Overview of Congenital CMV

Charleston Pediatric Update 2024

Eileen Raynor, MD FACS FAAP
Pediatric otolaryngology
HNS&CS

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

1

Disclosures

- Member NC CMV workgroup
- Board member NC BOESLPA

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

2

Objectives

- Differentiate between symptomatic and asymptomatic cCMV and identify methodology for CMV testing and implications for positive results
- Develop a plan for cCMV positive children
- Be a resource to educate families and PCPs on cCMV

Duke Head and Neck Surgery & Communication Sciences

3

Background

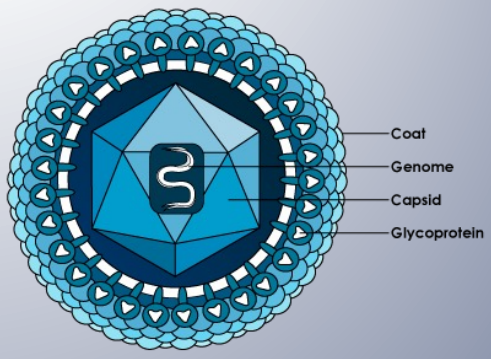
- Congenital CMV infection (cCMV) is an important public health issue
  - Most common congenital infection, affecting 1 of every 200 newborns
  - Major cause of hearing loss (HL) and disability in children
- Most cCMV infections are clinically not apparent - infants not identified at birth
  - ~ 50% of HL due to cCMV occurs after birth and will be missed by universal newborn hearing screening (NBHS)
- Diagnosis of cCMV relies on urine or saliva culture or PCR in the first 3 weeks of life
  - Universal testing of newborns will promote early detection of hearing loss
  - Targeted testing of newborns with hearing loss will help establish an etiology

Duke Head and Neck Surgery & Communication Sciences

4

What is Congenital CMV (cCMV)?

- Herpes family of viruses affecting from 60-90% of adults, usually minimal URI type symptoms
- Most common congenital infection and the leading cause of non-genetic hearing loss in the United States
- *Every* pregnant woman is at risk of transmitting CMV to her newborn
  - Only 9% of women know about CMV
- cCMV is common, serious, and *preventable*



Duke Head and Neck Surgery & Communication Sciences

5

Epidemiology of Congenital CMV

- Most common cause of congenital infection worldwide
  - 0.2 to 2.2 % of all births
- Result of both primary and recurrent maternal infection
  - Primary infection- risk is higher with primary infection (~40%)
  - Recurrent infection- risk is ~1%
    - Reactivation of latent virus
    - Reinfection with different strain
- Risk factors in mothers
  - Young maternal age (< 25 y)
  - Single marital status
  - Non-white race
  - Lower socioeconomic status

Duke Head and Neck Surgery & Communication Sciences

6

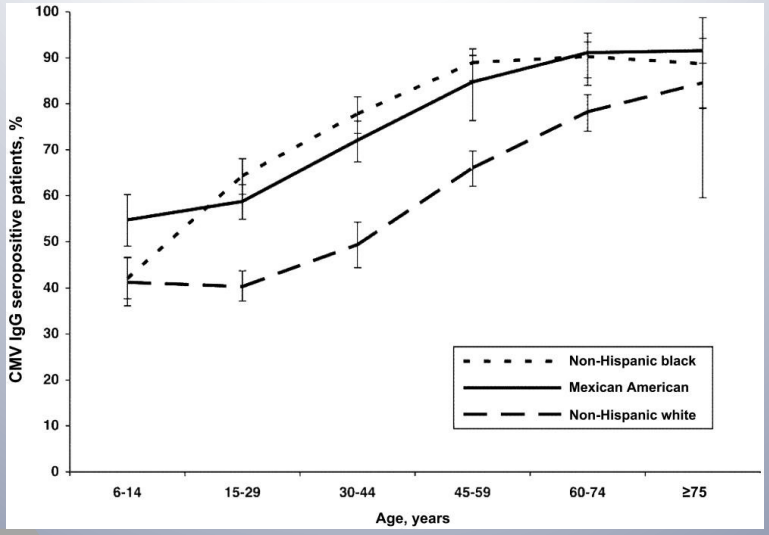
Influence of SoDH in cCMV

- Well established higher incidence in lower SES and non-white
- More children of younger age in home
- Closer living conditions
- Children in daycare
- Younger maternal age
  - More risk of getting primary infection
  - More chance of being around younger children

