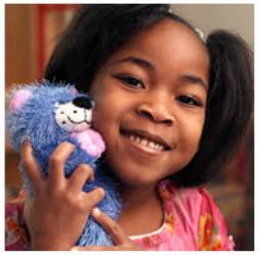






Texas Children's Hospital®

Baylor College of Medicine

Congenital Cytomegalovirus Infection
CMV 101 The Basics
The Elephant in Our Living Room

Gail J Demmler Harrison MD
Professor of Pediatrics, Section Infectious Diseases
Baylor College of Medicine
and
Texas Children's Hospital
Houston, Texas USA

Disclosures

- I will discuss off label use of ganciclovir, valganciclovir, valacyclovir, and CMV hyperimmune globulin, with findings supported by clinical trials, expert opinion, consensus panels, and guidance from AAP, ACOG, SOGC
- I have received research support from, and/or done consulting for, Merck, Moderna, and Microgen, and for other educational support from Elsevier, Wolters-Kluwer and WEBMED Medscape

Why ELEPHANTS and CMV?

CMV is a BIG problem that no one really talks about - CMV is the elephant in our living room.

Asian and African Elephants in human care and the wild are battling their own CMV-related virus, called Elephant Endotheliotropic Herpes Virus (EEHV), which causes lethal hemorrhagic disease in young elephants and threatens elephant babies survival

Elephants never forget!

Long, Latimer, Hayward ILAR 2016.

CMV 101 Elephant Friends as Helpers

Baby Tupelo & Mother Tess

Baby Baylor & Mother Shanti

OBJECTIVES CCMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- TREATMENT
- PREVENTION
- LOOK FOR THE ELEPHANT FOR NEW THINGS TO REMEMBER!

Texas Children's Hospital®

Baylor College of Medicine

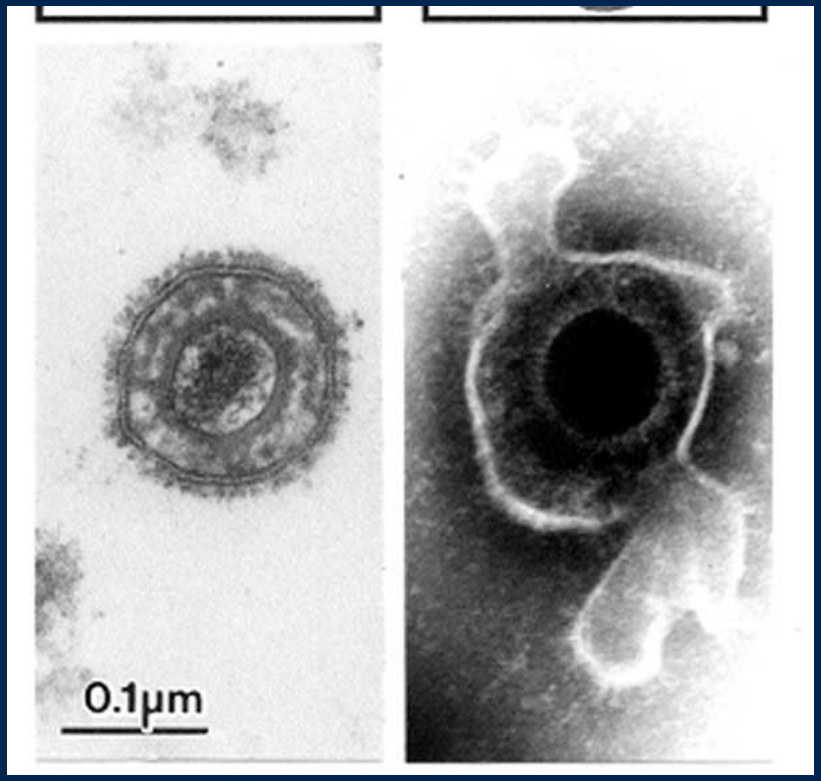
WHO IS CMV?

- CMV = CYTOMEGALOVIRUS
- AKA
  - Cyto= cell megalo= big virus= L. poison
  - “A ubiquitous virus with protean manifestations”
  - An “opportunistic virus”
  - A “stealth virus”
  - “The most common virus most people have never heard of”
  - “The elephant in our living room”

"I'm right there in the room, and no one even acknowledges me."

FACIAL RECOGNITION of CMV

- Large ds DNA virus
  - 240 KB genome
  - 162 capsomeres
  - Icosahedral symmetry
  - Enveloped



Biological Characteristics of CMV

- Primary or first infections or second reinfections
- Latency/Persistence
  - A resting, dormant, but also expressive phase of infection
  - Virus expresses numerous viral proteins and mRNAs which mediate immune evasion
  - A variety of human cells in our body
- Reactivation
  - An active infection with viral gene expression and production of viral particles

Biological Characteristics of CMV

- Asymptomatic infections
  - Active viral infection that produces no obvious outward symptoms in the person
  - Most of CMV infections
- Symptomatic infections
  - Active viral infection that produces symptoms and signs
  - Many different signs and symptoms can occur
  - A minority of CMV infections

Biological Characteristics of CMV

- Primary infections
  - First infection with CMV
- Recurrent infections
  - Reactivation
    - A CMV endogenous in your body reactivates the infection
    - Most recurrent infections are probably reactivations
  - Reinfection
    - A new CMV infects your body

OBJECTIVES CCMV 101 – COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- TREATMENT
- PREVENTION

EPIDEMIOLOGY

- CMV INFECTION IS COMMON
  - **CONGENITAL**
    - **Acquired from maternal transmission in utero**
  - POSTNATAL
    - Breast milk, perinatal secretions, person-to-person
  - TODDLER
    - Day care, play groups, family, sharing
  - ADOLESCENCE
    - Intimacy, sharing food/drinks
  - ADULTHOOD
    - Intimacy, sharing, contact with young children

THE FETUS AND NEWBORN WITH CMV

Approximately 4 Million Births

Annually in the U.S.A.

0.5 to 1% with cCMV

20,000 to 40,000 Congenitally Infected Infants Each Year

3-6,000 Symptomatic *in utero* or at birth; most neurologic or sensory sequelae common; fetal or neonatal death 8%

18-34,000 Asymptomatic or mildly symptomatic at birth; 25% hearing loss and 1-2% vision loss, may have developmental disabilities

Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

0.1% to 1% recurrent CMV maternal infection

CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

15% to 45% CMV seronegative

1% to 4% to 7% primary CMV maternal infection

40% CMV *in utero* fetus congenital CMV newborn

10% -15% have signs and symptoms of disease as fetus or newborn*

5% to 8% die
85% to 90% will have broad range disabilities

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

smaller size or GA
25%
hearing loss
other disabilities?

Texas Children's Hospital®

Baylor College of Medicine

OBJECTIVES CCMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- TREATMENT
- PREVENTION

Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

0.1% to 1% recurrent CMV maternal infection

CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

15% to 45% CMV seronegative

1% to 4% to 7% primary CMV maternal infection

40% CMV *in utero* fetus congenital CMV newborn

10% -15% have signs and symptoms of disease as fetus or newborn*

5% to 8% die
85% to 90% will have broad range disabilities

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

smaller size or GA
25%
hearing loss
other disabilities?

Texas Children's Hospital®

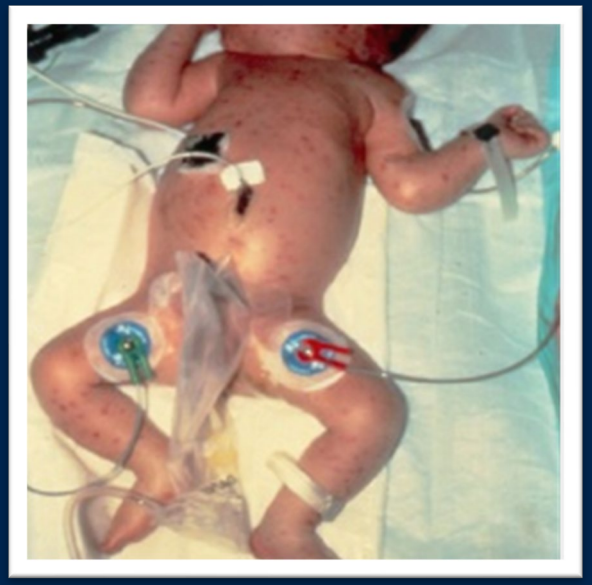
Baylor College of Medicine

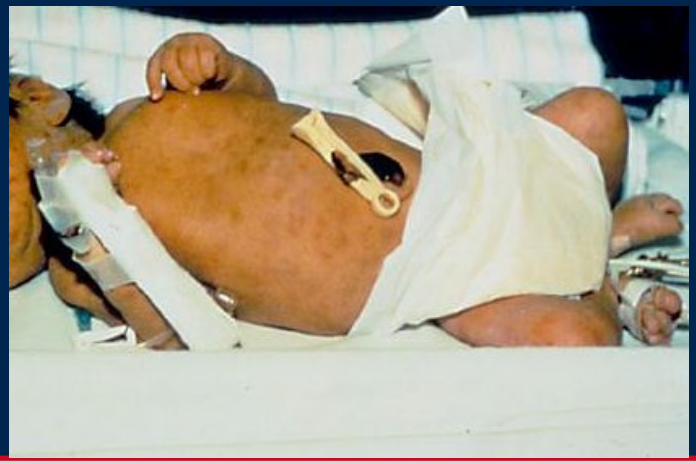
CONGENTIAL CMV (CCMV)

- SYMPTOMATIC CCMV
  - Symptoms at birth
- SYMPTOMATIC CCMV W/ CENTRAL NERVOUS SYSTEM OR BRAIN INVOLVEMENT
  - Clinical signs
  - Brain imaging
- PRIMARY NEUROPHENOTYPE SYMPTOMATIC CCMV
  - Only brain involved
  - May have sensory involvement too

SYMPTOMATIC CCMV

- "Tip of the iceberg"
- Classic signs and symptoms – body somatic- ONE OR MORE OF THESE
  - Growth restriction or small for gestational age -IUGR or SGA
  - Jaundice w/ direct hyperbilirubinemia at birth
  - Skin rash - petechiae or purpura
  - Enlarged liver and spleen
  - Low platelets
  - Abnormal liver enzymes





SYMPTOMATIC CCMV W/ CNS INVOLVEMENT- BRAIN IMAGING

- Enlarged ventricles
- Calcifications of brain – usually periventricular
- Periventricular white matter lucencies
- Cerebral atrophy
- Cortical maldevelopment of brain
  - Polymicrogyria
  - Fetal brain disruption sequence
- Lenticulostriate vasculopathy
- Cysts, especially temporal lobe

SYMPTOMATIC CCMV W/ CNS INVOLVEMENT

- Microcephaly- at birth or later in infancy
- Neurologic signs, focality, stroke
- Seizures or infantile spasms
- Hemiparesis
- Hydrocephalus
- Abnormal tone
  - Hypertonia
  - Hypotonia
  - Cerebral palsy

Pesch et al Pediatr Res 2023

SYMPTOMATIC CCMV W/ CNS INVOLVEMENT- OUTCOMES

- Developmental and speech language delays- variable
- Learning differences
- ADD and ADHD
- Autism and ASD

- Auditory and visual central processing disorders
- Food preferences/feeding differences
- Sleep disturbances/differences

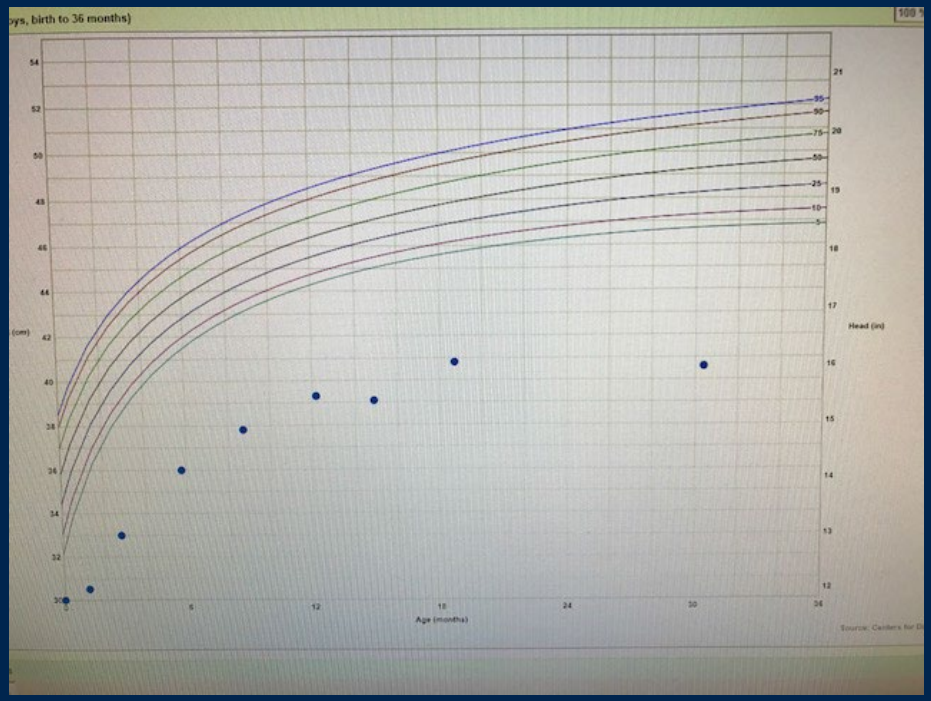
Pesch et al Pediatrics 2024 and Pesch et al Pediatri Res 2023, Topham J et al J Dev Behav Pediatr 2019; Connolly P,Jerger S, et al. Amer J Otol 1992

