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Chapter

Universal Screening for Congenital CMV Infection

Sara Lunardi, Francesca Lorenzoni and Paolo Ghirri

Abstract

Congenital cytomegalovirus (CMV) infection is an important public health problem. It is a leading cause of disability in children. Congenitally infected neonates often appear asymptomatic at birth or have nonspecific symptoms. An early diagnosis and subsequent early antiviral therapy associated to nonpharmacological therapy (e.g., hearing rehabilitation, speech-language therapy, and cochlear implants) can reduce long-term disability. Much research has been done in this field, but further studies are still necessary. Looking back at the most recent papers, we will draw a review on this topic trying to answer to the question: could universal CMV screening be a useful and cost-effective diagnostic tool?

Keywords: cytomegalovirus, universal screening, congenital infection, hearing loss, disability

1. Introduction

Congenital cytomegalovirus (CMV) infection is an important public health problem. It is a leading cause of disability in children. Even if it is a major public concern and a high cost, there is little awareness among the general public and medical officers. Most pregnant women are not aware of CMV and do not know how to prevent it. Congenitally infected neonates often appear asymptomatic at birth or have nonspecific symptoms. An early diagnosis and subsequent early antiviral therapy associated to nonpharmacological therapy (e.g., hearing rehabilitation, speech-language therapy, and cochlear implants) can reduce long-term disability.

Routine ultrasound scans fail to identify signs of cytomegalovirus infection till late gestation. Furthermore, most congenitally infected babies are asymptomatic at birth and thus will not be identified by routine clinical examination or hearing test (the majority of neonates with CMV-related sensorineural hearing loss will have late onset or progressive losses). Although congenital cytomegalovirus infection is more common than most screened newborn conditions, a routine cytomegalovirus screening at birth is not performed [1], even if the existence of reliable tests to early diagnose the condition, the improved outcomes following early diagnosis and the successful antiviral treatment could fulfill the criteria for universal screening [2, 3].

2. Congenital cytomegalovirus infection

2.1 Incidence, transmission routes, and clinical spectrum

The overall CMV seroprevalence in women of childbearing age depends on age, parity, ethnicity, and social status; differs between countries and regions; and changes over time.

The congenital infection prevalence varies according to the chosen diagnostic criteria and how tests are performed by the laboratory. It affects around the 0.5–0.7% of all live births in industrialized countries such as Western Europe, United States, Canada, and Australia. It affects even more babies (1–2% of all live births) in other countries such as Africa, Latin America, and most Asian countries [1, 4–11].

Cytomegalovirus (CMV) is a herpesvirus spread by almost all human fluids (blood, saliva, breast milk, urine, sperm, and vaginal fluids). Cytomegalovirus usually leads to unknown infection in immunocompetent adults, and so it happens in pregnant women. In Europe, 1–8% of women are exposed to primary infection [12].

Infants and toddlers often shed the virus for months or even years, and pregnant women could easily be infected by urine and saliva. Intrauterine infection leads to fetal infection with a transmission rate of 32% in primary maternal infection and 1.4% in recurrent maternal infection. Consequences are worst if the mother is primary infected (10–18% of newborns with symptomatic congenital CMV disease at birth and 10–58% rate of permanent and late sequelae), but also secondary infection (reactivation by a preexistent herpesvirus or infection by a new strand) can lead to neurological sequelae (8% circa of late sequelae) [12]. Due to the high overall prevalence, two-thirds of babies with congenital CMV infections are born to mothers with preexistent antibodies [13].

The clinical spectrum of congenital CMV varies from the absence of signs (85–90% of infected neonates are asymptomatic) to potentially life-threatening disease (10–15% are symptomatic at birth with a wide spectrum of disease expression: clinical manifestations may include sensorineural hearing loss, hepatomegaly, jaundice, petechiae, microcephaly, chorioretinitis, and intrauterine growth restriction) [14].

