Early Identification and Management of Congenital Cytomegalovirus

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KEYWORDS

• Congenital cytomegalovirus • Congenital CMV • Hearing loss • Valganciclovir

KEY POINTS

- Congenital cytomegalovirus (cCMV) is the most common nongenetic cause of sensorineural hearing loss.
- There is no universal screening for cCMV. Therefore, it is often not diagnosed in children who are otherwise asymptomatic.
- Hearing loss owing to cCMV is often delayed in onset, is progressive, and can be bilateral or unilateral.
- Children with cCMV with severe to profound sensorineural hearing loss in one or both ears are potential candidates for cochlear implant.

INTRODUCTION

Congenital cytomegalovirus (cCMV) is the most common intrauterine infection, resulting in an overall birth prevalence of approximately 0.7%.[1,2] Prevalence varies among populations and is considerably higher in the developing world.[3] The most common manifestation of cCMV is sensorineural hearing loss (SNHL), and for this reason, cCMV is the most common nongenetic cause of SNHL, accounting for approximately one-quarter of early childhood SNHL.[4,5] The recognition of cCMV as a cause of SNHL is underestimated in clinical practice because (1) most of the affected children are otherwise asymptomatic and therefore not tested and diagnosed with cCMV at birth;

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and (2) delayed onset of hearing loss is common with onset after the period within which definitive diagnosis can be made. This article aims to provide an overview of cCMV transmission, manifestations, and management of cCMV and its associated SNHL.

TRANSMISSION OF CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is a member of the herpesvirus family and is highly prevalent, infecting many people by childhood or early adulthood worldwide.[6] Prevalence among women of reproductive age is estimated at 79% in North America and 86% globally.[7] Infection spreads through contact with infected bodily fluids, including urine, saliva, blood, or genital secretions. Repeated reinfection with CMV is common. Infections generally cause mild symptoms, except in those with compromised immune systems and in the case of the developing fetus. Intrauterine transmission occurs because of primary (new) maternal infection or nonprimary infection in seropositive mothers who previously experienced CMV infection. Primary infection, although less common, confers a 40% risk of transmission to the fetus, whereas nonprimary infection confers a 1% to 2% risk. There is no universally recommended CMV screening of mothers during pregnancy and, to date, no proven intervention to decrease transmission to a fetus.

MANIFESTATIONS OF CONGENITAL CYTOMEGALOVIRUS

Manifestations of cCMV are highly variable and range from no apparent sequelae to multisystem involvement. Approximately 10% of cases are symptomatic at birth. The remaining 90% of infections are considered asymptomatic.[1,2] The central nervous system is commonly affected in symptomatic cases and can result in microcephaly, cortical malformations, developmental delay, cerebral palsy, and visual impairment. Additional systemic manifestations include hepatosplenomegaly, hyperbilirubinemia, petechiae, thrombocytopenia, and anemia, findings of which should prompt evaluation for cCMV. cCMV infection is associated with prematurity, low birth weight, and intrauterine growth restriction (IUGR). SNHL is the most common sequela of cCMV. If SNHL is the only symptom in a child with cCMV, these patients have traditionally been referred to in the literature as members of an “asymptomatic” subgroup.

HEARING LOSS

SNHL occurs in 20% to 65% of symptomatic cases and 6% to 25% of asymptomatic cases.[8,9] Among symptomatic cases of cCMV, IUGR, petechiae, microcephaly, and abnormal neuroimaging findings have been associated with SNHL.[10–13] Among asymptomatic cases, prematurity and low birth weight are associated with SNHL.[8,14,15] Increased risk of SNHL has also been found in infants with higher viral load at diagnosis.[16,17] Despite these findings, there is no reliable way to predict which children with symptomatic and asymptomatic cCMV will develop SNHL.

