15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW
AUGUST 17-21, 2024

CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

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7/1/2024

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Disclosures of Financial Relationships with Relevant Commercial Interests		
Company	Role	Details
Evrys	Consultant	CMV treatment in transplant
Kamada Biotest	Consultant, research	Immunoglobulins and organ transplant infection prevention
Merck	Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME)	Transplant infections CMV antiviral trial, adjudication Pneumococcal vaccine, adjudication
QIAGEN	Consultant, research	Novel diagnostics in transplant patients
Shire/Takeda	Consultant, Adjudication committee member	CMV management in transplant patients
Roche Diagnostics	Research	Review of risk factors for herpes viral infections after transplant

Human Herpesviruses Family

1. Herpes simplex virus type I (HSV-1)
2. Herpes simplex virus type 2 (HSV-2)
3. Varicella-zoster virus (VZV)
4. **Epstein-Barr virus (EBV)**
5. **Cytomegalovirus (CMV)**
6. **Human herpesvirus type 6 (HHV-6)**
7. Human herpesvirus type 7 (HHV-7)
8. **Human herpesvirus type 8 (HHV-8)**

Differential Diagnosis of Pharyngitis

Table 1. Differential Diagnosis of Pharyngitis.*

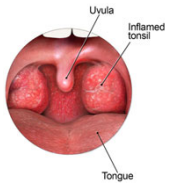
Pathogen	Affected Age Group	Season†	Associated Diagnosis and Distinguishing Feature‡
Respiratory viruses			
Rhinovirus	All	Fall and spring	Common cold
Coronavirus	Children	Winter	Common cold
Influenza virus	All	Winter and spring	Influenza
Adenovirus	Children, adolescents, and young adults	Summer (outbreaks) and winter	Pharyngoconjunctival fever
Parainfluenza virus	Young children	Any	Fever, cold, croup
Other viruses			
Epstein–Barr virus	Adolescents and adults	Any	Infectious mononucleosis (80%)
Cytomegalovirus	Adolescents and adults	Any	Heterophile antibody–negative mononucleosis (5 to 7%) No or mild pharyngitis, anicteric hepatitis
Herpes simplex virus	Children	Any	Gingivostomatitis
Coxsackievirus A	Children	Summer	Herpangina, hand–foot–mouth disease
Human immunodeficiency virus	Adolescents and adults	Any	Heterophile antibody–negative (<1%)
Human herpesvirus 6	Adolescents and adults	Any	Heterophile antibody–negative (<10%)
Bacteria			
Group A streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash, no hepatosplenomegaly
Group C and group G streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash
Arcanobacterium haemolyticum	Adolescents and young adults	Fall and winter	Scarlatiniform rash
Corynebacterium diphtheriae		Fall and winter	Tonsillar, pseudomembrane myocarditis
Neisseria gonorrhoeae	Adolescents and adults	Any	Tonsillitis
Mycoplasma pneumoniae	School-age children, adolescents, and young adults	Any	Pneumonia, bronchitis
Parasites			
Toxoplasma gondii	Adolescents and adults	Any	Heterophile antibody–negative (<3%) Small, nontender anterior lymphadenopathy

* Data are from Alcaide and Brizno.[58]
† Season is applicable only in temperate climates.
‡ Numbers in parentheses indicate the approximate percentage of mononucleosis cases due to the given pathogen.

* Luzuriaga K, Sullivan JL. N Engl J Med 2010;362:1993-2000.

Features of Common Causes of Mononucleosis Syndrome

	EBV	CMV	Toxo	HIV
Fever	++++	++++	++	++++
Myalgias / Arthralgias	++	+++	+	+++
Lymphadenopathy	++++	+	++++	+++
Sore throat	++++	++	+	+++
Exudative pharyngitis	++++	+	0	0
Headache	+++	++	+	++
Rash	+	+	+	+++
Splenomegaly	+++	++	+	++
Hepatomegaly	+	++	+	0
Atypical lymphocytes (>10%)	++++	+++	+	++
Elevated LFTs	++++	+++	0	+



Non-ID causes of mononucleosis syndrome with atypical lymphocytosis

- Drug hypersensitivity syndrome
- Can be induced by several drugs:
  - anticonvulsants such as **phenytion, carbamazepine**
  - antibiotics such as **isoniazid, minocycline**

