ABOUT THE AUTHORS

Maham Bushra, MD

Dr. Maham Bushra is currently a PGY-4 Gastroenterology resident at the University of Toronto (Toronto, Canada). She received her medical degree from the University of Toronto (2021) and completed her core Internal Medicine training at the University of Toronto in 2024. Upon completing her gastroenterology residency, Dr. Bushra is planning to pursue an advanced clinical fellowship in Inflammatory Bowel Diseases.

Affiliations: *Division of Gastroenterology and Hepatology, University Health Network, University of Toronto, Toronto, Ontario, Canada*

Parul Tandon, DO, PhD, FRCPC

Dr. Tandon is a gastroenterologist and clinician scientist at the University Health Network (UHN) in Toronto, Ontario and an Assistant Professor at the University of Toronto. He is also an adjunct scientist at ICES Central. He received his medical degree from Michigan State University and completed his Internal Medicine residency at the University of Ottawa and Gastroenterology residency at the University of Toronto. He further pursued a clinical and research fellowship in Advanced Inflammatory Bowel Diseases at the Mount Sinai Hospital in Toronto, Ontario, while completing a PhD in clinical epidemiology at the Institute of Health Policy, Management, and Evaluation, University of Toronto. He graduated from the Elliot Philipson Clinician Scientist Training Program at the Department of Medicine, University of Toronto, and the Clinician Investigator Training Program accredited by the Royal College of Physicians and Surgeons of Canada. His research interests include the care of inflammatory bowel disease (IBD) in racial and ethnic minorities, including immigrants navigating new healthcare systems. Dr. Tandon holds the David & Elyssa Feldberg and Family Professorship in IBD Research at UHN.

Affiliations: *Division of Gastroenterology and Hepatology, University Health Network, University of Toronto, Toronto, Ontario, Canada*

doi.org/10.58931/cibdt.2025.3245

Cytomegalovirus Colitis in Inflammatory Bowel Disease The Eternal Debate: Foe or Innocent Bystander?

Maham Bushra, MD
Parul Tandon, DO, PhD, FRCPC

Key Takeaways:

- The prevalence of CMV infection among patients with IBD ranges from 2 to 29%, with a higher prevalence in those with UC compared to CD.
- Immunohistochemistry and tissue PCR, or both, are the recommended tests for diagnosing active CMV colitis.
- CMV may be an active pathogenic participant in cases with a high density of CMV and severe disease activity. Thus, we recommend testing for CMV colitis in patients with a severe inflammatory burden who are not responding to conventional IBD therapy.
- Patients with low CMV viral burden can likely be treated with immunosuppression alone, while patients with high viral density or medically refractory disease should be treated with antiviral therapy.

Cytomegalovirus : Overview

Cytomegalovirus (CMV), also known as *Herpesvirus*-5, is a double-stranded deoxyribonucleic acid (DNA) virus and a member of the *Herpesviridae* family. Its global seroprevalence is approximately 83%, while in the Canadian population it is approximately 46%.[1] CMV may be transmitted horizontally through close contact with biological fluids,[2] vertically from mother to fetus, leading to viral congenital infections, or via solid organ or hematopoietic stem cell transplantation.[3,4]

CMV enters and replicates within numerous cell types, including fibroblasts, endothelial cells, epithelial cells, and monocytes. Entry into host cells is mediated by CMV glycoproteins on the surface of the virion, which interact with receptors on cell surfaces, leading to entry by various mechanisms depending on the cell type.[5] Once acquired, the virus persists in cells, resulting in lifelong viral latency. In healthy individuals, a combination of innate and adaptive immune responses work to prevent CMV reactivation and replication.[5] Therefore, CMV infection in healthy individuals is usually asymptomatic or results only in mild, self-limiting symptoms. However, factors leading to a compromised immune system, such as use of immunosuppressive medications, pregnancy, organ or hematopoietic stem cell transplantation, acquired immunodeficiency syndrome, chemotherapy, or severe sepsis can induce CMV reactivation. In these immunocompromised states, CMV infection can lead to end-organ disease including colitis, esophagitis, hepatitis, retinitis, pneumonia, encephalopathy, and disseminated CMV infection.[6]

