



PREVALENCE AND PREDISPOSITION FACTORS THAT CAUSE CYTOMEGALOVIRUS ESOPHAGITIS

MOHAMMED SALAH HUSSAIN ^{a,b*}, BATOOL MESFER M ALQAHTANY ^c,
SUKAINAH SALEH ALISMAIL ^d, FATIMAH HUSSAIN ALSHUHAYB ^e,
EYAD ABDULATIF ALMOHAISSEN ^e, WESAM KAMEL B. ALANAZI ^f,
YASSER MOHAMMED A. ALAMMARI ^g, ALI AHMED A. ALMARZOUQ ^g,
ABDULAZIZ MUQBIL FALEH ALSHAMMARI ^h,
GHADAH MOHAMMED ALHARBI ⁱ, A. ALJUHANI FAISAL GHAZI ^j
AND ZAINAB MOHAMMED ALFARAJ ^k

^a Department of Gastroenterology and Endoscopy, Dr Samir Abbas Hospital, Jeddah, Saudi Arabia.

^b Department of Internal Medicine, Faculty of Medicine, Alazhar University Hospitals, Cairo, Egypt.

^c Hurymila General Hospital, Saudi Arabia.

^d King Faisal General Hospital, Saudi Arabia.

^e King Faisal University, Saudi Arabia.

^f Tabuk University, Saudi Arabia.

^g Ibn Sina National College, Saudi Arabia.

^h University of Hail, Saudi Arabia.

ⁱ Batterjee Medical College, Saudi Arabia.

^j Ohud Hospital, Saudi Arabia.

^k King Fahad Hospital of the University, Saudi Arabia.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.56557/UPJOZ/2022/v43i243313

Editor(s):

(1) Dr. Ana Cláudia Correia Coelho, University of Trás-os-Montes and Alto Douro, Portugal.

Reviewers:

(1) Deepa PM, India.

(2) Rafael Machado de Araújo Alves, University Federal of Paraíba (UFPB), Brazil.

(3) Vicky Sumarki Budipramana, Universitas Airlangga, Indonesia.

Received: 19 October 2022

Accepted: 25 December 2022

Published: 27 December 2022

Systematic Review Article

ABSTRACT

Background: Cytomegalovirus (CMV)-associated gastrointestinal disorders are typically seen in immune-compromised patients; nevertheless, a few cases have been reported in healthy hosts, despite the fact that the pathogenic mechanisms are yet unknown. Various lesions, including erythematous mucosa, erosions, and ulcers,

*Corresponding author: Email: dr_msalahali@yahoo.com;

are brought on by CMV esophagitis, albeit these inflammatory alterations can also be seen in nearby or superficial esophageal malignancies. Cancer patients with late and/or terminal stages of the disease have also been known to develop CMV-associated esophagitis due to immunosuppression brought on by chemotherapy or the physiological demands of the cancer itself.

Objectives: To identify the prevalence of cytomegalovirus esophagitis, describe the evaluation of cytomegalovirus esophagitis and outline the causes of cytomegalovirus esophagitis.

Methods: For article selection, the PubMed database and EBSCO Information Services were used. All relevant articles relevant with our topic and other articles were used in our review. Other articles that were not related to this field were excluded. The data was extracted in a specific format that was reviewed by the group members.

Conclusion: Cytomegalovirus (CMV) esophagitis, which can result from illnesses including human immunodeficiency virus (HIV) infection and treatments like post-organ transplantation, long-term dialysis, and systemic steroid therapy, is mostly brought on by systemic immune deficiency. Primary CMV infection, however, can result in serious organ-specific consequences with high morbidity and fatality rates. In immune-competent people, severe CMV infections can have an impact on practically every system.

Keywords: Cytomegalovirus; immunosuppression; esophageal; immunodeficiency; esophagitis

1. INTRODUCTION

The second most frequent gastrointestinal symptom of cytomegalovirus (CMV) infection is esophagitis, behind colitis [1]. The Herpes viridae family, which contains the biggest genome of any herpes virus, includes the Cytomegalovirus (CMV). It is transmitted through bodily fluids, such as those exchanged during pregnancy or during sexual intercourse. Despite the fact that immune-competent people can contract the disease, it usually only shows symptoms in immune-compromised people, such as AIDS patients, organ transplant recipients, and chemotherapy patients [2]. Gastrointestinal cytomegalovirus (CMV) illness is uncommon in immune-competent hosts and typically develops in patients with immunodeficiency or immunosuppression [3].

CMV is a typical human viral infection. The incidence of sero-positivity for CMV strongly corresponds with socioeconomic position, ethnicity, and geographic region. Approximately 70% of the global human population has latent CMV infections. The most prevalent viral opportunistic infection in people with AIDS is CMV [4]. In tissues taken from the oesophagus of patients with acquired immunodeficiency syndrome (AIDS) who undergo esophagogastroduodenoscopy (EGD) for dysphagia or odynophagia, cytomegalovirus (CMV) cultures are found to be positive. EGD for unexplained nausea and vomiting is performed on 38% of bone marrow transplant recipients who test positive for CMV esophagitis and/or small intestine involvement. CMV esophagitis has no known racial or sexual predisposition. There are no published reports on age-related preference. However, older patients are more susceptible to developing CMV illness than younger patients since immune-competence often declines with age. After *Candida albicans* and the herpes

simplex virus, CMV is the third most frequent cause of infectious esophagitis in children (HSV) [5,6].

