

Cytomegalovirus

A common virus causing serious disease

BACKGROUND Human cytomegalovirus (CMV) is a herpes virus that causes severe illness and death in people whose immune systems are compromised, including organ and bone marrow transplant recipients, HIV infected people, those on immunosuppressive drugs and newborns infected during pregnancy.

OBJECTIVE This article aims to present a clear guide to diagnosis and treatment of CMV in at risk patients in the community.

DISCUSSION Cytomegalovirus is a common infection in the community, but diagnosis is often seen as difficult. The use of careful clinical assessment tests and a clear diagnostic algorithm can provide appropriate diagnosis in most immunocompromised patients, pregnant women and newborns with CMV. Treatment strategies and available antivirals are improving, complementing the advances made with diagnostic techniques and algorithms.

Cytomegalovirus (CMV) causes significant infection in immunocompromised patients with recognised syndromes of fever, hepatitis, pneumonitis, encephalitis and retinitis. Long term consequences of CMV infection such as allograft rejection, accelerated atherosclerosis, reduced effectiveness of anticancer drugs, secondary fungal and bacterial infections are less well recognised clinically. There is mounting evidence for the role of CMV in these chronic conditions, and for worse outcomes in the longer term for CMV infected patients. Also under recognised is that CMV is the leading infectious cause of congenital abnormalities in Australia with 200–600 babies born each year with deafness, mental disability, hepatitis, pneumonitis and blindness.¹ Recent advances in therapy hold some promise for improved treatment although trials are needed to confirm the clinical efficacy of newer treatments.

Epidemiology

Cytomegalovirus is an ubiquitous virus with 40–60% seropositivity in adults from western countries.² After primary infection with CMV, the virus becomes latent and can be reactivated to produce a secondary infection, particularly during episodes of immunosuppression.² Cytomegalovirus is secreted in saliva, urine and breast milk, and intermittent shedding of the virus is common, particularly in

infected infants, children and pregnant women.² In early life, CMV is predominantly transmitted via:

- breastfeeding
- fomite spread
- contact with other children, or
- the cervix during parturition.^{1–3}

Infection with CMV can also occur via:

- inhalation
- sexual contact (resulting in a peak of acute infection occurring in young adults)
- blood transfusions⁴
- transfer with transplanted organs, or
- vertical transmission from mother to unborn child.¹

Transmission of CMV also occurs by direct contact with infected urine or saliva, placing pregnant child care workers at particular risk of contracting CMV. Transmission of CMV can be significantly reduced in child carers by hand washing and the use of gloves while changing nappies; in adults by condom use; and in immunosuppressed patients by the use of leucocyte depleted or leucofiltered blood.⁴

Clinical features

Infection of mothers and babies

Congenital CMV infection occurs in 0.15–2.0% of newborns.¹ Approximately 30% of congenitally infected newborns develop symptomatic disease (including the most severe manifestation of

**William Rawlinson,
Gillian Scott**



William Rawlinson, BSc, MBBS, PhD, FRACP, FRCPA, GCM, FASM, is Senior Medical Virologist, South Eastern Sydney Area Health Service, Prince of Wales Hospital, Sydney Children's Hospital and Royal Hospital for Women, and Associate Professor, Faculties of Medicine and Science, the University of New South Wales.

Gillian Scott, BSc (Hons), is a research assistant, Virology Division, South Eastern Sydney Area Health Service, Prince of Wales Hospital, New South Wales.

cytomegalic inclusion disease and mental retardation) and 18% develop long term sequelae such as hearing loss.⁵ Children infected during the first trimester of pregnancy are at increased risk of complications, although infections at any stage of pregnancy can produce symptomatic disease.⁶ Prior maternal CMV antibodies are protective against transmission of the virus, but not against development of symptomatic disease once infection has occurred.^{5,6} Infection during pregnancy is often asymptomatic, however, when questioned closely, infected pregnant women often have greater than usual fatigue.⁷

Infection in children

The result of childhood infection with CMV is very different whether it occurs in the perinatal period (within one month of birth) or in early childhood (within five years of birth). Most perinatal infection is asymptomatic, although 10% of infants who develop symptoms can be severely affected, developing encephalitis, hepatitis and infections similar to those of immunocompromised adults (Table 1). Up to 60% of children are infected by the age of one year.⁸ Infection in older children is common but usually asymptomatic and predominantly results from contact with other children in the family or child care.

