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THERAPY AND MANAGEMENT OF CMV PATIENTS WITH HIV INFECTION

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TABLE OF CONTENTS

	Page
1. INTRODUCTION	Page 1
2. DIAGNOSTIC METHODS FOR CMV	Page 2
3. CLINICAL MANIFESTATIONS AND DIAGNOSIS OF CMV SYNDROMES	Page 4
Retinitis	Page 4
Pneumonitis	Page 5
Gastrointestinal CMV Infection	Page 6
Colitis	Page 6
Esophagitis/Gastritis	Page 7
Meningoencephalitis	Page 7
4. ANTIVIRAL AGENTS FOR TREATMENT OF CMV	Page 9
Ganciclovir (Cytovene-Syntex)	Page 9
Foscarnet (Foscavir-Astra)	Page 10
5. DRUG INTERACTIONS	Page 11
6. MANAGEMENT OF CMV DISEASE	Page 12
CMV Retinitis	Page 12
CMV Pneumonitis	Page 13
CMV Colitis/Esophagitis/Gastritis	Page 13
CMV Meningoencephalitis	Page 13
7. PATIENT MONITORING	Page 14
8. MANAGEMENT OF THE PATIENT WITH CMV DISEASE	Page 15
NOTES	Page 16

1. INTRODUCTION

There are many areas of controversy regarding the role of cytomegalovirus (CMV) and the optimal therapy for CMV diseases in patients infected with the human immunodeficiency virus (HIV). The methods of diagnosing CMV and the current therapies for the conditions caused by the virus are summarized in this document.

Approximately 50 percent of the general population has been infected with CMV. In people with normal immunity, CMV remains latent and therefore the patient remains symptomless. However, if immunity is impaired, as in HIV infection, a latent CMV infection may become reactivated. Of HIV-infected patients, 90 percent will develop an active CMV infection during their illness. Of AIDS patients, up to 25 percent will have life-or sight-threatening infections due to CMV.^{1,2,3}

CMV may be acquired at any stage of life. CMV's modes of transmission are similar to those for HIV (perinatal, sexual, and blood), but acquisition of CMV in young children—for example, those in daycare—probably occurs through oral secretions.⁴ As most HIV-infected patients have already acquired CMV, the conditions caused by CMV are chiefly the result of reactivation.

Many HIV-infected patients shed CMV intermittently, even when they show no symptoms attributable to CMV. Therefore, it is often difficult for clinicians to determine whether the presence of CMV indicates a new disease caused by CMV or a coincidental reactivation of latent CMV.

The diseases most commonly associated with CMV in HIV-infected patients^{1,2,3} are:

- Retinitis
- Pneumonitis
- Colitis/esophagitis/gastritis/mucositis
- Meningoencephalitis

This report explains briefly the clinical manifestations and diagnoses of HIV patients that have acquired these CMV diseases, as well as the antiviral agents that may be used for treatment and how these agents interact in HIV patients. The report also discusses the management and monitoring of the above CMV diseases and the patients that have acquired them.

2. DIAGNOSTIC METHODS FOR CMV

The diagnostic methods used to detect CMV include:

- **Cytology/histology.** The presence of large cells (25-35 μm - "cytomegalic") each containing a large, central, basophilic intranuclear inclusion are considered pathognomonic for CMV. Such cells may be seen not only in tissue specimens but also in bronchoalveolar lavage (BAL) specimens. However, this technique is not sensitive for detection of CMV.
- **CMV culture.** Culture is generally regarded as the definitive test for detecting CMV. Urine, blood, tissue, or fluid from a BAL may be cultured for CMV.

A single culture may fail to detect CMV if the quantity of virus in the sample is low. The virus yield may be increased by culturing several specimens over a period of time. In AIDS patients, the lack of sensitivity of culture is not a major problem, as these patients usually shed virus in their secretions at high rates.

A regular culture may take many days or weeks to become positive for CMV; more rapid results (24 to 48 hours) may be obtained by using the shell-vial culture technique.

- **CMV antigens.** CMV antigens in tissues may be detected using monoclonal antibodies and immunofluorescence techniques. The immunofluorescence technique is a rapid and sensitive (80 to 100 percent) diagnostic method; it is the method used in the shell-vial culture technique.
- **Serology.** Serology tests are usually not helpful in the diagnosis of CMV disease in HIV-infected patients. Most of these patients are already CMV seropositive. Furthermore, their IgG titres may be high, making the height of the IgG titre clinically useless (as a four-fold rise in this titre may not occur). Neither is CMV-specific IgM a useful diagnostic test; it exhibits low specificity and sensitivity in HIV-infected patients.