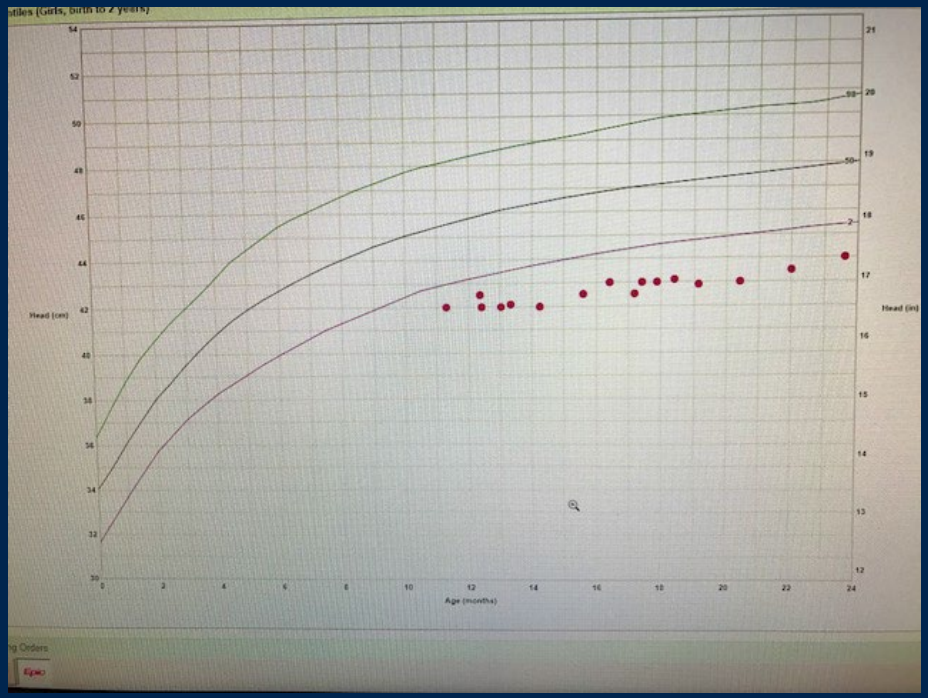
PRIMARY NEUROPHENOTYPE CCMV

<u>Emerging recognition</u> that CCMV can present with only microcephaly or neurologic findings on exam, or neuro-imaging abnormalities

- Microcephaly
- Cortical maldevelopment
- Neuronal migration abnormalities
- Polymicrogyria – PMG - unilateral or bilateral
- Ca+ not as common ?
- Diagnosis often delayed, neurogenetic/metabolic ?
- Suspect if isolated microcephaly develops over first months of life

HEAD CIRCUMFERENCE PLOTS SHOWING MICROCEPHALY

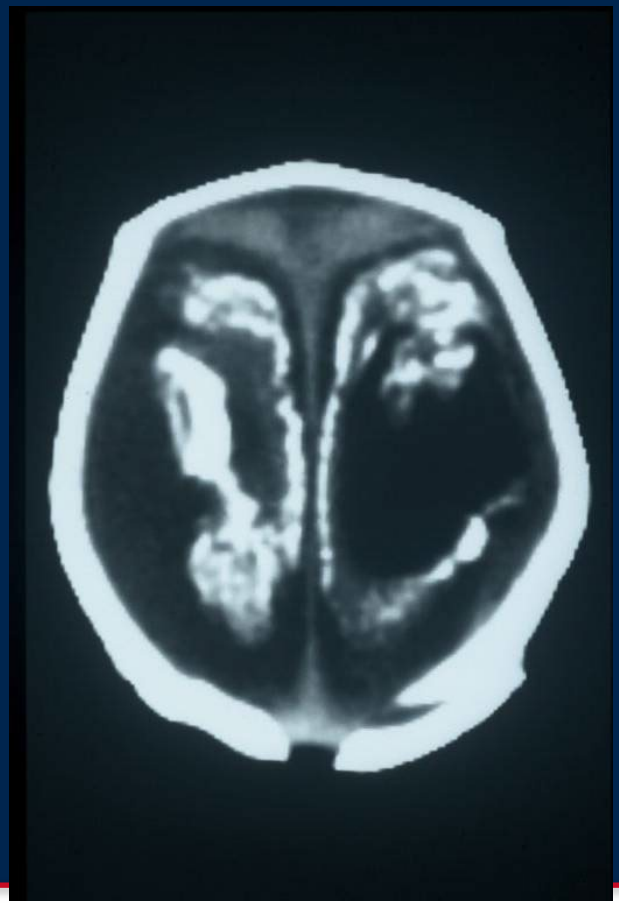




Texas Children's Hospital®

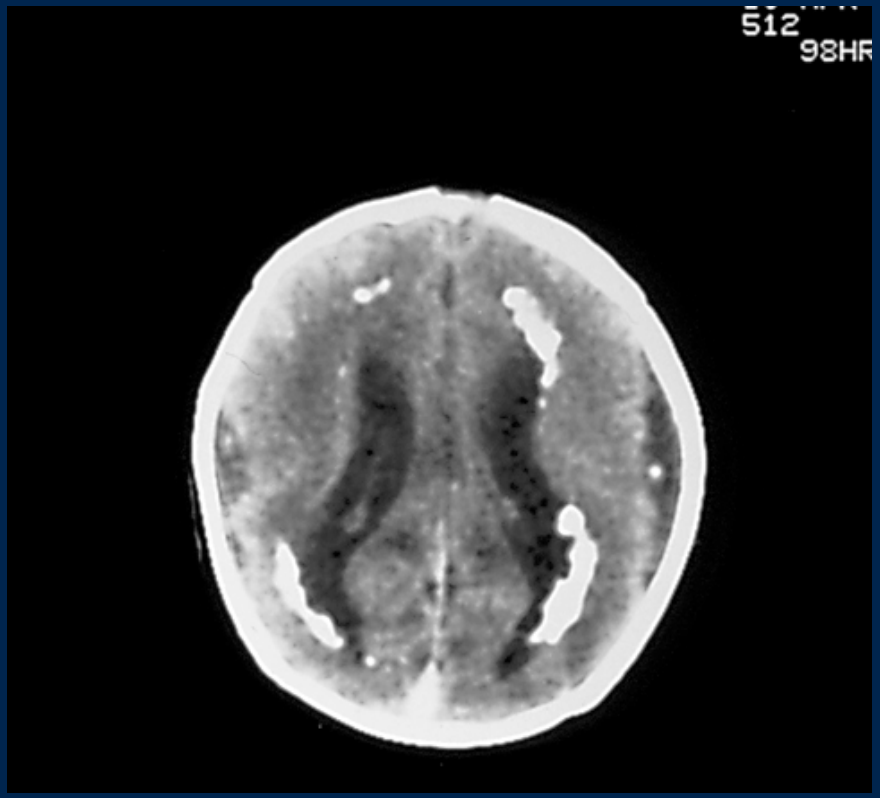
Baylor College of Medicine

SCCMV with CNS involvement- severe- fetal brain disruption sequence



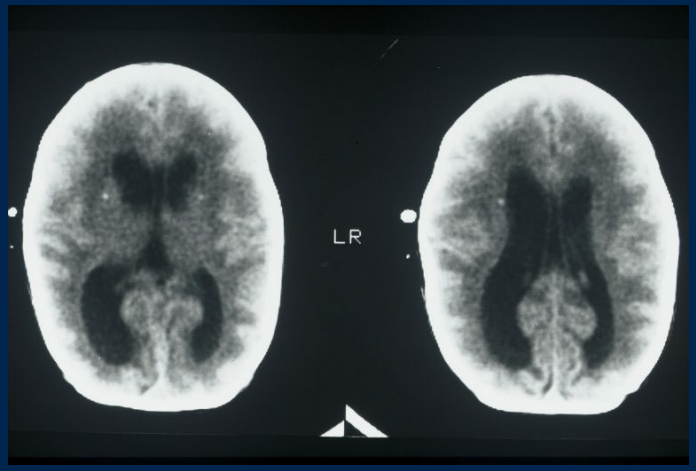
- Severe microcephaly with collapsed skull
- Severe brain malformation with periventricular Ca+

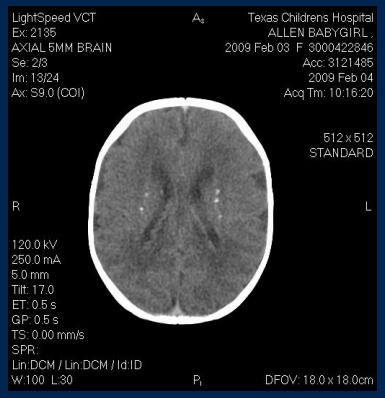
Classic congenital CMV with CNS involvement



- Unenhanced CT scan of brain showed ventriculomegaly, linear periventricular Ca+, cerebral atrophy

