THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
HEERSINK SCHOOL OF MEDICINE

Transplant Infectious Disease Update

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Transplant Infectious Diseases

Disclosures

- I have no financial disclosures.

Learning Objectives

- Differentiate level of risk for preventable infections amongst transplant recipients, specifically CMV and PJP.
- Recognize complications of prophylactic medications and identify next steps in management

Outline

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- Cytomegalovirus
  - Background
  - Prevention strategies
  - Cases
- Pneumocystis
  - Background
  - Prevention strategies
  - Cases

Cytomegalovirus

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- Member of herpes virus family
- Seroprevalence ~ 50% in US
  - Presence of antibody = latent infection
- Primary infection generally self-limited febrile illness in childhood

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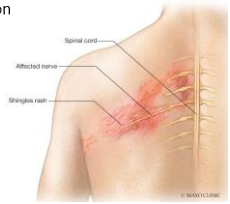
Where does CMV come from?

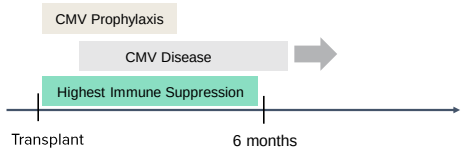
Why have I never heard of this before?

A helpful example
Varicella / Chickenpox

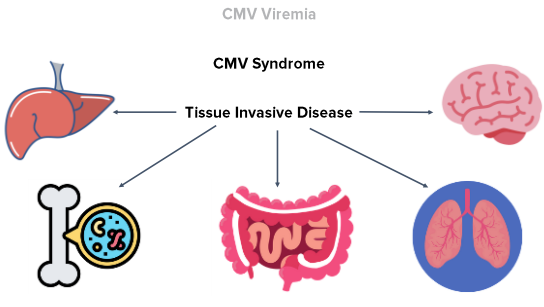
- Many patients have context of chickenpox and shingles rashes
- Example of viral latency and reactivation



Timing of Infection



CMV disease



CMV Syndrome

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Mono-like illness

- Fever, fatigue, myalgias
- Labs: LFT abnormalities (2-3X ULN), atypical lymphocytes, lymphopenia, thrombocytopenia

Transplant patients

~60% of CMV disease in transplant patients presents in this form

Fakhreddin et. al. GE Research and Practice
DOI: doi/10.1155/2019/6156581

Indirect Effects

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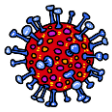
- Infections (bacterial, fungal, viral)
- PTLD
- Cardiovascular events
- New onset- diabetes mellitus
- Acute rejection
- Mortality



No clear consensus on viral load required for these indirect effects

Kotton Am J Tx doi.10.1111/ajt.12006

Who is at Risk

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Antibodies = Latency

CMV Risk

Donor (+) / Recipient (-)

Donor (+/-) / Recipient (+)

Donor (-) / Recipient (-) ***

*** Low risk initially – at risk for natural acquisition post- transplant

Additional Risk Factors

- Lymphocyte depletion
- Allograft rejection
- Type of transplant
  - Lung among highest risk
- Severe illness or infection

Prevention

- Virus persists lifelong, mostly in latency
- Transmission will occur with organ from CMV positive donor

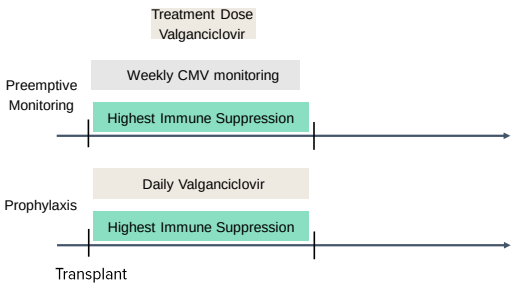
Tools

- No vaccine currently available

- Antivirals
  - Valganciclovir 900mg daily (preferred)
  - Letermovir 480mg daily

(there are additional antiviral options used for treatment of drug resistant infections Maribavir, Foscarnet, Cidofovir)

