Transplant Recipients

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Post-transplant *Pneumocystis jirovecii* Pneumonia

- Formerly *P. carinii* pneumonia
- Risk is 5-15% among SOT patients without prophylaxis
 - Greatest in lung, within 6 months post-transplant
- Risk factors
 - Lymphopenia, neutropenia
 - CMV
 - Hypogammaglobulinemia
 - Rejection
 - Age
 - Immunosuppression: corticosteroids, lymphocyte depleting agents, CNI's
- Characteristics
 - Fever, non-productive cough, hypoxia, chest x-ray findings, dyspnea

Clin Transplant. 2019 Sep;33(9):e13587.

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Management of post-transplant *Pneumocystis jirovecii* pneumonia

- **First-line treatment:** Trimethoprim-sulfamethoxazole (TMP-SMX) 15-20 mg/kg/day in 3-4 divided doses
 - Most effective therapy
- **Alternatives:**
 - Pentamidine 4 mg/kg/day IV
 - Pancreatitis, hypo/hyperglycemia, bone marrow suppression, renal failure, electrolyte disturbances
 - Primaquine 15-30 mg po QD + Clindamycin 600-900 mg IV/PO Q6-8h
 - Alternative for mild-moderate PJP
 - Atovaquone 750 mg po BID
 - Alternative for mild-moderate PJP
 - Dapsone 100 mg PO QD + Trimethoprim 15 mg/kg/day divided TID
 - Alternative for mild-moderate PJP

Clin Transplant. 2019 Sep;33(9):e13587.

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Management of post-transplant *Pneumocystis jirovecii* Pneumonia

- Adjunctive corticosteroids
 - Recommended despite conflicting data in non-HIV patients
 - Patients with $pAO_2 < 70$ mmHg on room air or alveolar-arterial DO_2 gradient ≥ 35 mmHg
 - Initiate early
 - Suggest 40-60 mg of prednisone equivalents BID or TID with taper after 5-7 days over a period of 1-2 weeks
 - Common regimen:
 - Prednisone 40 mg BID x 5 days
 - 40 mg QD x 5 days
 - 20 mg QD x 11 days
- Duration of therapy
 - Typically 14-21 days

Clin Transplant. 2019 Sep;33(9):e13587.
N Engl J Med. 1990 Nov 22;323(21):1451-7.

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Post-transplant Fungal Infections

	Yeasts	Molds	Dimorphic Fungi
Examples	<i>Candida</i> spp. <i>Cryptococcus</i> spp.	<i>Aspergillus</i> spp. <i>Rhizopus</i> spp.	Blastomycosis Histoplasmosis Coccidioidomycosis
Characteristics	Rounded single cells or budding organisms	Grow as filamentous forms (hyphae)	Grow as yeasts in tissue but in filamentous forms at room temperature

Clin Infect Dis. 2016 Feb 15;62(4):e1-50.
Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.

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Management of Post-transplant *Candida* infections

	Azoles	Echinocandins	Polyenes (Amphotericin)
<i>Candida spp.</i>	Good coverage for all <ul style="list-style-type: none"> - Voriconazole, posaconazole, isavuconazole, and itraconazole cover all - Fluconazole lacks <i>C. krusei</i> - <i>C. glabrata</i> can develop resistance to all azoles: only susceptible-dose-dependent category exists 	Good coverage for all <i>(C. parapsilosis and C. guilliermondi may have higher MICs)</i>	Good coverage for all <i>(C. lusitanae may have higher MICs)</i>

Clin Transplant. 2019 Sep;33(9):e13623.
Infect Dis Clin North Am. 2016 Mar;30(1):51-83.

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Management of Post-transplant *Candida* infections

Candidemia

- **First line therapy:** Echinocandin as initial therapy
 - Micafungin 100 mg daily / Anidulafungin 200 x 1 then 100 mg daily / Caspofungin 70 mg x 1 then 50 mg daily
- **Alternative:** Fluconazole for those not critically ill/no prior exposure OR step-down
 - Fluconazole 12 mg/kg x 1 then 6 mg/kg IV or PO daily
 - Dose adjustment required for renal dysfunction
- **Alternative:** Voriconazole can be used when mold coverage desired
- **Duration:** Minimum of 2 weeks after clearance of blood cultures
- **Special considerations:** Endocarditis & endophthalmitis evaluation, potential line removal

Clin Infect Dis. 2016 Feb 15;62(4):e1-50.
Clin Transplant. 2019 Sep;33(9):e13623.

