

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 data are yet to be translated into clinical practice. An informal International Congenital Cytomegalovirus Recommendations Group was convened in 2015 to address these questions and to provide recommendations for prevention, diagnosis, and treatment. On the basis of consensus discussions and a review of the literature, we do not support universal screening of mothers and the routine use of cytomegalovirus immunoglobulin for prophylaxis or treatment of infected mothers. However, treatment guidelines for infected neonates were recommended. Consideration must be given to universal neonatal screening for cytomegalovirus to facilitate early detection and intervention for sensorineural hearing loss and developmental delay, where appropriate. The group agreed that education and prevention strategies for mothers were beneficial, and that recommendations will need continual updating as further data become available.

Introduction

Many adverse fetal and neonatal outcomes have been prevented since the introduction of maternal screening for infectious diseases during pregnancy, and since the institution of routine rubella vaccination of women of reproductive age. In stark contrast, congenital cytomegalovirus infection remains largely unrecognised in the developed and developing world.¹ This is despite congenital cytomegalovirus now being the major infectious cause of sensorineural hearing loss and neurodevelopmental abnormalities in infants born in developed countries,² and second only to cerebral palsy in all causes of serious malformation in many parts of the world. The prevalence of congenital cytomegalovirus has been reported as 0.2% to 2.0% (average of 0.64%) of pregnancies.³ Many factors contribute to congenital cytomegalovirus mortality and morbidity, including the limited awareness of clinicians and parents about infection during pregnancy, low levels of routine testing of neonates at risk, the absence of maternal or neonatal screening programmes, the limited efficacy and toxicity of current treatments, and the absence of licensed vaccines. In part, because of these limitations, congenital cytomegalovirus and preventive measures for acquiring cytomegalovirus during pregnancy are not routinely or consistently discussed with pregnant women or women attempting conception. However, with evidence for efficacy of preventive actions,⁴ efficacy of early intervention for children with sensorineural hearing loss,⁵ evolving antiviral treatments, and recent availability of candidate vaccines for pregnant women and neonates,⁶ there is an emerging consensus that more attention must be directed to this infection by clinicians^{3,7}

researchers, and communities. In some states of the USA, legislation requires cytomegalovirus education as part of routine antenatal care.^{8–10}

To assist with clinical care, an informal International Congenital Cytomegalovirus Recommendations Group was convened as part of the 5th International Congenital Cytomegalovirus conference on April 19, 2015, to review and grade available evidence, and to draft recommendations that could be used to guide congenital cytomegalovirus diagnosis, prevention, and therapy. The International Congenital Cytomegalovirus Recommendations Group addressed whether pregnant women should be screened to aid diagnosis of maternal cytomegalovirus infection, and also addressed methods for diagnosis of maternal or fetal cytomegalovirus infection. Suggestions about who should be educated about congenital cytomegalovirus infections, and preventive measures for maternal cytomegalovirus infection, were considered. Whether cytomegalovirus hyperimmunoglobulin or antiviral therapy could be used routinely to prevent or treat congenital cytomegalovirus infection during pregnancy was discussed. Neonatal screening and the important questions of whether to treat infected neonates, and what form this therapy should consist of, were also addressed.

Methods to provide global recommendations on cytomegalovirus prevention, diagnosis, and treatment

Expert clinicians, opinion leaders for congenital cytomegalovirus, researchers with expertise in congenital cytomegalovirus infection, and representatives of the congenital cytomegalovirus community from Europe, the USA, and Australia were identified and invited to a

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workshop, organised as part of the 5th International Congenital Cytomegalovirus Conference in Brisbane, Australia (April 19, 2015). Identification of relevant participants was on the basis of publication track records about congenital cytomegalovirus, participation in or supervision of trials of diagnostic methods and therapies

for congenital cytomegalovirus, from lists of plenary speakers at international conferences, and from availability to attend the workshop and thereafter in drafting the recommendations. The International Congenital Cytomegalovirus Recommendations Group clearly could not embody all clinicians and researchers with expertise in congenital cytomegalovirus, but it did comprise internationally recognised experts with published expertise within diagnosis, prevention, and therapy.