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Epstein Barr Virus

Epstein Barr Virus: Epidemiology

- Majority of infections are asymptomatic in early childhood
- Adolescent seroprevalence:
  - Resource limited regions >95%
  - Higher resource regions ~40-50%
- Primary infection in adolescents or adults results in ~50% symptomatic disease (infectious mononucleosis)
- 500 cases/100,000 population/year in USA
  - incidence rate for those 15--19yo estimated 200 – 800 cases per 100,000
- Occasionally transmitted by transfusion or organ/stem cell transplant
  - High risk in EBV seronegative organ transplant recipients for infection, lymphoma
- Latently infected memory B lymphocytes serve as lifelong viral reservoirs
  - EBV is capable of transforming B lymphocytes, resulting in malignancy

Epstein-Barr virus Mononucleosis

- Transmission - saliva (due to prolonged shedding for months), sexual
- Long incubation period – 4 to 8 weeks
- Clinical – viral prodrome with **fever**, malaise, headache
  - **Pharyngitis** with tonsillar exudate
  - Symmetrical cervical **adenopathy**, posterior > anterior
  - Palatal petechiae, periorbital edema, and rash (maculopapular, urticarial, or petechial)
  - Splenomegaly in 15 to 65% of cases
  - Acute symptoms persist 1-2 weeks, fatigue can last for months
- Lab - **> 40% lymphocytosis** with atypical lymphocytes
- Diagnosis - **serology**
  - Non-specific heterophile Ab (“**monospot**”) sensitivity 87%, specificity 91%
  - EBV specific Ab panel
- EBV viral load/PCR - *not necessary for routine mononucleosis*, may be useful in transplant or other immunocompromised patients
- Therapy - supportive, no antiviral therapy, steroids for upper-airway obstruction, hemolytic anemia, and thrombocytopenia (rash with ampicillin)
- Prevention - no vaccine (Moderna mRNA vaccine phase 1 Eclipse Trial, ending 2025)
- EBV reactivation mostly asymptomatic; can reflect extent of immunosuppression

Complications of Primary EBV Infection/Infectious Mononucleosis

General:

- Splenic rupture in 0.5-1%, male > female, mostly w/in 3 weeks (up to 7 weeks)

****avoid contact sports for 4 weeks minimum****

- Prolonged fatigue/malaise (>6 mo. in 10%)
- Hepatitis, rarely with fulminant hepatic failure
- Pneumonitis
- Peritonsillar abscess
- Airway obstruction from massive adenopathy

Heme syndromes:

- Neutropenia
- TTP-HUS
- DIC
- Acquired hypogammaglobulinemia
- X-linked lymphoproliferative disease (EBV as trigger)
- Hemophagocytic lymphohistiocytosis (HLH) (estimated 50% of all HLH cases from EBV)

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Neurologic Complications of Primary EBV Infection/Infectious Mononucleosis (1 to 5% of cases)

- Viral meningitis
- Encephalitis
- Optic neuritis
- Transverse myelitis
- Facial nerve palsies
- Guillain–Barre syndrome
- Acute cerebral ataxia
- Hemiplegia
- Sleep disorders
- Psychoses

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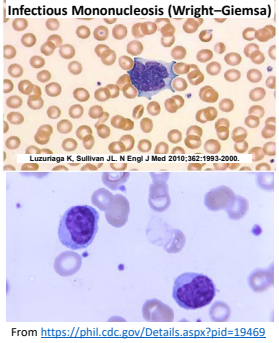
An Atypical Lymphocyte in a Patient with Infectious Mononucleosis (Wright–Giemsa)



From https://phil.cdc.gov/Details.aspx?pid=19469

Atypical lymphocytes

- Large pleomorphic, non-malignant peripheral blood lymphocytes
- **CD8+ cytotoxic T cells** activated by exposure to viruses (e.g., CMV, EBV, HIV, etc.) or other antigens (e.g., toxo)

General features:

- Low nuclear / cytoplasmic ratio
- Indented or lobulated nuclei with nucleoli
- Cytoplasm often basophilic; can be “sky blue”, with vacuoles and granules

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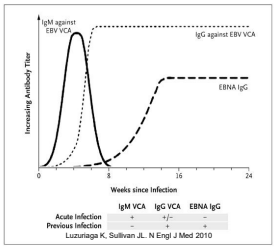
EBV Serology

- **Viral capsid antigen (VCA)**
  - Anti-VCA IgM appears early in EBV infection then disappears in 4-6 weeks
  - Anti-VCA IgG appears in the acute phase of EBV infection, peaks at two to four weeks after onset, declines slightly then **persists for the rest of a person's life.** → **"VCA is here to stay"**
- **EBV nuclear antigen (EBNA)**
  Antibody to EBNA, determined by the standard immunofluorescent test, is not seen in the acute phase of EBV infection but slowly **appears two to four months after onset of symptoms and persists for the rest of a person's life.**
- **Early antigen (EA)**
  Anti-EA IgG appears in the acute phase of illness and generally falls to undetectable levels after three to six months. In many people, detection of antibody to EA is a sign of active infection. However, 20% of healthy people may have antibodies against EA for years.
- **Monospot test**
  The Monospot test is not recommended for general use, poorly sensitive/specific. The antibodies detected by Monospot can be caused by conditions other than infectious mononucleosis.
- The antibody response occurs rapidly during primary EBV infection