Mild to moderate ScCMV - Variations of CNS involvement



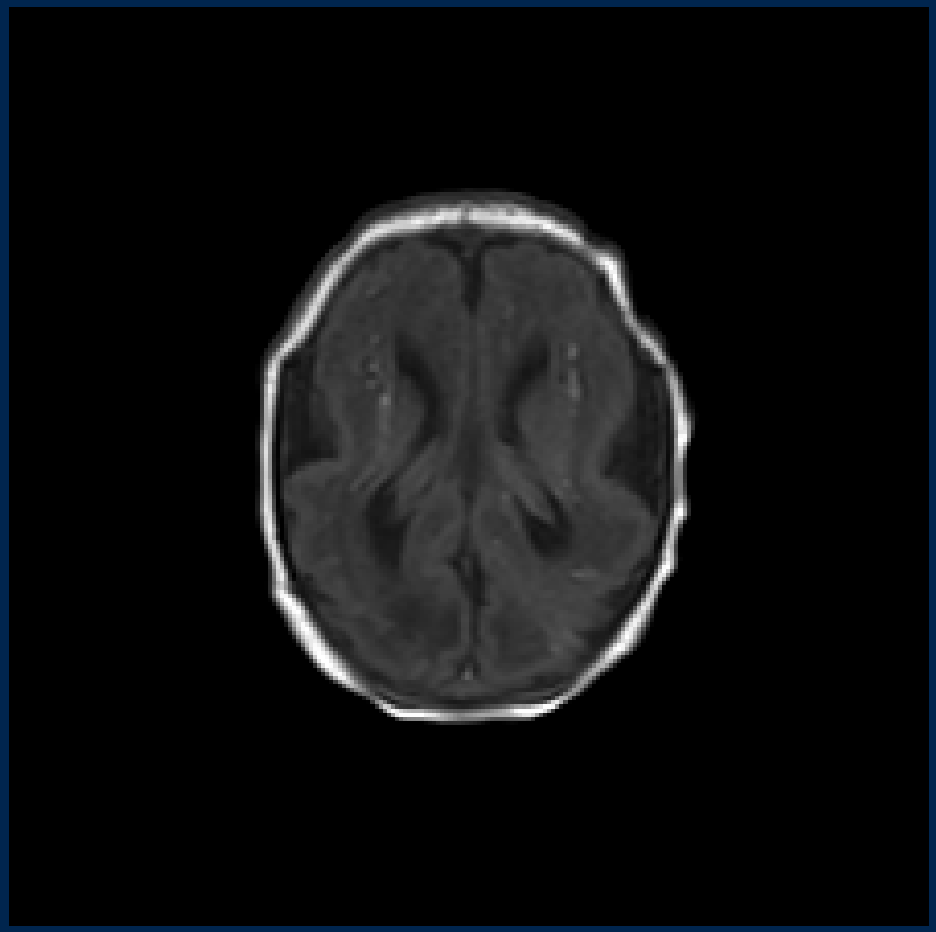


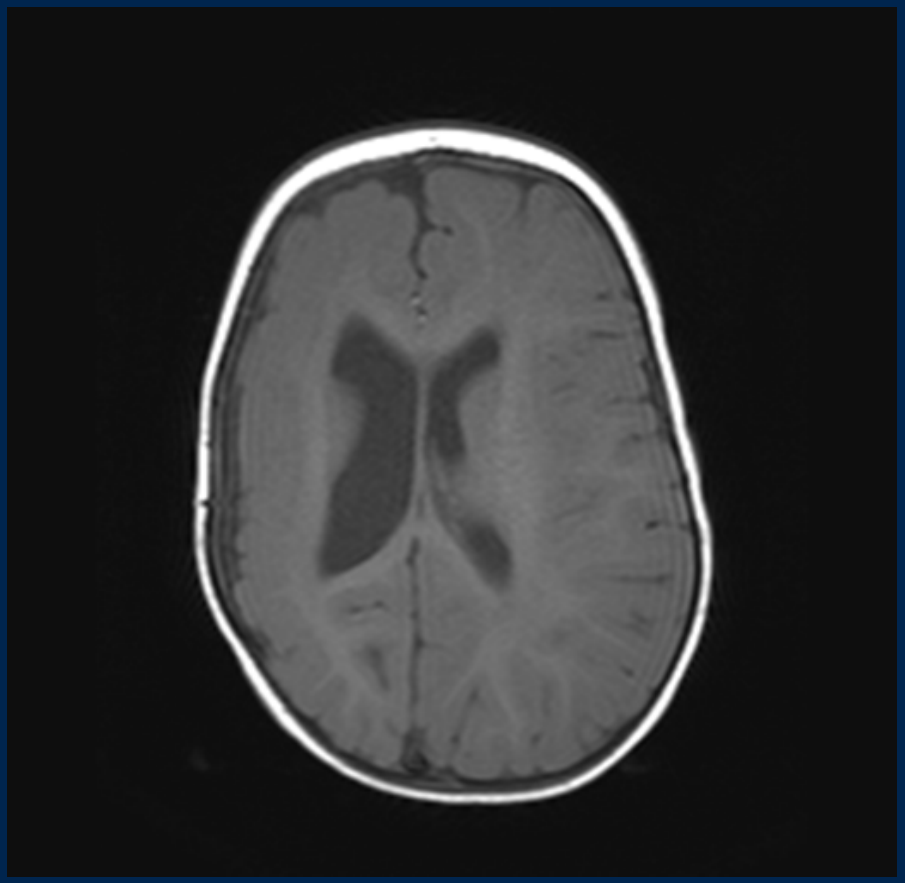
- Ventriculomegaly
- Punctate or beaded periventricular Ca+
- Periventricular leukomalacia

Texas Children's Hospital®

Baylor College of Medicine

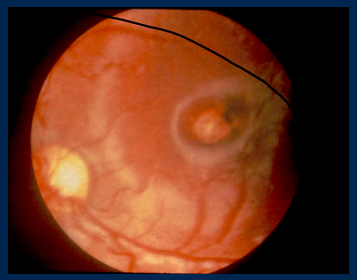
Cortical maldevelopment – unilateral or bilateral PMG

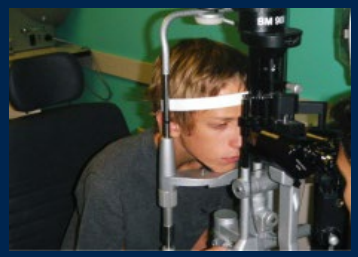




SYMPTOMATIC CCMV- VISION

- Active chorioretinitis
- Chorioretinal scars
- Optic nerve atrophy



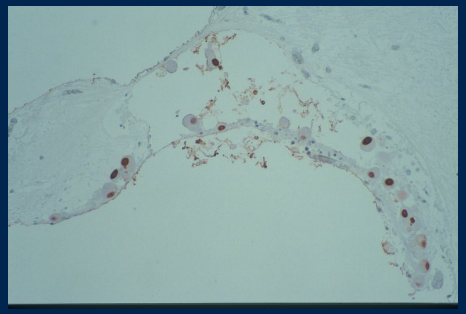


- Cortical blindness with central vision impairment (CVI)
- Strabismus
- Delayed vision maturation
- Can occur in asymptomatic CCMV also, rarely

Modrzejewska M et al J Clin Med 2024; Jin HD, et al Pediatr Infect Dis 2017

SYMPTOMATIC CCMV- HEARING

- Hearing loss- most common sequelae
  - Conductive with middle ear effusion
  - Sensorineural
  - Progressive, lifelong risk
  - Unilateral or bilateral
  - Congenital or later onset
  - Greatest risk emerges first 3-5 years



Lanzieri T et al Pediatrics 2017; Chung W Pediatr Infect Dis J 2021

SYMPTOMATIC CCMV-VESTIBULAR FUNCTION

- Vestibular Involvement
  - Can occur in asymptomatic and symptomatic CCMV
  - Can occur with or without hearing loss
  - Monitor head lag, hypotonia, delayed sitting, imbalance when learning to walk
  - Affects gross motor, coordination and QOL

Shears et al. Arch Dis Child Fetal Neonatal Ed 2022;107:F630; Pinninti S, et al. Pathogens 2024;

Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

0.1% to 1% recurrent CMV maternal infection

CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

15% to 45% CMV seronegative

1% to 4% to 7% primary CMV maternal infection

40% CMV *in utero* fetus congenital CMV newborn

10% -15% have signs and symptoms of disease as fetus or newborn*

5% to 8% die
85% to 90% will havebroad range disabilities

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

smaller size or GA
25%
hearing loss
other disabilities?

Texas Children's Hospital®

Baylor College of Medicine

ASYMPTOMATIC CONGENTIAL CMV (ACCMV)

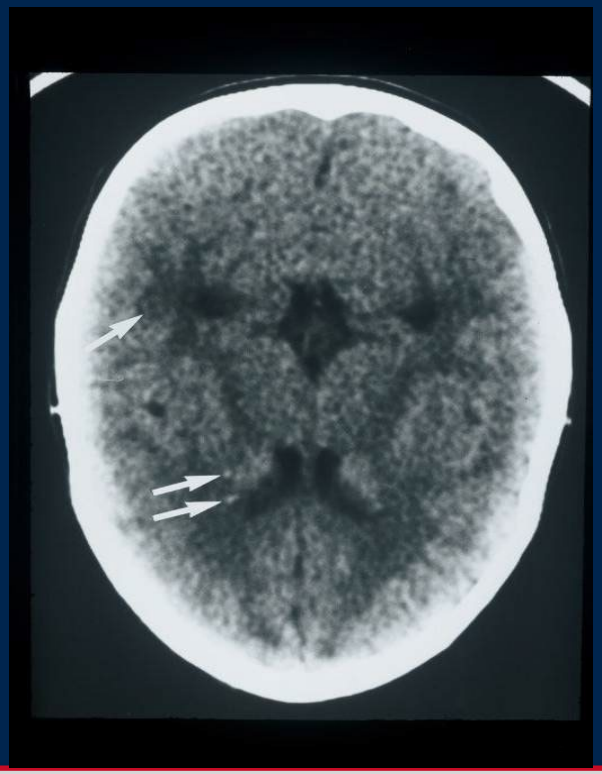
- **ASYMPTOMATIC CCMV**
  - No apparent symptoms at birth
  - Normal hearing at birth
  - At risk later onset hearing loss
- **ASYMPTOMATIC CCMV WITH ISOLATED HEARING LOSS**
  - No apparent symptoms at birth
  - Fail/refer newborn hearing screen
  - Congenital hearing loss
    - Unilateral one side
    - Bilateral both sides
    - At risk for hearing loss progression

ASYMPTOMATIC CCMV

- MAY HAVE BRAIN IMAGING FINDINGS OF SUBTLE CNS BRAIN INVOLVEMENT, ESP IF SNHL ALSO
  - Ventriculomegaly, or asymmetrical ventricles
  - Periventricular cysts
  - Temporal lobe or germinlytic cysts
  - White matter changes
  - Delayed myelination
  - Punctate tiny calcificatIons
  - Leticulostriate vasculopathy LSV

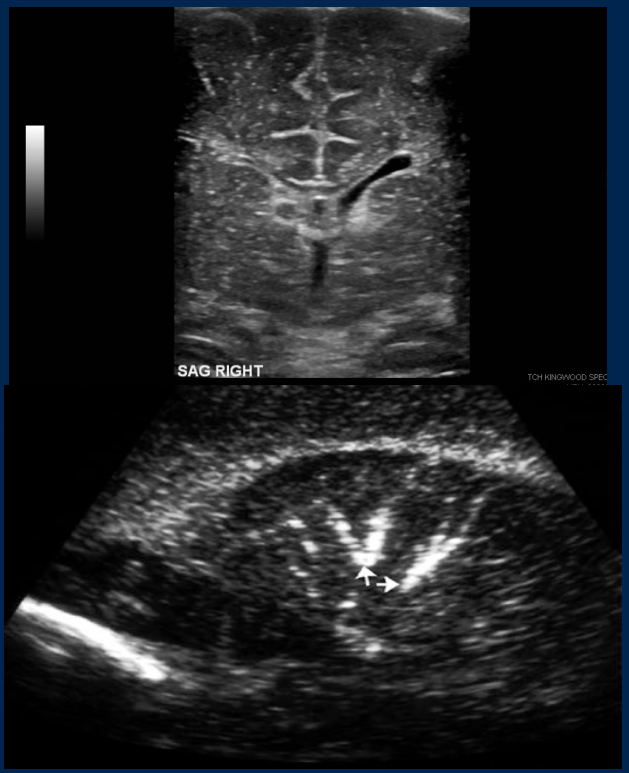
Valencak I et al Pathogens 2025, Lanzieri et al. Otolaryngol Head Neck Surg 2018

AcCMV Cranial CT images may have mild abnormalities 25%



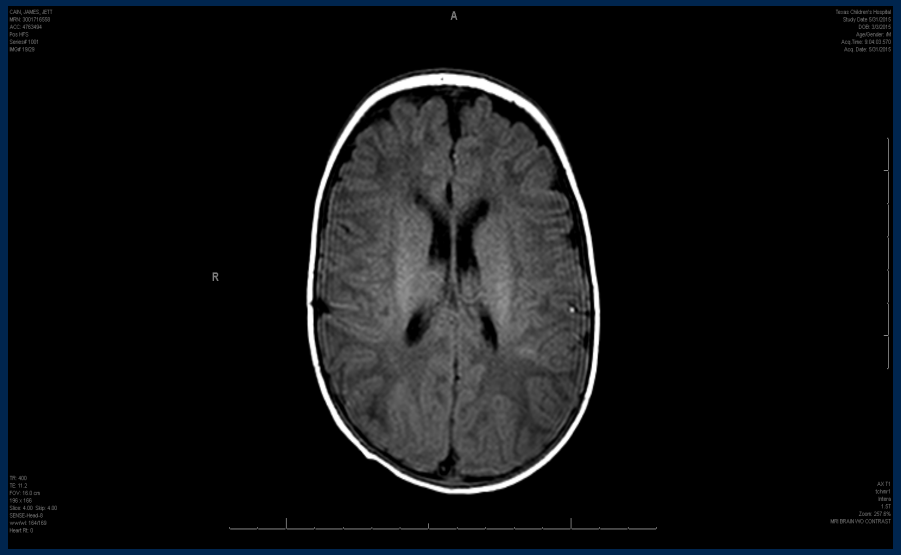
- Periventricular leukomalacia
- Punctate periventricular calcifications
- Mild enlargement of ventricles

AcCMV Cranial head ultrasounds may show subtle nonspecific abnormalities of brain



- Asymmetrical ventricles, periventricular cysts
- Lenticulostriate vascuopathy LSV

AcCMV Brain MRI may show subtle nonspecific abnormalities of brain



- Brain with delayed myelination, small germinolytic cysts, slightly enlarged ventricles

Texas Children's Hospital®

Baylor College of Medicine®

ACCMV long term outcomes

- Asymptomatic CCMV identified through newborn screening with normal hearing by age 2 years do not have significant IQ differences or academic achievement differences at 5 years and 18 years
- If hearing loss presents by age 2 years, full scale IQ and receptive vocabulary scores may be lower, and likely due to the SNHL
- Can early detection and interventions minimize this impact ?

Lopez, et al Pediatrics 2017 Nov; 140(5). Lanzieri T et al Pediatrics 2023

OBJECTIVES CMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- **DIAGNOSIS**
- **TREATMENT**
- **PREVENTION**

Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

0.1% to 1% recurrent CMV maternal infection

CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

15% to 45% CMV seronegative

1% to 4% to 7% primary CMV maternal infection

40% CMV *in utero* fetus congenital CMV newborn

10% -15% have signs and symptoms of disease as fetus or newborn*

5% to 8% die
85% to 90% will havebroad range disabilities

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

smaller size or GA
25%
hearing loss
other disabilities?

