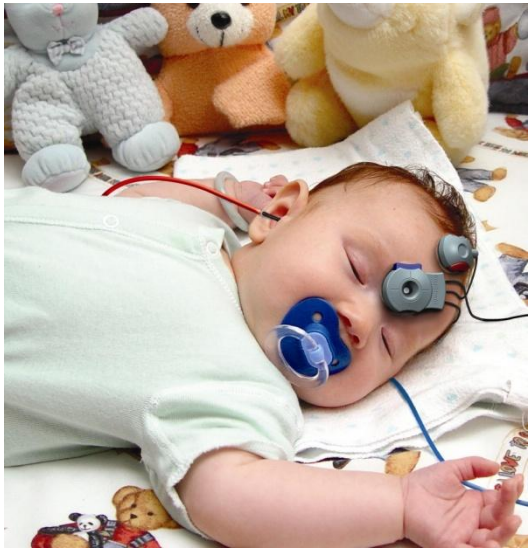
Congenital Cytomegalovirus Infection and hearing loss



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Introduction

- Most common congenital infection in many developed countries
- Congenital CMV infection as a cause of hearing loss in children has received increased attention in recent years due to
  - Advances in diagnosis
  - Possibilities of treatment
  - Prevention of developmental disabilities

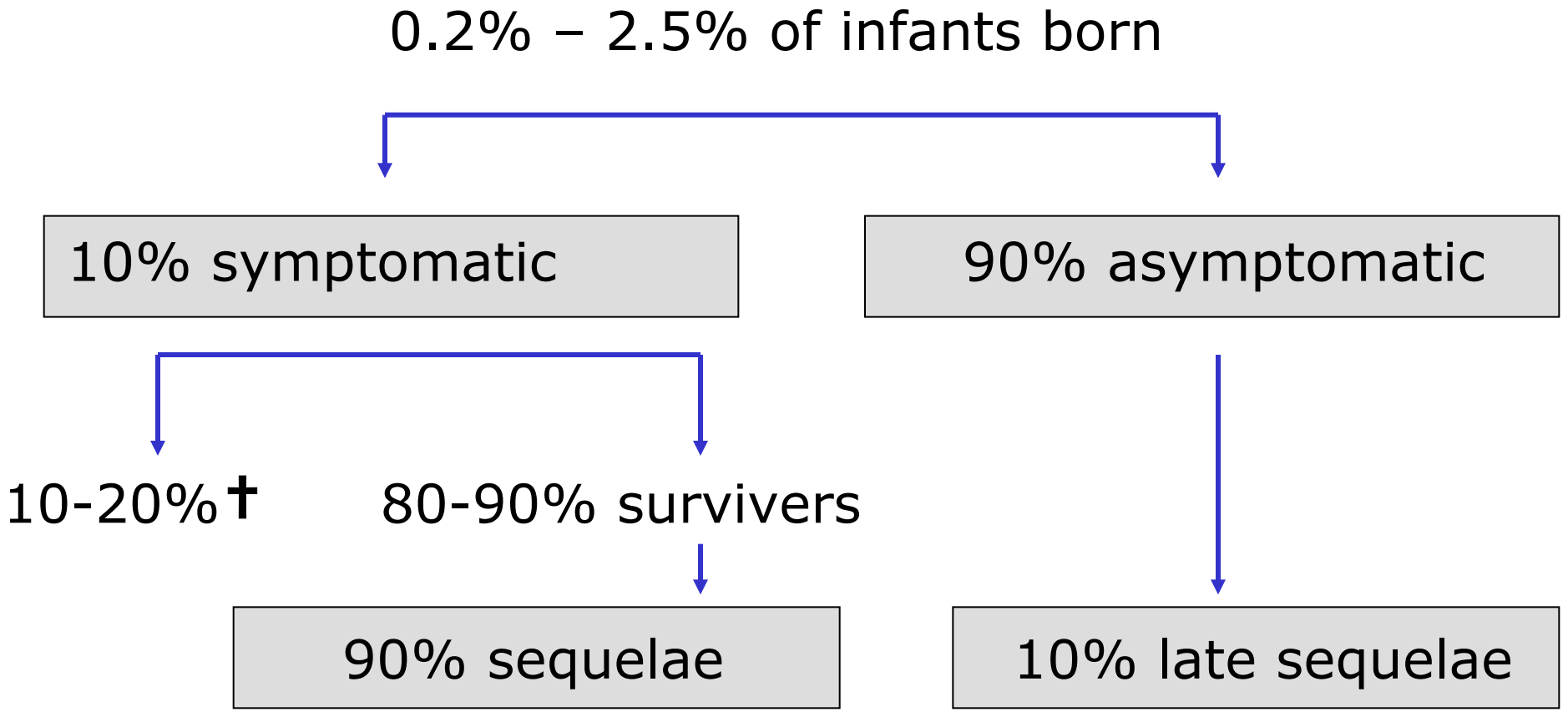
1. Prevalence of congenital CMV infection

- Congenital CMV infection is endemic
- Rates of congenital CMV infection will be relatively constant

Study	N° of screened newborns	Rate per1000 live births
Canada, 1980	15212	4.2
England, 1983	14200	3.0
Sweden, 1984	10328	4.8
USA, 1993		
Low SES	18343	11.8
Middle SES	11154	4.8