Endoscopic evidence and a histological analysis of the lesions are used to make a diagnosis of CMV esophagitis [7]. Hematoxylin and eosin (H&E) staining reveals hypertrophic cells with massive eosinophilic cytoplasmic inclusions surrounded by a distinct halo, or "owl's eye," which is referred to as [8,9]. The diagnostic sensitivity is increased by IHC to 93%, while the specificity is close to 100%. But it could take a few days for a histology analysis or PCR, delaying the confirmation of the diagnosis and the start of an antiviral regimen. Differential diagnosis of CMV esophagitis based on the endoscopic findings is critical in clinical practise since incorrect diagnosis and care may subject patients to excessive drug toxicity and raise medical costs [10]. The endoscopic results helped narrow down the possible causes of CMV esophagitis.

Although they are uncommon, tracheo-esophageal fistula, esophageal stricture, and haemorrhage are possible side effects of CMV ulceration of the oesophagus [11]. Wilcox (1999) identified only 6 patients with CMV esophagitis complicated by esophageal stricture within a sample of 160 HIV positive patients with esophagitis, one of them had an esophageal stricture at index endoscopy. Olmos and colleagues (2000) described 2 patients who developed stricture after receiving ganciclovir in a group of 21 HIV positive patients with CMV esophagitis. However, no cases of IRIS-related esophageal stricture associated with CMV have been documented [12].

High amounts of CMV DNA in plasma have a prognostic effect in HIV-infected people who are more prone to acquire CMV illness [13,14]. The measurement of CMV DNA and serology is not advised, nevertheless, as it cannot establish or

disprove the presence of CMV illness. The diagnosis of CMV disease is made conclusively by the typical symptoms of CMV gastrointestinal disease, endoscopic characteristics, and the presence of cellular inclusion bodies. High amounts of CMV DNA in plasma have a prognostic effect in HIV-infected people who are more prone to acquire CMV illness. The measurement of CMV DNA and serology is not advised, nevertheless, as it cannot establish or disprove the presence of CMV illness. The diagnosis of CMV disease is made conclusively by the typical symptoms of CMV gastrointestinal disease, endoscopic characteristics, and the presence of cellular inclusion bodies [13]. It takes 14–21 days of intravenous ganciclovir 5 mg/kg twice daily therapy for CMV esophagitis. 40% of patients will need more than two weeks of treatment, on average. It is not advised to use valganciclovir for maintenance therapy [15].

In all cases, anti-CMV medications such as ganciclovir and valganciclovir were utilized. According to Lim et al., these medicines are useful for preventing rebleeding from CMV-related lesions in the GI tract. Not only immunosuppressed patients, but also those with mild immunological dysfunction brought on by diabetes and hypo-albuminemia, can develop CMV esophagitis. Additionally, although it is uncommon, CMV can result in severe bleeding that compromises hemodynamics. Therefore, even in patients without obvious immunodeficiency, doctors should take CMV esophagitis into account when making a differential diagnosis of esophageal bleeding of unknown cause. The treatment of CMV esophagitis requires an early histological diagnosis and the use of anti-CMV medications [16].

1.1 Study Objective

To identify the prevalence of Cytomegalovirus Esophagitis, describe the evaluation of disease and identify the causes of cytomegalovirus esophagitis.

2. METHODS AND MATERIALS

2.1 Study Design

In order to define a coherent empirical research agenda that builds on prior knowledge, a systematic review of the current evidence on Cytomegalovirus Esophagitis is regarded as a reliable method of identifying and synthesizing the peer-reviewed articles for evidence in this area. Only qualitative evidence was used in this review to support an interpretation. Additionally, a synthesis of qualitative data aims to produce conclusions that are meaningful, pertinent, and appropriate for individuals. The review combined, integrate, and interpret the data from the

included papers using qualitative synthesis techniques, whenever possible.

The review aims to move beyond the aggregation of available data to provide further interpretive insights into Cytomegalovirus Esophagitis and define where future research can add to what is known.

2.2 Study Eligibility Criteria

Peer-reviewed qualitative studies were included in the review. Mixed-methods studies' qualitative data was screened for inclusion and added if the qualitative component is relevant. All peer-reviewed articles that discuss Cytomegalovirus Esophagitis from the viewpoint of the general public, healthcare professionals, and the healthcare delivery system and are published in English was included.

The studies had to have been published between January 2012 and August 2022 in order to be considered for the review, ensuring the work's currency and enabling the identification of emerging issues from a variety of perspectives.

2.3 Study Inclusion and Exclusion criteria

The project's relevance, the articles' English-language and quality all were taken into account when choosing which ones to use. All other articles, repeated studies, reviews of studies, and articles that did not have one of these topics as their primary end were disregarded. Studies not available in English, conference abstracts, books, grey literature, and editorial comments all were disregarded by the reviewers. Studies that only present qualitative data won't be considered.

2.4 Search Strategy

A systematic search strategy was developed using a combination of Medical Subject Headings (MeSH) and controlled vocabulary to identify peer-reviewed articles on cytomegalovirus. The PubMed/MEDLINE database was chosen for data collection.