Luzuriaga K, Sullivan JL. N Engl J Med 2010

https://www.cdc.gov/epstein-barr/laboratory-testing.html

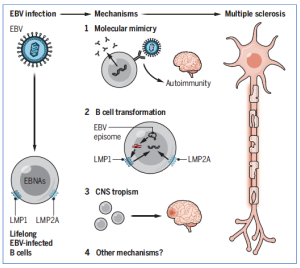
Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1†], Marianna Cortese[1†], Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[9], Stephen J. Elledge[9], David W. Nicholls[10], Ann I. Scher[11], Kassandra L. Munger[1‡], Alberto Ascherio[1,10,11‡]

Science 375, 296–301 (2022)

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

My interpretation:
- Interesting observation
- Nothing for us to do clinically, no antiviral treatments
- EBV vaccine could be helpful in the future (?)



Model for multiple sclerosis development
From Robinson & Steinman, Science, Jan 2022 Vol 375 Issue 6578

EBV after Organ/Stem Cell Transplantation

- High risk for EBV syndromes and proceeding to post-transplant lymphoproliferative disorder (PTLD), especially if donor seropositive/recipient seronegative (D+R-)
  - Best to monitor EBV viral load periodically for the first two years after transplant
  - If EBV viremia, reduce immune suppression whenever possible
- Low EBV viremia (<~5,000 IU/ml) may reflect immunosuppressed state
- No evidence that any currently available antiviral therapy is helpful
  - Valganciclovir only works in lytic phase (small %)
- WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis
- PTLD treatment may include (in order): reduction of immunosuppression, rituximab, and cytotoxic chemotherapy

Allen and Preiksaitis, Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, Clin Trans 2019
Preiksaitis et al, The IPTA Nashville Consensus Conference on Post-Transplant lymphoproliferative disorders after solid organ transplantation in children: III - Consensus guidelines for Epstein-Barr virus load and other biomarker monitoring, Pedia Transplant 2024

QUESTION — PREVIEW QUESTION

An 14-year-old female presents to your office with sore throat, fever, and malaise, with lymphadenopathy and pharyngitis on physical exam.

Her heterophile antibody test (Monospot) is **negative**. In addition to other tests, you order EBV-specific serology.

Which EBV-specific antibody profile would confirm a diagnosis of acute infectious mononucleosis?

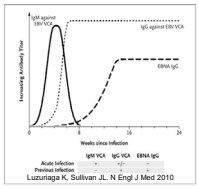
Response	VCA IgM	VCA IgG	EBNA IgG	EA IgG
A	+	+	+	+
B	+	+	-	+
C	-	+	+	+
D	-	-	+	-

QUESTION - ANSWER — PREVIEW QUESTION

The correct answer is B: VCA IgM positive, VCA IgG positive, EBNA IgG negative, EA IgG+.

Response	VCA IgM	VCA IgG	EBNA IgG	EA IgG
A	+	+	+	+
B *	+	+	-	+
C	-	+	+	+
D	-	-	+	-

Antibodies directed against the **viral capsid antigen (VCA), both IgM and IgG**, and also **EA IgG**, are usually detectable at the time of symptom onset. VCA IgG persists for life, while VCA IgM disappears after about a year. Epstein-Barr nuclear antigen (EBNA) IgG does not appear for several weeks after symptom onset and also persists for life.


Luzuriaga K, Sullivan JL. N Engl J Med 2010

CMV

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

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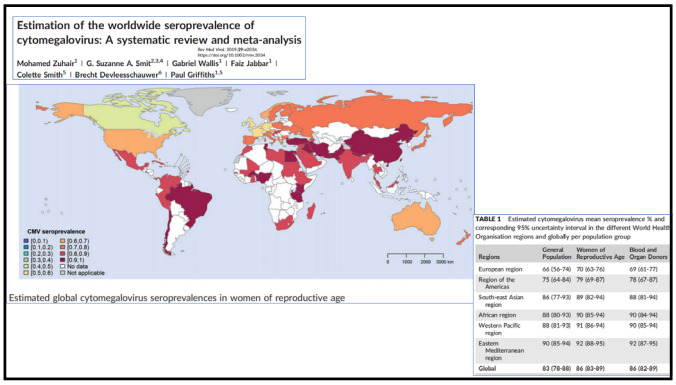
Epidemiology of CMV Infection