Texas Children's Hospital®

Baylor College of Medicine

DIAGNOSIS OF CCMV

- **Timing**
  - First 21-28 days of life
- **Specimen**
  - Saliva – good screening tool
  - Urine-best confirmatory test for CCMV
  - Blood/Plasma or Dried Blood Spot- may be negative in CCMV
  - Tissue
- **Method**
  - Culture/Shell vial- phasing out
  - PCR or other NAAT/LAMP- tests of choice now
  - Qualitative and quantitative PCRs

DIAGNOSIS OF CCMV

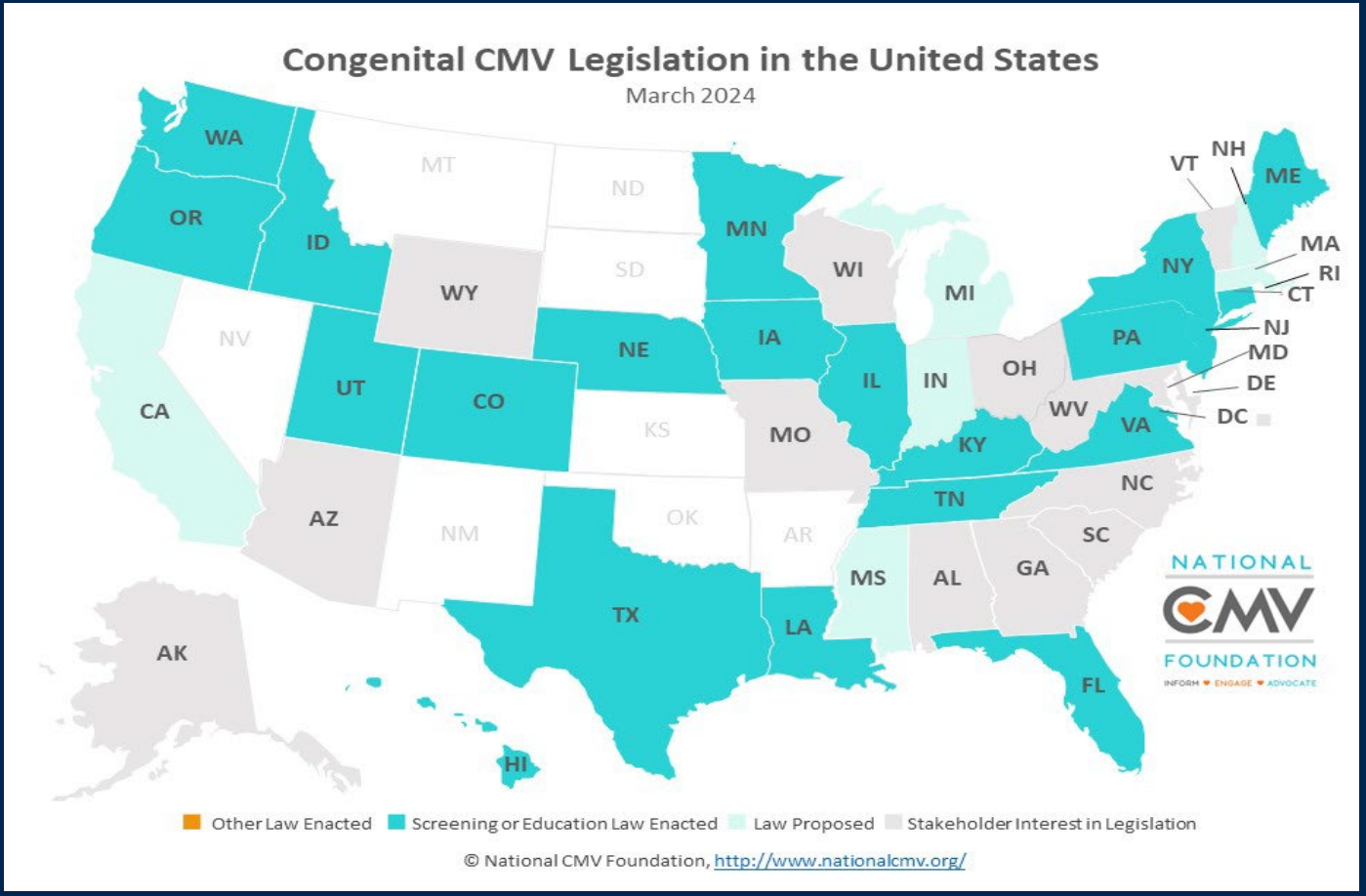
- **What not to do**
  - TORCH titers- non specific, broad
  - CMV IgG serology
    - CMV IgG antibody will be mostly maternal
    - High prevalence of CMV IgG antibody in general population
  - CMV IgM serology
    - Insensitive compared to viral detection
    - CMV IgM positive still needs confirmatory testing of urine/saliva by viral detection

NEWBORN CCMV DIAGNOSIS

- Diagnostic Testing- **NOW**
  - Newborns with signs or symptoms of CCMV tested
  - **Many are still missed**
- Targeted Newborn Screening-**EVOLVING**
  - Normal newborns with failed/referred NBHS tested
- Universal Newborn Screening-**EVOLVING !**
  - ALL newborns screened/tested for CCMV

UNIVERSAL NEWBORN SCREENING FOR CCMV- USA National

- RUSP application submitted March 27, 2019 by National CMV RUSP Multidisciplinary Nomination Team
- Under review by the Advisory Committee on Heritable Disorders In Newborns and Children – ACHDNC- Still……
- To support this effort go to www.nationalcmv.org website



TEXAS HEARING INSTITUTE

Texas Children's Hospital

Baylor College of Medicine

Targeted Newborn Screening for CCMV for Failed NBHS- USA

- Colorado, Connecticut, Florida, Illinois, Iowa, Kentucky, Louisiana, Maine, New York, Texas, Utah, and Virginia perform state based targeted testing
- Many birthing hospitals in many other states
- For a list of hospitals and states see
  - https://www.nationalcmv.org/overview/newborn-screening

Targeted Newborn Screening for CCMV and Failed NBHS-Canada

- British Columbia and Manitoba
  - Province wide
- Nova Scotia- selected screening
- New Brunswick-selected screening
- Birthing hospitals in other Provinces
- For a list of hospitals https://www.cmvcanda.com

www.cmvcanada.com

Universal Newborn Screening Strategies for CMV

- **Detection of CMV in urine**
  - DNA by PCR
  - Rapid POCT in newborn nursery
- **Detection of CMV in saliva**
  - DNA by PCR
  - Rapid POCT in newborn nursery
  - Breast milk feeds may produce a low false positive result
  - Confirm all saliva positives with urine CMV test
- **Detection of CMV in newborn screen DBS by DNA PCR**

Texas Children's Hospital

Baylor College of Medicine

Universal Newborn Screening for CCMV- USA

Minnesota

- First state to adopt routine universal newborn screening for cCMV January 2023
- Method NB DBS

- Connecticut

  - Passed Universal CMV screening newborn law June 2023; started 2025
  - Method NB DBS

- New York
  - Passed Universal screening newborn law Aug 2023- paused in 2025
  - Method NB DBS

Schleiss and Blazquez-Gamero. Lancet and Child & Adolescent Health Jan 2025.

Universal Newborn Screening for CCMV

- Canada- NB DBS
  - Ontario since 2019
  - Saskatchewan since 2022
  - Alberta- 2023 adopted, but not yet implemented
  - Manitoba- 2024 adopted; implementation pending soon?

DIAGNOSIS OF CCMV AFTER BIRTH- GOING BACK IN TIME

- **NEWBORN DRIED BLOOD SPOT CMV DNA DETECTION**
  - **NB DBS can be retrieved from state newborn screening labs with parental permission**
  - **Reference lab can test NB DBS samples for CMV DNA by PCR methods**
  - **If positive, confirms CCMV, may predict hearing loss**
  - **If negative, does not exclude CCMV, as false negatives occur**
  - **Time limitations of storage vary**

Del Valle Penella A, et al Int J Neonatal Screen 2023

Recommended Evaluations for NEWBORNS Who Screen Positive for CMV

- Labs
  - CMV PCR urine and saliva to confirm congenital CMV
- If CMV confirmatory labs positive, then additional investigations to see if end organ, sensory, or CNS disease present
- Assess if antivirals indicated

Recommended Evaluations for NEWBORNS Who Have Confirmed Congenital CMV Infection

- Labs
  - CMV PCR urine and saliva – these are positive and confirm congenital CMV
  - CBC diff plt, liver panel, creatinine
  - CMV quant PCR plasma/blood to assess level viremia- some experts recommend
- Imaging
  - Neonatal HUS
  - MRI brain if microcephaly or HUS abnormal or neurological abnormalities
  - If SNHL confirmed, then IAC BRAIN MRI also
- Ophthalmology evaluation for retinitis/optic nerve
- Audiology
  - Confirmatory ABR to fully assess hearing both ears
  - ENT referral if SNHL confirmed
- Exam includes HC,WT, L, newborn physical exam and newborn neurological exam

TEXAS HEARING INSTITUTE

Texas Children's Hospital®

Baylor College of Medicine

National Case Definition for CCMV

- Council of State and Territorial Epidemiologists
  - Standardized Surveillance Case Definition for CCMV infection and Disease Position Statement
    - Went into effect Jan 2024

  - Lays groundwork for defining and reporting a case of CCMV at state level
  - CCMV may be made a reportable condition in some states
  - Will support other position statements
  - Allows baseline and trends of CCMV pre and post vaccine

www.cste.org

Is CCMV Reportable?

- Los Angeles County – March 21, 2025- CCMV now reportable by laboratory or provider to LA County Dept of Public Health
- Minnesota
- Colorado
- Connecticut – soon?
- Other states under NBHS screening state programs-

https://www.health.state.mn.us https://publichealth.lacounty.gov

OBJECTIVES CMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- **TREATMENT**
- **PREVENTION**

Pregnant or Persons of Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative

0.1% to 1% recurrent CMV maternal infection

1% to 4% primary CMV maternal infection

CMV *in utero* fetus congenital CMV newborn

40% CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

Hearing loss
Disabilities ?

*

10% to 15% have hearing loss
other disabilities ?

Texas Children's Hospital®

Baylor College of Medicine

CCMV 101-ANTIVIRAL TREATMENT PROVIDES BENEFIT

- 1991-1999 Phase III randomized trial IV ganciclovir 6 mg/kg/dose every 12 hours for 6 week for CCMV w/ CNS involvement
- 2008-2011 Phase III randomized clinical trial oral valganciclovir 16 mg/kg/dose every 12 hours for 6 weeks vs 6 months
- Case Series and Retrospective Real World Studies
  - Kimberlin et al J Ped 2003, Kimberlin et al J Clin Virol 2010; Kimberlin et al N Engl J Med 2015; Chung et al J Pediatr 2024

Antiviral Treatment Congenital CMV American Academy Pediatrics Redbook 2024

- Moderate to severe symptomatic congenital CMV
- Obvious apparent signs to suggest congenital CMV disease, with OR without central nervous system involvement
- Valganciclovir given orally for 6 months
  - Valganciclovir 16 mg/kg/dose PO Q 12 hours
  - IV ganciclovir 5 mg/kg/dose IV Q 12 hours if unable to tolerate PO
  - Adjust dosage monthly for weight gain
  - **Off Label Use- Not FDA approved indication**
- Treatment should be started within the first 13 weeks following birth – NEW RECOMMENDATION

Chung J Pediatr 2024; AAP Redbook 2024; Kimberlin et al N Eng J Med 2015

Antiviral Treatment Congenital CMV American Academy Pediatrics Redbook 2024

- Absolute neutrophil counts should be measured weekly for 6 weeks, then at 8 weeks, then monthly for the duration of antiviral treatment; serum alanine aminotransferase concentration should be measured monthly during treatment.
- When it occurs, neutropenia is more common during the first 4 to 6 weeks of therapy;
- If the absolute neutrophil count reproducibly drops below 500 cells/mm3 , either treatment can be held until counts recover above 750 cells/mm3, or granulocyte colony-stimulating factor can be administered once daily for 1 to 3 consecutive days

CCMV 101- Antiviral treatment –

- Follow up in randomized clinical trials has been only for 6 months to 2 – 3 years
- Apparent short term benefits of antiviral therapy may not last long term

Hearing loss may start to progress and may continue to progress once antivirals are stopped

  - Lack of enduring benefits of early antiviral therapy now being shown
  - But will give benefits during critical periods of language acquisition and brain growth
- Do we need to treat longer than 6 weeks to 6 months for long term benefits?

Lanzieri, et al. J Ped Infect Dis Soc, 2022; Lanzieri, Pesch, Grosse, Pediatrics 2023.

CCMV 101- Antiviral treatment – unanswered questions

- Will use of two antivirals be beneficial?
  - Expedite CMV viremia and symptoms resolution?
  - Improve outcomes?
- Letermovir + valganciclovir for CCMV Phase I study
  - Both antivirals are orally administered
  - Safety data and PK data need to be collected first
    - www.clinicaltrials.gov

CCMV -Other interventions are also very helpful

- Hearing aids, cochlear implants
- Speech language therapy , ASL, communication aids

- Educational accommodations
- Physiotherapy, mobility aids, orthotics, orthopedics
- Seizure treatments
- Tone management- botox, baclofen
- Vision aids and therapies, strabismus surgery
- Nutritional interventions, diet and feeding therapies, G tube feedings, for growth disorders
- Vestibular therapies
- Vision therapies
- Family support and respite and private duty nursing

Pregnant or Person of Childbearing Age

55% to 85% CMV seropositive

0.1% to 1% recurrent CMV maternal infection

CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

Hearing loss Disabilities ?