The group first formulated which specific issues should be addressed (appendix) and assessed these before the workshop by reviewing the scientific literature. A systematic review of prevention and treatment of congenital cytomegalovirus⁴ was also undertaken before the workshop to ensure current published, and unpublished views were expressed in an unbiased manner. The use of a systematic review, combined with consensus meeting and discussion was on the basis of similar projects.^{11–13}

Recommendations were formulated after discussion and scientific evidence was graded (appendix). The quality of evidence on which recommendations were based was scored using the Oxford Centre for Evidence Based Medicine (OCEBM) levels of evidence.¹⁴ These are defined as: level 1, evidence from at least one properly randomised controlled trial; level 2a, controlled trials without randomisation; level 2b, cohort or case-control analytical studies; level 2c, multiple time series or uncontrolled experiments (including data on new therapies that were not collected in a randomised fashion); and level 3, evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. These recommendations then underwent a panel vote, with consensus declared if 100% of the group agreed to a recommendation. After the workshop, a draft document was distributed among the members of the group, with 4 weeks allowed for responses, all of which were collated to finalise the document of consensus recommendations.

The key findings of this workshop are summarised in panel 1. The definitions of congenital cytomegalovirus infection and disease used in this document were those previously used,⁶ with minor adjustments based on discussions of the group (panel 2), to provide retrospective comparability. The final document was reviewed by all authors, by other internationally recognised authors with obstetric, paediatric, infectious diseases, and virology expertise who were unable to participate in the original workshop or publication, and was sent to all members of the Australian and New Zealand Paediatric Infectious Diseases Group for comment.

Evidence and recommendations

Screening for maternal cytomegalovirus infection

Universal cytomegalovirus screening of pregnant women is not recommended by national public health bodies in any country. However, selective testing of pregnant

Panel 1: Key findings and recommendations

Diagnosis

- If maternal primary cytomegalovirus infection is diagnosed or fetal infection is suspected, referral to a clinician with experience in the diagnosis and management of fetal cytomegalovirus infection is recommended.
- Cytomegalovirus serology tests (cytomegalovirus-specific IgG, IgM, and IgG avidity) should be offered when a pregnant woman develops an illness with influenza-like symptoms (typically fever, fatigue, and headache) not attributable to another specific infection, or when imaging findings (ultrasound or the less frequently used MRI) are suggestive of fetal cytomegalovirus infection.
- For cytomegalovirus-seronegative pregnant women, the diagnostic assessment of primary cytomegalovirus infection should include the detection of cytomegalovirus-specific IgG in serum. When the immune status before pregnancy is unknown, the diagnosis of maternal primary cytomegalovirus infection should be on the basis of the detection of both cytomegalovirus IgM and cytomegalovirus IgG antibodies of low-to-moderate avidity.
- A confirmed diagnosis of fetal cytomegalovirus infection can be made after 20–21 weeks of gestation, and at least 6 weeks from the time of maternal infection, by testing amniotic fluid for cytomegalovirus using nucleic acid test assays such as real-time PCR.
- The diagnosis of congenital cytomegalovirus-infected neonates should include real-time PCR of saliva, urine, or both within the first 3 weeks of life, with saliva as the preferred sample.
- Consideration should be given to universal neonatal cytomegalovirus screening to enable early detection of congenital cytomegalovirus-infected infants allowing early intervention for sensorineural hearing loss and developmental delay where appropriate. However, universal screening of all pregnant women to assist in the diagnosis of primary cytomegalovirus infection is currently not recommended.

Prevention

- All pregnant women and health-care providers should be educated about congenital cytomegalovirus infection and preventive measures.
- Cytomegalovirus hyperimmunoglobulin should not be routinely administered to pregnant women with primary cytomegalovirus infection to prevent fetal cytomegalovirus infection.
- Routine antiviral therapy to prevent congenital cytomegalovirus infection during pregnancy is not recommended.

Therapy

- Cytomegalovirus hyperimmunoglobulin treatment should not be routinely administered for fetal cytomegalovirus infection.
- Routine antiviral therapy to treat fetal cytomegalovirus infection during pregnancy is not recommended.
- Valganciclovir treatment for 6 months is only recommended for congenitally infected neonates with moderately to severely symptomatic disease.
- Antiviral therapy should not be administered to neonates with asymptomatic congenital cytomegalovirus infections.
- Antiviral therapy is not routinely recommended for asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss, or for neonates with mildly symptomatic congenital cytomegalovirus infection.

women is done as part of population-based studies, and by some clinicians independently of formal screening programmes in parts of Europe, Israel, Australia, and the USA.^{15–17}