2.5 Selection of Study

The selection procedures and outcomes were presented in accordance with the ENTREQ guidelines for reporting qualitative systematic reviews. To help with duplication removal, all retrieved studies first imported into the Endnote library. The two reviewers shared the Endnote library after the duplicates have been eliminated in order to independently screen the articles by title and abstract while being guided by the eligibility requirements. The studies that the two reviewers would have selected was reviewed in full.

Any disagreements between the two reviewers were resolved by a third reviewer. Each eligible study had its entire text reviewed independently by the two reviewers. When there are disagreements between the two reviewers, the third reviewer was consulted to discuss the differences in order to reach a consensus. Finally, the full texts of all relevant studies found to meet the inclusion criteria was retained for the final framework synthesis.

2.6 Data Extraction

Two reviewers independently extracted data from eligible studies onto a customised data extraction form, filling it with variables related to the study population and the relevant phenomena. The third review author double-checked and confirm the extracted articles. Name of the first author, publication year, data collection period, and geographical location are just a few of the study characteristics that was extracted. Then, specific study information such as the study's design, population, sample size, sampling techniques, and data collection methods was recorded.

2.7 Data Synthesis and Analysis

No software was utilized to analyze the data. The reviewers sorted the data by theme and present the themes in the form of an analysis table (chart). The columns and rows of the table reflect the studies, and related themes and enable us to compare findings of the studies across different themes and subthemes.

The reviewers used charts to define the identified concepts and map the range and nature of the phenomena. Our review explored associations between the themes to help clarify the findings.

3. RESULTS

Fig. 1 shows the selection and identification of studies. The search of the mentioned databases returned a total of 240 studies that were included for title screening. 105 of them were included for abstract screening, which lead to the exclusion of 70 articles. The remaining 90 publications full-texts were reviewed. The full-text revision led to the exclusion of 39 studies due to difference in inclusion criteria, and 10 were enrolled for final data extraction (Table 1).

six studies out of 10 were prospective studies (searched hospital databases for Prevalence and Causes of Cytomegalovirus Esophagitis) and the three studies were from doctors' perspectives after face-to-face interview.

The results which reported in the collected studies stated that Patients with cancer who received chemoradiotherapy were more likely to develop CMV esophagitis.

Chemoradiotherapy side effects that could be related to the treatment should be taken into account include CMV esophagitis [1]. Patients with esophageal cancer who appear with fever or digestive symptoms while receiving chemotherapy and radiation therapy should be evaluated by doctors and pathologists for the possibility of CMV esophagitis.¹⁷ The diagnosis of CMV infection requires a biopsy of the affected tissues, and once the diagnosis is made, antiviral therapy should start. For severe CMV disease, advanced age, acute diseases, or immune-modulatory comorbidities, antiviral medication may be instituted [3,23].

Multiple organ dysfunction, hypoxia, and hypoperfusion result from immune-compromised status, which is also regarded as an immune-deficient condition and is, therefore, a risk factor for CMV esophagitis. Immune-compromised status includes concurrent chemoradiotherapy, hock, and respiratory failure. When inpatients have fever, hematemesis, odynophagia, diffuse or multiple esophageal ulcers, and esophageal candidiasis, symptoms and endoscopic findings should be considered [18]. also, the claim that Esophagogastroduodenoscopy used to healing esophagitis without using anti-viral medications or steroids [19]. Antifungal therapy might be used as a treatment any signs or gross CMV esophagitis [20]. CMV esophagitis responds well to induction ganciclovir therapy, and long-term remission may occur following just induction therapy. Despite the positive response to ganciclovir medication, the patients' low long-term survival reflects their extreme immunodeficiency [24].

Anther reported result in the collected studies stated that CMV-positive cells were seen in the cytologic smears [22]. Also Both immune-peroxidase staining for CMV infection and hematoxylin and eosin (H&E) staining for CMV antigens underwent reliability testing [21].

