World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i1.17

World J Gastroenterol 2013 January 7; 19(1): 17-25
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Juan-Ramón Larrubia, PhD, *Series Editor*

Clinical significance of cytomegalovirus infection in patients with inflammatory bowel disease

Elena Garrido, Elisa Carrera, Rebeca Manzano, Antonio Lopez-Sanroman

Elena Garrido, Antonio Lopez-Sanroman, Inflammatory Bowel Disease Clinic, Department of Gastroenterology, University Hospital Ramón y Cajal, 28034 Madrid, Spain
Elisa Carrera, Department of Gastroenterology, University Hospital of Guadalajara, 19002 Guadalajara, Spain
Rebeca Manzano, Department of Gastroenterology, Hospital Sureste, 28500 Madrid, Spain
Author contributions: Garrido E, Carrera E, Manzano R and Lopez-Sanroman A contributed equally to this work; and all authors have approved the final version of the manuscript.
Correspondence to: Dr. Elena Garrido, Inflammatory Bowel Disease Clinic, Department of Gastroenterology, University Hospital Ramón y Cajal, Carretera Colmenar K9.100, 28034 Madrid, Spain. elenagarridogomez@hotmail.com
Telephone: +34-913-368305 Fax: +34-913-368354
Received: May 29, 2012 Revised: August 3, 2012
Accepted: August 14, 2012
Published online: January 7, 2013

Abstract

Cytomegalovirus (CMV) infection is common in humans. The virus then enters a "latency phase" and can reactivate to different stimuli such as immunosuppression. The clinical significance of CMV infection in inflammatory bowel disease is different in Crohn's disease (CD) and ulcerative colitis (UC). CMV does not interfere in the clinical course of CD. However, CMV reactivation is frequent in severe or steroid-resistant UC. It is not known whether the virus exacerbates the disease or simply appears as a bystander of a severe disease. Different methods are used to diagnose CMV colitis. Diagnosis is classically based on histopathological identification of viral-infected cells or CMV antigens in biopsied tissues using haematoxylin-eosin or immunohistochemistry, other tests on blood or tissue samples are currently being investigated. Polymerase chain reaction performed in colonic mucosa has a high sensitivity and a positive result could be associated with a worse prognosis disease; further studies are needed to determine the most appropriate strategy with positive CMV-DNA in colonic mucosa. Specific endoscopic features have not been described in active UC and CMV infection. CMV colitis is usually treated with ganciclovir for several weeks, there are different opinions about whether or not to stop immunosuppressive therapy. Other antiviral drugs may be used. Multicenter controlled studies would needed to determine which subgroup of UC patients would benefit from early antiviral treatment.

Key words: Cytomegalovirus; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Hematoxylin and eosin; Immunohistochemical; Polymerase chain reaction; Ganciclovir; Infectious colitis

Garrido E, Carrera E, Manzano R, Lopez-Sanroman A. Clinical significance of cytomegalovirus infection in patients with inflammatory bowel disease. *World J Gastroenterol* 2013; 19(1): 17-25 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i1/17.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i1.17

NATURAL HISTORY OF CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) is a member of the *Herpesviridae* family which contains a double-stranded DNA. It often causes primary infection in humans, and later persists lifelong in a latent stage. In different situations of immunosuppression [birth, human immunodeficiency virus (HIV) infection, use of immunosuppressant therapy or chemotherapy] the virus can reactivate[1,2] and cause disease, but this may also occur in immunocompetent hosts.

In CMV infection, CMV antigens or antibodies can be detected in blood, whereas CMV disease symptoms

generally appear in a target organ[3]. The prevalence of CMV infection is high, ranging from 30%-100%[4-7], depending on age and race of population tested[8-10].

Primary CMV infection in immunocompetent individuals is usually asymptomatic, and rarely manifests itself as a mononucleosis-type disease similar to that caused by Epstein-Barr virus, consisting of fever, fatigue and cervical lymphadenopathy. Subsequently, the virus enters a latency phase in endothelial cells, macrophages or granulocyte stem cells[11-13]. Virus can reactivate in the healthy adult, this new activation being typically asymptomatic; however, this delicate balance can be disrupted in patients whose immune response is compromised, which may lead to development of symptoms in different organs, such as CMV colitis[13]. The use of highly active antiretroviral therapy in patients with HIV has decreased significantly CMV disease in these patients[14]; on the other hand, induced immunodeficiency in situations such as solid organ transplant or inflammatory bowel disease (IBD) sometimes allows CMV disease to develop, with significant morbidity and even mortality[15].

Antibody response to CMV infection reflects this relapsing-remitting pattern. In primary infection, an early increase of specific IgM antibodies occurs, which can be detected in the first week of infection[16], showing a sensitivity of 100% and a specificity of 99%[17]. Over the next 3-6 mo immunoglobulin M (IgM) antibodies fall to undetectable levels, although some may persist for up to 12-24 mo. Persistence of IgM antibodies could be related to concomitant immunosuppression[18]. Reactivation can cause again a rising IgM titers[17,19]. Immunoglobulin G (IgG) antibody production occurs within a few weeks of IgM increase[16]. When patients develop specific CMV IgG antibodies, they are considered "seropositives". In the reactivation of CMV, IgG antibody levels do not change, so that this situation can only be differentiated by the detection of an increase in IgM antibody titers that does not always occur. Thus, serology has a limited value in the diagnosis of reactivation[10]. Seronegative patients are not at risk for CMV disease, unless primoinfection occurs.

Gastrointestinal tract is a common site of CMV disease, with preference the esophagus and the colonic mucosa (especially at the right colon). The pouch mucosa behaves in a similar way to colon mucosa[20-22]. Clinical presentation of CMV colitis begins with watery diarrhoea that may be progress to rectal bleeding, abdominal pain, fatigue and fever. Other presentations such as fever of unknown origin, megacolon or digestive hemorrhage, are also possible.

It is unknown whether the virus remains in colon after a primary infection or if it disappears spontaneously[23]. A recent study[24] demonstrated persistence of colonic CMV [using polymerase chain reaction (PCR) method], following an acute ulcerative colitis (UC) flare-up despite remission of symptoms. The virus may disappear or not from the colon after an acute UC flare-up, but if it persists is detected only by PCR DNA, without displaying inflammatory changes in colonic mucosa or CMV antigens in infected colonic cells.

There have been reports of CMV colitis in immunocompetent hosts[25,26], especially in elderly patients with comorbidities in whom the disease followed a severe course with high mortality rate. Also, rare cases of CMV colitis preceding IBD have been reported[27].

RELATIONSHIP BETWEEN CMV AND IBD

The association between CMV and IBD was described long ago. The first case report dates from 1961, when Powell *et al*[28] described a patient with UC and cytomegalic inclusion disease. Since then, questions remain about the role of CMV in these patients: does CMV reactivation exacerbate the disease in patients with established IBD or is reactivation a consequence of IBD activity and its treatment with CMV acting as an innocent bystander[29-31]? Interpretation of existing results is limited because most studies are small and retrospective, different diagnostic methods of CMV detection are available and even different classifications are used for the severity of concomitant IBD[3].