- Age-specific peaks in incidence:
  - Children in USA: 10-15% infected before age 5
  - Young adults at onset of sexual activity
  - ~50% adults are CMV IgG+ (NHANES, *Bate et al, Clin Infect Dis 2010*)
  - In low-income regions, CMV seroprevalence approaches 100%
- Transplant:
  - Organ: highest risk is donor seropositive, recipient seronegative (D+R-)
  - Stem cell: highest risk is D-R+ (opposite)
  - Superinfection can occur (organ transplant D+R+ higher risk than D-R+)
- Immunocompromised hosts
  - Seen with inflammatory bowel disease
  - Can see atypical syndromes – worth checking



Transmission & Pathogenesis of CMV

- Beta herpesvirus
- Infection transmitted via:
  - body fluids (urine, semen, cervical secretions, saliva, breast milk)
  - transplanted tissue (blood, organs, stem cell transplant)
    - Reduced with routine use of blood filtered/WBC-depleted
- Primary infection usually asymptomatic/subclinical
  - Mononucleosis syndrome in <10%
- Viral replication in WBCs, epithelial cells (kidney, salivary glands, etc.)
- Following primary infection, prolonged viremia (weeks) and viruria (months) persist despite humoral and cellular immune responses.
  - Ongoing shed is important factor in transmission
- No vaccine available; several under development (Moderna mRNA CMV)

CMV Mononucleosis Syndrome

- CMV causes ~20% of mono syndrome cases in adults
- Presentation: fever, myalgias, atypical lymphocytosis.
  - High fever ("typhoidal"). Pharyngitis and lymphadenopathy (13-17%) less common than with EBV (80%).
  - Rash in up to 30% (variety of appearances)
  - May be clinically indistinguishable from mono syndrome caused by other pathogens
  - Complications: colitis, hepatitis, encephalitis, GBS, anterior uveitis
- Symptoms may persist > 8 weeks
- Diagnosis: IgM/IgG seroconversion (CMV blood PCR - can be confusing)
- Antiviral therapy not indicated (except for severe complications or in immunocompromised)

CMV: Congenital infection

- Leading cause of nonhereditary sensorineural hearing loss in USA
  - Can cause other long-term neurodevelopmental issues, including cerebral palsy, intellectual disability, seizures, vision impairment
- Congenital CMV 0.6% prevalence in high income countries
  - 40,000 children/year in USA
- Primary maternal CMV infection - 30-40% risk of congenital infection
  - Having children in daycare is major risk
- Reactivation maternal CMV infection - 0.9-1.5% risk of congenital infection
- Newborn screening under evaluation, sensitivity of dried blood spots for detecting congenital CMV infection is 73-78%

Cytomegalovirus: the troll of transplantation

Balfour HH, Jr. Arch Intern Med. 1979;139(3):279-80

Remember the tale of "The Three Billy Goats Gruff?" The transplant patient, like the billy goats, initially is on rocky ground and wants to cross the bridge over the rushing river to greener pastures on the other side. Cytomegalovirus is the troll under the bridge, hidden in shadows and often undetectable even by the most sophisticated diagnostic techniques. As we immunosuppress patients to help them cross the bridge, the troll comes out and threatens to devour them. Like the two smaller billy goats in the story, we clinicians are passing the buck to stall for time, hopeful that in the near future our patients, armed with either a vaccine or an effective antiviral agent, will be strong enough to throw the voracious CMV troll off the bridge and back into obscurity.

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CMV INFECTION AFTER ORGAN/STEM CELL TRANSPLANT: A SPECTRUM OF DISEASE

Direct Effects

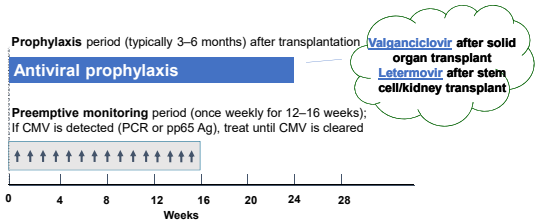
Asymptomatic Viremia

CMV Viral Syndrome
- Flu-like syndrome: fever, malaise, myalgia
- Leukopenia, thrombocytopenia

Tissue-Invasive Disease
- GI diseases: Colitis, Hepatitis
- Pneumonitis
- Myocarditis
- Myocarditis
- Nephritis
- Encephalitis, retinitis

Torres-Madriz G, Boucher HW. Clin Infect Dis. 2008;47(5):702-711;
Kotton CN, CMV: Prevention, Diagnosis and Therapy, AJT 2013