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Management of Post-transplant *Candida* infections

Fluconazole	Echinocandins (Micafungin, caspofungin, anidulafungin)
Eliminated renally	Eliminated primarily by liver/feces
Inhibits P450 (not as strong as other azoles)	Do not have P450/PGP interactions
Well tolerated	Well tolerated
May increase LFTs	May cause small increases in LFTs
Only covers about 50% of <i>C. glabrata</i> , <i>C. krusei</i> is intrinsically resistant	Covers most <i>Candida</i> spp.
Inexpensive	Expensive
Multiple formulations	IV only
Good CSF/eye/urine penetration	Poor CSF/eye/urine penetration

Clin Infect Dis. 2016 Feb 15;62(4):e1-50.

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Post-transplant Aspergillosis

- Filamentous mold
- Most common species isolated is *A. fumigatus*
 - *A. niger* / *A. flavus* / *A. terreus*
- Ubiquitous in the environment
 - Soil, air, water, food
- Cause infection through inhalation of conidia
- Most common site of invasive infection: lung (can also cause infection in sinuses and CNS)
- Risk factors in SOT recipients include: older age, renal failure, CMV disease, bacterial infection, chronic graft rejection, cancer related to immunosuppression

Clin Transplant. 2019 Sep;33(9):e13544.
Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.
J Natl Compr Canc Netw. 2016 Jul;14(7):882-913.

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Management of Post-transplant Aspergillosis

	Azoles	Echinocandins	Polyenes (Amphotericin)
<i>Aspergillus spp.</i>	Agents with activity from the class: <ul style="list-style-type: none"> - Voriconazole (1st line) - Isavuconazole - Posaconazole - Itraconazole 	Questionable coverage (Data not as strong, reserved for refractory or special cases)	Good coverage Elevated MICs for <i>A. terreus</i>

Clin Transplant. 2019 Sep;33(9):e13544.
Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.
J Natl Compr Canc Netw. 2016 Jul;14(7):882-913.

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Management of Post-transplant Aspergillosis

- **First line therapy:** Voriconazole
- **Dose:** 6 mg/kg IV q12h x 2 doses then 4 mg/kg IV q12h
 - Suggest adjusted body weight if obese
- **Target trough:** 1-5.5 µg/mL (Troughs >5.5 associated with toxicity), consider 2-6 µg/mL if poor prognosis or elevated MICs
- **Duration:** At least 6-12 weeks, highly variable
- **Alternatives**
 - Isavuconazole
 - Posaconazole
 - Amphotericin (liposomal/lipid complex formulations preferred), inhaled as adjunct therapy in lung transplant
 - High-dose echinocandin (use alone is controversial)
 - Itraconazole (mild disease)

Clin Transplant. 2019 Sep;33(9):e13544.
Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.
J Natl Compr Canc Netw. 2016 Jul;14(7):882-913.

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Management of Post-transplant Aspergillosis

Voriconazole	Isavuconazole	Posaconazole
Hepatic metabolism	Eliminated through urine and feces	Hepatic metabolism
Strong CYP3A4 inhibitor, moderate CYP2C19 inhibitor	Moderate CYP3A4 inhibitor and substrate	Strong CYP3A4 inhibitor, UGT1A4 substrate
Ocular toxicity, hallucinations, increase in LFT's	? Less liver toxicity No ocular toxicity/hallucinations	Increases in LFT's
TDM available, but non-linear kinetics	TDM not routine; unclear goals More predictable PK	TDM available, linear kinetics
Oral suspension, tablet, IV	Capsules and IV	Oral suspension, ER tablet, IV
Good CSF/eye penetration	Widely distributes to tissues	Low CSF/eye penetration
Relatively inexpensive	More costly	More costly

TDM = therapeutic drug monitoring

Clin Transplant. 2019 Sep;33(9):e13544.
Clin Infect Dis. 2016 Feb 15;62(4):e1-50

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Management of Post-transplant Aspergillosis

