Clinical and Hearing Management of infants identified on cytomegalovirus (CMV) screening with congenital CMV infection- what to do with all the babies?

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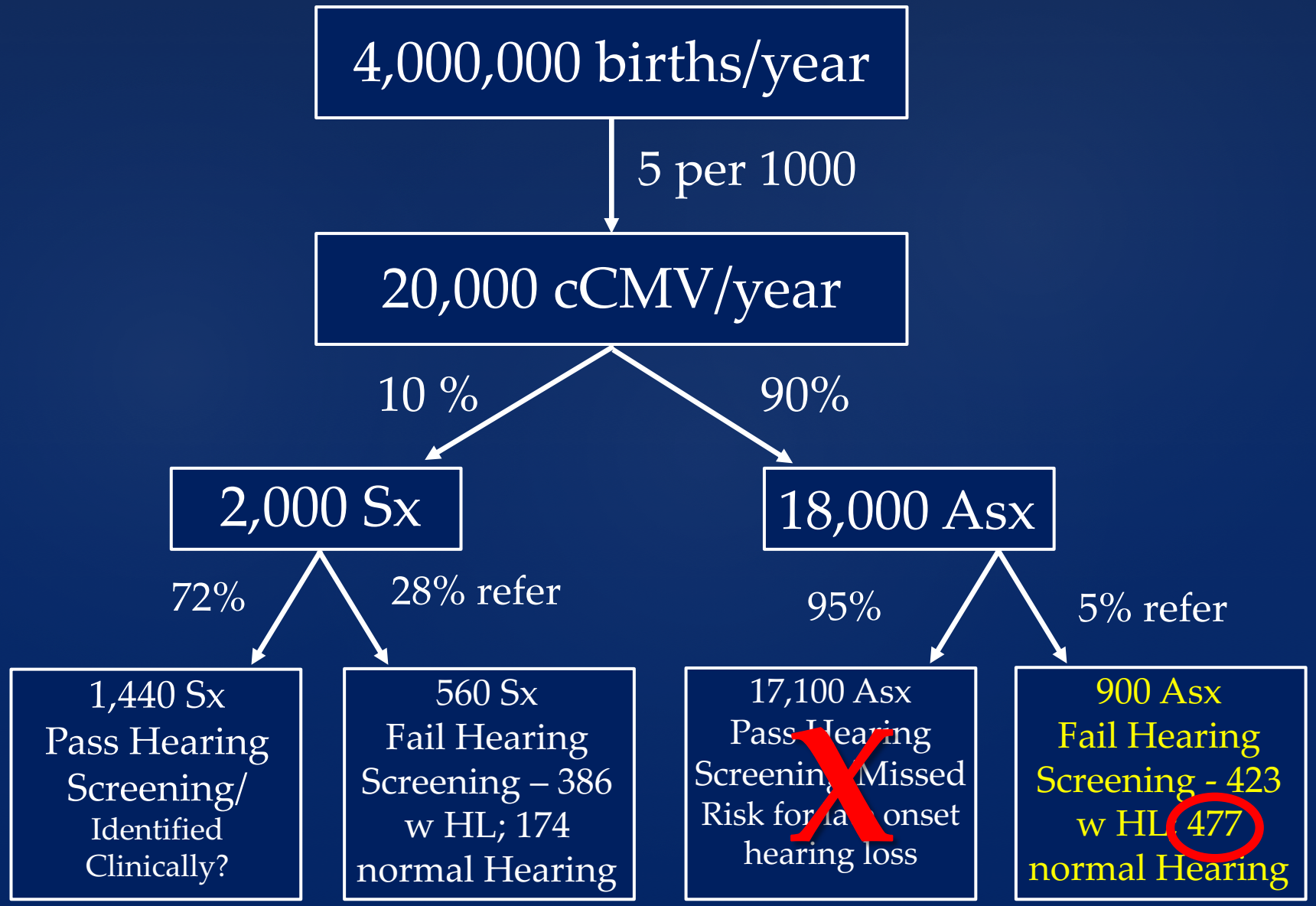
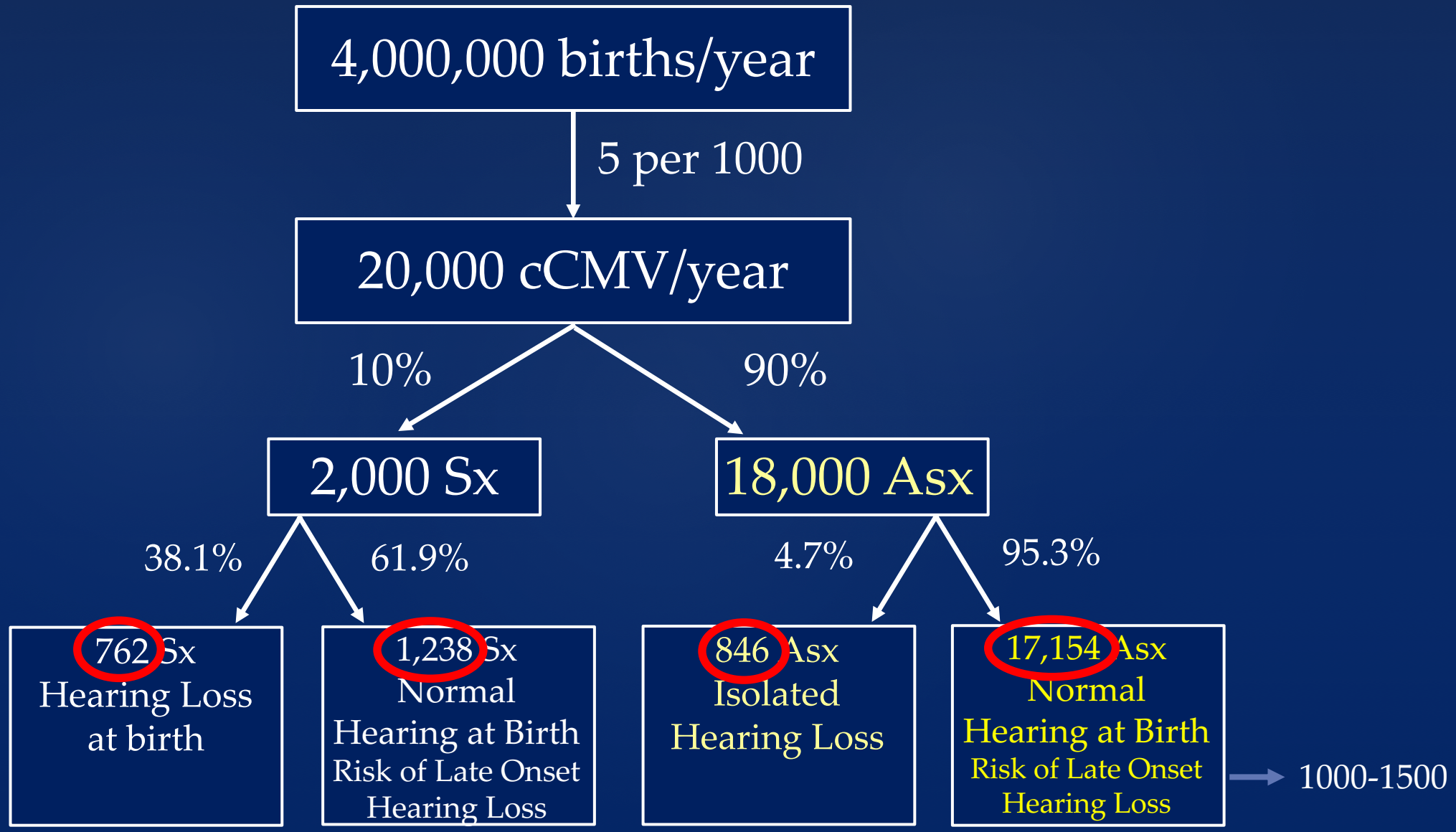
UAB MEDICINE
PEDIATRICS

