Cytomegalovirus (CMV), an encapsulated double-stranded DNA virus of the 
Betaherpesvirinae subfamily of herpesviruses, is a common, ubiquitous pathogen, generally innocuous in healthy individuals (O’Hara et al., 2017). Following primary infection, the virus establishes latency in haematopoietic progenitor cells and myeloid lineage cells (Goodrum et al., 2016). The latent state permits life-long persistence of the viral genome marked by sporadic bouts of reactivation, which allows for periods of typically subclinical virus shedding (Britt et al., 2008). Of all herpes viruses, CMV harbours the largest number of genes dedicated to evading innate and adaptive immunity in the host (Gupta et al., 2021). A broad range of cells are infected including the parenchyma and connective tissue cells of gastrointestinal (GI) organs. The varied manifestations of CMV disease are, in part, related to its diverse cellular tropism.

CMV transmission usually requires close and prolonged contact with body fluids, such as urine, saliva, semen, vaginal fluid, and breastmilk, but can occur through blood/tissue, and occupational exposure as well. Approximately 59% of the population older than six years of age has been exposed to CMV, with an increase in the population’s seroprevalence with advancing age and lower income (Bartlett et al., 2018).

Primary CMV infection is often asymptomatic or subclinical in immunocompetent individuals. When symptomatic, in adults it is often described as a self-limiting mononucleosis-like syndrome, characterised by fever, rash, and leukocytosis, with less prominent cervical lymphadenopathy than that caused by Epstein-Barr virus (Nolan et al., 2017).

Organ involvement is uncommon in immunocompetent hosts, although both disseminated and tissue-invasive CMV
have been documented and described (Karigane et al., 2014; Sue et al., 2016). In contrast, CMV is an important opportunistic pathogen in immunocompromised hosts, particularly those with acquired immunodeficiency syndrome (AIDS), recipients of solid and bone marrow transplants, those receiving immunosuppressive therapy, including patients with inflammatory bowel diseases (IBD), and patients with malignancies, especially those under chemotherapy or with haematological malignancies, causing significant morbidity and mortality (Ozaki et al., 2013; Wang et al., 2016). These patients tend to develop severe organ-specific or disseminated CMV manifestations, such as pneumonia, retinitis, and colitis.

Caution must be exercised whenever analysing published literature describing invasive CMV disease in immunocompetent patients as different studies include patients with endocrinopathies, for example, diabetes mellitus (DM), lymphoproliferative and nonhaematological malignancies, end-stage renal disease, autoimmune diseases, and pregnancy in the immunocompetent group, although such comorbidities could serve as potential immune-modulating and predisposing factors to severe CMV disease (Galiatsatos et al., 2005; Ko et al., 2015). Thus, with the increasing prevalence of such factors in the general population, further studies are warranted to clarify the underlying pathophysiology of CMV diseases in these “immunocompetent” (or “non-immunocompromised”) but high-risk populations.

In the context of CMV and GI tract, overall, the lower GI tract is the most common site of involvement, however, in the recent past, CMV disease with more involvement of the upper GI tract in both immunocompetent and immunocompromised individuals has been increasingly recognised (Hwang et al., 2006).

UPPER GI TRACT

CMV disease presents throughout the upper GI tract (the mouth, pharynx, oesophagus, stomach, and small intestine). Previous studies have shown that the most affected sites of upper GI CMV disease are the mid-distal oesophagus (88%) (Wang et al., 2016) and the gastric antrum (84%) (Bonetti et al., 2011).

The clinical presentation of upper GI CMV disease is highly variable and depends on its location and severity. Wang et al. (2016) found that odynophagia/dysphagia (44%) and epigastric pain (31%) were the most common symptoms in patients with CMV esophagitis, while according to another study (Péter et al. 2004), abdominal pain (39%), anaemia/GI bleeding (20%), and nausea/vomiting (13%) were the most frequent complaints in patients with CMV gastritis/duodenitis. Moreover, in up to 7% of the cases, upper GI CMV disease may be asymptomatic.

Patients with CMV disease in the small intestine often present with diarrhea and generalised abdominal pain (Karigane et al., 2014). Intestinal CMV disease may mimic IBD through endoscopy and imaging (Hsieh et al., 2016). Haemorrhage and perforation have been reported but are rare (Cha et al., 2010).

