

HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE VIRAL OPPORTUNISTIC INFECTIONS IN HIV-INFECTED ADULTS

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ABSTRACT : Despite the development of highly active antiretroviral therapy (HAART), opportunistic infections continue to be seen in HIV-infected patients throughout the world. The primary reason for this is the lack of access to HAART for most people living with HIV/AIDS. For patients that have access to HAART, some may not have an effective response to therapy, due to reasons such as medication toxicity, poor adherence, or drug-resistant strains of HIV. Viral infections, in particular, are a major cause of opportunistic infections in HIV-infected adults, and can lead to significant morbidity and mortality. We have reviewed the epidemiology, clinical manifestations, diagnosis, and treatment of the most common viral opportunistic infections, including cytomegalovirus, JC virus, varicella-zoster virus, herpes simplex virus, and human papillomavirus.

Opportunistic infections continue to be a major cause of disease in patients with HIV infection. Despite the development of highly active antiretroviral therapy (HAART), opportunistic infections continue to be seen in patients who do not have access to antiretrovirals, and in patients who do not have an adequate response to antiretrovirals [1]. Viral infections are a major cause of opportunistic infections in HIV-infected adults, and can lead to significant morbidity and mortality. Cytomegalovirus, JC virus, varicella-zoster virus, herpes simplex virus, and human papillomavirus are among the most common viral opportunistic infections and will be discussed in detail below.

1. CYTOMEGALOVIRUS

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus of the herpesvirus group. CMV typically affects HIV-infected patients whose CD4⁺ T-lymphocyte counts are < 100 cells/ μ L [2]. Manifestations of CMV infection include retinitis, colitis, esophagitis, pneumonitis, and neurological disease.

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Prior to the development of HAART, the estimated lifetime probability of developing CMV retinitis was approximately 30% in patients with AIDS [3]. After the development of HAART, the number of new cases of CMV retinitis declined by approximately 55%-75% [3]. The incidence of CMV gastrointestinal disease has also significantly decreased since the development of HAART, previously occurring in up to 5% of patients with AIDS in the pre HAART era [4]. Nevertheless, CMV infection still occurs in HIV-infected patients with CD4⁺ T-lymphocyte counts < 100 cells/ μ L [2], and must be considered in patients with characteristic symptoms of CMV disease.

Clinical manifestations

Retinitis is the most common clinical manifestation of CMV disease in patients with AIDS, and usually occurs when the CD4⁺ T-lymphocyte count is further suppressed to < 50 cells/ μ L [4]. Patients typically present with floaters, scotomata, or visual field deficits when there are peripheral retinal lesions, and decreased visual acuity if there are central retinal lesions [3]. On fundoscopic examination, perivascular fluffy yellow-white retinal infiltrates are seen, and intraretinal hemorrhage may be present [3]. Without HAART or anti-CMV therapy, retinitis progresses and can lead to blindness.

CMV colitis is the next most common manifestation after retinitis, and typical symptoms include fever, weight loss, diarrhea, and hematochezia [5]. CMV esophagitis typically leads to fever, dysphagia, and odynophagia [5]. CMV pneumonitis presents with dyspnea, cough, hypoxemia, and bilateral interstitial infiltrates on chest radiography [6]. CMV can lead to neurological disease, including ascending polyradiculomyelopathy, dementia, and ventriculoencephalitis [7]. Ascending polyradiculomyelopathy resembles Guillian-Barre syndrome, and patients with dementia typically present with fever, lethargy, and confusion. Patients with ventriculoencephalitis present with acute onset of focal neurological signs and can rapidly progress to death.