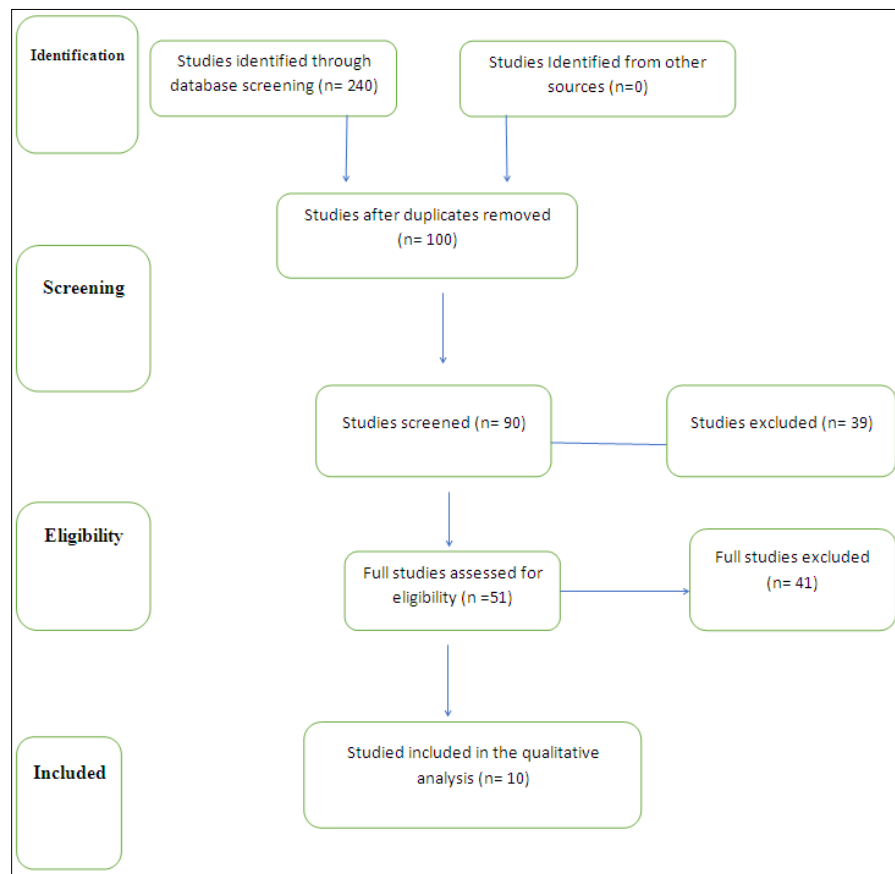


Fig. 1. The included studies had different study designs

Table 1. Author, country, year of publication, methodology and outcome

Author, Publishing Year	Methodology	Outcome
Wang HW et al. (2016) [1]	Retrospective analysis was performed on a total of 16 individuals who had esophageal ulcers and had histologically verified CMV infection (2006 to 2013). For further investigation, information on the patients' demographics (age, smoking and alcohol use), underlying systemic diseases (such as diabetes, end-stage renal disease, and chronic obstructive pulmonary disease), malignancy, indication for esophagogastroduodenoscopy, endoscopic features, and diagnostic techniques (such as pathological or serological findings) was gathered.	CMV esophagitis has been recorded in transplant recipients, dialysis patients, and people infected with the human immunodeficiency virus. The average age of those who had CMV esophagitis was 59.94 years (from 23 to 84 years). The ratio of men to women was 1.67:1. Epigastralgia and odynophagia were frequent symptoms. Of the 16 patients, 3 (18.75%) had HIV infection, and 9 (56.25%) had an underlying cancer, including 6 cases of lung cancer, 2 cases of esophageal cancer, 1 case of stomach cancer, 1 case of ampulla of Vater cancer, and 1 case of lymphoma (1 patient). Six of the nine cancer patients (66.7%) received concomitant chemotherapy and radiation treatment (CCRT).
Umemoto et al. (2016) [17]	Two patients acquired CMV esophagitis during chemoradiotherapy for esophageal	Based on an assessment of biopsy samples collected to gauge the effectiveness of anticancer treatments,

Author, Publishing Year	Methodology	Outcome
	cancer. On the basis of the discovery of intranuclear inclusions in tumour biopsy samples, cytomegalovirus esophagitis was identified. The two Japanese patients arrived with fever and anorexia.	CMV esophagitis was identified. Following two chemotherapy treatments (51–58 days after the start of treatment), CMV esophagitis manifested in both Japanese instances. Biopsy samples were taken from the tumour sites, which were seen endoscopically as ulcers with a white base. After receiving antiviral medication in both instances, test findings for CMV antigenemia turned out to be negative. These patients had nausea or fever, and therapy improved both endoscopic findings and symptoms.
Gravito-Soares E, et al.(2018) [3]	A 25-year-old Caucasian female was diagnosed with hypothyroidism, was a previous smoker, had infectious mononucleosis, and had left thoracic zoster. The patient was referred to a gastrointestinal consultation after experiencing odynophagia for a month without experiencing fever, nausea, or abdominal pain. Sucralfate plus a double dosage of a proton pump inhibitor were used in the treatment, with some clinical improvement.	Two months following the commencement of the symptoms, the patient steadily got better and eventually stopped having any symptoms. CMV IgM changed from positive to negative two months following the diagnosis, and a second endoscopy revealed that the oesophageal ulcers had completely healed.
Yeh, Pai-Jui, et al.(2022) [18]	148 individuals in total were enrolled, 44 of whom were in the CMV. All patients with esophageal CMV immunohistochemistry (IHC) staining results from the pathology database at the Linkou Chang Gung Memorial Hospital who had esophageal CMV immunohistochemistry (IHC) staining between 2003 and 2021 were enrolled in this retrospective cohort analysis. Based on positive CMV IHC staining of the esophageal tissue, with or without viral inclusion bodies, utilising hematoxylin and eosin staining, CMV esophagitis was identified. Monoclonal antibodies against the CMV pp65 antigen were used for CMV IHC.	The CMV group had a mean age of 59.5 18.5 years and was predominately made up of men (77.3%). 15.9% required ICU treatment, and 75% were hospitalized. The main underlying disorders in this group—which had an immune-compromised status up to 77.3%—were cancer, gastric reflux disease, and hypertension. The majority of cancers in the CMV group were found in the neck and chest region, including one orbital melanoma with thoracic spine metastases, seven esophageal cancers, six lung cancers, and two breast cancers. Each of the 16 patients in this group had radiation treatment, which exposed them to radiation near their esophagus. There were eight, three, and two patients with autoimmune illness, solid organ transplant, and HIV infection, respectively. In addition to hepatitis and retinitis, seven individuals also had CMV gastritis, extraalimentary disorders, hepatitis, and retinitis, with one patient also having retinitis and gastritis. Antibiotics (75%) proton pump inhibitors (PPIs) (63.6%), and steroids (52.3%) were the most often prescribed first drugs.

