Congenital Cytomegalovirus: A European expert consensus statement on diagnosis and management.

<u>**Introduction**</u>

Congenital CMV (cCMV) is the most common congenital infection in the developed world. Reported prevalence varies between cohorts but is approximately 7 per 1000 births.[1] About half of CMV-infected babies with clinically detectable disease at birth are destined to have significant impairments in their development and cCMV infection is implicated in around 25% of all children with sensorineural hearing loss (SNHL). [1,2] Meta-analysis shows that although long-term sequelae, especially SNHL, are more common in those with clinically detectable disease at birth they are also found in 13% of those without clinical features attributable to CMV on initial examination.[1]

Despite the significant long-term impact of cCMV infection there is limited evidence on which to base many treatment decisions in clinical practice. In an era of enhanced antenatal screening fetuses and newborns are increasingly tested for CMV following abnormalities detected during routine ultrasonography or maternal serology. Furthermore, otherwise "asymptomatic", congenitally CMV-infected, newborns are being identified following detection of SNHL through newborn hearing screening programs (NHSP).   Babies with cCMV now presenting to pediatricians therefore differ from those primarily included in clinical trials of treatment reported in the literature.

A symposium was convened during the 2015 conference of the European Society of Paediatric Infectious Diseases (ESPID) to discuss the current management of cCMV. In

attendance were clinicians from throughout Europe, many of whom are involved in policy for cCMV for their region/country.

This paper summarizes the discussions at this meeting alongside the evidence informing them. A balanced perspective of the controversies in this area is presented and areas of consensus highlighted. Finally where evidence is lacking suggestions are made for future research efforts to address areas of unmet medical need.

The authors acknowledge the coexisting need for studies on the management of babies with symptoms consistent with cCMV, but in whom this diagnosis cannot be firmly established, and of those with symptomatic postnatal CMV infection; this paper does not, however, address these groups.

The internationally accepted GRADE system for evaluating evidence has been used to illustrate points where relevant (Table 1).[3]

Definitions of Symptomatic disease

Classically cCMV infection is categorized as "symptomatic" or "asymptomatic" at birth. Differing definitions and opinions on what constitutes "symptomatic" CMV infection, however, makes interpreting the literature challenging. Indeed, some of the largest cohort studies include babies with SNHL at birth in the group described as being "asymptomatic" since no "clinically apparent disease" was detectable during newborn examination.[4] In modern healthcare systems, whereby cCMV is increasingly detected through screening for other conditions, alongside increased accessibility of investigations, such as MRI, the traditional dichotomy between clinically "apparent" and "inapparent" disease is becoming less meaningful. Table 2 summarizes the accepted clinical features of cCMV disease with

those symptoms detectable on newborn examination listed separately to those detectable only if specific investigations are conducted, for example, when cCMV is already suspected.[5-8]

Full consensus within this expert group was that:-

1) For the purposes of research and publication newborns identified as having cCMV disease following abnormal clinical examination at birth (such as microcephaly, small for gestational age (SGA), widespread petechiae, hepatosplenomegaly) should be differentiated from those babies identified through screening or investigation for other disorders e.g. those tested for CMV following known/likely maternal infection or abnormal newborn hearing screening. This differentiation would allow for more accurate assessment of the prognostic value of individual manifestations of "symptomatic" disease on longer-term outcomes as already shown in other publications.[9]

2) "Symptomatic" cCMV should be considered as 'severe', 'moderate' or 'mild' disease.

   a. 'Mild' disease includes those with isolated (one, or two at most), otherwise clinically insignificant or transient findings such as, petechiae, mild hepatomegaly or splenomegaly or biochemical/hematological abnormalities (such as thrombocytopenia, anemia, leukopenia, borderline raised liver enzyme abnormalities or conjugated hyperbilirubinemia) or SGA (defined as weight for gestational age < -2 standard deviations (SD)) without microcephaly.

   b. 'Severe' disease includes those with CNS involvement (abnormal neurological or ophthalmological examination, microcephaly and/or neuroimaging

consistent with cCMV disease (such as calcifications, moderate to severe ventriculomegaly, cysts, white matter changes, cerebral or cerebellar hypoplasia, hippocampal dysplasia, neuronal migration abnormalities))[10] and/or with life-threatening disease.