CMV colitis occurs in "seropositive" patients with IBD. CMV does not appear to interfere with the clinical evolution of Crohn's disease (CD), and its involvement in UC is debated, especially in severe flare-ups.

DIAGNOSTIC TECHNIQUES

Diagnostic techniques for CMV infection

Serology: Serology is useful to determine previous viral exposure and identify patients at risk, as only seropositive patients (positive IgG antibodies in blood) may develop CMV disease[30,31].

Antigenemia assay: It detects viral protein pp65 produced in peripheral blood polymorphonuclear leukocytes. It is a simple and rapid technique, with a sensitivity of 60%-100% and a specificity of 83%-100%[32,33]. However, it does not differentiate between latent infection and active disease[23], no association exists with virus reactivation in the intestinal mucosa[31,34], and false negatives can occur in neutropenic patients[35].

PCR DNA amplification assay in blood: This test is supplanting antigenemia. Sensitivity ranges 65%-100% and specificity ranges 40%-92%[32,36,37]. This diagnostic method cannot differentiate between latency and activity states, so it is necessary to determine a cut-off above which active infection is diagnosed in patients with IBD[30,35], as well as in solid organ transplantation, where a viremia > 1000 copies/100 000 leukocytes indicates symptomatic CMV infection[38]. This method can be used both to detect disease and to monitor treatment response; a slow or absent decline in DNA levels after treatment could be an early indicator of drug resistance[39], and positive result after therapy indicates continuing treatment[40]. Most studies in patients with IBD have reported a correlation between

identification of CMV by PCR in blood and detection colonic CMV by haematoxylin and eosin (HE) or immunohistochemistry (IHC)[34,41-43].

PCR assay in stool: A qualitative and quantitative PCR assay for CMV DNA has been performed on human faecal specimens from immunocompromised patients[44,45].

Diagnostic techniques for CMV colitis

Histological diagnosis is considered the "gold standard" for diagnosing CMV disease in the gastrointestinal tract[46-51]. Several methods are available.

Histology by HE: Typically reveals cytomegalic cells that are 2 or 4 fold larger than normal cells, containing basophilic intranuclear inclusions in eccentric location surrounded by a clear halo, giving it an "owl's eye" appearence. Cells show a thickened nuclear membrane and smaller granular intracytoplasmic inclusions. Colonic biopsies should be taken from inflamed mucosa near or within the ulcer. This method has very high specificity (92%-100%), but its main problem is a poor sensitivity (10%-87%), making the diagnosis requires many samples and a trained pathologist[46,47]. Anecdotally cytomegalic cells have been described in colon biopsies from normal mucosa in healthy individuals[48,49].

IHC in colon biopsies: It involves the identification of CMV antigens in infected cells. It has a higher sensitivity than HE (78%-93%)[50,51]. Other techniques, however, do not rely on histology.

PCR DNA amplification assay in colon mucosa: PCR DNA amplification assay in colon mucosa has the greatest accuracy for virus detection[29,52,53] and may be used as a qualitative or quantitative method. PCR DNA levels in the colon are not related to viremia levels measured in blood[31,43,54,55]. Some studies detected prevalences greater than 30% in IBD patients[56], although the significance of a positive result in absence of histological signs of CMV infection is unclear. Very few studies have shown a correlation between histology (HE/IHC) and PCR results[31,43]. This suggests that detection of low DNA levels could determine latent infection and requires a cut-off level of viremia to distinguish infection from disease[30]. In other words, a positive result in colon does not necessarily reflect the involvement of CMV in UC flare-ups. A recent study from France suggests a cut-off of > 250 copies/mg for CMV disease[54] with a sensitivity of 100% and a specificity of 66%. To avoid false positives, and awaiting further studies, this determination should be performed only in patients with active UC refractory to conventional treatment.

Viral culture: Viral culture was previously regarded as the gold standard in CMV detection. Culture has a sensitivity of 45%-78% and a very high specificity (89%-100%). The virus is placed in a fibroblast tissue culture and diagnosis is made once the virus causes cytopathic changes in fibroblasts. The problem is that the result takes days to weeks[10], so this method is not used in clinical practice[57].

Typical endoscopic findings of CMV colitis: Typical endoscopic findings of CMV colitis are microerosions, deep ulcers and pseudotumoral lesions[58]. Most studies in patients with IBD, specifically in active UC, have not found specific endoscopic features[43,54,59,60]. Anecdotal studies describe some characteristic endoscopic (large, irregular, punched-out or longitudinal ulcers) with virus[61]. Discrepancy can be explained by the different criteria used to define CMV infection or disease.

In conclusion, different methods of detection of CMV have different sensitivities and specificities. In the setting of a severe UC flare-up refractory to conventional treatment, colonic IHC or PCR in blood should be performed, PCR presents a good correlation with the results of HE and IHC[30]. Serology and antigenemia only are useful as negative predictors for CMV infection, since they do not correlate with actual CMV colitis. The role of PCR positivity in colon remains to be determined, it is not known how to interpret its positivity in the absence of histological changes. However, recent studies imply positivity of this method in the disease prognosis[54]. Current European guidelines[62] recommend the use of tissue PCR or IHC to detect CMV in patients with UC resistant to immunomodulators, whereas older American guidelines[63] recommend performing sigmoidoscopic biopsy and viral culture in refractory cases of UC.

CMV PREVALENCE IN IBD

Overall prevalence of CMV is unknown in IBD patients. Most of studies have been carried out using a selected patient group and using different diagnostic methods, so that the available data include a wide range of prevalences.

CMV prevalence in CD

Seropositivity in CD patients is as high as in other populations (70%)[64,65], however CMV disease is rare in CD, making the virus an unlikely etiological factor in the novo development of IBD[27,64,66,67].

In most surveys, IHC did not detect CMV in CD patients, and PCR in tissue or stool samples found a very small frequency (< 5% of patients)[27,66-69], except in one study that used a highly sensitive PCR (detection < 10 copies of DNA) which detected CMV in 66% of individuals with CD and in 29% of controls, showing no association between CMV DNA and disease activity, suggesting the authors that small quantities of viral DNA are not clinically relevant[29].

Recently some theories have been published that explain these findings based on small studies[70], so results should be interpreted with caution. Tumor necrosis factor-α (TNFα) would be significantly associated with CMV infection or reactivation in IBD. However interferon-γ (IFNγ), which is produced from CD4 + T

cells[71], could suppress CMV reactivation. CD is considered a Th1-type inflammatory process with high expression of IFNγ, which does no help the virus reactivation and may explain the different prevalence of CMV disease in UC and CD[70].