Duke Head and Neck Surgery & Communication Sciences

7

Prevalence of CMV Infection

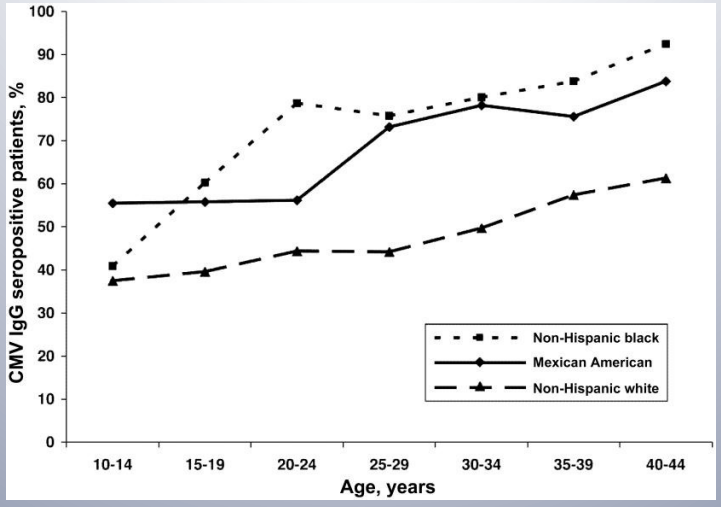


Duke Head and Neck Surgery & Communication Sciences

Clin Infect Dis 2006; 43: 1143-51

8

Seroprevalence of CMV in Women of Childbearing Age

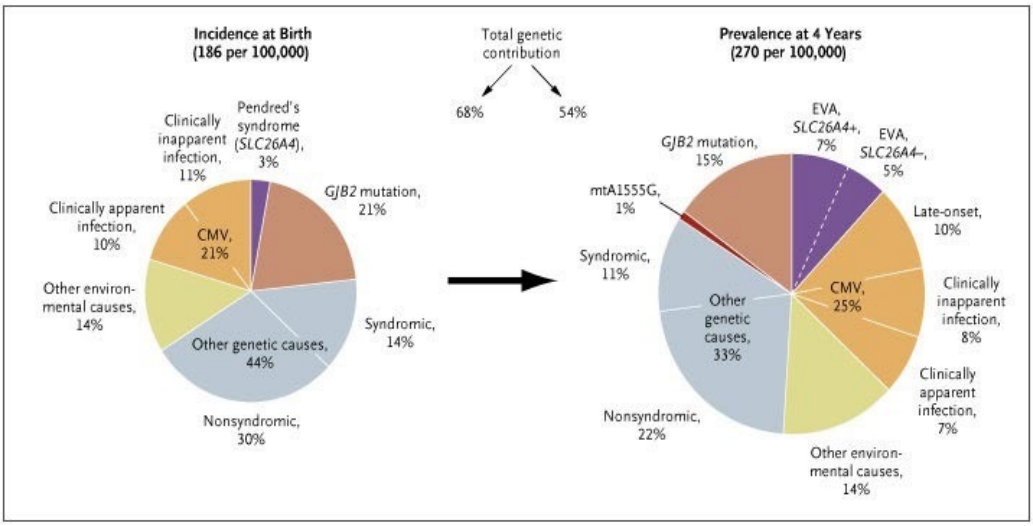


Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

Clin Infect Dis 2006; 43: 1143-51

9

Congenital CMV and Hearing Loss



Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

N Engl J Med 2006; 354: 2151-64

10

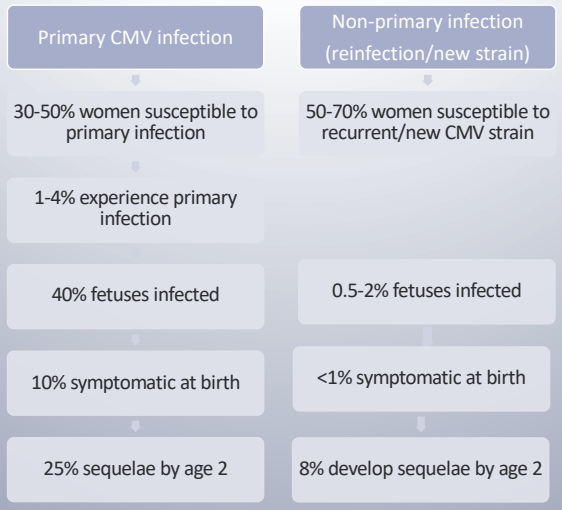
Estimated Annual U.S. Cases of Selected Fetal and Neonatal Viral Infections

Viral Etiology	Cases/Year
Cytomegalovirus	25,000
Herpes simplex	2000
Varicella-zoster	500
Human immunodeficiency virus	2000
Parvovirus B 19	13,000
Hepatitis B	6000
Rubella	0-31

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

11

Maternal and neonatal risks for CMV infection



Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

Fowler KB and Boppana SB. *ClinVirol.* 2006;35:226–231.
Naing ZW, Scott GM, Shand A, et al. *Aust N Z J Obstet Gynaecol.* 2016;56(1):9-18.
Society for Maternal-Fetal Medicine (SMFM), Hughes BL, Gyamfi-Bannerman C.. *Am J Obstet Gynecol.* 2016;214(6):B5-B11.

