Review Article

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Cytomegalovirus in Inflammatory Bowel Disease - Clinical Relevance.

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Abstract

Background: Cytomegalovirus is a common and self-limiting infection in general population, but in immunocompromised states it has been implicated in severe complications like pneumonia and colitis. It could also be an innocent bystander(coloniser) in colon. In Inflammatory bowel disease there has been an association with severe colitis and flares of disease,with a reported prevalence of 4.5–16.6%, and as high as 25% in patientsrequiring colectomy for severe colitis. The role of CMV in the deterioration of the IBD disease is still debatable. There is also no global consensus in defining this entity. The clinical relevance of the presence of CMV in IBD patients is our question-whether it is a bystander or clinically significant.

Aim: To analyse the clinical relevance of Cytomegalovirus in patients with inflammatory bowel disease, including epidemiology, clinical features, diagnosis and management options.

Methods: Literature search was made using Pubmed, EMBASE and the Cochrane resources with the search words: CMV in Inflammatory Bowel disease, cytomegalovirus colitis, CMV treatment.

Results: Cytomegalovirus infection is common in patients with Inflammatory Bowel Disease. CMV disease and CMV reactivation is common in patients with severe colitis, with a prevalence of 4.5–16.6%, and upto 25% in patients with severe colitis requiring colectomy. The clinical outcome of patients with reactivation is poorer compared to those without reactivation. However, 71-86% of patients who underwent treatment with antivirals showed disease remission.

Conclusions: From the literature review, we can infer that, testing for CMV should be considered in patients with flare of disease having moderate to severe activity, by doing biopsies for microscopic evidence of CMV activity, Immunohistochemistry, tissue for Real time Polymerase Chain reaction. Ganciclovir treatment showed good results in these group of patients.

Key Words: Cytomegalovirus infection, Cytomegalovrus Disease, Inflammatory Bowel Disease, Flare, Severe Colitis, Steroid Refractory Colitis, Clinical relevance.

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Introduction

Inflammatory bowel disease is a relatively immune compromised state and patients are prone for various infections. One among the infections is Cytomegalovirus related. CMV is usually an asymptomatic infection in healthy adults and may remain as a lifelong latent infection. Cytomegalovirus seroprevalence is noted to be high even in general population in Asia about 70%-90%.[1] It can cause serious complications in the immunocompromised individuals presenting clinically as Pneumonia and colitis.It is implicated as one of the cause of flare of IBD disease. The highest prevalence of CMV infection and CMV intestinal disease is noted in steroid refractory disease, for each definition of CMV used. CMV in IBD patients is an important clinical entity associated with high morbidity and mortality.

There is no gold standard definition for clinically relevant CMV infection in IBD patients. CMV infection is defined as isolation of the CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen

CMV gastrointestinal disease is defined by identification of a combination of

1. clinical symptoms
2. findings of macroscopic mucosal lesions on endoscopy and
3. demonstration of CMV infection (by culture, histopathology, IHC, or in situ hybridization) in a gastrointestinal tract biopsy specimen.

Clinically relevant describes the situation that symptoms appear, clinical deterioration occurs, and (antiviral) treatment should be initiated.

The recent ECCO guideline mentions that different techniques for diagnosis of CMV infection are available, but stops short of defining a gold standard. The guideline refers to histopathology combined with IHC (using monoclonal antibodies) as highly specific and sensitive for verifying CMV infection in tissue. In addition the guideline describes quantitative PCR in tissue and in blood as the most commonly used and advantageous technique for diagnosis of CMV infection.

Inclusion Criteria:

There are no prospective randomised control trials on this subject. Hence, observational, case control studies and retrospective studies have been included in the analysis.

Outcome assessment

The primary outcomes were: (1) all used definitions of CMV infection or CMV intestinal disease in IBD patients; and (2) the reported prevalence of CMV in IBD patients. Secondary outcomes were: (1) prevalence of CMV in subpopulations as ulcerative colitis (UC), Crohn's disease (CD), steroid refractory disease; and (2) prevalence of CMV in different regions of the world. There is also a summary of different diagnostic strategies for CMV infection in IBD patients.

Results

The search strategy generated 194 relevant articles published till now, of which only 52 eligible articles were chosen.

Review of literature:

Epidemiology of CMV:

Domenech et al. reported the prevalence of anti-CMV IgG antibodies in four groups of patients with UC and healthy controls from Spain.[7] The prevalence was similar in the five groups (61–76%). Prior exposure to CMV was, therefore, similar in patients and controls. Yi et al. reported different findings among patients and controls from China: 73% of patients with UC, 89% of those with Crohn's disease (CD) and 51% of controls had anti-CMV IgG antibodies.[8] The prevalence in the control group was much lower than expected and the results may not be generalisable.

If CMV reactivation were associated with a relapse of UC, then the prevalence of serum anti CMV IgM antibodies would be raised. Similarly, molecular techniques such a CMV-specific PCR would show the virus. To date, this has not been the case. Roblin et al. reported 16 patients with CMV colitis, all had serum anti-CMV IgG antibodies but none had anti-CMV IgM antibodies, although three had CMV DNA in their blood.[9] Iida et al. found none of the 79 patients they reported with moderate or severe UC, who were anti CMV IgG antibody positive, had serum IgM antibodies to CMV.[10] Recent exposure to CMV is unlikely to precipitate a relapse of UC and CMV in the intestine does not appear to invoke a systemic IgM antibody response.

