CMV Diagnosis and Management in children

Melissa Lawler

Paediatric Infectious Disease

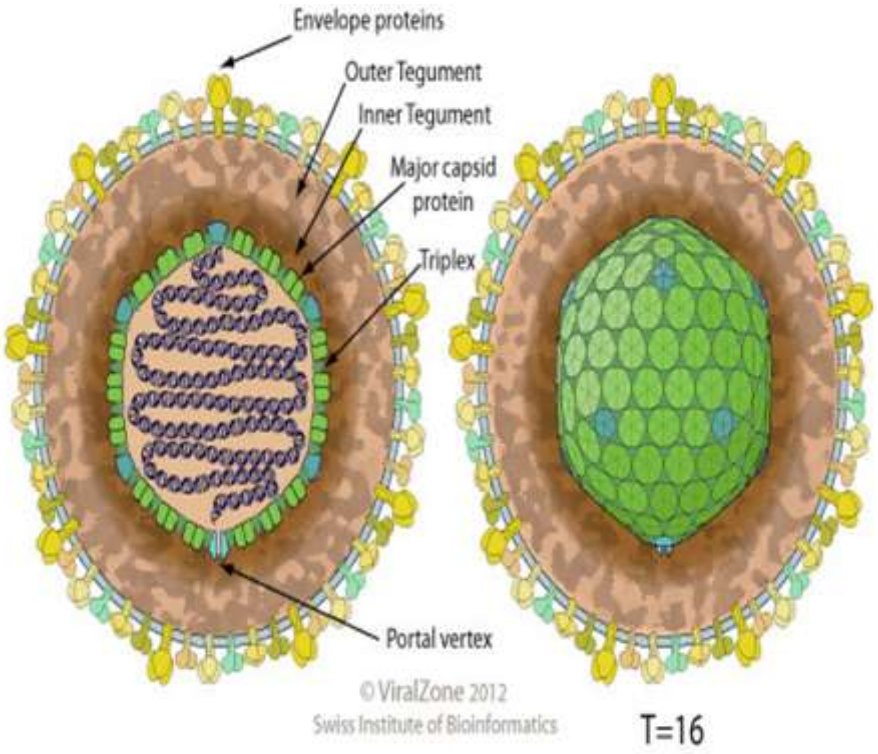
UKZN

Herpesviridae

Betaherpesvirinae

Human cytomegalovirus

double-stranded DNA



HCMV Pathophysiology

Site of inoculation in healthy host → mucosal surface in the upper respiratory or genital tract

Sources of infection: oropharyngeal secretions, urine,cervical and vaginal secretions, semen, breast milk,tears, feces and blood