The endoscopic appearance of upper GI CMV disease is often non-specific ranging from normal or minimal inflamed mucosa to deep ulceration (Bonetti et al., 2011; Ozaki et al., 2013). In CMV esophagitis, well-demarcated serpiginous ulcers are more common than mucosal inflammation (88% vs. 63%) (Wang et al., 2016), whereas in gastroduodenal disease inflammatory changes may exceed ulceration (54% vs. 18%) (Peter et al., 2004). Despite the location in the GI tract, erosions and ulcers tend to be multiple (Bonetti et al., 2011; Wang et al., 2016). Extensive and deep ulceration can also be present and may lead to serious GI complications, such as perforation and massive bleeding (Ozaki et al., 2013; Marques et al., 2017).

LOWER GI TRACT

The most common clinical presentation of GI CMV disease is colitis, which typically causes diarrhea, haematochezia, fever, tenesmus, urgency, and abdominal pain (Ko et al., 2015).

A meta-analysis (Galiatsatos et al. 2005) showed that 36% of critically ill “immunocompetent” patients in an intensive care unit had CMV end-organ disease. The mean age of “immunocompetent” patients with CMV disease was observed to range between 64 and 75 years and most patients had underlying immune-modulating conditions, such as chronic kidney disease, DM, or cardiomyopathy (Siciliano et al. 2014; Bernard et al. 2015). The in-hospital mortality of these patients, probably affected by comorbidities, was 71.4% despite treatment.

In IBD, the symptoms of CMV colitis tend to mimic IBD exacerbation [abdominal pain, anorexia, malaise, nausea, vomiting, diarrhea, and bleeding], and can potentially, although rarely (about 1% of cases), cause colonic perforation (Bontà et al., 2016).

RELATIONSHIP BETWEEN CMV AND IBD

The association between CMV and IBD was first described by Powell et al. (1961) in a patient with ulcerative colitis (UC) and cytomegalic inclusion disease. Since then, the question of whether CMV is an active pathogen or an innocent bystander in IBD patients remains controversial (Laurier et al., 2010). Interpretation of existing results is limited due to the small and retrospective design of most studies, different diagnostic methods for detecting CMV and different classifications for the severity of concomitant IBD.

CMV colitis occurs in “seropositive” patients with IBD. Generally, CMV does not appear to interfere with the clinical evolution of Crohn’s disease (CD), and its involvement in UC is still debatable, especially in severe flare-ups (Ayer et al., 2009).
CMV prevalence in CD. According to Hommes et al. (2002) and D’Ovidio et al. (2008), CMV seropositivity in CD patients does not differ from other populations and reaches 70%; however, CMV disease is rare in CD, making the virus an unlikely aetiological factor in the de novo development of IBD (Kim et al., 2010).

Most studies in the field consistently report that the majority of CD patients are negative for CMV upon immunohistochemistry (IHC) staining, the mainstay of tissue-invasive CMV diagnosis, while CMV DNA in tissue or stool sample is positive in < 5% of patients (Knösel et al., 2009; Kim et al., 2010). However, an exception was in a study (Wakefield et al., 1992) that used highly sensitive PCR (detection threshold < 10 copies of CMV DNA), detecting CMV in 66% of individuals with CD and in 29% of controls, and thus showing no association between CMV DNA and CD activity, along with the suggestion that small quantities of viral DNA are not clinically relevant even in patients with UC.

Nakase et al. (2010) proposed that these findings could be related to some pathophysiologic aspects of CD and CMV, specifically that tumour necrosis factor-α (TNFα) is significantly associated with CMV infection or reactivation in IBD, while interferon-γ (IFNγ) released from CD4+ Th1 cells (Fuss et al., 1996) could suppress CMV reactivation. As CD is considered a Th1-type inflammatory process with high expression of IFNγ, this could possibly explain the different prevalence of CMV disease in UC and CD.