SES, socio-economic scale

1.Prevalence of congenital CMV infection



2. Frequency of sequelae in children with congenital CMV infection

	Symptomatic (10%)	Asymptomatic (90%)
Infant death	**10%**	**0%**
Hearing loss	**35-65%**	**7–15%**
Mental retardation	**45%**	**2–10%**
Cerebral palsy	**35%**	**<1%**
Chorioretinitis	**15%**	**1–2%**

Hearing loss is the most common sequela of congenital CMV infection

Hearing loss is usually the only sequela in the asymptomatic group

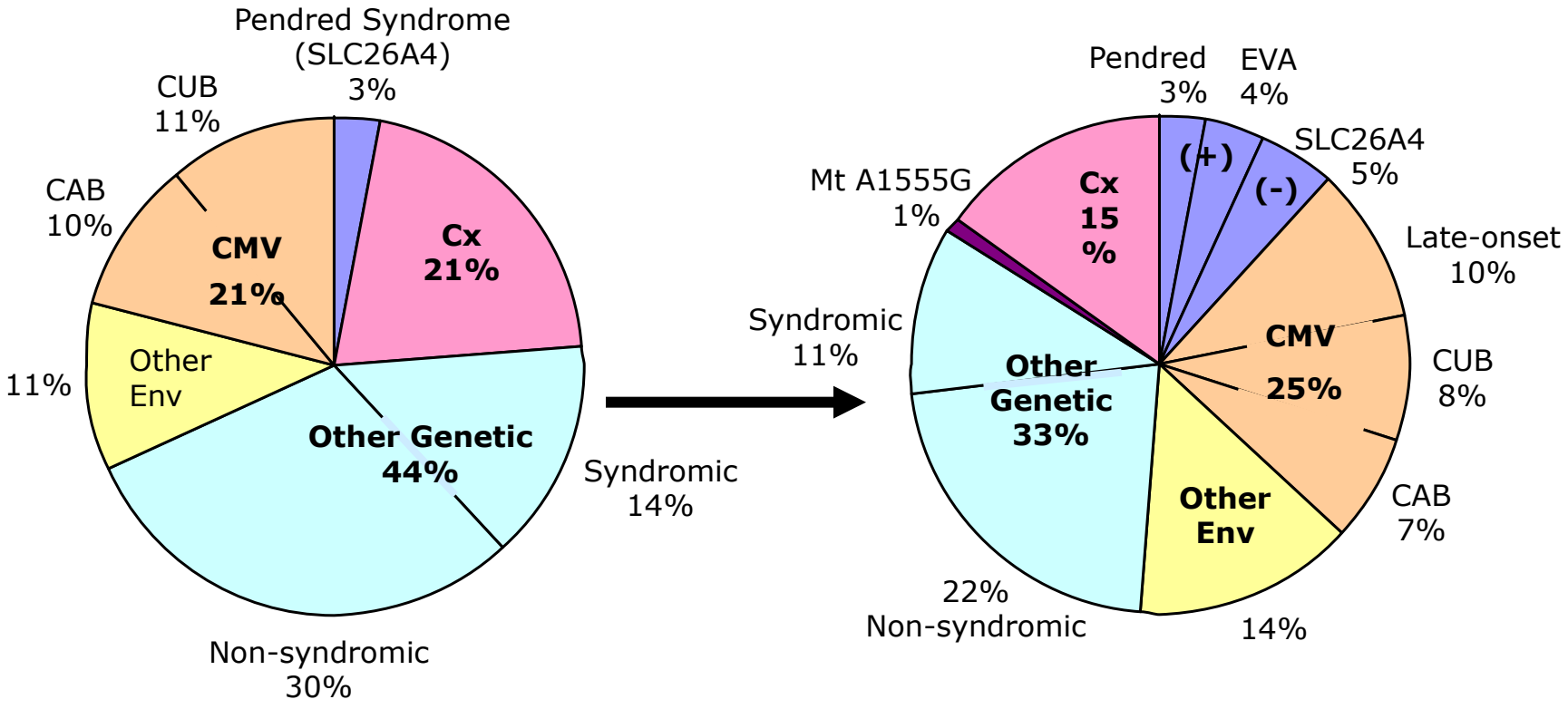
Population rates of SNHL due to congenital CMV infection

Incidence at birth
(1.9 per 1000)

TOTAL GENETIC

68% **55%**

Prevalence at 4 years
(2.7 per 1000)



Population rates of SNHL due to congenital CMV infection

Congenital CMV infection is nowadays the leading cause of non-genetic SNHL in childhood

3. Pathophysiology of hearing loss

Histopathology (guinea pig model)

- Labyrinthitis secondary to viremia via stria vascularis
- Labyrinthitis via meningeal or neural spread causing mostly nervous damage (degeneration of spiral ganglion)