Viraemia – dissemination

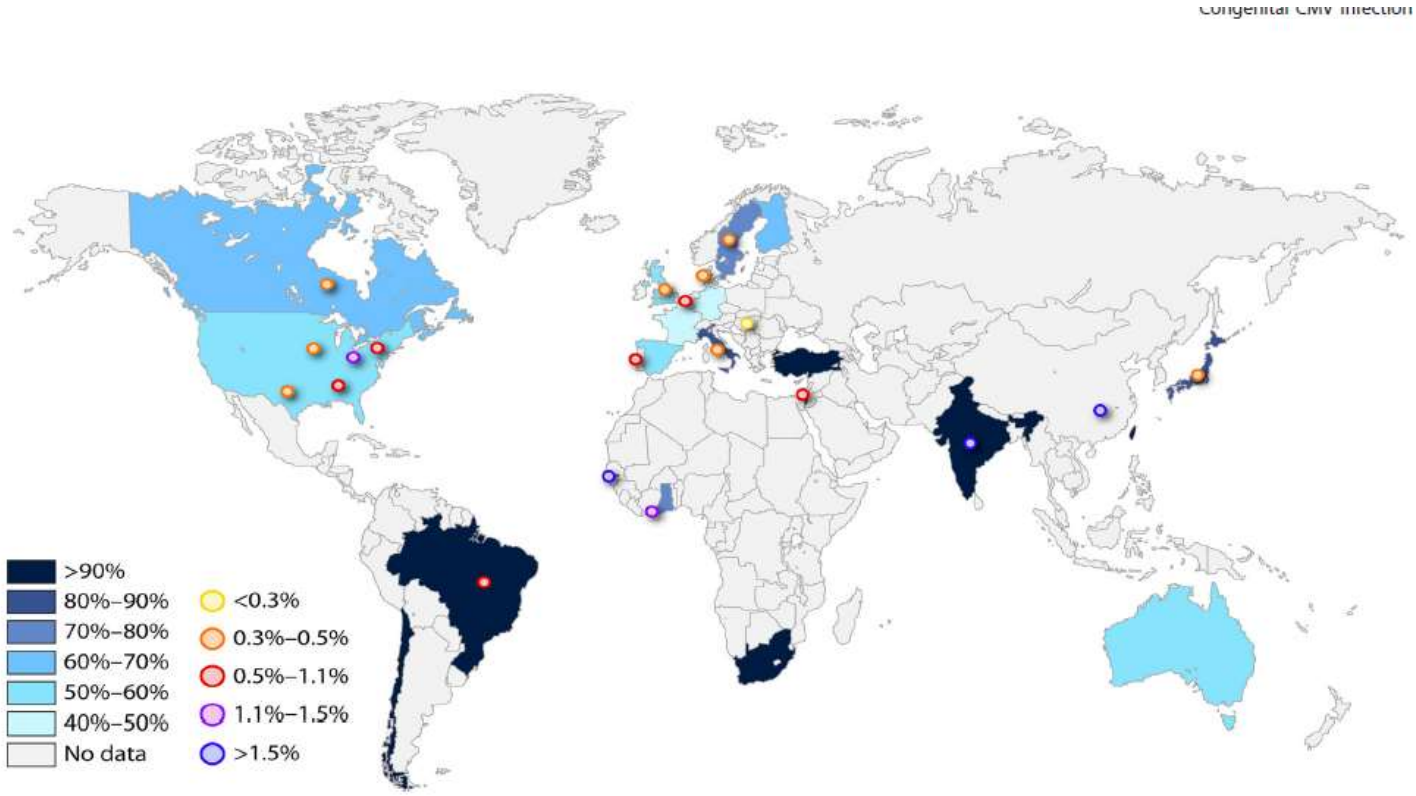
Shedding after 4 to 6 weeks

- continues for months to years

Latency

Disease = Reactivation/primary infection in disabled immune system

CMV Seroepidemiology



Clinical findings

NORMAL HOST

Early childhood – saliva in family or day care settings

Adulthood- sexually and via saliva ,urine, blood transfusions or transplanted organs

Mononucleosis (about 8% of infectious mononucleosis cases)

Rare complications include pneumonia, hepatitis and CNS disease

In children <7 years of age, CMV infection may result in severe liver or respiratory disease

Recurrent infection is rare in the normal host

Clinical findings

NEONATE

Congenital, intrapartum and postnatal routes of infection

Postnatal

- Cervical secretions during vaginal delivery
- Ingestion of CMV-infected breast milk
- Term - rarely result in significant symptoms or sequelae
- Low-birth weight premature infants
  - Worsening respiratory status, neutropenia, or sepsis
  - Long-term sequelae independent from prematurity unclear

Impact of HIV on congenital CMV

HIV-infected women

- CMV seropositive
- More frequent CMV recurrences

Increased risk for congenital CMV infection in neonates

HIV-infected - 3-fold higher risk for symptomatic congenital CMV infection

CMV may act as a cofactor for HIV disease progression

Risk for infant mortality is increased in HIV-CMV-coinfected infants

Accelerated progression of CNS disease in survivors

Resource-limited settings - high rate of coinfections in pregnant women with HIV-1

? influences the transplacental transmissibility of CMV

Placental Infection
- Extensive
- Reduced
- Suppressed

Primary

Recurrent

Fetal Transmission

20% – 40%

0.2% – 2.2%

Symptomatic (5% – 10%)
Intrauterine growth retardation, retinitis, microcephaly, jaundice, hepatosplenomegaly

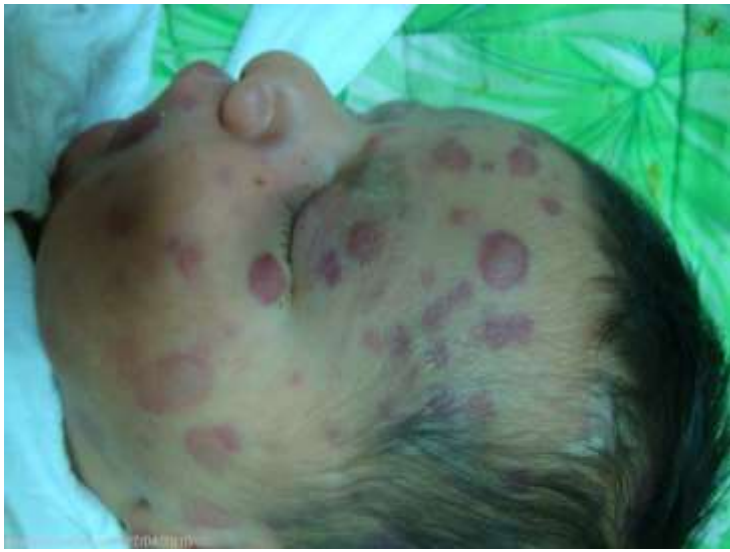
Asymptomatic (90% – 95%)