The majority agreed that:-

2b.   'Severe' disease also includes babies with evidence of severe single organ disease (including those with clinically significant liver enzyme abnormalities (liver 'failure') and marked hepatosplenomegaly) and/or those with significant multi-organ involvement. Babies with transient or otherwise clinically insignificant abnormalities (i.e. the babies are not 'sick') that resolve spontaneously over a few weeks are not included in this group even if these abnormalities are multiple.

2c.   A further group exists that may be considered to have 'moderate' disease. This group is heterogeneous and includes, for example, those with persistent (e.g. more than 2 weeks duration) abnormalities of hematological/biochemical indices and/or more than 2 'mild' disease manifestations (as listed above). Due to lack of evidence full consensus could not be reached on how to approach this group and treatment decisions are currently made on a case by case basis. Development of a validated clinical scoring system for disease severity at presentation and risk of sequelae would be beneficial for both counselling parents and informing treatment decisions.

3) Defining CNS involvement

a. It remains uncertain whether some, non-specific findings detected on cranial ultrasound (CrUSS) and MRI (particularly isolated lenticulostriatal vasculopathy (LSV)) constitute clinically significant CNS disease. LSV has been detected in 0.4%-5.8% of all neonates undergoing an ultrasound and only 5% has been associated with cCMV.[11;12] Some have suggested isolated LSV as a marker of risk for SNHL.[11] Others have found only more extensive neuroimaging abnormalities to be of prognostic value.[13;14] The majority at this meeting would not consider LSV in isolation to be a notable CNS manifestation of disease. It is suggested that neuro-radiological abnormalities not known to be clearly associated with CMV disease and adverse outcomes are discussed with a suitably experienced neuro-radiologist, particularly if the results of these discussions might influence treatment decisions.

b. The exact pathophysiology of SNHL is not clear but is likely secondary to infection and degradation of sensory structures within the inner ear [15;16]. It is therefore debated whether isolated SNHL should truly be considered a CNS-manifestation of infection and, as a consequence, whether such children should be considered comparable to those with CNS disease included in published clinical trials. No studies have addressed this specific population, but a non-randomized cohort study observing the effects of valganciclovir in isolated SNHL is in progress (clinicaltrials.gov NCT02005822). The majority of experts at this meeting would categorize babies with isolated, confirmed, SNHL in the 'severe'/CNS group since bilateral SNHL is not only associated with likely long-term impairments but was also included in the criteria for

recruitment in the only randomized controlled trials (RCTs) in cCMV.

However, consensus was not reached because the spectrum of hearing loss is wide and treatment of isolated SNHL has not been evaluated in any RCTs.

When should testing for congenital CMV be considered?

Indications for testing for cCMV are based on the presence of one or more of the most frequently observed clinical features (Table 3).[17] Unfortunately predictive values for each of these features are not available.

Full consensus within this expert group was that testing for cCMV should be performed in:-

1) Fetuses with ultrasound/MRI imaging consistent with cCMV disease (by appropriately timed antenatal testing of amniotic fluid). [18](Quality C, Level 1)

2) Newborns where there is a maternal history of suspected primary CMV infection during pregnancy. If antenatal testing of amniotic fluid has been conducted it is suggested that cCMV infection should still be confirmed at birth since both false positive and negative results have been reported.[18] (Quality C, Level 1)

3) Newborns with signs/symptoms consistent with cCMV disease (see Table 2) (including those with findings consistent with cCMV on antenatal imaging). (Quality B, Strength 1)

4) Children with confirmed SNHL.[16] Systems need to be established to ensure testing for cCMV occurs, where possible, in the first 21 days of life since dried blood spot (DBS) are not always readily available for testing (see below). (Quality B, Strength 1)

The majority agreed that:-

5) Newborns that are small for gestational age (SGA) should not routinely be tested.