Diagnosis

Diagnosis of CMV retinitis is usually made based on characteristic retinal abnormalities on fundoscopic examination [3]. In patients with CMV colitis and esophagitis, endoscopy usually shows ulcerations of the esophageal or colonic mucosa, and endoscopic biopsy specimens demonstrate characteristic intranuclear CMV inclusion bodies [5]. CMV pneumonitis can be diagnosed by finding CMV intranuclear inclusion bodies on

TABLE I
PREFERRED TREATMENT FOR CYTOMEGALOVIRUS (CMV) DISEASE [1]

DISEASE	Treatment
CMV RETINITIS	
For immediate sight-threatening disease [9]	<ul style="list-style-type: none"> ■ Ganciclovir (GCV) intraocular implant + valganciclovir 900 mg PO daily Initiate therapy promptly
For peripheral lesions [10]	<ul style="list-style-type: none"> ■ Valganciclovir 900 mg PO BID for 14-21 days, then 900 mg PO daily
Chronic maintenance therapy	<ul style="list-style-type: none"> ■ Valganciclovir 900 mg PO daily, OR ■ Foscarnet 90-120 mg/kg body weight IV daily
CMV ESOPHAGITIS OR COLITIS	
	<ul style="list-style-type: none"> ■ Ganciclovir IV OR Foscarnet IV for 21-28 days ■ Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption ■ Maintenance therapy is generally not necessary, but should be considered after relapse
CMV PNEUMONITIS	
	<ul style="list-style-type: none"> ■ Consider treatment in patients with histological evidence of CMV pneumonitis, who do not respond to treatment of other pathogens ■ Role of maintenance therapy is not established
CMV NEUROLOGICAL DISEASE	
	<ul style="list-style-type: none"> ■ Ganciclovir IV + Foscarnet IV, initially, start as promptly as possible ■ Maintenance therapy should be continued for life

PO : oral BID : twice daily IV : intravenous

lung tissue, and absence of other pathogens that commonly lead to pneumonia in patients with AIDS [6]. CMV neurological disease is diagnosed based on presenting symptoms and signs, and the presence of CMV in cerebrospinal fluid or brain tissue [7]. CMV viremia may be detected in patients with CMV end-organ disease by PCR, antigen assays, and blood culture, but viremia may also be seen in patients without end-organ disease [8].

Treatment

Treatment of CMV disease is outlined in Table I. Patients are typically treated with an induction course of antiviral therapy, followed by chronic maintenance therapy to decrease the risk of relapse.

The choice of therapy in CMV retinitis should be based on the severity and location of the lesions (see Table I). Following the induction course of therapy in CMV retinitis, chronic maintenance therapy is recommended for life, though discontinuation may be considered in patients with sustained (> 6 months) CD4⁺ T-lymphocyte counts > 100-150 cells/ μ L [11]. If chronic maintenance therapy is discontinued and the CD4⁺ T-lymphocyte count decreases to < 100-150 cells/ μ L, therapy should be reinstated to prevent relapse [11]. Patients should have dilated indirect ophthalmoscopy by an experienced ophthalmologist at least monthly throughout the treatment process.

Following the initiation of HAART, patients may develop immune recovery uveitis, which is characterized by an immunological reaction to CMV leading to posterior segment inflammation, vitreitis, macular changes, and/or papillitis [12]. It is generally seen 4-12 weeks

after initiation of HAART and manifests symptomatically with decreased vision and/or floaters. Treatment usually requires corticosteroids [1, 12].

Prophylaxis

Primary prophylaxis with oral ganciclovir in patients who have CD4⁺ T-lymphocyte counts < 50 cells/ μ L should be considered [13]. Potential adverse reactions to ganciclovir such as neutropenia and thrombocytopenia, conflicting reports of efficacy, and lack of proven survival benefit, need to be considered prior to starting therapy.

Most importantly, patients should be educated on the early manifestations of disease. Patients should be made aware that floaters or changes in visual acuity could be a sign of CMV retinitis, and should be reported to their health care provider.

2. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Introduction

Progressive multifocal leukoencephalopathy (PML) is a neurological disease caused by JC virus, a DNA virus of the papovavirus group. JC virus infects up to 90% of humans early in life, and initial infection with JC virus is usually asymptomatic [14]. In patients with AIDS, JC virus can reactivate leading to PML, which is characterized by demyelinating CNS white matter lesions. PML is usually seen in patients with AIDS who have a CD4⁺ T-lymphocyte count < 100 cells/ μ L [14].

Clinical manifestations

PML leads to CNS white matter lesions, and patients can present with hemiparesis, gait ataxia, cognitive dysfunction, speech deficits, and visual disturbances [14]. Computed tomography usually shows hypodense cerebral white matter lesions [15]. Magnetic resonance imaging typically shows areas of increased signal intensity without mass effect on dual echo MR images, and the lesions are most often located in the periventricular and subcortical white matter [15].

Diagnosis

Definitive diagnosis of PML requires the combination of a compatible clinical syndrome, characteristic radiographic findings, and brain biopsy [1]. Brain biopsy can be deferred in patients with characteristic signs, symptoms, and radiographic findings, who have JC virus detected via PCR in cerebrospinal fluid (CSF) [14]. The sensitivity of PCR for JC virus in CSF ranges from 42%-100%, and the specificity is approximately 95% [14]. Therefore, a positive CSF PCR for JC virus in the appropriate clinical setting is helpful in making the diagnosis of PML, though a negative test does not rule out PML.

Treatment

There is no therapy shown to be effective for PML. Vidarabine and cidofovir have been evaluated in clinical trials, though they have not been shown to be effective [16]. HAART has been shown to improve survival rates in patients with PML, and is considered the standard of care, though patients occasionally do not improve after the initiation of HAART despite having an increase in CD4⁺ T-lymphocyte count [14]. The prognosis of PML is poor, with the average survival time in one study estimated at 4 months [17].

3. VARICELLA-ZOSTER VIRUS

Introduction

Varicella-zoster virus (VZV) is a double-stranded DNA virus of the herpesvirus group. VZV mainly causes two syndromes, varicella (chickenpox) and herpes zoster (shingles) [18]. Chickenpox is due to primary infection with VZV and usually occurs in children, though may occur in adults. Herpes zoster is due to reactivation of latent VZV infection in dorsal root ganglia leading to a localized cutaneous rash. The incidence of herpes zoster is significantly higher in HIV-infected patients. In one cohort study, the relative risk of herpes zoster in HIV seropositive men was 16.9 compared with HIV seronegative men [19].

Clinical manifestations

Herpes zoster usually presents with an initial prodrome characterized by localized pain, itching, or tingling [18]. These symptoms usually precede the rash by 1-5 days. A maculopapular rash then develops in one or more contiguous dermatomes, which progresses to form clusters

of vesicles. The rash evolves over 3-5 days into pustules, ulceration, and crusting. Healing of the rash occurs over a 2-4 week period, and may result in scarring and pigmentation.

Progressive outer retinal necrosis (PORN) is an entity associated with VZV that usually occurs in AIDS patients whose CD4⁺ T-lymphocyte count is < 50 cells/ μ L [20]. It is characterized by a rapidly progressive necrotizing retinopathy, leading to a high rate of loss of vision and retinal detachment. Acute retinal necrosis (ARN) is also associated with VZV and is characterized by peripheral necrotizing retinitis, and also leads to a high rate of loss of vision and retinal detachment [21]. ARN usually occurs at higher CD4⁺ T-lymphocyte counts than PORN [1].

VZV may also lead to vasculitic stroke, encephalitis, and transverse myelitis, though the incidence of these complications in HIV-infected patients is not known [22].

Diagnosis

Herpes zoster and chickenpox are diagnosed clinically based on the characteristic appearance of the skin lesions. If lesions are atypical, which can occur in immunocompromised patients, a swab from a fresh lesion or a tissue biopsy sample can be submitted for viral culture, direct immunofluorescence, or PCR for VZV DNA [18]. PORN and ARN are diagnosed based on signs and symptoms, as well as characteristic funduscopic abnormalities [20-21].