CMV prevalence in UC

Prevalence of CMV infection is about 70%[31], a similar percentage to that of the general population.

Patients with inactive or mild-moderate UC did not show an increased risk of CMV colitis, using HE and IHC[27,31,41] or IHC in colectomy patients undergoing surgery for dysplasia or cancer[72].

The most extensive literature is on severe and/or steroid-refractory colitis. These two terms are used interchangeably in studies and are not defined clearly, so the results are difficult to interpret[30].

Severe colitis: The combination of serological tests and rectal biopsies found a CMV disease prevalence of around 20%[42,73]. Risk factors that have been identified are female gender, older age, pancolonic disease with active inflammation at histology and azathioprine therapy[60,72,73]. According only to antigenemia, prevalence increased to 34%[60], while using HE or IHC in colonic mucosa prevalence decreased to 3%[74].

Severe steroid-resistant colitis: In retrospective studies the prevalence according to HE was 0.5%[75]. The prevalence of CMV increased by combining HE and IHC with antigenemia (20%-40%)[31,41,72,76,77]. The prevalence using blood PCR was 60%[43], whereas PCR results in colon were lower (38%)[78]. There is a poor correlation between peripheral and colonic viral load, this can be explained by theory proposed by Criscuoli *et al*[24,42] about a specific genotype, which possibly has a particular colonic tropism and pathogenic character, whilst other genotypes are not pathogenic.

Urgent colectomy for colitis: A higher prevalence of CMV is expected in these patients because the greater severity of their disease, but the prevalence using HE or IHC ranged between 11.5% and 27%[77,79-82], which is similar to the previous groups.

Experimental studies have identified three factors that influence the reactivation of CMV infection in active colitis: (1) increased cell proliferation in inflamed tissue with ulcers that attract CMV; (2) inherent impaired natural killer cell activity presented by patients with IBD[83,84]; and (3) use of immunosuppressive drugs[31,42,69]. The third factor is controversial[73-75,80,85], since use of steroids may be either a risk factor or a surrogate marker of severity disease[41]. *In vitro* data suggest that steroids and cyclosporine could support the replication of CMV[76,86,87]. Infliximab treatment has not been associated with increased risk of CMV reactivation in IBD patients[66]. Moreover, TNFα has been identified as an activator of CMV, and thus infliximab (IFX) could promote viral latency, by lowering the levels of this cytokine[88,89]. This suggests that IFX could be used in patients with severe UC flare and CMV reactivation. However, some cases of tacrolimus-refractory UC that were treated with IFX did not have a favourable outcome[90].

CMV reaches the mucosa by way of monocytes and then colonize the colonic cells, acquiring particular affinity for the inflammatory sites, probably due to the presence of pro-inflammatory cytokines such as IFNγ and TNFα produced by macrophages and T-cells in active UC[91-94]. CMV avoids immune recognition of macrophages and uses immune specific functions to reactivate and spread[95]. Recent studies suggested CMV can appear only in inflamed tissue and is not found in healthy tissue[54].

Hommes *et al*[94] proposed the following sequence to explain the pathophysiology of CMV disease in patients with active UC: (1) initiation phase, mucosal inflammatory response induces expression of cytokines and chemokines which activates latently infected cells and the migration of monocytes and dendritic cells into the inflamed mucosa; (2) reactivation phase, in which infected monocytes differentiate into tissue macrophages and dendritic cells; and (3) consolidation phase, during which the virus causes an active replication predominantly in endothelial cells that likely exacerbates inflammation. The virus in the first and second phase has not led to histological damage and can only be detected by PCR-DNA. It would be appropriate to detect CMV in these phases, so the optimal treatment would be administered at an early stage before complicating the disease. They do not consider CMV as an innocent bystander but rather involved in resistance to immunosuppressive treatment.

In the same line, other authors suggest that the positivity of CMV DNA in the colonic mucosa in patients with refractory UC indicates uncontrolled intestinal inflammation, suggesting a change in immunosuppressive therapy[96].

Coincidental detection of primary CMV infection at the first appearance of IBD has been reported before[66,97], primary CMV infection in IBD patients without immunosupression[98,99], and even disseminated CMV infection in CD[100].

PROGNOSIS OF CMV COLITIS IN IBD

As discussed above, it is unclear whether CMV superinfection leads to a more aggressive course of pre-existing inflammatory disease[29,30].

Referring only to UC, case-reports and retrospective series[29,42,55,68,69] suggested that CMV may trigger a steroid-refractory flare-up and worsen disease prognosis[76,77,80,85,101], associated increased risk of toxic megacolon[81] and surgical intervention[31,77,82,102,103]. This hypothesis is supported by two prospective studies[41,54]. The second, a recent French study, relates positivity of CMV (PCR in colon > 250 copies/mg) to treatment resistance (steroids and other three line of treatment), demonstrating that early initiation of antiviral therapy in these cases delays treatment resistance

and improves prognosis[54].

However, other studies[3,27,34,43,72] that analyzed prognosis in patients with severe UC refractory to conventional treatments did not find increased disease severity nor increased rate of colectomy in CMV positive patients.

These conclusions are limited by differences in quality of existing studies.

TREATMENT OF CMV COLITIS IN IBD

It is difficult to draw conclusions about the role of antiviral therapy based on the available evidence[23], which is of varying quality.

Most authors recommend the use of antivirals[30,31,41,43,75] in steroid-refractory UC flare-up and CMV positive patients. Treatment can significantly decrease the mortality rate and need for surgery. However, some studies show that treatment of CMV does not alter disease course[80], and has even been shown the transience of positivity of serological tests (antigenemia, PCR) in patients with severe UC, but which as discussed earlier has little correlation with PCR determination in colon[34,94].

As CMV reactivation impact in clinical outcome is not yet elucidated, a rational approach would be to determine the CMV serology (IgG) when prescribing steroids in UC[31]. If steroid-refractoriness develops, rectal biopsies should be conducted only in seropositive patients, who are the ones who are at risk of developing CMV disease[31]. A detection of CMV (HE, IHC or PCR) in the inflamed mucosa should imply that standard therapies alone will not control intestinal inflammation, and make mandatory to consider alternative therapies[43], including CMV treatment[30]. If detection methods are not readily available, empiric therapy of IgG positive individuals with steroid-refractory disease is probably justified.

An original study recommended only antiviral treatment in severe UC with large ulcers (> 5 mm) and positive PCR in colon, all patients with positive PCR and no large ulcers in endoscopy responded to conventional therapy[104].