Methods of Prevention



Preemptive Monitoring vs Prophylaxis

TABLE 2 Characteristics of antiviral prophylaxis and preemptive therapy

	Antiviral prophylaxis	Preemptive therapy
Clinical efficacy	Yes (based on large randomized controlled clinical trials)	Yes (based on fewer and smaller trials), including D+/R− kidney and liver recipients
Ease of application	Easier to coordinate	More difficult to coordinate Viral load thresholds not defined; each program should develop viral load thresholds for various clinical indications
Delayed-onset CMV disease	Common in CMV D+/R− transplant recipients (post-prophylaxis delayed-onset CMV disease)	Less common
Cost	Higher drug costs	Higher laboratory costs
Toxicity	Greater drug toxicity (myelosuppression)	Lesser drug toxicity with shorter courses of antiviral therapy
Indirect effects (graft loss, mortality, and opportunistic infections)	Positive impact (meta-analyses and limited comparative trials)	Very limited data
Drug resistance	Yes	Yes

Razonable et. al. DOI: 10.1111/ctr.13512

Case 1

65 year-old with liver transplant for MASLD 5 months prior returns to clinic for routine follow-up. He has done well. CMV serologies Donor (+) / Recipient (-).

He is having leukopenia and you are concerned valganciclovir is contributing.

Which of the following would be your next step in management?

A) Stop prophylaxis as sufficient course has been provided
B) Stop prophyaxis and move to preemptive monitoring protocol
C) Transition prophylaxis to letermovir
D) Decrease to low dose valganciclovir (450mg daily)
E) Provide dose filgastrim

How long for prophylaxis?

	Liver	Kidney	Heart	Lung
D + / R -	3-6	6	3-6	6-12
R +	3	3	3	6

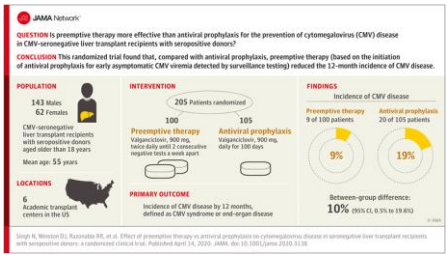
Values in Months

Kotton et. al. *DOI:* 10.1097/TP.0000000000002191

If moving to preemptive protocol when would we treat?

Population	Threshold	Comments	Reference
High risk D+R–			
39 D+R– SOT (23 kidney, 15 liver, 1 heart)	1500 IU/mL in plasma	No episodes of symptomatic CMV disease were diagnosed in patients with viral loads below 1500 IU/mL. Very high rate of infection (36/59).	195
Mixed risk D+R– and R+			
689 kidney (n = 368) and liver (n = 321), 11% D+R–, 71% R+	3000 copies/mL in whole blood, twice a week (same group later converted this to 2520 IU/mL [1g] see below)	More of a study of preemptive therapy and effect of immunity than analysis of threshold	172
3/45 D+R– 42/45 D+R+ SOTR	2275 IU/mL (2500 copies/mL) in plasma	This threshold allowed for discrimination between self-clearing infections and those requiring therapy. Focus of study on use of CMV DNAemia vs antigenemia.	197
59 Kidney, liver, HSCT patients (minority were higher risk)	2520 IU/mL (3000 copies/mL) of whole blood	Whether antiviral treatment needed for PET @ 2520 IU/mL (yes); not an analysis of best threshold, but whether 2520 IU/mL is an effective threshold (yes).	196
Lower risk R+			
252 R+ SOTR	3983 IU/mL threshold resulted in 99.6% NPV, "the great majority of patients at lower risk will not develop CMV disease without specific antiviral therapy"	Analysis of best threshold; single center and only seropositive recipients	198

Kotton et. al. *DOI:* 10.1097/TP.0000000000002191



Letermovir Prophylaxis?