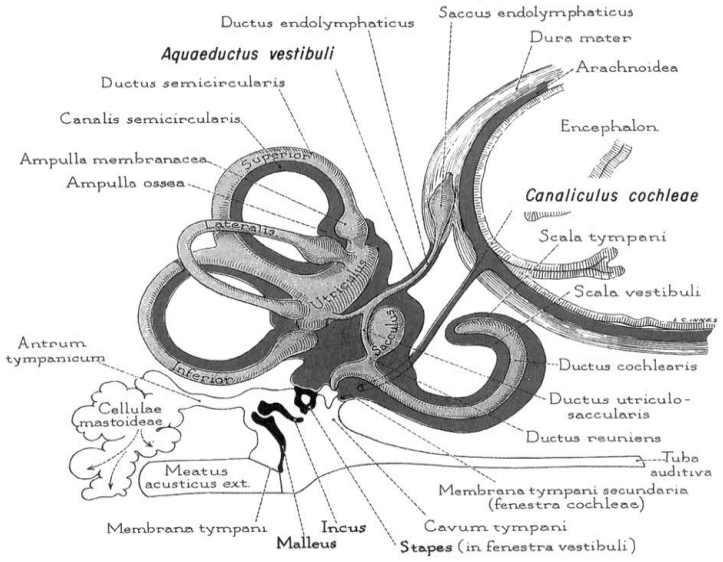


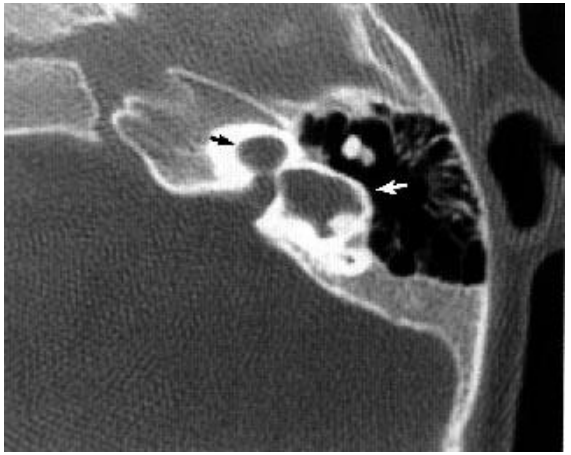
Figure 4–1 Schematic diagram of major components of the middle and inner ear. The organs of the membranous labyrinth *(in blue)* are shown enclosed within the various cavities of the bony labyrinth *(in red)*. (From Anson et al [1973], with permission.) ***(See Color Plate 2.)***

(DeBiasi 2002: apoptosis as a result of direct viral injury to neurons)

- typical **inclusion cells** in the endolabyrinth (demonstrated in the of children who died of a symptomatic congenital infection)

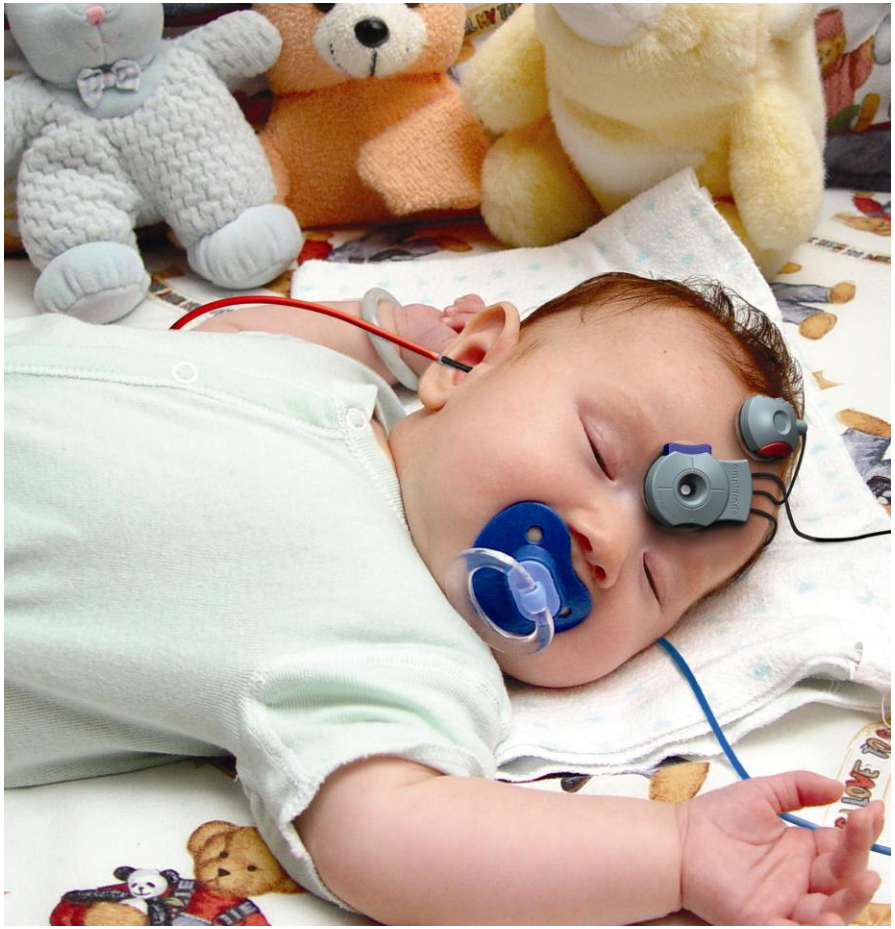
3. Pathophysiology of hearing loss

- <u>CMV occurring in early pregnancy (7-8th week):</u>
  cochlear malformation comparable to mondini dysplasia (short cochlea, enlarged vestibular aqueduct, short and wide internal auditory canal)