CMV prevalence in UC. Although prevalence of latent CMV in UC is similar to CD, approximately 70% (Domènech et al., 2008), recent data have suggested that CMV infection increased the risk of hospitalisation attributable to UC exacerbation 8.2-fold, and patients with histories of CMV colitis within the three months prior to commencement of infliximab therapy were 6.47-fold more likely not to respond to such therapy (Park et al., 2013; Matsumoto et al., 2014).

Patients in remission or with mild-moderate UC did not show an increased risk of CMV colitis, determined by negative haematoxylin and eosin (HE) and IHC findings (Domènech et al., 2008; Kim et al., 2010) or IHC in colectomy patients undergoing surgery for dysplasia or cancer (Kojima et al., 2006).

The most extensive literature is on severe and/or steroid-refractory UC. As these terms are used interchangeably in different studies and are not defined clearly, the results are difficult to interpret (Lawlor et al., 2010).

Severe colitis. According only to CMV antigenaemia, prevalence of CMV disease is reported around 34% (Wada et al., 2003), while with HE or IHC alone in colonic mucosa prevalence decreased to 3% (Vega et al., 1999). The combination of both serological tests and rectal biopsies found a CMV disease prevalence of around 20% (Criscuoli et al., 2004; Kishore et al., 2004). Identified risk factors include female gender, older age, pancolonic disease with active inflammation at histology and azathioprine therapy (Kojima et al., 2006).

Severe steroid-resistant colitis. Retrospective study by Papadakis et al. (2001) showed a 0.5% prevalence of CMV disease according to HE, which increased dramatically when combining HE and IHC with antigenaemia (20%–40%) (Maconi et al., 2005; Kojima et al., 2006; Domènech et al., 2008). As there is a poor correlation between blood and colonic viral DNA load (60% and 38%, respectively), possibly due to a specific CMV genotype with a particular colonic tropism and pathogenic character, as proposed by Criscuoli et al. (2011), a blood test alone should not guide clinical decision-making whether to start or withhold antiviral treatment (Pofelski et al., 2007; Yoshino et al., 2007).

Urgent colectomy for colitis. A higher prevalence of CMV could be expected in these patients due to a more severe course of their disease, but the prevalence studies using HE or IHC for CMV detection in mucosal samples ranged between 11.5% and 27% (Alcalá et al., 2000; Maconi et al., 2005), similarly to the previous groups.

Experimental studies suggest that CMV reaches the intestinal mucosa through persistence in migrating monocytes and then colonises the colonic cells, acquiring particular affinity for the inflammatory sites, probably due to the presence of pro-inflammatory cytokines (IFNγ and TNFα) produced by macrophages and T-cells in active UC (Hommes et al., 2004; Simon et al., 2005). Robin et al. (2011) proposed that CMV can appear only in inflamed tissue and is not found in healthy tissue, thus leading other authors to suggest that the positivity of CMV DNA in the colonic mucosa in patients with refractory UC indicates uncontrolled intestinal inflammation, necessitating a change in immunosuppressive therapy (Hakase et al., 2011).

Coincidental detection of primary CMV colitis at the first manifestation of IBD (Diepersloot et al., 1990; Orvar et al., 1993), in IBD patients without immunosuppression (Rachima et al., 1998; Streetz et al., 2003), and even disseminated CMV infection in CD (Hellingbl et al., 2002) has been rarely reported.

ESTABLISHING DIAGNOSIS

To the best of our knowledge, there are more than 20 different methods to diagnose CMV infection and/or intestinal disease, mainly caused by the fact that still no single gold standard exists for establishing clinically relevant CMV disease in IBD (Table 1). As CMV-seropositive patients receiving immunosuppressants are at risk of end-organ reactivation, the latest European Crohn’s and Colitis Organisation (ECCO) guidelines on the prevention, diagnosis, and management of infections in IBD recommend measurement of CMV-specific IgG antibodies for all IBD patients, preferably at disease diagnosis or at least before starting or while being treated with immunosuppressive agents, if baseline measurements are missing (Kucharzik et al., 2021), in order
to potentially identify patients who are at risk of acquiring a new CMV infection (seronegative) or reactivation (seropositive) (Liu et al., 2014). However, serology has no diagnostic value for CMV colitis due to high seroprevalence of CMV within the adult population and thus cannot replace invasive endoscopic procedures for pathological confirmation of CMV colitis (McCoy et al., 2014).

