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

Speaker: Camille Kotton, MD

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

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Disclosures of Financial Relationships with Relevant Commercial Interests

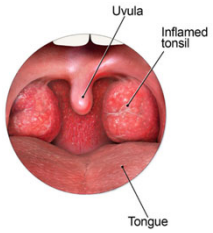
Company	Role	Details
Biotest	Consultant	Scientific advisory board, medical education (CMV immunoglobulins)
Hookipa	Consultant	CMV Vaccine trial
Merck	Consultant	Clinical trial adjudication, scientific advisory board (CMV)
Oxford Immunotec	Consultant	Scientific advisory board (CMV), medical education (TB)
Takeda	Consultant	Clinical trial adjudication, scientific advisory board (CMV)

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)**

"Mononucleosis Syndrome"

- Clinical Features:
  - Fever
  - Malaise
  - Myalgias, arthralgias
  - Pharyngitis
  - Lymphadenopathy
  - Hepatomegaly / splenomegaly
- Laboratory Findings:
  - Lymphocytosis (>50%; >4500/mm3)
  - Atypical lymphocytes (>10%)
  - Abnormal LFTs



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Differential Features of Most 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	++++	+++	+	++
Elevated LFTs	++++	+++	0	+

Differential Diagnosis of Pharyngitis

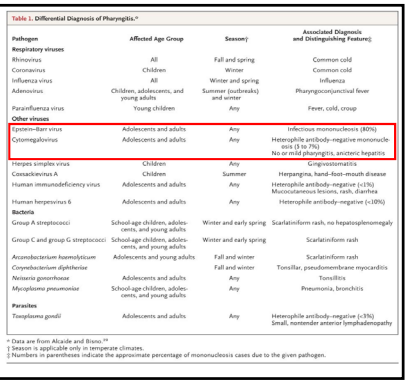

Table 1. Differential Diagnosis of Pharyngitis.*

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 (3 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%) Mucocutaneous lesions, rash, diarrhea
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 Bisno.[19]
† 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.

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Non-ID causes of mononucleosis syndrome with atypical lymphocytosis

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

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 dz (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

EBV Infection: Pathogenesis

- Gamma herpesvirus; HHV-4
- Infectious virus intermittently shed from oropharyngeal epithelial cells
  - Up to 6 months or longer after disease, then intermittently
- Transmission by saliva ("kissing disease"), sexual transmission possible
- Long incubation period – 4 to 8 weeks
- Latently infected memory B lymphocytes serve as lifelong viral reservoirs
  - EBV is capable of transforming B lymphocytes, resulting in malignancy
- EBV reactivation mostly asymptomatic

Infectious Mononucleosis

- Etiology - primary Epstein-Barr virus infection
- Transmission - saliva (due to prolonged shedding for months)
- 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 - lymphocytosis with atypical lymphocytes
- Diagnosis - serologic. Non-specific heterophile Ab ("monospot"); specific Ab (VCA, EBNA)
- Therapy - supportive, no antiviral therapy, steroids for upper-airway obstruction, hemolytic anemia, and thrombocytopenia (rash with ampicillin)
- Prevention - no vaccine

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

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

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

Heme syndromes:

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

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

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

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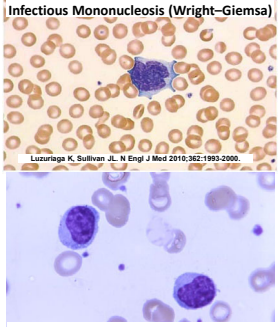
Laboratory Findings in EBV Infectious Mononucleosis

- CBC - elevated lymphocytes, often >50%
- Atypical lymphocytes = range 10-90% (manual differential only)
  - >=10% atypical lymphocytes in a pharyngitis patient --> sensitivity of 75% and specificity of 92% for the diagnosis of infectious mononucleosis (Ebell MH Am Fam Physician 2004)
- Total white blood cell count averages 12,000 to 18,000/microL
- Elevated liver function tests
  - AST, ALT (90%), alkaline phosphatase (60%)
  - Elevated bilirubin less common (45%, but jaundice in <10%)
- EBV viral load/PCR - *not necessary for routine mononucleosis*, may be useful in transplant or other immunocompromised patients