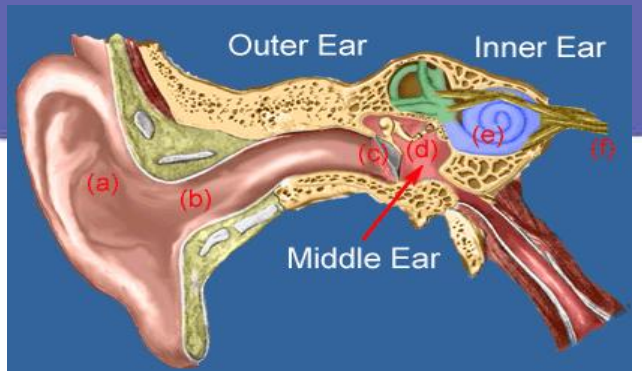


- <u>Infection after week 12</u>: no morphological changes to the cochlea, however, disturbance of maturation and growth is still possible. (Bauman 1994)

4. Characteristics of hearing loss due to congenital CMV infection



Configuration of hearing loss



	Symptomatic (N=209)	Asymptomatic (N=651)
SNHL	41 %	7 %
Unilateral	33 %	52 %
Bilateral	67 %	48 %
High-Frequency Only (4000-8000 Hz)	13 %	37 %

Dahle et al., 2000

Degree of Loss

	Symptomatic (N=209)	Asymptomatic (N=651)
Mild (21-45 dB HL)	12%	17%
Moderate (46-70 dB HL)	13%	15%
Severe (71-90 dB HL)	31%	17%
Profound (> 90 dB HL)	44%	51%

Dahle et al., 2000

Delayed Onset Loss

	Symptomatic (N=209)	Asymptomatic (N=651)
Delayed Onset Loss	27 %	37 %
Median age (range) of delayed onset	33 mo (6-197)	44 mo (24-182)

Dahle et al., 2000

Progression/fluctuation of hearing loss

	Symptomatic (N=209)	Asymptomatic (N=651)
Progressive Loss	54%	54 %
Median age (range) of First Progression	26 mo (2-209)	51 mo (3-186)
Fluctuating Loss	29 %	54 %
Improvement of Loss	21 %	48 %

It is unclear whether progressive hearing loss is caused by
- reactivation of the virus
- immunological response of the host
- the delayed clinical appearance of damage already present