Permanent Damage (50% – 80%)
Mental retardation, deafness, blindness

Death (20%)

Late Sequelae (7% – 25%)
Deafness, learning deficiencies

Clinical clues



IUGR

Hydrops

generalized petechiae, purpura

Thrombocytopenia

Jaundice

Hepatosplenomegaly

Pneumonitis

Microcephaly,periventricular calcifications, seizures

Chorioretinitis

sensorineural hearing loss

Bone abnormalities, abnormal dentition, and hypocalcified enamel

Children with HIV

Associated with T cell activation in HIV infected children

Often other opportunistic infection

CMV pneumonia

- Increased mortality and treatment failure in HIV-infected infants
- Viraemia peaks around 3–4 months of age
- Interstitial pneumonitis

CMV GI disease

Colitis – stool occult blood or frank bloody

CMV retinitis

Children- relatively rare (developed world)

Necrotic rapidly progressing retinitis with brushfire retinitis

Children- strabismus or failure to fix and follow objects may be important clues to the diagnosis

Diagnostic methods for CMV

Serology

Antigenaemia

PCR

Cytology/Histology

Culture

Immunohistochemistry

Diagnostic methods for CMV

Serology

Antigenaemia

PCR

Cytology/Histology

Serology

CMV IgG - Past infection

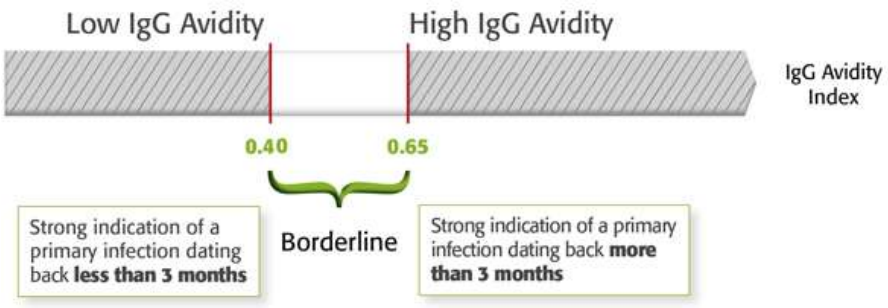
CMV IgM - Acute or recent infection

- ELISAs are the most widely used and are based on crude viral preparations
- Lack specificity for primary infection
  - *false-positive results*
  - *can persist for months after primary infection*
  - *reactivated CMV infections*
  - *Inaccurate in immunocompromised*
  - *Pregnant women*

Serology

IgG avidity assays distinguish primary from non-primary CMV infection

- Avidity increases over time reflecting maturation of the immune response
- Reported as the avidity index



Antigenemia

Detect the viral pp65 antigen

Structural late protein expressed in blood leukocytes during the early phase of the CMV replication cycle

Immunoflurescence assay for the CMV

Limited to detection of the virus in leukocytes

Qualitative result and quantitative

Correlating closely with viraemia and clinical disease severity in immunosupressed populations

Figure 4 CMV pp65 antigens detected in nuclei of peripheral blood neutrophils

Disadvantages

- Labor intensive with low throughput
- Not amenable to automation
- Subjective bias
- Have to be immediately processed
  (within 6 hours)

Neutropenic patients- false-negative results

Polymerase Chain Reaction Amplification

Widely available rapid and sensitive method of CMV detection based

- amplification of nucleic acids
- target major immediate early and late antigen genes in their well conserved regions

DNA can be extracted from

- whole blood, leucocytes, plasma, or any other tissue (tissue biopsy samples) or fluid (urine, CSF, BAL)