CMV colitis is typically treated with ganciclovir, although other antivirals have been used as foscarnet, valganciclovir and cidofovir[105-107]. Ganciclovir has a poor oral bioavailability so initially it has to be administered intravenously[105,106]. The recommended dosage is 5 mg/kg twice daily for at least 3 wk[107]. After some days of initial treatment the patient can switched to oral ganciclovir (1 g three times daily), although its value is uncertain. Treatment benefits must outweigh the risks associated with the medications used, as this drug can trigger significant adverse effects such as bone marrow suppression, particularly neutropenia[105]. Other side effects include headaches, somnolence, psychosis, elevated transaminases, fever and rash[105]. Foscarnet can be used when ganciclovir is contraindicated (90 mg/kg intravenously twice daily for 3-6 wk)[107]. Its main adverse effect is nephrotoxicity.

Response rate to antiviral therapy is 72% (range 50% to 83%)[31,41,43,75], but these data should be interpreted with caution because "response" was not uniformly defined in these studies and patients were treated concomitantly with immunosuppressants[30], although some authors decreased the dose of immunosuppressive drug[75]. Other authors consider to increase immunosuppressive therapies (other than corticosteroids) if CMV-DNA in colonic mucosa is detected, because a positive finding of CMV-DNA in inflamed colonic mucosa of patients with refractory UC suggests uncontrolled intestinal inflammation[96]. Antiviral treatment should be considerate in disseminated disease[108] which has very poor prognosis.

ECCO guides[62] and American College of Gastroenterology[63] recommend treatment when CMV is detected in colon tissue. Immunosuppressive therapy is stopped only in case of severe systemic CMV reactivation[62].

A multicenter randomized controlled trial with a large number of patients, using homogeneous diagnostic methods, including endoscopic evaluation, would be required to determine in which subgroup of patients early antiviral treatment would be useful[23,96].

REFERENCES

1 **Alford CA**, Stagno S, Pass RF, Britt WJ. Congenital and perinatal cytomegalovirus infections. *Rev Infect Dis* 1993; **12** Suppl 7: S745-S753 [PMID: 2173104 DOI: 10.1093/clinids/12.Supplement_7.S745]

2 **Nelson MR**, Erskine D, Hawkins DA, Gazzard BG. Treatment with corticosteroids--a risk factor for the development of clinical cytomegalovirus disease in AIDS. *AIDS* 1993; **7**: 375-378 [PMID: 8097096 DOI: d10.1097/00002030-199303000-00011]

3 **Ayre K**, Warren BF, Jeffery K, Travis SP. The role of CMV in steroid-resistant ulcerative colitis: A systematic review. *J Crohns Colitis* 2009; **3**: 141-148 [PMID: 21172262 DOI: 10.1016/j.crohns.2009.03.002]

4 **Krech U**. Complement-fixing antibodies against cytomegalovirus in different parts of the world. *Bull World Health Organ* 1973; **49**: 103-106 [PMID: 4363395]

5 **Staras SA**, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. *Clin Infect Dis* 2006; **43**: 1143-1151 [PMID: 17029132 DOI: 10.1086/508173]

6 **Zhang LJ**, Hanff P, Rutherford C, Churchill WH, Crumpacker CS. Detection of human cytomegalovirus DNA, RNA, and antibody in normal donor blood. *J Infect Dis* 1995; **171**: 1002-1006 [PMID: 7706776 DOI: 10.1093/infdis/171.4.1002]

7 **Colugnati FA**, Staras SA, Dollard SC, Cannon MJ. Incidence of cytomegalovirus infection among the general population and pregnant women in the United States. *BMC Infect Dis* 2007; **7**: 71 [PMID: 17605813 DOI: 10.1186/1471-2334-7-71]

8 **Mcgavran MH**, Smith MG. Ultrastructural, cytochemical, and microchemical observations on cytomegalovirus (salivary gland virus) infection of human cells in tissue culture. *Exp Mol Pathol* 1965; **76**: 1-10 [PMID: 14297550 DOI: 10.1016/0014-4800(65)90019-5]

9 **Pass RF**. Epidemiology and transmission of cytomegalovirus. *J Infect Dis* 1985; **152**: 243-248 [PMID: 2993429 DOI: 10.1093/infdis/152.2.243]

10 **de la Hoz RE**, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. *J Clin Virol* 2002; **25** Suppl 2: S1-12 [PMID: 12361752 DOI: 10.1016/S1386-6532(02)00091-4]

11 **Crough T**, Khanna R. Immunobiology of human cytomegalovirus: from bench to bedside. *Clin Microbiol Rev* 2009; **22**: 76-98 [PMID: 19136435 DOI: 10.1128/CMR.00034-08]

12 **Grefte A**, van der Giessen M, van Son W, The TH. Circulating cytomegalovirus (CMV)-infected endothelial cells in patients with an active CMV infection. *J Infect Dis* 1993; **167**: 270-277 [PMID: 8380609 DOI: 10.1093/infdis/167.2.270]

13 **Jacobson MA**, Mills J. Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS). Clinical findings, diagnosis, and treatment. *Ann Intern Med* 1988; **108**: 585-594 [PMID: 2831765 DOI: 10.7326/0003-4819-108-4-585]

14 **Macdonald JC**, Torriani FJ, Morse LS, Karavellas MP, Reed JB, Freeman WR. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. *J Infect Dis* 1998; **177**: 1182-1187 [PMID: 9593001 DOI: 10.1086/515281]

15 **Ho M**. Virus infections after transplantation in man. Brief review. *Arch Virol* 1977; **55**: 1-24 [PMID: 200197 DOI: 10.1007/BF01314475]

16 **Van der Giessen M**, van den Berg AP, van der Bij W, Postma S, van Son WJ, The TH. Quantitative measurement of cytomegalovirus-specific IgG and IgM antibodies in relation to cytomegalovirus antigenaemia and disease activity in kidney recipients with an active cytomegalovirus infection. *Clin Exp Immunol* 1990; **80**: 56-61 [PMID: 2157567 DOI: 10.1111/j.1365-2249.1990.tb06441.x]

17 **Revello MG**, Zavattoni M, Furione M, Lilleri D, Gorini G, Gerna G. Diagnosis and outcome of preconceptional and periconceptional primary human cytomegalovirus infections. *J Infect Dis* 2002; **186**: 553-557 [PMID: 12195384 DOI: 10.1086/341831]

18 **Nagington J**. Cytomegalovirus antibody production in renal transplant patients. *J Hyg* (Lond) 1971; **69**: 645-660 [PMID: 4332511 DOI: 10.1017/S0022172400021926]

19 **Rawlinson WD**. Broadsheet. Number 50: Diagnosis of human cytomegalovirus infection and disease. *Pathology* 1999; **31**: 109-115 [PMID: 10399165 DOI: 10.1080/003130299105287]

20 **Moonka D**, Furth EE, MacDermott RP, Lichtenstein GR. Pouchitis associated with primary cytomegalovirus infection. *Am J Gastroenterol* 1998; **93**: 264-266 [PMID: 9468256 DOI: 10.1016/S0002-9270(97)00068-3]