Dahle et al., 2000

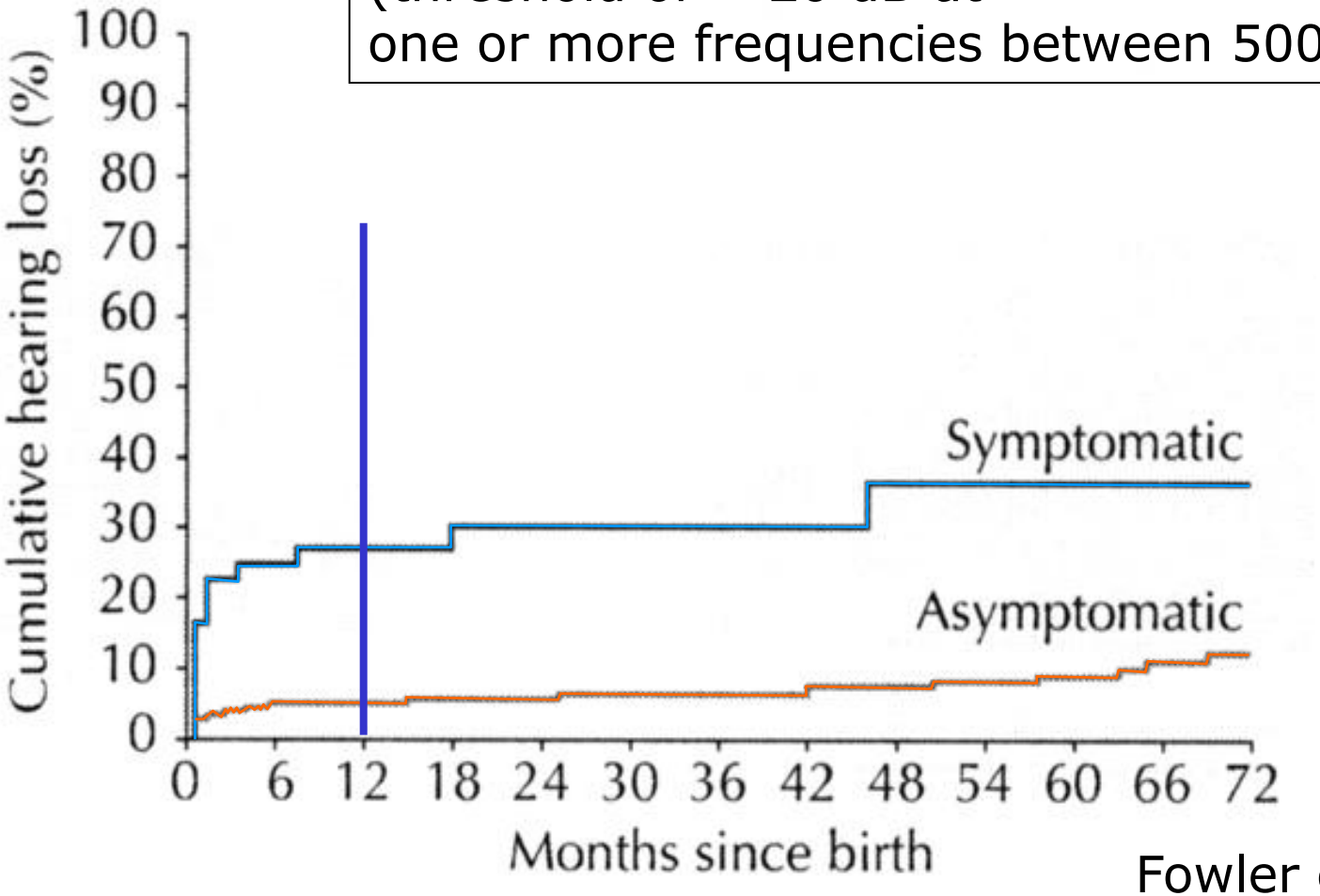
Hearing loss and CMV

- Uni- or bilateral
- Majority severe to profound
- Delayed onset is possible in 20-40%
- Progression of hearing loss in 50% during the first 6 years of life
- Fluctuating hearing loss in 20-50%

Williamson et al., 1990
K.B. Fowler et al., 1999
Dahle et al., 2000
Rivera et al., 2002

Increase with age in the rates of hearing loss due to Congenital CMV infection

Hearing loss:
(threshold of > 20 dB at
one or more frequencies between 500-4000 Hz)