Infection in adults

Infection with CMV is most often asymptomatic in immunocompetent individuals although adults with primary CMV infection may present with a mononucleosis-like syndrome, encephalitis or hepatitis (Table 1). Retinitis and gastrointestinal disease are common manifestations of CMV infection in HIV infected patients, however, highly active antiretroviral therapy in these patients has significantly decreased the incidence of CMV induced disease (particularly retinitis) in recent times.⁹ The incidence of CMV infection in HIV positive patients is close to 100%, and coinfection with multiple strains is common.¹¹ Bone marrow and stem cell transplant recipients are at increased risk of life threatening CMV pneumonitis,¹² whereas solid organ recipients are more likely to develop CMV induced hepatitis.¹³ Cytomegalovirus infection is also associated with chronic rejection, particularly in solid organ transplant recipients with CMV related end organ disease.¹⁴ Receipt of an organ from a CMV seropositive donor by a seronegative recipient (D+/R-) is a significant risk factor for the development of CMV disease and increases the risk of secondary bacterial and fungal infection.^{15,16}

Diagnosis

The diagnosis of CMV infection is straightforward

| Table 1. Clinical presentations of adults with primary (first) or secondary (reactivation) CMV infection | | |
|--|--------------------|--|
| Patient group | Symptoms | Clinical features |
| Healthy | Asymptomatic (70%) | <ul style="list-style-type: none">• Fever• Mononucleosis syndrome indistinguishable from glandular fever• Rarely meningoencephalitis, hepatitis, pancreatitis |
| Immunosuppressed | Often symptomatic | <p>Acute</p> <ul style="list-style-type: none">• Acute CMV syndrome with fever + malaise + myalgia + falling white cell count ± leukopaenia ± thrombocytopaenia• Acute chorioretinitis, encephalitis, hepatitis, myocarditis (rare), pancreatitis, pneumonitis <p>Chronic</p> <ul style="list-style-type: none">• Chronic accelerated atherosclerosis (heart transplants), hepatitis (liver transplants), bronchiolitis obliterans (lung transplants), bacterial infection (esp. Staphylococcus and streptococcal), fungal infection (esp. aspergillosis)• Organ rejection• Graft versus host disease |

using current techniques (Table 2, 3). Serological tests are highly specific and sensitive, and although antibody can decline with age and severe immunosuppression, IgG seropositivity is usually lifelong. Techniques for detecting the virus itself are improving rapidly, and nucleic acid tests such as the polymerase chain reaction (PCR), branch DNA (bDNA) and nucleic acid sequenced based amplification (NASBA) are now available at larger centres. All the nucleic tests are useful and choice largely depends upon the laboratory preference and the tests being commercially developed at any given time.

The same cannot be said for diagnosis of invasive CMV disease (Table 2, 3). Although direct detection of virus is straightforward, the lack of association between the presence of virus and the presence of disease means that it is extremely important to place the result of the diagnostic test in the clinical setting in which the patient finds him or herself. Sophisticated tests with quantitation of the amount of virus in blood (eg. quantitative PCR on plasma or white cells derived from EDTA anticoagulated blood) are increasingly available. Such quantitative measures of CMV are useful in directing therapy in immunocompromised adults and children,¹³ are a surrogate measure of the development of clinical resistance^{17,18} and provide prognostic guides for the outcome of congenital CMV infection of pregnancy when testing is

carried out on amniotic fluid.^{1,19,20} Quantitative tests are currently only available in reference laboratories, although it is likely they will become available in other laboratories as the cost per test decreases.

Table 2. How CMV causes diseases

Latent CMV

- Virus present lifelong in the resting phase
- Indicated by the person being IgG seropositive
- Not eliminated by any currently available treatment
- Virus can reactivate with suppressed immunity (pregnancy, HIV-AIDS, immunosuppressive treatment) or spontaneously (healthy adults)

CMV infection

- Isolation of the virus from any site or serological evidence of recent infection
- May be primary or secondary
- Primary infection occurs in a person who is IgG negative and is followed by IgM production with persistence of IgM for up to 2–3 years
- Reactivation infection occurs when CMV is isolated from a person known to be IgG seropositive

CMV disease

- Invasive or symptomatic infection with biopsy evidence of viral cytopathic effect
- Most commonly diagnosed on the basis of evidence of recent infection plus clinically consistent illness, eg. CMV detected in blood by PCR, in a renal transplant patient with fever, thrombocytopenia and deteriorating renal function