PREVENTION: Prophylaxis vs. Preemptive Therapy



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

CMV Diagnostics

- Serology
  - To diagnose acute infection in normal host, detect IgM or IgM-->IgG seroconversion
  - CMV IgG establishes donor/recipient serostatus/risk in transplantation (no IgM)
  - Serology has no role in diagnosis of acute infection in transplant setting
- Molecular diagnostics – for immunocompromised
  - **Quantitative PCR – detects CMV DNA in blood, other fluids, tissues**
    - Lower (somewhat) sensitivity of blood PCR for CMV GI disease, pneumonitis, retinitis
    - Variations between whole blood and plasma, different testing platforms – pick one and use that to trend results, don't compare across different specimen types/testing platforms
- Histopathology of biopsied tissue
  - Basophilic intranuclear inclusion bodies surrounded by a clear halo – "owl's eye" cells
  - CMV-specific immunohistochemical stains
- Viral culture
  - Specimens: BAL, GI biopsy, etc.
  - Tissue culture: slow; cytopathic effect in 3-21 days (shell vial technique is faster); expensive; sensitivity/specificity not optimal (viral shed vs true infection)

Treatment of CMV after Transplant

Determine severity of infection

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

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

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

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

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

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

* Kotton et al, International CMV Guidelines, Transplantation 2018

Ensure Correct CMV Resistance Testing Ordered

Detects Resistance to:	UL97 Phosphotrans-ferase	UL54 Polymerase	UL27	UL56 Terminase
Maribavir, Letermovir, Ganciclovir, Foscarnet, Cidofovir	x			
Maribavir, Ganciclovir, Foscarnet, Cidofovir		x		
Maribavir			x	
Letermovir				x

What is the definition of resistant/refractory CMV?

Resistant CMV infection: The presence of a ***known viral genetic mutation(s)*** that decreases the susceptibility to one or more anti-CMV medications.

Refractory CMV infection: Persistent signs and symptoms of CMV disease and/or persistent CMV viremia that fails to improve [<1 $\log_{10}$ (<10x) decrease in CMV viral load] or increases after **at least 2 weeks** of appropriately dosed antiviral therapy.

Chemaly R *et al*, Definitions of Resistant and Refractory Cytomegalovirus Infection and Disease in Transplant Recipients for Use in Clinical Trials. CID 2018

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Maribavir: Current State of Regulatory Approval

- Approved by Federal Drug & Food Administration (FDA) in December 2021 (≥ 12 years old) and European Medicines Agency in September 2022 (adults) for **treatment of resistant/refractory CMV disease after SOT/HSCT**
- **Not yet approved for treatment outside of resistant/refractory CMV disease**
  - "A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the **Treatment of Asymtomatic Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients**", ClinicalTrials.gov: NCT02927067 → did not reach non-inferiority endpoint
- **Unlikely to move forward as prophylaxis** in the near future
  - Prior failure in stem cell and liver transplant (likely due to doses used)
- / JOAJMPN® R IIC M®CII IIDINIJM$ / 4 ?IN®<N®

Clinically significant drug interactions with maribavir

Cytochrome-P450 (CYP)/P-glycoprotein	Concomitant medication	Clinical implication of interaction	Clinical management of interaction
CYP-3A4 substrate/ P-glycoprotein substrate	Cyclosporine	Increase cyclosporine concentration	Patients concomitantly receiving maribavir and CYP-3A4/ P-glycoprotein substrates (cyclosporine, everolimus, tacrolimus, sirolimus) should have plasma levels monitored starting at initiation through discontinuation of maribavir.
	Everolimus	Increase everolimus concentration	
	Tacrolimus	Increase tacrolimus C_{max} 38% and AUC 51%	
	Sirolimus	Increase sirolimus concentration	
	Digoxin	Increase digoxin concentrations	Digoxin plasma concentrations should be monitored starting at initiation through discontinuation of maribavir.
	Rosuvastatin	Increase rosuvastatin concentrations	Monitor for myopathy and rhabdomyolysis
CYP-3A4/ P-glycoprotein strong-moderate inhibitor	Diltiazem	Increase maribavir C_{max} 6% and AUC 9%	Can consider co-administering maribavir with strong CYP3A4 inhibitors without dose adjustment, based on lack of toxicities associated with doses up to 1200mg twice daily in studies and lack of 3-fold increase in AUC with strong-moderate CYP-3A4 inhibitors.
	Erythromycin	Increase maribavir C_{max} 26% and AUC 44%	
	Ketoconazole	Increase maribavir C_{max} 17% and AUC 54%	
	Ritonavir	Increase maribavir C_{max} 37% and AUC 63%	
CYP3A4/P P-glycoprotein strong-moderate inducer	Carbamazepine	Decrease maribavir C_{max} 23% and AUC 29%	Consider increasing maribavir doses to 800-1200 mg twice daily
	Efavirenz	Decrease maribavir C_{max} 25% and AUC 42%	Consider increasing maribavir doses to 1200-1600 mg twice daily
	Phenobarbital	Decrease maribavir C_{max} 27% and AUC 39%	Consider increasing maribavir doses to 800-1200 mg twice daily
	Phenytoin	Decrease maribavir C_{max} 31% and AUC 42%	Consider increasing maribavir doses to 1200mg twice daily
	Rifampin	Decrease maribavir C_{max} AUC 61%	Co-administration should be avoided and alternative antimicrobial or antituberculosis therapy should be considered if alternative CMV agents cannot be used.
CYP2C19 substrate	Voriconazole	No effect	Maribavir and voriconazole may be co-administered without dose adjustment. Unknown if interactions with posaconazole, itraconazole, and isavuconazole, exist, but unlikely based on voriconazole data.