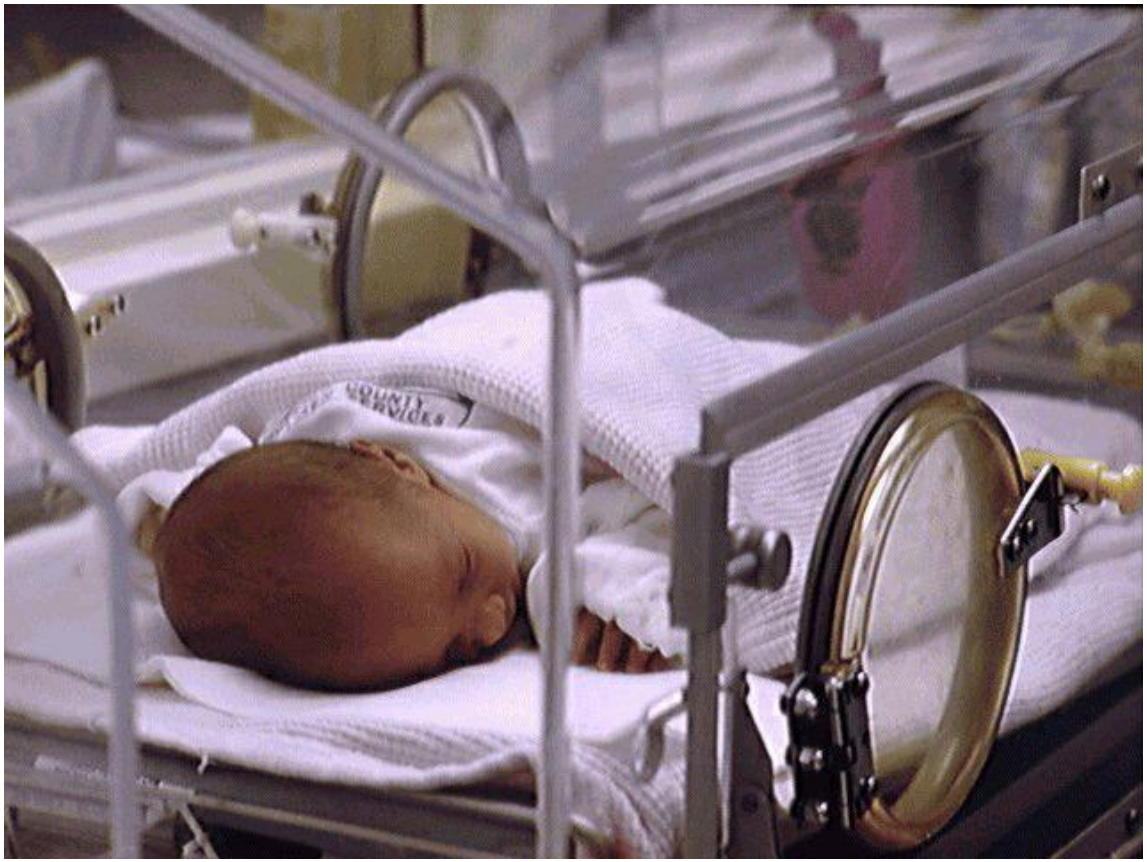


Fowler et al., 1999

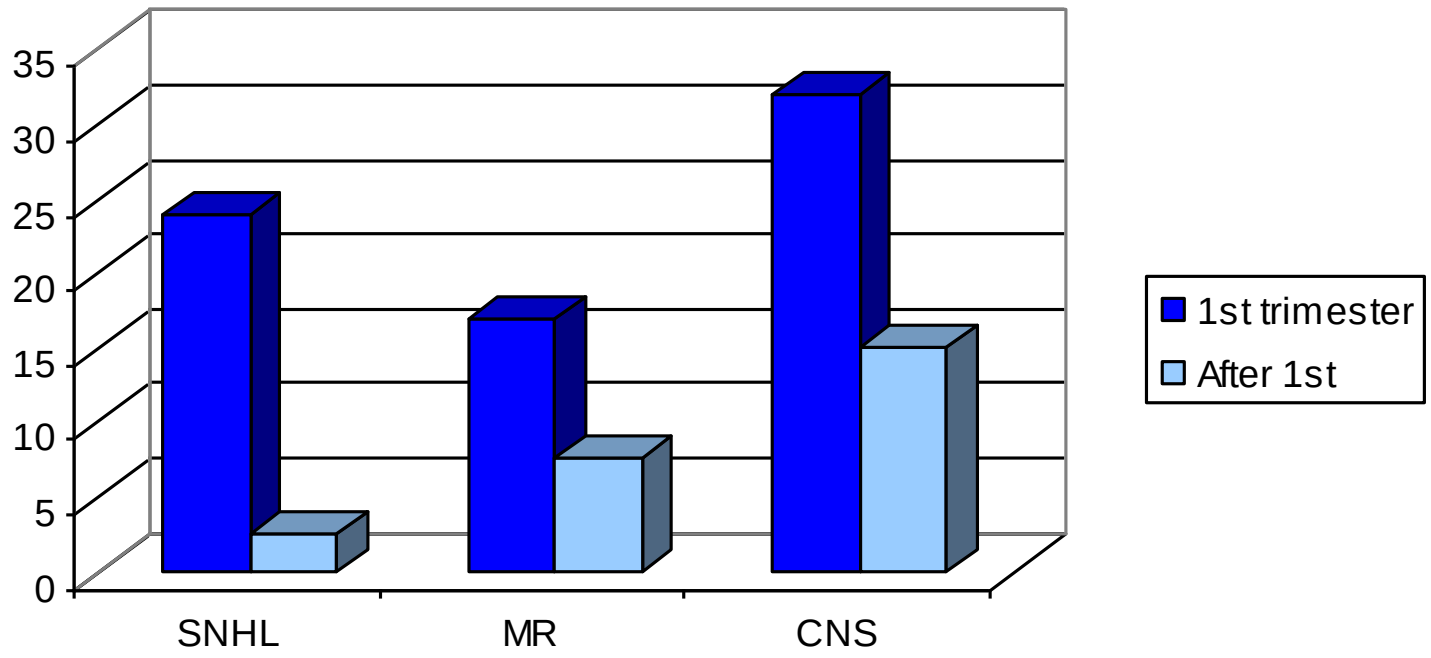
Increase with age in the rates of hearing loss due to Cong CMV infection

- Most important decline in hearing occurs during the first year of life
- Most progressive and late onset hearing loss occurs between birth and 12 months of age
- No patient with normal hearing at 2 years of age progresses to bilateral hearing loss with a threshold of >30dB in the better ear
- A small number of normal hearing infants still develop a unilateral high-frequency hearing loss after 3 years of age

5. Predictive factors



Gestational age at the time of maternal infection



SNHL: sensorineural hearing loss
MR: mental retardation
CNS: central nervous system problems

Pass et al. 2006

Risk Factors for HL in Symptomatic Infants

N=180 children with congenital CMV

Characteristic	*OR (95% CI)*
IUGR	2.2 (1.1-4.1)
Petechiae	3.1 (1.5-6.3)
Hepatosplenomegaly**	2.0 (1.1-3.9)

**After adjusting based on regression analyses, hepatosplenomegaly was not shown to be an independents predictor of hearing loss.

Rivera et al., 2002

Risk Factors for HL in Symptomatic Infants

	Hearing Loss N=87 %	Normal Hearing N=93 %	Crude OR (95% CI)
Direct Bilirubin > 4 mg/ml	58	33	2.8 (1.2-6.4)
Platelet Count < 100,000 mm3	62	41	2.4 (1.3-4.5)
Intracerebral Calcifications	69	28	5.8 (1.8-19)