- **CMV DNA hybridization.** Cloned subgenomic fragments of CMV have been used as probes to detect CMV DNA.⁶ Tests such as dot blot, Southern blot, *in situ* hybridization, or polymerase chain reaction can use these probes to detect CMV DNA in the tested specimens. The role of these tests in the management of CMV disease in HIV-infected patients remains to be determined.

3. CLINICAL MANIFESTATIONS AND DIAGNOSIS OF CMV SYNDROMES

This section describes the incidence, clinical presentation, clinical findings, and diagnosis for those diseases that are related to CMV in HIV-infected patients.

Retinitis

Incidence

Retinitis occurs in 5 to 40 percent of patients with AIDS.⁷

Clinical Presentation

In the initial manifestation of AIDS,^{1,2,3} retinitis occurs in less than 10 percent of HIV-infected patients. More commonly, retinitis presents itself months or years after a diagnosis of HIV infection. Retinitis usually presents unilaterally but may progress to bilateral involvement.

The patient's presenting complaint may be floaters, decreased visual acuity, or unilateral visual-field loss, although peripheral lesions may be asymptomatic.

Retinitis in AIDS patients may be rapidly progressive.

Clinical Findings

Ophthalmologic examination of the patient reveals large creamy, granular areas with perivascular exudates and hemorrhages ("cottage cheese and ketchup" appearance) in the retina. The initial lesions are usually peripheral and progress to involve the macula and optic disc.

"Cotton wool spots" also occur in CMV retinitis but are non-specific and do not progress.

Diagnosis

The diagnosis of retinitis is based on clinical findings, because it is not practical to obtain fluid or tissue from the eye. Patients with suspected retinitis but without CMV in other body fluids should be referred to an experienced ophthalmologist to confirm the clinical impression.

Pneumonitis

Incidence

CMV has been found in the lungs of 17 percent of AIDS patients with pneumonia, but only in 4 percent of those patients was CMV the single pathogen found. The role of CMV in the pathogenesis of pulmonary disease in AIDS is controversial⁸.

Clinical Presentation

An AIDS patient with pneumonitis experiences worsening dyspnea and a dry, non-productive cough.

Pneumonitis may appear to be indistinguishable from the symptoms of pneumonia caused by *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* intracellulare (MAI), or other viruses.

Clinical Findings

In pneumonitis patients, the physician will find tachypnea and tachycardia, with minimal findings on auscultation. Hypoxemia will also be evident.

The chest radiographs will show diffuse interstitial infiltrates similar to those of PCP, MAI, or other viruses.

Diagnosis

The diagnosis for CMV pneumonia is made when the following factors combine:

- 1) a positive CMV culture from lung tissue or BAL,

- 2) the absence of other pathogenic organisms, and
- 3) the presence in tissue either of cells with intranuclear inclusion bodies, or of CMV antigens, or of CMV DNA.

Gastrointestinal CMV Infection

Colitis

Incidence

Colitis occurs in 5 to 10 percent of AIDS patients.

Clinical Presentation

A patient with CMV colitis will present with a fever, diarrhea (sometimes bloody), abdominal pain, anorexia, and weight loss.

Clinical Findings

In colitis patients, abdominal radiographs may show thumbprinting. On sigmoidoscopy or colonoscopy, diffuse erythema, submucosal hemorrhages, and diffuse mucosal ulceration are seen.

Diagnosis

The diagnosis of CMV colitis is supported by the presence of CMV inclusions or CMV antigens, or a positive culture of the biopsy tissue.

To exclude other pathogens, have the stool examined by staining, culture, ova and parasite examination, and assay for *C. difficile* toxin. If these test results are negative, then sigmoidoscopy or colonoscopy should be performed, as well as a biopsy and culture for virus. The physician should keep in mind that stool specimens are not suitable for culture of CMV.

Esophagitis/Gastritis

Incidence

Esophagitis in AIDS patients is most commonly caused by *Candida* or *Herpes simplex* virus (HSV) and, less frequently, by CMV.

Clinical Presentation

The patient has severe pain on swallowing, as well as substernal or epigastric pain.

