Congenital CMV infection

current strategies and future perspectives

1. Introduction
2. Clinical features
3. Diagnosis
4. Treatment
5. Outcome

Herpesviridae - linear dsDNA

- Alpha (HSV group)
  - Herpes Simplex 1 (HSV1)
  - Herpes Simplex 2 (HSV2)
  - Varicella-zoster Virus (VSV, "chickenpox")
- Beta (CMV group)
  - Human cytomegalovirus (CMV or HCMV)
  - Human herpesvirus 6 (HHV6)
  - Human herpesvirus 7 (HHV7)
- Gamma (lymphoproliferative group)
  - Epstein-Barr Virus (EBV, "mono")
  - Human herpesvirus 8 (HHV8)

TABLE 135-1 Biologic Features of Herpesviruses That Infect Humans

Virus	Genome: Subfamily	Genome: Size (kbp)	Receptor(s)	Sites of Latency
Human Virus				
HSV-1 (HHV-1)	α	152	Nectin-1, nectin-2 TNFRSF14, 3-OS-HS	Sensory and cranial nerve ganglia
HSV-2 (HHV-2)	α	152	Nectin-1, nectin-2 TNFRSF14	Sensory and cranial nerve ganglia
Varicella-zoster virus (HHV-3)	α	125	IDE	Sensory and cranial nerve ganglia
Cytomegalovirus (HHV-5)	β	229	PDGFRα, EGFR? $\alpha_2\beta_1$, $\alpha_6\beta_1$, $\alpha_v\beta_3$	Monocytes, macrophages CD34⁺ cells
HHV-6	β	165	CD46	CD34⁺ cells, monocytes, macrophages
HHV-7	β	145	CD4?	CD4 cells
Epstein-Barr virus (HHV-4)	γ	172	CD21, MHC class II	Memory B cells
Kaposi's sarcoma–associated herpesvirus (HHV-8)	γ	165	Integrin $\alpha_3\beta_1$ XCT, DC-SIGN	B cells
Simian Virus				
Herpes B virus (cercopithecine herpesvirus 1)	α	150	Unknown	Sensory and cranial nerve ganglia

CMV

- Mainly establishes latency in mononuclear leukocytes, such as monocytes and macrophages.
- Very widespread virus, 60 - 70% in US and 100% in Africa population produce anti-CMV antibodies by adulthood.
- Primary/secondary infection are generally asymptomatic and are characterized by shedding of virions.

TABLE 135-2 Features of Herpesvirus Infections and Seroepidemiology

Virus	*Primary Infection in Healthy Persons*	*Infection in Immunocompromised Persons*	Seroprevalence (%)		
			Healthy Children	Healthy Adults	
				United States	*Developing World*
Herpes simplex virus 1	Gingivostomatitis Keratoconjunctivitis Cutaneous herpes Genital herpes	Gingivostomatitis Keratoconjunctivitis Cutaneous herpes Visceral infections	20-40	50-70	50-90
Herpes simplex virus 2	Genital herpes Cutaneous herpes Gingivostomatitis Aseptic meningitis Neonatal herpes	Genital herpes Cutaneous herpes Disseminated infection	0-5	20-50	20-60
Varicella-zoster virus	Varicella	Disseminated infection	50-75	85-95	50-80
Cytomegalovirus	Mononucleosis Hepatitis Congenital cytomegalic inclusion disease	Hepatitis Retinitis Other visceral infections	10-30	40-70	40-80
Epstein-Barr virus	Mononucleosis Hepatitis Encephalitis	Polyclonal and monoclonal lymphoproliferative syndromes Oral hairy leukoplakia	10-30	80-95	90-100
Human herpesvirus 6	Exanthem subitum, infantile fever and seizures, encephalitis	Fever and rash Encephalitis Bone marrow suppression	80-100	60-100	60-100
Human herpesvirus 7	Exanthem subitum, childhood fever and seizures, encephalitis	Encephalitis?	40-80	60-100	40-100
Kaposi's sarcoma–associated herpesvirus	Febrile exanthem Mononucleosis?	Kaposi's sarcoma, Castleman's disease, primary effusion lymphoma	<3	<3	10-60
Herpes B virus	Mucocutaneous lesions Encephalitis	?	0	<<1	<<1

Clinical features

- Jaundice (62%), petechie (58%), hepatosplenomegaly (50%)
- Sensorineural hearing loss, oligohydramnios, polyhydramnios, intrauterin growth retardation, non-immune hydrops, fetal ascites, hypotonia, cerebral ventriculomegaly, microcephaly, intracranial calcifications,…
- Increased risk of congenital malformations

Diagnosis

- Virus isolation/PCR: urine, blood, saliva and cerebrospinal fluid before 3ws of age
- Antigen CMV-IgM in blood

Table I. Diagnostic methods available for the diagnosis of maternal, fetal and neonatal CMV infection. Adapted from Ref. 5.