In an observational study, CMV genome was detected using PCR on intestinal tissue samples in 32.9% of the inflammatory bowel disease (IBD) patients and only in 2.4% of the controls. The

individuals in the control group were patients who had colonoscopy for other reasons such as anaemia or non-IBD.[11] The exact prevalence of CMV disease in IBD patients is not entirely clear; mainly due to selection bias and methods used to diagnose CMV infection, but histological prevalence has been reported between 4.5 and 16.6% (see Table 1).[12]

Table 1: Prevalencebydefinitionofcytomegalovirus-infection

Definition	Studies,*n*	Median	Range
Antigenemia[17-21]	5	32%	6%-34%
TissuePCR[22-25]	4	11%	1%-32%
IHC1[26-29]	4	13%	9%-23%
HE[30-32]	3	17%	5%-36%
HEorIHC[33,34]	2	8%	5%-11%
HEandIHC[35,36]	2	19%	12%-27%
IgMorHEorIHC2[37,38]	2	9%	5%-13%
Antigenemia or Tissue PCR[39]	1	NA	NA
Serum PCR[40]	1	84%	-
(HE and IHC) or tissue PCR[41]	1	4%	-
Tissue PCR 10 copies/µg; OR histology OR Antigenemia[42]	1	54%	-
Antigenemia (2 tests: C7-HRP OR C10/C11) OR histology[43]	1	9%	-
Antigenemia or blood PCRquantitative[44]	1	36%	-
IgM or serum PCR or HE[45]	1	78%	-
IgM or tissue PCRqualitative or HE[46]	1	16%	-
IgG and (blood culture, antigenemia or histology or IgM or urine culture)[47]	1	6%	-
IgM or serum PCRqualitative or feces PCR[48]	1	5%	-
Inclusions: HE[49]	1	13%	-
Active infection: tissue PCR[50]	1	13%	-
Active replication: (HE or IHC) and antigenemia[51]	1	36%	-
Blood dissemination: (viremia, antigenemia, RNAemia) or (viremia or tissue culture)[52]	1	16%	-
Total:21	Total:36		

One study defined a clinically relevant infection as > 10 IHC + cells/section but also recognized "scattered" positivity as 1-9 cells per section[29]; 2Once mentioned as "acute infection". PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IHC: Immunohistochemistry; IgM: Immunoglobulin M; IgG: immunoglobulin G; NA: Not applicable.

Table 2: Prevalence by definition of cytomegalovirus-intestinal disease

Definition	Studies,*n*	Median	Range
HE or IHC1[38,44,53,54]	4	6%	2%-29%
HE[20,55]	2	9%	0%-17%
Tissue PCRquantitative > 10 copies/mg[56,57]	2	34%	-
Serology and (IHC or antigenemia or serum PCR or tissue PCR)[58]	1	6%	-
IHC[59]	1	0%	-
HE or IHC or tissue PCR[51]	1	33%	-
(Pp65 antigenemia or tissue PCRquantitative) and IHC and intestinal symptoms[39]	1	NA3	-
IHC positive when inflammation present[52]	1	1%	-
Total:8	Total:13		

[1]One study tested both before and after iv-steroid administration; 2No data on prevalence: definition is used as the gold standard to compare other diagnostics;

[3]No prevalence is reported in this study. PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IHC: Immunohistochemistry.

Table 3: Prevalence by definition of cytomegalovirus-reactivation

Definition	Studies,*n*	Median	Range
IgM or HE or PCR1[60]	1	10%	-
Serum PCR in IgG positive patients[61]	1	0%	-
Antigenemia or plasma PCR[62]	1	36%	-
Total:3	Total:3		

1Not specified what material is used for PCR testing. PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IgM: Immunoglobulin M; IgG: Immunoglobulin G

Clinical and endoscopic features

Clinical suspicion of CMV viraemia should be directed towards IBD patients presenting with

prominent systemic symptoms, especially fever, lymphadenopathy,

splenomegaly, leucopenia and mild hepatitis.[17] However, CMV colitis need not have such features.

Iida et al.[10] reported the endoscopic features of patients with UC and CMV. Patients were subdivided according to the presence of CMV antigen. There were no features that were diagnostic of CMV infection, but 'punched-out ulcers' and 'geographic ulcers' were more common in steroid-refractory patients' with CMV than those without CMV (P = 0.055 and 0.087, for punched-out and geographical ulcers respectively); however, these ulcers were substantially more common in steroid-refractory disease than in patients not receiving steroid therapy suggesting that ulceration was a manifestation of disease severity and not of CMV infection. Suzuki et al.[18] found an association between CMV anti-genaemia and longitudinal ulceration; they claimed that such ulceration was 100% sensitive and 95% specific for CMV.

Omiya et al.[19] took a different approach to a series of 20 in-patients being treated for UC: they treated 10 patients with deep ulceration with anti-viral therapy, but gave standard therapy to the others; all the patients on standard therapy responded, but the outcome for those with deep ulceration was less good: three underwent colectomy. They concluded that the absence of deep ulceration was predictive of latent CMV. This is partially true, 5/10 patients with deep ulceration had CMV DNA in mucosal biopsies, while only 2/10 patients without deep ulceration had CMV DNA. The risk of colectomy appeared greater in those with CMV, 2/7 underwent colectomy, compared with 1/13 without CMV. Arguably the CMV, like deep ulceration, was a marker of severe disease.