15% to 45% CMV seronegative

1% to 4% primary CMV maternal infection

40% CMV *in utero* fetus congenital CMV newborn

10% -15% have signs and symptoms of disease as fetus or newborn

5 to 8% die - 85% to 90% survivors neurodevelopmental

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

Texas Children's Hospital

Baylor College of Medicine

Antiviral Treatment Congenital CMV American Academy Pediatrics Redbook 2024- Asymptomatic at birth

- Asymptomatic congenital CMV with isolated sensorineural hearing loss
- No clinically apparent signs to suggest congenital CMV disease, but sensorineural hearing loss
- Valganciclovir may be offered and given orally for 6 weeks – NEW RECOMMENDATION
- Treatment should be started within the first 13 weeks following birth- NEW RECOMMENDATION

Chung J Peds 2024; AAP Redbook 2024; Kimberlin et al N Eng J Med 2015

Antiviral Treatment Congenital CMV American Academy Pediatrics Redbook 2024- Asymptomatic at birth

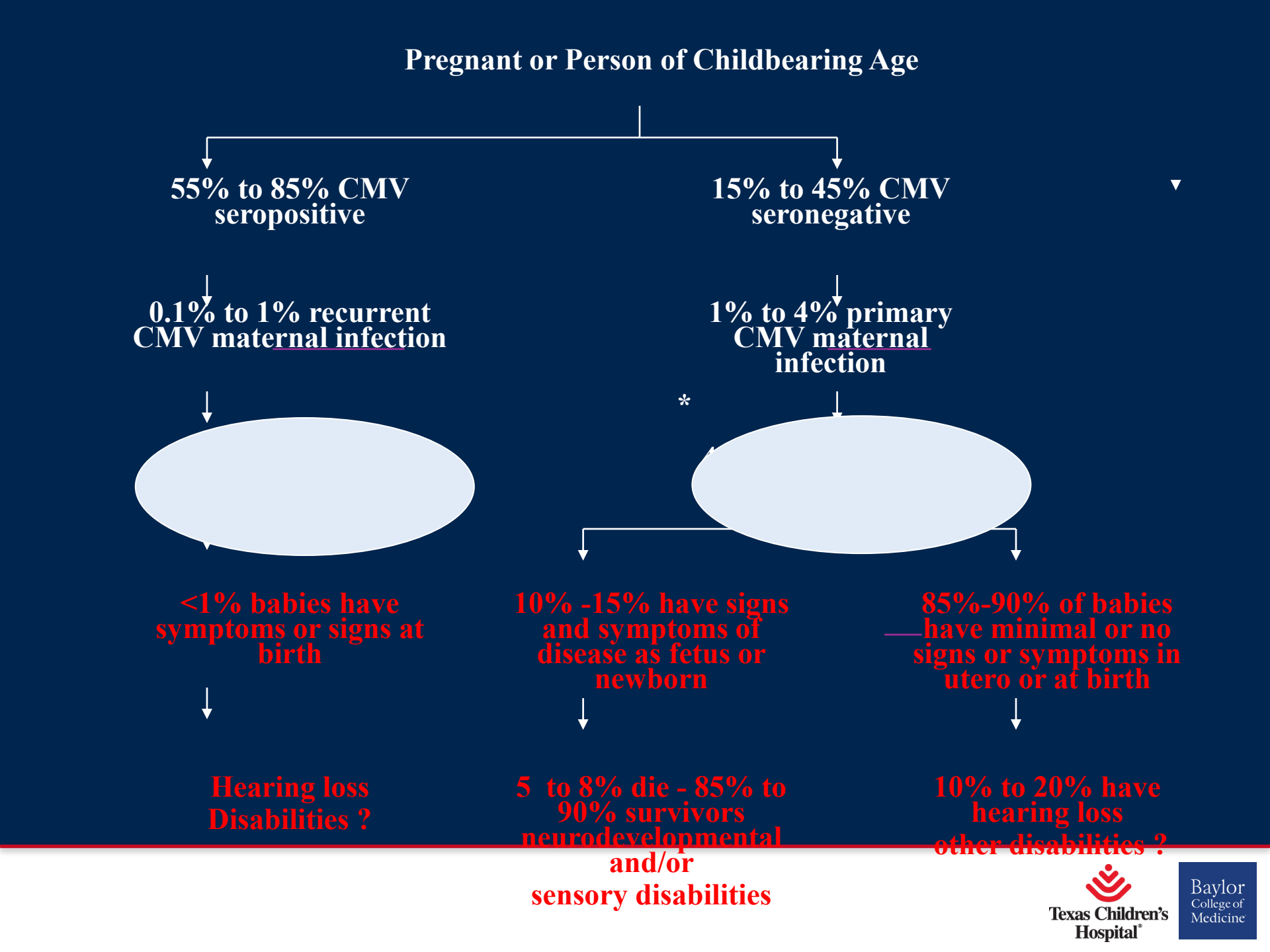
- Asymptomatic No apparent signs to suggest congenital CMV disease, and normal hearing at birth,
- Antiviral therapy not recommended outside of a research study
- Some experts may consider antiviral therapy if CMV viremia levels high because risk for hearing loss may be greater in these infants

Chung J Peds 2024; AAP Redbook 2024; Kimberlin et al N Eng J Med 2015

Asymptomatic CCMV-Other Management

- Anticipatory guidance – at risk for progressive and later onset SNHL
- Regular hearing evaluations
  - Every 3-6 months for first year, then every 6 months age 3 to 5 years, then annually, or as needed if clinical change or suspicion of hearing loss progression, until age 6 to18 yr, life long if hearing loss detected
  - Hearing aids or cochlear implants, as indicated
- Vestibular and developmental screening
- Speech/language therapy if needed
- Educational accommodations if needed
- Sign language -education/awareness/inclusion- if needed

Alde M et al Children(Basel) 2024 ; Amer Acad Aud Pos Statement on CMV in Newborns 2023



Prenatal Testing or Screening to Diagnose Maternal CMV Infection during Pregnancy

- Maternal Serology – NOT ROUTINE USA BUT IS AVAILABLE
- CMV IgG positive – CMV infection at some time
- Seroconversion (IgG negative to IgG positive)- primary infection
- CMV IgM positive
  - May mean recent primary infection, or recurrent infection, or false positive, or prolonged positive IgM serostatus
  - CMV IgG avidity index
    - Low indicates recent infection < 4 months ago
    - High indicates CMV infection > 4 -6 months ago

Revello et al J Clin Virol 2011; Lazzarotto et al Clin Microbiol 2011; Yinon J Obstet Gynaecol Can 2010

Prenatal Testing or Screening to Diagnose Maternal CMV Infection during Pregnancy

- ACOG- Not Recommended
- SOGC- In provinces where CMV IgG avidity testing is available, screening for CMV primary infection in the first trimester (using IgG and IgM antibodies followed by IgG avidity testing if the patient is IgM-positive) can be offered, especially in women at high risk (those who have a child under 3 years at home). CMV screening in pregnancy is not recommended in provinces where CMV IgG avidity testing is unavailable
- International CMV Consensus Reports- Not Recommended
- ECCI - prenatal or 1st trimester screening for CMV pregnancy now recommended;

Rawlinson et al Lancet, 2017; ACOG Practice Bulletin 2015; SOGC Clinical Practice Guideline 2021; Leruez-Ville M et al. The Lancet Europe, 2024

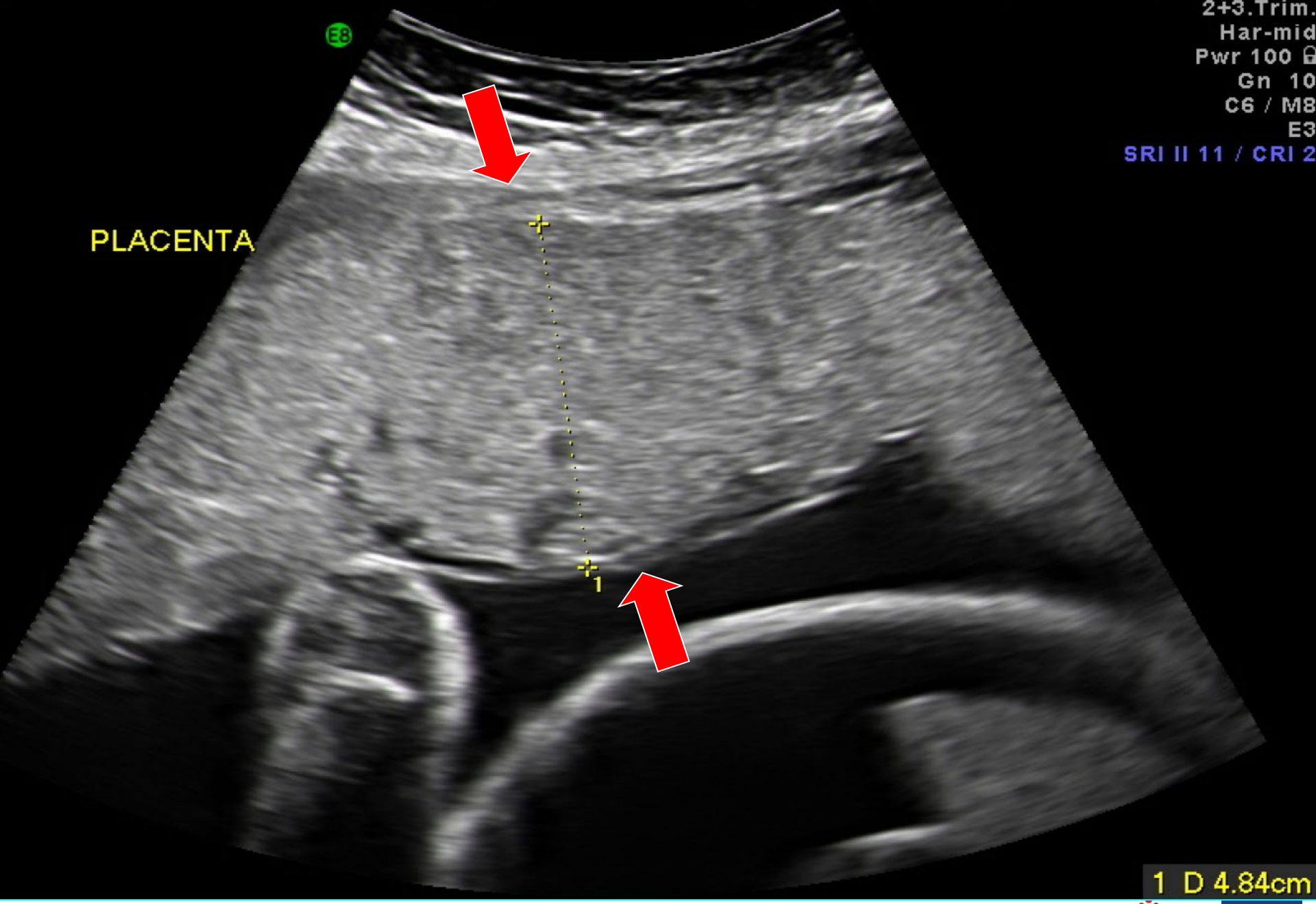
Prenatal Testing or Screening to Diagnose Maternal CMV Infection during Pregnancy