12

Congenital CMV Infection

- Birth prevalence of CMV in US is 0.65%
  - 25,000 newborns annually in the US
- **Symptomatic infection** (10-15%)
  - Risk of sequelae is 45-60%
  - Evaluation at birth/diagnosis and monitoring for sequelae
- **Asymptomatic infection** (85-90%)
  - Risk of sequelae is 10-15%
  - Role of screening, evaluation and monitoring for sequelae is evolving

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

13

Symptomatic cCMV

- Typical clinical symptoms include:
  - Petechiae
  - Thrombocytopenia
  - Microcephaly
  - Hepatosplenomegaly
  - Jaundice
  - Chorioretinitis
- Neurodevelopmental sequelae include SNHL, intellectual disability, motor impairment, vestibular problems and visual impairment
- Failed hearing screen now under definition of symptomatic cCMV

Baby born with petechiae

(Kadambari et al., 2011)

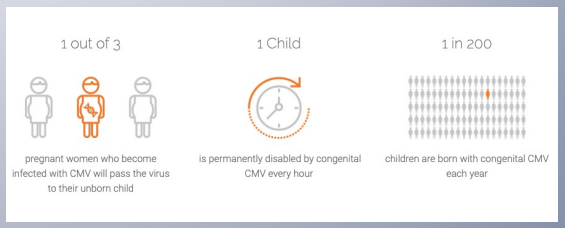
Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

14

Potential Outcomes

- **Hearing loss**
- Vision loss
- Intellectual disability
- Microcephaly, intracranial calcifications
- Cerebral palsy
- Feeding issues/failure to thrive
- Sleeping, behavior, sensory issues
- Delayed motor milestones/vestibular problems
- Seizures
- Death

1 out of 5 children born with congenital CMV will develop permanent health problems with as many as 400 infant deaths annually.



Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

15

Asymptomatic cCMV

- Children born with *asymptomatic* CMV may also develop sequelae in childhood including:
  - SNHL (most common)
  - Vision loss
  - Neurological problems
  - Developmental delay including speech/language
  - Vestibular dysfunction
- In general, these children have a better long-term prognosis than those who are symptomatic at birth

Early Hum Dev 2011: 87: 723-8

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

16

Diagnosis of cCMV

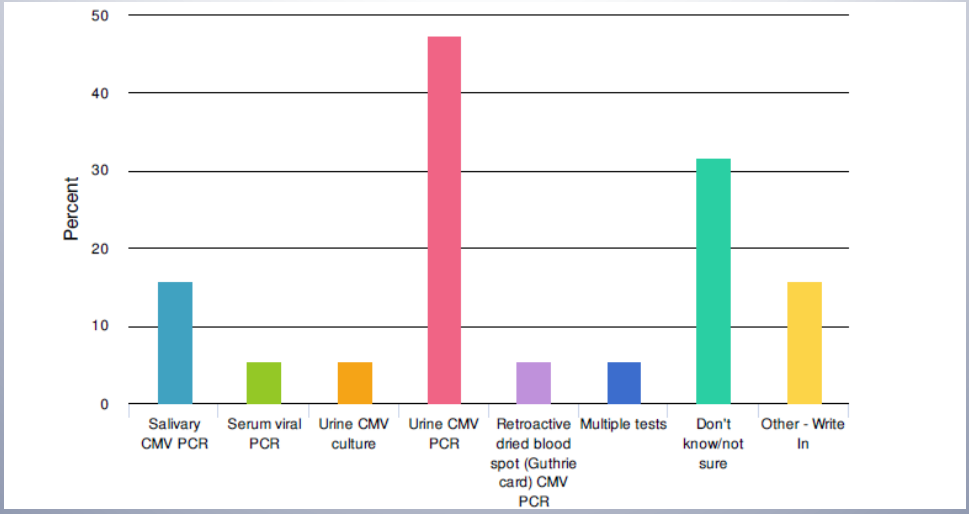
- Viral culture or PCR (polymerase chain reaction) of urine or saliva within the first 3 weeks of life
  - After 3 weeks, diagnosis difficult to confirm-may be congenital or acquired
- Serology (blood tests, IgG) after 3 weeks are not helpful unless negative (acquired from breast milk or other children)
- Dried blood spots (Guthrie card)
  - Sample of baby's blood taken at birth to screen for serious medical problems such as phenylketonuria (PKU), congenital hypothyroidism, cystic fibrosis etc.
  - Allows retrospective diagnosis of CMV for older children
  - Historically demonstrated poor sensitivity (40-60%) for detecting cCMV, however recent study with new DNA extraction showed up to 78% sensitivity and 100% PPV
  - Many states do not keep these cards long (6 months up to 27 years)
- *Difficult to confirm cCMV infection as etiology of hearing loss after newborn period*

Early Hum Dev 2011: 87: 723-8
Dollard, Jama pediatrics 2021: 175(3)

Duke Head and Neck Surgery & Communication Sciences

17

NC survey: How is cCMV tested for at your center?