Diagnosis

Latent or subclinical CMV infection has a high prevalence in the population.[1,2] Serum anti-CMV IgG antibodies have high specificity and sensitivity for latent infection, and IgM antibodies for acute infection or reactivation of CMV infection with viraemia, but this does not correlate with active CMV colitis.[20] There is no clinical role for measuring antibodies to CMV unless viraemia is suspected, when qPCR for CMV DNA would be a more useful investigation.

Cytomegalovirus may be found in the colon. Techniques used to demonstrate the virus include haematoxylin and eosin (H&E) staining, immune histochemistry (IHC) and PCR.[7, 9, 21] Each has been used to attempt to quantify the infection, qPCR being the most appropriate to determine viral load.

Haematoxylin and eosin staining may demonstrate typical CMV inclusions. The hallmark histological feature being cells that are larger than normal with intranuclear inclusions which can be surrounded by clear cytoplasm giving the 'owl's eye' appearance (Figure 1a). Although this method is highly specific (92–100%) the sensitivity can be as low as 10–87%, resulting in false negative biopsies.[22, 23] However, sensitivity may be increased to 78–93% [22, 23] by the use of IHC with antibodies to CMV early antigen.

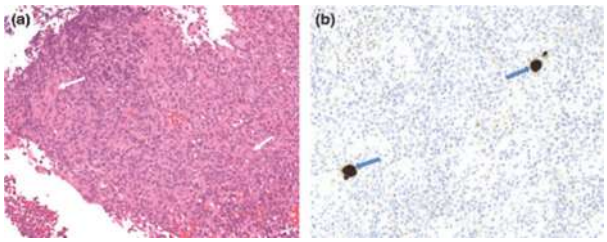

Fig. 1

(a) Haematoxylin and eosin staining of colonic mucosa in CMV disease from a patient with ulcerative colitis demonstrating typical CMV inclusions (arrows). (b) Immune histochemistry of colonic mucosa in CMV disease from a patient with ulcerative colitis demonstrating CMV inclusions (arrows). Courtesy of Professor Fiona Campbell, Royal Liverpool University Teaching Hospital.

Qualitative and quantitative PCR for CMV DNA from colonic tissue is a highly specific (93–98.7%) and sensitive test (92–96.7%).[24, 25] Qualitative PCR can detect viral DNA in the colon, although the significance of a positive result and differentiating between CMV infection and disease is unclear. Quantitative PCR may be more accurate; however, no cut off value has yet been defined. It has been suggested that a CMV DNA load >250 copies/mg of tissue in moderate to active UC is predictive of resistance to steroids, infliximab and cyclosporine.[9]

The European Crohn's and Colitis Organisation recommend tissue PCR or immunohistochemistry for diagnosing CMV colitis in IBD.[26]

Monocyte recruitment and CMV

In the colon, CMV is considered to be reactivation of latent infection. In latent disease, CMV resides in mononuclear cells. In the presence of inflammation, there is monocyte recruitment to the colon. Hommes et al.[27] proposed that the cytokine milieu of the colon, rich in TNFα and interferonγ in

active UC, leads to differentiation of CMV-infected monocytes into macrophages with reactivation of the latent disease. It has been argued that the risk of CMV reactivation differs in UC and CD, because the relative amounts of TNFα and interferonγ favours reactivation in UC more than in CD.20 This is supported by reports showing that CMV colitis is uncommon in CD,[28-30] although others have been less persuasive.[21]

Severe colitis and steroid resistance

Kojima et al. reviewed 126 surgical specimens of patients with UC to explore the clinicopathologic features of CMV and concluded that the clinical prevalence of CMV is higher (15% and 25% for HE and IHC respectively) in patients with severe UC undergoing surgery than in those with refractory UC (1.3% and 8.3%, $P < 0.05$) and much lower in patients with UC-related dysplasia (0% for both HE and IHC).[31] These results suggest that CMV is associated with the severity of colitis rather than its treatment.

There are many case reports which suggest that colonic CMV superinfection in existing IBD causes more symptoms with increased prevalence of toxic megacolon and surgical intervention,[32] but the issue remains controversial. Domenech et al. reported a colectomy in three out of six patients with active steroid-refractory UC and CMV disease, compared with only 2 of 13 steroid-refractory cases without associated CMV disease.[7] A case–controlled study by Kambhm et al.[33] linked unrecognized and therefore untreated CMV infection in steroid-refractory UC with higher surgical intervention risk.

Matsuoka et al.[34] reported the clinical outcomes in 69 patients with moderate to severe UC, who were tested for CMV reactivation every 2 weeks for 8 weeks using the CMV anti-genemia assay and serum quantitative real-time PCR assay for CMV: 48 patients were sero-positive for CMV but the study showed that clinical outcomes including rates of remission and colectomy were not significantly different among the CMV reactivation-positive and negative patients. These data, then, suggest CMV does not influence the course of the relapse.