Treatment

Localized dermatomal herpes zoster is typically treated with valacyclovir 1 gram orally three times per day or famciclovir 500 mg orally three times per day, for a total duration of 7-10 days [1]. Acyclovir may also be used at a dose of 800 mg five times per day, for 7-10 days. If there is extensive cutaneous involvement or evidence of visceral involvement, acyclovir 10 mg/kg IV every 8 hours is recommended until cutaneous and/or visceral disease is clearly resolving [1]. Corticosteroids are not recommended for localized dermatomal herpes zoster.

PORN can rapidly lead to loss of vision. Emergent ophthalmological consultation and rapid initiation of treatment is necessary [20]. Acyclovir 10 mg/kg IV every 8 hours in combination with foscarnet 60 mg/kg IV every 8 hours is recommended [1]. ARN will typically respond to acyclovir IV, followed by oral valacyclovir [1].

Patients who develop primary VZV infection (chickenpox) should be treated with acyclovir 10 mg/kg IV every 8 hours for 7-10 days, and conversion to oral therapy may be considered once visceral involvement has been ruled out [1].

In patients with herpes zoster or chickenpox who do not respond within 10 days of initiating antiviral therapy, acyclovir resistant VZV should be considered [23]. A culture of the lesion should be performed and submitted

for susceptibility testing. Treatment with foscarnet is the recommended alternative therapy if resistance is documented.

4. HERPES SIMPLEX VIRUS

Introduction

Herpes simplex virus (HSV) is a double-stranded DNA virus of the herpesvirus group. The prevalence of adults in the general population with serum antibodies to HSV-1 and/or HSV-2 is estimated to be between 60%-80% [24] and the seroprevalence of HSV-2 among those

12 years of age was found to be 21.9% in one study [25]. In HIV-infected patients, up to 95% are seropositive for either HSV-1 or HSV-2 [24] and are at risk for reactivation disease.

Clinical manifestations

The most common clinical manifestation of HSV-1 infection is HSV orolabialis [26]. Patients typically present with a prodrome of sensory symptoms, followed by oral lesions that progress from papules, to vesicles, to ulcers, then to crusting lesions. In patients that are untreated, the rash typically resolves after 7-10 days. Lesions can recur multiple times per year.

HSV genitalis is the usual manifestation of HSV-2 infection [27]. Following a prodromal syndrome of pain and pruritis, lesions similar to HSV orolabialis appear in the perineal area. Patients may also complain of dysuria, urethral discharge, and vaginal discharge. In patients that are severely immunosuppressed including HIV-infected patients, lesions may appear in atypical locations including the buttocks and low back, may be more necrotic and painful than in normal hosts, and tend to heal slower [28].

HSV can also cause acute retinal necrosis [29], HSV keratitis [30], HSV encephalitis [31] and herpetic whitlow [32], in HIV-infected patients.

Diagnosis

HSV infections are diagnosed clinically based on the characteristic skin and mucous membrane lesions. If lesions are atypical, which may occur in patients that are immunosuppressed, a swab from a fresh lesion or a tissue biopsy sample can be submitted for Tzanck smear, viral culture, antigen detection, or PCR for HSV DNA [33].

Treatment

HSV orolabialis and initial or recurrent HSV genitalis can be treated with acyclovir 400 mg orally three times per day, famciclovir 500 mg orally two times per day, or valacyclovir 1 gram orally two times per day, for a total of 7-14 days [1, 34].

For moderate to severe mucocutaneous HSV infections, initial therapy should be acyclovir 5 mg/kg IV every 8 hours [1, 34]. Once lesions regress, therapy can be changed to oral therapy with acyclovir 400 mg orally

three times per day, famciclovir 500 mg orally two times per day, or valacyclovir 1 gram orally two times per day. Therapy should be continued until lesions have completely healed. HSV keratitis is treated with trifluridine 1% ophthalmic solution, 1 drop into the eye every two hours, not to exceed 9 drops per day, for no longer than 21 days [1]. The recommended treatment for HSV encephalitis is acyclovir 10 mg/kg IV every 8 hours for 14-21 days [1].