Duke Head and Neck Surgery & Communication Sciences

18

Table 1. Comparison of Urine Real-Time Polymerase Chain Reaction (PCR) and Urine Rapid Culture and Saliva Real-Time PCR and Saliva Rapid Culture for the Diagnosis of Congenital Cytomegalovirus Infection

	Result, by Test		
Result, by Test	Positive	Negative	Total
Urine rapid culture[a]		Urine PCR	
Positive	76	0	76
Negative	3	1	4
Total	79	1	80
Saliva PCR		Saliva Rapid Culture	
Positive	78	0	78
Negative	2	0	2
Total	80	0	80

[a] $P = .688$ for discordant results.

Table 2. Comparison of Urine and Saliva Real-Time Polymerase Chain Reaction (PCR) and Urine and Saliva Rapid Culture for the Diagnosis of Congenital Cytomegalovirus Infection

	Result, by Test		
Result, by Test	Positive	Negative	Total
Saliva PCR		Urine PCR	
Positive	79	1	80
Negative	0	0	0
Total	79	1	80
Saliva rapid culture[a]		Urine Rapid Culture	
Positive	74	4	78
Negative	2	0	2
Total	76	4	80

[a] $P = .688$ for discordant results.

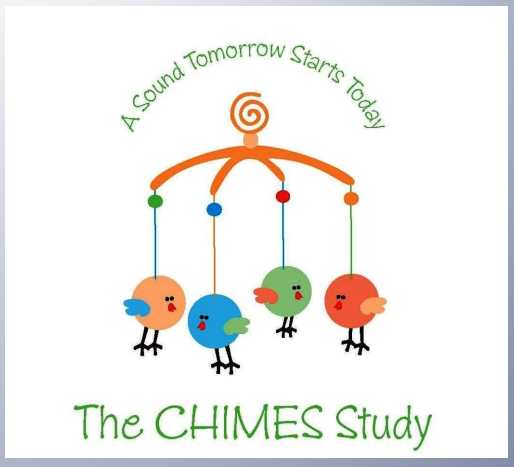
Duke Head and Neck Surgery & Communication Sciences

J Infect Dis 2014; 210: 1415-8)

19

CMV and Hearing Multicenter Screening (CHIMES) Study

- Determine the validity and clinical utility of screening tests for cCMV
  - Screen 100,000 newborns for cCMV
- Define the long-term audiologic outcome in children with cCMV
  - Sequential audiologic follow-up of those with cCMV until age 4 years



Duke Head and Neck Surgery & Communication Sciences

20

CHIMES Findings

- 100,332 newborns screened for cCMV
  - 391/100,333 (0.4%) CMV-positive
- Overall SNHL in 47/391 (12%) with cCMV
  - SNHL in 16/39 (41%) of symptomatic and 31/352 (8.8%) of asymptomatic children
  - Substantial portion had late onset hearing loss
- Burden of hearing loss in cCMV
  - 7.0% of CMV-positive infants did not pass NHS versus 0.9% CMV-negative
- Renewed interest in targeted and universal screening for cCMV
  - DBS with newer techniques to extract DNA as a result of prior studies showing < 40% sensitivity

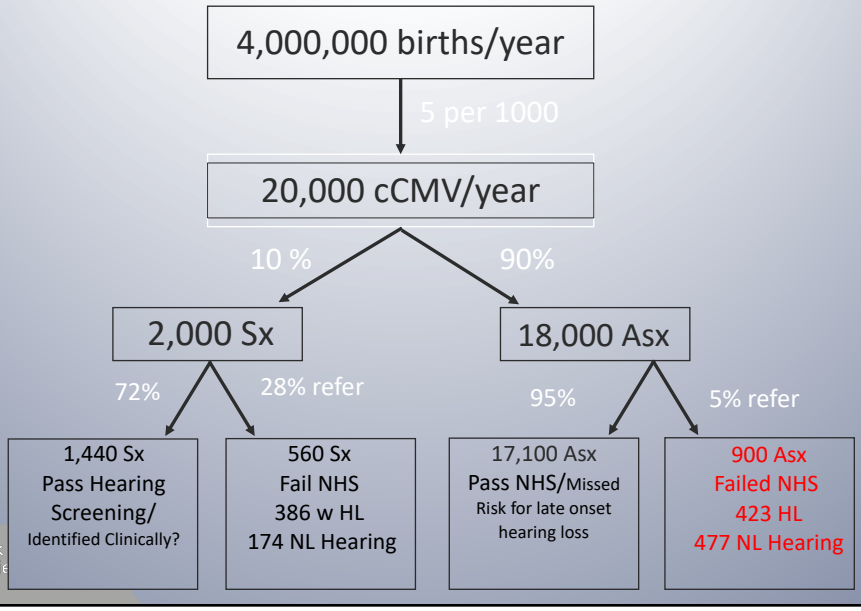
Duke Head and Neck Surgery & Communication Sciences

JAMA 2010; 808: 1875-82;
N Engl J Med 2011; 864: 2111-18
Pediatrics 2017; 139: e20162128