Generally, patients with refractory IBD should be tested for CMV colitis, especially if they are failing immunosuppressive therapy, as multiple studies have concluded that concurrent CMV colitis is associated with a major risk of poorer outcomes, including toxic megacolon, colectomy, rescue therapy, and increased rate of disease flares (Lee et al., 2016; Cohen et al., 2018; Schenk et al., 2019).

Active CMV colitis is usually diagnosed by endoscopic CMV detection in colonic tissue, histological tests including HE and IHC stains, and/or tissue PCR, although blood-based CMV antigenemia assay and blood PCR (bPCR) have been extensively studied recently and could have some practical implications as well.

Typical endoscopic findings of CMV colitis are microerosions and deep ulcers (Ljungman et al., 2002). Pseudotumoral lesions as an endoscopic finding for CMV GI tract infection have been reported by others and are postulated to be due to infection of stromal and epithelial cells resulting in hyperplastic changes (Bonetti et al., 2015). However, most studies in patients with IBD, specifically in active UC, have not found specific endoscopic features (Yoshino et al., 2007; Roblin et al., 2011).

When assessing for CMV colitis, biopsy location and number appear to be important. Zidar et al. (2015) compared specimens collected from the colonic ulcer base and edge, and from uninvolved mucosa, which showed no significant difference between the ulcer base and edge in terms of the highest densities of CMV-positive cells. However, the uninvolved mucosa was IHC-negative for CMV and either PCR-negative, or very low (0 to 3 viral copies/mg tissue), supporting previous findings of Roblin et al. (2011), and suggesting that the most appropriate biopsy sites seem to be ulcer base and edge.

Left-colon biopsies identify most UC patients with CMV. Conversely, in CD many patients had CMV detectable only in right-colon biopsies. In terms of the adequate specimen number, McCurdy et al. (2015) proposed that 11 sigmoidoscopic biopsies be taken for UC diagnosis, and 16 colonoscopic biopsies for CD diagnosis to achieve an 80% probability of CMV detection. However, such high numbers are associated with risks of haemorrhage and perforation, thus highlighting the importance of the location of biopsies.

HE staining is the primary diagnostic test performed in patients suspected of having invasive CMV disease and has the ability to show the typical viral inclusions highly specific for CMV colitis known as “owl’s eye” inclusions — the nuclei of cytomegalic cells containing CMV inclusion bodies are surrounded by clear cytoplasm (Park et al., 2017). However, the HE method has been shown to have lower sensitivity compared to IHC and tissue polymerase chain reaction (tPCR), possibly due to the rarity of finding these inclusion bodies within the relatively small amount of

**Table 1. Characteristics of diagnostic tests for CMV colitis (adapted from Römkins et al., 2016; Park et al., 2017)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Pros</th>
<th>Cons</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus IgG class</td>
<td>Helps to distinguish patients with risk for CMV colitis</td>
<td>Systemic, not providing information about intestinal disease</td>
<td>98–100</td>
<td>96–99</td>
</tr>
<tr>
<td>Antigen (pp65) detection</td>
<td>Takes a short time to perform (24 hour)</td>
<td>Systemic, not providing information about intestinal disease</td>
<td>47–67</td>
<td>82–90</td>
</tr>
<tr>
<td>CMV DNA PCR in tissue</td>
<td>Non-invasive method (endoscopy not required)</td>
<td>No cut-off value for the diagnosis yet established</td>
<td>44</td>
<td>88</td>
</tr>
<tr>
<td>CMV DNA PCR in stool</td>
<td>Very high sensitivity for CMV detection in colon</td>
<td>Cut-off value not yet clear</td>
<td>65–100</td>
<td>40–100</td>
</tr>
<tr>
<td>CMV DNA PCR in stool</td>
<td>Non-invasive method (endoscopy not required)</td>
<td>Little experience with the method</td>
<td>83</td>
<td>93</td>
</tr>
<tr>
<td>Viral culture</td>
<td>High sensitivity and specificity</td>
<td>Long turnaround time (2–4 weeks)</td>
<td>45–78</td>
<td>89–100</td>
</tr>
<tr>
<td>Histological examination –</td>
<td>Highly specific, proves intestinal disease</td>
<td>Invasive</td>
<td>10–87</td>
<td>92–100</td>
</tr>
<tr>
<td>IHC staining</td>
<td>Requires several tissue samples and skilled pathologist</td>
<td>Time-consuming</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological examination –</td>
<td>Highly specific, proves intestinal disease</td>
<td>Invasive</td>
<td>93</td>
<td>92–100</td>
</tr>
<tr>
<td>HE staining</td>
<td>Helps to distinguish patients with risk for CMV colitis</td>
<td>Systemic, not providing information about intestinal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HE staining</td>
<td>Requires several tissue samples and skilled pathologist</td>
<td>Time-consuming</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV DNA (PCR in blood)</td>
<td>Very high sensitivity for CMV DNA (PCR in blood)</td>
<td>Cut-off value not yet clear</td>
<td>65–100</td>
<td>40–100</td>
</tr>
<tr>
<td>CMV DNA (PCR in blood)</td>
<td>Highly specific, proves intestinal disease</td>
<td>Little experience with the method</td>
<td>83</td>
<td>93</td>
</tr>
<tr>
<td>CMV DNA (PCR in stool)</td>
<td>Non-invasive method (endoscopy not required)</td>
<td>Quantification possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV DNA (PCR in stool)</td>
<td>Very high sensitivity for CMV DNA (PCR in stool)</td>
<td>Quantification possible</td>
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</table>

