Gastrointestinal Cytomegalovirus Disease in the Immunocompromised Patient

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Cytomegalovirus (CMV) has emerged as a significant opportunistic pathogen in the era of immunosuppression. CMV was a common cause of gastrointestinal disease in AIDS patients, but the introduction of highly active antiretroviral therapy has led to a dramatic decline in AIDS-related disease. Among patients with solid organ transplants, CMV has become an increasingly important cause of gastrointestinal disease as more routine use of early CMV prophylaxis has increased delayed-onset disease, which is often tissue invasive at presentation. The role of CMV in inflammatory bowel disease is controversial; treatment may be indicated in selected cases of steroid-refractory disease with evidence of CMV. Diagnosis of gastrointestinal CMV disease generally requires endoscopic biopsy with histologic confirmation. CMV culture of biopsy material may be falsely positive because of contamination from latently infected cells. The standard induction treatment of gastrointestinal CMV disease uses intravenous ganciclovir, though the use of oral valganciclovir is increasing, especially for long-term maintenance or suppression therapy.

Introduction

Before the era of immunosuppression, cytomegalovirus (CMV) infection in adults was rarely more than a benign viral syndrome, with only sporadic case reports of more severe disease. With the advent of organ transplantation and the onset of the AIDS epidemic, however, CMV quickly demonstrated its pathogenic potential as a deadly opportunist in immunocompromised hosts. Since the 1980s, efforts to improve both the diagnosis and therapy of CMV disease have led to significant decreases in morbidity and mortality.

CMV is a DNA virus, a member of the Betaherpesvirinae family. It has a seroprevalence in adults of 80% to 90% worldwide, with some geographic variability. In the United States, 50% to 80% of people are infected before age 40, most without symptoms [1]. Primary infection in healthy adults typically occurs during the first two decades of life, ranging from asymptomatic to a "mono-like" illness. As with all the Herpesviridae family, CMV can establish a latent infection following the primary infection. Latent CMV exists in a nonreplicating or slowly replicating state in a wide host of cells, including polymorphonuclear leukocytes, T lymphocytes, endothelial vascular tissue, renal epithelial cells, and salivary glands. Secondary infection occurs by reactivation of latent virus or by new infection with a second CMV strain; it is typically associated with less viral replication, and thus less severe disease, than primary infection [2].

Gastrointestinal CMV disease has been associated primarily with AIDS, organ transplantation, and malignancy, and more recent literature describes a role in inflammatory bowel disease (IBD). CMV also has been described in case reports of patients with rheumatologic disorders, particularly lupus, and common variable immunodeficiency, as well as in the elderly. This article focuses on the role of CMV in AIDS, organ transplantation, malignancy, and IBD.

AIDS

Epidemiology of CMV disease

The introduction of the protease inhibitors in 1995 and of nonnucleoside reverse transcriptase inhibitors in 1996, used as part of a combination drug regimen termed *highly active antiretroviral therapy* (HAART), has led to a marked decline in opportunistic infections such as CMV [3]. Between 1995 and 2005, researchers documented a dramatic reduction of newly diagnosed CMV disease in a Canadian cohort, from 40 cases to 4 cases per 1000 person-years; most new cases were attributed to newly diagnosed HIV or nonadherence to therapy [4•]. Among patients in a European HIV cohort with an initial CD4 count of 200 cells/μL or less, 1.8% of patients using HAART developed CMV disease within a 24-month period, compared with 14.3% without treatment [5]. Despite these advances, 88% of patients in whom AIDS

is diagnosed report at least one gastrointestinal symptom in their lifetime; 39% report diarrhea [6]. When considering CMV as a possible cause, it is critical to assess the degree of immunocompromise and adherence to therapy. Gastrointestinal opportunistic infections typically are not seen until CD4 counts fall below 200 cells/μL, and CMV disease is rarely seen without severe T-cell impairment, typically associated with a CD4 count below 50 cells/μL [7]. In patients who are adherent to HAART, the risk for CMV disease is low: it was estimated that at least 40% of opportunistic gastrointestinal infections, including CMV disease, in patients on HAART are due to nonadherence [8••]. Even among patients with an inadequate response to therapy (defined as a persistent viral load > 100,000 copies/mL or a CD4 count < 100 cells/μL), a retrospective cohort study demonstrated a significant reduction in opportunistic infections, including CMV, in patients who continued HAART. Relapse of gastrointestinal CMV in AIDS is also low once a patient's immune system is reconstituted on HAART: the European HIV cohort reported 0.54 relapses per 100 person-years [9]. Current guidelines recommend discontinuing CMV treatment after CD4 counts improve to more than 100 cells/μL. Thus, in patients adherent to HAART and with a CD4 count greater than 100 cells/μL, CMV disease is highly unlikely and another diagnosis should be strongly considered.