21

Targeted Congenital Cytomegalovirus Infection (cCMV) Screening

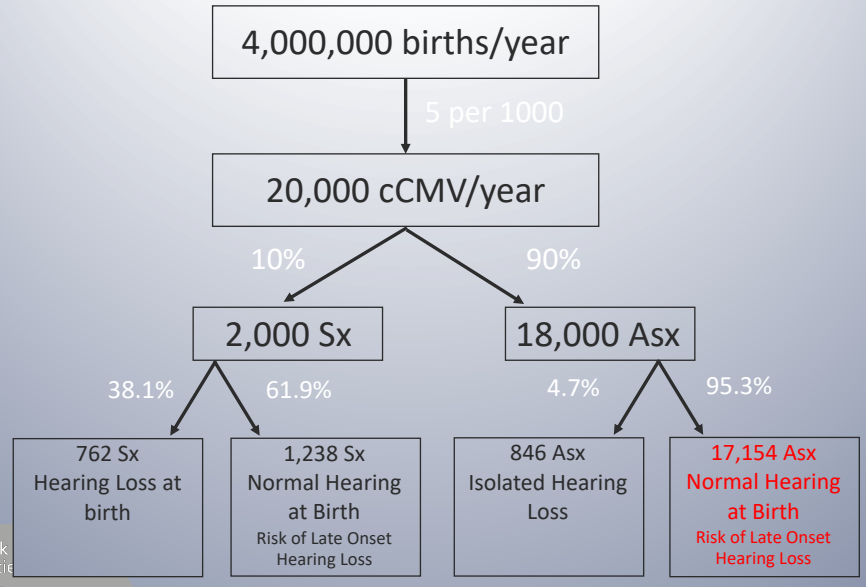
The CHIMES Study



Duke Head and Neck & Communication Sci

22

Universal Congenital Cytomegalovirus Infection (cCMV) Screening



23

Medical Management of cCMV

- Treatment
  - Ganciclovir (IV) or valganciclovir (oral)
  - May prevent progression or development of hearing loss
  - Impacts developmental outcomes
  - Currently recommended for symptomatic infants only
  - Infants receiving these antivirals should be monitored for toxicity
  - Significant side effect profile with these meds
- **Both asymptomatic and symptomatic babies born with cCMV should have hearing and vision monitored closely**

24

Congenital Cytomegalovirus (cCMV) and Hearing Loss

- 22-65% of *symptomatic* children will have hearing loss following cCMV infection
- 6-23% of *asymptomatic* children will have HL following cCMV infection
- Variability in severity ranges from unilateral high frequency hearing loss to profound bilateral hearing loss

Fowler and Boppana JClin Virol 2006 Feb;335 (2):226-31

Duke Head and Neck Surgery & Communication Sciences

25

Congenital Cytomegalovirus (cCMV) and Hearing Loss

- Both asymptomatic and symptomatic children may experience:
  - Delayed onset of HL
  - Fluctuating HL
  - Progressive HL
  - Asymmetric HL
- Necessitates continued monitoring of hearing status

J Dahle AJ, Fowler KB, Wright, JD Boppana SB, Britt WJ, Pass RF. J Am Acad Audiol. 2000 May;11(5):283-90

Duke Head and Neck Surgery & Communication Sciences

26

26

Comparison of hearing findings in asymptomatic cCMV by study

Author	year	N	Asymptomatic SNHL	Severe-profound	Unilateral	Progressive	Fluctuating	Delayed
Goderis	2014	379	10%	77%	56.9%	20.3%	24%	9%
Foulon	2008	28	21%	60%	14%	38%	54%	23%
Ross*	2006	300	11%	63%	58%	63%	43%	53%
Fowler	2006	860	7.4%	68%	NR	50%	NR	15%
Williamson	1992	59	100% **	77%	11%	62%	11%	9%

*data for primary maternal CMV infection; **only cCMV with SNHL included in study; NR not reported in study

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

Raynor, et al: triological thesis 2022

27

Characteristics of cCMV SNHL

- Delayed Onset (Approximately 33-50%)
  - Usually occurs before 6 years of age, but later onset, even in adolescence has been reported
- Progressive (Approximately 50% of cases)
  - About the same rate for symptomatic and asymptomatic
  - Symptomatic have greater degree of severity and earlier progression
- Fluctuating
  - Not explained by middle ear problems
  - May occur in one or both ears
- Asymmetric
  - Symptomatic more likely to be bilateral
  - Asymptomatic more likely to be unilateral

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

Fowler et al.,1999, 2006
Fowler, 2018 & Goderis et al, 2014

28

Newborn hearing screen results

- Follow up of refer or failed hearing test
  - Should be audiology driven (JCIH 2019 recommendations)
  - May be impacted by distance from birth center
  - If there is not an audiology or ENT/audiology practice nearby, need to identify sites for follow up
  - https://www.ncnewbornhearing.org/files/ApprovedInfantDiagnosticSiteList-03182020.pdf

Link to list of audiology practices statewide that can do diagnostic testing for newborns

Raynor, et al IJPORL 2021

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

29

Management of HL in cCMV: What's different?