Hearing loss varies from mild to profound and can be unilateral or bilateral, with most children ultimately progressing to severe or profound SNHL.[18–20] The most common audiometric configurations are flat and down-sloping SNHL.[19,20] Hearing loss in symptomatic children tends to be more severe and more often bilateral than in asymptomatic children.[18,21,22]

Hearing loss can be stable, progressive, fluctuating, or rarely, might improve over time. Progression of hearing loss occurs in many (over 50%) of both symptomatic and asymptomatic patients.[18,23,24] Progression can occur at any time, even after years of stability, necessitating long-term audiological follow-up in all patients with cCMV-

related hearing loss. In 1 study, progression was first documented on average 51 months (range, 3–186) after diagnosis for asymptomatic infections and 26 months (range, 2–209) for symptomatic infections. Fluctuating hearing loss is also common.[18,23]

Onset of hearing loss is delayed in up to 50% of patients.[25] Median age of onset of delayed hearing loss in a large observational study was 33 months (range, 6–197) and 44 months (range, 24–182) for asymptomatic and symptomatic cases, respectively.[18] In addition, cCMV patients with unilateral hearing loss are at risk of developing SNHL in the contralateral ear.[9]

DIAGNOSTIC TESTING FOR CONGENITAL CYTOMEGALOVIRUS

Testing for cCMV should be done within the first 3 weeks of life to conclusively distinguish congenital infection from postnatally acquired infection. As there is no universal screening for cCMV, prompt testing of children who do not pass newborn screening in one or both ears would identify cCMV in children with SNHL at birth. Viral CMV cultures have been replaced by CMV DNA polymerase chain reaction (PCR) of saliva or urine. Saliva is the simplest to obtain but has more false positive results than urine testing. A positive saliva PCR should be confirmed with a repeat PCR test (preferably urine), ideally within the neonatal period. For children who have not undergone neonatal PCR testing within the optimal time window for accurate testing, another approach is to perform CMV PCR testing on the dried blood spot (DBS). The DBS is routinely collected at birth on all children to screen for a series of disorders and stored by state health departments for varying time periods. Previous studies have reported lower sensitivity of cCMV diagnosis based on blood spot testing, but more recent studies show improved sensitivity.[26,27] Thus, PCR testing of stored DBS might be a useful retrospective means of determining if SNHL and other symptoms are related to cCMV.

TARGETED AND HEARING TARGETED SCREENING

A “targeted screening” approach to cCMV testing is currently in use in some locations wherein infants with symptoms that could be related to cCMV undergo PCR testing. Indications for cCMV testing include thrombocytopenia, transaminitis, conjugated hyperbilirubinemia, IUGR, small for gestational age, microcephaly, rash consistent with cCMV, abnormal head ultrasound with ventriculomegaly or periventricular calcification, hepatosplenomegaly, known maternal infection during pregnancy, and SNHL. Although SNHL as an isolated symptom is not defined as symptomatic cCMV, isolated SNHL is included as an indication for targeted screening given the frequency of which cCMV causes SNHL and the implications for management. The approach to routine cCMV screening in infants with a failed newborn hearing screen (unilateral or bilateral) is referred to as hearing-targeted early cytomegalovirus (HT-CMV) screening. In 2013, Utah became the first state to legislate that CMV testing be accomplished by age 3 weeks for infants who fail newborn hearing screening. Since then, a growing number of medical centers have voluntarily adopted similar institutional policy, and more states have instituted legislation requiring discussion of cCMV testing with parents. HT-CMV policies are useful but do not identify the significant number of children with delayed onset of SNHL owing to cCMV.

BENEFIT OF UNIVERSAL CONGENITAL CYTOMEGALOVIRUS NEWBORN SCREENING

Implementation of targeted screening for cCMV in combination with universal newborn hearing screening has resulted in improved early detection of cCMV-related SNHL. However, as noted previously, a significant proportion of cases will

be missed because of delayed presentation of hearing loss beyond the newborn period.[25] For this reason, many experts advocate for universal newborn cCMV screening.[28–30] Universal cCMV screening of all newborns, independent of hearing screening or evidence of symptomatic disease, would enable audiologic monitoring of children at risk of developing SNHL because of this congenital infection. Because early diagnosis and treatment of hearing loss positively impact language, universal cCMV screening has the potential to benefit those children at risk for SNHL.

COMPREHENSIVE EVALUATION OF INFANTS DIAGNOSED WITH CONGENITAL CYTOMEGALOVIRUS

Infants with cCMV, with or without SNHL, benefit from a comprehensive evaluation (**Box 1**) that includes brain imaging by ultrasound or MRI. Characteristic findings include intracranial calcifications, ventriculomegaly, cerebral and cerebellar volume loss, and white matter disease. Findings might be useful in confirming diagnosis of cCMV, in guiding counseling about prognosis, and in identifying candidates for antiviral treatment. In addition, newly diagnosed infants should have laboratory testing to assess for cytopenia and hepatitis and ophthalmologic evaluation to rule out ocular manifestations of cCMV.