Clinical manifestations and diagnosis

CMV disease can occur anywhere in the gastrointestinal tract, from the mouth to the anus. The most commonly described manifestation is colitis, accounting for about half of all CMV gastrointestinal disease; esophagitis and enteritis are the next most common. A rare but often overlooked manifestation is cholangiopathy. Oral, pharyngeal, and anal lesions are rare and can be readily diagnosed with biopsy of suspicious lesions.

Colitis and enteritis

CMV colitis in AIDS is nearly always associated with diarrhea, which is typically chronic, though it may be intermittent in up to 30% of patients [10,11]. Abdominal pain, weight loss, and fever are also frequently reported. Hematochezia is an unusual finding [12]. Endoscopic studies have found colitis alone in 20% of patients, ulcer alone in 38%, and both colitis and ulcerative disease in 39% [10,11]. Focal or diffuse subepithelial hemorrhage is a prominent finding, though it is seldom seen alone [10]. However, up to 25% of patients may have normal-appearing colonic mucosa, so blind biopsies may be needed to establish the diagnosis when the disorder is clinically suspected [11]. Multiple biopsies are often needed, as only 13% of initial biopsies from lesions later proven to be secondary to CMV were positive [13,14].

The use of flexible sigmoidoscopy versus colonoscopy for lower endoscopy to evaluate diarrhea in the AIDS patient has been controversial. Though Kearney et al. [15] found 100% sensitivity for the diagnosis of CMV colitis on flexible sigmoidoscopy, the sensitivity of left colon biopsies for all pathogens was 77%; combined biopsies of the right colon, left colon, and terminal ileum increased sensitivity to 100%. In a study comparing the sensitivity of colonoscopy versus flexible sigmoidoscopy in the evaluation of chronic diarrhea in 317 patients with AIDS, 30% of pathogens and 75% of lymphomas were identified only with colonoscopy. CMV, the most commonly identified pathogen (accounting for 24% of all those found), was identified only in the proximal colon in 34% of patients [16]. Of the pathogens found only in the proximal colon, 94% were organisms for which effective therapy is available, further demonstrating the superiority of colonoscopy in evaluating diarrhea in HIV-positive patients.

Enteritis, which has been described in about 4% of patients with CMV disease, can rarely cause perforation. When CMV infects small bowel, it tends to invade a particular region rather than becoming a panenteric process [17].

Esophagitis

CMV esophagitis occurs primarily in patients with AIDS and a CD4 count less than 50 cells/μL. It presents clinically as dysphagia, odynophagia, or both. The diagnostic gold standard for CMV esophagitis remains endoscopic biopsy. In patients without oral candidiasis or those in whom a course of antifungal therapy for odynophagia fails, the sensitivity of biopsy is 97.5% and the specificity is 100% [18]. When ulcerative esophagitis is seen on endoscopy, the differential diagnosis has historically included CMV, aphthous ulcerations (nonviral), or herpes simplex virus, which tends to cause smaller ulcerations. Overall, ulcerations or erosions were 60% predictive of CMV esophagitis. In a prospective evaluation of 110 patients, Bonacini et al. [19] discovered a higher incidence of viral culture positivity (52%–58%) than suspected by histologic examination (42%), suggesting that chronic shedding of CMV in some patients may contaminate biopsy specimens. These authors also demonstrated that *Candida* is a frequent co-pathogen, occurring in 27% of AIDS patients with viral esophagitis.