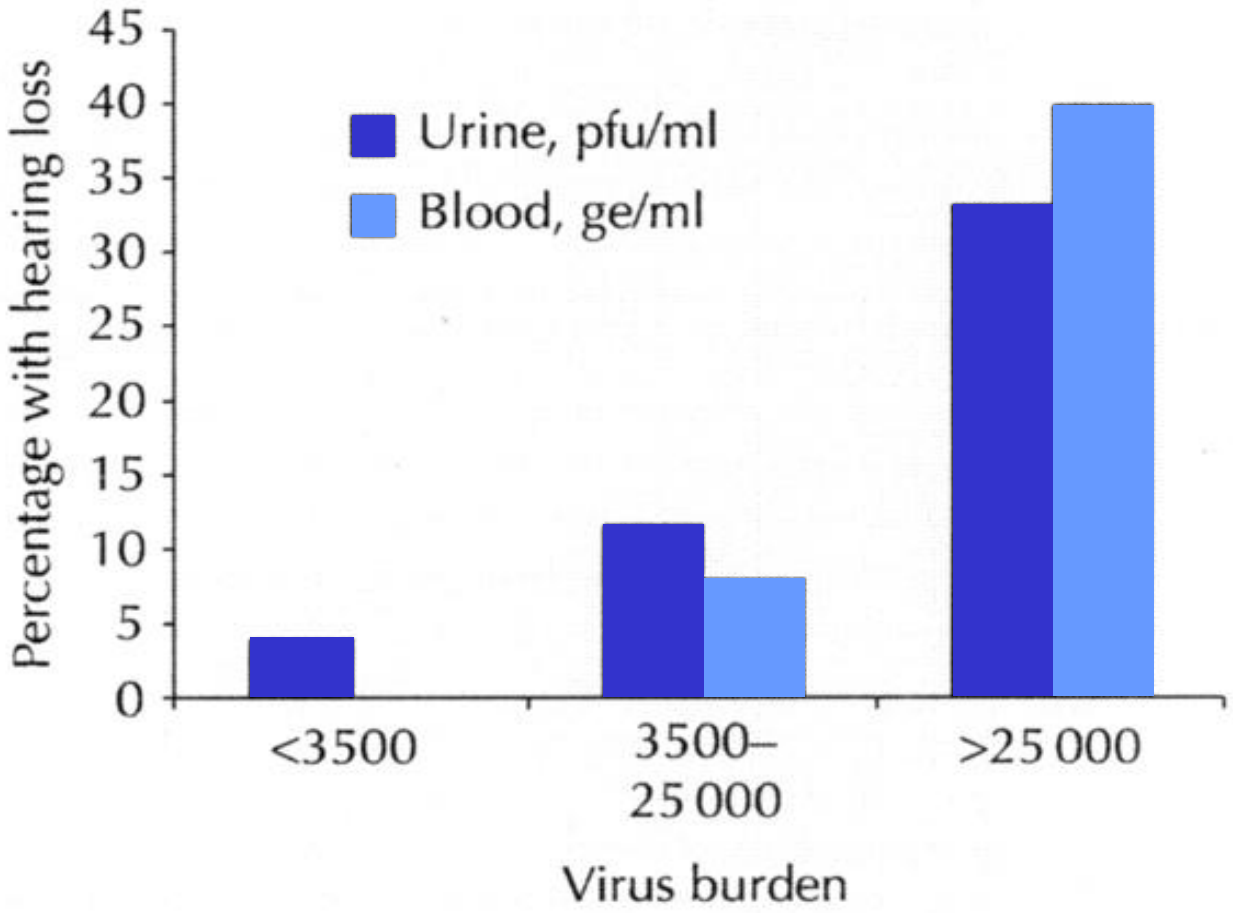
Rivera et al., 2002

Possible Risk Factors for HL in Asymptomatic Infants

	Hearing Loss N=48	Normal Hearing N=456	
Mechanical Ventilation	4 %	3%	
Apgar < 7 at 5 min	2 %	2 %	
Jaundice	10 %	10 %	
Hypoglycemia	4 %	2 %	
Ototoxic Medications	8 %	14 %	
Birth Weight, g	2,888 ± 674	3,061 ± 746	p=0.15
Preterm < 37 weeks	15 %	9 %	p=0.07

Fowler, unpublished data

Relationship between viral burden and hearing outcome in children with congenital CMV infection



Boppana et al., 2005

Lanari et al., 2006

Predictive factors

- First trimester maternal infection is more likely to cause SNHL
- Disseminated infection at birth with or without CNS involvement is associated with HL in symptomatic infants
- Maternal and perinatal factors do not predict hearing loss in children with asymptomatic congenital CMV infection
- Linear relationship between viral load and risk of hearing loss (?)

Early identification of hearing loss and developmental outcome

Congenital deafness is common (0.4-1/1000 live births)

Impact is considerable

Delayed identification, even of mild HL results in

- language delays
- developmental skill delays
- behavior problems.
- subsequent delays in literacy, and academic performance

Early identification and early habilitation will improve speech and language ability, school performance