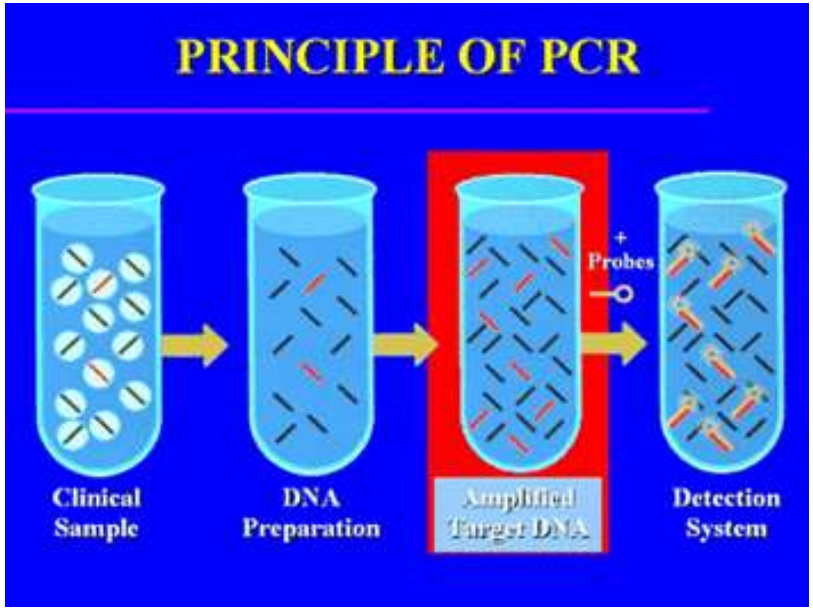
Specimen deterioration with time after sample collection is not as problematic with PCR assays

Qualitative or quantitative

Threshold of the qualitative method calibrated to prevent over-detection

Quantitative PCR (Real-Time PCR)

- more expensive compared to the antigaenemia assay
- rapid and can be automated



Cytology/ Histology

Characteristics intranuclear inclusions in specimens

Saliva, milk, cervical and tracheal secretions, and in touch preparations from biopsy or necropsy tissues

Hallmark of CMV infection "owl's eye"

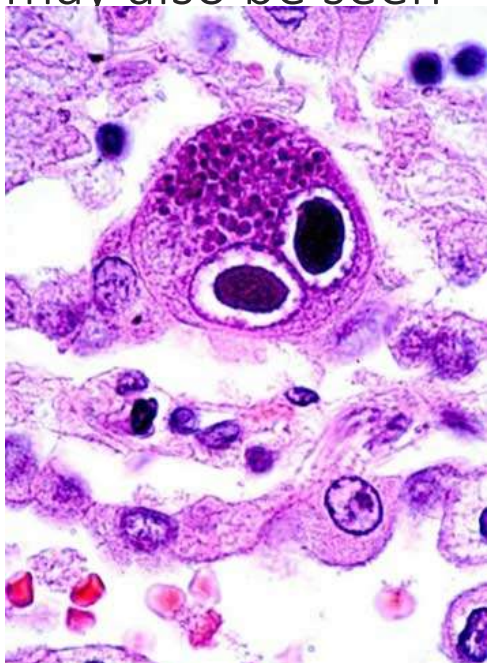
Papanicolaou or hematoxylin-eosin stains