COOCCURRENCE OF CONGENITAL CYTOMEGALOVIRUS AND GENETIC CAUSE OF HEARING LOSS

In light of the relatively high incidence of cCMV in the general population, there is reason for concern that it could cooccur with genetic causes of SNHL, which are

Box 1
Evaluation, treatment, and monitoring of infants with congenital cytomegalovirus infection

Initial evaluation:
- Diagnosis by saliva or urine CMV PCR within the first 3 weeks of life (positive saliva followed by confirmatory urine) or positive DBS CMV PCR
- If cCMV diagnosed:
  Brain imaging (US or MRI), ophthalmology examination, hearing assessment, laboratory tests (cytopenias hepatitis, kidney function), consider consultation with Infectious Diseases

Antiviral therapy candidates:
- Infants with moderate to severe symptomatic cCMV
- Consider mildly symptomatic infants/isolated SNHL on case-by-case basis

Initiation of treatment:
- Ideally within first month of life

Treatment regimen:
- Oral valganciclovir 16 mg/kg/dose twice daily

Duration of treatment:
- 6 months

Monitoring during treatment:
- Absolute neutrophil counts followed closely (weekly to biweekly) for first 2 months, then monthly for the duration of therapy
- Transaminases and kidney function monthly for the duration of therapy

Follow-up as indicated:
- Ophthalmology
- Audiology (see **Fig. 1**) and Otolaryngology
- Case-by-case: Infectious Diseases, Neurology, developmental assessment, and therapy

Abbreviation: US, ultrasound.

known to account for more than half of childhood hearing loss. This raises the question of whether children with cCMV diagnosed with bilateral SNHL should also undergo comprehensive genetic testing. To date, cooccurrence of genetic causes of hearing loss has been reported in a small percentage of this population.[31,32] However, consensus on the genetic testing for children with bilateral SNHL and cCMV is currently lacking.

HEARING LOSS SCREENING AND MONITORING

Although only a minority of children with cCMV develop SNHL, prediction of which children will develop hearing loss is not possible. Therefore, it is necessary that children known to have cCMV infection receive ongoing audiologic surveillance (Fig. 1). The Joint Committee on Infant Hearing has stated that "early and more frequent assessment" might be indicated for children with cCMV infection as compared with their recommendation of "at least one" additional audiology assessment by 24 to 30 months of age for children who pass newborn hearing screening but have risk factors for hearing loss.[33] Other monitoring recommendations for delayed onset of hearing loss in children with cCMV vary from every 6 to 12 months until age 4 to 6 years (see Fig. 1).[4,20,34] The risk of delayed-onset SNHL is reported to return to a level comparable to non-cCMV-infected controls by age 5 years.[9] Children with cCMV and confirmed SNHL, whether onset is at birth or delayed, require ongoing audiologic