Studies in SGA newborns have shown the prevalence of cCMV to be 0-5.2%.[19-22]

However, the majority of studies report a prevalence of 1.4-1.8%, which is not

significantly higher than the prevalence of cCMV in the general population.

Therefore evidence is insufficient to justify screening all newborns with isolated

SGA for cCMV. None of these studies distinguish between asymmetrical (with

normal head circumference) and symmetrical SGA but, when head circumference

was mentioned, most SGA babies with cCMV had microcephaly (head

circumference < -2 SD).[21;22] Because of this, and the poor prognostic outcome of

children with cCMV and microcephaly, many present at this meeting test those

babies with symmetrical SGA but not those with preserved head

growth.[14](Quality C, Strength 2)

6) Prematurity.

Evidence that premature babies have a higher incidence of cCMV is limited.[20;23]

Testing extremely premature babies (<28 weeks gestational age) at birth does,

however, assist in differentiating between congenital and postnatal infection.

This may be very helpful in guiding the management of these babies that are

particularly vulnerable to symptomatic postnatal infection. However, consensus

was not reached regarding practice in this area with cost being a factor amongst

other considerations.[24] (Quality C, Strength 2)

7) Testing of babies born to mothers who are known to be CMV seropositive at the

establishment of pregnancy.

Although maternal non-primary CMV infection is known to be important when considering the overall burden of cCMV disease testing all babies born to these women, particularly in populations with high maternal seroprevalence, is tantamount to universal neonatal screening.[25;26] Identifying women with non-primary CMV who are at highest risk of transmitting infection to their fetus remains elusive. It was agreed that individual case discussion and local policy should therefore dictate practice in this area. Further research is clearly needed.

Laboratory diagnosis of congenital CMV infection

Testing for cCMV using CMV-PCR in urine is highly reliable; sensitivity is 100% and specificity 99%.[27] One negative urine specimen in a neonate is therefore sufficient to exclude infection and repeat sampling is not necessary. After 21 days a urine positive for CMV could be due to CMV acquired postnatally from, for example, passage through the birth canal or through breast milk. As CMV PCR techniques are becoming more sensitive earlier testing, before the age of 14 days, is recommended. [27]

CMV PCR testing of saliva is an alternative and is easy to perform. Samples should be taken immediately before feeding in breastfed newborns, and confirmed with urine, as false positive results have been reported.[28-31]

PCR assay of neonatal DBS can be performed retrospectively in an attempt to diagnose cCMV after the first 21 days of life. Sensitivity is around 84% in meta-analysis but is highly variable depending on the laboratory techniques used and the population being tested; a negative DBS PCR cannot therefore be used to definitively exclude a diagnosis of cCMV.[32]

Full consensus within this expert group was that:-

1) Testing for cCMV should be performed using a single CMV PCR of urine obtained within 21 days of birth but ideally within 14 days of birth (Quality B, Strength 1).

2) Saliva PCR testing can be an alternative but a positive result should be confirmed using urine (Quality B, Strength 1).

3) After the age of 21 days CMV DNA PCR of stored DBS can be used to diagnose cCMV retrospectively; sensitivity is relatively low and a negative test cannot be used to definitively exclude a diagnosis of cCMV (Quality B, Strength 1).

Recommended investigations after confirming a diagnosis of congenital CMV infection

After a virological diagnosis of cCMV infection has been made, additional investigations are necessary to evaluate the extent of disease and to assist with discussions regarding prognosis and treatment.

Full consensus within this expert group was that:-

1) The investigations below are conducted in any baby in whom a diagnosis of cCMV is confirmed looking specifically for the manifestations of disease (Table 2):

- Complete blood count, liver enzymes, (conjugated) bilirubin

- Renal function (before initiating therapy)

- Cranial ultrasound (CrUSS). (Quality A, Strength 1)

- Audiological testing (brainstem evoked response; some screening tests such as otoacoustic emissions are not sufficient to detect central auditory hearing loss in cCMV). (Quality A, Strength 1)

- Ophthalmic assessment. (Quality A, Strength 1)

2) If additional imaging to CrUSS is felt to be indicated then MRI is the preferred

   neuroimaging modality. MRI can be successfully performed in neonates without the

   need for sedation and is therefore both highly sensitive and free of the risks of

   radiological exposure which accompany computed tomography (CT). (Quality C,

   Strength 1)

3) MRI should be performed in babies with clinically detectable neurological findings or

   CrUSS abnormalities.