The pathogenesis of CMV in the gastrointestinal tract is not entirely understood. It is possible that CMV infection in the colon leads to vascular endothelial changes, resulting in ischemic damage to the colonic mucosa and localized ulceration.[7] Additionally, CMV replication may cause disruption of epithelial tight junctions, leading to translocation of gut bacteria and ultimately intestinal inflammation.[8]

CMV in Inflammatory Bowel Disease

The prevalence of CMV infection among patients with inflammatory bowel disease (IBD) ranges from 2 to 29%, with a higher prevalence observed in those with ulcerative colitis (UC) compared to Crohn's Disease (CD).[9] In these

individuals, CMV disease may result from reactivation of a latent virus, primary infection with a new virus, or reinfection with a different viral strain.

The involvement of CMV in IBD has been widely debated, with two competing hypotheses: **1)** CMV is an innocent bystander, reactivating in response to intestinal inflammation or **2)** CMV plays an active pathogenic role, where viral reactivation leads to disease exacerbation and worse clinical outcomes.

Data supporting the innocent bystander hypothesis predominantly stems from retrospective studies. Prior studies assessing colonic biopsies from patients experiencing IBD flares have reported that CMV DNA was detected in only 10% of all biopsies.[10] Furthermore, no correlation was found between the severity of IBD and the CMV viral load levels in the colonic mucosa.[10] In most CMV-positive patients, CMV cleared spontaneously upon IBD remission without the need for antiviral therapy.[10] Finally, CMV reactivation has been observed in steroid-naïve patients with UC, suggesting that severe inflammation of the colonic mucosa itself could act as a trigger for CMV reactivation.[11]

In contrast, other studies have associated CMV infection in IBD with worse clinical outcomes, such as increased hospitalizations, longer hospital stays, increased risk of surgical intervention, higher rates of rescue therapy, and increased mortality.[12,13] In a recent meta-analysis of over 2000 patients with UC, risk factors for CMV reactivation included severe phenotypes, pancolitis, older age, and prior exposure to corticosteroids or azathioprine.[14] Use of 5-aminosalicylic acid was the only protective factor against CMV reactivation.[14] Interestingly, infliximab therapy was not found to increase the occurrence of CMV reactivation in patients with UC.[14] A subsequent meta-analysis demonstrated that IBD patients with concurrent CMV infection had an overall poorer prognosis than patients without CMV.[13]

The true impact between CMV reactivation in IBD likely depends not only on its presence in colonic tissue, but on the viral density.[15] In a case-control study, among patients with CMV who were treated with antivirals, those with high density of CMV inclusions (defined as ≥5 inclusions per biopsy fragment) had lower colectomy rates compared to those with lower density of CMV.[15] Another study demonstrated that a dense CMV burden, specifically >10 inclusions per histologic section, was predictive of increased steroid resistance, higher rates of emergency surgery, and longer postoperative hospital stays.[16] Additionally, a retrospective multicentre analysis of patients with acute severe UC (ASUC) revealed that patients with elevated levels of mucosal CMV DNA (>2,000 copies/mg) faced a significantly higher risk of steroid failure and colectomy, independent of other prognostic indicators.[17] These results suggest that CMV may be an active pathogenic participant in cases with a high density of CMV and severe disease activity. Therefore, it is reasonable to consider and test for CMV colitis in patients with a severe inflammatory burden who are not responding to conventional IBD therapy.