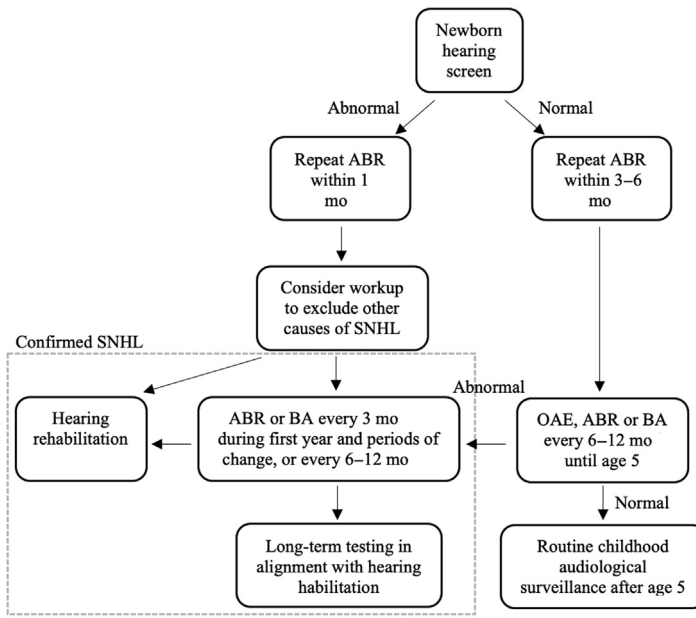

Fig. 1. Flowchart of hearing screening and monitoring in patients with cCMV. ABR, auditory brainstem response; BA, behavioral audiometry; OAE, otoacoustic emissions. (*Adapted from* Foulon I, Vleurinck L, Kerkhofs K, Gordts F. Hearing configuration in children with ccmv infection and proposal of a flow chart for hearing evaluation.Int J Audiol. 2015;54(10):714-9. copyright ©BritishSociety of Audiology; International Society of Audiology; Nordic Audiological Society, reprinted by permissionof Informa UK Limited, trading as Taylor & Francis Group, www.tandfonline.com on behalf of British Society of Audiology; International Society of Audiology; Nordic Audiological Society.)

monitoring for stability of hearing loss and management. To optimize amplification, more frequent audiologic testing is often necessary during the first year of life and during periods whereby hearing is fluctuating or progressing.[4,20]

Techniques used to screen for hearing loss and to perform diagnostic audiologic evaluations will vary based on the age and development of the patient (see **Fig. 1**). Evaluation and management by an experienced pediatric audiologist are ideal. Auditory brainstem response testing is necessary for young infants, as well as older children who are difficult to test by behavioral techniques. Further information on audiologic approach to diagnosis of hearing loss in children can be found in Linda J. Hood's article, "Auditory Neuropathy / Auditory Synaptopathy," in this issue.

MANAGEMENT OF SENSORINEURAL HEARING LOSS

Hearing habilitation should be pursued for children with SNHL, regardless of cause, to minimize the impact of hearing loss on speech, language, and cognition. The first line of treatment is amplification for children with bilateral SNHL or unilateral SNHL of mild to moderate degree (see Sampat Sindhar and Judith E.C. Lieu's article, "Overview of Medical Evaluation of Unilateral & Bilateral Hearing Loss in Children," in this issue). Amplification should not be delayed by antiviral treatment. To maximize listening and spoken language, early intervention therapy that includes listening and spoken language therapy is beneficial.

COCHLEAR IMPLANTATION

Cochlear implantation (CI) is the only medical treatment of SNHL when amplification does not provide adequate access to spoken language. Benefits of CI in patients with cCMV are well established, with multiple series showing improvement in auditory thresholds, speech perception, and expression.[32,35–40] Some studies have shown equivalent progress among implanted patients with cCMV compared with controls with other causes of SNHL, whereas others have shown comparatively slower or poorer progress.[32,36,38,39,41]

Children with cCMV, especially those with symptomatic cCMV, can have comorbidities and developmental delays placing them at increased risk for cognitive impairment. In the past, children with these comorbidities have been viewed as poor candidates for CI. However, CI candidacy has evolved to include children with significant additional disabilities, and the benefits have been well established.[42–44] Early access to CI can be critical to these children to fully develop their hearing, language, and cognitive potential.

For children with cCMV and single-sided deafness, or asymmetric hearing loss with severe to profound loss in 1 ear, CI is also a consideration. Having useful hearing from only 1 ear is associated with many disadvantages, including increased difficulty hearing in background noise and poor sound localization. The risk of progression or onset of hearing loss in the better hearing ear also makes early implantation of the poorer ear more compelling. In addition, for the subpopulation of children with symptomatic cCMV who also have visual impairment, improvement of hearing is especially important.[13,45]

ANTIVIRAL TREATMENT FOR CONGENITAL CYTOMEGALOVIRUS

Over the last 3 decades, antiviral medications have emerged as a viable treatment option. Several early studies of children with symptomatic CMV treated with 6 weeks of intravenous ganciclovir provided promising evidence of positive impact on hearing

preservation in the short term.[46,47] In addition, antiviral treatment might also improve neurodevelopmental outcomes.[48] The most significant risk of antiviral treatment is significant neutropenia, which is dose-dependent and reversible. Possible side effects of antiviral therapy include thrombocytopenia, anemia, and kidney and liver dysfunction.