Author, Publishing Year	Methodology	Outcome
Murakami et al. (2021) [19]	Esophagogastroduodenoscopy (EGD) was performed on a 77-year-old male. An EGD using standard white-light imaging showed a middle-distal esophageal lesion that was somewhat depressed and reddish with whitish exudate. An iodine-unstained lesion was visible on lugol chromoendoscopy. Atypical squamous epithelium with CMV-positive granulation tissue and macrophage clusters were seen in the biopsies of the reddish lesion. Additional than gender and age, he had no other risk factors for esophageal cancer and was a social drinker who never smoked. He also had no underlying diseases that would have made him more susceptible to CMV infection.	After EGD, he didn't get either antiviral medications or steroids to avoid strictures, and a 4-month follow-up revealed no evidence of esophagitis.
Laine, L et al.(1992) [20]	Retrospective analysis was performed on 48 individuals who had previously participated in a prospective endoscopic study looking at the causes of esophageal symptoms in HIV infection and had been confirmed to have both Candida and CMV infection. Patients engaged in a trial of antifungal medication for Candida esophagitis who also had CMV esophagitis were prospectively evaluated.	Of the 48 patients who had Candida esophagitis, 10 (21%) showed signs of esophageal CMV (nine by culture, one by histology). After 4 weeks of therapy, one person passed away with little retrosternal pain. After receiving antifungal therapy, none of the remaining nine patients displayed any signs or gross CMV esophagitis. In the retrospective analysis, thirteen additional individuals with CMV and Candida were included (mean follow-up of 8 months). Eight patients got just antifungal therapy: six (symptomatic resolution in six; CMV determined by histology in three and by culture in three); one (symptomatic resolution in one; CMV determined by culture in one); and one (symptomatic resolution in one but negative repeat endoscopy in one); Due to concomitant CMV retinitis, two patients passed away without getting treatment, while three others underwent combined antifungal and anti-CMV medication (esophageal symptoms resolved in all three).
Theise, N D et al.(1991) [21]	Over the course of one year, we evaluated 28 esophageal biopsies from 28 AIDS patients. The persistence of dysphagia after antifungal medication and/or radiologic indications of an esophageal ulcer were indicators for esophageal biopsy. Hematoxylin and eosin (H&E) staining for CMV antigens and immune-peroxidase staining for CMV infection were	13 samples included just squamous epithelium, and both procedures revealed negative results in all of them. No CMV inclusions were found by H&E in the remaining 10 instances. In three of these biopsies, viral antigens were stained. Numerous cells positive for viral antigens in all cases by immune-peroxidase did not exhibit any of the morphologic diagnostic criteria for CMV. Malignant lymphoma, Kaposi's

Author, Publishing Year	Methodology	Outcome
	tested for their ability to reliably identify CMV infection. By H&E stain and immune-peroxidase, five samples tested positive for CMV. Granulation tissue and, in one particularly severe example, stromal papillae of the intact mucosa were frequently found to contain infected cells.	sarcoma, and candidiasis were some of the additional concomitant diagnoses.
Teot, L A et al.(1991) [22]	Three AIDS-related CMV esophagitis patients had cytologic smears from esophageal brushings that contained diagnostic cells that had marginated chromatin, large, basophilic intranuclear inclusions surrounded by a clear halo, and granular, eosinophilic intracytoplasmic inclusions. These cells also had nuclear and cytoplasmic enlargement.	In one instance, the biopsies were used to make the initial diagnosis, and it was only after thorough study that the cytologic smears revealed cells indicative of CMV infection. Numerous cells in the patient had herpes simplex virus-related alterations, which most likely concealed the existence of the CMV-infected cells. While the cytologic preparations revealed cells with the distinctive CMV inclusions, the biopsies from another patient only revealed necrotic debris and inflammatory cells.
Akın, Sibel et al.(2013) [23]	Following varying intervals of corticosteroid therapy, CMV esophagitis manifested in three cases of giant cell arteritis. Immuno-compromised patients with GI disease should have CMV infection considered in the differential diagnosis, and the doctor should seek appropriate diagnostic and therapeutic measures aggressively.	Because immune function often declines with age, older individuals are more likely than younger ones to get CMV illness. Adults with immune-competent status are very rarely infected with CMV. After colitis, esophagitis is the second most typical gastrointestinal symptom of CMV infection.
Wilcox, C M et al.(1995) [24]	All patients with HIV having endoscopy were prospectively identified, and 44 patients with CMV esophagitis confirmed endoscopically and histopathologically were included. Ganciclovir was administered intravenously during induction therapy at a dose of 10 mg/kg every day for about 14 days. For those who didn't respond to ganciclovir, foscarnet was given at a dose of 60 mg/kg every 8 hours.	Of these patients, 35 underwent induction ganciclovir therapy, with a total response rate of 77%, consisting of 17 complete responses (49%) and 10 partial responses (29%). Following treatment with foscarnet, 5 out of the 7 nonresponders had a clinical response. Seven (39%) of the 18 people who eventually completely responded to ganciclovir or foscarnet and were monitored without maintenance medication reverted at a median time of four months (range 2 to 18 months). Recurrent odynophagia was always a sign of relapse.