There have been two recent studies reporting viral load and outcomes. In 2010, Leveque et al.[21] reported no relationship between colonic CMV DNA load and disease severity in seven patients; in five of six cases not treated with anti-viral therapy, immunosuppression was increased and resulted in clinical improvement. A year later, Roblin et al.[9] reported that there was no correlation between detection of CMV DNA and the Mayo endoscopic score; furthermore the 'threshold of CMV load did not influence the results'. However, Roblin et al. did find a relationship between CMV DNA load and clinical outcome: a positive colonic CMV load was associated with steroid resistance (Likelihood ratio 3, sensitivity 50% and specificity 100%); CMV DNA >250 copies/mg tissue was predictive of resistance to steroids and two immunosuppressives (Likelihood ratio 4.3, sensitivity 100% and specificity 66.6%). They recruited 42 consecutive patients exhibiting moderate to severe flare ups of UC in a prospective observational study. All patients underwent a colonoscopy or flexible sigmoidoscopy <24 h after inclusion and colonic biopsies were taken to measure CMV DNA viral load by real-time PCR. CMV DNA was detected in inflamed tissue of 16 patients. All 42 patients were treated as established by the European guidelines. They received i.v. steroids and those who were steroid resistant at day 7 received second line therapy with either ciclosporin or Infliximab. If clinical remission was not observed then one therapy was switched to another. Eight of the 16 patients positive for colonic CMV DNA failed to respond and were commenced on i.v.Ganciclovir for 10 days followed by oral valganciclovir for 15 days along with immunosuppressive therapy. One patient did not achieve clinical remission and required emergency colectomy. The other seven patients all achieved clinical remission and remained in remission at 6 months with no CMV DNA detected on repeat colonic biopsies at day 30 ± 5 days.

Delvincourt et al.[35] reported that CMV reactivation does not appear to alter the course of IBD flares and that treatment directed at CMV does not impact on IBD course. They carried out a retrospective case–controlled study comparing a population of UC patients (n = 26) with relapses and PCR evidence of CMV viraemia without anti-viral treatment to matched patients with blood negative CMV PCR. They found no difference between the two groups, regarding length of stay (8.7 days vs 9.7 days for CMV+ and CMV− patients respectively; $P = 0.42$) and colectomy rate (15.4% and 23.1% for CMV+ and CMV− patients respectively; $P = 0.48$). The same group also looked at 110 hospitalisations for relapse of UC with CMV reactivation (80 diagnosed on blood PCR, 33 on tissue PCR) in three French referral centres; evolution following CMV reactivation diagnosis was compared between those receiving anti-viral treatment and those who

did not. There were no differences in the treated and untreated groups of patients with regard to age, gender, IBD type, immunosuppressant, CRP and haemoglobin level. They reported that no differences were observed in CRP level decrease at 10 days and colectomy rate at 3 months (10.6% vs. 13.3%; P = 0.7) between the two groups. They also reported that the group receiving anti-viral treatment had a longer period of hospitalisation (16.3 days vs. 8.3 days; P < 0.001). The findings in this study suggest that patients with latent CMV or reactivation with evidence of CMV viraemia, who are treated with anti-virals have no difference in acute colitis outcomes when compared to those who are not treated with anti-virals. These findings are similar to those of Matsuoka et al.'s[34] study. However, as we have mentioned earlier, latent or subclinical CMV does not correlate with CMV colitis which requires colonic tissue for diagnosis. Delvincourt's group did compare 33 patients who had positive colonic tissue CMV PCR, and reported no difference in outcomes (CRP level drop, length of hospital stay and colectomy rate) between those treated and not treated with anti-virals. However, the CMV DNA cut-off value for diagnosing CMV colitis was not stated and the positive PCR results if low values may have reflected latent CMV detected in colonic tissue.

In general, the prevalence is negligible in healthy controls. We found a higher prevalence in UC than in CD both for CMV infection (median 14% vs 2.5%) and CMV intestinal disease (median 19.5% vs 11%). The prevalence is highest in steroid refractory disease for CMV infection (median 32.5%) and intestinal disease (median 32.5%.).

Diagnostic tests for CMV

More than 10 different tests were used to diagnose CMV (active) infection and intestinal disease, which can be found in the definition Tables Tables22 and and3.3. Histology, with or without immunohistochemistry (IHC), is most widely used to diagnose CMV disease (infection and/or intestinal disease; n = 30/48). PCR on tissue is used in almost one third of the included studies (14/48). In Table Table55 we present an overview of the test characteristics as described earlier in literature[24,63-70].

Table 4: Testcharacteristicsdifferentdiagnostictoolsforcytomegalovirus

Test	Pro	Con	Sens	Spec
Serology	Fast, quantificationpossible	Systemic,notprovingintestinaldisease;	98%-100%	96%-99%
Antigenemia	Fast, quantificationpossible	Systemic,notprovingintestinaldiseaselaborintensive	60%-100%	83%-100%
SerumPCR	Fast, quantificationpossible	Systemic,notprovingintestinaldisease	65%-100%	40%-94%
HEHistology (goldstandard?)	Specific,proofsintestinaldisease	Slow;lowsensitivity	10%-87%	92%-100%
HistologywithIHC	Specific,proofsintestinaldisease	Slow	93%	92%-100%
TissuePCR	Quantificationpossible	Cut-offpointunclear,uncertainclinicalsignificance	65%-100%	40%-100%
StoolPCR	Quantificationpossible	Littleexperience	83%%	93%
ViralCulture	Veryspecific	Veryslow	45%-78%	89%-100%
RapidVialculture	Veryspecific	Littleexperience	68%-100%	89%-100%
Rapid Vial culture	Very specific	Little experience	68%-100%	89%-100%

Sens: Sensitivity; Spec: Specificity; PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IHC: Immunohistochemistry.