Gandhi RG & Kotton CN, Evaluating the Safety of Maribavir for the Treatment of CMV, Therapeutics and Clinical Risk Management 2022:18 223–232

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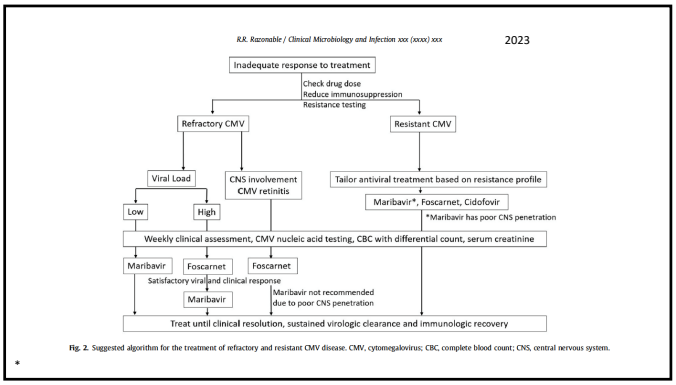

Fig. 2. Suggested algorithm for the treatment of refractory and resistant CMV disease. CMV, cytomegalovirus; CBC, complete blood count; CNS, central nervous system.

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JAMA | Original Investigation

Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients

A Randomized Clinical Trial

June 2023

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

- D+R- kidney transplants
- Compared letermovir 480mg, orally daily (with acyclovir) or valganciclovir 900mg, orally daily (adjusted for kidney function) for up to 200 days after transplant
- **Confirmed CMV disease: 10.4% on letermovir vs 11.8% on valganciclovir = SAME**
- **Leukopenia or neutropenia** by week 28 lower w/ letermovir vs valganciclovir (26% vs 64%; P < .001)
- Quantifiable CMV DNAemia detected in 2.1% on letermovir vs 8.8% on valganciclovir by week 28
  - Of participants evaluated for suspected CMV disease or CMV DNAemia, none (0/52) who received letermovir and 12.1% (8/66) who received valganciclovir had resistance-associated substitutions.
- Fewer participants in the letermovir group than the valganciclovir group discontinued prophylaxis due to adverse events (4.1% vs 13.5%) or drug-related adverse events (2.7% vs 8.8%)

MERCK

Media > News releases > News release

June 6, 2023

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

*previously approved for stem cell transplant prophylaxis

important drug interactions
Tacrolimus
Cyclosporine
Azoles

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

----------RECENT MAJOR CHANGES----------

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

----------INDICATIONS AND USAGE----------

PREVYMIS is a CMV DNA terminase complex inhibitor indicated for:

- Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (1.1)
- Prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]). (1.2)

----------DOSAGE AND ADMINISTRATION----------

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

Pseudotumor presentation of CMV disease: Diagnostic dilemma and association with immunomodulating therapy

"Cytomegalo-tumor"

Olivia C. Smibert[1,2] | Cody C. Allison[3] | Marcel Doerflinger[3] | Marc Pellegrini[3] | Danny Rischin[4] | Alesha Thai[4] | Monica A. Slavin[3,5] | Camille N. Kotton[3]

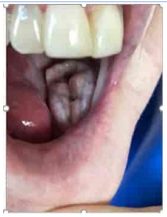

FIGURE 1 Fungating ulcerated lesion on oral mucosa of the left lower mandible at the site of prior SCC resection and marginal mandibulectomy

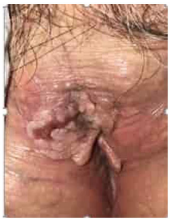

FIGURE 3 Six centimeter cluster of verrucous papules in a cluster encompassing the entire right labia minora, the right clitoral hood, and the margin of the right labia majora and sparing the periurethral area

Transpl Infect Dis. 2020;00:e13535.
https://doi.org/10.1111/tid.13535

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

QUESTION

A kidney transplant recipient (D+R-) gets 6 months of valganciclovir prophylaxis. Three months later, presents with fevers, malaise, low WBC, atypical lymphocytes, low platelets, hepatitis. What do you recommend?