Type of patient	Diagnostic method	Comments
Maternal infection	IgG seroconversion (appearance of virus-specific IgG in the serum of a pregnant woman who was previously seronegative) Presence of anti-CMV IgM and IgG antibodies Anti-CMV IgG avidity test	Two consecutive maternal blood samples need to be collected 2-3 weeks apart. IgM can be detected in: reactivations or reinfections; until more than one year after CMV primary infection; interference due to rheumatoid factor of the IgM class or cellular antigen; false positive during other viral infections (B19 Virus, Epstein Barr Virus, etc.). Low avidity means recent maternal infection, but threshold differs between virological methods.
Fetal infection	Amniocentesis to assess the presence of CMV by PCR	Perform the test after the 21st week of gestation and after 5-6 weeks from the estimated onset of infection. Indications are: woman with compatible clinical signs of primary CMV infection; compatible ultrasound abnormalities; serologic suspicion of a recent maternal infection.
Neonatal infection	Culture or CMV-DNA testing by PCR in urine, blood, throat and CSF.	If infection is confirmed, classify as symptomatic or asymptomatic and follow-up at 1, 3, 6 and 12 months and annually until school age in order to detect sequelae with delayed onset.

CMV

- varied in humans infected : no disease in healthy hosts and congenital CMV syndrome in neonates, which is frequently fatal, to infectious mono-nucleosis syndrome in young adults.
- In the patient with immunocom- promise, CMV produces its most significant and severe disease syndromes in lung, liver, kidney, and heart transplant recipients

Treatment

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Congenital cytomegalovirus infection: current strategies and future perspectives

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Group 1 was treated with GCV 5 mg/kg twice daily for two weeks. Group 2 was treated with GCV 7.5 mg/kg twice daily for 2 weeks, followed by 10 mg/kg three times a week for 3 months. In group 1 viral shedding disappeared in 3/6 infants, whereas in group 2 all six infants showed cessation of viruria. In all babies viral shedding reappeared after treatment was discontinued. Two infants in group 1 and four in group 2 had normal neurologic outcomes at 18 months