- Matched control paper (small numbers)
  - Noninferior in preventing CMV disease
  - Leukopenia improved
  - Tacrolimus increased (recommended 50% reduction when starting)
- RCT in JAMA for high risk Renal Transplant Recipients
  - Noninferior in preventing CMV disease
  - Less leukopenia

Winstead et. al. *DOI:* 10.1111/tid.13570 Limaye et. al. doi:10.1001/jama.2023.9106

Letermovir Side Effects

- Drug-drug interactions with tacrolimus
- Nausea / abdominal pain
- Peripheral edema

Cost and coverage may be a barrier

Does not cover other herpes viruses

Low Dose Valganciclovir

- Practice sometimes called "mini-dosing"
- AST guidelines recommend against this practice in any circumstance
- Consensus guidelines from 2018 qualify that data is very limited to retrospective studies in low risk patients & also do not recommend

Would avoid this approach given the risk for drug resistance development and alternatives available.

Management of leukopenia beyond stopping valganciclovir

- Filgastrim administration
- Reduction of IS if able, particularly MMF
- Addressing other marrow suppressive medications

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Case 2

35 year-old with kidney transplant for PKD 2 years prior who presented for routine outpatient follow-up.
Stable immune-suppression and course uncomplicated. Feeling a little under the weather for the last 24 hours with some URI symptoms. Reports something is going through the elementary school and both children have been sick. Routine labs unremarkable.

72 hours later a CMV quant from whole blood returns 500 IU/mL. You call and learn she feels back to normal.

Initial Serologies Donor + / Recipient + and completed 3 months of prophylactic valganciclovir. She lives in Mobile.

What would be your next step in management?

A) Nothing further, 6 month follow-up
B) Arrange for CMV DNA in Mobile in 1 week
C) Initiate valganciclovir at prophylactic dose
D) Initiate valganciclovir at treatment dose

CMV testing options

- CMV IgM/ IgG – mainly used pre-transplant, occasionally look for seroconversion post
- CMV T-cell immunity assay – used to assess immune response,
- CMV viral culture – costly and poor sensitivity
- CMV antigenemia – limitations in leukopenia, technically complicated, difficulty to standardize
- CMV QNAT testing (DNA) –the current "gold standard"

CMV QNAT

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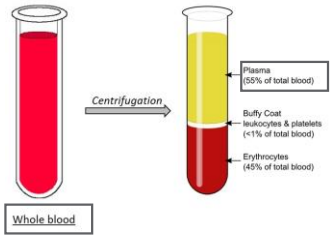
Whole Blood
- Positive earlier
- Higher quantity/ mL

Plasma
- Better predictor for relapse when positive

UAB testing runs on whole-blood

Consistency is key



CMV QNAT Standards

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- Standard should be reported as IU/mL
  - 1 IU/ mL = 1.72 copies/ mL
- Check values 1-week apart
  - 3 fold increase (0.5 log) required to be significant
  - 5 fold increase (0.7 log) required when viral load ≤ 1000
- WHO standard for Lower Limit of Quantification is 200 IU/mL

Limaye et. al. CMR https://doi.org/10.1128/CMR.00043-19.

Reasons to Order CMV QNAT

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- Concern for Tissue invasive disease
  - Beware false negatives
    - GI disease
    - Lung Transplant with pneumonitis
    - Very rare in highest risk patients
- Concern for CMV syndrome
- Pre-emptive Protocol
- Monitoring response to therapy
- Surveillance after prophylaxis
  - no data to support, general consensus (if done) ≤ 12 weeks

Sent as part of work-up for acute event with better alternative found.

Approach to Positive Result

1, Determine pre-test probability

- Reason test was sent
- Patients risk factors for CMV
- Is there an alternative explanation

2, Consider CMV QNAT value

- Some pre-emptive protocols begin 1,500-3,000 IU/mL
- UAB uses highly sensitive assay (200 IU/mL standard LLD)
- Trend most valuable piece of information

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Case 3

55 YO with heart transplant for NICM 9 months prior was found to have CMV QNAT 2,000 IU/mL. Serologies D(+) / R (-) and he completed 6 months of prophylaxis with valganciclovir. You restart valganciclovir at treatment dose and schedule follow-up labs in one week.