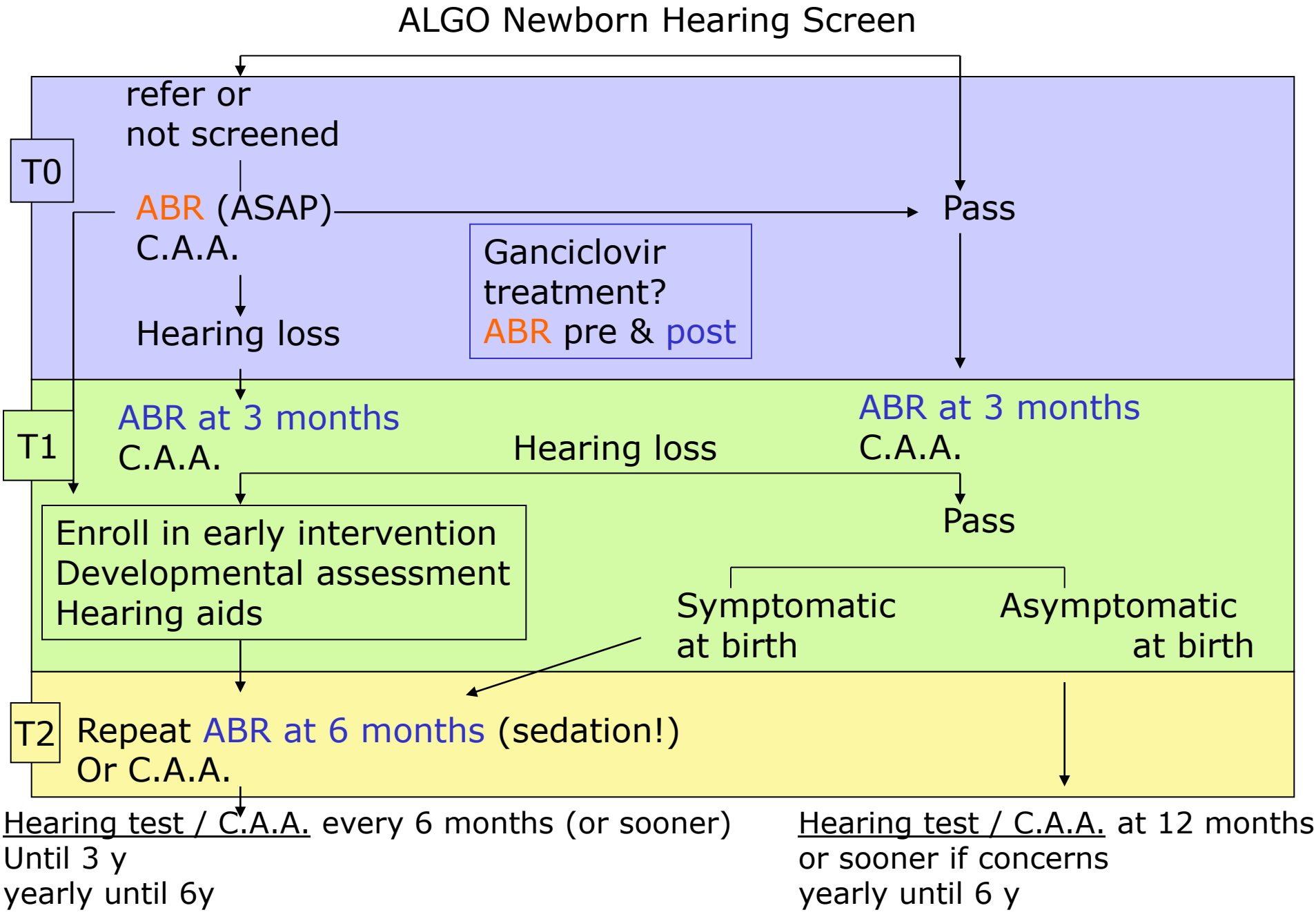
Early identification of hearing loss neonatal hearing screening programs

- The infection is not apparent at birth in 90% of children
- Hearing loss is only detectable in the first month in 50-60% of cases
- Over half will be missed by neonatal hearing screening programs !

- Up to 15% of asymptomatic children risk will have or develop SNHL during childhood
- the epidemiological weight of the infection in asymptomatic children is greater than in symptomatic newborns were the incidence of hearing loss may reach 60%

Only neonatal identification of the infection and consequent audiological monitoring wil permit prompt detection of hearing loss and its correction

Audiological Follow up for infants with congenital CMV



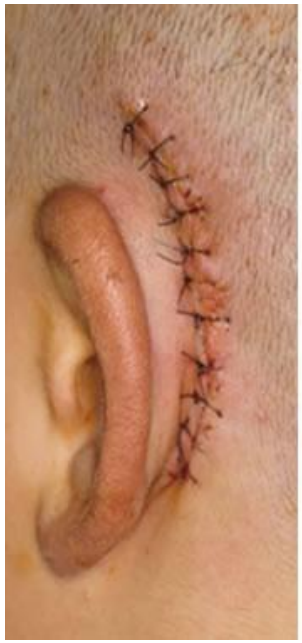
AUDIOLOGICAL MANAGEMENT

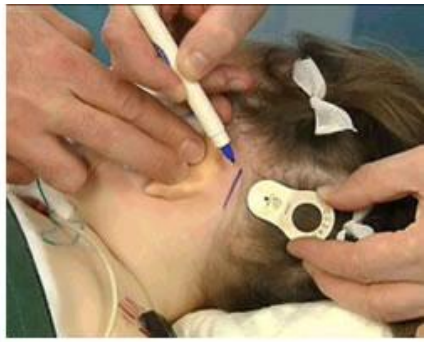
- Interdisciplinary assessment to identify any additional conditions
- Early intervention program referral

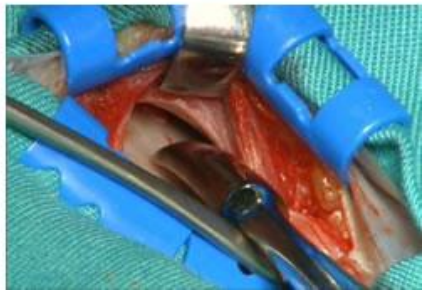
- Frequent audiological monitoring
- Hearing aids
- Training in communication methods that accommodate changing hearing levels

Rehabilitation of severe hearing loss

Cochlear implantation in children with profound deafness







Conclusions

- Cong CMV infection is the leading non-genetic cause of neurosensory hearing loss.
- The Hearing loss can be uni- or bilateral, fluctuating, progressive or late onset in nature.
- Most important decline in hearing occurs during the first year of life
- Disseminated infection at birth is associated with hearing loss in symptomatic infants
- There seems to be a linear relationship between viral load and risk of hearing loss
- Over half of the hearing impaired children will be missed by neonatal hearing screening programs !

Worldwide CMV seroprevalence among women of reproductive age (Cannon et al, 2010)