CMV, cytomegalovirus; IgG, immunoglobulin G; PCR, polymerase chain reaction; HE, hematoxylin and eosin; IHC, immunohistochemistry.
tissue biopsied (Gauss et al., 2015; Tandon et al., 2017). Atypical features such as eccentric or smudged nuclei, perinuclear amphiphilic zones (Yan et al., 2014), and cells with basophilic inclusions that are up to twice the size of their non-infected neighbours and do not have the classic halo appearance (Zidar et al., 2015), have been documented as well.

Numerous studies have confirmed that the gold standard for detection of CMV in GI mucosal biopsies is CMV-specific IHC staining, labelling CMV antigen in infected cells (Mills et al., 2013; Zidar et al., 2015; Juric-Sekhar et al., 2017), which is a highly sensitive and specific test. Thus, according to ECCO guidelines, IHC should be performed in any clinical suspicion or consistent findings in the HE staining (Kucharzik et al., 2021). The inclusions in IHC tend to be nuclear, occasionally cytoplasmic, mainly within endothelial cells.

Whereas quantitative CMV bPCR implies for diagnosis of systemic infection, tpPCR has been shown to be more sensitive than IHC, and ECCO guidelines recommend it as, possibly, the standard test for confirming active CMV infection [colitis] in IBD patients, along with IHC (Kucharzik et al., 2021). This method is fast and objective, although not well standardised yet (Bernard et al., 2015). However, using tpPCR for diagnosis of CMV colitis is controversial (Zidar et al., 2015). One source of controversy is related to the difference between fresh and formalin-fixed, paraffin-embedded tissue (FFPE) when performing tpPCR, as fresh tissue is often hard to obtain in clinical practice. A study by Mills et al. (2013) showed that CMV PCR on FFPE GI biopsies complements IHC, and therefore can be used instead of fresh tissue. Another aspect to consider is that CMV remains latent within leukocytes after a primary infection, meaning that a positive result does not necessarily indicate an active infection due to very high sensitivity, although tpPCR is crucial when IHC is negative in patients with strong clinical suspicion of active CMV colitis. Overall, authors agree that there is still a need to define a cut-off for PCR within GI biopsies as no clear criteria differentiating between a latent CMV infection and CMV disease are yet available. According to Ciccióippo et al. (2015), a mucosal viral load greater than 10^5 copies/10^5 cells was associated with refractoriness to treatment, whereas Robin et al. (2011) found that a viral load of 250 copies/mg of tissue predicted the resistance of patients with active UC to continuous intravenous (IV) steroids, infliximab, and cyclosporine.