Amphotericin	Echinocandins	Itraconazole
Primary elimination unknown	Eliminated primarily by liver/feces	Hepatic metabolism
No P450 interactions	No P450 interactions	Strong P450 inhibitor, P-gp
Infusion-related reactions, electrolyte abnormalities, nephrotoxicity	May cause small increases in LFTs	Increases in LFTs, heart failure exacerbations
No TDM available	No TDM available	TDM available
IV only: Ambisome®, Abelcet®, Ampho B deoxycholate	IV only: micafungin, caspofungin, anidulafungin	Capsules, oral solution, SUBA-capsules
Some CSF/eye penetration	Poor CSF/eye/urine penetration	Poor CSF/eye/urine penetration
More costly	More costly	Dependent on formulation

Clin Infect Dis. 2016 Feb 15;62(4):e1-50, *Clin Transplant.* 2019 Sep;33(9):e13544.

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Post-transplant Mucormycosis

- Also known as Zygomycosis
- Most common species: *Rhizopus*, *Mucor*, *Rhizomucor* sp.
- Rare prevalence
 - ~2% incidence of all IFI's in SOT recipients
 - 66-96% mortality in immunocompromised patients
- Risk factors include: diabetes, corticosteroids, neutropenia
 - Also includes renal failure, prior voriconazole use, and prior caspofungin use in SOT
- Common sites of infection: sinuses, pulmonary, CNS/eye, disseminated
- Angioinvasion and tissue necrosis is common
 - Early tissue debridement is key

Lancet Infect Dis. 2019 Dec;19(12):e405-e421.
Clin Transplant. 2019 Sep;33(9):e13525.
Clin Infect Dis. 2005 Sep 1;41(5):634-53.
Clin Infect Dis. 2010 Apr 15;50(8):1101-11.
J Infect Dis. 2009 Sep 15;200(6):1002-11.

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Management of Post-transplant Mucormycosis

	Azoles	Echinocandins	Polyenes (Amphotericin)
<i>Zygomycetes</i>	Agents with activity from the class: <ul style="list-style-type: none"> - Posaconazole - Isavuconazole 	No coverage Activity <u>only synergistic</u> with posaconazole or amphotericin in <i>Rhizopus</i> (expresses $\beta(1,3)$ -D-glucan synthase)	Good coverage for all

Lancet Infect Dis. 2019 Dec;19(12):e405-e421.
Clin Transplant. 2019 Sep;33(9):e13525.

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Management of Post-transplant Mucormycosis

- Amphotericin B
 - Liposomal or lipid-complex amphotericin B at 5-10 mg/kg per day
 - Aggressive dosing, combination therapy may be warranted
- Alternatives
 - Posaconazole
 - Isavuconazole
 - +/- Echinocandin
- Non-drug Treatments
 - Surgical debridement* → Key for cure because of tissue necrosis
 - Management of underlying predisposing conditions

Lancet Infect Dis. 2019 Dec;19(12):e405-e421.
 Clin Transplant. 2019 Sep;33(9):e13525.
 J Antimicrob Chemother. 2015 Nov;70(11):3116-23.
 J Infect Dis. 2009 Sep 15;200(6):1002-11.

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Question 6: Which of the following is an appropriate treatment option against *Zygomycetes*?

- a) Voriconazole
- b) Micafungin
- c) Amphotericin B
- d) Voriconazole + micafungin

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Question 6: Which of the following is an appropriate treatment option against *Zygomycetes*?

- a) Voriconazole
- b) Micafungin
- c) Amphotericin B**
- d) Voriconazole + micafungin

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Post-transplant Histoplasmosis/Blastomycoses

- **Blastomycosis:**
 - Endemic to the Ohio and Mississippi River Valleys, Midwest region
 - Rare in SOT patients (~incidence 0.14%)
 - Pulmonary, disseminated infection common
 - Osteoarticular, CNS, genitourinary can also occur
- **Histoplasmosis:**
 - Endemic to the Ohio and Mississippi River Valleys, Central/South America
 - Rare in SOT patients (incidence 0.1%)
 - Disseminated infection most common in SOT

Clin Transplant. 2019 Sep;33(9):e13553.
 Transpl Infect Dis. 2007;9(4):310-317.
 Transpl Infect Dis. 2014;16(2):213-224.