Targeted Congenital Cytomegalovirus Infection (cCMV) Screening



Fowler, et al Pediatrics 2018

Universal Congenital Cytomegalovirus Infection (cCMV) Screening



Fowler, et al Pediatrics 2018

Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy

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Congenital cytomegalovirus is the most frequent, yet under-recognised, infectious cause of newborn malformation in developed countries. Despite its clinical and public health importance, questions remain regarding the best diagnostic methods for identifying maternal and neonatal infection, and regarding optimal prevention and therapeutic strategies for infected mothers and neonates. The absence of guidelines impairs global efforts to decrease the effect of congenital cytomegalovirus. Data in the literature suggest that congenital cytomegalovirus infection remains a research priority, but

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Panel 2: Definitions of congenital cytomegalovirus infection and disease

Moderately to severely symptomatic congenital cytomegalovirus disease

- Multiple manifestations attributable to congenital cytomegalovirus infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin), or
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with cytomegalovirus central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or the detection of cytomegalovirus DNA in cerebrospinal fluid

Mildly symptomatic congenital cytomegalovirus disease

- Might occur with one or two isolated manifestations of congenital cytomegalovirus infection that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations. However, the difference is that they occur in isolation

Asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss

- No apparent abnormalities to suggest congenital cytomegalovirus disease, but sensorineural hearing loss (≥21 decibels)

Asymptomatic congenital cytomegalovirus infection

- No apparent abnormalities to suggest congenital cytomegalovirus disease, and normal hearing

Moderately to Severely Symptomatic Congenital Cytomegalovirus Infection

Panel 4: **Recommended treatment regimen and monitoring of the congenitally cytomegalovirus-infected neonate**

Who to treat

- Neonates with moderately to severely symptomatic congenital cytomegalovirus disease[6,139]

When to treat

- Within the first month of life[6]

What to treat with

- Oral valganciclovir 16 mg/kg per dose orally, twice a day[6,139]

How long to treat

- Treatment duration for the goal of improving audiological or developmental outcomes should not exceed 6 months[6]

Monitoring during treatment

- Absolute neutrophil counts should be followed weekly for 6 weeks, then at week 8, then monthly for the duration of therapy[6,139]
- Levels of transaminases should be followed monthly throughout therapy[6,139]

Follow up

- An ophthalmological examination should be done early in the course of treatment, with follow-up eye examinations as suggested by the ophthalmologist
- Audiological testing should be done at 6-month intervals for the first 3 years of life, and annually thereafter through adolescence (ages 10–19).
- Developmental assessments beginning at the first year of life might be helpful in some children with symptomatic congenital cytomegalovirus disease, and should be employed on a case-by-case basis

Consensus Recommendations for Treatment of Congenital CMV

- Antiviral therapy NOT routinely recommended for mildly symptomatic congenital CMV disease
- Antiviral therapy NOT routinely recommended for asymptomatic congenital CMV with isolated SNHL
- Antiviral therapy NOT recommended for babies with asymptomatic congenital CMV
- Antiviral therapy NOT routinely recommended in infants <32 weeks gestational age

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Asymptomatic congenital cytomegalovirus (cCMV) infection

~90% have no clinical findings at birth and ~10% symptomatic at birth

10-15% of asymptomatic infants develop SNHL
- Approximately 1/3 of SNHL is delayed-onset

Asymptomatic Congenital CMV Infection

Lab/Neuroimaging	# abnormal (%, Exact CI)
Platelets < 100,000*	7/105 (6.7%, 2.7 – 13.2)
ALT > 80 U/L	0/55 (0%)
Direct Bilirubin >3.0mg/dL	0/149 (0%)
CNS Calcifications**	7/104 (6.7%, 2.8 – 13.4)
Chorioretinitis	0/77 (0%)

*Among the infants with Platelets<100,000, 7/7 were in the NICU with a mean gestation age of 32.7 wk ga (±4.6), all < 2500 g

**3 < 37 wks; 2 with petechial rash only on face

Ross et al CHIMES data unpublished

Asymptomatic Congenital CMV Infection

Association between CNS calcifications and SNHL			
	SNHL	Normal hearing	
Calcifications	2	5	7
No Calcifications	8	89	97
	10	94	104
P=0.14 Fisher's exact test			

HL – 35 wk, 2170 g; 39 wk, 2809 g

Asymptomatic Congenital CMV Infection

SNHL following asymptomatic cCMV	
Characteristics	N=31 (8.8%) # (%)
Unilateral loss	19 (61)
Late Onset Loss	8 (26)
Months, median (range)	24 mo (7-48 mo)
Progressive loss	15 (48)
Months at first progression, median (range)	24 mo (7-48 mo)
Fluctuating loss	8 (26)
High frequency loss only (4-8kHz)	3 (10)