21 **Casadesus D**, Tani T, Wakai T, Maruyama S, Iiai T, Okamoto H, Hatakeyama K. Possible role of human cytomegalovirus in pouchitis after proctocolectomy with ileal pouch-anal anastomosis in patients with ulcerative colitis. *World J Gastroenterol* 2007; **13**: 1085-1089 [PMID: 17373744 DOI: 1007-9327/13/1085.asp]

22 **Muñoz-Juarez M**, Pemberton JH, Sandborn WJ, Tremaine WJ, Dozois RR. Misdiagnosis of specific cytomegalovirus infection of the ileoanal pouch as refractory idiopathic chronic pouchitis: report of two cases. *Dis Colon Rectum* 1999; **42**: 117-120 [PMID: 10211531 DOI: 10.1007/BF02235196]

23 **Criscuoli V**, Rizzuto MR, Cottone M. Cytomegalovirus and inflammatory bowel disease: is there a link? *World J Gastroenterol* 2006; **12**: 4813-4818 [PMID: 16937462 DOI: 1007-9327/12/4813.asp]

24 **Criscuoli V**, Rizzuto MR, Montalbano L, Gallo E, Cottone M. Natural history of cytomegalovirus infection in a series of patients diagnosed with moderate-severe ulcerative colitis. *World J Gastroenterol* 2011; **17**: 633-638 [PMID: 21350712 DOI: 10.3748/wjg.v17.i5.633]

25 **Galiatsatos P**, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. *Dig Dis Sci* 2005; **50**: 609-616 [PMID: 15844689 DOI: 10.1007/s10620-005-2544-6]

26 **Ng FH**, Chau TN, Cheung TC, Kng C, Wong SY, Ng WF, Lee KC, Chan E, Lai ST, Yuen WC, Chang CM. Cytomegalovirus colitis in individuals without apparent cause of immunodeficiency. *Dig Dis Sci* 1999; **44**: 945-952 [PMID: 10235602]

27 **Kim CH**, Bahng S, Kang KJ, Ku BH, Jo YC, Kim JY, Chang DK, Son HJ, Rhee PL, Kim JJ, Rhee JC, Kim YH. Cytomegalovirus colitis in patients without inflammatory bowel disease: a single center study. *Scand J Gastroenterol* 2010; **45**: 1295-1301 [PMID: 20568970]

28 **Powell RD**, Warner NE, Levine RS, Kirsner JB. Cytomegalic inclusion disease and ulcerative colitis; report of a case in a young adult. *Am J Med* 1961; **30**: 334-340 [PMID: 13737621 DOI: 10.1016/0002-9343(61)90105-X]

29 **Wakefield AJ**, Fox JD, Sawyerr AM, Taylor JE, Sweenie CH, Smith M, Emery VC, Hudson M, Tedder RS, Pounder RE. Detection of herpesvirus DNA in the large intestine of patients with ulcerative colitis and Crohn's disease using the nested polymerase chain reaction. *J Med Virol* 1992; **38**: 183-190 [PMID: 1287131 DOI: 10.1002/jmv.1890380306]

30 **Lawlor G**, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis* 2010; **16**: 1620-1627 [PMID: 20232408 DOI: 10.1002/ibd.21275]

31 **Domènech E**, Vega R, Ojanguren I, Hernández A, Garcia-Planella E, Bernal I, Rosinach M, Boix J, Cabré E, Gassull MA. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. *Inflamm Bowel Dis* 2008; **14**: 1373-1379 [PMID: 18452205 DOI: 10.1002/ibd.20498]

32 **Boivin G**, Handfield J, Toma E, Murray G, Lalonde R, Tevere VJ, Sun R, Bergeron MG. Evaluation of the AMPLICOR cytomegalovirus test with specimens from human immunodeficiency virus-infected subjects. *J Clin Microbiol* 1998; **36**: 2509-2513 [PMID: 9705384]

33 **Lazzarotto T**, Dal Monte P, Landini MP. Recent advances in the diagnosis of cytomegalovirus infection. *Ann Biol Clin* (Paris) 1996; **54**: 259-265 [PMID: 8949423 DOI: 10.1016/j.humimm.2004.02.006]

34 **Matsuoka K**, Iwao Y, Mori T, Sakuraba A, Yajima T, Hisamatsu T, Okamoto S, Morohoshi Y, Izumiya M, Ichikawa H, Sato T, Inoue N, Ogata H, Hibi T. Cytomegalovirus is frequently reactivated and disappears without antiviral agents in ulcerative colitis patients. *Am J Gastroenterol* 2007; **102**: 331-337 [PMID: 17156136 DOI: 10.1111/j.1572-0241.2006.00989.x]

35 **Nakase H**, Matsumura K, Yoshino T, Chiba T. Systematic review: cytomegalovirus infection in inflammatory bowel disease. *J Gastroenterol* 2008; **43**: 735-740 [PMID: 18958541 DOI: 10.1007/s00535-008-2246-x]

36 **Michaelides A**, Liolios L, Glare EM, Spelman DW, Bailey MJ, Walters EH, Williams TJ, Snell GI, Kotsimbos TC. Increased human cytomegalovirus (HCMV) DNA load in peripheral blood leukocytes after lung transplantation correlates with HCMV pneumonitis. *Transplantation* 2001; **72**: 141-147 [PMID: 11468549]

37 **Rowshani AT**, Bemelman FJ, van Leeuwen EM, van Lier RA, ten Berge IJ. Clinical and immunologic aspects of cytomegalovirus infection in solid organ transplant recipients. *Transplantation* 2005; **79**: 381-386 [PMID: 15729162 DOI: 10.1097/01.TP.0000148239.00384.F0]

38 **Gerna G**, Lilleri D. Monitoring transplant patients for human cytomegalovirus: Diagnostic update. *Herpes* 2006; **13**: 4-11 [PMID: 16732996 DOI: 10.1111/j.1600-6143.2006.01488.x]

39 **Roberts TC**, Brennan DC, Buller RS, Gaudreault-Keener M, Schnitzler MA, Sternhell KE, Garlock KA, Singer GG, Storch GA. Quantitative polymerase chain reaction to predict occurrence of symptomatic cytomegalovirus infection and assess response to ganciclovir therapy in renal transplant recipients. *J Infect Dis* 1998; **178**: 626-635 [PMID: 9728529 DOI: 10.1086/515383]

40 **Einsele H**, Ehninger G, Steidle M, Vallbracht A, Müller M, Schmidt H, Saal JG, Waller HD, Müller CA. Polymerase chain reaction to evaluate antiviral therapy for cytomegalovirus disease. *Lancet* 1991; **338**: 1170-1172 [PMID: 1682592 DOI: 10.1016/0140-6736(91)92032-W]

41 **Cottone M**, Pietrosi G, Martorana G, Casà A, Pecoraro G,

Oliva L, Orlando A, Rosselli M, Rizzo A, Pagliaro L. Prevalence of cytomegalovirus infection in severe refractory ulcerative and Crohn's colitis. *Am J Gastroenterol* 2001; **96**: 773-775 [PMID: 11280549 DOI: 10.1016/S0002-9270(00)02413-8]