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Post-transplant Histoplasmosis/Blastomycoses

- **Mild/localized first line therapy:** Itraconazole 200 mg Q8H x 3 days load, then 200 mg BID maintenance x 12 months
- **Moderate/severe/disseminated:** Amphotericin (lipid formulation) x 1-2 weeks then itraconazole x 12 months
- **CNS Blastomycosis:** Amphotericin (lipid formulation) x 4-6 weeks then voriconazole (200-400 bid) x 12 months
 - Alternative stepdown: fluconazole 800 mg daily

Clin Transplant. 2019 Sep;33(9):e13553.
Clin Infect Dis. 2008 Jun 15;46(12):1801-12.

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Post-transplant Histoplasmosis/Blastomycoses

- **Itraconazole therapeutic drug monitoring:** Goal Itraconazole + hydroxyitraconazole level >1-2 mcg/mL for treatment (level after 10-14 days)
 - **Itraconazole capsules:** requires acidity, better with food and non-diet cola drinks
 - **Itraconazole solution:** absorption not affected by pH, better fasted, increased compared to conventional capsules
 - **SUPER-BioAvailable (SUBA)-itraconazole capsules:** absorption better fasted, absorption increased compared to conventional capsules
 - Formulations should not be interchanged
- **Alternatives**
 - Voriconazole, posaconazole, isavuconazole have in-vitro activity but limited clinical evidence
- Antigen enzyme immunoassay (EIA) levels are commonly elevated at diagnosis, can be followed during treatment

Clin Transplant. 2019 Sep;33(9):e13553.
Clin Infect Dis. 2008 Jun 15;46(12):1801-12.

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Post-transplant Coccidioidomycosis

- Caused by *C. immitis* and *C. posadasii*
- Endemic to the American Southwest, areas of Central/South America
- Pulmonary infection is most common
 - Can also involve meningitis, skin and osteoarticular infections
- Serologic testing includes immunodiffusion-based and complement-fixing anti-coccidioidal antibodies and EIA testing
- Can be transmitted from donor to recipient (~43% transmission rate in one report)
 - Recipients should receive prophylaxis if donor has active/past infection
 - SOT recipients living in endemic areas should receive azole prophylaxis (fluconazole 200 mg daily if seronegative/400 mg daily if seropositive) x 6-12 months post-transplant

Clin Transplant. 2019 Sep;33(9):e13553.
Am J Transplant. 2016 Dec;16(12):3562-3567.
Clin Infect Dis. 2016 Sep 15;63(6):e112-46.

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Management of Post-transplant Coccidioidomycosis

- Mild-moderate
 - Fluconazole 400 mg daily x 6-12 months*
- Severe
 - Amphotericin (lipid formulation) followed by fluconazole x 6-12 months*
- CNS disease
 - Fluconazole 400-1200 mg daily x 6-12 months*

*Recommended to continue suppressive therapy indefinitely in SOT patients

Clin Transplant. 2019 Sep;33(9):e13553.
Clin Infect Dis. 2016 Sep 15;63(6):e112-46.

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Post-transplant *Cryptococcus*

- Organ transplantation is associated with an increased risk for cryptococcal infections
 - Third most common invasive fungal infection in SOT patients
 - Overall incidence ~2.8%
 - Potentially higher incidence in heart and small bowel transplant recipients
 - Mortality in solid-organ transplant: 30-50%
- Predilection for the CNS
 - Can also involve pulmonary, skin/soft-tissue/bone, fungemia
- Serum cryptococcal antigen is commonly positive
 - 88-91% of SOT recipients with meningitis

Clin Transplant. 2019 Sep;33(9):e13543.
Transpl Infect Dis. 2002 Dec;4(4):183-8.
Clin Infect Dis. 2010 Feb 1;50(3):291-322.
Clin Infect Dis. 2008 Nov 15;47(10):1321-7.