The majority agreed that:-

4) Cranial MRI should be performed in any babies with cCMV and evidence of CMV

   disease (see table 2). (Quality C, Strength 1).

5) CMV PCR quantitation should be performed in blood at baseline.

   Several studies have shown the absence of CMV viremia to be associated with better

   long-term outcomes and this may be reassuring when evaluating babies without any

   other manifestations of cCMV disease.[33-35] Blood CMV PCR should not, however, be

   used to rule out cCMV infection since paradoxically the absence of CMV in blood has

   been described even in babies with severe cCMV disease.[33;36] (Quality C, Strength 2)

6) Examination of cerebrospinal fluid:

   No current evidence supports examination of cerebrospinal fluid (CSF) as part of

   routine diagnostic work up. Studies have shown detectable CMV DNA in CSF and

   elevated biomarkers such as beta2-microglobulin suggest a poor prognosis.[13;37]

   However, others have shown no additional prognostic value from CSF specimens

   obtained in the clinical setting.[37] Despite this lack of evidence there was a majority

view that, although a possible area of interest for future research, lumbar puncture should not be performed routinely in babies with cCMV infection (Quality C, Strength 1).

Only a minority agreed that:-

7) Cranial MRI should be performed in all CMV-infected babies.

    Although there is no conclusive evidence that performing MRI gives additional prognostic information to CrUSS in those without evidence of CMV disease at birth some argued that it is desirable to conduct MRI in all cCMV infected babies since additional pathology can be identified as compared to CrUSS.[38-40] (Quality D, Strength 2)

Treatment

No antiviral drugs are currently licensed for the treatment of cCMV. Although many case reports and cohort studies have reported on treatment for cCMV there are results from only 2 randomized controlled trials (RCTs).[7;41-44] The first of these studies evaluated 6 weeks' intravenous ganciclovir treatment in neonates (< 1 month of age), gestational age ≥32 weeks, and clinically apparent disease in the newborn period with evidence of CNS disease (including microcephaly, intracranial calcification, abnormal CSF indices for age, hearing deficit and chorioretinitis).[7] Improved hearing and neurodevelopmental outcomes were shown but there was significant loss to follow-up.[7;44] A more recent trial compared 6 weeks to 6 months treatment with oral valganciclovir and included babies with any evidence of symptomatic (including non-CNS) cCMV disease.[41] Few babies enrolled, however, had isolated, mild clinical features and none in the 6 month treatment group had isolated SNHL (D Kimberlin 2015, personal email correspondence, 28 April). A modest benefit on both 2

year hearing and neurodevelopmental outcomes was shown with the 6 month treatment course. The longer treatment course improved likelihood of better hearing outcomes most notably in those with pre-existing CNS involvement. Longer duration of therapy was only statistically significant, however, for 'total ear' hearing as opposed to 'best ear' hearing (which is of greater functional significance) and only once adjusted for baseline CNS involvement. Given the natural resolution of some features of cCMV disease in published cohorts, alongside the delayed onset of hearing loss and fluctuations in SNHL reported in cCMV, it is even more challenging to draw any conclusions regarding treatment effect from uncontrolled studies.[7;16;45]

Clinical trials to date do not, therefore, provide good evidence on which to base treatment decisions for many of the infants presenting to clinicians in everyday clinical practice.