4. DISCUSSION

The second most prevalent CMV disease of the gastrointestinal tract is cytomegalovirus (CMV) esophagitis [25,26]. It is most commonly diagnosed in immune-compromised people, but it can also occur in immune-competent persons [27,28]. Due to the small number of occurrences, most research focused on

CMV illness of the upper gastrointestinal tract or infectious esophagitis rather than CMV esophagitis [27,29,30].

The American Joint Committee on Cancer's cancer staging manual was used to categorize the sites of esophageal lesions (upper, middle, and lower third) [31]. According to recommendations from the

American College of Gastroenterology, Barrett's esophagus was identified [32]. Patients were deemed to be "immune-compromised" if they had primary immunodeficiency, human immunodeficiency virus (HIV) infection, an underlying cancer that had been treated with radiation or chemotherapy within the previous six months, the use of immune-suppressants like corticosteroids, or had undergone solid organ or bone marrow transplantation [33,34].

The majority of CMV patients are asymptomatic or have minor symptoms, making it a prevalent infectious disease. The reactivation of a latent infection is thought to be the primary cause of the pathological problems that can be life-threatening that are associated with a CMV infection in an immune-compromised patient [35,36]. Immune-competent patients have also had CMV reactivation. CMV reactivation was discovered in 13–33% of patients in the intensive care unit, and its risk factors include men, repeated transfusions, and high CRP levels [38,39]. The bulk of CMV esophagitis cases, however, involved people who were immunocompromised [35,37,40,41]. According to Wilcox et al., CMV alone was responsible for 45% of the esophageal ulcers detected in HIV patients [35].

Dysphagia and odynophagia can lead to malnutrition, which can be devastating in the presence of serious conditions like AIDS and organ failure necessitating a transplant [42]. Perforation and severe GI bleeding may occur spontaneously or as a side effect of endoscopy if the ulcerations that form grow sufficiently deep and broad [43,2]. Despite receiving treatment with ganciclovir and foscarnet and even as the initial symptom of CMV esophagitis without previous ulcers, stricture development has been documented to happen occasionally. In one case report, a patient who had finished anti-viral therapy and had post-treatment pathology samples that were negative for CMV experienced stricture formation severe enough to completely obliterate the esophageal lumen. This case report illustrates that strictures can still form even after the disease has been treated and resolved [44].

It is recognized that specific endoscopic and clinical characteristics can assist distinguish CMV esophagitis from HSV esophagitis. Patients with HSV esophagitis were more likely to have endoscopic findings of discrete ulcers, the presence of vesicles or bullae, shouldered margins, coalescent or geographic ulcers, whereas patients with CMV esophagitis were more likely to have punch-out ulcers, serpiginous ulcers, ulcers with an uneven base, friability, and with a circumferential distribution [45,46].

Patients with cytomegalovirus (CMV) esophagitis may want to think about maintenance therapy, especially if they need reinduction medication therapy for relapse. Patients with human immunodeficiency virus (HIV) infection whose CD4+ T-lymphocyte counts have grown to more than 100-150 cells/L and whose HIV plasma ribonucleic acid (RNA) levels have been reduced may want to stop receiving long-term maintenance medication. There are CMV vaccines under development. The benefits of preventative esophageal screening have not been proven [47].

Patients should have a complete history and physical examination as well as an evaluation for the presence of risk factors by primary care physicians if there is a suspicion of CMV esophagitis. Patients should be referred to gastroenterologists for an upper endoscopy so that pathologists can examine biopsy samples. The primary care doctor should go over the findings with the patient. The patient's induction treatment should be started by the primary care physician, who should also follow up with them. If treatment problems arise, experts in infectious diseases should be included in the debate as well [48].

5. CONCLUSION

Patients receiving organ transplants, those undergoing protracted renal dialysis, those with HIV infection or AIDS, as well as those suffering from other incapacitating illnesses, have all been documented to experience this condition. The most frequent gastrointestinal (GI) symptom of cytomegalovirus (CMV) infection is esophagitis. Of all herpes viruses, it possesses the biggest genome. It spreads through bodily fluids, such as those exchanged during pregnancy or during sexual intercourse.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wang HW, Kuo CJ, Lin WR, Hsu CM, Ho YP, Lin CJ, Su MY, Chiu CT, Wang CL, Chen KH. The clinical characteristics and manifestations of cytomegalovirus esophagitis. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2016; 29(4):392–399. Available: <https://doi.org/10.1111/dote.12340>
2. Goodgame RW. Gastrointestinal cytomegalovirus disease. *Ann Intern Med*. 1993;119(9):924-35.