Clusters of small intracytoplasmic inclusions may also be seen

Sensitivity of the standard cytologic

techniques is low relative to virus isolation

Irrespective of the type of specimen



Diagnosing Congenital CMV

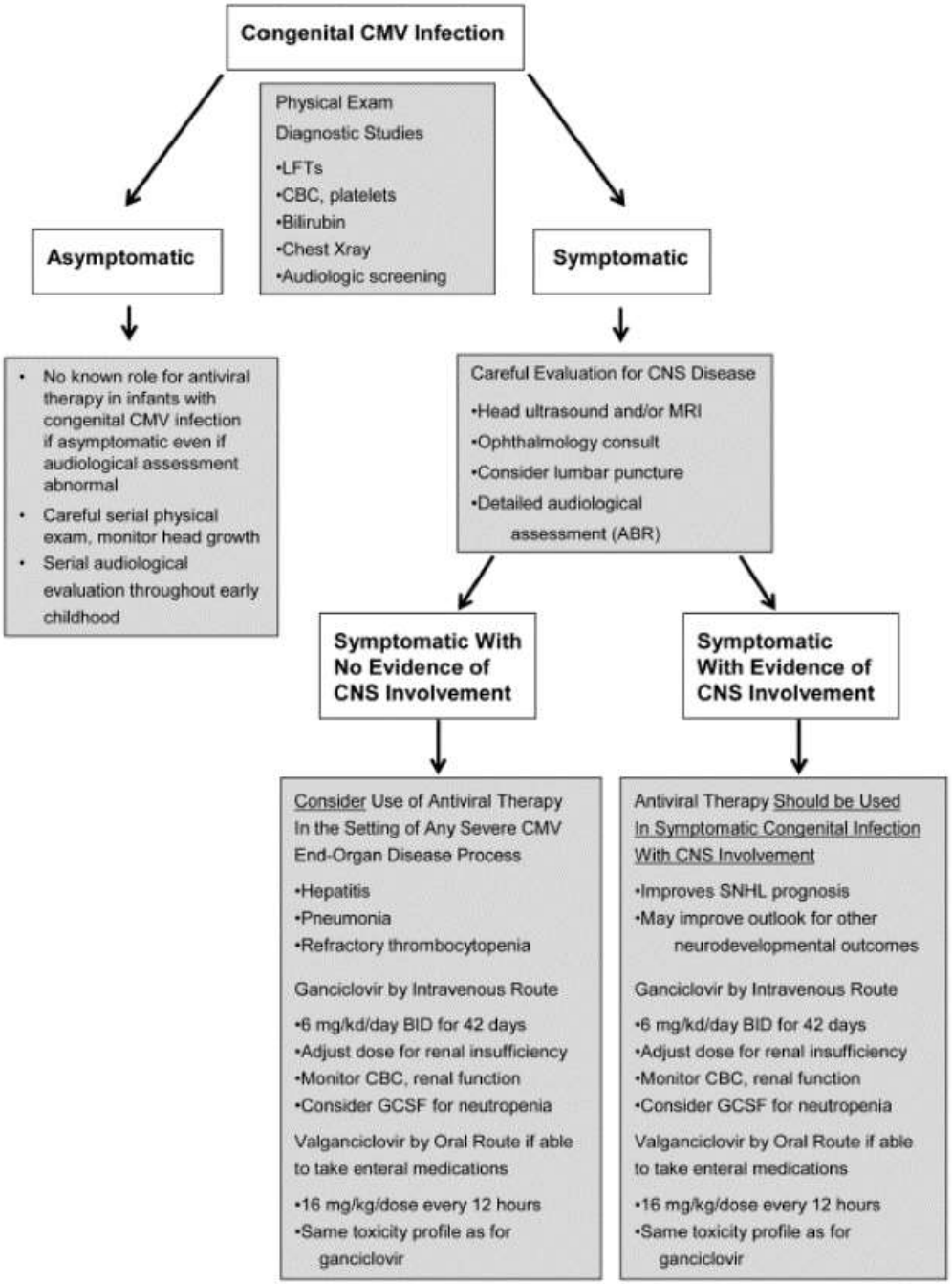
Antibody titers
- maternal CMV IgG crosses the placenta
- neonates mount weak IgM responses

Viral detection in body fluids
- PCR, culture, or antigen testing (pp65 antigen)
- first 3 weeks of life

>3 weeks – Congenital vs postnatally acquired infection

Saliva and urine - newborns shed high levels of the virus

Saliva samples
- more easily obtained
- As reliable as urine samples in diagnosing CMV


Congenital CMV Infection
Physical Exam
Diagnostic Studies
•LFTs
•CBC, platelets
•Bilirubin
•Chest Xray
•Audiologic screening
Asymptomatic
Symptomatic
• No known role for antiviral therapy in infants with congenital CMV infection if asymptomatic even if audiological assessment abnormal
• Careful serial physical exam, monitor head growth
• Serial audiological evaluation throughout early childhood
Careful Evaluation for CNS Disease
•Head ultrasound and/or MRI
•Ophthalmology consult
•Consider lumbar puncture
•Detailed audiological assessment (ABR)
Symptomatic With No Evidence of CNS Involvement
Symptomatic With Evidence of CNS Involvement
Consider Use of Antiviral Therapy In the Setting of Any Severe CMV End-Organ Disease Process
•Hepatitis
•Pneumonia
•Refractory thrombocytopenia
Ganciclovir by Intravenous Route
•6 mg/kd/day BID for 42 days
•Adjust dose for renal insufficiency
•Monitor CBC, renal function
•Consider GCSF for neutropenia
Valganciclovir by Oral Route if able to take enteral medications
•16 mg/kg/dose every 12 hours
•Same toxicity profile as for ganciclovir
Antiviral Therapy Should be Used In Symptomatic Congenital Infection With CNS Involvement
•Improves SNHL prognosis
•May improve outlook for other neurodevelopmental outcomes
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Diagnostic Assessment and Subspecialty Consultations in Infants with Suspected Congenital CMV Infect