One proposed approach to reducing the incidence of congenital cytomegalovirus infection is universal cytomegalovirus screening of pregnant women to assist diagnosis of primary infection.¹⁸ Primary maternal cytomegalovirus infection has been associated with the highest individual risk of in-utero transmission and clinical consequences for the fetus.^{2,19} Several studies have used serological screening (cytomegalovirus-specific IgG testing) to identify those seronegative pregnant women with a higher risk of seroconversion.^{20–27} The results of studies showed that providing these women with advice regarding appropriate precautions to reduce their risk might prevent primary maternal cytomegalovirus infection. However, universal screening of all pregnant women to identify those who are cytomegalovirus-seronegative is not recommended as part of routine antenatal screening in any country known to the expert group. This arises from health-economical, practical, and jurisdictional reasons, and because congenital cytomegalovirus infection can occur in infants born to women who were cytomegalovirus-seropositive before pregnancy (non-primary maternal cytomegalovirus infection).^{28–33} Estimates suggest that more than two-thirds (about 75%) of all congenital cytomegalovirus cases in the USA (and by implication in other developed countries) occur in infants born to women with non-primary cytomegalovirus infection, presumably due to reactivation of latent virus, reinfection with a new cytomegalovirus strain, or both.^{28,29,34} Additionally, increasing evidence shows that the risk of symptomatic infection, especially that resulting in hearing loss, is similar after maternal primary or non-primary cytomegalovirus infection.^{1,35–40} Data from nationwide registries for congenital cytomegalovirus (such as those in France and the USA) could assist further investigation of this risk and the effect of maternal primary and non-primary cytomegalovirus infection.

The members of the group did not recommend universal screening of pregnant women to diagnose primary cytomegalovirus infection (on the basis of level 2b evidence).

Diagnosis of maternal cytomegalovirus infection

When maternal primary cytomegalovirus infection is clinically suspected, then cytomegalovirus testing can assist in determining the risk of transmission to the fetus. The diagnosis of maternal primary cytomegalovirus infection cannot be made on the basis of clinical symptoms alone, because these are non-specific (typically fever, fatigue, and headache), and 25–50% of mothers have no symptoms.^{29,41–43} When maternal primary cytomegalovirus infection is suspected, diagnostic testing should include detection of de-novo cytomegalovirus-specific IgG in the

serum of previously seronegative pregnant women (seroconversion). In practice, the diagnosis by seroconversion alone is rarely achieved because of the frequent absence of an appropriate baseline cytomegalovirus-specific IgG negative sample. However, comparison with stored pre-pregnancy or early pregnancy serum, where available, is ideal.

When cytomegalovirus immune status before pregnancy is unknown, isolated detection of cytomegalovirus IgG avidity (maturity) or detection of specific IgM antibodies are inadequate single measures to diagnose maternal primary infection.^{43–45} However, the concurrent use of both measures improves identification of primary infection,⁴⁴ with the detection of cytomegalovirus IgM antibodies and low–moderate cytomegalovirus IgG avidity serving as good indicators of recent primary infection.⁴⁶ When these antibodies are detected using validated assays,^{47,48} particularly before 12–16 weeks of gestation, they indicate a higher risk for symptomatic congenital infection.^{44,49}

Consensus recommendations from the group were that cytomegalovirus serology tests (for cytomegalovirus-specific IgG, IgM, and IgG avidity) should be offered when a pregnant woman develops an illness with influenza-like symptoms (typically fever, fatigue, and headache) not attributable to another specific infection, or when imaging findings (ultrasound or MRI⁵⁰) are

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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

Definitions as published by Kimberlin and colleagues,⁶ with minor emendation from discussions of the International Congenital Cytomegalovirus Recommendations Group

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For more on cytomegalovirus
education in Australia see
<http://www.cmv.org.au>

For more on cytomegalovirus
education in the USA see
<http://www.nationalcmv.org>

For more on cytomegalovirus
education in the UK see
<http://www.cmvaction.org.uk>

See Online for appendix

suggestive of fetal cytomegalovirus infection (level 3 evidence). For cytomegalovirus-seronegative pregnant women, the diagnostic assessment of primary cytomegalovirus infection should include the detection of cytomegalovirus-specific IgG in serum (level 2b evidence). When the immune status before pregnancy is unknown, the diagnosis of maternal primary cytomegalovirus infection should be based on the detection of both cytomegalovirus IgM and low–moderate avidity cytomegalovirus IgG antibodies (level 2b evidence).