Table 4 provides guidance on which infants should be offered treatment following a risk versus benefit discussion with the family. This table and associated text indicate areas where consensus was reached. Much discussion focused around the treatment of babies with less severe cCMV disease and whether the minimal additional benefit shown in the 6 month treatment course was sufficient to justify such a prolonged course of treatment. Although clinical findings such as SGA and petechiae have been shown in historical cohorts to predict risk for SNHL, more recent re-analysis of data indicates that these findings in isolation are generally associated with disease-free outcomes in babies presenting without other manifestations of symptomatic disease.[9;46] Opinion on the severity, or number, of symptoms justifying antiviral treatment remains divided and it is therefore strongly recommended that clinicians discuss treatment initiation and duration with an expert in this area.

Full consensus within this expert group was that:-

1) Babies with evidence of CNS disease should receive antiviral treatment (Quality A, Strength 1).   Treatment should be preferably for 6 months duration (Quality B, Strength 2)

2) Babies with no clinical/laboratory findings consistent with CMV disease should not receive treatment since no evidence exists to support treatment in this group (Quality D, Strength 1 (not to treat)).

3) Babies with evidence of life-threatening disease or severe single organ disease and/or multi-organ involvement should receive treatment. Although evidence is limited, particularly for life-threatening disease, consensus was that treatment should be considered in this group (Quality B, Strength 1). Consensus could not be reached on duration of treatment in this group.

4) Oral valganciclovir is now the drug of choice. IV ganciclovir should be used in babies unable to tolerate oral drug or where gastrointestinal absorption is uncertain. (Quality A, Strength 1)

The majority agreed that:-

5) Babies with 'mild' cCMV disease (as defined earlier) should not receive treatment. No studies have clearly addressed treatment in this group. Most present at this meeting would not, therefore, treat babies with one or two isolated or transient, clinically insignificant, manifestations of disease. (Quality C, Strength 2)

6) Babies with 'moderate' cCMV disease (as defined earlier). Evidence for treating babies with multiple, but not severe, manifestations of disease (including

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jaundice, hepatosplenomegaly without significantly raised liver enzymes, SGA) is limited. It is therefore recommended that these cases are discussed on a case-by-case basis with a clinician with experience of managing babies with cCMV (such as a pediatric infectious disease specialist)(Quality B, Strength 2).

7) Treatment of isolated SNHL: The majority at this meeting would include SNHL at birth in their indications for treatment since this was in the inclusion criteria for treatment in previous RCT's. Furthermore the main benefit of treatment is in preserving hearing rather than improving hearing once damage exists with good outcomes reported in observational studies (with likely bias).[7;41;47] There was not, however, consensus and it is acknowledged that no RCT's have specifically addressed treatment effect in this group of babies who are usually now identified through NHSPs (Grade C, Strength 1).

8) Drug dose and formulation: Although oral valganciclovir is now first line treatment in most cases it is currently unknown whether valganciclovir reaches target areas as effectively as ganciclovir or, indeed, where drug should be targeted (e.g. CNS or inner ear) since no studies have directly compared the two drugs. In those with severe disease, particularly if absorption is uncertain, IV ganciclovir is therefore preferred by some in early stages of treatment until oral therapy can be reliably tolerated (Quality C, Strength 1).

9) Treatment duration in cases without CNS involvement: In those infants in whom the decision is taken to give antiviral treatment, the majority would treat for 6 months. However, there was not consensus on this point in light of the modest benefit shown for longer treatment courses in the only RCT (Quality B, Strength 2).

10) Treating babies older than 28 days: Treatment of older children has not been addressed in any RCTs although it is acknowledged that the 28 day cut-off is also not evidence-based. Retrospective case series of small numbers of babies treated outside the newborn period have reported good outcomes.[48;49] Babies found to have SNHL following hearing screening at birth often do not have a diagnosis of cCMV confirmed until outside the one month 'window of evidence' for treatment. No consensus was reached on how late it might be acceptable to start treatment in this scenario, and/or in the eventuality of hearing deterioration. Two RCT's are currently evaluating the use of treatment in older children with cCMV and SNHL (clinicaltrials.gov NCT01649869 and NCT02606266) which may clarify this debate. (Evidence for treating outside the newborn period Quality D, Strength 2)

Side effects of antiviral treatment:

Much of the debate around treating less severely affected babies relates to the potential side effects of currently available antiviral drugs.