A. Could be many things – send for many different cultures and viral load testing
B. This is probably CMV – send CMV viral load testing and routine cultures, and start treatment with valganciclovir 900mg po twice a day (renally adjusted as needed) (plan if not better, will check additional diagnostics)
C. Call a transplant ID colleague for guidance

QUESTION - ANSWER

A kidney transplant recipient (D+R-) gets 6 months of valganciclovir prophylaxis. Three months later, presents with fevers, malaise, low WBC, atypical lymphocytes, low platelets, hepatitis. What do you recommend?

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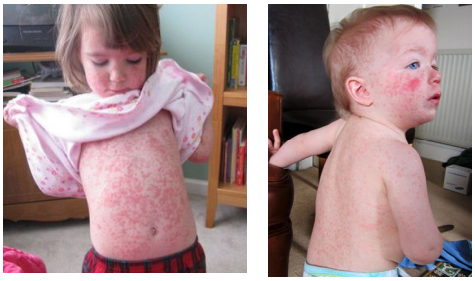
HHV-6

Human Herpesvirus Type 6

- Beta herpesvirus, discovered in 1986
- Two subgroups:
  - HHV-6A – uncommon pathogen, little known about clinical impact or epidemiology
  - HHV-6B – frequent infection in healthy children, etiology of roseola (exanthem subitem), & cause of reactivation disease
- Primary infection common in first year of life, >60% infected by 12 months
- Transmission by saliva; incubation period ~9 days (5-15 days)
- Replicates and establishes latency in mononuclear cells, esp. activated T-lymphocytes
- Can integrate into human germline cells (1%); chromosomally inherited, will be viral load/PCR high level positive forever; can reactivate from integrated state
- No vaccine available or under development

Exanthem subitum (roseola, sixth disease)



Slide courtesy of John W. Gnann Jr., MD, Medical University of South Carolina

Human Herpesvirus Type 6: Normal hosts

- Associated syndromes
  - Exanthem subitum (roseola infantum, sixth disease*)
    - children < 4 y.o.; high fever for 5 days (febrile seizures), followed by a rash
  - Primary infection in adults (very rare) – mononucleosis syndrome
  - *Reactivation disease in transplant patients, esp. encephalitis and pneumonitis*
  - Mesial temporal lobe epilepsy association
  - Not the cause of MS, chronic fatigue, myocarditis, some others
- Diagnosis
  - Classic rash and clinical setting (early childhood)
  - IgG seroconversion
  - PCR from plasma (cell free), CSF, tissue → *immunocompromised patients*
- Therapy
  - Supportive care

**because it was the sixth common childhood rash that scientists named: measles, scarlet fever, rubella, Dukes' disease (now same as scarlet fever), and erythema infectiosum (parvovirus B19)*

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

HHV-6: Immunocompromised Hosts

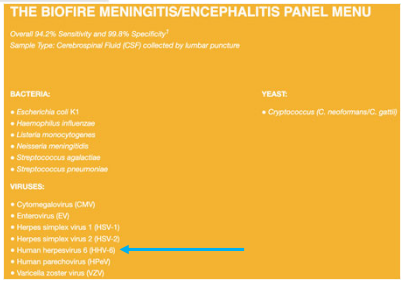
- Associated syndromes
  - Reactivation disease in transplant patients
  - **Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days**
    - 1% of those with HHV-6 viremia
    - Acute memory loss, altered mental status, and seizures; fever is rare
  - Bone marrow suppression (maybe also GVHD?)
  - Pneumonitis (rare, harder to prove)
- Diagnosis
  - PCR from plasma (cell free), CSF, tissue
    - High prevalence of viral DNA in peripheral blood mononuclear cells limits the use of PCR to discriminate between latency and active infection, chromosomal integration can be confusing
    - CSF typically normal or only mildly abnormal, slightly elevated WBC and protein, HHV-6 PCR 15,000-30,000 copies/ml
    - Encephalitis – Mild CSF lymphocytic pleocytosis, temporal abnormalities shown on EEG, and MRI hyperintense lesions in the limbic system
- Therapy
  - Ganciclovir or foscarnet x ≥ 3 weeks; decide based on toxicities; cidofovir last choice
  - Treat if encephalitis; not all need treatment, not if just low level HHV-6+ in blood/CSF
  - Reduce immunosuppression if possible; do not use steroids

The BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel

Distinguishing bacterial from viral meningitis based on clinical presentation alone is challenging. Getting fast, pathogen-specific answers can help save lives and guide appropriate therapy.