In Europe, congenital cytomegalovirus infection is a leading cause of neurological disabilities in children such as sensorineural hearing loss (it is the main cause of nongenetic sensorineural hearing loss), blindness, neurodevelopment delays, and cerebral palsy. Permanent impairments mainly target the central nervous system.

Hearing loss may be present at birth or has a delayed onset. About 50% of sensorineural hearing loss further deteriorates during childhood [14]. At present, no definite markers have been identified to predict which infants with mild signs or asymptomatic disease will develop sensorineural hearing loss: viral load as determined by polymerase chain reaction could probably be useful for this purpose [15].

Even if congenital cytomegalovirus infection is a major public concern and a high cost, there is little awareness among the general public and medical officers.

While cytomegalovirus is a routine test for pregnant women in eight European countries and Israel, it is not a mandatory test in Italy and most obstetrics do not recommend it [16, 17] probably due to lack of definite and universally accepted intervention for pregnant women with a primary infection and to the fact that most infected babies are born to mothers experiencing a nonprimary maternal infection [14].

2.2 Diagnostic timing

Routine ultrasound scans fail to identify signs of cytomegalovirus infection till late gestation. Furthermore, most congenitally infected babies are asymptomatic

at birth and thus will not be identified by routine clinical examination or hearing test (the majority of neonates with CMV-related sensorineural hearing loss will have late onset or progressive losses). Early, reliable, and relatively inexpensive tests should be defined in order to identify these babies at risk at an early stage.

To make diagnosis of congenital infection, tests should be performed within the first 2–3 weeks of age. The Joint Committee on Infant hearing states that all babies with hearing loss of uncertain origin, based on an initial evaluation, should be tested for cytomegalovirus [18].

But if CMV diagnosis is reliable and if the test is performed within the first 3 weeks of age, then waiting for a complete audiological and medical evaluation often means that it is too late to diagnose congenital CMV infection.

2.3 Universal screening: pro and cons

According to the American College of Medical Genetics Newborn Screening Expert Group "To be included as a primary target condition in a newborn screening program, a condition should meet the following minimum criteria: It can be identified at a period of time (24 to 48 hours after birth) at which it would not ordinarily be clinically detected, a test with appropriate sensitivity and specificity is available, there are demonstrated benefits of early detection, timely intervention, and efficacious treatment" [19]. Earlier on the Wilson and Jungner criteria for newborn screening had stated that the condition should represent a public health problem and a well-known condition, a suitable test should exist to early diagnose it and the benefit should outweigh the risks and costs of early intervention [20, 21].

Although congenital cytomegalovirus infection is more common than most screened newborn conditions, a routine cytomegalovirus screening at birth is not performed [1], even if the existence of reliable tests to early diagnose the condition, the improved outcomes following the early diagnosis and the successful antiviral treatment could fulfill the criteria for universal screening [2, 3].

In Italy, the prevalence of congenital CMV infection is lower than other countries (0.15–0.51% according to Italian Higher Health Institute data) but still higher than other conditions that are routinely screened at birth (e.g., cystic fibrosis that occurs in about one over 2500–3000 healthy neonates, phenylketonuria with an incidence of 1:10.000 newborns, or congenital hypothyroidism with a prevalence of 1/2000–4000).

According to the informal International Congenital Cytomegalovirus Recommendations Group that convened in 2015, "consideration must be given to universal neonatal screening for cytomegalovirus to facilitate early detection and intervention for sensorineural hearing loss and developmental delay" [22].

Cannon et al. in a study published in 2014 estimated the number of babies with the most common CMV-related disabilities (such as hearing loss, visual impairment, and cognitive deficits) in the United States. For each disability, they analyzed the existence of useful therapeutic intervention. They found evidence of benefits of nonpharmacological treatments in babies with cognitive deficits and in babies with delayed hearing loss with onset within the first 2 years of age. No benefits were found for babies with visual impairment [23]. Improved language development should result by a prompt detection and management of late onset hearing loss (e.g., use of hearing aids or cochlear implants).

The economic burden caused by congenital CMV is substantial as many affected babies require ongoing care, special therapeutic, and educational services [23].