Finally, given the reduced sensitivity of HE staining, ECCO guidelines consistently propose that IHC, possibly tpPCR, or both are essential for detecting CMV colitis in IBD and should be considered as standard tests (Tandon et al., 2017; Kucharzik et al., 2021).

Blood-based CMV detection tests studied in patients with IBD include CMV antigenaemia assay and bPCR, although both tests are of limited value in UC patients, as such patients have lower levels of CMV than do transplant recipients. The CMV antigenaemia assay semi-quantitatively detects the pp65 antigen in polymorphonuclear leucocytes (PMNs) of peripheral blood. CMV antigen-positive PMNs develop when antigens produced by CMV-infected cells are absorbed by the nuclei of PMNs, indicating systemic CMV reactivation. A positive result is defined as at least one pp65-positive cell per 2 × 10^5 PMNs and may depend on disease severity and the doses of immunosuppressants prescribed; no cut-off value for diagnosis of CMV colitis has yet been established (Park et al., 2017). It should be noted that false negative results can occur in neutropenic patients (Nakase et al., 2008).

CMV DNA in serum, measured by bPCR, may be diagnostic, but no cut-off value separating latent from active infection has yet been defined. Cut-offs in post-transplant patients vary from 4000 to 10 000 IU/ml (Emery et al., 2013; Kotton et al., 2013). In a study by Kim et al. (2013) on diagnosing suspected CMV colitis in patients with moderate-to-severe UC, serum CMV DNA PCR positivity was defined as > 250 copies/ml. Notably, both the CMV antigenaemia assay and bPCR were diagnostically useful in UC patients with endoscopically significant ulcers; the tests predicted CMV colitis with 67.3% sensitivity and 75.7% specificity in such patients. Furthermore, CMV antigenaemia-positivity was significantly associated with the need for subsequent colectomy in patients with UC and CMV colitis, suggesting that the test usefully predicted the clinical course of the disease. Similarly, Chun et al. (2015) found that two pp65-positive cells on CMV antigenaemia assay were significantly associated with refractoriness to corticosteroid therapy, affording a sensitivity of 66.7% and a specificity of 90.3%.

These findings suggest that while the low sensitivity of the CMV antigenaemia assay renders it difficult to replace endoscopic biopsy with the assay, the high specificity might aid in early diagnosis of severe CMV colitis cases that require prompt treatment prior to time-consuming IHC staining. According to Chang et al. (2015), as CMV infection is associated with poor responses to steroids and infliximab, CMV antigenaemia-positivity prior to the administration of such drugs in the acute exacerbation of UC might usefully predict candidates for early CMV rescue therapy, while ECCO guidelines suggest that blood-based CMV tests may be performed in addition to tissue-based tests when considering cessation of immunosuppressive therapy (Kucharzik et al., 2021).

Viral culture was previously regarded as the gold standard in CMV detection, and despite its relatively high sensitivity and specificity to identify CMV in colonic tissue, this method is not used in clinical practice anymore as results take 2 to 4 weeks to obtain (Garrido et al., 2013).

Furthermore, there is a need to develop non-invasive molecular tests for diagnosis of CMV colitis, and stool PCR may become the non-invasive diagnostic test of choice (Goodman et al., 2015), but to date, the sensitivity of the assays is too low, leading to false-negative results, even in allograft patients with high viral load in the tissue (Sun et al., 2021).
2015). Either way, a high index of suspicion is needed for diagnosis of CMV colitis in immunocompromised as well as immunocompetent patients.

TREATMENT — FEASIBLE OR FUTILE?

CMV is frequently detected in colonic tissue of IBD patients who are refractory to immunosuppressants, and thus could be involved in the pathophysiology of steroid refractoriness (Lee et al., 2016; Nowacki et al., 2018). There have been no studies specifically designed to address immunosuppressive treatment in this clinical scenario.

In a study by Shukla et al. (2017), corticosteroids (OR = 2.10, 95% CI = 1.31–3.37) and azathioprine (OR = 1.76, 95% CI = 1.21–2.57) were shown as independent predictive factors of CMV reactivation in the colon, which in turn may aggravate moderate or severe attacks of IBD.

