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# Evidence based management guidelines for the detection and treatment of congenital CMV

S. Kadambari [a,*], E.J. Williams [b,1], S. Luck [c], P.D. Griffiths [c], M. Sharland [a]

[a] Paediatric Infectious Diseases Unit, St George's University of London, Cranmer Terrace, London SW17 0RE, United Kingdom
[b] Royal Victoria Infirmary Hospital, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom
[c] University College London, Division of Infection and Immunity, Royal Free Hospital, Rowland Hill Street, London NW3 2PF, United Kingdom

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ABSTRACT

CMV is the most common congenital infection in newborns worldwide. Congenital CMV causes sensorineural hearing loss in a significant proportion of infected newborns, while the majority of newborns are asymptomatic. In the last three years there have been significant advances in the diagnosis and treatment of congenital CMV. We have developed practical evidence based guidelines for the management of congenital CMV.



## 1. Introduction

Congenital CMV (cCMV) is the leading non-genetic cause of sensorineural hearing loss [1,2]. Worldwide, the birth prevalence of cCMV is estimated at 7 per 1000 [2]. Approximately 12.7% of infected newborns are symptomatic at birth [2]. Around 13.5% of infants who are asymptomatic then develop sequelae including sensorineural hearing loss (SNHL) in childhood [2]. An accurate diagnosis has to be made within the first three weeks of life as virological and serological tests taken after this time no longer clearly distinguish between congenital and acquired infection.

Vertical transmission of CMV infection can occur through three main routes: (i) intrauterine; (ii) intrapartum and (iii) post-natal. Intrauterine transmission is the most important route as it may result in major neurological sequelae. Primary maternal infection, maternal reinfection with a different viral strain or reactivation of latent maternal infection can all cause in utero transmission. The most common source of virus for pregnant women is from young children [3]. Postpartum acquisition is mainly through breast milk. One study found infants who breast feed from seropositive mothers have an estimated rate of infection of up to 38% [4].

Congenital CMV is an important illness that is a common cause of hearing loss in newborns and a major cause of disability in children. The annual costs of CMV disease to the US health care system were estimated in the 1990's to be 1.86 billion dollars [5]. There is currently no universal screening programme for CMV but there is interest in the feasibility of linking screening for cCMV to the Newborn Hearing Screening Programme [6]. This report will discuss recent advances in detection and treatment and propose pragmatic management guidelines for congenital CMV. There is a very limited evidence base to guide the management of cCMV. We therefore conducted a systematic and comprehensive literature review using MEDLINE (1990 to May 2011) and EMBASE (1990 to May 2011) using the following terms as the Medical Subject Heading (MeSH) and text words: neonate, infant, cytomegalovirus, CMV, antiviral agents, valganciclovir, ganciclovir, management and treatment. Standard levels of evidence and grades of recommendations are used (Table 1).

## 2. Making the diagnosis

### 2.1. Clinical features

#### 2.1.1. Symptomatic congenital CMV infection

The typical physical signs of symptomatic disease include blueberry muffin rash, petechiae, IUGR, microcephaly, hepatosplenomegaly and jaundice. Laboratory results are consistent with hepatic

*Abbreviations:* CNS, Central nervous system; CMV, Cytomegalovirus; CrUSS, Cranial Ultrasound; DBS, Dried blood spot; FBC, Full blood count; IUGR, Intrauterine growth restriction; LFT, Liver Function Test; MRI, Magnetic Resonance Imaging; PCR, Polymerase Chain Reaction; SNHL, Sensorineural hearing loss.

* Corresponding author. Tel.: +44 208 725 5382; fax: +44 208 725 0716.
*E-mail addresses:* skadamba@sgul.ac.uk (S. Kadambari), eleri.williams@nuth.nhs.uk (E.J. Williams), sluck@doctors.org.uk (S. Luck).
[1] Tel.: +44 191 233 6161.