H&E, haematoxylin and eosin; IHC, immune histochemistry; PCR, polymerase chainreaction.

Role of immunosuppression

The role of immunosuppression has been addressed by several groups. It is common to see CMV complicating acute severe colitis in patients who are taking immunosuppressives. In a large retrospective observational study by Raed Al-Zafiri which compares the outcome of IBD patients with and without CMV infection in patients with acute relapse, all the patients with CMV were on standard immunomodulators in addition to steroids.36

In a systematic review of nine case series and 33 case reports over a period of 40 years, CMV was detected in the setting of acute severe

Table 5: Histological prevalence of CMV disease in IBD patients

Study	Patient group	Prevalence	Diagnostic test
Kim et al.[50]	New onset UC	4.5% (3/65)	H&E and IHC
Leveque et al.[17]	IBD exacerbations	10.4% (7/53)	Colonic tissue PCR
Kim et al.[51]	Acute IBD exacerbation	8% (12/142)	IHC
Domenech et al.[7]	UC patients	5% (6/114)	H&E and IHC
Criscuoli et al.[38]	Acute colitis (IBD) admissions	16.6% (7/42)	H&E
Kambham et al.[29]	Severe UC	13.8% (11/80)	H&E and IHC

colitis. All cases received corticosteroids for a prolonged period of time before CMV infection was diagnosed. In five of nine studies, patients also received some form of immunosuppression with thiopurines or cyclosporine.[27] It is well known that CMV infection can be re-activated in patients on immunosuppression. For example, in patients with organ transplants or HIV patients with acquired immunodeficiency it has a clear pathogenic role causing systemic or organ specific disease. HIV patients who are treated with anti-retroviral therapy have a reduction in the CMV related disease.[37]

In a prospective study of 63 patients (61 ulcerative colitis and two CD) treatment with azathioprine in addition to steroids was found to be a significant risk factor associated with CMV infection.[38]

Patients receiving anti-TNF agents have also been studied[39]; these agents might lead to a reduction in macrophage differentiation and CMV reactivation. This clinical approach is supported by the experience of D'Ovidio et al. in which nine patients with CMV viraemia, three of whom had CMV colitis: neither the CMV infection nor the colitis worsened with infliximab therapy.[40]

Despite the clear association, it is difficult to prove that CMV is a causative factor in the pathogenesis of severe colitis or whether it simply represents a surrogate marker of a severe or steroid-refractory disease. There is an extensive literature concerning CMV complicating acute severe colitis, the role of CMV in CD is less established, although this group of IBD patients is expected to be on some form of immunosuppression in addition.

Treatment of CMV colitis

Colitis remission rates after antiviral treatment in IBD patients with CMV infection range from 67% to 100% (Table 2).37-40 When the full course of antiviral therapy is completed, immunosuppressant therapies including thiopurines 41 may be safely recommenced.

Table 6: Outcome of IBD patients with CMV colonic disease following treatment with anti-viral therapy

Study number (*n*)	Patient group	Colonic CMV Diagnostic test	Anti-viral treatment	Outcome/ results
Delvincourt et al.31(n = 33)	Acute UC and CMV colonic disease	Semi-quantitative PCR	22 received anti-viral treatment 11 did not receive anti-viral treatment	No difference between two groups in CRP drop, length of stay, colectomy rate
Roblin et al.9(n = 8)	Moderate to severe UC and CMV colonic disease who failed to respond to medical therapy with i.v. steroids and IFX or CsY	Quantitative PCR	All eight received anti-viral treatment	Seven achieved clinical remission and remained in remission at 6 months 1 required colectomy
Cottone et al.37(n = 7)	Admissions with acute colitis and CMV colonic disease (5UC, 2CD colitis)	H&E/IHC	Six received anti-viral treatment	Five achieved clinical remission One required colectomy
Vega et al.40(n = 7)	Acute IBD admissions refractory to i.v.steroids and CMV colonic disease (6 UC, 1 CD)	H&E/IHC	All seven received anti-viral treatment	Five achieved clinical remission One required colectomy One achieved remission with CsY

- CMV, cytomegalovirus; UC, ulcerative colitis; CD, Crohn's disease; PCR, polymerase chain reaction; CRP, C reactive protein; IFX, Infliximab; CsY, cyclosporine; H&E, haematoxylin and eosin; IHC, immune histochemistry.