Follow-up labs in one week return with CMV QNAT of 5,000 IU/mL. Patient remains asymptomatic and is otherwise doing well.

What is your next step in management?

A) Continue valganciclovir at current dose
B) Review valganciclovir dosing with pharmacist
C) Admit for IV Ganciclovir
D) Admit for IV Foscarnet
E) Start oral Maribavir

Case 3

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B) Review valganciclovir dosing with pharmacist

- Dosing is titrated significantly based off GFR
- Cerner is a poor predictor of GFR
- If kidney dysfunction present, would consider reviewing dosing before starting – underdosing may predispose to drug resistance

Drug Resistant CMV

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- Foscarnet
  - High nephrotoxicity, electrolyte wasting
  - IV only, requires inpatient monitoring
- Cidofovir
  - High nephrotoxicity
  - IV only
- Maribavir
  - Oral and minimal toxicity
  - Altered taste in $^{\sim}$ half of patients although to varying degree
  - May fail with high viral replication

Case 3

36

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What is your next step in management?

A) Continue valganciclovir at current dose

(assuming you checked with pharmacy already)

May take 2 weeks to reach plateau

CMV Key Points

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- Risk defined by Serologies and Type of Transplant
  - D+ / R - highest risk
  - Lung transplant highest risk
- Prevention strategies include Prophylaxis vs Preemptive monitoring
  - UAB uses prophylaxis, which makes it the best option for our patients
  - There is a role for monitoring though in select cases
- Valganciclovir may worsen leukopenia
  - There are numerous strategies to address this, guided by patient factors
  - There are some institutional guidelines in place, but low threshold to engage TxID if concerns or questions

Case 4

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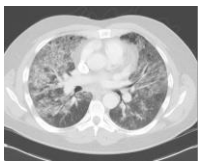
40 y/o female with liver transplant 9 months prior for AIH presents with dyspnea.

Transplant course complicated by CMV syndrome at 8 months and recent elevated liver enzymes treated with increased steroids.

She has 1 week of fatigue, dry cough, and increasing dyspnea. She was admitted and quickly escalated to 6L NC.

You are the overnight admitting team & can send one test to confirm your suspicion- What would you send?

A) CMV QNAT
B) Beta-D-Glucan
C) Urine histoplasma antigen
D) I can't answer till I complete my med-rec



Pneumocystis

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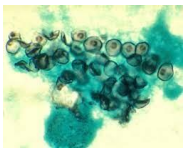
- Opportunistic fungal pathogen
- Transmitted through person-person spread
- Symptomatic disease limited to severely immune-suppressed



Timing of Infection

- Without prophylaxis
  - Most occurred within first 6 months
  - Rates 5-15%
- Prophylaxis now universal immediately post-transplant so disease occurring later, typically at times of increased risk

PJP Risk Factors

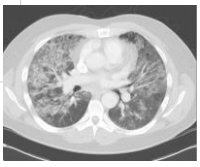
- Lung transplant
- Lymphopenia
- CMV infection
- Hypogammaglobulinemia
- Graft rejection
- Older age
- Corticosteroids

Fishman et. al. DOI: 10.1111/ctr.13587

PJP Clinical Presentation

Table 2. Signs and symptoms of *Pneumocystis* pneumonia

Sign or Symptom of PJP	Incidence
Fever	81%-87%
Dyspnea	66%-68%
Cough	71%-81%
Chest pain	23%-24%
Abnormal lung auscultation on examination	30%-34%
Abnormal chest radiography	92%-96%
Hypoxemia	78%-91%



Presentations often more rapid in development and severe than case studies describing disease in patients with AIDS

Fishman et. al. DOI: 10.1111/ctr.13587

Case 4

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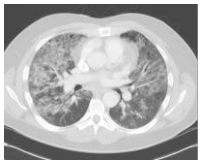

Prophylaxis

- All SOT recipients should receive 6-12 months
- Lung transplant – lifelong
- Prior PJP – lifelong
- Heart may extend to lifelong
- Any SOTR with risk factors (rejection, CMV disease, flare of autoimmune disease) may consider restarting

Bactrim is the preferred agent. Would not expect PJP disease if on Bactrim prophylaxis.