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**Table 1**
Levels of evidence and recommendations.

| Study design | Evidence level | Recommendation grade |
|---|---|---|
| Good recent systematic review | Ia | A+ |
| One or more vigorous studies | Ib | A− |
| One or more prospective studies | II | B+ |
| One or more retrospective studies | III | B− |
| Formal combination of expert opinion | IVa | C |
| Informal expert opinion | IVb | D |

**Table 2**
Summary of key recommendations for the management of congenital CMV.

| | Recommendation grade |
|---|---|
| Who to treat | |
| 1. CNS disease – SNHL, cerebral disease, chorioretinitis | B+ [15] |
| 2. Severe focal organ disease – severe hepatitis, severe anaemia, neutopaenia, throbocytopaenia, colitis, pneumonitis | D |
| When to treat | B+ [15] |
| Start treatment within the first 28 days of life | |
| What to treat with | |
| Ganciclovir 6 mg/kg IV BD | B+ [15] |
| Valganciclovir 16 mg/kg PO BD when clinically appropriate | B+ [18] |
| How long to treat | B+ [15] |
| Total duration of treatment 6 weeks | |
| Monitoring during treatment | B+ [18] |
| Weekly FBC, U&E, LFT's | |
| Neutrophil count drops $<0.5\times10^9$/L stop medication till count reaches $>0.75\times10^9$/L | |
| Platelet count drops to $<50\times10^9$/L stop medication till count reaches $>50\times10^9$/L | |
| Creatinine clearance between 10 and 19 ml/mim/1.73 $m^2$ should lead to once daily dosing until creatinine clearance returns to above 20 ml/mim/1.73 $m^2$ | |

and reticuloendothelial involvement. Findings include conjugated hyperbilirubinaemia, thrombocytopaenia and elevated hepatic transaminases in the majority of symptomatic newborns [7]. Long term studies have shown that almost half of symptomatic newborns will develop SNHL, learning difficulties and microcephaly and, rarely, visual loss [7].

*2.1.2. Asymptomatic congenital CMV infection*

Congenital CMV is most commonly asymptomatic. Approximately 10% of asymptomatic children will develop SNHL over the first 5–7 years of life, whilst the incidence of hearing loss in the general population is only 0.1–0.4% [1]. Hearing loss can be bilateral, and is often progressive or with delayed onset therefore requiring prolonged audiological follow up [1]. Because hearing is often normal at birth, only 50% of cases of SNHL caused by CMV are expected to be detected by neonatal hearing screening programmes [1].

*2.2. Laboratory confirmation of infection*

*2.2.1. Urine vs saliva CMV PCR*

Polymerase chain reaction (PCR) amplification of viral DNA is rapidly replacing viral culture as the most sensitive and efficient method for the detection of CMV. Detection of CMV in the urine or saliva is relatively easy because newborns shed high levels of the virus from these fluids and both are amenable to rapid testing using PCR [8]. The gold standard for the diagnosis of cCMV infection in newborns has been isolation of the virus in the urine within the first three weeks of life. Collection of urine from newborns is however difficult, time consuming and not an easy method for routine diagnosis. For example, technical difficulties prevented one third of urine samples from being analysed in a comparison study assessing the diagnostic accuracy between saliva and urine PCR, whilst saliva samples were more easily obtained [8]. The authors concluded that saliva samples are as reliable and more convenient in the diagnosis of cCMV.

The most recent study on diagnosing cCMV found that real time PCR of both liquid and dried saliva showed very high rates of specificity and sensitivity [9]. This prospective multicentre study found 177 out of the 34, 989 infants recruited to be positive for CMV. The liquid saliva PCR assay detected 85 out of 17,662 infants (0.5%; 95% CI, 0.4 to 0.6) positive for CMV on both culture and PCR assay. The dried saliva PCR assay detected 74 out of 17,327 (0.4%; 95% CI, 0.3 to 0.5) positive for CMV and 76 were CMV positive on rapid culture. Real time PCR assays of both liquid and dried saliva samples had sensitivities of >97% and 99.9% respectively compared with saliva rapid culture. False positive results can cause considerable anxiety for parents but the frequency of false positive results of both liquid and dried saliva was less than 0.03%. Saliva was shown to be more sensitive in diagnosing cCMV than the use of Dried Blood Spots.

Obtaining saliva samples is easy, practical and they can be readily stored and transported to the laboratory. The high sensitivity and specificity of dried saliva PCR make this method of testing a readily applicable approach to accurately diagnose cCMV. Saliva specimens are also potentially a simple method to use in any future newborn screening programmes [10]. The most recent advances in detection of CMV have therefore demonstrated that saliva PCR is highly sensitive and specific and should now be considered as the investigation of choice to detect cCMV.