Based on this indirect information, several therapeutic schedules have been proposed, such as rapid steroid tapering (Inokuchi et al., 2014; Cohen et al., 2018) or administration of infliximab, which is considered to have a lower risk of CMV reactivation compared to other immunosuppressants (McCurdy et al., 2015; Shukla et al., 2017). Recently, case reports by Rawa-Gołąbiowska et al. (2019) and Hommel et al. (2020) proposed vedolizumab for the treatment of steroid-resistant UC with CMV reactivation, although its efficacy has not been previously shown in large cohorts.

Although immunosuppressants could theoretically worsen the outcome of CMV colitis, numerous case series and retrospective cohorts have shown that they are still mostly maintained for control of disease activity (McCurdy et al., 2015; Cohen et al., 2018; Nowacki et al., 2018). Moreover, in patients with low CMV viral load and a low number of IHC-positive cells in the colon, CMV clearance may parallel the achievement of remission induced by immunosuppressants, even in patients who do not receive antivirals (Clos-Parals et al., 2019). A case-control study by Levin et al. (2017) reported that immunosuppressant discontinuation and administration of antivirals achieved remission and colectomy rates similar to refractory patients without CMV managed with standard rescue therapy. Thus, the best therapeutic schedule for CMV reactivation in refractory UC remains to be determined.

Case reports have described primary disseminated CMV infection, characterised by a mononucleosis-like syndrome with positive serum CMV DNA PCR, fever, leukopenia, thrombocytopenia, and transaminitis, in UC patients receiving immunosuppressants (Torres et al., 2018; Fakhreddine et al., 2019). In such cases, discontinuation of immunosuppressive therapy is recommended.

Meta-analyses by Kopylov et al. (2014) and Shukla et al. (2015) revealed contradictory results regarding the benefits of antiviral therapy in CMV reactivation in IBD, probably due to differences in CMV burden, and thus supporting the concept that CMV is ‘an innocent bystander’ in patients with low CMV burdens but an active pathogen in those with high CMV burdens. The latest ECCO guidelines state that there is limited information on the relationship between the evolution of UC and tissue viral load, as measured by number of viral inclusions in IHC (Jones et al., 2015; Zagórówicz et al., 2016) or CMV DNA copies (Roblin et al., 2011). Although some studies demonstrated that the higher the colonic viral load, the higher the risk of colectomy in patients with UC, supporting the benefit of antiviral therapy in cases of CMV reactivation, an exact threshold to determine which patients might benefit from antiviral therapy is currently unknown.

For example, a study by Jones et al. (2015) classified IBD patients into a high-grade CMV density group (five or more viral inclusions on IHC in each biopsy specimen); a low-grade CMV density group (fewer than five inclusions); and a control group (CMV-negative). The colectomy rates for patients in the low-grade CMV density group did not differ, regardless of whether antiviral therapy was prescribed. However, in the high-grade CMV density group, the colectomy rates were significantly higher in patients not on antiviral therapy (83% compared to 44% in those on therapy). Therefore, antiviral therapy may be indicated for cases of steroid-refractory or -dependent UC with high-grade CMV infection, and for those with > 250 CMV DNA copies/mg of tissue or low-grade CMV infection (evidenced by few inclusions or 10 to 250 DNA copies/mg of tissue) with endoscopically large ulcers (> 5 mm) (Fig. 1) (Shukla et al., 2015; Pillet et al., 2016).

The drug of choice for CMV colitis in adults is intravenous ganciclovir (5 mg/kg twice daily) for 5–10 days, followed by oral prodrug valganciclovir (900 mg twice daily) for the remainder of the 2–3-week course. An earlier transition to oral treatment is possible depending on the treatment response (Kucharzik et al., 2021).

In paediatric patients, it is recommended to complete a full 2–3-week course of intravenous ganciclovir, as an early switch to oral treatment could promote CMV reactivation (Jain et al., 2016).

The common side effects of ganciclovir, namely neutropenia and thrombocytopenia [also manifestations of systemic CMV], can add complexity to management. Such situations require a multidisciplinary approach, including engagement with infectious disease specialists. Hence, full blood count must be monitored regularly in patients on ganciclovir. Foscarnet, administered intravenously (90 mg/kg) twice daily for 2 to 3 weeks, may serve as a secondary treatment for ganciclovir-intolerant patients or in uncommon cases of ganciclovir-resistant CMV, mostly due to mutations in the viral UL97 kinase gene; the principal side-effect is nephrotoxicity. Concomitant administration of normal saline may reduce the risk of irreversible renal damage (Kucharzik et al., 2021).