Cholangiopathy

Though declared "an endangered disease" [20] in the HAART era, cholangiopathy may still occur in patients with advanced AIDS. Before HAART, cholangiopathy occurred in 3% to 11% of patients with CMV retinitis or gastrointestinal disease, with a nonjaundiced, cholestatic enzyme pattern [21]. Elevated alkaline phosphatase levels and coexisting opportunistic infections (especially cryptosporidiosis) portend a poor prognosis. Ultrasound and CT frequently demonstrate biliary dilatation. Endoscopic retrograde cholangiopancreatography (ERCP) is more specific and also provides palliation, but no survival benefit has been shown [22].

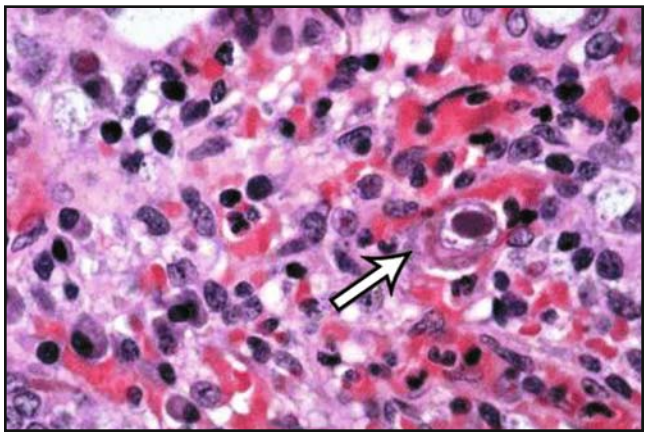

Figure 1. Cytomegalovirus inclusions are shown in an isolated colonic lamina propria cell from ulcerative colitis. In addition to the classic cytoplasmic and Cowdry type A nuclear inclusions, the infected cell (*arrow*) is markedly enlarged, illustrating the cytomegaly for which this virus is named. The nuclear inclusion consists of a large central amphophilic inclusion surrounded by a halo with peripheral chromatin condensation at the perimeter of the nucleus. The cytoplasmic inclusions consist of the amphophilic granular material at the periphery of the cytoplasm and the eosinophilic, ropelike inclusion closer to the nucleus. (*From* Kandiel and Lashner [53], with permission of Wiley-Blackwell Publishing.)

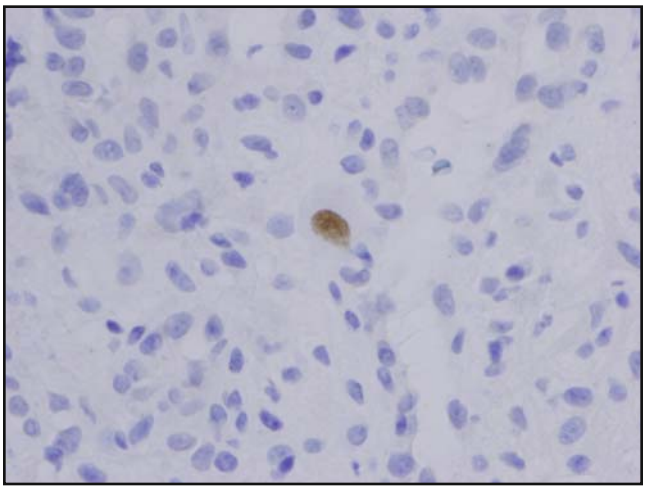

Figure 2. Colonic cell infected with cytomegalovirus in a solid-organ transplant patient (immunohistochemical [IHC] staining, original magnification ×400). (*Courtesy of* Dr. Stephanie Spingarn.)

Histology

The gold standard for diagnosing CMV disease remains the finding of cytomegalic cells on mucosal biopsy specimens using hematoxylin and eosin (H&E) staining; the cells appear as Cowdry type A intranuclear inclusions with a surrounding halo ("owl's eye" inclusions) (Fig. 1) [13]. Immunohistochemical (IHC) staining with monoclonal antibodies directed toward early antigen is also frequently used in histopathologic diagnosis (Fig. 2). Both IHC and H&E staining have been shown to have 97% sensitivity and 100% specificity, suggesting no benefit for IHC staining despite its markedly higher cost [23]. However, there is some evidence that the specificity of IHC staining is superior among the subset of patients with clinically suspected disease and normal findings on colonoscopy [24].