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Management of Post-transplant *Cryptococcus* Infections

	Azoles	Echinocandins	Polyenes (Amphotericin)
<i>Cryptococcus neoformans, gattii</i>	Agents with activity from the class: <ul style="list-style-type: none"> - Fluconazole - Alternatives: <ul style="list-style-type: none"> - Voriconazole - Posaconazole - Isavuconazole - Itraconazole* 	No coverage	Good coverage for all

*Less effective than fluconazole for cryptococcal meningitis

Clin Transplant. 2019 Sep;33(9):e13543.
Clin Infect Dis. 2010 Feb 1;50(3):291-322.
Clin Infect Dis. 1999 Feb;28(2):291-6.

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Management of Post-transplant *Cryptococcus* Infections

Disseminated/CNS/Moderate-severe Cryptococcal infection

- Induction with Amphotericin B (liposomal or lipid complex preferred, 3-4 mg/kg/day or 5 mg/kg/day respectively) } 2 weeks
 - Plus flucytosine 100 mg/kg/day in 4 divided doses
- Consolidation with fluconazole 400-800 mg/day } 8 weeks
- Maintenance with fluconazole 200-400 mg/day } 6-12 months

Mild/moderate pulmonary Cryptococcal infection

- Fluconazole 400 mg/day } 6-12 months

Clin Transplant. 2019 Sep;33(9):e13543.
Clin Infect Dis. 2009 Dec 1;49(11):1721-8.
Clin Infect Dis. 2010 Feb 1;50(3):291-322.

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Management of Post-transplant *Cryptococcus*

Treatment Pearls

- Fluconazole
 - Requires renal dose adjustment
- Flucytosine
 - Requires renal dose adjustment
 - Levels recommended: Peak level (~2 hours post-dose) on Day 3 of therapy
 - Goal peak 30-80 mcg/mL: levels >100 associated with myelosuppression and liver toxicity
- Adjunctive steroids: NOT recommended for meningitis treatment
- Alternative treatments: voriconazole, posaconazole and isavuconazole have limited clinical evidence yet are active in-vitro
- Reduction in immunosuppression recommended

Clin Transplant. 2019 Sep;33(9):e13543.
Clin Infect Dis. 2010 Feb 1;50(3):291-322.
N Engl J Med. 2016 Feb 11;374(6):542-54.
Clin Infect Dis. 2005 Jun 15;40(12):1756-61.

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Adverse Effects of Systemic Antifungal Agents

Antifungal	LFT elevations	Nephrotoxicity	Neurotoxicity /visual	QTc prolongation	Photosensitivity /rash	Infusion reactions
Fluconazole	x			x	x	
Itraconazole	x			x (heart failure warning)	x	
Voriconazole	x		x	x	x	
Posaconazole	x			x	x	
Isavuconazole	x			QTc shortening		
Echinocandins	x				x	
Amphotericin	x	x				x

Mayo Clin Proc. 2011 Aug;86(8):805-17.

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Drug-drug Interactions with Systemic Antifungal Agents

- Voriconazole/itraconazole/posaconazole
 - Severely increases levels of CNI, mTORi via CYP3A4 inhibition
 - Mild-moderate increases in steroid levels
 - Voriconazole: decrease CSA dose by 50% TAC by 2/3, mTORi by 75-90%
 - Itraconazole: decrease TAC & mTORi by ~50%, CSA by 25-50%
 - Posaconazole: decrease CSA by 25%, TAC by 2/3, mTORi by 75-90%
- Isavuconazole
 - Moderately increases levels of CNI, mTORi via CYP3A4 inhibition
 - Consider decrease of TAC, mTORi by 25-50%
 - Monitor CSA levels

Clinical Transplant. 2019;33:e13510.

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Drug-drug Interactions with Systemic Antifungal Agents

- **Fluconazole**
 - Moderately increases levels of CNI, mTORi via CYP3A4 inhibition
 - Consider decrease of TAC, mTORi by 25-50%
 - Monitor CSA levels, consider decrease by 25%
- **Echinocandins**
 - CSA may increase caspofungin levels (unknown mechanism)
 - Monitor for adverse events
- **Amphotericin**
 - Additive nephrotoxicity with CNI
 - Monitor for adverse events

Clinical Transplant. 2019;33:e13510.