Significant neutropenia is frequently observed during antiviral treatment in infants. This is reported less commonly with valganciclovir than with ganciclovir (21% compared to 65%).[7;41;44;50] Neutropenia generally occurs during the first month of treatment with no increased toxicity observed after 6 weeks in those randomized to receive 6 months treatment compared to placebo in the only RCT evaluating this.[41] The oral administration of valganciclovir also removes the burden of hospitalization and risk of nosocomial infections and central line complications observed during treatment with ganciclovir. Hepatotoxicity has been reported in up to 30% of those treated with ganciclovir and thrombocytopenia in a

similar proportion.[51] In the most recent study of treatment with valganciclovir deranged liver function was observed but this was neither clinically nor statistically significant when compared to placebo. In all studies abnormal biochemical and hematological parameters resolved following drug discontinuation.

Long-term side effects have not been evaluated in neonates treated with ganciclovir or valganciclovir. Animal studies raise the theoretical risk of gonadotoxicity and carcinogenicity.[52;53] Although this has not been observed in humans to date parents should be counselled about these potential risks, particularly when considering treatment in those groups in which benefit has not been clearly shown. No adverse long-term effects have been documented in a small cohort of babies treated in early neonatal studies and followed up to puberty (NCT00031421 – unpublished data).

Monitoring of babies during treatment:

Table 5 summarizes a proposed monitoring strategy for babies treated for cCMV. These recommendations are based on the safety monitoring and data obtained from the published RCTs.[7;41]

There are no data to support therapeutic drug monitoring (TDM).[54] TDM may, however, have a role when toxicity is a concern (for example in those with impaired renal function) or where there are concerns about treatment response.

Full consensus within this expert group was that:-

1) Where treatment is given babies should have regular weight measurement and safety monitoring to enable appropriate dose adjustment of medication (see Table 5).(Quality A, Strength 1)

2) Where treatment is given parents should be fully counselled about both the known and potential side effects of treatment with current antivirals. (Quality A, Strength 1 for short-term side effects; Long-term no published studies)

3) Although there are theoretical risks of longer term treatment toxicity no large cohorts have been followed up to enable this to be fully evaluated in humans treated during early life. Where possible children receiving antiviral treatment should therefore be entered into a registry to enable ongoing pharmacovigilance.

Only a minority agreed that:-

1) Viral load monitoring: Some centers report monitoring viral load to assist in decisions regarding adequate drug dosing and detection of potential drug resistance; however, most experts at this meeting do not conduct this routinely. Treatment duration is not altered by any viral parameters and rebound of virus after treatment discontinuation is well-documented with no demonstrable association with long-term outcomes. (Quality D, Strength 2) If viral load is checked after discontinuing drug it is suggested that parents are forewarned of the likelihood that virus will be detectable and that this is of unknown significance.

Follow-up

Table 5 summarizes recommended follow-up of babies with cCMV (both treated and untreated).

The recommendation for audiological follow-up is based on long-term surveillance studies of SNHL in cCMV.[4;16] Frequent follow-up is suggested during the first two years of life since this is the period of highest risk for development of cCMV-associated hearing loss and a critical period for language development. Early detection of SNHL during this period is also most likely to improve long-term outcomes. [55] Monitoring should continue into early childhood, however, since deterioration in hearing continues throughout early life.[55] (Quality B, Strength 1)

Neurodevelopmental follow-up is suggested at one and two years of age ideally with formal neurodevelopmental assessment. This is not, however, routinely conducted in all centers and there is no evidence-based benefit in this particular group although early detection of functional impairments is generally agreed to be beneficial.

Ophthalmic follow-up is recommended annually at least until children can talk in those with clinically detectable disease at birth, but not in those without, since deterioration in vision has been observed in this group. (Quality C, Strength 1).[6]

Families should be given information for local/national support groups where these exist (see acknowledgements). Where cCMV parent groups are not easily accessible parents of children with hearing loss may find support from groups for those with hearing impairment.

Recommendations for future pediatric research

1) Clinical trials addressing treatment of those with more 'minor' manifestations of disease/no clinically detectable disease at birth and those with isolated SNHL.