Organ Transplantation and Malignancy

Epidemiology

CMV disease is estimated to occur in 8% to 39% of solid-organ transplant recipients, with a predilection for the organ transplanted. The lowest rates tend to be in kidney transplantation, with the highest seen in pancreas and heart-lung transplantation [25]. Seronegative recipients receiving an organ from a CMV-seropositive donor (D+/R-) are at the highest risk; without prophylaxis, about 85% will develop primary CMV disease [25].

Before the era of prophylaxis, CMV disease usually followed the period of maximal immunosuppression, the first 6 months after transplantation or after treatment of acute rejection. The use of prophylactic antiviral agents in high-risk and intermediate-risk patients for 1 to 3 months after transplantation has reduced the overall incidence of CMV disease in these subgroups, but delayed-onset disease is becoming more prevalent. Despite prophylaxis with ganciclovir for 12 weeks, 10% of patients develop delayed-onset disease after discontinuing prophylaxis [26]. The highest-risk group remains D+/R- patients, with a cumulative incidence of 30% in the 36 months after discontinuation of prophylaxis. Of those D+/R- patients who develop disease, 40% will develop tissue-invasive gastrointestinal disease [27••,28,29]. Delayed-onset CMV disease is an independent risk factor for death, partly owing to delay in diagnosis [30]. Other risk factors increasing the risk of CMV reactivation are organ rejection [31], induction immunosuppressive therapy, bacterial sepsis and fungal disease within the first month after transplantation [27••], female gender, and younger age at time of transplantation [27••]. Despite the occurrence of delayed-onset CMV disease, antiviral prophylaxis has been accompanied by decreases in opportunistic infections, allograft rejection, and overall mortality [32].

Clinical manifestations

Patients with CMV gastrointestinal disease may present with a variety of symptoms, which are usually related to the organ affected. In our experience, fever and malaise accompany most cases. Transplant patients can present with signs and symptoms of organ rejection. Laboratory findings associated with CMV disease include thrombocytopenia, leukopenia, and transaminitis. However, in tissue-invasive disease (especially if it is late-presenting), many of these markers may be within normal ranges. Fica et al. [33•] evaluated 31 patients with tissue-invasive disease (71% with gastrointestinal manifestations) and found thrombocytopenia in 50% and leukopenia in 35.5%. The authors commented that the frequencies of leukopenia and thrombocytopenia were lower than expected, but they did not report the frequency of antiviral prophylaxis in this subgroup.

Disease can occur anywhere in the gastrointestinal tract, but colitis is most frequent, followed by gastritis, and it may range from asymptomatic to perforation or hemorrhage. Among transplant patients with gastrointestinal CMV disease, Fica et al. [33•] found that over half reported "esophagitis-gastritis" symptoms, 41% reported diarrhea, and 32% reported epigastric or thoracic pain. Gastrointestinal hemorrhage or perforation occurred in less than 10%.

CMV hepatitis, a clinical entity of CMV disease most commonly seen in liver transplant patients, occurred in up to 17% of these patients before the prophylaxis era [34]. It continues to occur in 10% to 16% of liver transplant patients, with delayed onset [28,30]. CMV hepatitis occurs less often in patients with other organ transplants and malignancies, representing less than 5% to 9% of patients diagnosed with CMV disease [27••,29,33•,35]. Pathologically, CMV hepatitis appears as microabscesses surrounding the liver lobule. Laboratory studies demonstrate transaminitis followed by an increase in γ-glutamyltransferase and alkaline phosphatase levels [25].

CMV in patients with cancer

Gastrointestinal CMV disease is rare in malignancy. In a recent review from a tertiary cancer referral center covering 236,113 cancer patients over a 10-year period, only 47 patients (0.02%) developed gastrointestinal CMV disease [35]. Of these patients, 72% had a hematologic malignancy, and most had additional factors contributing to their immunocompromised state, including AIDS or iatrogenic immunosuppression following stem cell transplantation. Among hematopoietic stem cell transplantation (HSCT) patients, the overall incidence of CMV disease is 296 per 100,000 patients. It is more frequent with allogeneic HSCT than with autologous HSCT (incidence of 608 versus 58 per 100,000) [35,36]. Graft-versus-host disease affecting the gastrointestinal tract was seen in 38% of patients with gastrointestinal CMV after allogeneic HSCT. With HSCT, CMV tissue-invasive disease most often presents as pneumonia or gastrointestinal disease, with a predilection for the stomach (48%) and esophagus (19%) [35]. Gastrointestinal CMV disease was associated with increased mortality (67%–71%), with 23% to 35% of deaths attributed to CMV itself. Predictors of increased mortality included AIDS, disseminated CMV disease, and an absolute lymphocyte count less than 1000 cells/μL [35].