Prenatal diagnosis of fetal cytomegalovirus infection

Prenatal diagnosis of fetal cytomegalovirus infection can be made via testing of amniotic fluid for cytomegalovirus by amniocentesis, since the virus is excreted into the amniotic fluid through fetal urine. An amniocentesis for cytomegalovirus can be recommended in two situations: when there is maternal primary cytomegalovirus infection during pregnancy, or when there are abnormalities on ultrasound that are compatible with fetal cytomegalovirus infection. There is a low risk of miscarriage associated with amniocentesis, with a population-based study⁵¹ suggesting minimal or no increased rates of miscarriage in women who underwent amniocentesis by a fetal medicine expert. Amniocentesis for cytomegalovirus achieves the best sensitivity after 20–21 weeks' gestation, once fetal urination is well established, and at least 6 weeks from the time of maternal cytomegalovirus infection.⁵² The sensitivity of amniocentesis before 20 weeks can be as low as 45%,⁵³ but it might be warranted in certain circumstances, particularly when ethical and practical difficulties limit management options after 21 weeks of gestation. The use of amniocentesis for the diagnosis of fetal infection has been tested in a number of studies.⁵⁴ The presence of cytomegalovirus can be detected using PCR, other nucleic acid test assays, or virus culture.^{52,55–57} Most studies confirm that nucleic acid test assays such as real-time PCR are the most sensitive methods for the detection of cytomegalovirus in amniotic fluid. If cytomegalovirus is detected in the amniotic fluid, fetal infection is confirmed. Perinatal outcome following confirmed fetal cytomegalovirus infection ranges from healthy asymptomatic livebirth to stillbirth or postnatal survival with severe disability. Several methods have been investigated to predict the perinatal outcome of fetal infection, including prenatal ultrasound and fetal MRI,^{58–64} cytomegalovirus DNA quantification in amniotic fluid^{56–58,65,66} or fetal blood,^{58,67,68} examination of the amniotic fluid peptidome,⁶⁹ fetal blood platelet counts,^{61,70} and IgM levels in fetal blood samples.^{61,67,68,71,72} Although these methods are available now, larger studies are needed to verify their clinical efficacy in predicting clinical outcomes of a cytomegalovirus-infected fetus after birth.

The group recommended that if maternal primary cytomegalovirus infection is diagnosed or fetal infection is suspected, referral to a clinician with experience in prenatal diagnosis and management of fetal cytomegalovirus

infection is recommended (level 3). As noted previously, a confirmed diagnosis of fetal cytomegalovirus infection can be made after 20–21 weeks' gestation, and at least 6 weeks from the time of maternal infection, by testing amniotic fluid for cytomegalovirus using nucleic acid test assays, such as real-time PCR (level 2b evidence).

Prevention of maternal cytomegalovirus infection during pregnancy

Prevention of maternal cytomegalovirus infection through vaccination has been tested in a phase 2 trial of a recombinant glycoprotein B vaccine in seronegative women, which showed 50% efficacy for maternal seroconversion.⁷³ However, waning immunity was observed, which questions the long-term efficacy of this vaccine formulation. A randomised, double-blind, placebo-controlled phase 2 study testing this glycoprotein B vaccine in cytomegalovirus-negative adolescent girls produced similar results, with 45% efficacy for seroconversion after two doses.⁷⁴ Several cytomegalovirus vaccines are under development and completion of several clinical trials is anticipated between 2017 and 2019 (ClinicalTrials.gov trial registry numbers NCT02594566, NCT02396134, NCT02506933, and NCT01877655). A particular risk factor for maternal cytomegalovirus infection is close contact with children younger than 2 years of age, since cytomegalovirus excretion in saliva and urine can continue for months or years in young children.^{24–27} Children can shed high levels of cytomegalovirus, and frequently acquire cytomegalovirus from other children, including those attending daycare.^{24,75} Approximately 30% of mothers with a cytomegalovirus-infected child younger than 2 years old at day care seroconvert within 1 year of their child attending day care.²⁴ Therefore, hygienic and behavioural interventions (panel 3) have been investigated to prevent cytomegalovirus infection in pregnant women.

Results from two cluster randomised trials^{20,23} and one single-group study²² showed that behavioural measures that reduce contact with bodily fluids from young children reduced cytomegalovirus seroconversion in pregnant women. These trials probably have selection and detection biases,⁷⁹ and control data are missing in the single-group study. However, a more recent interventional and observational controlled trial²¹ has provided further evidence that a prevention strategy based on provision of information to pregnant women at risk for cytomegalovirus infection is effective. In a 2015 study by Revello and colleagues,²¹ pregnant women in the prospective intervention group received the same information and behavioural instructions as mothers in the 1996 study by Adler and colleagues,²⁰ with the exception of using gloves and avoiding co-sleeping with the infant. Seroconversion occurred in four (1.2%) of 331 pregnant women in the intervention group, at a lower rate compared with 24 (7.6%) of 315 in the comparator, non-instructed group (absolute risk reduction [Δ]=6.4% [95% CI 3.2–9.6]; $p<0.001$ [exact value not reported]).²¹

Adler and colleagues²³ described that all (n=106) mothers reported these behavioural interventions as being done easily, indicating that this approach was not difficult to implement. However, results from seven studies^{80–86} have shown that a large proportion (61.0% to 87.5%) of pregnant women are unaware and uninformed about congenital cytomegalovirus infection, and the results of four studies^{87–90} suggested that health-care providers, such as doctors, obstetricians, and midwives, do not possess sufficient knowledge of this infection.