2) Clinical studies of antenatal therapies to decrease transmission of infection and cCMV disease once infection is established.

3) Publications relating to cCMV should make it clear how those included were identified (i.e. babies presenting with clinically detected "symptoms" vs "screened" babies identified through existing antenatal or postnatal screening pathways including hearing screening programs), or following further investigation of abnormalities, such as thrombocytopenia, found incidentally when blood sampling is performed for other indications.

4) Development of clinical prediction models to better categorize severity of disease (CNS vs non-CNS and babies with single vs multiple findings of disease) and associated outcomes to assist counselling of parents.

5) Studies of neuroimaging, particularly MRI, and added-value with regards to predicting long-term impairments particularly in those without clinically detectable disease at birth through studies involving unselected cCMV cohorts.

6) Clinical trials of alternative treatment durations and new anti-CMV therapies when available.

7) Biomarkers. It seems unlikely that a pre-defined duration of treatment will be similarly beneficial in babies with such varying clinical manifestations of disease and likely variable viral burden and host immune function. The development of both host and virological biomarkers of long-term outcomes would greatly enhance design of future RCTs and enable more accurate counselling, and resource allocation.

8) All children receiving treatment should be captured in a registry to enable ongoing pharmacovigilance for any long-term effects of antiviral medication.

9) Identification of risk factors for maternal virus transmission, particularly in those mothers with previous known exposure to CMV (CMV IgG seropositive).

Conclusions

As stated at the outset this article represents the consensus opinion of a group of professionals with a particular interest in cCMV. It highlights that much of our practice is based on limited data, but identifies areas where there is nonetheless consensus amongst experts. Recent publications have shown potential cost effectiveness of screening at birth for cCMV although these calculations are constrained by the issues raised in this article regarding true quantification of benefits of treatment and agreed treatment duration in certain patient groups.[56;57]   It will be challenging to address many of the research questions raised through RCT's given the significant resources and long-term follow-up required alongside potential difficulties in recruiting into such studies when treatment is anecdotally being offered more freely. Collecting accurate data on disease manifestations and treatment outcomes in different patient groups alongside maternal demographics can, however, inform treatment strategies as previously shown very effectively for the management of pediatric HIV. This requires a unified approach to initial diagnostic tests, definitions of symptomatology and follow-up which is currently being addressed by a network of clinicians with an interest in this area through both national and European initiatives such as PENTA-ID, the ECCI and ESPID. It should also be reiterated that this article focusses on postnatal aspects of diagnosis and treatment. There is an associated and simultaneous need for work alongside obstetric and fetal medicine colleagues to address similar uncertainties in aspects of antenatal care. It is hoped that through such

collaborations progress will be made in decreasing infection and disease in fetuses,

newborns and subsequently older children with cCMV.

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Table 1: GRADE OF EVIDENCE (3)

Quality rating	Definition	Example methodology	Depiction in text
Strength of recommendation	Definition		Depiction in text

Strength of recommendations is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resource use

Table 2: Possible signs and symptoms in children with congenital CMV [5-8]

CLINICALLY DETECTABLE SYMPTOMS/SIGNS

ABNORMALITIES DETECTED INCIDENTALLY OR THROUGH SUBSEQUENT INVESTIGATION/SPECIALIST EXAMINATION

<u>Table 3:</u> Clinical features that should lead to testing for congenital CMV

Neonates

Older children

Features in bold are those where there is consensus for testing
Features in italics, are those that might lead to testing in individual circumstances and depending on local practice.

[1] Seek expert clinical virology advice for interpretation of virological investigations in pregnancy

[2] Baseline screening, to differentiate between congenital and postnatal CMV infection is helpful for extremely premature infants (<28 weeks gestational age), who are at increased risk of symptomatic postnatal infection.

Table 4: Summary of treatment recommendations

Disease manifestation	Treatment recommendation	Level of evidence

Table 5: **Monitoring and follow up according to treatment status**

No treatment offered   **Treatment offered**