Valganciclovir is an orally administered antiviral medication that has supplanted ganciclovir as the drug of choice for treatment of symptomatic cCMV. It offers equivalent pharmacokinetics, ease of oral administration, and a lower side-effect profile.[49,50] A 6-month course of oral treatment is more effective to optimize hearing outcomes than 6 weeks of therapy. Neutropenia occurs less frequently with oral than with intravenous antiviral treatment.[51] In some cases, improvement in auditory thresholds has been noted, more commonly in ears with less hearing loss. In addition, infants treated with 6 months of oral valganciclovir have been found to have improved neurodevelopmental scores at 24 months.[51]

It is standard care to offer antiviral treatment (see **Box 1**) for infants with moderate to severe symptomatic cCMV.[52] Moderately to severely symptomatic cCMV disease includes infants with multiple manifestations of cCMV disease or who have central nervous system involvement beyond SNHL. Treatment should ideally be initiated within the first month of life, and standard length of treatment is 6 months. Whether there is also benefit when treatment is initiated after the first month of life is an area of active study.[53,54]

Several trials are underway to determine the benefit of antiviral therapy for asymptomatic cCMV, with and without SNHL, and the timing of treatment initiation (ClinicalTrials.gov Identifiers: NCT01649869, NCT03107871, NCT03301415). Results of these studies might support expanded indications and windows for treatment.

At the Ann and Robert H. Lurie Children's Hospital of Chicago, antiviral therapy is offered on a case-by-case basis to children with mild symptomatic or asymptomatic disease with SNHL. Children are comprehensively evaluated by their Infectious Disease specialists (see **Box 1**) and counseled as to the potential benefits and risks of oral antiviral therapy and required monitoring. Ideally, these children are treated within the setting of a clinical trial; however, treatment is offered outside of a trial for those who do not qualify or decline participation. The primary goal of antiviral therapy in these children is stabilization of hearing loss as well as prevention of hearing loss in the normal hearing ear, if present. In discussing antiviral therapy, parents are informed about (1) current level of evidence of treatment effectiveness, (2) applicability to the individual child's history, and (3) potential known and unknown side effects.

SUMMARY

cCMV is the most common nongenetic cause of SNHL. Hearing loss caused by cCMV is often bilateral but can be asymmetric or unilateral and of varying degree. Children with cCMV may pass newborn hearing screening because almost half present with delayed onset of hearing loss. Those with residual hearing are at significant risk for progression and, therefore, require careful audiologic monitoring. The role of antiviral therapy to address SNHL in children with otherwise mild or asymptomatic disease is emerging. Children with cCMV and significant SNHL in one or both ears may be excellent candidates for CI.

CLINICS CARE POINTS

- Targeted hearing screening for congenital cytomegalovirus with polymerase chain reaction testing completed before 3 weeks of age for infants who fail newborn hearing screening is

an effective policy to increase diagnosis of congenital cytomegalovirus–related sensorineural hearing loss. This approach also enables the option of antiviral therapy to preserve hearing for this population.

- Children with congenital cytomegalovirus–related sensorineural hearing loss require monitoring for progression of hearing loss and appropriate hearing technology to address their unilateral or bilateral loss in order to maximize language and developmental outcome.
- Congenital cytomegalovirus should be considered as a possible cause of postnatal sensorineural hearing loss. Definitive diagnosis of congenital cytomegalovirus as the cause of postnatal sensorineural hearing loss might not be possible beyond the neonatal period and especially in otherwise asymptomatic children unless polymerase chain reaction testing of the dried blood spot is positive. However, at this time, children with delayed onset sensorineural hearing loss are not candidates for antiviral therapy because evidence of benefit to hearing or overall development is lacking for treatment initiated after the neonatal period.
- Cochlear implantation is an effective treatment for congenital cytomegalovirus–related sensorineural hearing loss when amplification does not provide access to spoken language. Candidates include children with complicating conditions and developmental delays in addition to hearing loss. The benefit of binaural hearing provided by an implant for children with congenital cytomegalovirus–related single-sided deafness is also of consideration, especially given the risk for sensorineural hearing loss in the only hearing ear.