The consensus recommendations from the group were that health-care providers, including midwives, obstetricians, and paediatricians, should be educated about congenital cytomegalovirus infection and preventive measures (panel 3; level 2b evidence). Given the potential risk of congenital cytomegalovirus in all pregnancies, albeit at low risk in the individual cytomegalovirus-seropositive woman,^{1,19,91} all pregnant women should be educated about congenital cytomegalovirus infections and preventive measures (level 2b evidence). The group also concluded that research is needed to identify the education content and methods that are most effective in preventing cytomegalovirus infection in pregnant women. Educational resources should be developed and used locally, and preferably shared online.

Prevention of vertical transmission of cytomegalovirus infection

Passive immunisation with cytomegalovirus hyperimmunoglobulin has been investigated as a potential means to prevent cytomegalovirus transmission to the fetus in pregnant women with primary cytomegalovirus infection. Four studies evaluated the efficacy of hyperimmunoglobulin treatment to prevent fetal cytomegalovirus infection. Although a non-randomised controlled phase 1 and 2 study,⁹² a double-blinded, randomised placebo-controlled study,⁹³ and two observational studies^{94,95} report some evidence of benefit and a trend towards efficacy of hyperimmunoglobulin, the results from these studies are inconsistent and not definitive, which could be related to suboptimal doses used or the application interval.⁹⁶ No serious adverse events due to hyperimmunoglobulin therapy were reported in the three non-randomised studies.^{92,94,95} Results from a randomised trial⁹³ showed no significant benefit for treatment, but reported obstetric complications (preterm delivery, preeclampsia, and fetal growth restriction) in seven (13%) of 53 women in the group receiving hyperimmunoglobulin, compared with one (2%) of 51 women in the placebo group (p=0.06). At least one randomised clinical trial is underway (NCT01376778), which might clarify the role for prophylactic hyperimmunoglobulin treatment.

The benefits and harms of antiviral drugs used to prevent vertical transmission in pregnant women are being studied in one randomised, phase 2, double-blinded clinical trial that is planned to evaluate the efficacy of valaciclovir to prevent vertical transmission of

Panel 3: Hygiene precautions and behavioural interventions that could prevent cytomegalovirus infection in pregnant women, based on published findings^{20–23}

- Do not share food, drinks, or utensils used by young children
- Do not put a child's dummy/soother/pacifier in your mouth
- Avoid contact with saliva when kissing a child
- Thoroughly wash hands with soap and water for 15–20 seconds, especially after changing nappies/diapers, feeding a young child, or wiping a young child's nose or saliva
- Other precautions that can be considered, but are likely to less frequently prevent infection, include clean toys, countertops, and other surfaces that come into contact with children's urine or saliva, and not sharing a toothbrush with a young child^{76–78}

cytomegalovirus after maternal primary infection during pregnancy (NCT02351102). The results of this trial might provide much-needed evidence for antiviral safety and efficacy in the prevention of congenital cytomegalovirus acquisition during pregnancy.

The group recommended that hyperimmunoglobulin should not be routinely administered to pregnant women with primary cytomegalovirus infection for prevention of congenital cytomegalovirus, on the basis of insufficient evidence (level 2c evidence). If such patients are treated, their data should be tracked to contribute to understanding of the safety of this approach. Routine antiviral therapy to prevent congenital cytomegalovirus infection during pregnancy is also not recommended, on the basis of insufficient current evidence (level 3 evidence).

Treatment of the cytomegalovirus-infected fetus during pregnancy

Treatment options for fetal cytomegalovirus infection during pregnancy to prevent or reduce the severity of fetal cytomegalovirus-associated symptoms are limited. Management options of the infected fetus include therapy with cytomegalovirus hyperimmunoglobulin or antiviral drugs. However, because there is insufficient evidence for the efficacy of antiviral drugs, they should currently all be regarded as investigational, and therefore should not be used outside of a clinical trial setting.⁹⁷