Diagnosis

In contrast with AIDS-associated CMV disease, the workup of CMV disease related to transplantation or malignancy includes polymerase chain reaction (PCR) and CMV pp65 antigen. However, because of the decreased sensitivity of both markers' ability to predict CMV disease, especially in late disease, the diagnosis of tissue-invasive disease still relies on an aggressive diagnostic approach, including endoscopy with multiple biopsies of affected regions and histopathologic examination with special stains.

Endoscopy with biopsy

On endoscopy, lesions range from patchy erythema, exudates, and microerosions to edematous mucosa, multiple erosions, deep ulcers, and pseudotumors [37]. To diagnose CMV disease in transplant patients, current definitions require histologic findings of characteristic inclusion bodies on H&E staining, positive IHC staining, culture, or in situ hybridization, in addition to macroscopic lesions on endoscopy.

Using CMV DNA qualitative PCR, Peter et al. [38] tested 227 esophagogastroduodenal biopsies performed over 5 years at a single center and found that 91 specimens were PCR-positive, but only 20 (22%) had characteristic histologic findings. This study raises the same concerns as raised by viral cultures: PCR positivity is a sensitive marker, but it does not always correlate with clinical disease, probably because of contamination from latently infected cells.

Serologic markers: advances and pitfalls

Serologic testing (CMV IgG) is used during the initial assessment of a transplant patient to determine the posttransplantation risk of disease and duration of prophylaxis. Unfortunately, serology is an otherwise ineffective tool to diagnose CMV disease, particularly because most cases present as reactivation of latent virus [39]. However, CMV-seronegative recipients who receive seropositive organs are at a higher risk of developing CMV disease if they do not seroconvert [40], suggesting a decreased ability to mount an immune response to this viral infection. Serial CMV IgG measurements in D+/R- patients may help the clinician monitor those at highest risk of progression to disease.

Because of the increased morbidity and rejection associated with CMV, CMV PCR or testing for pp65 antigenemia is used in an effort to detect CMV before the onset of end-organ disease. The late CMV antigen (pp65) and quantitative CMV PCR assays both have 89% to 100% sensitivity for CMV viremia [41], but they are poor predictors of CMV disease [42]. Among patients with a positive quantitative PCR, those with persistently elevated viremia (20,000–70,000 copies/mL) are more likely to progress to disease than those with a low level of viremia [43]. Furthermore, in patients who are viremic at the time of diagnosis of tissue-invasive disease, PCR is useful for monitoring clinical response and the risk of recurrent disease. Viremia and antigenemia can often be detected 2 to 5 days before clinical symptoms, making it possible to initiate preemptive therapy for patients at risk for CMV disease [44]. These markers are also useful in identifying probable CMV disease in the first 6 months after transplantation [33•].

The routine prophylaxis of high-risk patients after solid-organ transplantation has diminished the usefulness of monitoring with PCR. Humar et al. [45] evaluated the clinical utility of CMV PCR and, using a positive cutoff value of 400 copies/mL, found a sensitivity of 38% and specificity of 60% for prediction of CMV disease in the first year after transplantation. The test characteristics were not improved by changing the viral load cutoff point for defining a positive result. Overall, the authors found that 17.6% of CMV D+/R- patients developed CMV disease, though routine PCR monitoring identified only 38% of those patients. Therefore, negative serum PCR should not exclude end-organ CMV disease, especially in the setting of new gastrointestinal complaints in the year following the end of prophylaxis.