Congenital CMV disease (cCMVd) is associated with a substantial economic burden, not only at birth and throughout the first year of life, but also during childhood, adolescence, and adulthood. Although a lot has been published about the

clinical outcomes and sequelae associated with congenital CMV infection, less data are available regarding health care resource utilization and costs associated with cCMVd.

The Committee to Study Priorities for Vaccine Development estimated in 2000 that there were 40,000 infants born every year in the United States with CMV infection and assumed 400 deaths annually from the congenitally acquired CMV infection and about 8000 children with permanent disabilities [24]. Assuming that these children require diagnostics, hospitalization, long-term care such as regular visits to a specialist for the lifetime and special schooling expense, the estimated annual direct economic cost for caring for these children was estimated at about 1–2 billion dollars [14, 24, 25]. Lifetime costs of hearing impairment are available, and in 2007, costs including devices, medical costs, special education, and lost productivity were estimated to be over 700.000 euro per person with bilateral hearing impairment [20].

Ronchi et al. defined congenital CMV infection a huge public health problem with an estimated annual cost of up to 4 billion dollars in the United States alone [26].

A recent study by Clinthera et al., in line with previously published US data, revealed inpatient costs associated with cCMVd in infants. They focused on birth admission describing a mean long of stay (LOS) between 22.1 and 37.5 days with mean costs between $46,994 and $98,126, corresponding to accrue costs at birth about 1.5–2.1 times greater than control infants for cesarean and vaginal deliveries. Moreover, during the first year of life, infants with cCMVd had costs about 7 times greater than control infants. The key cost driver among the cCMVd population is represented by inpatient visits. Beyond the direct economic impact, other aspects of congenital CMV (cCMV) infection affect both the patient and the society. In the same study, the annual economic costs, both direct and indirect, associated with care of children with disabilities due to cCMV infection (hearing loss and cognitive disabilities), range between $20,000 and $60,000, with an average of $30,000 per family [27].

Both universal screening and targeted screening have shown to be cost-effective, but the first one probably provides large net savings and better care [26, 28–29].

As already underlined by Gantt et al., introducing a screening program for cCMV at birth would allow for identification of asymptomatic newborns with cCMV, who would previously have gone undiagnosed and provide potentially early treatment and ongoing neurodevelopmental monitoring, including hearing surveillance. With their well-designed cost-effectiveness study, they provide key support for the healthcare system benefits, especially cost savings, for either a targeted or universal approach to screening cCMV. The potential benefits described by this study, in particular those provided by universal screening, when loss of productivity costs is taken into account, make it the most attractive form of screening, compared to targeted screening [30].

Among all infants born in the United States, identification of 1 case of cCMV infection by universal screening was estimated to cost $2000 to $10,000 and by targeted screening, $566 to $2832. Net savings from universal screening were estimated to be greater than those from targeted screening, although screening costs are higher. Savings from screening strategies are derived not only from improved hearing with antiviral treatment of affected newborns but also from earlier detection of late-onset hearing loss [28].

The importance of the economic burden of CMV has started to be recognized also in Europe, where a recent Dutch study by Korndewal et al. confirmed that children with cCMV have higher average healthcare costs in the first 6 years of life than cCMV-negative children. The difference in total healthcare costs between these

groups is more than €2500 per child. This study again revealed that the large and usually unrecognized groups of children with cCMV who are asymptomatic at birth are responsible for half of the costs, underestimating the real impact. Other causes of underestimation are the fact that children who died were not included and that the evaluation of the costs is only up to 6 years of age, while, at a later follow-up, the difference between cCMV-positive and cCMV-negative children might become even larger. Finally, other costs related to the impairment of children with cCMV, such as special needs education, future reduced productivity, and potential productivity loss of parents, were not taken into account [31].