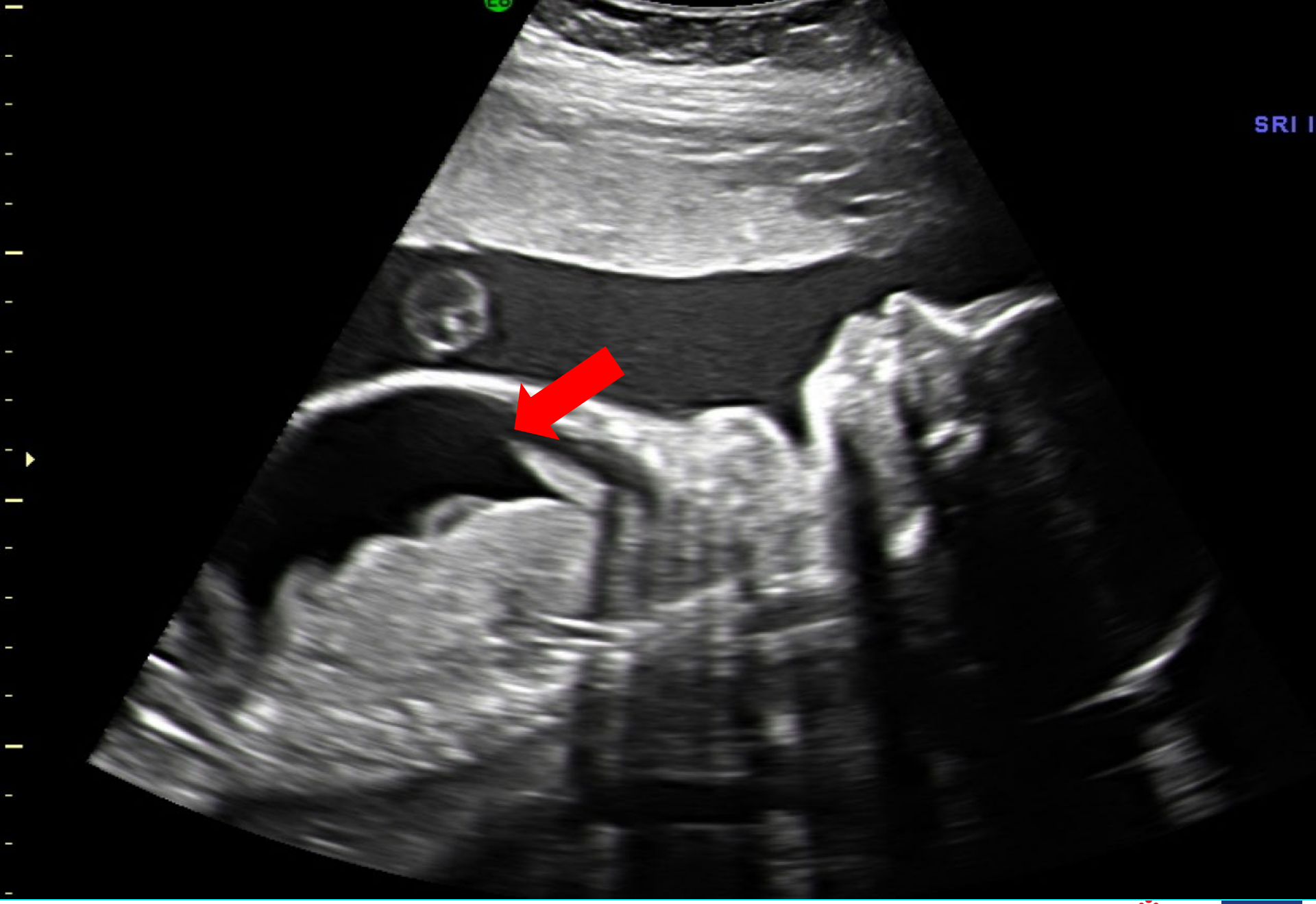
- Second Trimester- Fetal Ultrasound- ROUTINE
  - Echogenic bowel, IUGR, hydrops, brain abnormalities may be first indication of CMV infection *in utero*
  - Warrants CMV testing in mother and possibly fetus

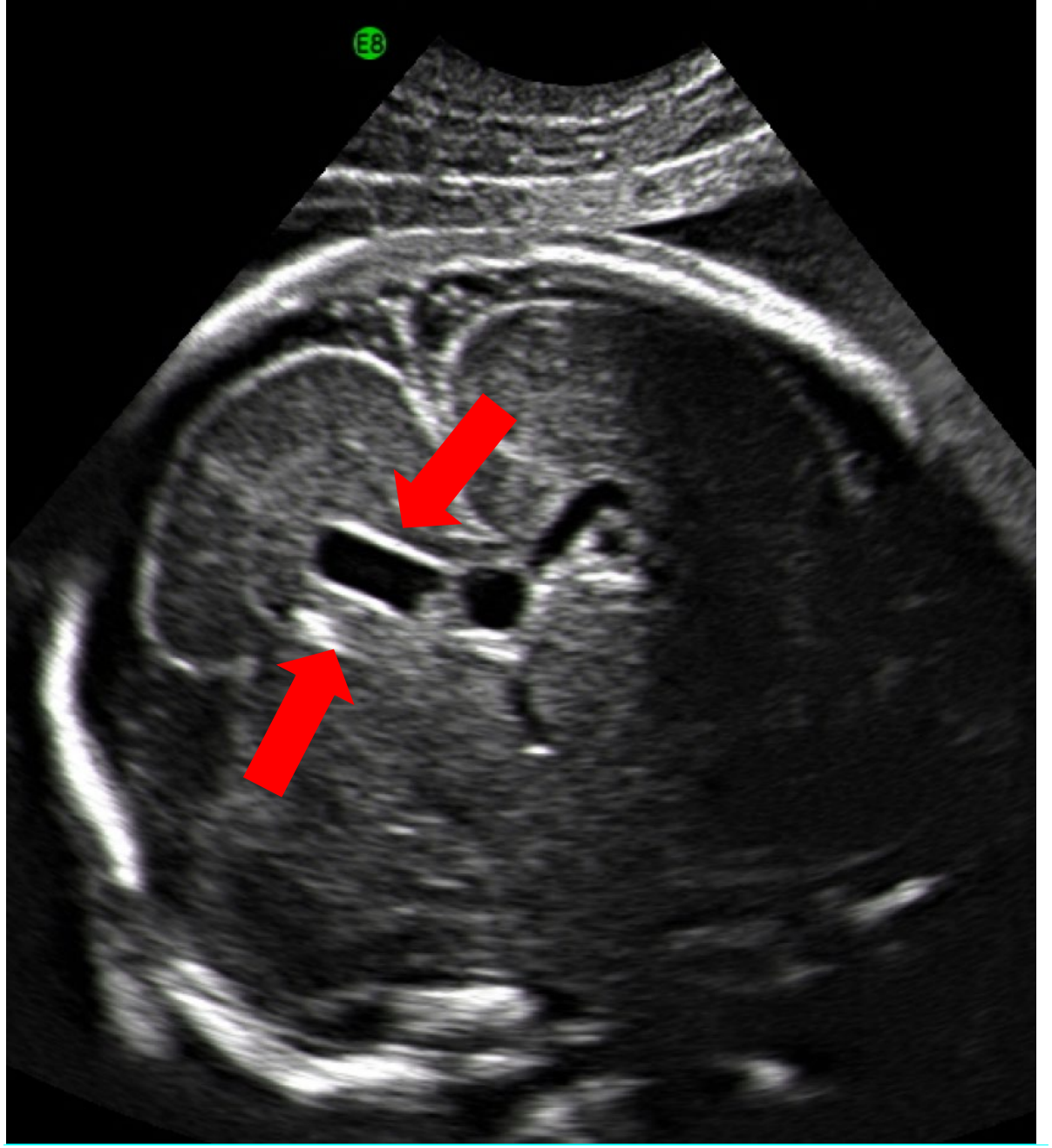
Goetzinger et al Obstet Gynecol 2011

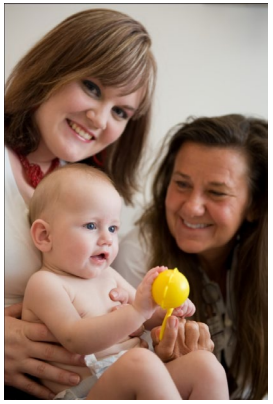
Case
Cytomegalovirus Infection of a Fetus

- 24 y.o G2P1Ab0
- Ultrasound 20 weeks screening fetal anatomy scan and repeat 24 weeks gestation- thickened placenta, cerebral echogenic foci, fetal ascites, hepatosplenomegaly
- Maternal studies: CMV IgG +, CMV IgM +, CMV avidity high - Recent primary infection? Or not?
- Amniocentesis: + PCR/culture for CMV; viral load > 1 X 10^6 copies/ml




SRI



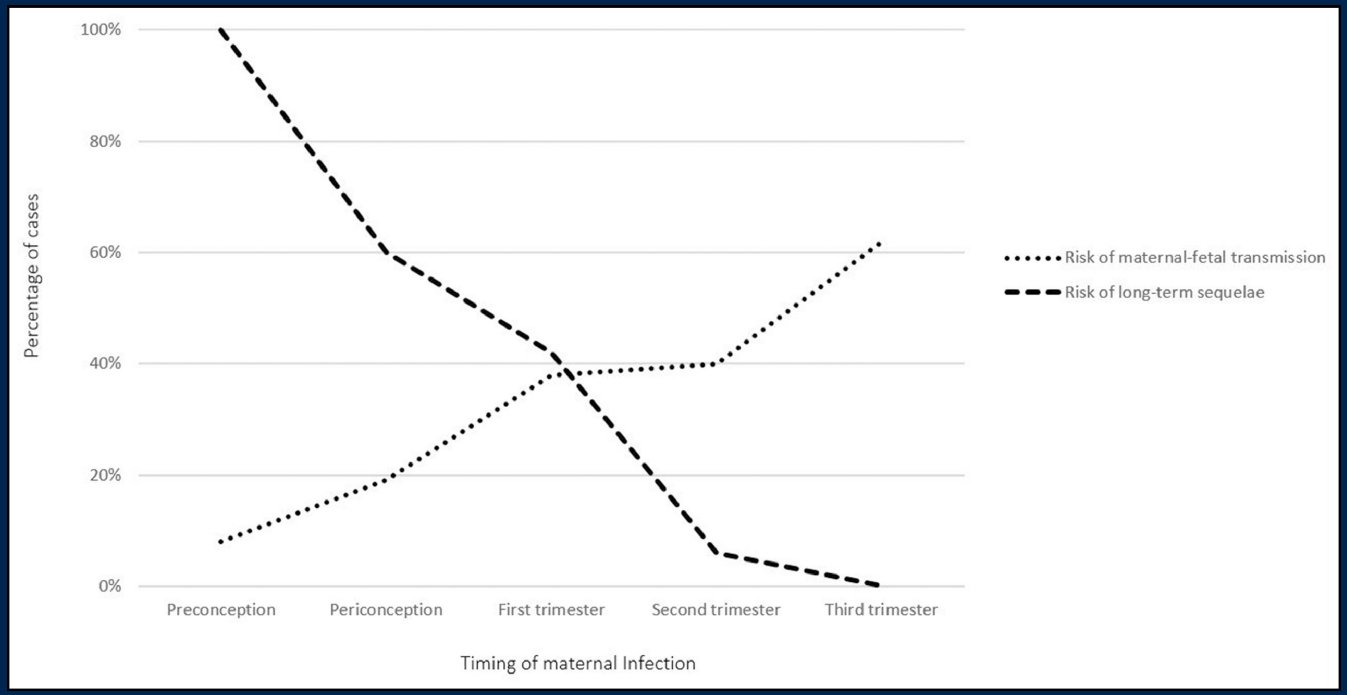


Texas Children's Hospital®

Baylor College of Medicine

Figure 2

Risk of fetal infection and risk of long term infant sequelae in relation to gestation age
SOGC Clinical Practice Guideline NO. 420 2021



Prenatal Prevention/Treatment for In UTERO CCMV

- **CMV Hyperimmune Globulin Treatment**
  - Four prospective observational studies were promising and showed reduction in maternal fetal transmission and severity of CCMV disease in baby
  - RCTs did not demonstrate a significant benefit
  - Remains investigational and research
  - It is not standard treatment at this time
  - Not recommended by ACOG, SOGC, or International Consensus Guidelines at this time
  - **Not being done anymore in most practices.**

Prenatal Prevention/Treatment for IN UTERO CCMV

- **Valacyclovir high dose treatment**
  - Randomized, double blind placebo controlled study of pregnant women with serologic evidence of primary CMV infection in early pregnancy-foundational evidence
  - 8 grams daily valacyclovir vs placebo
  - Reduced rate of fetal CMV infection by 71%
  - 29.8% PLACEBO VS 11.1% VALACYCLOVIR
    - (P= 0.027; OR 0.29; 95% ci 0.09-0.9)

Shahar-Nissan et al Lancet, 2020.

Zammarchi L, et al Amer J Obstet Gynecol, 2023, Chatzakis C et al. Amer J Obstet Gynecol, 2024, Nye et al CID, 2023

Prenatal Treatment/Prevention for IN UTERO CCMV

- **Valacyclovir high dose treatment**
  - NOT FDA approved; Off label use
  - Appears safe; used for HSV in pregnancy
  - Rare reports of acute, reversible renal failure
    - 4% if 4 gm BID dosing
    - Nil if 2 gm QID dosing, with hydration

  - Not recommended routinely by ACOG, or some International Consensus Guidelines at this time
  - Can be considered per SOGC
  - **<u>Now recommended by ECCI</u>**
  - Being used clinically in many centers/practices

Shahar-Nissan et al Lancet, 2020; Guideline 420 CMV in Pregnancy, JOGC 2021; Zammarchi, et al Clin Microbiol Infect 2020 and J Obstet Gynecol 2023; Leruez-Ville M et al. Lancet Review 2024.Chatzakis, Amer J Obstet Gynecol 2024, Faure-Bardon V et al. Ultrasound Obstet Gynecol 2021; Egloss C et al Ultra sound Obstet Gynecol c 2023; Shurder J et al. Ultra sound Obstet Gynecol 2021 Ville Y, Leruez-Ville M. Ultrasound Obstet Gynecol 2021; D'Antonio F, et al. Ultrasound Obstet Gynecol 2022; ACOG Prac Bulletin 151; 2015

Pregnant or Persons of Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative

*

CMV *in utero* fetus congenital CMV newborn

40% CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

Hearing loss
Disabilities ?

5 to 8% die - 85% to 90% survivors neurodevelopmental

10% to 15% have hearing loss
other disabilities ?