- [PubMed] [Reference list]
3. Gravito-Soares E, Gravito-Soares M, Camacho E, Tomé L. Cytomegalovirus ulcerative oesophagitis in a young healthy immunocompetent patient. *Case Reports*. 2018; bcr-2017.
4. Emery VC. Cytomegalovirus: recent progress in understanding pathogenesis and control. *QJM*. 2012;105(5):401-5. [PMC free article] [PubMed] [Reference list]
5. Patel NC, Caicedo RA. Esophageal infections: an update. *Curr Opin Pediatr*. 2015;27(5):642-8. [QxMD MEDLINE Link].
6. Ahuja NK, Clarke JO. Evaluation and management of infectious esophagitis in immunocompromised and immunocompetent individuals. *Curr Treat Options Gastroenterol*. 2016;14(1):28-38. [QxMD MEDLINE Link].
7. Feiden W, Borchard F, Burring KF, et al. Herpes oesophagitis. I. Light microscopical and immunohistochemical investigations. *Virchows Arch A Pathol Anat Histopathol*. 1984;404:167-76.
8. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis*. 2010;16:1620-7.
9. Reddy N, Wilcox CM. Diagnosis & management of cytomegalovirus infections in the GI tract. *Expert Rev Gastroenterol Hepatol*. 2007;1: 287-94.
10. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol*. 2006;101:2857-65.
11. Wilcox CM. Esophageal Strictures complicating ulcerative esophagitis patients with AIDS. *Am J Gastroenterol*. 1999;94(2) [PubMed] [Google Scholar]
12. Olmos M. Esophageal strictures complicating cytomegalovirus ulcers in patients with AIDS. *Unusual Cases Tech Notes*. 2000;822 [PubMed] [Google Scholar]
13. Steininger C, Puchhammer-Stöckl E, Popow-Kraupp T. Cytomegalovirus disease in the era of highly active antiretroviral therapy (HAART) *J Clin Virol*. 2006;37(1):1-9. [PubMed] [Google Scholar]
14. Pector SA, Wong R, Hsia K, Pilcher M, Stempien MJ. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. *J Clin Invest*. 1998; 101(2):497-502. [PMC free article] [PubMed] [Google Scholar]
15. Blanshard C, Benhamou Y, Dohin E, Lernestedt J. Treatment of AIDS-associated gastrointestinal cytomegalovirus infection with foscarnet and ganciclovir - a randomized comparison. *J Infect Dis*. 1995;172:622-628. [PubMed] [Google Scholar]
16. Lim LG, Rajnakova A, Yan B, Salto-Tellez M, Lim LL. Recurrent lower gastrointestinal bleeding secondary to cytomegalovirus associated colonic ulcer in a non human immunodeficiency virus infected patient: timely diagnosis and treatment averted surgery. *Colorectal Dis*. 2009;11:984-985.
17. Umemoto K, Kojima Y, Nagata N, Yokoi C, Sakurai T, Kobayakawa M, Akiyama J. Cytomegalovirus esophagitis developing during chemoradiotherapy for esophageal cancer: two case reports. *Journal of Medical Case Reports*. 2016;10(1):1-4.
18. Yeh PJ, Wu RC, Chen CM, Chiu CT, Lai MW, Chen CC, Le PH. Risk Factors, Clinical and Endoscopic Features, and Clinical Outcomes in Patients with Cytomegalovirus Esophagitis. *Journal of Clinical Medicine*. 2022;11(6):1583.
19. Murakami D, Harada H, Yamato M, Amano Y. Cytomegalovirus-associated esophagitis on early esophageal cancer in immunocompetent host: a case report. *Gut pathogens*. 2021;13(1):1-8.
20. Laine L, Bonacini M, Sattler F, Young T, Sherrod A. Cytomegalovirus and Candida esophagitis in patients with AIDS. *Journal of Acquired Immune Deficiency Syndromes*. 1992;5(6):605-609.
21. Theise ND, Rotterdam H, Dieterich D. Cytomegalovirus esophagitis in AIDS: diagnosis by endoscopic biopsy. *The American Journal of Gastroenterology*. 1991;86(9):1123-1126.
22. Teot LA, Ducatman BS, Geisinger KR. Cytologic diagnosis of cytomegaloviral esophagitis. A report of three acquired immunodeficiency syndrome-related cases. *Acta Cytological*. 1993;37(1):93-96.
23. Akin S, Tufan F, Bahat G, Saka B, Erten N, Karan MA. Cytomegalovirus esophagitis precipitated with immunosuppression in elderly giant cell arteritis patients. *Aging Clinical and Experimental Research*. 2013; 25(2):215-218. Available: <https://doi.org/10.1007/s40520-013-0019-8>
24. Wilcox CM, Straub RF, Schwartz DA. Cytomegalovirus esophagitis in AIDS: a prospective evaluation of clinical response to ganciclovir therapy, relapse rate, and long-term outcome. *The American Journal of Medicine*. 1995;98(2):169-176.