42 **Criscuoli V**, Casà A, Orlando A, Pecoraro G, Oliva L, Traina M, Rizzo A, Cottone M. Severe acute colitis associated with CMV: a prevalence study. *Dig Liver Dis* 2004; **36**: 818-820 [PMID: 15646428 DOI: 10.1016/j.dld.2004.05.013]

43 **Yoshino T**, Nakase H, Ueno S, Uza N, Inoue S, Mikami S, Matsuura M, Ohmori K, Sakurai T, Nagayama S, Hasegawa S, Sakai Y, Chiba T. Usefulness of quantitative real-time PCR assay for early detection of cytomegalovirus infection in patients with ulcerative colitis refractory to immunosuppressive therapies. *Inflamm Bowel Dis* 2007; **13**: 1516-1521 [PMID: 17828781 DOI: 10.1002/ibd.20253]

44 **Boom R**, Sol C, Weel J, Lettinga K, Gerrits Y, van Breda A, Wertheim-Van Dillen P. Detection and quantitation of human cytomegalovirus DNA in faeces. *J Virol Methods* 2000; **84**: 1-14 [PMID: 10644082 DOI: 10.1016/S0166-0934(99)00127-5]

45 **Michel D**, Marre E, Hampl W, Roczkos J, Müller S, Hertenstein B, Kern P, Heymer B, Salzberger B, Arasteh K. Intestinal cytomegalovirus disease in immunocompromised patients may be ruled out by search for cytomegalovirus DNA in stool samples. *J Clin Microbiol* 1995; **33**: 3064-3067 [PMID: 8576379]

46 **Wu GD**, Shintaku IP, Chien K, Geller SA. A comparison of routine light microscopy, immunohistochemistry, and in situ hybridization for the detection of cytomegalovirus in gastrointestinal biopsies. *Am J Gastroenterol* 1989; **84**: 1517-1520 [PMID: 2556912]

47 **Cotte L**, Drouet E, Bissuel F, Denoyel GA, Trepo C. Diagnostic value of amplification of human cytomegalovirus DNA from gastrointestinal biopsies from human immunodeficiency virus-infected patients. *J Clin Microbiol* 1993; **31**: 2066-2069 [PMID: 8396587]

48 **Dieterich DT**, Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. *J Acquir Immune Defic Syndr* 1991; **4** Suppl 1: S29-S35 [PMID: 1848619]

49 **Franzin G**, Muolo A, Griminelli T. Cytomegalovirus inclusions in the gastroduodenal mucosa of patients after renal transplantation. *Gut* 1981; **22**: 698-701 [PMID: 6271652 DOI: 10.1136/gut.22.9.698]

50 **Beaugerie L**, Cywiner-Golenzer C, Monfort L, Girard PM, Carbonnel F, Ngô Y, Cosnes J, Rozenbaum W, Nicolas JC, Châtelet FP, Gendre JP. Definition and diagnosis of cytomegalovirus colitis in patients infected by human immunodeficiency virus. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; **14**: 423-429 [PMID: 9170416 DOI: 10.1097/00042560-199704150-00005]

51 **Kandiel A**, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol* 2006; **101**: 2857-2865 [PMID: 17026558 DOI: 10.1111/j.1572-0241.2006.00869.x]

52 **Rahbar A**, Boström L, Lagerstedt U, Magnusson I, Söderberg-Naucler C, Sundqvist VA. Evidence of active cytomegalovirus infection and increased production of IL-6 in tissue specimens obtained from patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2003; **9**: 154-161 [PMID: 12792220 DOI: 10.1097/00054725-200305000-00002]

53 **Robey SS**, Gage WR, Kuhajda FP. Comparison of immunoperoxidase and DNA in situ hybridization techniques in the diagnosis of cytomegalovirus colitis. *Am J Clin Pathol* 1988; **89**: 666-671 [PMID: 2833851]

54 **Roblin X**, Pillet S, Oussalah A, Berthelot P, Del Tedesco E, Phelip JM, Chambonnière ML, Garraud O, Peyrin-Biroulet L, Pozzetto B. Cytomegalovirus load in inflamed intestinal tissue is predictive of resistance to immunosuppressive therapy in ulcerative colitis. *Am J Gastroenterol* 2011; **106**: 2001-2008 [PMID: 21788989 DOI: 10.1038/ajg.2011.202]

55 **Kou T**, Nakase H, Tamaki H, Kudo T, Nishio A, Chiba T. Cytomegalovirus infection in patients with ulcerative colitis diagnosed by quantitative real-time PCR analysis. *Dig Dis Sci* 2006; **51**: 1052-1055 [PMID: 16865568 DOI: 10.1007/s10620-006-8006-y]

56 **Dimitroulia E**, Spanakis N, Konstantinidou AE, Legakis NJ, Tsakris A. Frequent detection of cytomegalovirus in the intestine of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2006; **12**: 879-884 [PMID: 16954807 DOI: 10.1097/01.mib.0000231576.11678.57]

57 **Landry ML**, Ferguson D. Comparison of quantitative cytomegalovirus antigenemia assay with culture methods and correlation with clinical disease. *J Clin Microbiol* 1993; **31**: 2851-2856 [PMID: 8263166]

58 **Ljungman P**, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002; **34**: 1094-1097 [PMID: 11914998 DOI: 10.1086/339329]

59 **Sakamoto I**, Shirai T, Kamide T, Igarashi M, Koike J, Ito A, Takagi A, Miwa T, Kajiwara H. Cytomegalovirus enterocolitis in an immunocompetent individual. *J Clin Gastroenterol* 2002; **34**: 243-246 [PMID: 11873105 DOI: 10.1097/00004836-200203000-00010]

60 **Wada Y**, Matsui T, Matake H, Sakurai T, Yamamoto J, Kikuchi Y, Yorioka M, Tsuda S, Yao T, Yao S, Haraoka S, Iwashita A. Intractable ulcerative colitis caused by cytomegalovirus infection: a prospective study on prevalence, diagnosis, and treatment. *Dis Colon Rectum* 2003; **46**: S59-S65 [PMID: 14530660 DOI: 10.1097/01.DCR.0000087486.21981.C6]

61 **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**: 1245-1251 [PMID: 20222169 DOI: 10.3748/wjg.v16.i10.1245]

62 **Rahier JF**, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domènech E, Eliakim R, Eser A, Frater J, Gassull M, Giladi M, Kaser A, Lémann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, Van Assche G, Viget N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009; **3**: 47-91 [PMID: 21172250 DOI: 10.1016/j.crohns.2009.02.010]

63 **Kornbluth A**, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004; **99**: 1371-1385 [PMID: 15233681 DOI: 10.1111/j.1572-0241.2004.40036.x]