Evidence for potential efficacy of hyperimmunoglobulin treatment to reduce disease from congenital cytomegalovirus has been reported in four prospective and two retrospective studies, each treating between three and 31 pregnant women diagnosed prenatally with congenital cytomegalovirus infection.^{92,94,98–101} Nigro and colleagues⁹² observed that pregnant women with cytomegalovirus-positive amniotic fluid, treated with 200 U/kg of hyperimmunoglobulin intravenously, gave birth to infants with a reduced rate of symptomatic disease (one [3%] of 31) compared with women who declined hyperimmunoglobulin treatment (seven [50%] of 14). A partly

randomised case-control study by Visentin and colleagues⁹⁹ reported that fewer infants had poor outcomes (such as sensorineural hearing loss) at 1 year of age when the mother was treated with 200 U/kg hyperimmunoglobulin intravenously at 20–24 weeks' gestation (four of 31 [13%]), compared with infants from untreated mothers (16 of 37 [43%]). However, the findings of these studies are not definitive because of the small number of women treated with hyperimmunoglobulin, and other methodological issues, as reviewed previously.⁴

Antiviral drugs such as ganciclovir, the oral pro-drug valganciclovir, foscarnet, and cidofovir have been used extensively to treat cytomegalovirus in immunocompromised patients. However, foscarnet and cidofovir are unsuitable therapeutics during pregnancy because of nephrotoxicity and potential carcinogenicity, with minimal safety or efficacy data in pregnancy.¹⁰² Additionally, there are limited safety and efficacy data for ganciclovir and valganciclovir in pregnancy, with four case reports describing ganciclovir use in pregnancy for transplant recipients and in a woman with HIV/AIDS without teratogenic effects.^{103–106} Ganciclovir is not recommended for use in pregnancy because of reported risks of gonadal dysgenesis in animal studies, and the inability to monitor for fetal toxicities, including neutropenia. Ganciclovir, valganciclovir, foscarnet, and cidofovir are currently classified by the US Food and Drug Administration (FDA) as category C.

Aciclovir and the oral pro-drug valaciclovir have been used as prophylaxis for cytomegalovirus infection in transplant recipients and patients with HIV/AIDS.¹⁰⁷ The premise for use in pregnancy is that although they have weak activity against cytomegalovirus, they have very low rates of adverse effects in pregnancy on the basis of two small observational studies and one large registry-based study managed by the drug manufacturer.^{108–110} A subsequent registry-based study provided additional evidence that aciclovir, valaciclovir, and famciclovir are not teratogenic.¹¹¹ Results from a pilot observational study by Jacquemard and colleagues⁹⁷ showed that oral valaciclovir was tolerated by pregnant women with confirmed fetal cytomegalovirus infection and might decrease viral load in fetal blood, without clear improvement in fetal outcome, possibly due to the small sample size or lack of efficacy. One non-randomised, single group assignment phase 2 clinical trial evaluated the efficacy of valaciclovir in treatment of confirmed fetal cytomegalovirus infection in 41 women with 43 moderately symptomatic congenital cytomegalovirus-infected fetuses.¹¹² Mothers were treated with 8 g/day oral valaciclovir, analysed using Simon's optimal two-stage design, whereby valaciclovir was assumed to have a positive effect if at least 31 of 43 neonates were asymptomatic at birth. In total, 34 of 43 neonates were born asymptomatic, which suggests efficacy of valaciclovir treatment, although these findings are not conclusive due to the design of the study, and the small number of

valaciclovir-treated women to date. Further evaluation of the use of aciclovir, valaciclovir, and famciclovir (FDA category B) is of interest. However, they cannot be recommended routinely because current data on antiviral efficacy and safety profiles during pregnancy are limited.

The consensus recommendations from the group were that antenatal cytomegalovirus hyperimmunoglobulin should not be routinely recommended as therapy for fetal cytomegalovirus infection (level 2b evidence). If such patients are treated, their data should be tracked to contribute to the overall understanding of the safety of such an approach. Routine antiviral therapy to prevent or treat congenital cytomegalovirus infection during pregnancy is also not recommended, on the basis of insufficient evidence for safety and effectiveness of antiviral drugs on clinical outcomes (level 2c evidence).

Neonatal cytomegalovirus screening

Congenital cytomegalovirus-infected neonates might be asymptomatic or symptomatic at birth (panel 2). The severity of long-term adverse outcomes varies substantially, from minimal deficits with unilateral sensorineural hearing loss, to major neurodevelopmental complications and death for a minority of neonates. Universal newborn hearing screening, which is now done in many developed countries, successfully detects many neonates with congenital hearing impairment at birth. However, nearly 10% of initially asymptomatic cytomegalovirus-infected neonates later develop hearing loss,¹¹³ at which point the capacity for cytomegalovirus diagnosis and opportunities for early intervention are lost or substantially reduced.