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



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

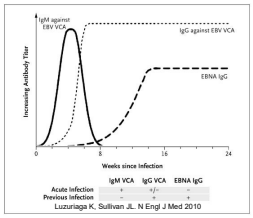
- Large pleomorphic, non-malignant peripheral blood lymphocytes
- **CD8+ cytotoxic T cells** activated by exposure to viruses (e.g., CMV, EBV, HIV, etc.) or other antigens (e.g., toxo)

General features:

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

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**.
- **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

EBV after Solid Organ 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 periodically for the first two years after transplant
- If EBV viremia, reduce immune suppression whenever possible
- No evidence that any current 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

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?

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

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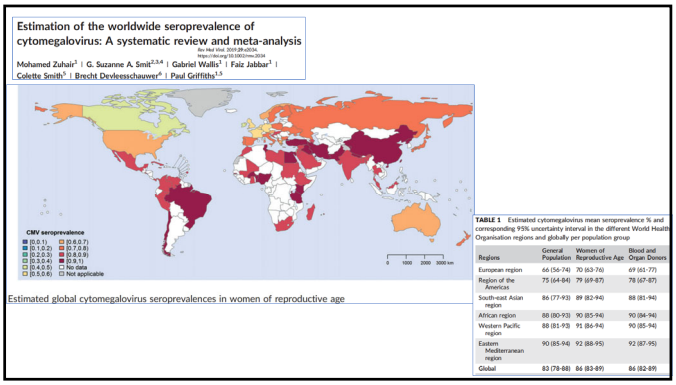
Epidemiology of CMV Infection

- 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*)
- Seroprevalence of CMV correlates inversely with socioeconomic development
  - In the developing world, 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+)



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 back 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.

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

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)

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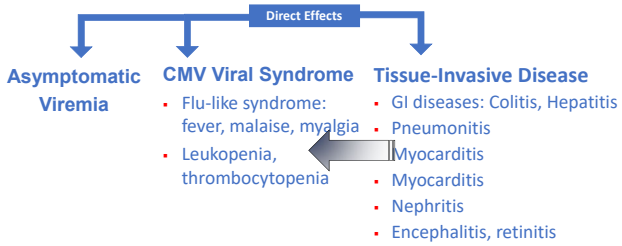
CMV: Congenital infection

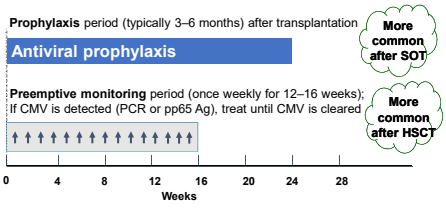
- Leading cause of nonhereditary sensorineural hearing loss
  - Can cause other long-term neurodevelopmental issues, including cerebral palsy, intellectual disability, seizures, vision impairment
- Congenital CMV 0.6% prevalence in developed countries
  - 40,000 children/year in USA
- Primary maternal CMV infection - 30-40% risk
  - Having children in daycare is major risk
  - Infants more likely to have symptoms at birth & long-term sequelae
- Reactivation maternal CMV infection - 0.9-1.5% risk
- Hearing loss similar in both primary and reactivation cohorts
- Newborn screening under evaluation, sensitivity of dried blood spots for detecting congenital CMV infection is 73-78%

CMV INFECTION AFTER ORGAN TRANSPLANT: A SPECTRUM OF DISEASE



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, 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
  - 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 for Transplant Recipients: Consensus Recommendations (Kotton et al, CMV Guidelines, Transplantation 2018)