64 **Hommes DW**, Sterringa G, Boom R. Incidence and outcome of cytomegalovirus infection in patients with inflammatory bowel disease. *Gastroenterology* 2002; **122**: A1287

65 **D'Ovidio V**, Vernia P, Gentile G, Capobianchi A, Marcheggiano A, Viscido A, Martino P, Caprilli R. Cytomegalovirus infection in inflammatory bowel disease patients undergoing anti-TNFalpha therapy. *J Clin Virol* 2008; **43**: 180-183 [PMID: 18614396 DOI: 10.1016/j.jcv.2008.06.002]

66 **Orvar K**, Murray J, Carmen G, Conklin J. Cytomegalovirus infection associated with onset of inflammatory bowel disease. *Dig Dis Sci* 1993; **38**: 2307-2310 [PMID: 8261839 DOI: 10.1007/BF01299914]

67 **Knösel T**, Schewe C, Petersen N, Dietel M, Petersen I. Prevalence of infectious pathogens in Crohn's disease. *Pathol Res Pract* 2009; **205**: 223-230 [PMID: 19186006 DOI: 10.1016/j.prp.2008.04.018]

68 **Takahashi Y**, Tange T. Prevalence of cytomegalovirus infection in inflammatory bowel disease patients. *Dis Colon Rectum* 2004; **47**: 722-726 [PMID: 15037934 DOI: 10.1007/

s10350-003-0117-3]
69 **Kaufman HS**, Kahn AC, Iacobuzio-Donahue C, Talamini MA, Lillemoe KD, Hamilton SR. Cytomegaloviral enterocolitis: clinical associations and outcome. *Dis Colon Rectum* 1999; **42**: 24-30 [PMID: 10211516 DOI: 10.1007/BF02235178]
70 **Nakase H**, Yoshino T, Honzawa Y, Chiba T. Low prevalence of CMV infection in patients with Crohn's disease in comparison with ulcerative colitis: effect of different immune response on prevalence of CMV infection. *Dig Dis Sci* 2010; **55**: 1498-1499 [PMID: 20198427 DOI: 10.1007/s10620-010-1162-0]
71 **Fuss IJ**, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, Fiocchi C, Strober W. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol* 1996; **157**: 1261-1270 [PMID: 8757634]
72 **Kojima T**, Watanabe T, Hata K, Shinozaki M, Yokoyama T, Nagawa H. Cytomegalovirus infection in ulcerative colitis. *Scand J Gastroenterol* 2006; **41**: 706-711 [PMID: 16716970 DOI: 10.1080/00365520500408584]
73 **Kishore J**, Ghoshal U, Ghoshal UC, Krishnani N, Kumar S, Singh M, Ayyagari A. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance and outcome. *J Med Microbiol* 2004; **53**: 1155-1160 [PMID: 15496396 DOI: 10.1099/jmm.0.45629-0]
74 **Vega R**, Bertrán X, Menacho M, Domènech E, Moreno de Vega V, Hombrados M, Cabré E, Ojanguren I, Gassull MA. Cytomegalovirus infection in patients with inflammatory bowel disease. *Am J Gastroenterol* 1999; **94**: 1053-1056 [PMID: 10201482 DOI: 10.1016/S0002-9270(99)00068-4]
75 **Papadakis KA**, Tung JK, Binder SW, Kam LY, Abreu MT, Targan SR, Vasiliauskas EA. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 2137-2142 [PMID: 11467645 DOI: 10.1016/S0002-9270(01)02512-6]
76 **Kambham N**, Vij R, Cartwright CA, Longacre T. Cytomegalovirus infection in steroid-refractory ulcerative colitis: a case-control study. *Am J Surg Pathol* 2004; **28**: 365-373 [PMID: 15104299 DOI: 10.1097/00000478-200403000-00009]
77 **Maconi G**, Colombo E, Zerbi P, Sampietro GM, Fociani P, Bosani M, Cassinotti A, Casini V, Russo A, Ardizzone S, Porta M, Bianchi Porro G. Prevalence, detection rate and outcome of cytomegalovirus infection in ulcerative colitis patients requiring colonic resection. *Dig Liver Dis* 2005; **37**: 418-423 [PMID: 15893280 DOI: 10.1016/j.dld.2005.01.011]
78 **Pofelski J**, Heluwaert F, Roblin X, Morand P, Gratacap B, Germain E, Brion JP, Salon C, Bonaz B. Cytomegalovirus and cryptogenic inflammatory bowel disease. *Gastroenterol Clin Biol* 2007; **31**: 292-296 [PMID: 17396088 DOI: GCB-03-2007-31-3-0399-8320-101019-200520007]
79 **Mendez JC**, Espy MJ, Smith TF, Wilson JA, Paya CV. Evaluation of PCR primers for early diagnosis of cytomegalovirus infection following liver transplantation. *J Clin Microbiol* 1998; **36**: 526-530 [PMID: 9466770 DOI: 0095-1137/98/$04.0010]
80 **Eyre-Brook IA**, Dundas S. Incidence and clinical significance of colonic cytomegalovirus infection in idiopathic inflammatory bowel disease requiring colectomy. *Gut* 1986; **27**: 1419-1425 [PMID: 3026932 DOI: 10.1136/gut.27.12.1419]
81 **Cooper HS**, Raffensperger EC, Jonas L, Fitts WT. Cytomegalovirus inclusions in patients with ulcerative colitis and toxic dilation requiring colonic resection. *Gastroenterology* 1977; **72**: 1253-1256 [PMID: 192627]
82 **Alcalá MJ**, Casellas F, Pallarés J, de Torres I, Malagelada JR. Infection by cytomegalovirus in patients with ulcerative colitis requiring colonic resection. *Med Clin* (Barc) 2000; **114**: 201-204 [PMID: 10757099]
83 **Targan SR**, Karp LC. Defects in mucosal immunity leading to ulcerative colitis. *Immunol Rev* 2005; **206**: 296-305 [PMID: 16048556 DOI: 10.1111/j.0105-2896.2005.00286.x]
84 **Ginsburg CH**, Dambrauskas JT, Ault KA, Falchuk ZM. Impaired natural killer cell activity in patients with inflammatory bowel disease: evidence for a qualitative defect. *Gastroenterology* 1983; **85**: 846-851 [PMID: 6884709]
85 **de Saussure P**, Lavergne-Slove A, Mazeron MC, Alain S, Matuchansky C, Bouhnik Y. A prospective assessment of cytomegalovirus infection in active inflammatory bowel disease. *Aliment Pharmacol Ther* 2004; **20**: 1323-1327 [PMID: 15606394 DOI: 10.1111/j.1365-2036.2004.02273.x]
86 **Widmann T**, Sester U, Gärtner BC, Schubert J, Pfreundschuh M, Köhler H, Sester M. Levels of CMV specific CD4 T cells are dynamic and correlate with CMV viremia after allogeneic stem cell transplantation. *PLoS One* 2008; **3**: e3634 [PMID: 18982061 DOI: 10.1371/journal.pone.0003634]
87 **Forbes BA**, Bonville CA, Dock NL. The effects of a promoter of cell differentiation and selected hormones on human cytomegalovirus infection using an in vitro cell system. *J Infect Dis* 1990; **162**: 39-45 [PMID: 1693943 DOI: 10.1093/infdis/162.1.39]
88 **Lavagna A**, Bergallo M, Daperno M, Sostegni R, Costa C, Leto R, Crocellà L, Molinaro G, Rocca R, Cavallo R, Pera A. Infliximab and the risk of latent viruses reactivation in active Crohn's disease. *Inflamm Bowel Dis* 2007; **13**: 896-902 [PMID: 17345605 DOI: 10.1002/ibd.20131]
89 **Adler SP**, Hempfling SH, Starr SE, Plotkin SA, Riddell S. Safety and immunogenicity of the Towne strain cytomegalovirus vaccine. *Pediatr Infect Dis J* 1998; **17**: 200-206 [PMID: 9535246 DOI: 10.1097/00006454-199803000-00006]
90 **Nakase H**, Yamamoto S, Matsuura M, Honzawa Y, Chiba T. Cytomegalovirus affects clinical outcome of infliximab in ulcerative colitis refractory to tacrolimus. *Aliment Pharmacol Ther* 2010; **32**: 510-511 [PMID: 20636704 DOI: 10.1111/j.1365-2036.2010.04372.x]
91 **Hahn G**, Jores R, Mocarski ES. Cytomegalovirus remains latent in a common precursor of dendritic and myeloid cells. *Proc Natl Acad Sci USA* 1998; **95**: 3937-3942 [PMID: 9520471 DOI: 10.1073/pnas.95.7.3937]
92 **Söderberg-Nauclér C**, Fish KN, Nelson JA. Interferon-gamma and tumor necrosis factor-alpha specifically induce formation of cytomegalovirus-permissive monocyte-derived macrophages that are refractory to the antiviral activity of these cytokines. *J Clin Invest* 1997; **100**: 3154-3163 [PMID: 9399963 DOI: 10.1172/JCI119871]
93 **Simon CO**, Seckert CK, Dreis D, Reddehase MJ, Grzimek NK. Role for tumor necrosis factor alpha in murine cytomegalovirus transcriptional reactivation in latently infected lungs. *J Virol* 2005; **79**: 326-340 [PMID: 15596827 DOI: 10.1128/JVI.79.1.326-340.2005]
94 **Hommes DW**, Sterringa G, van Deventer SJ, Tytgat GN, Weel J. The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. *Inflamm Bowel Dis* 2004; **10**: 245-250 [PMID: 15290919 DOI: 10.1097/00054725-200405000-00011]
95 **Söderberg-Nauclér C**, Nelson JY. Human cytomegalovirus latency and reactivation - a delicate balance between the virus and its host's immune system. *Intervirology* 1999; **42**: 314-321 [PMID: 10702712]
96 **Nakase H**, Yoshino T, Matumura K, Honzawa Y, Yamamoto S, Matsuura M, Chiba T. Positive finding of colonic polymerase chain reaction for cytomegalovirus DNA is not false positive but a warning for treating patients with ulcerative colitis refractory to immunosuppressive therapies. *Inflamm Bowel Dis* 2011; **17**: E13-E14 [PMID: 20629104 DOI: 10.1002/ibd.21401]
97 **Diepersloot RJ**, Kroes AC, Visser W, Jiwa NM, Rothbarth PH. Acute ulcerative proctocolitis associated with primary