Delayed Onset:

- Diagnostic challenge: If HL not identified at time of NBHS, may not be screened again until school age
- Parents more likely to return for follow up of failed hearing screen and regular monitoring if they know child has cCMV and is at risk for late onset HL
- Better speech/language/cognitive outcomes when HL identified and treated early

Progressive:

- Frequent monitoring of hearing needed to ensure that technology is appropriate
  - If HL progresses, HA settings will need to be adjusted to insure adequate audibility
  - Are HAs sufficient, or is CI needed?

Fluctuating:

- Difficult to manage hearing aid settings when hearing loss is fluctuating
  - May require multiple programs (parents need to manage for young child)
  - Adjustable volume control may also be helpful
  - Unexplained fluctuating HL in unknown etiology may trigger unnecessary diagnostic tests and treatments

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

30

Hearing Loss in Congenital CMV

- Characterized by progression and fluctuation
  - Onset may be delayed for months to years
  - Critical to have regular audiologic follow up
- SNHL present at birth in 5-10% of infected newborns
  - Accounts for <50% of SNHL in cCMV
  - Emphasizes need for identification of the asymptomatic cCMV infant
- The majority of SNHL due to cCMV not detected at birth
  - Confirmation of cCMV as etiology **after** 3 weeks of life is difficult
  - DBS testing only about 60% sensitivity
- Parent education and advocacy for their child is *critical*. Avoids delay in management and speech and language development

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

31

Universal Newborn Hearing Screening: Will children with SNHL caused by cCMV be missed?

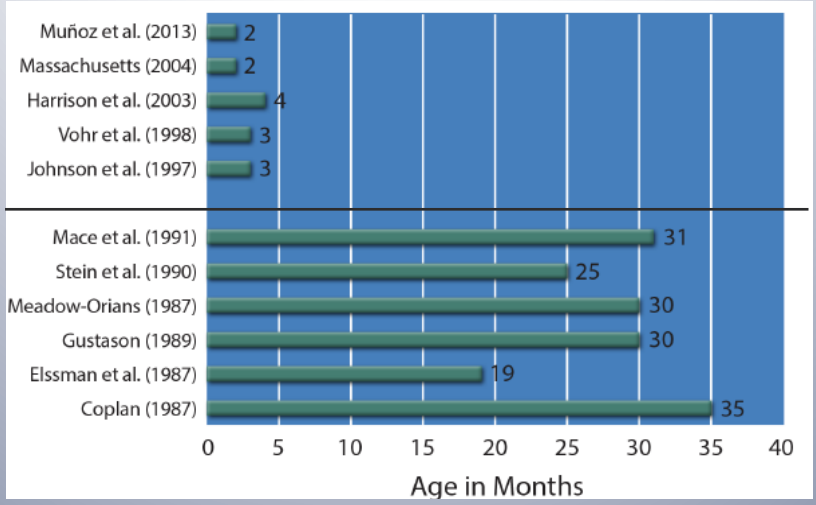
- 388 neonates identified with cCMV (1980-1996)
  - Audiologic exam at birth because of identified cCMV (prior to universal hearing screening)
- SNHL in 5.2% of newborns with cCMV
- By age 72 months - 15% with SNHL
  - Symptomatic- 36%
  - Asymptomatic- 11%
  - Would not have been tracked or ID'd otherwise

J Pediatr 1999; 135: 60-4

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

32

Age at Which Permanent HL Diagnosed… Before and After Newborn Hearing Screening



Duke Head and Neck Surgery & Communication Sciences

K.White, 2012

33

Age at Detection of SNHL in cCMV Infection

Age of Child	Cumulative incidence of all SNHL (%)*	Cumulative incidence of SNHL (%) †
< 1 mo	5.2	3.9
3 mo	6.5	5.3
12 mo	8.4	6.8
24 mo	9.9	7.2
36 mo	10.8	7.6
48 mo	11.3	7.6
60 mo	12.4	7.6
72 mo	15.4	8.3

*≥ 20 dB loss † ≥ 30 dB loss

Duke Head and Neck Surgery & Communication Sciences

J Pediatr 1999; 135: 60-4

34

Diagnostic audiological follow up

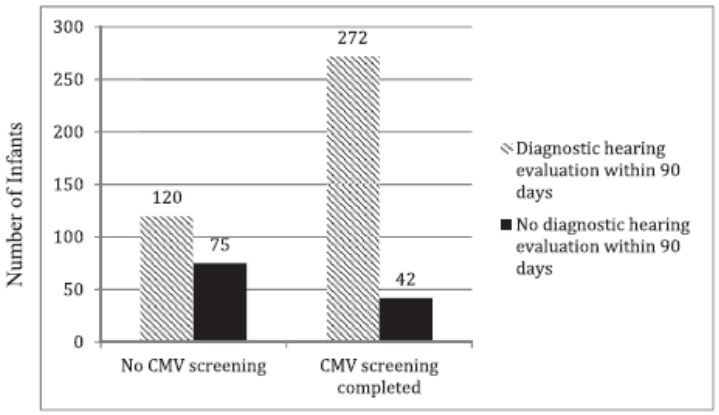


FIGURE 3
Numbers of infants who completed diagnostic hearing evaluations within 90 days by CMV testing status.