In patients who do not show signs of resolution of lesions within 7-10 days after starting therapy, acyclovir resistant HSV should be considered [23]. A lesion culture should be obtained and submitted for susceptibility testing. Treatment with foscarnet is recommended if resistance is documented.

Prophylaxis

Chronic suppressive therapy may be indicated in patients with frequent or severe recurrences. Acyclovir 200 mg orally three times per day or 400 mg orally two times per day, and famciclovir 250 mg orally two times per day are recommended treatments [1, 24]. Valacyclovir 500 mg orally two times per day may also be given.

5. HUMAN PAPILLOMAVIRUS

Introduction

Human papillomavirus (HPV) is a DNA-containing virus of the papillomavirus group. Manifestations of HPV can range from anogenital warts to squamous cell carcinoma. The large majority of cases of anogenital warts are associated with HPV types 6 and 11, though HPV types 40, 42, 53, and others are also associated with anogenital warts [35-36]. The incidence of anogenital warts is significantly increased in HIV-infected women compared with women not infected with HIV. The relative risk of developing condyloma acuminata in HIV-infected women was noted to be 13.8 in one study [37].

HPV is also associated with cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN). The HPV types that are most commonly associated with CIN and AIN are types 16 and 18, though types 31, 33, 35, 45, and others are also associated with CIN and AIN [35-36]. HIV-infected women have approximately a five-fold greater risk of developing squamous intraepithelial lesions or AIN than HIV-seronegative women [38]. HIV-infected women may also develop cervical carcinoma, which is an AIDS defining illness.

Men having sex with men (MSM) in general have higher rates of anal HPV infection and AIN, and those patients that are infected with HIV are at even higher risk [39].

Clinical manifestations

Anogenital warts due to HPV infection present as pedunculated lesions that are cauliflower-like in the anogenital region [40]. Lesions may also be papular, keratotic, or irregularly shaped. Lesions may have varying colors,

including lesions that are skin colored, white, or hyperpigmented. Lesions are usually multiple and often found in clusters. Patients may or may not have symptoms, such as perianal or perivulvar itching. Depending on the grade of the lesion, patients with CIN and AIN may or may not have symptoms, which may include bleeding or itching.

Diagnosis

HPV-associated anogenital lesions are usually diagnosed based on clinical examination. In women, a thorough examination of the vulvar, vaginal, cervical, perianal region, and anal canal should be performed [1]. In men, examination of the perianal area and anal canal, as well as the genital area, should be performed. If dysplasia or malignancy in anogenital lesions is suspected or if there is uncertainty, diagnosis can be confirmed by biopsy, and biopsy should be performed earlier in HIV-infected patients due to the increased risk of dysplasia [1]. There are currently no guidelines for testing of anogenital warts for HPV DNA.

Guidelines for routine Pap smear in women should be followed [41]. There are currently no formal guidelines for anal Pap smear testing in HIV-infected men and women, though anal Pap smear can be considered in high risk men [39]. If a visible lesion is present, biopsy should be performed to evaluate for invasive anal cancer.

Treatment

Treatment of anogenital warts in HIV-infected patients is similar to treatment in patients without HIV infection [1, 42]. Patient-applied treatments are recommended for uncomplicated external lesions, and consist of topical Podofilox and topical Imiquimod. Provider-applied treatments are recommended for complex or inaccessible lesions, and treatment options include : cryotherapy with liquid nitrogen, topical trichloroacetic or bichloroacetic acids, surgical excision or electrocautery, laser surgery, and topical podophyllin resin.

Management of CIN in HIV-infected patients is not different from published guidelines [41]. There are currently no guidelines for the management of AIN, though treatment of AIN may consist of one or more of the provider-applied treatments described above for anogenital warts [1].

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