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Key Takeaways

- All potential transplant recipients should undergo recommended serologic testing and vaccination/treatment if necessary
- There are many options for antibacterial prophylaxis, antiviral prophylaxis, and antifungal prophylaxis – patient and facility specific factors should be considered
- Risk of infection in transplant recipients varies based on organ type, donor and recipient factors, and timeline from transplant
- Both opportunistic infections and non-opportunistic infections can affect transplant recipients; including bacterial, viral, fungal, and parasitic
- Drug-drug interactions and considerations of toxicity are highly important in managing the treatment of Infectious Diseases in the transplant population

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References

- Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283.
- Am J Transplant. 2009 Dec;9 Suppl 4:S173-9.
- Am J Transplant. 2014 Dec;14(12):2765-76.
- Am J Transplant. 2015 Jan;15(1):180-9.
- Am J Transplant. 2015 May;15(5):1162-72.
- Am J Transplant. 2016 Dec;16(12):3562-3567.
- Ann Intern Med. 2005;143:870-880.
- Antimicrob Agents Chemother. 2013 Dec;57(12):6097-105.
- Case Rep Nephrol Dial. 2015;5:96-105.
- Cidofovir [package insert]. Rockford, IL: Mylan Institutional LLC; 2012.
- Clin Infect Dis. 2019;68:1420-26.
- Clin Infect Dis. 1999 Feb;28(2):291-6.
- Clin Infect Dis. 2005 Jun 15;40(12):1756-61.
- Clin Infect Dis. 2005 Sep 1;41(5):634-53.
- Clin Infect Dis. 2008 Jun 15;46(12):1801-12.
- Clin Infect Dis. 2008 Nov 15;47(10):1321-7.
- Clin Infect Dis. 2009 Dec 1;49(11):1721-8.
- Clin Infect Dis. 2010 Apr 15;50(8):1101-11.
- Clin Infect Dis. 2010 Feb 1;50(3):291-322.
- Clin Infect Dis. 2011 Mar 1;52(5):e103-20.
- Clin Infect Dis. 2013 Jan;56(2):258-66.
- Clin Infect Dis. 2013;56:367-73.
- Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.
- Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.
- Clin Infect Dis. 2016 Feb 15;62(4):e1-50.
- Clin Infect Dis. 2016 Sep 1;63(5):e61-e111.
- Clin Infect Dis. 2016 Sep 15;63(6):e112-46.
- Clin Infect Dis. 2017 Jan 15;64(2):111-115.
- Clin Infect Dis. 2017;64:97-91.
- Clin Infect Dis. 2019 May 2;68(10):1611-1615.
- Clin Infect Dis. 2020;71:905-13.
- Clin Infect Dis. 2020 Jan 9. pii: ciz1113.
- Clin Infect Dis. 2021 Dec 2;ciab988.
- Clin Microbiol Rev. 2010;23:689-712.
- Clin Transplant. 2019 Sep;33(9):e13507.
- Clin Transplant. 2019 Sep;33(9):e13509.
- Clin Transplant. 2019 Sep;33(9):e13511.
- Clin Transplant. 2019 Sep;33(9):e13512.
- Clin Transplant. 2019 Sep;33(9):e13513.
- Clin Transplant. 2019 Sep;33(9):e13525.
- Clin Transplant. 2019 Sep;33(9):e13526.
- Clin Transplant. 2019 Sep;33(9):e13528.
- Clin Transplant. 2019 Sep;33(9):e13543.
- Clin Transplant. 2019 Sep;33(9):e13544.
- Clin Transplant. 2019 Sep;33(9):e13545.
- Clin Transplant. 2019 Sep;33(9):e13547.
- Clin Transplant. 2019 Sep;33(9):e13548.
- Clin Transplant. 2019 Sep;33(9):e13552.
- Clin Transplant. 2019 Sep;33(9):e13553.
- Clin Transplant. 2019 Sep;33(9):e13553.
- Clin Transplant. 2019 Sep;33(9):e13587.
- Clin Transplant. 2019 Sep;33(9):e13589.
- Clin Transplant. 2019 Sep;33(9):e13589.
- Clin Transplant. 2019 Sep;33(9):e13595.
- Clin Transplant. 2019 Sep;33(9):e13622.
- Clin Transplant. 2019 Sep;33(9):e13623.
- Clin Transplant. 2019 Sep;33(9):e13623.
- Clin Transplant. 2019;33:e13510.
- Clin Transplant. 2019;33:e13514.
- Clin Transplant. 2019;33:e13588.
- Clin Transplant. 2019;e13544. Clin Transplant. 2019 Sep;33(9):e13652.
- Clinical Transplant. 2019;33:e13510.
- Clinical Transplantation. 2019;33:e13514.
- Clinical Transplantation. 2019;33:e13587.
- Clinical Transplantation. 2019;e13499.
- Clinical Transplantation. 2019;e13499.
- Clinical Transplantation. 2019;e13526.
- Clin Microbiol Infect. 2022 Feb 18:S1198-743X(22)00078-7.
- Foscavir [package insert]. Lake Forest, IL: Hospira Inc; 2017.
- Ganciclovir [package insert]. Lenoir, NC: Exela Pharma Sciences; 2017.
- Hepatology. 2020;71:686:721.
- Infect Dis Clin North Am. 2016 Mar;30(1):51-83.