Make sure that the pathogen you detect fits the clinical scenario

https://www.biofiredx.com/products/the-filmarray-panels/filmarrayme/



HHV-8

Human Herpesvirus Type 8

- Gamma herpesvirus, discovered 1994
- Kaposi sarcoma-associated herpesvirus (KSHV)
- Four variants have been described:
  - classic
  - endemic (Africa, Mediterranean regions)
  - iatrogenic or immunosuppression-associated
  - epidemic or AIDS- associated
- HHV-8 seroprevalence in the US (highly variable internationally):
  - Blood donor populations: 1-5%
  - MSM: 8-25%
  - HIV-positive MSM: 30-77%
  - HIV-positive with KS: 90%
- Route of transmission unknown – Sexual, saliva?
  - Transmission via SOT documented (rare).
- 1° infection usually asymptomatic, some with febrile rash syndrome

HHV-8 Associated Diseases

- **Kaposi sarcoma**. 4 types:
  - Classic: indolent cutaneous proliferative disease, mainly affecting the lower extremities of elderly men of Mediterranean and Ashkenazi Jewish origin
  - Endemic: all parts of equatorial Africa, affecting both children and adults, can be more aggressive than classic
  - Transplant-associated: more often donor-derived (D+R-), can be reactivation
  - Epidemic/AIDS-related): KS is the most common tumor arising in people living with HIV; an AIDS-defining illness
- **Primary effusion lymphoma (body cavity-based lymphoma)**
  - Non-Hodgkin B-cell lymphoma, usually in HIV+. Involves pleural, pericardial, or peritoneal spaces
- **Castleman's disease (HIV+ and HIV-)**
  - Unicentric or Multicentric; hyaline vascular or plasma cell variants – all HHV-8 related. Fever, hepatomegaly, splenomegaly, massive lymphadenopathy
- **KSHV Inflammatory Cytokine Syndrome (KICS) in HIV+.**
  - Fever, elevated IL-6 & IL-10, high HHV-8 VL. High mortality rate.

HHV-8 Diagnosis and Treatment

- Diagnosis
  - HHV-8 IgG
  - HHV-8 PCR on plasma, tissue
  - Biopsy/pathology for primary effusion lymphoma, Castleman's disease, etc
    - HHV-8 immunohistochemistry
- Treatment
  - Reduction of immunosuppression (watch for rejection)/start antiretroviral therapy
  - mTor inhibitors (sirolimus/rapamycin, etc) for transplant patients
  - Antiviral therapies +/- efficacy, not usually recommended, can be considered
  - Intralesional therapy or adjuvant chemotherapy may be required if unresponsive to these conservative measures or for more aggressive disease
  - Kaposi's sarcoma treated as a cancer

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Antiviral Prophylaxis & Treatment Agents

*acyclovir/valacyclovir/famciclovir and letermovir *for prophylaxis only*

**foscarnet, cidofovir, maribavir not usually used for prophylaxis

Antiviral agent	CMV	EBV	HHV-6	HHV-8	HSV	Varicella	BK	Adeno-virus
Commercially available								
acyclovir/valacyclovir/famciclovir*	high dose +/-				x	x		
ganciclovir IV/valganciclovir PO	x		x	+/-	x	x		
foscarnet**	x		x	+/-	x	x		
cidofovir**	x		x	+/-	x	x	poor	+/- IC50
letermovir (prophylaxis only)	x							
maribavir (treatment only)	x	*in vitro*						
Novel/investigational antiviral agents (SOT)								
brincidofovir (not available)	*x*	*x*			*x*	*x*	*x*	*x*
pritelivir (phase III)					*x*			

Modified from Kotton CN, Updates on antiviral drugs for cytomegalovirus prevention and treatment, Curr Opin Organ Transplant 2019, 24:469–475

Summary: EBV, CMV, HHV-6, HHV-8

- Common childhood infections
- All human herpesviruses establish latency
- Serology useful, viral load detection more helpful in immunocompromised
- Infection from donor → recipient usually major risk factor
- Varied spectrum of clinical manifestations, from infectious syndromes to malignancies (EBV, HHV-8)
- Antiviral prophylaxis/treatment – best for CMV, more limited utility for others
- No vaccines available

Questions? ckotton@mgh.Harvard.edu

@KottonNelson

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