DISCLOSURE

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REFERENCES

1. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17(4):253–76.
2. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007;17(5):355–63.
3. Lanzieri TM, Dollard SC, Bialek SR, et al. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. Int J Infect Dis 2014;22:44–8.
4. Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. Clin Infect Dis 2013;57(Suppl 4):S182–4.
5. Morton CC, Nance WE. Newborn hearing screening–a silent revolution. N Engl J Med 2006;354(20):2151–64.
6. Manicklal S, Emery VC, Lazzarotto T, et al. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev 2013;26(1):86–102.
7. Zuhair M, Smit GSA, Wallis G, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta-analysis. Rev Med Virol 2019;29(3):e2034.
8. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. J Clin Virol 2006;35(2):226–31.
9. Lanzieri TM, Chung W, Flores M, et al. Hearing loss in children with asymptomatic congenital cytomegalovirus infection. Pediatrics 2017;139(3):e20162610.
10. Ito Y, Kimura H, Torii Y, et al. Risk factors for poor outcome in congenital cytomegalovirus infection and neonatal herpes on the basis of a nationwide survey in Japan. Pediatr Int 2013;55(5):566–71.

11. Boppana SB, Fowler KB, Vaid Y, et al. Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. Pediatrics 1997;99(3):409–14.
12. Rivera LB, Boppana SB, Fowler KB, et al. Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. Pediatrics 2002;110(4):762–7.
13. Lanzieri TM, Leung J, Caviness AC, et al. Long-term outcomes of children with symptomatic congenital cytomegalovirus disease. J Perinatol 2017;37(7):875–80.
14. Fowler K. Do perinatal factors predict hearing loss in children with asymptomatic congenital (CMV) infection? Am J Epidemiol 2003;157:S84.
15. Dimopoulou D, Kourlaba G, Antoniadou A, et al. Low birth weight and head circumference as potential biomarkers of sensorineural hearing loss in asymptomatic congenitally CMV-infected infants. J Clin Virol 2020;129:104471.
16. Boppana SB, Fowler KB, Pass RF, et al. Congenital cytomegalovirus infection: association between virus burden in infancy and hearing loss. J Pediatr 2005;146(6):817–23.
17. Yamaguchi A, Oh-Ishi T, Arai T, et al. Screening for seemingly healthy newborns with congenital cytomegalovirus infection by quantitative real-time polymerase chain reaction using newborn urine: an observational study. BMJ Open 2017;7(1):e013810.
18. Dahle AJ, Fowler KB, Wright JD, et al. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol 2000;11(5):283–90.
19. Madden C, Wiley S, Schleiss M, et al. Audiometric, clinical and educational outcomes in a pediatric symptomatic congenital cytomegalovirus (CMV) population with sensorineural hearing loss. Int J Pediatr Otorhinolaryngol 2005;69(9):1191–8.
20. Foulon I, Vleurinck L, Kerkhofs K, et al. Hearing configuration in children with cCMV infection and proposal of a flow chart for hearing evaluation. Int J Audiol 2015;54(10):714–9.
21. Riga M, Korres G, Chouridis P, et al. Congenital cytomegalovirus infection inducing non-congenital sensorineural hearing loss during childhood; a systematic review. Int J Pediatr Otorhinolaryngol 2018;115:156–64.
22. Goderis J, De Leenheer E, Smets K, et al. Hearing loss and congenital CMV infection: a systematic review. Pediatrics 2014;134(5):972–82.
23. Fowler KB, McCollister FP, Dahle AJ, et al. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. The J Pediatr 1997;130(4):624–30.
24. Williamson WD, Demmler GJ, Percy AK, et al. Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. Pediatrics 1992;90(6):862–6.
25. Fowler KB, Dahle AJ, Boppana SB, et al. Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed? J Pediatr 1999;135(1):60–4.
26. Leruez-Ville M, Vauloup-Fellous C, Couderc S, et al. Prospective identification of congenital cytomegalovirus infection in newborns using real-time polymerase chain reaction assays in dried blood spots. Clin Infect Dis 2011;52(5):575–81.
27. Dollard SC, Dreon M, Hernandez-Alvarado N, et al. Sensitivity of dried blood spot testing for detection of congenital cytomegalovirus infection. JAMA Pediatr 2021;175(3):e205441.