Bactrim (Trimethoprim/ sulfamethoxazole)

Side Effects

- Bone Marrow Suppression
- Rash (including SJS)
- Hyperkalemia
- Creatinine rise

Dosing

SS-daily

DS – 3 X week

Benefit of covering Toxoplasma as well

Case 5

65 YOF with history of heart transplant 3 months prior presents to ED. She was on valganciclovir and Bactrim for prophylaxis, but post-transplant course complicated by leukopenia so Bactrim switched to Dapsone a couple weeks ago.

She presents now with several days of weakness, headache and dyspnea. She has blue discoloration of her lips and nails.

O2 sat 86% on RA and 87% on 6L NC.

ABG: performed with O2 sat 99% measured

What is the most likely cause of this patients illness?

A) Toxoplasmosis
B) Pneumocystis
C) Drug Side Effect

Dapsone

- Second line prophylactic agent
- Not sufficient for Toxoplasma prevention– (pyrimethamine added)

Side Effects

- Hemolytic Anemia
- Methemoglobinemia

(both more common in patients with G6PD deficiency)

Dosing

50-100mg daily

Atovaquone

- Suspension with bad taste
- May be sufficient for Toxoplasma prevention

Side Effects

- Diarrhea

- Breakthrough infections common if under-dosed

Dosing

1500mg daily

Pentamidine

- Aerosolized delivery
- Not sufficient for Toxoplasma prevention

Likely inferior for PJP prevention as compared to Bactrim and Dapsone

Case 4

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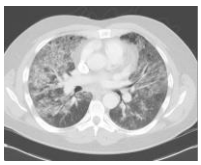

PJP Lab Testing

Beta D- Glucan
- Polysaccharide that is a constituent of the cell wall in most fungi.
- Elevated with pneumocystis (and other invasive fungi)
- Sensitivity & Specificity (outside of HIV) 70-80%
- False positives: blood transfusions, Dialysis, IVIG

LDH
- Helpful in HIV, but specificity low in other IC populations

PCR testing
- Our assay validated for BAL samples
- **Most valuable when high pre-test probability**

Silver Staining
- Path testing performed on BAL samples

PJP Management

- Bactrim 15-20mg/kg (preferred)
- Primaquine / Clindamycin (second line)
- Adjunctive steroids?

Original Article

Adjunctive glucocorticoid therapy for *Pneumocystis jirovecii* pneumonia in solid organ transplant recipients: A multicenter cohort, 2015-2020

Seyed M. Hosseini-Moghaddam [1], Sagar Kothari [1], Atul Humar [1], Hanan Albasata [1], Zachary A. Yetmar [2], Raymund R. Razonable [2], Dionysios Neofytos [3], Matilde D'Asaro [3], Katia Boggian [4], Cedric Hirzel [5], Nina Khanna [6], Oriol Manuel [7], Nicolas J. Mueller [8], Hannah Imlay [9], Dima Kabbani [10], Varalika Tyagi [10], Olivia C. Smibert [11,12,13,14,15], Mohamed Nasra [11,12,16], Lauren Fontana [17], Karam M. Obeid [17], Jay A. Fishman [18]

PJP Key Points

- Risk defined by state of immune-suppression
  - Lung transplant highest risk
  - Rejection, steroids, lymphopenia, hypogammaglobulinemia, infection
- Primary prophylaxis in all for 6-12 months
  - Consider extension in those with risk factors
- Bactrim is preferred agent for prophylaxis
  - Breakthrough infections exceedingly rare with Bactrim & Dapsone
  - Recognizing side effects of Bactrim and alternative agents is important

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Thank you!