Studies reviewed by Cannon and colleagues¹¹⁴ reported evidence that cytomegalovirus screening of all neonates could significantly improve the outcome of those infected with cytomegalovirus with delayed hearing loss. It is well established that infants with an early diagnosis of hearing loss develop better receptive and expressive language¹¹⁵ with improved cognitive function than do infants with a later diagnosis. Therefore, targeted cytomegalovirus screening of newborn infants (eg, testing of infants who fail newborn hearing screening) and cytomegalovirus screening of all neonates has been the focus of investigations over the past few years.^{116–122} A 2015 cost-benefit analysis reported a net public benefit for targeted cytomegalovirus testing of neonates with hearing loss.¹¹⁸ A separate cost-effectiveness analysis based on data derived from large prospective cohorts reported that both universal and targeted newborn cytomegalovirus screening were cost-saving.¹¹⁹ Additional prospective studies and cost-effectiveness studies would further inform any recommendation regarding universal or targeted cytomegalovirus testing of neonates.

The group recommended that consideration should be given to universal neonatal cytomegalovirus screening to enable early detection of congenital cytomegalovirus-infected infants, facilitating early detection and intervention for sensorineural hearing loss and

developmental delay where appropriate (level 2b evidence).

Diagnosis of the cytomegalovirus infected neonate

A large prospective study reported that real-time PCR analysis of dried blood spots had low sensitivity for newborn cytomegalovirus testing.¹²³ Results from a 2015 study¹²⁴ that included testing of a small number of dried blood spots spiked with blood specimens from transplant recipients showed that DNA yield from dried blood spots was improved by using different extraction methods; however, the sensitivity of these methods in identifying infants with congenital cytomegalovirus has not been evaluated in screening of unselected neonates. Yamamoto and colleagues¹²⁵ showed that both urine and saliva are reliable specimens for neonatal cytomegalovirus screening using PCR, and a prospective multicentre study reported that real-time PCR of saliva showed high sensitivity (>97%) and specificity (99%) for detecting congenital cytomegalovirus infection.¹²⁶ Similar to other newborn screening assays, a positive cytomegalovirus screening result should be confirmed by testing a subsequent sample (either saliva or urine) collected within the first 3 weeks of life. Testing for cytomegalovirus in saliva, urine, or both, as early as possible, appears optimal since diagnostic tests do not distinguish congenital from postnatal cytomegalovirus infection in newborn babies older than 3 weeks of age, who might have acquired the virus at birth or through breastmilk.^{127,128} Obtaining a saliva sample at least 1 hour after breastfeeding to avoid potential contamination with cytomegalovirus from breastmilk has been practised and described.¹²⁹

The consensus recommendations from the group were that the diagnosis of congenital cytomegalovirus infection in neonates should include real-time PCR of saliva, urine, or both, as soon as possible after birth but within the first 3 weeks of life, with saliva as the preferred sample (level 2b evidence).

Treatment of congenitally cytomegalovirus infected neonates

Because of noteworthy toxicities of cytomegalovirus antivirals, consideration of their use in congenitally infected neonates must balance known risks (such as neutropenia) and possible risks (eg, gonadal dysgenesis, carcinogenicity) with potential benefits. Among currently available antivirals, intravenous ganciclovir and oral valganciclovir have been studied for the treatment of infants with congenital cytomegalovirus infection. Results from a phase 2 trial published in 1997, comparing 8 mg/kg and 12 mg/kg daily doses for 6 weeks, showed that ganciclovir treatment significantly improved or stabilised hearing in five (16%) of 30 infected infants with a daily dose of 12 mg/kg.¹³⁰ A subsequent phase 3 randomised clinical trial assessed the outcome of ganciclovir treatment in symptomatic

congenital cytomegalovirus-infected neonates with neurological deficits.¹³¹ This study had a large number of children who could not be evaluated for the primary endpoint because of loss to follow-up, but still found that ganciclovir treatment might have prevented hearing deterioration at 6 months and less than 1 year of life. However, this study also observed an association of ganciclovir treatment with neutropenia. Additional analyses of this trial suggested that ganciclovir might also improve neurodevelopmental outcome.¹³² Two case reports and two pilot observational studies provided additional evidence that ganciclovir treatment improves or prevents hearing loss in infants with symptomatic congenital cytomegalovirus infection.^{133–136}

Evidence that oral valganciclovir improves or preserves hearing in infants with symptomatic congenital cytomegalovirus infection has been reported in three case studies.^{117,137,138} More recently, results from a randomised placebo-controlled trial showed statistically significant benefit of valganciclovir treatment in symptomatic neonates.⁶ All symptomatic cytomegalovirus-infected neonates received valganciclovir for