Even in the United Kingdom, a cost model had been proposed, but, due to the scarcity of robust data preventing inclusion of many expected costs, it is likely that this model underestimates the "true" cost. It estimated that the cost of cCMV to the United Kingdom in 2016 was £732 million, of which approximately 40% of the costs were direct and 60% indirect. Acute management of cCMV was the lowest contributing cost (estimated at £1.2 million), with costs for management of long-term sequelae being orders of magnitude greater. As well as in the United States, also in the United Kingdom, both universal and targeted newborn screening would be cost-effective options for detecting and reducing hearing loss and other consequences caused by cCMV [32].

Many studies have already evaluated the benefits of a targeted screening program in the United Kingdom. Williams et al. estimated that the cost of "protecting" a case of childhood SNHL from cCMV identified and treated through a national targeted screening program would be ~£14,000. In comparison, detailed health economic analysis suggests that the societal cost of bilateral hearing impairment in children aged 7–9 years rises from £9120 to £21,179 per year from moderate to severely affected children, and the lifelong cost of a pediatric cochlear implant is £82,000–108,000. The cost of identifying a case of cCMV-related SNHL varied between £9224 and £5413, and the cost of "protecting" a case of cCMV-related SNHL varied between £19,601 and £11,502, taking into account only the healthcare costs and no family and wider societal costs [33].

Based on these economic data, it could be the right time to introduce also in Europe a universal screening program even if larger studies to determine the cost-effectiveness and utility of this policy would be helpful.

Commonsense says that screening should be performed only if potential benefits outweigh the costs and potential harms. Potentially negative aspects of Universal Screening could be parental stress linked to a positive diagnosis in those CMV infected babies who will never develop clinical problems related to the congenital infection or costs of unnecessary visits or tests. But, on the other hand, a definite diagnosis could reduce parental (and medical) stress and anxiety caused by an uncertain diagnosis in babies with nonspecific symptoms (and could also save anxiety and costs linked to the diagnostic odyssey that is often linked to without-definite-cause late onset hearing or neurological impairment). In studies, universal screening has shown to be well accepted by parents. Early diagnosis could be important, but it is fundamental that children and parents are not left alone after such a diagnosis [23, 34].

2.4 Diagnostic tests

Early, reliable, and relatively inexpensive tests should be defined in order to identify these babies at risk at an early stage (**Table 1**).

Traditional isolation of the virus by culture of urine or saliva is the gold standard test, but it is not suitable as a mass screening because it cannot be automated, and it is labor- and resource-intensive and requires tissue culture facilities [35]. On the

Test	It could be performed on	Pro		Cons
Traditional isolation of the virus by culture	Urine	Reliable, it is the gold standard to diagnose CMV infection.		It is not suitable as a mass screening because it cannot be automated, and it is labor- and resource-intensive and requires tissue culture facilities.
	Saliva			
PCR (real-time polymerase chain reaction)	Urine	PCR could be automated, and it is low cost and does not seem to be affected by sample storage and transport.	CMV is largely excreted in urine, and quantification of urinary CMV load could even predict the incidence of late-onset sequelae.	Collecting urine for a universal screening could be difficult.
	Saliva		Saliva swabs are easy to collect.	False positive results could be related to contamination by CMV in maternal milk.
	Dried blood spot samples		It could be useful for retrospective diagnosis in late-onset hearing loss.	Studies reported variable sensitivity of PCR on DBS.
Detection of CMV specific immunoglobulin M antibodies	Neonatal serum	—		Only 20–70% of infected neonates show specific IgM

Table 1.
Diagnostic tests.

other hand, PCR (real-time polymerase chain reaction) could be automated, and it is low cost and does not seem to be affected by sample storage and transport. PCR tests could then be suitable as a mass screening and could be performed on urine, saliva, and dried blood spot samples. CMV is largely excreted in urine; thus, PCR on urine is largely used to diagnose congenital CMV infection with a cost per child of about 22 € (based on rough **cost** estimations by our own facilities). According to the study published by Yamaguchi et al. in 2016, quantification of urinary CMV load could even predict the incidence of late-onset sensorineural hearing loss (SNHL) and neurological disorders because urinary CMV copy number seemed to be associated with SNHL and central nervous system damage: CMV viral load in urine not only could so be diagnostic of congenital infection but also predict sequelae [36]. The problem is that collecting urine for a universal screening could be more difficult (and use of cotton balls or filter cards is still to be evaluated in large studies) than PCR on saliva.