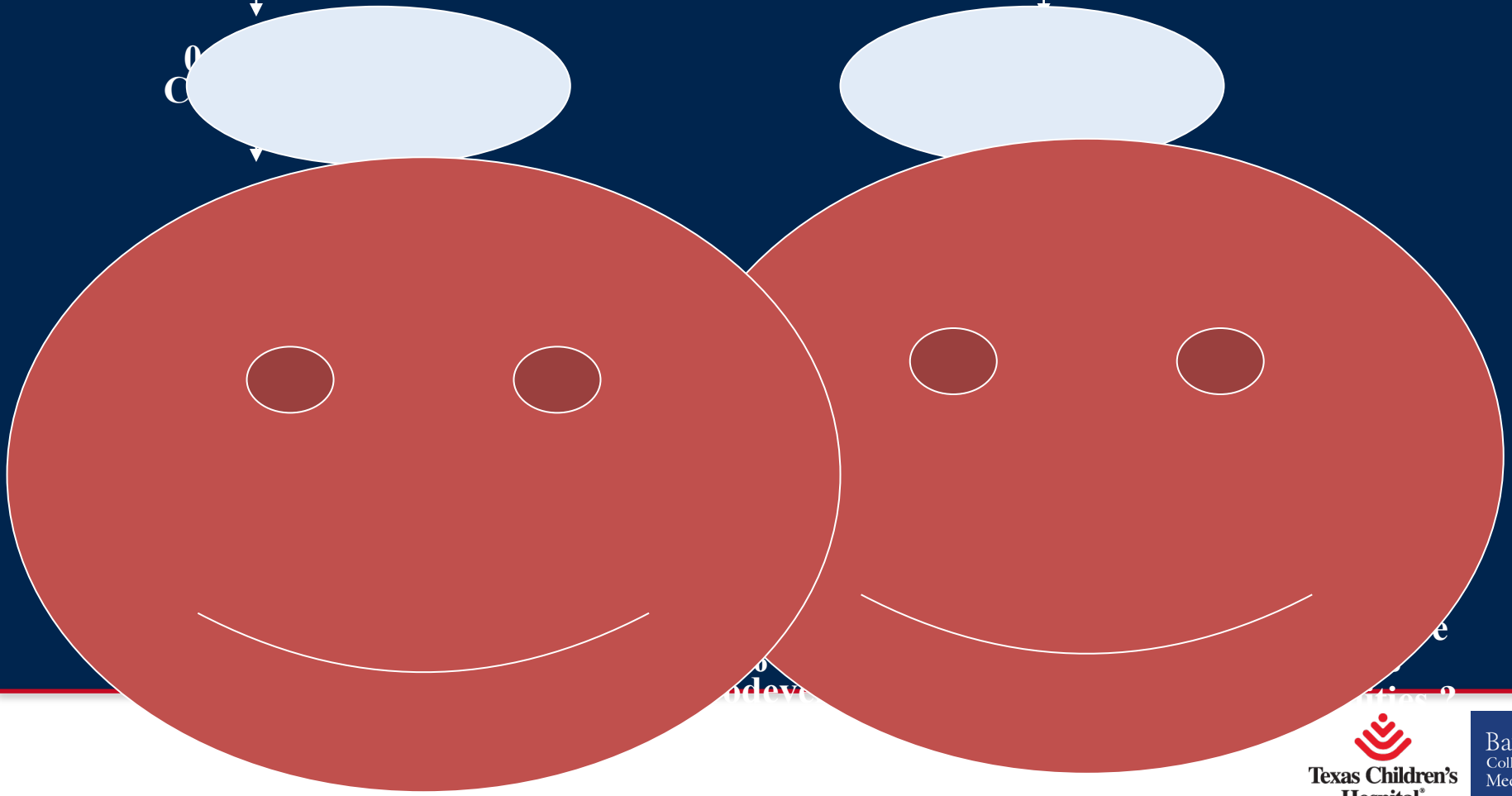
Texas Children's Hospital®

Baylor College of Medicine

Pregnant or Persons of Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative



Texas Children's Hospital®

Baylor College of Medicine

OBJECTIVES CMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- TREATMENT
- **PREVENTION**

CCMV Prevention

- **CMV vaccine to prevent maternal CMV infection and CCMV in the baby**
  - **CMV vaccine research ongoing since 1970s, many candidates evaluated**
  - **CMV Vaccine a priority for 21st Century in USA by Institute of Medicine***
  - **Many CMV vaccine candidates under evaluation, active R&D pipeline, currently clinical trials with results**
  - **NO licensed CMV vaccine available yet**

* IOM Committee to Study Priorities for Vaccine Development for 21st Century Nat Academics Press 2000; **www.clinicaltrials.gov, www.cmvictory.com

Texas Children's Hospital®

Baylor College of Medicine

CMV vaccine conundrums

- Natural immunity to infection, re infection, and reactivation incomplete
- Correlates of immunity not well understood
- Subunit, DNA, mRNA, and viral-vectored vaccines all being studied
- gB protein vs trimeric or pentameric complexes important ?
- Prevent primary or recurrent infection important?
- Target populations?
- Endpoints for efficacy?

CMV Vaccines in Clinical Trials

- mRNA 1647- Moderna
- V160 -Merck
- Triplex -MVA vector expressing three CMV genes – City of Hope Med Center
- gB/pentamer – GSK
- gB/VLP and VBI 1901- VBI
- SPYVLP01/VLP SpyBiotech Inc
- Others?

Permar S, Schleiss M, Plotkin S. J Clin Invest Review, 2025; www.clinicaltrials.gov

Can we prevent maternal CMV through other ways ?

- CMV is transmitted through close contact with others who have CMV infected body fluids
- Toddlers are “HOT ZONES” for CMV
- Annual seroconversion rates 15% day care workers and 50% in households with toddlers shedding CMV in saliva/urine
- Reduce risk by reducing contact with CMV infected secretions

Texas Children's Hospital®

Baylor College of Medicine

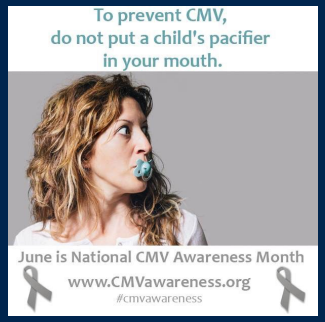
“CMV Knowledge Vaccine”
“Information Vaccination”

- An Ounce of CMV Awareness
- Three Simple Precautions –
  - Do not kiss young children on or near mouth
  - Do not share food or drink or pacifiers or toothbrushes with young children
  - Wash hands after <u>all</u> diaper changes and after wiping runny noses/drooling

<u>Not</u> recommended now routinely by obstetricians and by ACOG – “too burdensome” “unproven”<u>-? reconsidering</u>

Recommended by CMV experts, International Consensus Guidelines, AAP, SOGC, CDC, supported by clinical trials

Adler et a J Pediatr 2004; Cannon Br Med J 2005; Harvey et al 2008; Revello et al J Clin Virol 2011; Vauloop-Fellous et al J Clin Virol 2009, Rawlinson et al Lancet ID, 2017; SOGC Guideline 420 JOGC CMV Pregnancy, 2021; ACOG Practice Bulletin 151 CMV etc Pregnancy, 2015; www.cdc.gov/cmv.



Texas Children's Hospital®

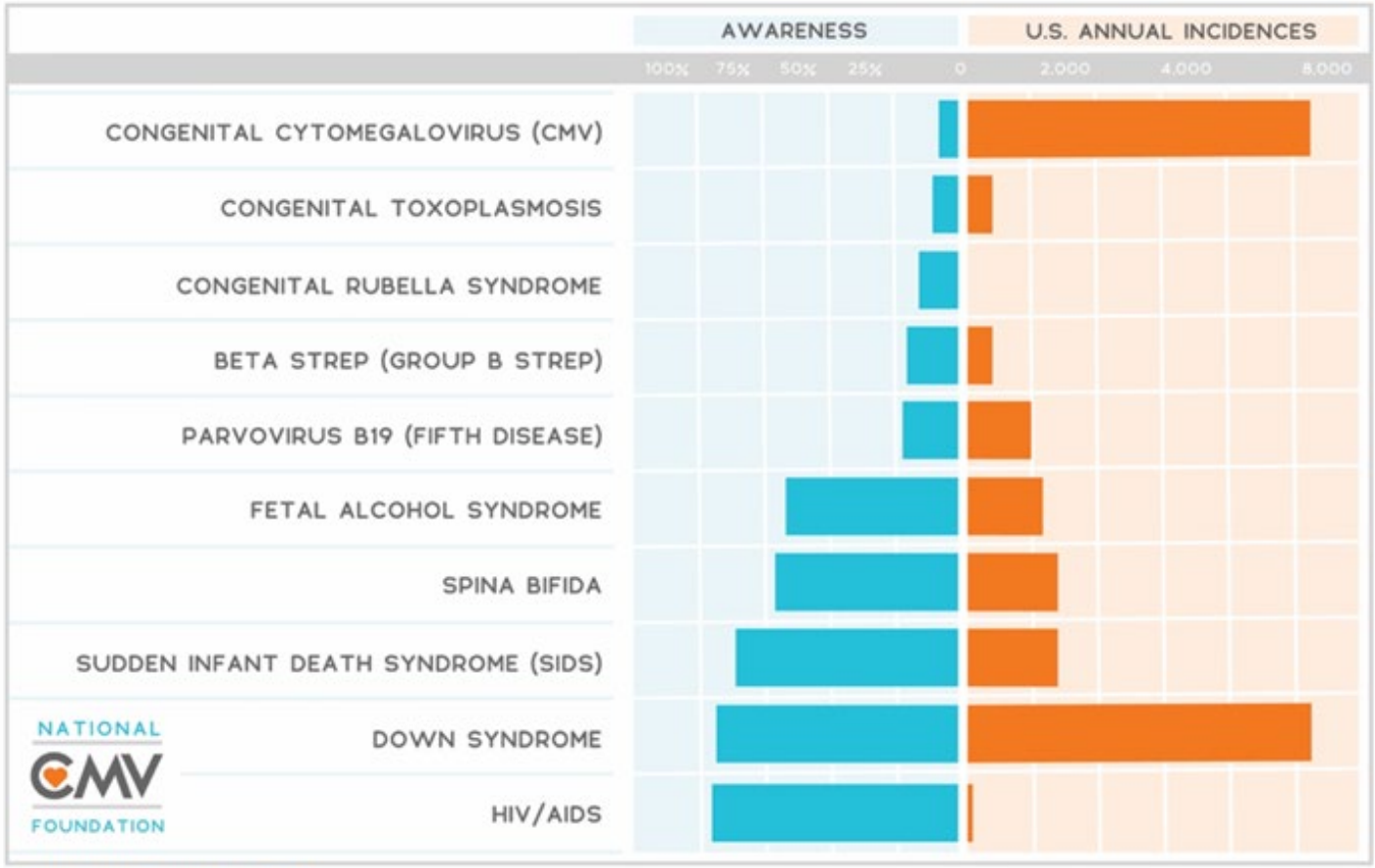
Baylor College of Medicine

Who should know?

- Pregnant persons with contact with young children
  - Toddlers/ pre schoolers in household or extended family or babysitters or caretakers
  - Day care center workers
    - Should CMV information be required for licensure?
  - Pre school teachers
  - Speech/language therapists
  - Health care workers- routine universal precautions sufficient to prevent transmission in hospital- but there may be special circumstances