Evaluation and Follow-up of Infants with Asymptomatic Congenital CMV

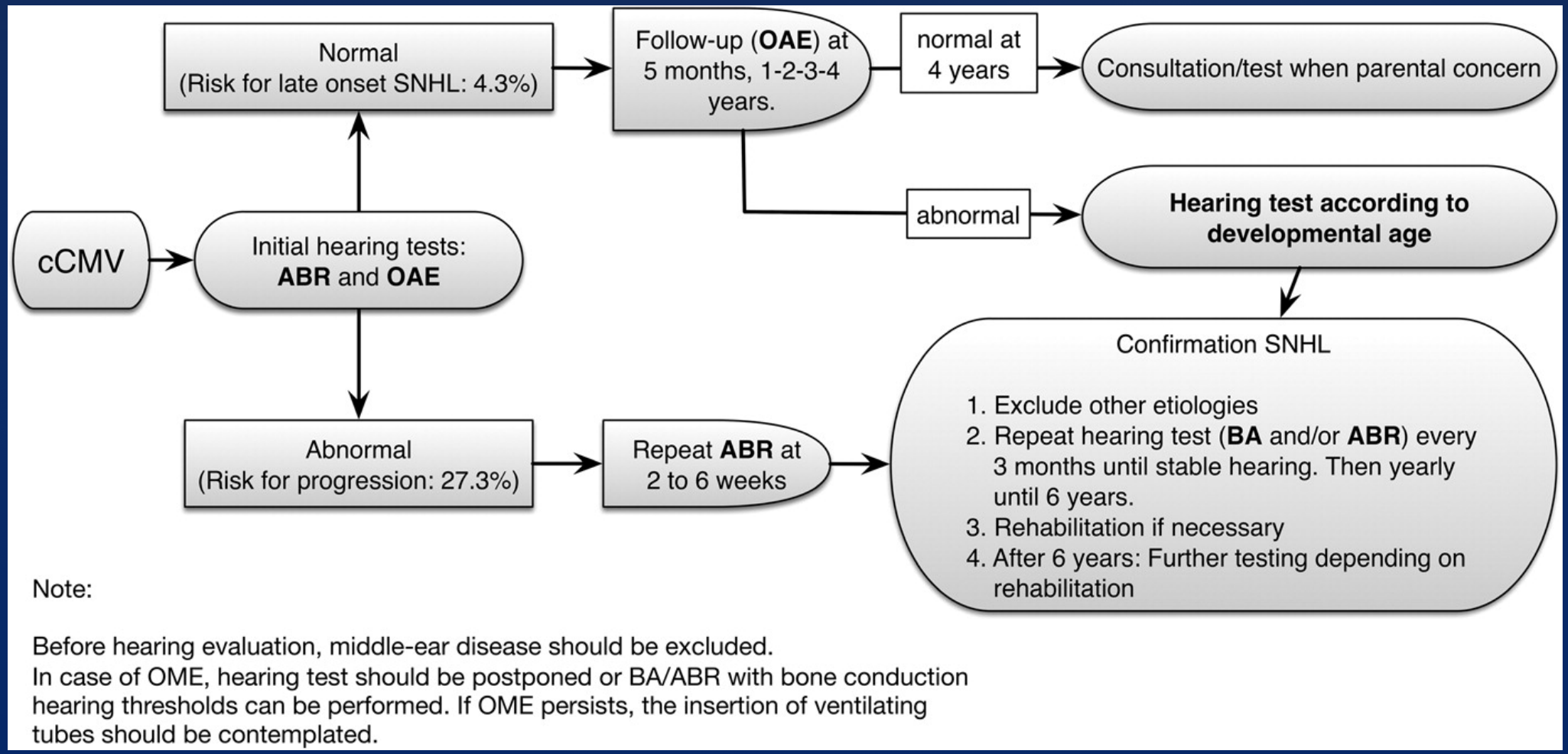
At Birth

- Thorough physical exam to assess for symptoms
- Ophthalmologic examination (at some point)
- No laboratory evaluation (CBC, LFTs)
- Neuroimaging?
- Diagnostic audiological testing (OAE and ABR)