Ganciclovir is a nucleoside analogue that acts by inhibiting viral DNA polymerase. It is the first line treatment for CMV infection which is given intravenously, at a dose of 5 mg/kg, twice per day, initially. If there is a clinical response then it may

Revised Rates for 2019 (Institutional)

Title of the Journal	Frequency	India(INR) Print Only	India(INR) Online Only	Outside India(USD) Print Only	Outside India(USD) Online Only
Dermatology International	Semiannual	5500	5000	430	391
Gastroenterology International	Semiannual	6000	5500	469	430
Indian Journal of Anatomy	Quarterly	8500	8000	664	625
Indian Journal of Anesthesia and Analgesia	Bi-monthly	7500	7000	586	547
Indian Journal of Cancer Education and Research	Semiannual	9000	8500	703	664
Indian Journal of Communicable Diseases	Semiannual	8500	8000	664	625
Indian Journal of Dental Education	Quarterly	5500	5000	430	391
Indian Journal of Diabetes and Endocrinology	Semiannual	8000	7500	597	560
Indian Journal of Genetics and Molecular Research	Semiannual	7000	6500	547	508
Indian Journal of Hospital Administration	Semiannual	7000	6500	547	508
Indian Journal of Hospital Infection	Semiannual	12500	12000	938	901
Indian Journal of Medical & Health Sciences	Semiannual	7000	6500	547	508
Indian Journal of Pathology: Research and Practice	Bi-monthly	12000	11500	938	898
Indian Journal of Preventive Medicine	Semiannual	7000	6500	547	508
International Journal of Neurology and Neurosurgery	Quarterly	10500	10000	820	781
International Physiology	Triannual	7500	7000	586	547
Journal of Cardiovascular Medicine and Surgery	Quarterly	10000	9500	781	742
Journal of Global Medical Education and Research	Semiannual	5900	5500	440	410
Journal of Global Public Health	Semiannual	12000	11500	896	858
Journal of Microbiology and Related Research	Semiannual	8500	8000	664	625
Journal of Organ Transplantation	Semiannual	26400	25900	2063	2023
Journal of Orthopedic Education	Triannual	5500	5000	430	391
Journal of Pharmaceutical and Medicinal Chemistry	Semiannual	16500	16000	1289	1250
Journal of Practical Biochemistry and Biophysics	Semiannual	7000	6500	547	508
Journal of Radiology	Semiannual	8000	7500	625	586
New Indian Journal of Surgery	Bi-monthly	8000	7500	625	586
Ophthalmology and Allied Sciences	Triannual	6000	5500	469	430
Otolaryngology International	Semiannual	5500	5000	430	391
Pediatric Education and Research	Quarterly	7500	7000	586	547
Physiotherapy and Occupational Therapy Journal	Quarterly	9000	8500	703	664
Urology, Nephrology and Andrology International	Semiannual	7500	7000	586	547
Indian Journal of Maternal-Fetal & Neonatal Medicine	Semiannual	9500	9000	742	703
Indian Journal of Obstetrics and Gynecology	Quarterly	9500	9000	742	703
Indian Journal of Emergency Medicine	Quarterly	12500	12000	977	938
Indian Journal of Trauma and Emergency Pediatrics	Quarterly	9500	9000	742	703
Journal of Emergency and Trauma Nursing	Semiannual	5500	5000	430	391
Indian Journal of Forensic Medicine and Pathology	Quarterly	16000	15500	1250	1211
Indian Journal of Forensic Odontology	Semiannual	5500	5000	430	391
Indian Journal of Legal Medicine	Semiannual	8500	8000	664	625
International Journal of Forensic Sciences	Semiannual	10000	9500	781	742
Journal of Forensic Chemistry and Toxicology	Semiannual	9500	9000	742	703
Community and Public Health Nursing	Triannual	5500	5000	430	391
Indian Journal of Surgical Nursing	Triannual	5500	5000	430	391
International Journal of Pediatric Nursing	Triannual	5500	5000	430	391
International Journal of Practical Nursing	Triannual	5500	5000	430	391
Journal of Gerontology and Geriatric Nursing	Semiannual	5500	5000	430	391
Journal of Nurse Midwifery and Maternal Health	Triannual	5500	5000	430	391
Journal of Psychiatric Nursing	Triannual	5500	5000	430	391
Indian Journal of Ancient Medicine and Yoga	Quarterly	8000	7500	625	586
Indian Journal of Law and Human Behavior	Semiannual	6000	5500	469	430
Indian Journal of Medical Psychiatry	Semiannual	8000	7500	625	586
Indian Journal of Biology	Semiannual	5500	5000	430	391
Indian Journal of Library and Information Science	Triannual	9500	9000	742	703
Indian Journal of Research in Anthropology	Semiannual	12500	12000	977	938
Indian Journal of Waste Management	Semiannual	9500	8500	742	664
International Journal of Political Science	Semiannual	6000	5500	450	413
Journal of Social Welfare and Management	Triannual	7500	7000	586	547
International Journal of Food, Nutrition & Dietetics	Triannual	5500	5000	430	391
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be switched to oral therapy; however, some authors advocate a full 14 day course of intravenous treatment.[12,41] Valganciclovir, the pro-drug of ganciclovir, has superior oral absorption and may be preferred for out-patient management, although most patients requiring therapy will be in-patients. The most frequent side effects of ganciclovir are neutropenia, thrombocytopenia, rash, hypotension, nausea, vomiting and headache.[42]

Ganciclovir resistance is an evolving issue and should be considered if patients fail to respond to treatment. After 3 months of therapy, the emergence of ganciclovir resistant strains approaches 10% and after 12 months 30%.[43-45] Ganciclovir resistance usually arises as a result of a mutation in the UL97 CMV phosphotransferase gene.