CMV
INSPECTION
STATION
3/4 MILE

WE DO NOT PASS INSPECTION FOR CMV AWARENESS WWW.NATIONALCMV.ORG



Texas Children's Hospital

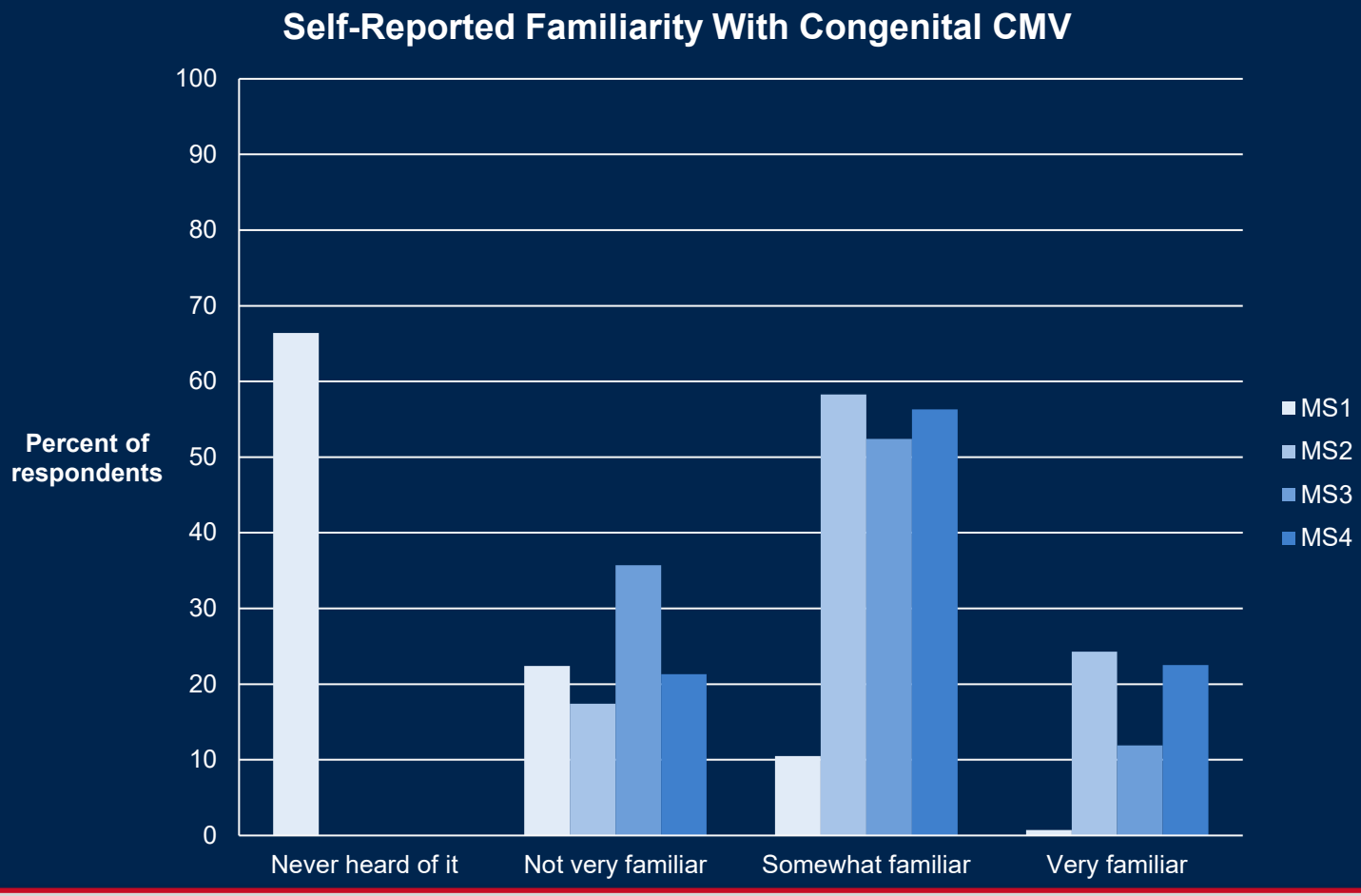
Baylor College of Medicine

Survey of Congenital Cytomegalovirus (cCMV) Knowledge Among BCM Medical Student, Houston Texas

Most “young doctors to be” have never even heard of CMV !

More awareness amongst medical teams needed!

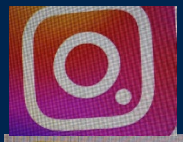
Baer HR, Corwin HE, Caviness AC, Demmler-Harrison GJ, J Clin Virol 2014

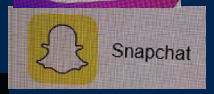


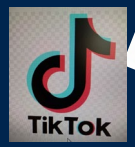
Texas Children's Hospital®

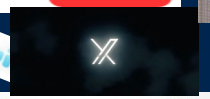
Baylor College of Medicine

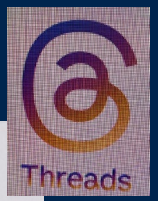
CMV Advocacy

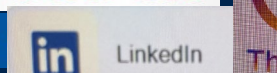


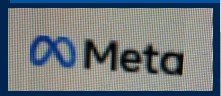


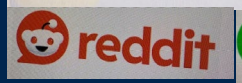


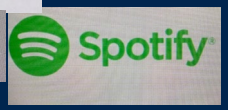


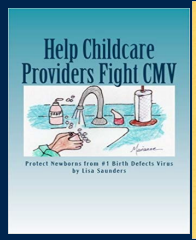


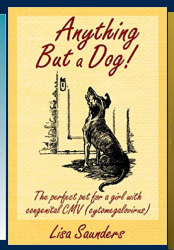


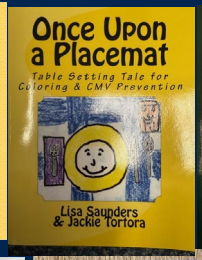


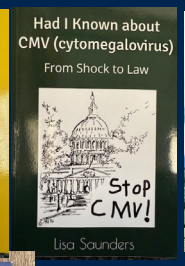


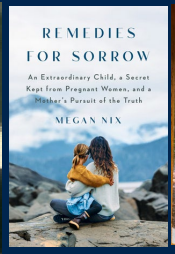


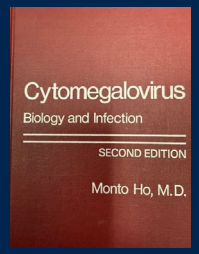


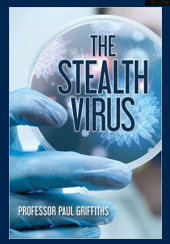


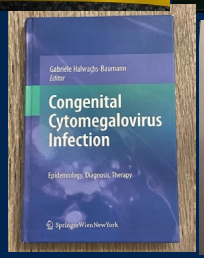


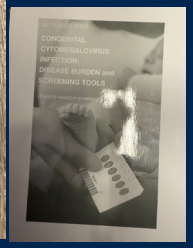










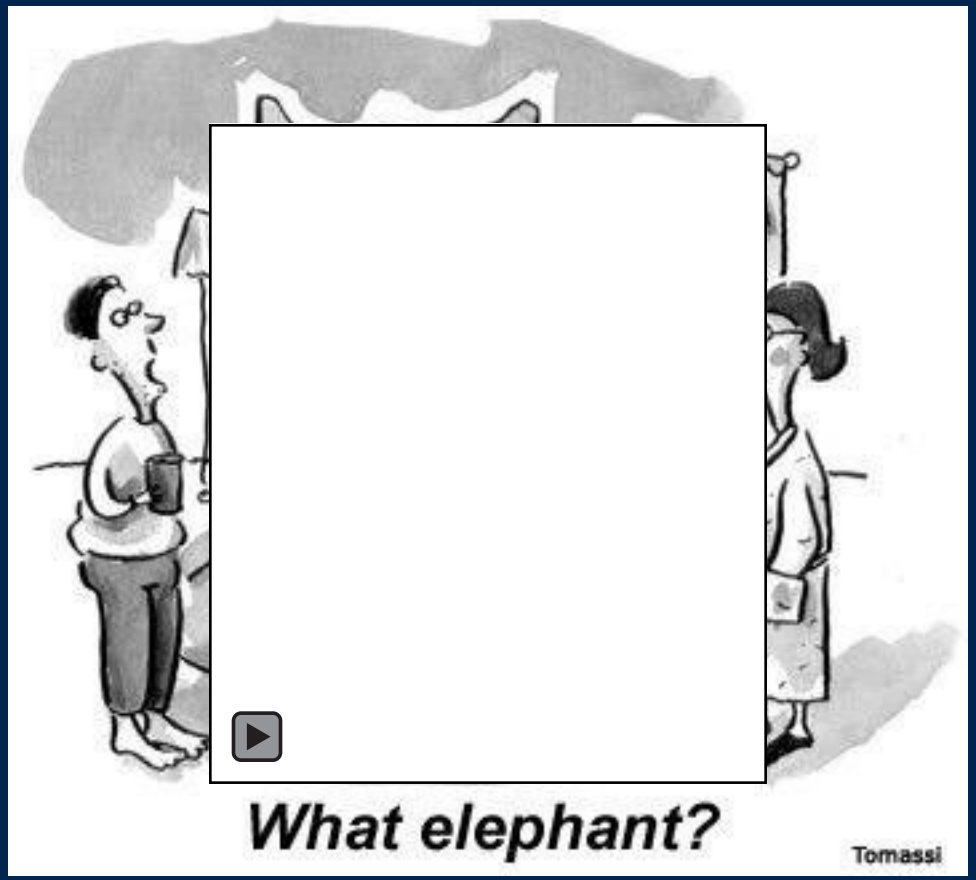


CMV ADVOCACY GROUPS ON LINE WEB

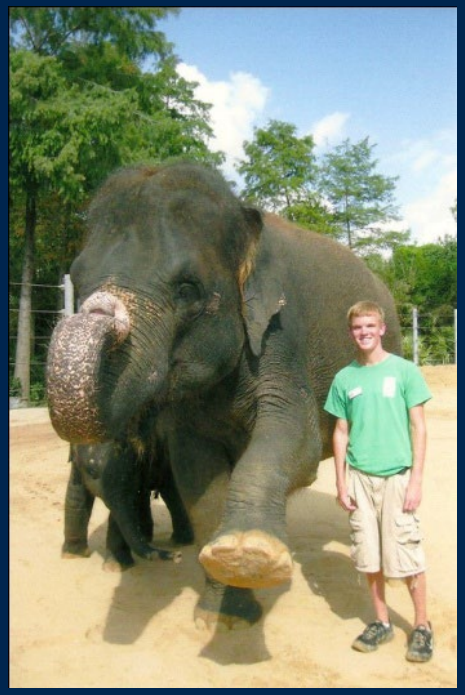
- Anti Cito (Italy)
- Chanter Marcher Vivre (France)
- Congenital CMV Association (Australia)
- CMV Action (UK)
- National CMV Foundation (USA)
- Idaho CMV Advocacy Project (USA)
- Utah CMV Council (USA)
- Congenital CMV News (USA)
- CMV Canada (Canada)
- Many Others !!

Texas Children's Hospital®

Baylor College of Medicine


What elephant?
Tomassi

Congenital CMV challenge…….. to take the next steps forward !



"If we stumble, it will not be because we lack for technology, vision or motivation.

It will be because we cannot set a direction and march collectively into the future."

History of the Future 2004

Maternal CMV Screening in Pregnancy

CMV Knowledge Vaccine - Information Vaccination

Newborn cCMV Screening for Early Diagnosis

Antiviral Treatments for cCMV

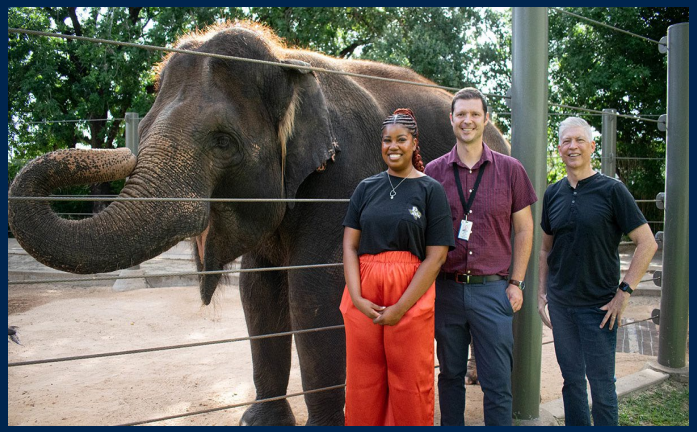
CMV Vaccine

Texas Children's Hospital®

Baylor College of Medicine

What about EEHV and our Elephant Friends?

- EEHV PCR diagnostics available in USA Europe Asia
- EEHV treatment antivirals- famciclovir; acyclovir, ganciclovir
- EEHV mRNA vaccines now appear effective –Mother Tess age 40 yr Asian Elephant from Houston Zoo received first ever mRNA EEHV vaccine in 2024!



www.houstonzoo.org
EEHVinfo.org

Ling P et al in Vaccines 2022 and 2024 and J Zoo Wildl Med 2023

Texas Children's Hospital®
Baylor College of Medicine

“Good Bye”
It’s time to say “good-bye” to the elephant in our living room !

Texas Children’s Hospital®

Baylor College of Medicine

The Houston Congenital CMV Longitudinal Study and my CMV Research, Clinic and Outreach Programs have been supported for over 40 years by grants and contributions from the following sources – Thank you!

- Baylor College of Medicine CMV Research Fund Donors
- The Woman's Hospital of Texas Research Foundation
- Office of Research Resources at Texas Children's Hospital
  - Audiology testing and GCRC outpatient visits
- General Clinic Research Center at Texas Children's Hospital
  - National Institutes of Health NIH – MOI RR 001-88-33
- Mental Retardation Research Center at Baylor College of Medicine
  - National Institutes of Health NIH – CHHD5—P30 HD 24064
- NIH NIAID CASG
- NIH NIDCD
- Research to Prevent Blindness, Inc. New York, NY
- Deafness Foundation, Houston, TX
- Vale Ashe Foundation, Houston, TX
- Maddie's Mission, Katy, TX
- Naymola Charitable Foundation, Beaumont, TX
- Merck & Co
- Moderna Inc
- Microgen Inc
- Centers for Disease Control
  - CDC Cooperative Agreement FOA IP 10-006
  - CDC Contract No. 0009280120/8454RU92
  - CDC Contract No. 0009184031/8403R491
- APS-SPR Summer Student Research Program
  - National Institutes of Health NIH – CHHD
- Donations of the time and talents of numerous volunteers
- Dedication of the "CMV Kids" and their families and physicians

Texas Children's Hospital®

Baylor College of Medicine

Thank you!

Texas Children's Hospital®

Baylor College of Medicine®

The End