*2.2.2. Problems with testing Dried Blood Spots (DBS)*

The detection of CMV DNA on DBS using PCR has enabled the retrospective diagnosis of cCMV in older children who present with compatible clinical features such as SNHL. The most recent studies however have unfortunately produced inconclusive findings on whether CMV DNA PCR on DBS would accurately identify the majority of newborns with cCMV. The four largest published studies now report sensitivities ranging from 34% to 100% for the detection of CMV PCR on DBS as a confirmatory test for cCMV. The size of DBS used, differences in DNA extraction methods and PCR assay protocols as well as variations in populations tested could account for the wide range of sensitivities noted in these studies.

A recent large prospective study assessed the diagnostic accuracy of DBS PCR as a universal screening tool [8]. Infants born at seven hospitals across the U.S were recruited between March 2007 and May 2008. Saliva specimens tested by rapid culture for detection of early antigen fluorescent foci were compared with a single primer and a two primer DBS PCR. Ninety two out of 20,448 newborns had confirmed cCMV infection (0.45%; 95% CI 0.36 to 0.55), 91 of whom had positive antigen detection on saliva. The single primer DBS PCR detected 17 out of 60 (28%) infants with confirmed cCMV of the 11,422 infants screened. However, the two primer DBS PCR assay identified 11 out of 32 infants (34%) of the 9026 newborns screened. The authors concluded that DBS PCR has low sensitivity for accurate diagnosis of cCMV because approximately two-thirds of infections were missed using this method. The sensitivities for detecting cCMV on DBS PCR were much lower than in other studies. In summary, a positive DBS CMV PCR taken in the first 3 weeks of life confirms the diagnosis of cCMV,

but a negative result cannot reliably exclude cCMV. DBS PCR now looks a poor screening test for the diagnosis of cCMV unless it can be shown to preferentially detect those at risk of developing SNHL in the future.

### 2.3. Further investigations required in a baby with confirmed cCMV

#### 2.3.1. Blood tests

Full Blood Count (FBC) and Liver Function Tests (LFTs) are essential because CMV can cause pancytopenia and hepatitis. Coagulation studies should be performed in the presence of hepatomegaly or hepatitis. Renal function should also be measured as a baseline prior to commencing treatment because ganciclovir (GCV) is renally excreted.

#### 2.3.2. Choice of neuroimaging

Congenital CMV can manifest with intracranial calcification, migrational abnormalities (usually microgyria and cystic changes), ventriculomegaly and white matter loss. Cranial ultrasound has been shown to be a good predictor of outcomes in symptomatic newborns with cerebral abnormalities and is a useful first imaging investigation in newborns with suspected cCMV [11].

A recent study assessing MRI findings in symptomatic newborns found that white matter involvement is variable, difficult to evaluate and not clearly related to clinical outcome. However, cortical malformations, ventriculomegaly and hippocampal dysplasia were all found to be predictors of a poor neurological outcome [12]. A Dutch group has shown that MRI provides important information including polymicrogyria, hippocampal dysplasia and cerebellar dysplasia all of which are difficult to visualize on computed tomography [13].

Cranial ultrasound scans are easily obtainable and and so now should be used as a primary screening tool to assess for intracerebral abnormalities including calcification for all babies with confirmed cCMV. MRI should then subsequently be performed for all symptomatic newborns and in asymptomatic newborns with any intracerebral abnormalities detected on cranial ultrasound.

#### 2.3.3. Ophthalmic assessment

Ophthalmic assessment should be performed for all newborns with cCMV at the time of diagnosis. Retinal scarring, strabismus, and cortical visual loss may be seen in symptomatic infants.

#### 2.3.4. Audiological assessment

A baseline audiological assessment should be performed on all newborns with cCMV. Hearing loss can be progressive or late onset and so audiological follow up is essential and will be discussed later on.

#### 2.3.5. Deciding whether the baby is Symptomatic or Asymptomatic

Following a full clinical, radiological, audiology and ophthalmology assessment with blood investigations a clear decision has to be made and documented in the notes, as to whether the baby with cCMV is Asymptomatic, or is Symptomatic. Symptomatic disease can then be defined as either mild/moderately symptomatic disease, or severe focal symptomatic organ disease, or symptomatic CNS disease. The evidence base for these definitions is as yet limited and the predictive power of different symptoms and signs on ultimate clinical outcomes needs further evaluation in larger international data sets.