CMV in IBD: Diagnosis

The most recent guidelines from both the European Crohn's and Colitis Organisation (ECCO) and the American College of Gastroenterology (ACG) recommend testing for CMV in IBD patients who present with steroid-refractory or severe colitis.[18,19]

Typical endoscopic features of CMV infection may include well-defined and longitudinal ulcers and a cobblestone-like mucosal appearance.[20] However, endoscopic examination alone is not sufficient to confirm CMV colitis, necessitating tissue sampling for a definitive diagnosis. The location and number of colonic biopsies during endoscopic assessment are important, with preference for tissue samples from the ulcer base and margins when present.[18] To avoid false negatives and achieve an 80% probability of CMV detection in appropriate clinical settings, it is recommended to obtain a minimum of 11 biopsies for UC and 16 biopsies for CD.[18]

Commercially available tests for detecting CMV include blood-based tests such as the pp65 antigenaemia assay and blood polymerase chain reaction (PCR), as well as colonic tissue-based tests such as haematoxylin and eosin staining (H&E), immunohistochemistry (IHC) and tissue PCR (tPCR). Blood-based PCR tests offer excellent specificity of approximately 99.9% but poor sensitivity at 50.8%, limiting their use in diagnosing CMV colitis in IBD.[21] Blood-based PCR testing is also not reliable for distinguishing latent versus pathologic reactivation states. Given that CMV reactivation initially occurs locally within the colonic mucosa of patients with IBD, current clinical guidelines recommend tissue-based CMV

diagnostic techniques for accurate detection.[18,19] In a study of patients with active UC, tissue CMV PCR was positive in 63% of these patients, while plasma PCR was positive in 59%. However, histologic confirmation using IHC was rare, with only 10% showing positive staining.[22] Thus, while high rates of CMV DNA are frequently detected in the active colonic mucosa of IBD patients, this does not always indicate true tissue-invasive infection. On H&E staining of the colonic mucosa, the presence of "owl-eye" inclusion bodies is considered pathognomonic for CMV infection. However, given the low sensitivity of H&E staining, IHC (which allows semi-quantification of viral infection), tPCR, or both are the recommended tests for diagnosing active CMV colitis.[18]

No specific viral cut off for CMV PCR in colonic tissue has been established. Currently, the assays used for PCR-based CMV testing have not been standardized, and as a result, cut-off values may not be directly comparable or generalizable across different institutions and testing platforms. A case-control study of steroid-refractory UC patients found that CMV positivity, defined as a tissue PCR viral load of >250 copies/mg of tissue, was associated with resistance to steroids and also to three additional lines of treatment. These findings suggest that initiating antiviral therapy early in the disease course in these patients may delay treatment resistance and thus improve the overall prognosis.[23]

Treatment of CMV Infection in IBD

Treatment of CMV infection with antiviral therapy may not be required for all IBD patients. A prospective study of 31 patients with UC and CMV infection found that those with symptom improvement while on steroids did not require antiviral therapy.[24] However, the remaining patients who did not respond to steroid therapy required ganciclovir treatment.[24] Another prospective series of IBD patients found positive CMV-DNA via colonic biopsy in 3 patients before receiving Infliximab; however after Infliximab, conventional histology and immunohistochemistry for CMV was negative in all.[25] Thus, patients with low viral burden demonstrated by only a few inclusions who are responsive to medical therapy can likely be treated with immunosuppression alone. In contrast, patients with high viral density or those with medically refractory disease should be treated with anti-viral therapy. For tissue-invasive CMV colitis, the recommended treatment includes induction therapy with intravenous ganciclovir at 5 mg/kg twice daily for 5–10 days, followed by oral valganciclovir at 900 mg daily to complete a 2–3 week course.[18] Protocols to determine CMV clearance and thus cessation of therapy are not well-defined and may require input from infectious disease colleagues. For patients who are intolerant to ganciclovir, or in rare cases of ganciclovir-resistant CMV, foscarnet may be used as an alternative treatment. Throughout antiviral treatment, patients should be carefully monitored for side effects, notably neutropenia, anemia, thrombocytopenia, renal injury, and electrolyte imbalances.[18]

The ECCO guidelines recommend that immunosuppressive therapy should generally be continued in IBD patients experiencing intestinal CMV reactivation, given its crucial role in controlling disease activity.[18] However, in cases of symptomatic, severe disseminated CMV infection, all immunosuppressive agents should be discontinued.[18] Given the substantial increased risk of CMV reactivation associated with glucocorticoid use, a steroid taper is recommended.[18]