Dried blood spots (DBS) are already collected routinely for metabolic screening worldwide and have been suggested as the optimal choice, but according to 2010 Boppana et al. study [35], CMV testing with DBS real-time PCR compared with tests on saliva had low sensitivity, limiting its value as a screening test. Other studies reported variable sensitivity of PCR on DBS, probably due both to technical

issues and to the fact that not all congenitally infected neonates have detectable viremia at birth. For this reason, it is not suitable for universal screening but could be useful for retrospective diagnosis in late onset hearing loss (even if a positive test is diagnostic while a negative test does not rule out a congenital CMV infection). Detection of CMV specific immunoglobulin M antibodies in neonatal serum may as well disclose congenital infection, but only 20–70% of infected neonates show specific IgM [37].

In a multicenter screening study published on New England Journal of Medicine in 2011, Boppana et al. concluded that PCR assays of both liquid and dried saliva showed high sensitivity and specificity and could be used as a potential screening test for congenital CMV infection. The rate of false positive results in both swabs was less than 0.03%: in case of positive test, a confirmation test within 3 weeks of age could then rule out a false positive result [14, 38]. Barkai et al. concluded in their report of clinical experience [39] that universal CMV screening using real-time PCR saliva is a feasible and easy-to-use method for newborn infants.

The ease of saliva swab collection makes the PCR on saliva the preferred test for newborn screening (probably with costs similar to those of PCR on urine), but if the test gives a positive result, then confirmation should be obtain by PCR or culture test on urine in order to rule out false positive results due, for example, to contamination by CMV in maternal milk.

2.5 Antiviral therapy

The treatment of symptomatic congenital CMV infection with intravenous ganciclovir for 6 weeks has shown to improve audiological outcome at 6 months. Treated infants had fewer development delays than untreated babies according to Denver Developmental evaluation. The Collaborative Antiviral Study Group determined the dose of oral valganciclovir resulting in systemic exposure similar to that with intravenous ganciclovir, so that actually therapy with intravenous ganciclovir or oral valganciclovir for 6 weeks is an accepted therapy for symptomatic CMV [40–42]. Given that the results seemed to wane after 2 years of age, a recent study [2] was performed by Kimberlin et al. in 2015 comparing the 6 weeks versus a 6-month therapy. It concluded that treating the condition with oral valganciclovir (16 mg/kg/dose twice a day) for 6 months appeared to improve developmental and hearing outcomes in the longer term: this is now considered an effective and well-tolerated therapeutic option for symptomatic neonates, while currently evidence of benefit of antiviral therapy in asymptomatic babies is still lacking [14] (**Table 2**). Asymptomatic babies are the majority of congenital CMV infected neonates, and since these babies are at risk of late-onset sequelae, further studies are needed in order to define the best pharmacological and nonpharmacological strategies. For these babies, a universal screening would be fundamental for an early diagnosis as early rehabilitation treatments are vital. Symptomatic neonates, instead, would probably not benefit of a screening program (for example, they would probably be already detected by universal hearing screening), apart from the advantages of a more immediate diagnosis with consequent parental and physician peace of mind.

2.6 Prevention

Handwashing and other preventive measures to avoid contact with potentially contaminated body fluids are likely to be effective in preventing seroconversion in pregnant women [12]. Toddlers can shed the virus through saliva and urine for a long period of time, so women dealing with young children are at particular risk. Most women have not ever heard of CMV infection.

• Treating the condition with oral valganciclovir (16 mg/kg/dose twice a day) for 6 months is now considered an effective and well-tolerated therapeutic option for symptomatic neonates, while currently evidence of benefit of antiviral therapy in asymptomatic babies is still lacking.

Table 2.
Antiviral therapy for congenital CMV infection.