At present pragmatic definitions with a limited evidence base could include:

CNS symptomatic disease – microcephaly, radiological abnormalities on MRI or CrUSS, abnormal csf parameters or a positive CMV csf PCR, chorioretinitis, or a sensorineural hearing loss diagnosed by brain stem evoked responses (BSER).

Severe Focal Organ Disease includes severe hepatitis, severe bone marrow suppression (anaemia, neutropenia, thrombocytopenia), colitis or pneumonitis.

This decision influences treatment and follow up decisions because at present we would only recommend treatment for symptomatic CNS disease or severe focal organ disease (Table 2).

## 3. Treating and monitoring cCMV

### 3.1. Treating symptomatic organ disease

#### 3.1.1. Who to treat

As discussed above, currently antiviral treatment with GCV and valganciclovir (VGCV) is only recommended for symptomatic newborns (in the first 30 days of life) with severe symptomatic focal organ disease, or CNS disease. Since the failure of maribavir in a recent phase III trial, there are limited new anti CMV drugs under development (these include liposomal cidofovir and the AiCuris inhibitor AIC246 which is currently undergoing phase IIb testing).

### 3.2. Ganciclovir – GCV

Ganciclovir has been used to treat cCMV for the last twenty years [14]. Only one phase III randomised trial by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG 102 study) has been conducted to assess the outcome of GCV treatment in symptomatic congenitally affected infants [15]. The study recruited 100 newborns less than a month old with symptomatic cCMV over a 10 year period. These babies were randomised to receive 6 weeks of IV GCV 6 mg/kg/dose every 12 h or no treatment. Treatment was started within the first month of life and was shown to prevent hearing deterioration at 6 months and ≥1 year of life. The phase III trial also showed short term improvements in weight gain, head circumference and resolution of liver abnormalities. Follow up of these babies was shown to reduce developmental delays at 6 and 12 months compared to untreated infants [16]. Infants treated with GCV have been shown to have more normal neurological outcomes but were still developmentally behind at 6 weeks, 6 months and 12 months.

There are however still only limited data regarding the pharmacokinetics, safety profiles and adverse effects of GCV, especially in premature or older infants. Ganciclovir induced neutropaenia and the risks associated with an indwelling central venous catheter are two primary problems associated with treatment, making a safer and convenient alternative desirable. Current data has only demonstrated treatment efficacy of GCV in symptomatic newborns with CNS disease. These data cannot be inferred to advocate treatment for newborns without CNS disease or asymptomatic babies. The current recommended treatment regimen is published in the British National Formulary of Children (BNFC www.bnfc.org) and used by the CASG: 6 mg/kg/dose IV 12 hourly for 6 weeks [15,17].

### 3.3. Valganciclovir – VGCV

The pharmacokinetic parameters of 24 neonates receiving 6 weeks of GCV (6 mg/kg) were similar to those receiving VGCV, the oral prodrug, (16 mg/kg) in a randomised study [18]. Lombardi and colleagues studied the effects of VGCV on 13 neonates with symptomatic cCMV [19]. The group used a 15 mg/kg twice daily regimen for six weeks with similar results. There have been no studies in either adults or children to compare csf levels in patients receiving VGCV or GCV.

It is our experience that six weeks of intravenous GCV in a baby usually requires a central line insertion, although this can often be a peripherally inserted CVC. In the absence of any direct evidence a pragmatic compromise has to be made between the morbidity associated with prolonged central line use and the potential added benefit of intravenous GCV. This risk/benefit analysis has altered with the availability in Europe of the Roche VGCV liquid formulation (Valcyte oral syrup – 50 mg/ml). This has only been licensed by the FDA for prevention of CMV disease in high risk kidney or heart transplant children aged 4 months to 16 years of age (www.valcyte.com). But this preparation is also being used as an off license indication in Europe for the management of cCMV disease. Extemporaneous preparations of crushed VGCV tablets should no longer be used due to the marked variation in pharmacokinetics seen with this method.

Until further clinical trial data are available, one possible approach is to treat all babies with severe CNS or focal organ disease initially with IV GCV for at least 2–3 weeks where possible. There is then the possibility of switching to oral VGCV to complete the 6 weeks of therapy, if the baby is tolerating oral medication well, there has been a significant virological response and venous access is becoming a problem. Families should be fully informed that oral VGCV is then being used as an off licence medicine under the guidance of a consultant paediatrician.