Duke Head and Neck Surgery & Communication Sciences

Pediatrics 2017; 139 (2): e20160789

35

Audiologic Monitoring for cCMV

- Since infants with cCMV are at risk for delayed onset or progressive HL they require periodic monitoring.
  - The Joint Committee on Infant Hearing (JCIH) recommendation for follow-up audiologic assessment of infants with cCMV is no later than 3 months of age. (JCIH, 2019)
- Recommendations for monitoring every 3 months in first year;
  - Every 6 months until age 3;
  - Annually until age 6
  - More frequent monitoring may be needed if hearing is fluctuating

Dahle et al, 2000
Fowler, 2013

Duke Head and Neck Surgery & Communication Sciences

36

JCIH 1, 3, 6 initiative

- Repeat screening testing within **1 month**
- Diagnostic testing (ABR) within **3 months** *(ideally should be within 2 mo)*
- Intervention within **3-6 months** (hearing amplification, initiate cochlear implant referral for profound SNHL) and referral to early intervention
- If *confirmed* to be congenital CMV, it is critical to counsel families regarding regular, consistent audiology follow up due to risk of **progressive and/or fluctuating SNHL** over time

Journal of Early Hearing Detection and Intervention. JCIH 2019. *J Early Hear Detect Interv*. 2019;4(2):1-44.

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

37

Otologic Work-up of SNHL

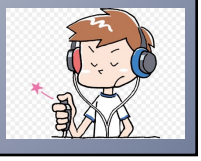
- Diagnostic ABR
  - Under 3-4 months of age in natural sleep
  - Additional confirmation may be needed with sedation or GA
- Good history important
  - Known hearing loss in family
  - Prenatal and birth history
- EKG (r/o long QT syndrome)
- CMV saliva or urine if < 3 weeks at ID
- MRI for inner ear anatomy
- Genetics evaluation (insurance may not cover testing)
- Ophthalmology evaluation if severe (50% may have associated visual issues)

Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

38

Tests of Hearing Function

Developmental Age	Test/ Average Time	Type of Measurement
All ages	OAE 10 min	Cochlear response to stimulus
Birth to 9 mo	BAER or aABR 15 min	Test of CN VIII function
6 mo to 2.5 y	VRA 30 min	Behavioral response
2.5 y – 4 or 5 y	Play audiometry 30 min	Behavioral response
5 y to Adolescence	Routine audiometry 30 min	Raise hand



Duke Head and Neck Surgery & Communication Sciences

39

Advocacy

Duke Head and Neck Surgery & Communication Sciences

40

State Legislation and Workgroups

- Feb 2022: Minnesota 1st state to do universal cCMV screen, Connecticut to start in 2025.
  - Indiana, Mississippi, Massachusetts, Michigan and New Hampshire – proposed legislation for universal screening. WA has opt-in screening program
- 18 U.S. states mandate education or targeted screening:
  - Connecticut, Hawaii, Idaho, Illinois, Iowa, Oregon, Tennessee, Texas, New York, Louisiana, Kentucky, Virginia, Colorado, Minnesota, Maine, Pennsylvania, Florida and Utah. NJ started a public awareness campaign
- Multiple states have workgroups or taskforces working on legislation
- 2019 American Academy of Pediatrics leadership forum resolution passed regarding support for education of pediatricians and parents on cCMV and its effects

About CMV.org

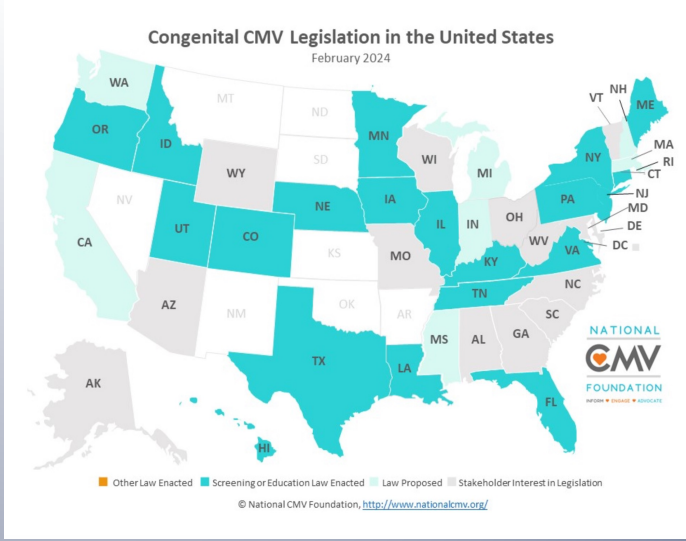
41

CMV and North Carolina

- Currently no rules or legislation for CMV education or testing exist in North Carolina or South Carolina
- Some hospitals test for CMV when babies do not pass hearing screen but no statewide mandate.
  - Duke, UNC, Atrium doing HT-testing
  - Universal screen for NICU at Duke
- Workgroup has been formed to evaluate the best options for our state
- Strong professional and parent support for the project