Potential Diagnostic Studies
• Diagnostic virology
• PCR and/or culture of infant urine, blood and saliva
• Specimens must be obtained prior to day 21 of life to confirm congenital infection (versus post-natal acquisition)
• Neurodiagnostic imaging
• Head ultrasound good screening exam in neonatal period
• MRI of brain more definitive for symptomatic/affected infants
• Ophthalmological evaluation
• Audiological evaluation
• Newborn hearing screening in nursery
• Definitive auditory evoked response (ABR) on follow-up evaluation
• CBC, platelet counts, transaminases, bilirubin for symptomatic infants
• EEG if seizures clinically evident or suspected

Neuroimaging assessment

Cerebral ultrasound, CT, and MRI for suspected or proven congenital infection

Before 19 weeks post menstrual age

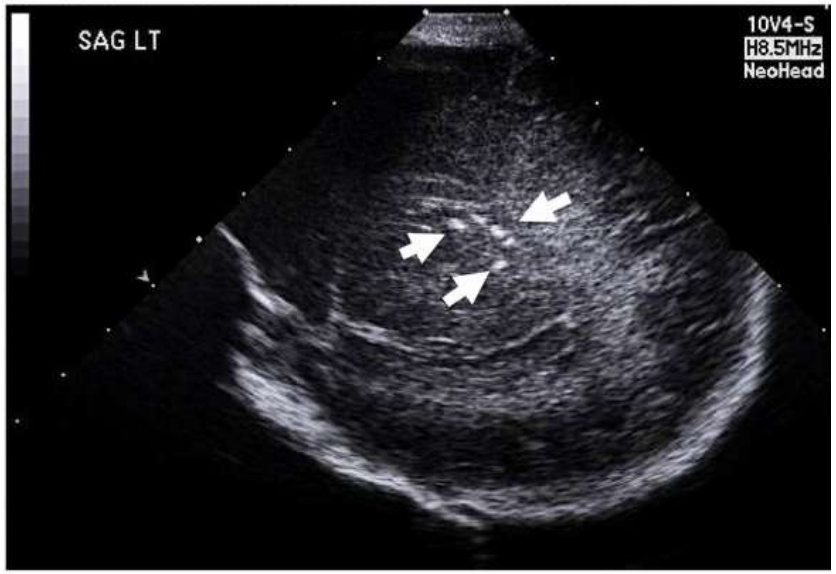
Lissencephaly with a thin cortex, cerebellar hypoplasia, ventriculomegaly, periventricular calcification and delayed myelination