CMV and gastrointestinal tumors

Since the 1980s, CMV has also been implicated as a causative agent in de novo gastrointestinal tumors. Reactivation of CMV and the Epstein-Barr virus (EBV) is an established risk factor in developing malignancies after transplantation, but only EBV, as the etiologic agent of posttransplantation lymphoproliferative disorder, has been directly associated with malignancies [46]. A recent case series by Adani et al. [47] reported four patients who developed gastrointestinal tumors following transplantation; all had CMV and EBV reactivation within 3 months after the procedure.

Inflammatory Bowel Disease

The role of CMV in IBD remains controversial. An association between CMV and IBD was first reported by Powell in 1961 [48]; by 2004, a systematic review had found 33 case reports and 9 case series evaluating the association of CMV and IBD [49]. Although some earlier studies suggest CMV as the cause of IBD, this conclusion is not generally supported by evidence. Most commonly reported is a CMV diagnosis in patients with previously diagnosed severe or refractory IBD who are using corticosteroids or other immunosuppressants.

The diagnosis of CMV disease remains particularly challenging in IBD, because biopsy results are similar in both disorders. The inflammation present in active Crohn's disease and ulcerative colitis often makes the typical intranuclear inclusions of CMV disease difficult to identify. However, in one series of 19 patients not responsive to intravenous corticosteroids, biopsies in 7 patients revealed characteristic intranuclear inclusions on H&E staining, confirmed with IHC staining [50]. In a study of 40 patients with steroid-refractory ulcerative colitis, CMV was identified in 2 patients using H&E staining, and in 10 patients using IHC staining, demonstrating an increased sensitivity of IHC staining in steroid-refractory patients [51]. Of the 10 patients with positive specimens, 6 had already undergone proctocolectomy, but 2 patients were given ganciclovir and were able to taper immunosuppression and avoid surgical intervention. In a study of 85 patients with IBD, Dimitroulia et al. [52] identified CMV in intestinal tissue samples from 10 patients (11.8%) using IHC staining and from 28 patients (32.9%) using CMV PCR.

The pathogenic role of CMV in IBD patients remains controversial, as its presence may simply represent viral shedding from latently infected cells localized to previously inflamed areas. However, there is some evidence that treatment of CMV infection in IBD patients may lead to clinical improvement, especially in patients with steroid-refractory disease. A review of five case series found a colitis remission rate of 67% to 100% among IBD patients with CMV infection after treatment with antivirals [53]. In the study by Dimitroulia et al. [52], 6 of the 10 patients with positive IHC staining of intestinal tissue were treated with ganciclovir, and all improved. Conversely, however, Criscuoli et al. [54] demonstrated in a small cohort of patients with severe acute colitis that 9 of 42 patients had biopsies with findings of CMV, but 4 were steroid-responsive and did not require antiviral therapy, suggesting that the presence of CMV does not always lead to steroid resistance [55]. Nonetheless, for IBD patients who are colonized with CMV and are worsening with immunosuppressive treatment, a trial of ganciclovir to treat a presumed superimposed CMV infection may be warranted. Based on these and similar anecdotal reports, CMV disease in an IBD host may best be defined as a patient with refractory IBD on immunosuppression with the presence of CMV inclusion bodies or positive IHC staining, in whom antiviral therapy allows a reduction in immunosuppression. As with transplant patients, a larger cohort is necessary to further define this clinical entity.

Treatment of Gastrointestinal CMV Disease

Intravenous ganciclovir remains the treatment of choice for induction therapy of gastrointestinal disease, but recent studies have explored the use of oral valganciclovir for the treatment of CMV disease. Valganciclovir is a valine ester of ganciclovir with a bioavailability of about 60% after oral ingestion. Absorption is facilitated by the intestinal peptide transporter PEPT1; then the drug is converted by intestinal and hepatic esterases to ganciclovir. A 900-mg dose of valganciclovir achieves serum levels comparable to 5 mg/kg of intravenous ganciclovir, though the peak tends to be lower with valganciclovir [55]. Treatment with valganciclovir has proven efficacious in AIDS patients with CMV retinitis [56]. Since its introduction, valganciclovir has been used for prophylaxis and preemptive treatment of CMV disease, but studies only recently have validated its use as a reasonable alternative to intravenous ganciclovir [57•,58•]. Although these studies have provided insight into treating those with viremia or CMV syndrome, they fail to specifically address gastrointestinal CMV disease.