Conclusion

CMV colitis remains a significant challenge in IBD given its overlapping features with severe disease, often leading to delays in both diagnosis and initiation of appropriate antiviral therapy. The longstanding debate over whether CMV acts as an "innocent bystander versus foe" debate likely can be settled by focusing on the density of CMV in intestinal tissue, with increasing viral loads suggesting pathogenicity. In the setting of severe, steroid-refractory IBD, CMV colitis may be a significant risk factor for poor clinical outcomes, including mortality. As such, maintaining a high index of suspicion in the appropriate clinical context will lead to achieving an accurate tissue diagnosis of CMV colitis and initiating appropriate treatment.

Correspondence

Parul Tandon, DO, PhD, FRCPC
Email: parul.tandon@uhn.ca

Financial Disclosures

M:B.: None declared.
P.T.: Advisory Boards: Takeda, Johnson & Johnson; **Speaker fees:** Abbvie, Johnson & Johnson, Takeda

References:

1. Zuhair M, Smit GSA, Wallis G, Jabbar F, Smith C, Devleesschauwer B, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta-analysis. Rev Med Virol. 2019;29(3):e2034. doi:10.1002/rmv.2034
2. Staras SA, Flanders WD, Dollard SC, Pass RF, McGowan JE Jr, Cannon MJ. Influence of sexual activity on cytomegalovirus seroprevalence in the United States, 1988–1994. Sex Transm Dis. 2008;35(5):472–479. doi:10.1097/OLQ.0b013e3181644b70
3. LeruezVille M, Foulon I, Pass R, Ville Y. Cytomegalovirus infection during pregnancy: state of the science. Am J Obstet Gynecol. 2020;223(3):330–349. doi:10.1016/j.ajog.2020.02.018
4. Atabani SF, Smith C, Atkinson C, Aldridge RW, RodriguezPerálvarez M, Rolando N, et al. Cytomegalovirus replication kinetics in solid organ transplant recipients managed by preemptive therapy. Am J Transplant. 2012;12(9):2457–2464. doi:10.1111/j.1600-6143.2012.04087.x
5. Griffiths P, Reeves M. Pathogenesis of human cytomegalovirus in the immunocompromised host. Nat Rev Microbiol. 2021;19(12):759–773. doi:10.1038/s41579-021-00582-z
6. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. Clin Infect Dis. 2017;64(1):87–91. doi:10.1093/cid/ciw668
7. D'Cruz RT, Lau CC-L, Thamboo TP. Severe ischemic cytomegalovirus proctocolitis with multiple perforation. Arch Virol. 2018;163(7):1927–1931. doi: 10.1007/s00705-018-3792-z
8. Maidji E, Somsouk M, Rivera JM, Hunt PW, Stoddart CA. Replication of CMV in the gut of HIV-infected individuals and epithelial barrier dysfunction. PLoS Pathog. 2017;13(6):e1006202. doi:10.1371/journal.ppat.1006202
9. Römkens TEH, Bulte GJ, Nissen LHC, Drenth JP. Cytomegalovirus in inflammatory bowel disease: A systematic review. World J Gastroenterol. 2016;22(3):1321–1330. doi:10.3748/wjg.v22.i3.1321
10. Lévêque N, Brixi-Benmansour H, Reig T, Renois F, Talmud D, Brodard V, et al. Low frequency of cytomegalovirus infection during exacerbations of inflammatory bowel diseases. J Med Virol. 2010;82(10):1694–1700. doi:10.1002/jmv.21877.
11. Kim YS, Kim YH, Kim JS, Cheon JH, Ye BD, Jung SA, et al. Cytomegalovirus infection in patients with new onset ulcerative colitis: a prospective study. Hepatogastroenterology. 2012;59(117):1098–1101. doi:10.5754/hge10217