Pharmacokinetic and pharmacodynamic properties of antiviral medications are not discussed as it is beyond the scope of this paper.
Follow-ups and monitoring standards after treatment of CMV colitis remain to be established. According to ECCO guidelines, blood-based CMV tests may be performed in addition to tissue-based tests when considering cessation of immunosuppressive therapy, although no cut-offs have yet been established (Kucharzik et al., 2021). It is unclear whether follow-up endoscopy is required to confirm clearance of CMV antigens after treatment of CMV colitis.

Whether medical treatment is necessary for other immunocompetent patients is debatable. Antiviral medications have considerable side effects, however, untreated CMV disease is associated with higher morbidity and mortality. Fyock et al. (2014) suggested that an immunocompetent patient should only be given antiviral treatment if it is a male over 55 years of age or if the patient has immune-modulating comorbidities. As many reports have described a rapid clinical improvement after starting therapy (Hasegawa et al., 2015; Levin et al., 2017), it is a common practice to treat “immunocompetent” patients who have severe CMV colitis, at least until further studies can be done.

CONCLUSIONS

CMV is a common infection in the general population, and a relatively common end-organ infectious complication in both immunocompromised and “non-immunocompromised” patients. In IBD, especially UC, patients, reactivation of CMV is associated with severe colitis, often leading to deterioration in their clinical evolution. As reactivation is triggered by clinical stimuli, including the use of immunosuppressants and exacerbation of mucosal inflammation, CMV screening is required only for a subset of patients, thus a high index of suspicion is crucial. Diagnosis of CMV colitis generally relies on histological IHC staining and colonic tissue PCR; blood-based tests such as the CMV antigenemia assay or PCR may aid in early diagnosis and predict the clinical course, although no clear cut-offs have yet been established. Prescription of antiviral medications may be based on the colon viral load or number of inclusions seen on IHC staining. However, when such assessment is practically difficult, an endoscopically large ulcers may aid in decision-making. Anti-TNF agents as a step-up therapy may be considered to treat CMV reactivation-associated flare-ups in UC patients with high CMV burden, in combination with antiviral treatment. Non-invasive CMV diagnostic tests are being developed and will hopefully improve the care of patients with CMV colitis.

REFERENCES


ISS CELVEDIS CITOMEGALOVĪRUSA ZARNU INFEKCIJAS DIAGNOSTIKAI UN ĀRSTĒŠANAI: ŠĪ BRĪZA DILEMMAS

Citomegalovīruss ir visušņāko herpes grupas viruss, kas pēc bieži vien asimptomātiskas primāras infekcijas pāriet latentē stāvoklī dažādos orgānos, tostarp zarnām. Tā kā pastāv cieša sinerģiskā saīniešana starp gluotāda iekaisumu un virusa ekspresiju, īpaši pacientiem ar iekaisīgām zarnu slimībām, bieži ir grūti atšķirt subklinisku citomegalovīrusa replikāciju no citomegalovīrusa izraisītā kolīta. Šī jautājuma izstrāde nav labprātīga, dažādas patoloģiskās situācijas ir mēģinājumi izmantot vietas metodes kā citomegalovīrusa dzīvības uzņēmumiem. Pētījumi ir iespējams mēģinājums ievērot, ka citomegalovīruse manifestācijas var būt tiešā saistība ar dažādām patoloģiskām situācijām, tostarp artrozīm, mazsukumiem un dzīvības uzņēmumiem, kas var izraisīt citomegalovīrusa izraisīto slimību. Ir iespējams mēģinājums izveidot patoloģiskā darbības izstādē, kas varētu palīdzēt izprast citomegalovīrusa ietekmē un radīt iespēju izveidot dažādu patoloģisku situāciju. Dažādi patoloģiskie procesi var izraisīt citomegalovīrusa izraisīto slimību, kas var būt atkarīgs no dažādām patoloģiskām situācijām.