As yet there have been no published data directly comparing VGCV with GCV for clinical endpoints. A placebo-controlled, double blind, randomized study comparing 6 weeks versus 6 months of oral VGCV is currently being conducted by the CASG (CASG 112) and has just closed to recruitment. The primary objectives of the study are to compare hearing outcomes, safety profiles, assess neurological outcomes and monitor CMV viral loads in symptomatic neonates up to one month of life who received 6 weeks versus 6 months of VGCV. Robust evidence is warranted before committing babies to long term courses of treatment with associated morbidity and cost to healthcare systems, so we currently recommend that treatment duration is fixed at six weeks unless the CASG 112 study demonstrates that a longer duration is both safe and effective. Currently no other phase III randomised controlled trials are recruiting to assess antiviral efficacy for the treatment of cCMV.

#### 3.3.1. Treating older children

In the absence of a newborn screening programme, cCMV is often diagnosed in infancy after children have been found to have hearing impairment. There is a clear need to establish whether treatment would be of clinical benefit in these children. Studies assessing viral load parameters and audiological outcomes with VGCV treatment in this group are essential.

### 3.4. Monitoring

#### 3.4.1. Safety parameters

Once treatment has started close monitoring of adverse effects including neutropaenia, thrombocytopenia and anaemia are essential. Neutropaenia should be monitored at least weekly during the course of antiviral treatment. If the neutrophil count drops to $<0.5\times10^9$/L then medication should stop until the neutrophil count recovers to $>0.75\times10^9$/L. If the platelet count drops to $<50\times10^9$/L then antiviral treatment should be stopped until the platelet count returns to $>50\times10^9$/L.

Liver function tests need to be monitored weekly during the treatment as cCMV can cause hepatitis. Creatinine clearance should also be monitored weekly as GCV is renally excreted. Creatinine clearance recorded between 10 and 19 ml/mim/1.73 $m^2$ should lead to once daily dosing of GCV or VGCV until creatinine clearance returns to above 20 ml/mim/1.73 $m^2$ .

#### 3.4.2. Viral loads

Whole blood CMV viral loads (VL) should be taken weekly during the course of treatment to assess treatment efficacy and monitor disease progression. Blood CMV viral loads usually drop between 1 and 2 logs during treatment, while urine and saliva VL are usually significantly higher at baseline and fall around 3–4 logs. Viral loads then rise again sharply usually once treatment has stopped. In the absence of any clinical disease progression, a rise in VL alone is not a reason to continue treatment over 6 weeks.

#### 3.4.3. Drug levels

Therapeutic drug monitoring (TDM) can be performed on a weekly basis during the course of treatment to help ensure treatment efficacy. Trough samples should be taken in serum clotted bottles an hour prior to administration and levels aimed at 0.5–1.0 mg/L. Ganciclovir peak levels should be taken one hour after administration in clotted serum bottles. In the U.K, currently the only reference laboratory to perform GCV levels is the Bristol Centre for Antimicrobial Research and Evaluation (http://www.bris.ac.uk/bcare) Ganciclovir peak levels should be between 7 – 9 mg/L [20]. Adjusting dose levels should not be necessary in the presence of adequate trough levels and a good virological response. As GCV/VGCV is renally excreted drug levels often fall during therapy due to newborn renal maturation increasing drug clearance.

#### 3.4.4. Resistance assays

Resistance in CMV is usually due to mutations in gene UL97 which encodes the viral protein kinase or in the viral polymerase gene UL54. Treatment failure and the emergence of some resistance mutations have been associated with the use of valganciclocvir [21]. Clinicians who are treating newborns with persistent high level viraemia should liaise with their local virology department to consider performing resistance assays for common gene mutations.

## 4. Planning long term follow up

### 4.1. Audiology

The National Deaf Children's Society guidelines (http://www.ndcs.org.uk) recommend hearing assessment for babies with cCMV should be performed every 3–6 months in the first year until age 3 and then yearly until 6 years old.

### 4.2. Neurodevelopmental

Clinical and neurodevelopmental follow up should be performed at 6 months and at least one year in general paediatric clinics. All CNS symptomatic infants should have a neurodevelopmental assessment at one year. Further referral to long term neurodevelopmental services will then be based on clinical need and neuroimaging findings.