Clinical Findings

The physician may observe ulcers on the tongue, buccal mucosa, and oropharynx.

On endoscopy, there is erythema, edema, mucosal erosion, and ulceration.

Diagnosis

Diagnose using endoscopy and biopsy. If the only pathogen detected is CMV, then the patient should be treated as CMV esophagitis or CMV gastritis.

Meningoencephalitis

Incidence

Although CMV inclusions were found at autopsy in the brains of 24 percent of patients with AIDS, the respective roles of HIV and CMV infection in the neurologic complications of AIDS have yet to be clarified.

Therapy and Management of CMV
in Patients with HIV Infection

Clinical Findings

Acute meningoencephalitis may be associated with CMV, whereas HIV is the pathogen more likely associated with the subacute changes of dementia and polyneuropathy.

Retinitis is present in most patients with CMV meningoencephalitis.

CMV may sometimes be isolated from the cerebrospinal fluid (CSF).

4. ANTIVIRAL AGENTS FOR TREATMENT OF CMV

Ganciclovir (Cytovene-Syntex)

Ganciclovir⁵ is an analogue of deoxyguanosine. It is similar in structure to acyclovir but is 50 times more active against CMV *in vitro* than acyclovir. Ganciclovir is phosphorylated by a cellular kinase in CMV-infected cells. The triphosphate form is a competitive inhibitor of viral DNA polymerase.

Ganciclovir is available only as an intravenous preparation, but it has been used as intravitreal therapy in some patients. The usual doses are: for treatment, 5 mg per kilogram of body weight twice a day (BID) for 14 to 21 days; and, for maintenance, 5 mg per kilogram of body weight daily or 6 mg per kilogram of body weight for five days per week. Because ganciclovir is excreted mostly unchanged in the urine, the dose must be adjusted if renal failure occurs.

The virologic response to ganciclovir tends to precede the clinical response. From 70 to 80 percent of sites positive on culture for CMV become negative on treatment for CMV. Development of ganciclovir resistance by CMV has been described in patients on ganciclovir.

The main side effects of ganciclovir treatment are neutropenia (in -40 percent) and thrombocytopenia (in -20 percent). Other side effects also associated with ganciclovir are rash (in -2 percent), central nervous system abnormalities (in -5 percent), and gastrointestinal symptoms (in -5 percent). Azoospermia, mutagenesis, and teratogenesis have been reported as side effects in animal experiments.

Foscarnet (Foscavir-Astra)

Foscarnet is a pyrophosphate analogue that has *in vitro* activity against CMV. Its mode of action is to inhibit viral DNA polymerase. Foscarnet also has anti-reverse transcriptase activity. It is also possible that foscarnet affects HIV activity. At present, foscarnet is not licensed for prescription in Canada; it is available, however, in open clinical trials with broad inclusion criteria for the treatment of CMV. Foscarnet is available as an intravenous preparation only. The dose of foscarnet must be adjusted if renal failure occurs.

The main side effect of foscarnet is nephrotoxicity, with a reversible increase in serum creatinine in about one third of foscarnet-treated patients.

5. DRUG INTERACTIONS

Because both zidovudine and ganciclovir are myelosuppressive, the two drugs should be given concurrently only with extreme caution and frequent hematologic monitoring. Owing to the myelosuppression, the physician should consider discontinuing zidovudine during induction therapy with ganciclovir. The zidovudine could be restarted at 300 mg per day when maintenance therapy begins, or the zidovudine could be changed to another anti-HIV agent with less bone marrow toxicity, such as 2',3'-dideoxyinosine (ddI). The addition of drugs such as granulocyte macrophage colony stimulating factor (GM-CSF), which may counteract the hematologic effects, are being evaluated.

6. MANAGEMENT OF CMV DISEASE

CMV Retinitis

Suspected or confirmed CMV retinitis^{9,10,11} should be treated with ganciclovir. The initial course is 5 mg per kilogram of body weight BID for 14 to 21 days. Initial response with improvement or stabilization in vision, or in ophthalmoscopic appearance, or both, occurs in 80 percent of treated patients. This response compares to retinitis progression in 90 percent of untreated patients.

Relapse occurs almost inevitably; maintenance therapy is required indefinitely to suppress the CMV. The optimal maintenance has not been established, but the data suggests that 25 to 35 mg per kilogram of body weight per week is required for sustained remission. Relapse occurs (despite maintenance therapy) in up to 50 percent of patients.