For those patients who are intolerant, or lack clinical response, to ganciclovir, foscarnet is the second choice. Foscarnet is an inhibitor of DNA polymerase of all herpes viruses. Foscarnet does not require phosphorylation by UL97 and so is most often active against ganciclovir resistant strains.[46,47] Foscarnet is given at 90 mg/kg, intravenously, twice per day for 2–3 weeks. Foscarnet toxicity includes renal impairment, central nervous system side effects, hypomagnesaemia, hypocalcaemia, hypophosphataemia and anaemia.[48]

An alternative strategy for dealing with concerns about CMV colitis is to treat all patients with severe UC with ganciclovir. Kim et al.[49] reported a series of 72 patients with moderate to severe UC treated with glucocorticoids. In patients with steroid resistance (defined as absence of clinical improvement 7–14 days after intravenous steroid treatment) ganciclovir was administered for 2 weeks: remission was achieved in 11 of 14 patients treated, the remainder undergoing colectomy. This strategy might be appropriate when there is reasonable clinical suspicion of CMV, without risking the inherent delays of a laboratory assessment of CMV in colonic tissue samples, however, the two studies by Delvincourt et al. mentioned earlier suggest this is actually unnecessary.[35]

Discussion

This review describes the prevalence of both CMV infection and intestinal disease in Inflammatory bowel disease patients. The prevalence varies with the definition used and there is no standard definition worldwide. In case of diagnosing CMV intestinal disease, the highest prevalence applies for tissue PCR (> 10 copies/mg tissue). The prevalence of CMV infection or disease was highest in group of patients with steroid refractory disease and in East Asia. In general, CMV infection or intestinal disease is seen more frequently in UC compared to CD.

CMV infection is described as (incidental) finding of positive PCR or detection of CMV antigens or antibodies in serum, whereas CMV disease is a clinical syndrome where CMV infection is accompanied by manifest clinical symptoms. Subclinical reactivation of CMV, without symptoms, is seen in approximately 50% of active UC cases on immunosuppressive therapy. There has been no unified definition in this regard in clinical trials and many times CMV infection and disease have been used interchangeably.

Population based CMV seroprevalence studies are lacking, but a review found seroprevalence highest in South America, Africa and Asia, and was also higher in parts of Europe and the Middle East[6]. The most likely explanation is the use of different diagnostic methods for CMV infection in different regions of the world. CMV infection and more importantly CMV colitis is unusual in the healthy population[13,28,29,54] as described before in a systematic review. Only one study reported presence of CMV DNA in 29% of asymptomatic control samples, but strong evidence is lacking[14]. There was a lower prevalence of CMV infection (and to a lesser extent in intestinal disease) for CD compared to UC[13,34]. The most frequently studied population in relation to CMV is those with steroid resistant IBD or refractory UC. There was highest prevalence of CMV infection and CMV intestinal disease in steroid refractory disease, for each definition of CMV used[54]. Whether or not CMV reactivation has a role in the process of steroid resistance, is still under debate.

The surveyed literature contains 29 different methods to diagnose CMV infection and/or intestinal disease, probably mainly caused by the fact that still no single gold standard exists for (clinically relevant) CMV infection in IBD. In general, the literature recommends to process biopsies for HE and IHC[33] and/or if available by CMV DNA real-time PCR, with a cut off value that is yet to be identified. The recent ECCO guidelinementions that different techniques for diagnosis of CMV infection are available, but stops short of defining a gold standard. The guideline refers to histopathology combined with IHC (using monoclonal antibodies) as highly specific and sensitive for verifying CMV infection in tissue. In addition the guideline describes quantitative PCR in tissue and in blood as the most commonly

used and advantageous technique for diagnosis of CMV infection. Quantitative PCR has a low sensitivity for diagnosing CMV colitis in patients with moderate to severe UC, and cannot substitute histopathology diagnosis[44]. CMV infection in general and for all organ specific involvements in transplant recipients, there was a guideline developed which has been updated in 2002. CMV infection was defined as isolation of the CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen. There CMV (gastro) intestinal disease was defined by identification of a combination of (1) clinical symptoms; (2) findings of macroscopic mucosal lesions on endoscopy; and (3) demonstration of CMV infection (by culture, histopathology, IHC, or in situ hybridization) in a (gastro)intestinal tract biopsy specimen. According to this guideline detection of CMV by PCR alone