• **Assume** that all toddlers and young children could be secreting the virus through saliva and urine.
• **Remember** hand washing with soap after activities such as changing diapers, bathing or feeding a baby, wiping running nose, touching baby's toys, or surfaces contaminated by saliva or urine.
• **Avoid** kissing babies on the mouth, sharing kitchen utensils, toothbrushes, or towels

Table 3.
Information should be given to all women of reproductive age about simple hygiene measures and change of behavior that could prevent seroconversion.

Of 643 women surveyed by Jeon et al. in their study published in 2006 [43], only 22% had heard of congenital CMV, while in a national mail survey of the US population, only 14% of female respondents had heard of CMV [44].

In our Neonatal Units (University Hospital of Pisa and S Luca Hospital of Lucca), we just started a survey asking mothers of healthy term newborns if they had ever heard of CVM (first question), if they knew their CMV status (second question), and if they knew how to prevent CMV infection (third question). From the few data we have collected since, 65% of women had somewhere heard of CMV, but 82% did not know their CMV status, and, most importantly, 90% of women did not know how to prevent CMV infection.

Information should be given to all women of reproductive age about simple hygiene measures and change of behavior that could prevent seroconversion. All women who are pregnant or planning to become pregnant should be fully informed, especially if dealing with children. They should be educated about hygienic practices to reduce the risk of CMV infection, assuming that all toddlers and young children could be secreting the virus through saliva and urine. Hygienic measures include not only hand washing with soap after activities such as changing diapers, bathing or feeding a baby, wiping running nose, touching baby's toys, or surfaces contaminated by saliva or urine, but also avoiding kissing babies on the mouth, sharing kitchen utensils, toothbrushes, or towels [25] (**Table 3**).

In 2015, Revello et al. published a mixed interventional and observational controlled study to measure the effectiveness of hygiene information among pregnant seronegative women at risk of primary CMV infection: 1.2% of women who had been given hygiene information at 11–12 weeks of gestation seroconverted versus 7.6% in the comparison group, and three newborns were diagnosed with congenital infection in the intervention group versus eight neonates in the group of women who had not been informed [45].

3. Conclusion

It is difficult to estimate, on the basis of precise numbers, the potential benefit of a congenital CMV screening, and surely further studies are urgently needed, but we could probably say that it could be an useful tool for an early intervention on those babies whose congenital infection would have never been detected at an early stage on a clinical basis. The main value of a universal screening is to pick up congenitally infected babies who are asymptomatic or with mild symptoms unrevealed

by clinical examination that pass neonatal hearing screening. These babies may develop late onset hearing impairment or other neurological sequelae and being diagnosed at an early stage by neonatal screening could improve their outcome, before it is too late for a successful rehabilitation [46]. Babies with symptomatic infection should be readily diagnosed by clinical examination (there should be no need for a universal screening in these babies), but sometimes awareness on congenital CMV even among health care professionals is relatively low so that too often being "small for gestational age" or other signs of possible CMV infection are attributed to other conditions and CMV test is not performed [26].

In a study we published in 2014 [47] we found an association between congenital CMV infection and preterm births (3.03%), and with SGA condition (3.7%), suggesting that routine CMV urine detection should be at least performed in all babies born before 37 weeks of gestational age and in term SGA newborns. Today, we could say that both universal screening and targeted screening have shown to be cost-effective, but the first one provides large net savings and better care [26, 28–29].

None of the benefits of newborn CMV screening will occur if the universal screening is not associated with an adequate follow-up program for an early detection and intervention of hearing loss, visual impairment, and cognitive deficits. Only if families are fully informed and never left alone in this journey, but thoroughly supported, then the potential parental stress, linked to a universal screening, could be outweigh by well-demonstrated advantages of an early diagnosis. But, even more important than universal screening is to clearly and thoroughly inform pregnant women about what CMV is, how it is transmitted, and how to prevent it: early diagnosis is fundamental, but prevention, whereas a vaccination has yet to come, is even more fundamental.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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