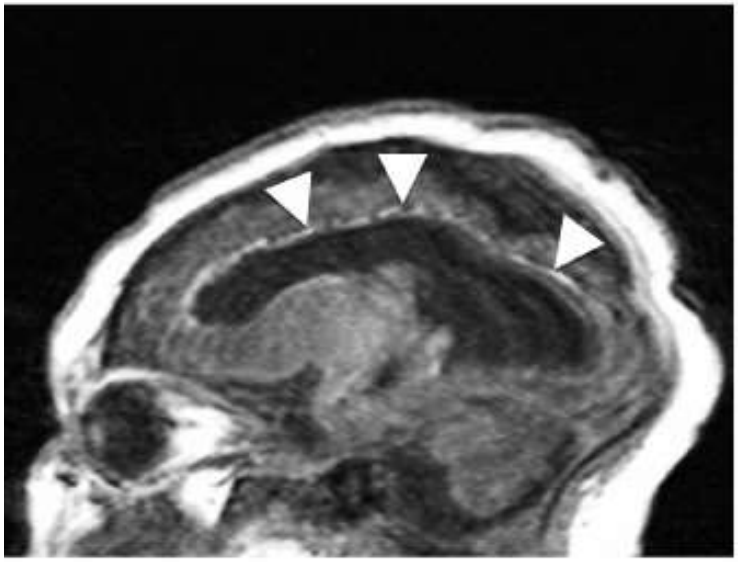
18-24 weeks

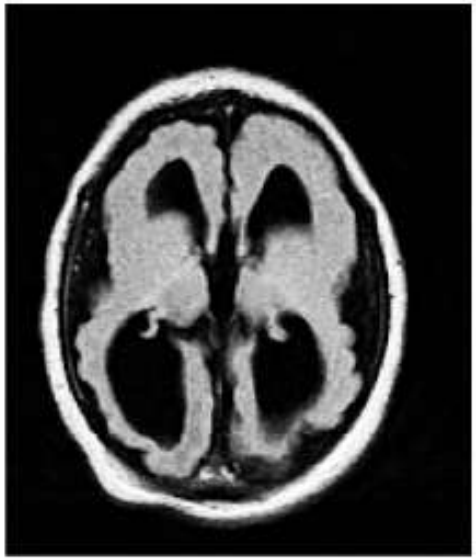
Migrational abnormalities

CNS lesions may include delayed myelination, dysmyelination and white matter disease

All cases, calcification is a common finding


SAG LT
10V4-S
H8.5MHz
NeoHead





Ophthalmologic and audiology assessment

Opthalmology

- chorioretinitis, optic atrophy, and cortical visual impairment
- Strabmismus is also a common long-term ophthalmologic complication

Audiological assessment

- SNHL may be absent at birth
- progressive in nature
- frequent evaluations are required throughout childhood

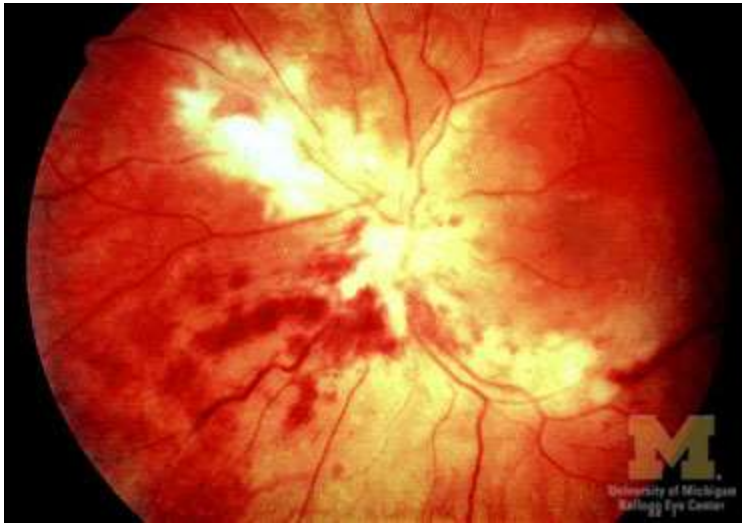
Diagnosis in HIV

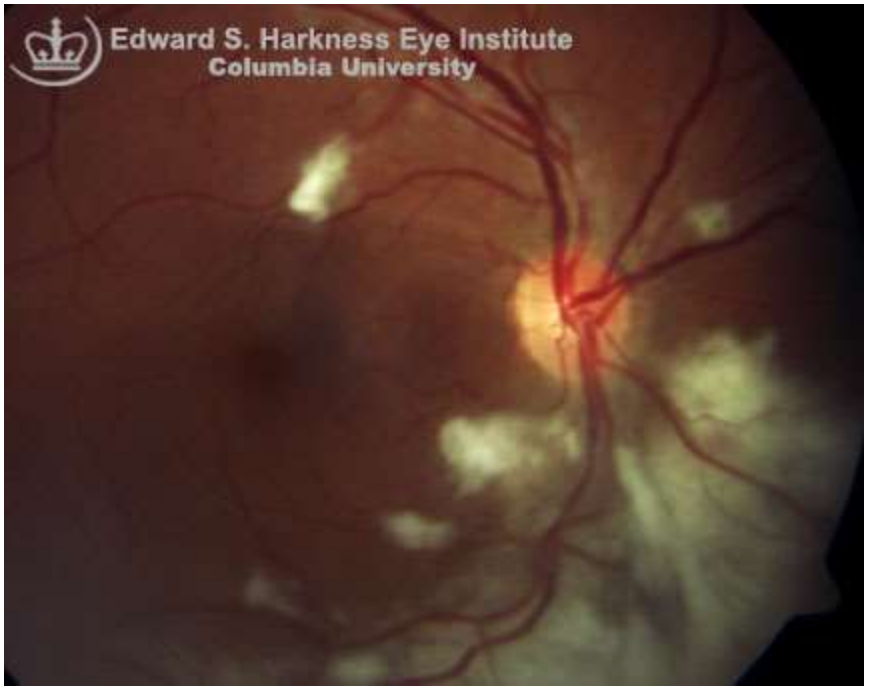
CMV viraemia

- Usually present in end-organ disease
- Low CD4 cell counts in the absence of end-organ disease
- Negative serum or plasma PCR assay also does not rule out CMV end-organ disease
- Not recommended for diagnosis of CMV poor PPV