Furthermore, these studies allowed clinicians to select intravenous ganciclovir or valganciclovir for treatment of disease, introducing the possibility of allocation bias.

In cases of gastrointestinal CMV disease involving severe compromise in function, valganciclovir is not recommended because of the likelihood of decreased absorption. In addition to concerns about treatment failure with inadequate absorption of valganciclovir, there is also a potential risk of developing resistance. Though resistance is rare, the most common mutations in the CMV genes *UL97* or *UL54* related to resistance have been shown to occur when a patient is exposed to an inadequate serum level of ganciclovir over an extended period [59]. Although further studies are needed, available evidence suggests that valganciclovir may be useful in mild cases of gastrointestinal CMV disease as initial treatment, or in more severe cases following intravenous induction therapy.

Adverse events associated with ganciclovir and valganciclovir are similar. Pancytopenia is the most common. Others are headache, nausea, diarrhea, lower limb edema, and peripheral neuropathy. Solid-organ transplant recipients may be more prone to neutropenia or leukopenia with valganciclovir and intravenous ganciclovir than with oral ganciclovir, although the use of oral ganciclovir is currently limited to prophylaxis [60].

For ganciclovir-resistant CMV disease, other therapeutic options are foscarnet and cidofovir. Nephrotoxicity is associated with both agents. Though virustatic, foscarnet has proved efficacious in cases of ganciclovir-resistant CMV disease. Cidofovir is infrequently used because of the risk of iritis, which occurs in as many as 41.2% of patients (especially those with higher CD4 counts) and presumably is due to immune reconstitution [61].

CMV immunoglobulin, either alone or in combination with antiviral medications, is not currently indicated for the treatment of CMV gastrointestinal disease. A small mortality benefit may exist, but there is significant heterogeneity among the studies evaluating its use in CMV disease [62].

In summary, first-line induction treatment for gastrointestinal CMV in both organ transplantation and AIDS is currently intravenous ganciclovir, 5 mg/kg every 12 hours for 14 to 21 days or until there is documented clearance of viremia or significant clinical improvement. The best duration of oral valganciclovir maintenance therapy to prevent relapse after intravenous induction remains unknown. A large international randomized study comparing valganciclovir with intravenous ganciclovir for treatment of CMV disease in transplant patients focused on patients with CMV viremia [58•]. Because of variability in treatment approaches, consultation with a local transplant infectious disease specialist is recommended. For patients with AIDS, initiation of ganciclovir is the primary treatment, with the long-term goal of restoring immune function with HAART. In the *MMWR* 2004 guidelines, Benson et al. [7] suggest that some HIV specialists may withhold or discontinue anti-CMV therapy in cases of mild gastrointestinal disease if prompt immune restoration is expected. However, in our experience, because patients with CMV are often nonadherent, long-term maintenance therapy or suppressive treatment is indicated to prevent progression of disease.

Conclusions

Over the past decade, mortality due to CMV disease has significantly decreased in immunocompromised patients because of better knowledge of the disease and improved diagnostic and treatment modalities. Among HIV-positive patients, the advent of HAART has led to the near-elimination of CMV disease in the developed world. Therefore, evaluation for CMV should generally be limited to newly diagnosed patients presenting with advanced AIDS and those nonadherent to antiretroviral therapy who have a CD4 count less than 50 cells/μL.

Today, the immunocompromised patient who develops gastrointestinal CMV disease will most likely be a transplant patient presenting with delayed-onset disease. Delayed-onset CMV disease is associated with more potent antiviral prophylaxis and remains an independent predictor of mortality. Serologic markers such as PCR are frequently negative 6 months after transplantation, so clinicians must remain vigilant for new gastrointestinal symptoms in the 12 months following CMV prophylaxis. Recent case series have focused on the role of CMV disease in patients with refractory IBD. Although successful uses of antiviral treatment have been reported, a controlled trial is needed to fully define the impact of antiviral therapies.

Clinical manifestations and diagnostic techniques were well characterized in AIDS patients in the pre-HAART era; further studies in transplant and IBD patients are needed to better describe clinical manifestations and guide diagnostic techniques.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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have been highlighted as:

- • Of importance
- •• Of major importance

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