Table 3. Diagnostic tests for CMV

| Laboratory test | | Indication for use | Discussion |
|----------------------------------|---------------------|---|---|
| Serology | IgM | Diagnosis of primary CMV infection | Rise 2–6 weeks after infection. May persist for two years. Detectable at low levels during |
| | IgG | Determination of serostatus. Diagnosis of recurrent infections | Diagnosis of recurrent infections requires demonstration of rising IgG titres and sequential specimens |
| | IgM and IgG avidity | Confirmatory test allowing improved diagnosis of primary infections | Useful in detecting primary infection in pregnancy (low avidity = recent infection within three months) |
| Nucleic acid (NA) testing | DNA PCR | Sensitive test for determining presence of CMV | Sensitivity allows detection of low numbers of virus (? 200 viral particles) |
| | Quantitative PCR | Detection of different levels. Correlates well with disease | Currently expensive |
| Virus cultures | Standard | Noninvasive urine testing Diagnosis of viral shedding | Delay of results – can take up to two weeks |
| | IFA* | In conjunction with standard culture | Do not have isolate for further analysis (eg. resistance testing) |

• Indirect immunofluorescence

Most diagnostic problems can be resolved reasonably well by using established algorithms for diagnosis of congenital CMV,¹⁹ appropriate tests in different settings (Table 3), and clinical guidance as to the patient's condition. The specific diagnostic problems of the pregnant woman with possible primary CMV infection, the older child with hearing impairment and possible CMV infection, and the immunocompromised adult with positive CMV PCR or culture, but no clinical evidence of CMV infection, are difficult, but not impossible to resolve using available algorithms. The need to provide definitive answers to questions in such patients is increasing and the use of increasingly refined tests such as quantitation and detection of strain variation²¹ is improving diagnostic outcomes. However, the clinical acumen of the general practitioner in determining CMV organ disease (Table 2) is paramount in directing early commencement of appropriate treatment.

Therapeutics

Antivirals currently used in the treatment of CMV disease include:

- nucleoside analogues ganciclovir (GCV) and cidofovir (CDV)
- pyrophosphate analogue foscarnet (PFA), and
- antisense oligonucleotide fomivirsen.²²

Ganciclovir, CDV and PFA are administered intravenously, whereas fomivirsen is administered intraocularly.²³ An oral pro-drug of GCV (valganciclovir [valGCV]) is now available and is well tolerated in adults and children.^{24,25} Valaciclovir (VCV), the oral pro-drug of aciclovir, provides broad spectrum control of herpes viral infections and has also successfully been used as a prophylactic agent for the prevention of CMV disease.¹⁵ New antivirals that target different processes in the viral life cycle are in development, and one of these (maribavir) is showing potential as a future option for antiviral therapy.²³

Treatment and prevention

Until recently, treatment of CMV disease was primarily instigated upon discovery of related symptoms and laboratory findings. The current treatment choices in immunosuppressed patients is between long term prophylaxis at times of high risk of disease, and pre-emptive treatment guided most often by nucleic acid testing.^{19,27} The increasing availability of antiviral pro-drugs (VCV and most recently valGCV) that can be taken orally with

decreased toxic side effects has expanded the treatment options available and antiviral prophylaxis using VCV is now standard practice for the management of some groups of transplant recipients.^{15,26}

There is ongoing debate over the efficacy of pre-emptive versus prophylaxis therapy.^{26,27} Pre-emptive therapy minimises the number of patients unnecessarily receiving long term antiviral, thus reducing the incidence of toxic side effects and emergence of antiviral resistant strains.²⁷ Despite this, some comparative studies have indicated prophylaxis is superior to pre-emptive therapy for the prevention of CMV disease in renal and lung transplant recipients and delays the onset CMV disease in bone marrow recipients.^{12,13,15} More comparative studies are required to definitively determine the best management strategies for different patient groups and the long term consequences of CMV infection need to be evaluated, even if such infection is appropriately treated.

Conclusion

Infection with CMV remains an important cause of disease in Australia. Diagnostic tests and therapies have improved, and with better diagnosis, alternative mechanisms of preventing and treating CMV are emerging. There will be increasing numbers of immunosuppressed patients on oral prophylaxis or treatment for CMV in the community, and with increased education, it is likely more women will be requesting CMV testing during pregnancy. These are positive steps in reducing the burden of CMV in the Australian community, and an increased understanding of the way CMV causes disease in our patients can only improve our diagnosis and treatment of disease due to this common, serious infection.

SUMMARY OF IMPORTANT POINTS

- CMV causes serious, common infections in pregnant women, neonates and immunosuppressed patients.
- Patients infected with CMV may present with a mononucleosis-like syndrome, 'flu-like' symptoms or infections of the gastrointestinal tract.
- Methods for the laboratory diagnosis of CMV infection are readily available.
- Antivirals are available and new oral agents are being released.

Conflict of interest: none declared.

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AFF

CORRESPONDENCE

Email: w.rawlinson@unsw.edu.au