Relapsed patients should be given a repeated course of the initial therapy (reinduction).

An indwelling line (such as a Hickman or Portacath) should be placed in those patients that have a prolonged need for intravenous therapy.

Intravitreal injection of 200 µg ganciclovir may be used for patients in whom neutropenia precludes use of systemic ganciclovir. However, intravenous therapy is the preferred treatment, because CMV is a disseminated disease in AIDS patients.

Foscarnet should be considered for patients who cannot tolerate ganciclovir or have developed resistant strains of CMV. The efficacy of foscarnet in initial treatment of CMV retinitis is similar to that of ganciclovir.

Foscarnet is administered as a continuous infusion of 20 mg per kilogram of body weight over 30 minutes, followed by 0.16 mg of kilogram of body weight per minute for two to three weeks. Recent studies have suggested that foscarnet given as 60 mg per kilogram of body weight every eight hours (Q8H) for two weeks may be as effective as continuous infusion, but further studies are necessary to confirm this finding. As with ganciclovir, maintenance therapy is necessary after the initial treatment of CMV retinitis with foscarnet. Maintenance therapy using foscarnet as a two-hour infusion, once daily, five days per week, is currently being studied.

Close ophthalmologic follow-up is essential with CMV retinitis patients.

CMV Pneumonitis

Therapy with ganciclovir should be considered when a patient has a deteriorating pulmonary status and a documented pulmonary infection,⁵ with CMV as the only pathogen identified. Of the patients treated for CMV pneumonia with ganciclovir (5 mg per kilogram of body weight BID for 14 to 21 days), 50 to 60 percent improve.

Maintenance therapy may not be required after the resolution of the CMV pneumonia.

CMV Colitis/Esophagitis/Gastritis

Potential pathogens isolated from the stool should be treated first.

If symptoms persist, an endoscopy and a biopsy should be performed. The tissue should be examined for viruses, bacteria, and ova and parasites. If CMV colitis¹² is confirmed, then treatment with ganciclovir (5 mg per kilogram of body weight BID for 14 to 21 days) will frequently lead to improvement.

Maintenance therapy is not usually necessary, although it may be considered for CMV colitis, as relapses may occur.

CMV Meningoencephalitis

Subacute encephalitis is unlikely to be due to CMV.

Acute meningoencephalitis may be associated with CMV¹³ infection of the central nervous system. Although there are no studies on the efficacy of CMV therapy in this situation, treatment with ganciclovir may be beneficial.

7. PATIENT MONITORING

All symptomatic HIV patients should have a thorough ophthalmologic examination (including dilatation for funduscopy) at regular intervals.

In the treatment of CMV disease in HIV-infected patients, the response to therapy is clinical. Virologic response to therapy does not correspond well to the clinical response. Patients on ganciclovir with persistent symptoms may be infected with organisms resistant to ganciclovir. The main side effect of ganciclovir is bone-marrow toxicity, which usually occurs early in therapy. Neutrophil and platelet counts should therefore be monitored at least twice weekly during BID dosing and weekly during daily dosing.

- If the patient's neutrophil count falls below $1000 \times 10^6/L$, ganciclovir should be reduced. If the count is less than $500 \times 10^6/L$, then the ganciclovir should be held until the counts have risen to more than $750 \times 10^6/L$.
- If the platelet count is less than $25,000 \times 10^6/L$, then the ganciclovir should be reduced or held.

The dose of ganciclovir (and foscarnet) must be modified if renal impairment occurs. Serum creatinine or creatinine clearance should therefore be monitored every two weeks.

8. MANAGEMENT OF THE PATIENT WITH CMV DISEASE

The patient will usually require hospital admission for

- confirming the diagnosis of CMV disease, if a diagnostic procedure such as a biopsy is required.
- initial intravenous therapy.
- initial monitoring of response to therapy by clinical parameters.
- initial monitoring of adverse effects by laboratory parameters.

Patients on maintenance require daily intravenous therapy, which may be arranged on an outpatient basis. Long-term venous access (such as a Hickman or Portacath) is necessary as part of this therapy.

Patients on ganciclovir should be warned about

- hematologic effects, which may be compounded by the use of zidovudine or cotrimoxazole.
- potential for carcinogenicity.
- temporary or permanent infertility.
- the mutagenic potential of ganciclovir, which is an additional reason for practising safe sex.

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