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

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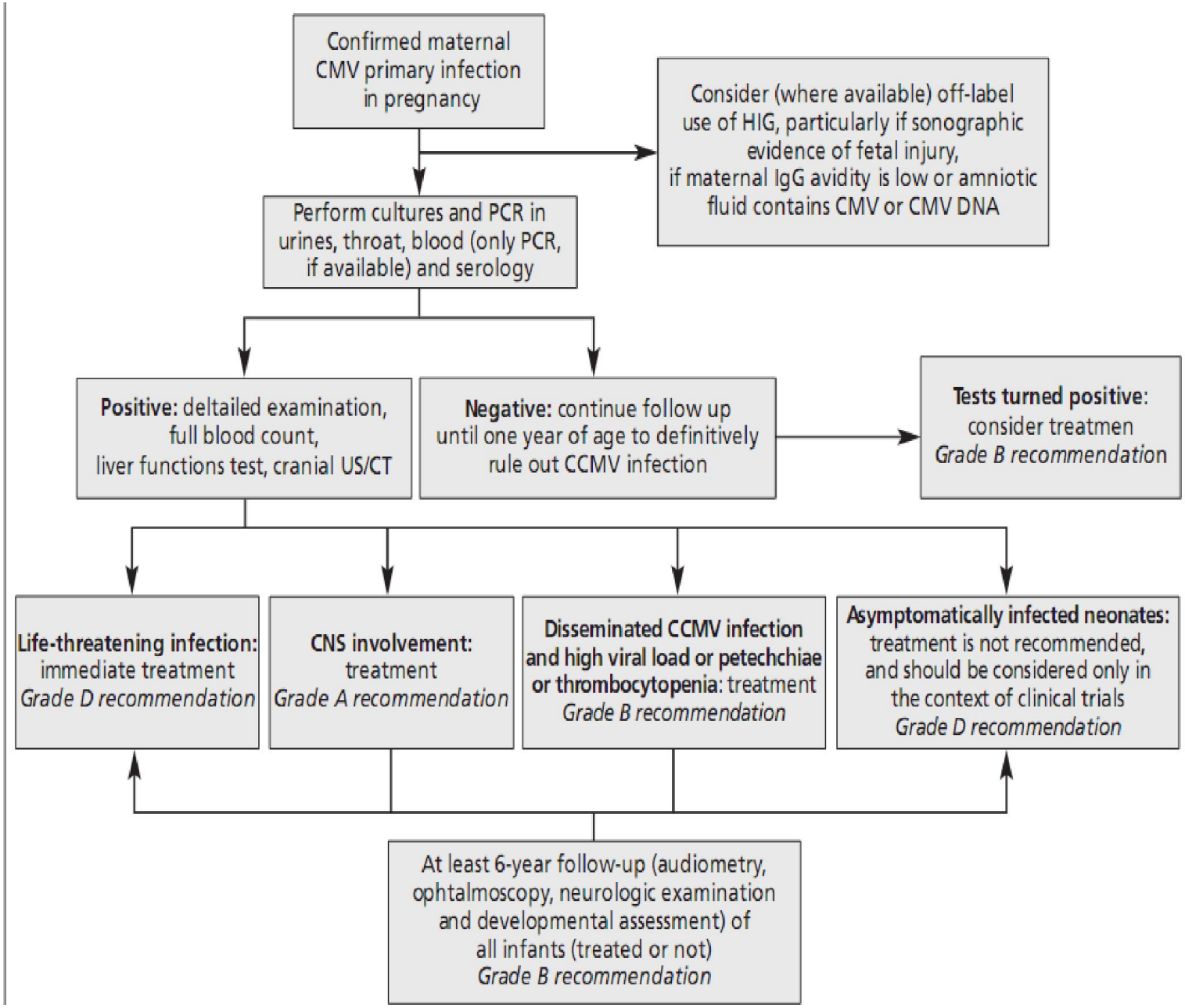
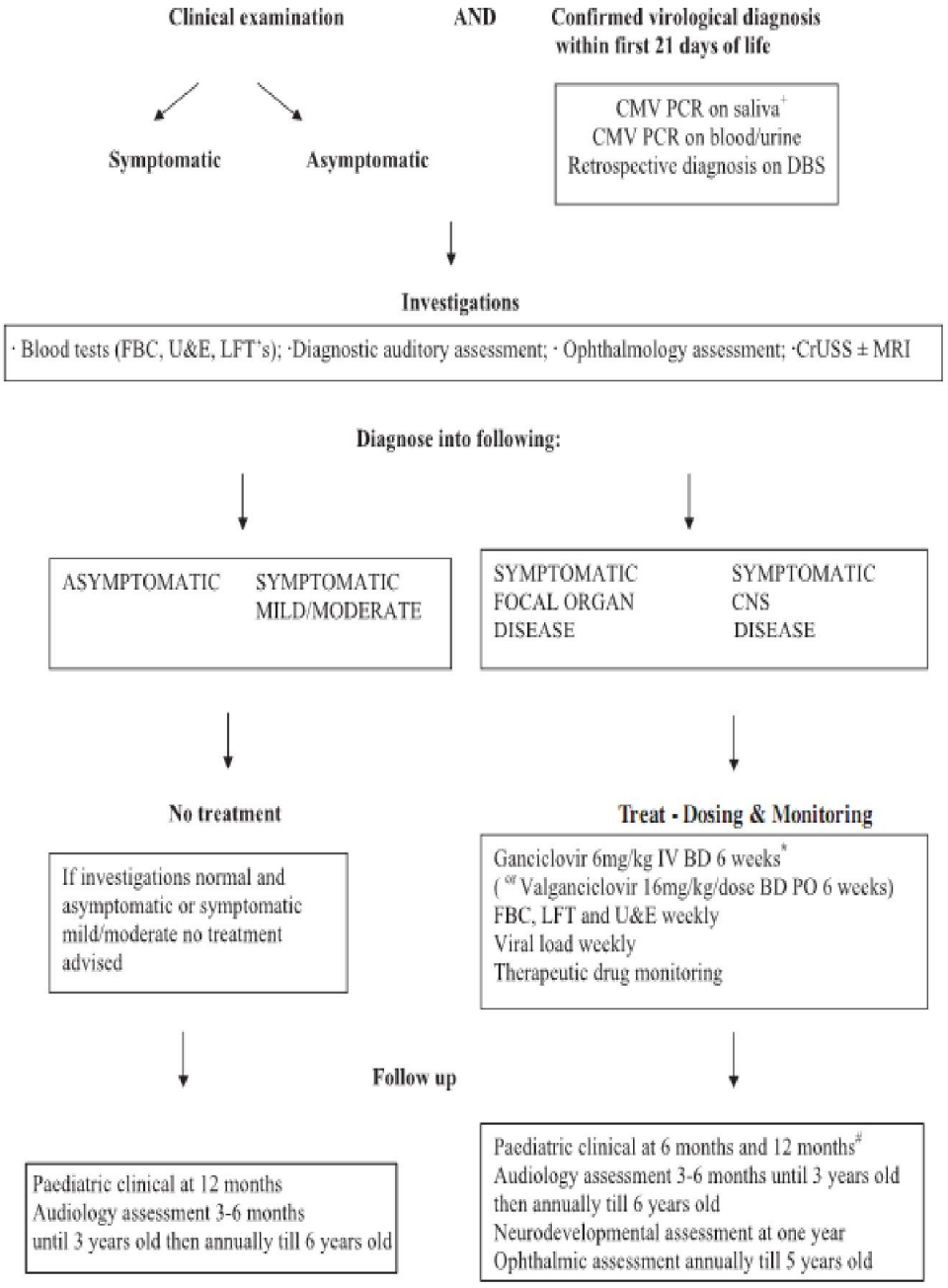
Table 2
Summary of key recommendations for the management of congenital CMV.