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 life⁶

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 months⁶

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

Search strategy and selection criteria

We published a systematic review on this topic before the meeting, which informed the consensus discussions at the April 2015 conference. Additionally, before this conference, additional relevant scientific literature was identified through searches of MEDLINE, Embase and ClinicalTrials.gov for articles published from Jan 1, 1968 to Feb 28, 2015, and updated after the meeting to Oct 31, 2016. Search terms included “congenital cytomegalovirus” and “treatment”, “screening”, “therapeutic”, “prevention”, “diagnosis”, “prophylaxis”, “intervention”, “antiviral”, and “hyperimmune globulin”. Studies were eligible for inclusion if they were of human pregnant women or neonates; were randomised controlled trials, a controlled trial, observational study, or case series; the full text was available; and the report was in English. Studies were excluded if they were review articles, abstracts, letters, or conference proceedings. Articles resulting from these searches and relevant references cited in those articles were reviewed and graded using the Oxford Centre for Evidence Based Medicine (OCEBM) levels of evidence (see Methods).

6 weeks, and were then randomised to placebo or valganciclovir treatment. Neonates receiving 6 months of valganciclovir had a 2.6-times increased likelihood of improved total hearing at 24 months than those who received only 6 weeks of valganciclovir treatment. Neurodevelopmental outcomes were improved with longer duration of therapy. Valganciclovir treatment was associated with neutropenia, although the incidence was markedly lower than previously observed with intravenous ganciclovir.⁶ As described in panel 4, valganciclovir treatment for 6 months is recommended for congenitally infected neonates with moderately to severely symptomatic disease.

Currently, there is no definitive evidence about the potential benefit of antivirals for treatment of mildly symptomatic or asymptomatic infants with isolated sensorineural hearing loss. Although isolated sensorineural hearing loss was an eligibility criterion,⁶ only one infant (randomised to the 6 week group) in this category enrolled in the study,⁶ meaning the benefit of treating these infants is unclear. One non-randomised, single-blind clinical trial is investigating whether early treatment with oral valganciclovir of infants up to 12 weeks of age with congenital cytomegalovirus infection and sensorineural hearing loss can prevent progression of hearing loss (NCT02005822).

Evidence from randomised trials to inform the initiation of antiviral therapy beyond the first month of life is absent. The Collaborative Antiviral Study Group is, as of 2016, recruiting participants for a phase 2 randomised, controlled trial of valganciclovir therapy in children up to 4 years of age with congenital cytomegalovirus infection and hearing loss (NCT01649869). A randomised efficacy study is planned to evaluate the

benefit of antiviral treatment with valganciclovir on hearing and balance in children aged 6 months to 12 years with congenital cytomegalovirus (NCT02606266), which might provide evidence to inform treatment options.

The group recommended that valganciclovir treatment for 6 months should only be for congenitally infected neonates with moderately to severely symptomatic disease as defined in panel 2 (level 1 evidence). Neonates with asymptomatic congenital cytomegalovirus infection should not be given antiviral therapy (level 3 evidence). Neonates with mildly symptomatic congenital cytomegalovirus infection should not routinely be given antiviral therapy (level 3 evidence). If such patients are treated on a case-by-case basis, their data should be accumulated to contribute to the overall understanding of the safety of such an approach. Antiviral therapy is not routinely recommended for congenital cytomegalovirus infection with isolated sensorineural hearing loss and otherwise asymptomatic, based on insufficient evidence (level 3 evidence). If such patients are treated, their data should be tracked to contribute to the overall understanding of the safety and efficacy of such an approach.

Conclusions

This Review summarises current data on the efficacy of prevention, the significant improvements in diagnostic capacity globally (particularly in molecular detection and characterisation of infection), and data showing utility of antiviral therapy in some infected neonates. These, and other published data, can now be used to inform jurisdictional policy, and practice, in reducing the global impact of congenital cytomegalovirus.

Contributors

All authors contributed to the discussions leading to the consensus document, and to review of the document during drafting. WDR and WvZ wrote the first draft. WDR, WvZ, SA, SBB, LG, MLG, GJH, WR, CAJ, DWK, PP, LH, AWS, SA, STH, MRS, TL, and KBF contributed to editing and writing of subsequent drafts. All authors approved the final version of the manuscript.

Declaration of interests

KBF reports personal fees from Merck, Sharp & Dohme Corp, outside the submitted work. DWK reports grants from NIH during the conduct of the study that fund research on congenital cytomegalovirus, but these grants did not directly contribute to this work; DWK also reports grants from Alios and GSK, outside the submitted work, for participation in clinical trials of respiratory syncytial virus and influenza, with all monies going to his university. WDR, SBB, SA, KD, TL, SD, LG, MLG, JG, STH, GJH, LH, CAJ, PP, MRS, AWS, and WvZ declare no competing interests.

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