More information available at

https://www.nationalcmv.org/



42

Mission Statement of North Carolina Workgroup

- Determine collaborative approaches to support the prevention and reduction of CMV infections in women, infants and children
- Timely diagnosis of congenital CMV infection
- Ensure access to care
- Support outreach and education for providers and patients



National CMV Foundation Legislative Goals

- To educate women of childbearing age, general public, healthcare providers, and departments of health about congenital CMV
- To implement a national program to screen every newborn for congenital CMV
- To increase funding for CMV research and clinical advances in treatment and interventions
- To advocate for vaccine development

Screening for cCMV

45

Targeted vs Universal Screening for cCMV

- SNHL is an important consequence of cCMV
  - Universal *newborn hearing screening* will detect <50% of SNHL caused by cCMV
- A different approach is needed to detect hearing loss as early as possible for these children
  - Screening for cCMV may effectively identify children at risk for SNHL caused by cCMV
  - Timing for reliable cCMV screening still presents practical difficulties
  - Earlier identification leads to earlier intervention

46

Targeted vs Universal Screening for cCMV

- Several states have legislation for mandatory cCMV testing in babies who *fail* newborn hearing screen – targeted testing (HT-CMV)
- Minnesota only state with universal CMV screening; CT to start in 2025. IN, MA MS, MI all have proposed legislation
- Canada currently undergoing evaluation of universal screening for cCMV
- Up to 15% of children with cCMV who *Pass* their newborn hearing screen will develop delayed onset hearing loss
- In NC several of the larger health systems have employed HT-CMV testing
  - Duke, UNC, Atrium/Novant

47

CMV education

48

CMV counseling and education

2019 AAP passed resolution supporting counseling and education on CMV

90% of expectant mothers have *never* heard of cCMV

Not regular curriculum in OB/Gyn training programs

How to increase awareness?

Provide expectant mothers information on prevention, symptoms and risks

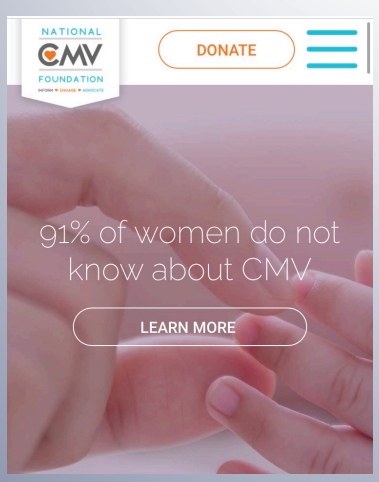
Provide pediatricians and family practitioners resources for where to refer for audiologic follow up

Educate the public on prevention: similar to that of COVID-19!!

Duke Head and Neck Surgery & Communication Sciences

49

Prevention



Duke Head and Neck Surgery & Communication Sciences

50

View web version.

Sponsored by moderna

Contemporary OB/GYN

CMV: In the Know

Our experts discuss the following key topics:

- CMV-associated risks of congenital transmission
- Key strategies for discussing transmission with patients
- Approaches to CMV screening
- Prevention tips for providers and patients

Gain expert insight about this research and more today on *Contemporary OB/GYN®*.

Duke Head and Neck Surgery & Communication Sciences

51

AAO-HNSF position statement (Feb 2024)

Universal newborn congenital cytomegalovirus (cCMV) screening

POSITION STATEMENT

is necessary to best accomplish these goals. References: Fowler KB, McCollister FP, Sabo DL, et al. A targeted approach for congenital cytomegalovirus **screen**ing within newborn hearing **screen**ing. Pediatrics. 2017;139(2):e20162128.

Care of Children Infected with Cytomegalovirus

POSITION STATEMENT

Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings includes hand hygiene and personal protective equipment (gloves). Since not all children undergo **CMV** testing and most with **CMV** show no signs of this infection, workers and staff must follow these precautions for

Duke Head and Neck Surgery & Communication Sciences

52

Take away messages

- Congenital CMV infection is an important public health issue
  - Most common cause of congenital infections
  - Major cause of hearing loss and disability in children
- The majority of cCMV infections are inapparent at birth and infected infants will not be identified at birth
  - ~ 50% of hearing loss due to cCMV occurs after birth and will be missed by universal newborn hearing screening
  - Rapid, reliable and relatively inexpensive methods to screen newborns for cCMV infection are needed for early identification of HL to prevent delays in language and learning
  - Education of the public on the risks of cCMV can change the trajectory of this disease
  - Audiologists can play an important role in identifying children with cCMV, providing earlier intervention and improved outcomes

53

Questions???

54