- For [illegible] oral valganciclovir (900 mg every 12 hours) or intravenous GCV (5 mg/kg every 12 hours) are recommended as first-line treatment in adults with normal kidney
- Valganciclovir is recommended in patients with mild to moderate CMV disease
- Intravenous GCV is recommended in life-threatening & severe disease; after clinical response, intravenous GCV may be transitioned to VGCV
- In patients without concomitant rejection, reduction of immunosuppression is suggested in the following settings: severe CMV disease, inadequate clinical response, high viral loads, and cytopenia
- [illegible]

Risk Factors

- **Inadequate antiviral drug dose or delivery**
- **Prolonged antiviral drug exposure**
- **Ongoing active viral replication (often seen w/ lack of prior CMV immunity D+/R-)**
- **Strongly immunosuppressive therapy**
- **Drugs with lower barrier to resistance**

Rates

- **Among solid organ recipients the usual incidence of resistance after ganciclovir therapy is 5% to 12%, but up to 18% in lung and 31% in intestinal and multivisceral organ transplant recipients**
- **Incidence of resistance is lower, in the 0% to 3% range, with 100 to 200 days of ganciclovir or valganciclovir prophylaxis in D+/R- kidney recipients (IMPACT trial, Humar AJT)**

MASSACHUSETTS GENERAL HOSPITAL TRANSPLANT CENTER

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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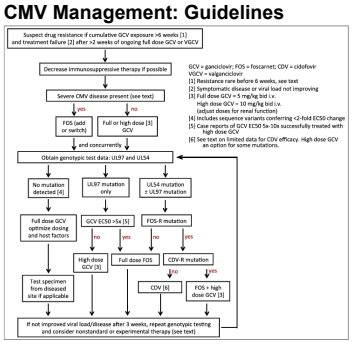
Resistant CMV Management: Guidelines



Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.

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

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

"Cytomegalo-tumor"

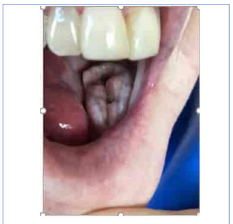


FIGURE 1 Fungating ulcerated lesion on oral mucosa of the left lower mandible at the site of prior SCC resection and marginal mandibulectomy

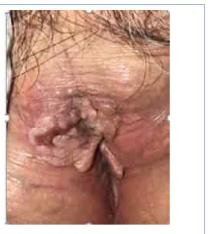


FIGURE 3 Six centimeter cluster of verrucous papules in a cluster encompassing the entire right labia minora, the right clitoral hood, and the margin of the right labia majora and sparing the periurethral area

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

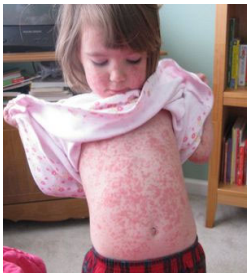
A kidney transplant recipient (D+/R-) gets 3 months of valganciclovir prophylaxis. Three months later, presents with fevers, malaise, low WBC, atypical lymphocytes, low platelets, hepatitis. What do you recommend?

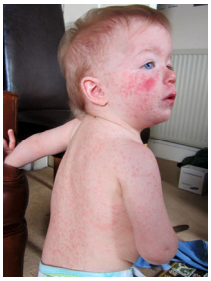
A. Could be many things – send for many different cultures and viral load testing
B. This is probably CMV – send CMV viral load testing and routine cultures, and start treatment with valganciclovir 900mg po twice a day (renally adjusted as needed) (plan if not better, will check additional diagnostics)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

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

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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

HHV-6: Immunocompromised Hosts

- Associated syndromes
  - Reactivation disease in transplant patients
  - Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days
  - 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 – MRI, EEG
- Therapy
  - Ganciclovir or foscarnet; likely decide based on toxicities; cidofovir last choice
  - Treat encephalitis; not all need treatment, not low level HHV-6+ in blood
  - Reduce immunosuppression if possible

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

31 – 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 not usually used for prophylaxis

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

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

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