CMV retinitis

- 70% in the blood
- Rest diagnosed by clinical criteria plus response to therapy
- CMV DNA detected in the vitreous in ~80% of cases


University of Michigan
Kellogg Eye Center


Edward S. Harkness Eye Institute
Columbia University

Pneumonitis

Diagnosis difficult

Consistent clinical and radiological findings

- Multiple CMV inclusion bodies associated with inflammation in lung tissue or cytology
- Absence of any other pathogens

Isolation of CMV from isolates including BAL does not prove that the child has CMV pneumonia

Co-infection with both PJP and CMV is common

Lung biopsy → gold standard

pp65 - sensitivity and specificity 73% and 50%

VL

Hsiao et al

- Significantly higher CMV viral load in infants with probable CMV pneumonia
- No cut-off identified
- Whole blood HCMV viral load above 4.1 log copies/ml is useful in clinical practice
- HIV infected with probable HCMV pneumonia
- Ganciclovir treatment

Management of Congenital Infections

Who???

- Central nervous system (CNS) involvement, including SNHL
- Considered in infants with serious end-organ disease
- First month of life

What????

- Ganciclovir
- Valganciclovir

Management of congenital cytomegalovirus infection: an evidence-based approachRS Gandhi et al Acta Pædiatrica 2010 99, pp. 509–515

Ganciclovir

Synthetic acyclic nucleoside analogue

Safe and well-tolerated in newborns

No sustained effect on CMV shedding

May be long-term neurodevelopmental benefit for some infants with congenital CMV

6 weeks of intravenous ganciclovir therapy is recommended in the management of babies with symptomatic congenital CMV disease involving the CNS

6 mg/kg/dose IV 12 hourly

Monitor for toxicity

- Full blood counts
- serum electrolytes and renal function

Neutropenia

- H- GCS factor therapy can be administered

Dosage adjustments made, when treating infants with impaired renal function

Realistic expectations-will not reverse established CNS injury

Valganciclovir

Oral prodrug of ganciclovir

Neonates who can take enterally

Very well absorbed following oral administration

Rapidly metabolized following oral dosing into ganciclovir

Studies in neonates have demonstrated stable drug levels following oral administration

Dose – 16mg/kg/dose 12 hourly po

6 weeks versus 6 months of valganciclovir performed by the collaborative antiviral study Group

Retinitis

Systemic therapy
- Disease part of systemic infection

FDA – Ganciclovir,Foscarnet and Cidofovir

Higher induction dose for 2-3 weeks

Maintenance to prevent relapse
- Stop once CD4 > 100cells/uL for 3-6 months

Antivitreal therapy
- Ganciclovir/Foscarnet
- Sight threatening disease
- Induction – 2-3 x weekly
- Implant – no longer available

Long – term suppression of CMV retinitis – HAART

Recommendations for Treating Cytomegalovirus (CMV) Infections (page 2 of 2)

Managing CMV Esophagitis or Colitis

- Doses are the same as for CMV retinitis.

Preferred Therapy:

- Ganciclovir 5 mg/kg IV q12h, may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy **(BI)**

Alternative Therapy:

- Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h **(BI)**—for patients with treatment limiting toxicities to ganciclovir or with ganciclovir resistance, *or*
- Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption **(BII)**, *or*
- For mild cases: If ART can be initiated or optimized without delay, withholding CMV therapy may be considered **(CIII)**.

Duration of Anti-CMV Therapy:

- 21–42 days or until signs and symptoms have resolved **(CII)**

Note: Maintenance therapy is usually not necessary, but should be considered after relapses **(BII)**

Managing Well-Documented CMV Pneumonitis

- Doses are the same as for CMV retinitis.
- Treatment experience for CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable **(CIII)**.
- The role of oral valganciclovir has not been established.
- The duration of therapy has not been established.

Managing CMV Neurological Disease

- Doses are the same as for CMV retinitis.
- ***Treatment should be initiated promptly.***
- Combination of ganciclovir IV + foscarnet IV to stabilize disease and maximize response; continue until symptomatic improvement **(CIII)**.
- Continue therapy until resolution of neurologic symptoms.
- Optimize ART to achieve viral suppression and immune reconstitution **(BIII)**.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: CDC and IDSA