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References

- J Am Soc Nephrol. 2020 Nov;31(11):2678-2687.
- J Antimicrob Chemother. 2015 Nov;70(11):3116-23.
- J Heart Lung Transplant. 2010;29:914-56.
- J Heart Lung Transplant. 2017 Oct;36(10):1137-1153.
- J Heart Lung Transplant. 2019;38:1296-1305.
- J Infect Dis. 2009 Sep 15;200(6):1002-11.
- J Natl Compr Canc Netw. 2016 Jul;14(7):882-913.
- Lancet Infect Dis. 2019 Dec;19(12):e405-e421.
- Mayo Clin Proc. 2011 Aug;86(8):805-17.
- MMWR Recomm Rep. 2020 Jun 26;69(4):1-16.
- MMWR Recomm Rep. 2021 Jul 23;70(4):1-187.
- N Engl J Med. 1990 Nov 22;323(21):1451-7.
- N Engl J Med. 2007 Dec 20;357(25):2601-14.
- N Engl J Med. 2016 Feb 11;374(6):542-54.
- N Engl J Med. 2019 Apr 25;380(17):1606-1617.
- N Engl J Med. 2022 Feb 10;386(6):509-520.
- N Engl J Med. 2021 Mar 4;384(9):795-807.
- N Engl J Med. 2022 Feb 16;NEJMoa2118542.
- N Engl J Med. 2022 Jan 27;386(4):305-315.
- Maribavir [package insert]. Lexington, MA: Takeda Pharmaceuticals America, Inc; 2021.
- Public Health Rep. 2013 Jul;128(4):247-343.
- Transpl Infect Dis. 2002 Dec;4(4):183-8.
- Transpl Infect Dis. 2007;9(4):310-317.
- Transpl Infect Dis. 2014;16(2):213-224.
- Transpl Infect Dis. 2015;17:163-173.
- Transpl Infect Dis. 2019 Dec;21(6):e13166.
- Transpl Infect Dis. 2020;e13483.
- Transpl Infect Dis. 2021 Jun;23(3):e13515.
- Transpl Infect Dis. 2021 Aug;23(4):e13570.
- Transplantation. 2010 May 15;89(9):1057-70.
- Transplantation. 2018 Jun;102(6):900-931.
- Transplantation. 2020;104:404-09.
- Valganciclovir [package insert]. San Francisco, CA: Genentech USA, Inc; 2017.
- Virazole [package insert]. McPherson, KS: Hospira Inc; 2019.
- <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>
- <https://www.fda.gov/media/154701/download>
- <https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html>
- https://www.myst.org/sites/default/files/Donor%20Testing%20Document_07.07.21.pdf
- <https://www.myst.org/sites/default/files/AST%20Statement%20on%20Oral%20Antiviral%20Therapy%20for%20COVID%20Jan%204%2028%29.pdf>
- <https://www.hep-druginteractions.org/checker>
- <https://www.hiv-druginteractions.org/checker>

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Infection Prevention and Management in Solid Organ Transplant Patients

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