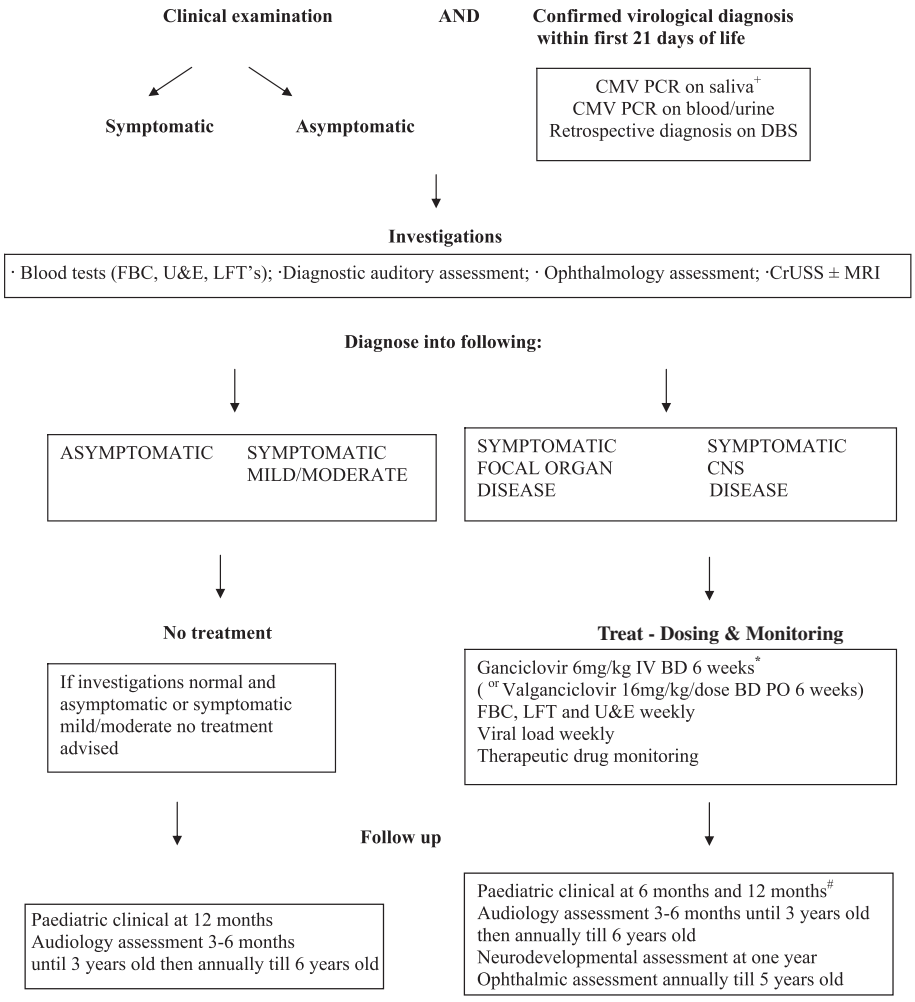
### 4.3. Ophthalmology

Initial ophthalmology assessment is required at diagnosis to evaluate the presence of retinal scarring. Asymptomatic newborns do not require further examinations. However, symptomatic newborns should undergo annual ophthalmology assessment until the age of 5 to detect the presence of delayed or progressive chorioretinitis.

### 4.4. Family support

In the U.K the congenital CMV association (www.cmvsupport.org) is run on a voluntary basis by the parents of children with cCMV. The association offers very helpful advice and support to families affected by cCMV.

## 5. Management algorithm for the treatment of congenital CMV




Key:

+ Where possible to perform in first instance.

* Where tolerated and clinically appropriate.

# Follow up should be sooner if clinically required.

## 6. Conclusion

In the absence of any imminent vaccine becoming available and new antiviral agents on the market, treatment with GCV and VGCV will remain the only therapy for some time. We know very little still about the long term outcomes of these drugs, so post treatment surveillance of newborns treated with GCV/VGCV remains very important. A novel web based registry for cCMV infected infants treated with GCV/VGCV is being piloted in the U.K as part of a pan-European treatment initiative to facilitate long term post treatment surveillance (www.ecci.ac.uk). Future research should concentrate on developing alternative antiviral agents which are more effective and have less toxicity.

## Conflict of interest

None.

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