  - Every 6 months at least until 3 years of age, then annually thereafter

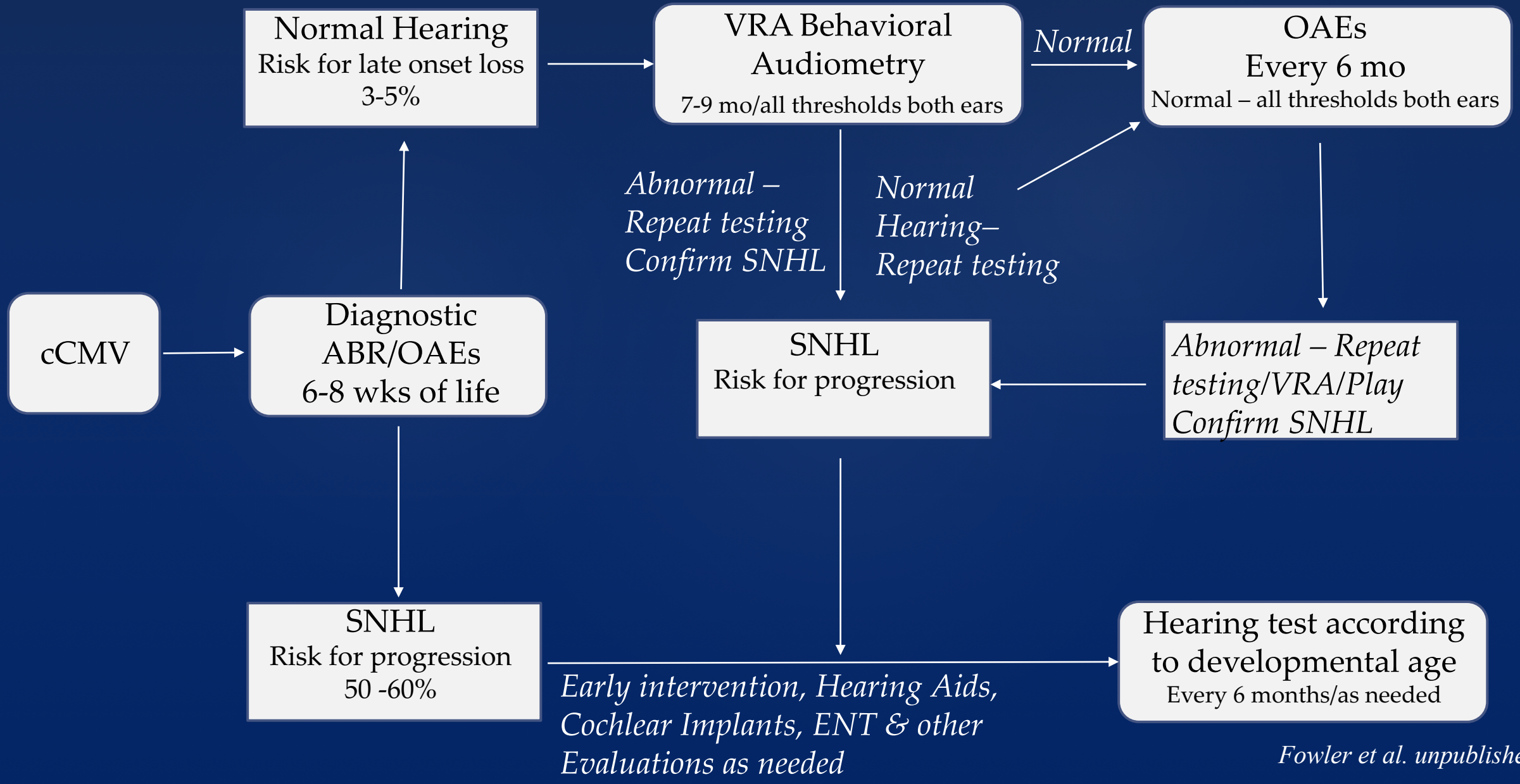
Ross et al unpublished

Proposed Hearing Algorithm



Published in: Ina Foulon; Leen Vleurinck; Kristin Kerkhofs; Frans Gordts; *International Journal of Audiology* **2015,** 54, 714-719.
DOI: 10.3109/14992027.2015.1046506

Proposed Hearing Algorithm for Asymptomatic cCMV Infants



Fowler et al. unpublished

Proposed Hearing Algorithm

Caveats:

- Before hearing evaluations, middle ear disease should be excluded
- Two full hearing evaluations for all thresholds bilaterally that confirm normal hearing by both ABR/OAEs and Behavioral (VRA)/OAEs before going to a Follow up OAE protocol every 6 months
- Follow up OAEs every 6 months (bilaterally, all thresholds) – not a screening. At least until school age, followed by annual evaluations after 5 or 6 years of age
    - Thresholds and OAEs concordant in 11/13 children with late onset HL
    - OAEs abnormal with normal thresholds (visit before abn thresholds) in
    - 2/13 children with late onset HL
- Parental concern triggers a fuller evaluation with appropriate hearing test appropriate for developmental age (other triggers – not meeting developmental milestones, etc.)

Proposed Hearing Algorithm

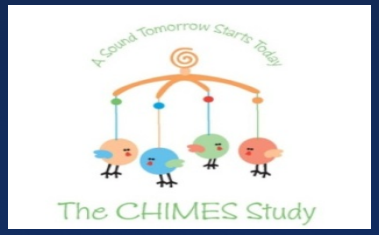
Reasons to Consider this approach:

- After the newborn period, most asymptomatic infants will not have subsequent hearing loss
- Burden to child, parents, and health care system to test children repeatedly with full hearing assessments (assuming universal screening)
- Limit costs

Summary

- Through targeted CMV screening (and universal screening), many infants with asymptomatic cCMV will be identified
- Laboratory abnormalities are rare in asymptomatic cCMV
- Should all babies undergo neuroimaging? Further study needed.
- No evidence at this time for antiviral treatment for asymptomatic infants (NCT03107871; NCT03301415)
- Hearing algorithm proposed

The CHIMES study Investigators and Personnel
Sponsor: NIDCD



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Questions?