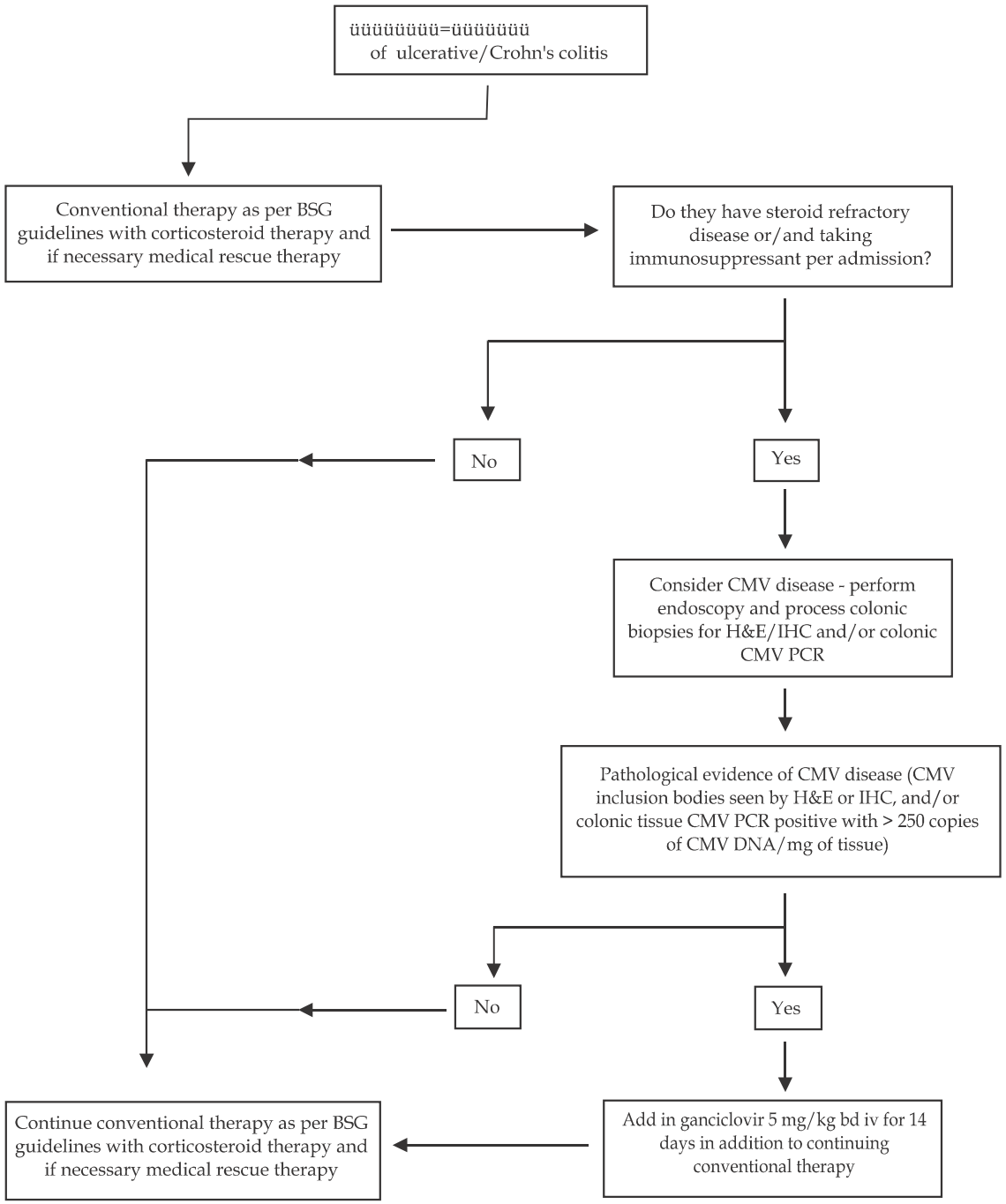

Fig 2: Proposed algorithm for diagnosis and management of CMV colitis in IBD

is insufficient for diagnosis of CMV gastrointestinal disease. Applying these criteria to IBD patients can be more complicated, since ulceration can also be caused by the underlying IBD. Since then, multiple more sensitive diagnostic tests have been developed to detect CMV, but a threshold or definition of clinical relevant CMV infection or intestinal disease remains to be established. There is an urgent need to have a global consensus meeting to have a unified definition for the CMV disease in IBD and the guideline could be useful in managing these patients successfully.

The limitation of the study is that there are no randomised trials in this aspect andthe heterogeneity of the design of included studies and wide variations in used definitions for both CMV infection and intestinal disease to perform a meta-analysis on these data.

Recommendations for diagnosis and treatment

We suggest that CMV colitis be considered for all patients presenting with moderate to severe UC (Figure 2). Early diagnosis should be considered especially in those patients who are resistant to first line treatment with corticosteroids or second line treatment with immunosuppressants. Diagnosis requires demonstrating CMV in colonic tissue. We recommend processing biopsies for H&E and IHC or/and if available CMV DNA real-time PCR. The cut off value for CMV DNA is yet to be identified but values >250 copies/mg tissue seem to predict resistance to steroids and two immunosuppressants and treatment has been shown to increase chance of achieving clinical remission and remaining in remission for 6 months.[9] Once diagnosed, we recommend treatment with i.v.ganciclovir 5 mg/kg twice daily for 14 days. The initial treatment for UC should continue alongside anti-viral therapy with corticosteroids and if necessary medical rescue therapy with immunosuppressants.

Conclusion

There is wide variation in defining the CMV infection and clinically relevant disease in the IBD patients. Cytomegalovirus reactivation is common in patients with severe ulcerative or severe Crohn's colitis. It seems likely that the reactivation is mediated by the both the inflammatory state of the mucosa and the immunosuppressive drugs administered to such patients. The outcome for patients with CMV reactivation appears worse than that for patients without reactivation, but it is not entirely clear that CMV is a contributor or a bystander. However, treatment of CMV in patients with severe colitis might reduce the colectomy rate suggesting that the virus is playing a role in the otherwise poor outlook for patients with severe ulcerative colitis. There is a need to have a global consensus definition for the CMV infection and disease in the IBD patient group.

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