	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 $<0.5 \times 10^9$/L stop medication till count reaches $>0.75 \times 10^9$/L	
Platelet count drops to $<50 \times 10^9$/L stop medication till count reaches $>50 \times 10^9$/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	

Table II. Treatment of CCMV infection. Adapted from Gandhi et al, 2010; 99: 509-515[82].

Drug	Regimen	Monitoring	Comments
Ganciclovir	6 mg/kg twice daily, intravenous, per 6 weeks.	Full blood count, liver function tests, creatinine, urea and electrolytes	Suspend treatment if absolute neutrophil count < 500 cells/μL or platelet count < 25 000 cells/μL
Valganciclovir	15 mg/kg twice daily, per os, per 6 weeks.	Full blood count, liver function tests, creatinine, urea and electrolytes	Suspend treatment if absolute neutrophil count < 500 cells/μL or platelet count < 25 000 cells/μL


Confirmed maternal CMV primary infection in pregnancy
Consider (where available) off-label use of HIG, particularly if sonographic evidence of fetal injury, if maternal IgG avidity is low or amniotic fluid contains CMV or CMV DNA
Perform cultures and PCR in urines, throat, blood (only PCR, if available) and serology
Positive: deltailed examination, full blood count, liver functions test, cranial US/CT
Negative: continue follow up until one year of age to definitively rule out CCMV infection
Tests turned positive: consider treatmen Grade B recommendation
Life-threatening infection: immediate treatment Grade D recommendation
CNS involvement: treatment Grade A recommendation
Disseminated CCMV infection and high viral load or petechchiae or thrombocytopenia: treatment Grade B recommendation
Asymptomatically infected neonates: treatment is not recommended, and should be considered only in the context of clinical trials Grade D recommendation
At least 6-year follow-up (audiometry, ophtalmoscopy, neurologic examination and developmental assessment) of all infants (treated or not) Grade B recommendation


Clinical examination
AND
Confirmed virological diagnosis within first 21 days of life
Symptomatic
Asymptomatic
CMV PCR on saliva+
CMV PCR on blood/urine
Retrospective diagnosis on DBS
Investigations
· Blood tests (FBC, U&E, LFT's); ·Diagnostic auditory assessment; · Ophthalmology assessment; ·CrUSS ± MRI
Diagnose into following:
ASYMPTOMATIC
SYMPTOMATIC MILD/MODERATE
SYMPTOMATIC FOCAL ORGAN DISEASE
SYMPTOMATIC CNS DISEASE
No treatment
Treat - Dosing & Monitoring
If investigations normal and asymptomatic or symptomatic mild/moderate no treatment advised
Ganciclovir 6mg/kg IV BD 6 weeks*
(or Valganciclovir 16mg/kg/dose BD PO 6 weeks)
FBC, LFT and U&E weekly
Viral load weekly
Therapeutic drug monitoring
Follow up
Paediatric clinical at 12 months
Audiology assessment 3-6 months until 3 years old then annually till 6 years old
Paediatric clinical at 6 months and 12 months#
Audiology assessment 3-6 months until 3 years old then annually till 6 years old
Neurodevelopmental assessment at one year
Ophthalmic assessment annually till 5 years old

Long term follow up

- Audiology: every 3-6ms in the first year until age 3, then yearly until 6
- Neurodevelopmental: 6m, 1y
- Ophthalmology: retinal scarring, annual until 5
- Family support

CMV infection in critically ill patient

Research

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Cytomegalovirus infection in critically ill patients: a systematic review

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- CMV infection occurs in 0 to 36% (median 25%) of critically ill patients between 4 and 12 days after ICU admission, especially those with sepsis, requiring mechanical ventilation, and receiving transfusion.
- CMV infection is associated with poor outcomes; however, it is not known whether the causal association exists, that is, CMV is truly a pathogen or CMV infection is just an indicator of immunosuppression.
- It remains to be determined whether CMV produces febrile syndrome or end-organ disease directly in critically ill patients.
- Further studies are warranted to identify subsets of patients who are at high risk of developing CMV infection and to determine the role of antiviral agents on clinically important outcomes in critically ill patients.

Discussion

- cCMV: common cause of congenital infection
- Its management is not yet well defined.
- GCV, Val-GCV: prolonged or repeated treatment?

- *Thanks for your attention!*