- Available: [https://doi.org/10.1016/s0002-9343\(99\)80400-8](https://doi.org/10.1016/s0002-9343(99)80400-8)
25. Wang HW, Kuo CJ, Lin WR, Hsu CM, Ho YP, Lin CJ, Su MY, Chiu CT, Wang CL, Chen KH. The clinical characteristics and manifestations of cytomegalovirus esophagitis. *Dis. Esophagus*. 2016;29:392–399. [CrossRef] [PubMed]
 26. Hoversten P, Kamboj AK, Katzka DA. Infections of the esophagus: An update on risk factors, diagnosis, and management. *Dis. Esophagus*. 2018;31:doi094. [CrossRef] [PubMed]
 27. Hoversten P, Kamboj AK, Wu TT, Katzka DA. Risk Factors, Endoscopic Features, and Clinical Outcomes of Cytomegalovirus Esophagitis Based on a 10-year Analysis at a Single Center. *Clin. Gastroenterol. Hepatol*. 2020;18:736–738. [CrossRef] [PubMed]
 28. Li L, Chakinala RC. Cytomegalovirus Esophagitis. In *StatPearls*; StatPearls Publishing LLC.: Treasure Island, FL, USA; 2021.
 29. Iwamuro M, Kondo E, Tanaka T, Hagiya H, Kawano S, Kawahara Y, Otsuka F, Okada H. Endoscopic Manifestations and Clinical Characteristics of Cytomegalovirus Infection in the Upper Gastrointestinal Tract. *Acta Med. Okayama*. 2017;71:97–104. [CrossRef] [PubMed]
 30. Jung KH, Choi J, Gong EJ, Lee JH, Choi KD, Song HJ, Lee GH, Jung HY, Chong YP, Lee SO, et al. Can endoscopists differentiate cytomegalovirus esophagitis from herpes simplex virus esophagitis based on gross endoscopic findings? *Medicine*. 2019;98:e15845. [CrossRef] [PubMed]
 31. Esophagus. In *AJCC Cancer Staging Manual*; Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M. (Eds.) Springer: New York, NY, USA. 2002;91–98.
 32. Shaheen, N.J.; Falk, G.W.; Iyer, P.G.; Gerson, L.B. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. *Off. J. Am. Coll. Gastroenterol. ACG*. 2016;111:30–50. [CrossRef] [PubMed]
 33. Le PH, Lin WR, Kuo CJ, Wu RC, Hsu JT, Su MY, Lin CJ, Chiu CT. Clinical characteristics of cytomegalovirus colitis: A 15-year experience from a tertiary reference center. *Ther. Clin. Risk Manag*. 2017;13:1585–1593. [CrossRef]
 34. Chaemsupaphan T, Limsrivilai J, Thongdee C, Sudcharoen A, Pongpaibul A, Pausawasdi N, Charatcharoenwithaya P. Patient characteristics, clinical manifestations, prognosis, and factors associated with gastrointestinal cytomegalovirus infection in immunocompetent patients. *BMC Gastroenterol*. 2020;20:22. [CrossRef] [PubMed]
 35. Wilcox CM, Schwartz DA, Clark WS. Esophageal ulceration in human immunodeficiency virus infection causes, response to therapy, and longterm outcome. *Ann Intern Med*. 1995;123:143–9.
 36. Lemonovich TL, Watkins RR. Update on cytomegalovirus infections of the gastrointestinal system in solid organ transplant recipients. *Curr Infect Dis Rep*. 2012;14:33–40.
 37. You DM, Johnson MD. Cytomegalovirus infection and the gastrointestinal tract. *Curr Gastroenterol Rep*. 2012;14:334–42.
 38. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. *JAMA*. 2008;300:413–22.
 39. Frantzeskaki FG, Karampi ES, Kottaridi C, et al. Cytomegalovirus reactivation in a general, nonimmunosuppressed intensive care unit population: incidence, risk factors, associations with organ dysfunction, and inflammatory biomarkers. *J Crit Care*. 2015;30:276–81.
 40. Rosołowski M, Kierzkiewicz M. Etiology, diagnosis and treatment of infectious esophagitis. *Prz Gastroenterol*. 2013;8:333–7.
 41. Wilcox CM, Straub RF, Schwartz DA. Prospective endoscopic characterization of cytomegalovirus esophagitis in AIDS. *Gastrointest Endosc*. 1994;40:481–4.
 42. Wang HW, Kuo CJ, Lin WR, Hsu CM, Ho YP, Lin CJ, Su MY, Chiu CT, Wang CL, Chen KH. The clinical characteristics and manifestations of cytomegalovirus esophagitis. *Dis Esophagus*. 2016;29(4):392-9. [PubMed] [Reference list]
 43. Marques S, Carmo J, Pinto D, Bispo M, Ramos S, Chagas C. Cytomegalovirus Disease of the Upper Gastrointestinal Tract: A 10-Year Retrospective Study. *GE Port J Gastroenterol*. 2017;24(6):262-268. [PMC free article] [PubMed] [Reference list]
 44. Sheth A, Boktor M, Diamond K, Lavu K, Sangster G. Complete esophageal obliteration secondary to cytomegalovirus in AIDS patient. *Dis Esophagus*. 2010;23(6):E32-4. [PubMed] [Reference list]
 45. Genereau T, Rozenberg F, Bouchaud O, et al. Herpes esophagitis: a comprehensive review. *Clin Microbiol Infect*. 1997;3:397–407.
 46. Wang HW, Kuo CJ, Lin WR, et al. The clinical characteristics and manifestations of

- cytomegalovirus esophagitis. Dis Esophagus. 2016;29:392–9.
47. Available:<https://emedicine.medscape.com/article/1952121-overview#showall>
48. Li L, Chakinala RC. Cytomegalovirus Esophagitis. In Stat Pearls. Stat Pearls Publishing; 2022.