cytomegalovirus infection. *Arch Intern Med* 1990; **150**: 1749-1751 [PMID: 2166491 DOI: 10.1001/archinte.150.8.1749]
98 **Rachima C**, Maoz E, Apter S, Thaler M, Grossman E, Rosenthal T. Cytomegalovirus infection associated with ulcerative colitis in immunocompetent individuals. *Postgrad Med J* 1998; **74**: 486-489 [PMID: 9926125 DOI: 10.1136/pgmj.74.874.486]
99 **Streetz KL**, Buhr T, Wedemeyer H, Bleck J, Schedel I, Manns MP, Göke MN. Acute CMV-colitis in a patient with a history of ulcerative colitis. *Scand J Gastroenterol* 2003; **38**: 119-122 [PMID: 12608474 DOI: 10.1080/00365520310000546]
100 **Helbling D**, Breitbach TH, Krause M. Disseminated cytomegalovirus infection in Crohn's disease following antitumour necrosis factor therapy. *Eur J Gastroenterol Hepatol* 2002; **14**: 1393-1395 [PMID: 12468964 DOI: 10.1097/00042737-200212000-00018]
101 **Farmer GW**, Vincent MM, Fuccillo DA, Horta-Barbosa L, Ritman S, Sever JL, Gitnick GL. Viral investigations in ulcerative colitis and regional enteritis. *Gastroenterology* 1973; **65**: 8-18 [PMID: 4352745]
102 **Minami M**, Ohta M, Ohkura T, Ando T, Ohmiya N, Niwa Y, Goto H. Cytomegalovirus infection in severe ulcerative colitis patients undergoing continuous intravenous cyclosporine treatment in Japan. *World J Gastroenterol* 2007; **13**: 754-760 [PMID: 17278199]
103 **Goodrich J**, Khardori N. Cytomegalovirus: the taming of the beast? *Lancet* 1997; **350**: 1718-1719 [PMID: 9413457 DOI: 10.1016/S0140-6736(97)22050-7]
104 **Omiya M**, Matsushita M, Tanaka T, Kawamata S, Okazaki K. The absence of large ulcer predicts latent cytomegalovirus infection in ulcerative colitis with positive mucosal viral assay. *Intern Med* 2010; **49**: 2277-2282 [PMID: 21048360 DOI: 10.2169/internalmedicine.49.3657]
105 **Faulds D**, Heel RC. Ganciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. *Drugs* 1990; **39**: 597-638 [PMID: 2161731 DOI: 10.2165/00003495-199039040-00008]
106 **Markham A**, Faulds D. Ganciclovir. An update of its therapeutic use in cytomegalovirus infection. *Drugs* 1994; **48**: 455-484 [PMID: 7527763 DOI: 10.2165/00003495-199448030-00009]
107 **Heuman DM**. Cytomegalovirus colitis. Available from: URL: http://emedicine.medscape.com/article/173151-overview
108 **Eddleston M**, Peacock S, Juniper M, Warrell DA. Severe cytomegalovirus infection in immunocompetent patients. *Clin Infect Dis* 1997; **24**: 52-56 [PMID: 8994755 DOI: 10.1093/clinids/24.1.52]

P- Reviewers Naito Y, Abraham P **S- Editor** Gou SX
L- Editor A **E- Editor** Li JY