28. Cannon MJ, Griffiths PD, Aston V, et al. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? Rev Med Virol 2014; 24(5):291–307.
29. Grosse SD, Dollard S, Ross DS, et al. Newborn screening for congenital cytomegalovirus: options for hospital-based and public health programs. J Clin Virol 2009;46(Suppl 4):S32–6.
30. Demmler GJ. Screening for congenital cytomegalovirus infection: a tapestry of controversies. J Pediatr 2005;146(2):162–4.
31. Peterson J, Nishimura C, Smith RJH. Genetic testing for congenital bilateral hearing loss in the context of targeted cytomegalovirus screening. Laryngoscope 2020;130(11):2714–8.
32. Ramirez Inscoe JM, Nikolopoulos TP. Cochlear implantation in children deafened by cytomegalovirus: speech perception and speech intelligibility outcomes. Otol Neurotol 2004;25(4):479–82.
33. American Academy of Pediatrics JCoIH. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics 2007;120(4):898–921.
34. Royackers L, Christian D, Frans D, et al. Hearing status in children with congenital cytomegalovirus: up-to-6-years audiological follow-up. Int J Pediatr Otorhinolaryngol 2011;75(3):376–82.
35. Lee DJ, Lustig L, Sampson M, et al. Effects of cytomegalovirus (CMV) related deafness on pediatric cochlear implant outcomes. Otolaryngol Head Neck Surg 2005;133(6):900–5.
36. Iwasaki S, Nakanishi H, Misawa K, et al. Cochlear implant in children with asymptomatic congenital cytomegalovirus infection. Audiol Neurootol 2009;14(3): 146–52.
37. Yoshida H, Takahashi H, Kanda Y, et al. Long-term outcomes of cochlear implantation in children with congenital cytomegalovirus infection. Otol Neurotol 2017; 38(7):e190–4.
38. Ciorba A, Bovo R, Trevisi P, et al. Rehabilitation and outcome of severe profound deafness in a group of 16 infants affected by congenital cytomegalovirus infection. Eur Arch Otorhinolaryngol 2009;266(10):1539–46.
39. Philips B, Maes LK, Keppler H, et al. Cochlear implants in children deafened by congenital cytomegalovirus and matched connexin 26 peers. Int J Pediatr Otorhinolaryngol 2014;78(3):410–5.
40. Hoff S, Ryan M, Thomas D, et al. Safety and effectiveness of cochlear implantation of young children, including those with complicating conditions. Otol Neurotol 2019;40(4):454–63.
41. Yoshida H, Kanda Y, Takahashi H, et al. Cochlear implantation in children with congenital cytomegalovirus infection. Otol Neurotol 2009;30(6):725–30.
42. Young N, Weil C, Tournis E. Redefining cochlear implant benefits to appropriately include children with additional disabilities. In: Young N, Kirk K, editors. Pediatric cochlear implantation. New York, NY: Springer-Verlag; 2016. p. 213–26.
43. Wiley S, Jahnke M, Meinzen-Derr J, et al. Perceived qualitative benefits of cochlear implants in children with multi-handicaps. Int J Pediatr Otorhinolaryngol 2005;69(6):791–8.
44. Waltzman S, Scalchunes V, Cohen N. Performance of multiply handicapped children using cochlear implants. Am J Otolaryngol 2000;21(3):329–35.
45. Coats DK, Demmler GJ, Paysse EA, et al. Ophthalmologic findings in children with congenital cytomegalovirus infection. J AAPOS 2000;4(2):110–6.

46. Whitley RJ, Cloud G, Gruber W, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis 1997;175(5):1080–6.
47. Kimberlin DW, Lin C-Y, Sánchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr 2003;143(1):16–25.
48. Oliver SE, Cloud GA, Sanchez PJ, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. J Clin Virol 2009;46(Suppl 4):S22–6.
49. Acosta EP, Brundage RC, King JR, et al. Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. Clin Pharmacol Ther 2007;81(6):867–72.
50. Kimberlin DW, Acosta EP, Sanchez PJ, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. J Infect Dis 2008;197(6):836–45.
51. Kimberlin DW, Jester PM, Sanchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med 2015;372(10):933–43.
52. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. The Lancet Infect Dis 2017;17(6):e177–88.
53. Dorfman L, Amir J, Attias J, et al. Treatment of congenital cytomegalovirus beyond the neonatal period: an observational study. Eur J Pediatr 2020;179(5):807–12.
54. del Rosal T, Baquero-Artigao F, Blazquez D, et al. Treatment of symptomatic congenital cytomegalovirus infection beyond the neonatal period. J Clin Virol 2012;55(1):72–4.