12. Gholami Shahrebabak M, Kouchaki H, Gholami Shahrebabak A, Ravankhah M, Abdollahi M, Akbari M, et al. Systematic review and meta-analysis of cytomegalovirus-associated adverse outcomes and healthcare resource utilization in hospitalized patients with inflammatory bowel disease. Int J Colorectal Dis. 2025;40(1):101. doi:10.1007/s00384-025-04886-x
13. Zhang WX, Ma CY, Zhang JG, He F, Liu QM, Cheng A, et al. Effects of cytomegalovirus infection on the prognosis of inflammatory bowel disease patients. Exp Ther Med. 2016;12(5):3287–3293. doi:10.3892/etm.2016.3763
14. Qin Y, Wang G, Kong D, Li G, Wang H, Qin H, et al. Risk factors of cytomegalovirus reactivation in ulcerative colitis patients: a metaanalysis. Diagnostics (Basel). 2021;11(11):1952. doi:10.3390/diagnostics11111952
15. Jones A, McCurdy JD, Loftus EV Jr, Bruining DH, Enders FT, Killian JM, et al. Effects of antiviral therapy for patients with inflammatory bowel disease and a positive intestinal biopsy for cytomegalovirus. Clin Gastroenterol Hepatol. 2015;13(5):949-955. doi: 10.1016/j.cgh.2014.09.042
16. Kuwabara A, Okamoto H, Suda T, Ajioka Y, Hatakeyama K. Clinicopathologic characteristics of clinically relevant cytomegalovirus infection in inflammatory bowel disease. J Gastroenterol. 2007;42:823–829. doi:10.1007/s00535-007-2103-3
17. Jain S, Namdeo D, Sahu P, Kedia S, Sahni P, Das Pet al. High mucosal cytomegalovirus DNA helps predict adverse shortterm outcome in acute severe ulcerative colitis. Intest Res. 2021;19(4):438–447. doi:10.5217/ir.2020.00055
18. Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, et al. ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. [published correction appears in J Crohns Colitis. 2023 Jan 27;17(1):149. doi: 10.1093/ecco-jcc/jjac104.]. J Crohns Colitis. 2021;15(6):879-913. doi:10.1093/ecco-jcc/jjab052
19. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD; ACG Clinical Guideline Committee. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114(3):384–413. doi:10.14309/ajg.0000000000000152
20. Suzuki H, Kato J, Kuriyama M, Hiraoka S, Kuwaki K, Yamamoto K. Specific endoscopic features of ulcerative colitis complicated by cytomegalovirus infection. World J Gastroenterol. 2010;16(10):1245–1251. doi:10.3748/wjg.v16.i10.1245
21. Tandon P, James P, Cordeiro E, Selvanderan S, Aruljothy A, Nguyen TM, et al. Diagnostic accuracy of blood-based tests and histopathology for cytomegalovirus reactivation in inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2017;23(4):551–560. doi: 10.1097/MIB.0000000000001073
22. Esen S, Saglik I, Dolar E, Cesur S, Ugras N, Agca H, et al. Diagnostic utility of cytomegalovirus DNA quantitation in ulcerative colitis. Viruses. 2024;16(5):691. doi:10.3390/v16050691
23. Roblin X, Pillet S, Oussalah A, Berthelot P, Del Tedesco E, Phelip JM, et al. Cytomegalovirus load in inflamed intestinal tissue is predictive of resistance to immunosuppressive therapy in ulcerative colitis. Am J Gastroenterol. 2011;106(11):2001-2008. doi:10.1038/ajg.2011.202
24. Kim YS, Kim YH, Kim JS, Cheon JH, Ye BD, Jung SA, et al. The prevalence and efficacy of ganciclovir on steroid-refractory ulcerative colitis with cytomegalovirus infection: a prospective multicenter study. J Clin Gastroenterol. 2012;46(1):51-6. doi:10.1097/MCG.0b013e3182160c9
25. D'Ovidio V, Vernia P, Gentile G, Capobianchi MR, Marcheggiano A, Viscido A, et al. Cytomegalovirus infection in inflammatory bowel disease patients undergoing anti-TNFα therapy. J Clin Virol. 2008;43(2):180-3. doi:10.1016/j.jcv.2008.06.002