Post Sepsis Cytomegalovirus Syndrome in Critically Ill Patients

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ABSTRACT

Cytomegalovirus (CMV) has been recognized as a pathogen in immune compromised hosts. With regard to immune competent patients, the precise roles of CMV in the pathogenesis to those with critical illness are increasingly highlighted but remain unclear. CMV infection occurs in roughly one-third of immune competent patients during critical illness at a median of 7-12 days after ICU admission, and that such reactivation is associated with prolonged duration of mechanical ventilation, days in ICU stay and higher mortality. Important risk factors for CMV infection include sepsis, prolonged mechanical ventilation and duration of ICU stay. Furthermore, the incidence of sepsis and the number of sepsis-related deaths appear to be increasing. Patients may experience transient immune compromise during late or recovery phase of the sepsis. Although sepsis could trigger CMV reactivation, CMV syndromes occurring in the post-sepsis stage are not easily recognized as the syndromes mimicking ongoing sepsis. From our perspectives, the most common CMV syndromes during post-sepsis stage in immune competent ICU patients are unexplained thrombocytopenia, pneumonia, bloody stool and jaundice. Therefore, the intensivists are increasingly facing a challenge of identifying such patients with CMV syndromes that might
require therapy as early as possible. Nonetheless, no definitive conclusions can be made regarding the beneficial effect of antiviral therapy in immune competent individuals. In this review, we also include 10 cases as demonstrations of various manifestations of post-sepsis CMV syndrome.

INTRODUCTION

Cytomegalovirus (CMV) is a double-stranded DNA virus and a member of the Herpesviridae family. It is a common herpes virus that persists in the host in a latent state following primary infection in 50-90% of populations worldwide [1]. In otherwise healthy persons, CMV infection is generally asymptomatic or with mild symptoms, although it may cause mononucleosis, fever, and hepatitis [2]. After primary infection with CMV the virus becomes latent in monocytes and macrophages and multiple organs and can later be reactivated during severe dysregulation of the immune system [3]. CMV could reactivate in the immune suppressed patients and has been an important pathogen of the immune compromised hosts, such as solid organ transplant recipients on immune suppressive therapy, patients with human immunodeficiency virus infection and malignant hematological patients receiving chemotherapy. In the immune compromised patients, CMV can be pathogenic and causes direct effects (for example, viral syndrome, pneumonia, meningo encephalitis, gastrointestinal tract diseases, pancreatitis, hepatitis, cholangitis and cholecystitis) and indirect effects of the suppressive immune modulation of host immunity [4,5].

CMV could also reactivate in the immune competent hosts who are sero positive and hospitalized in an intensive care unit (ICU) due to critical illness, such as surgical events, major trauma, shock, burns, acute lung injury and sepsis [3]. Critical illness can induce transient immune compromise, especially in those patients with steroid use or with underlying systemic chronic disorders, such as solid cancers, chronic kidney disease, liver cirrhosis, congestive heart failure and diabetes mellitus [6-10]. Usually CMV is not considered a clinically meaningful risk factor for the outcomes of critically ill ICU patients who have no evidence of immune suppression before or on ICU admission. However, some evidence may suggest a causal pathogenic link between CMV-related complications and inflammatory diseases in the immune competent patients staying in ICUs [11]. In fact, CMV may serve as a biological hallmark reflecting the severity of underlying disease or play an active role in the development of certain adverse complications alone or by interacting with coincident bacterial infection [12]. Moreover, CMV could be associated with higher mortality and may play a significant role in the outcomes of ICU patients.

Sepsis is defined as systemic inflammatory response syndrome to a bacterial infection. In the initial phase, sepsis is characterized by a short pro-inflammatory state, whereas in the late stage, sepsis enters an anti-inflammatory status with protracted immune suppression which favors dormant CMV to reactivation [13]. Meanwhile, CMV infection would accentuate the sepsis-induced immunologic effects increasing the risk of host vulnerable for infections by other microorganisms, leading to a vicious circle. CMV may also enhance the body’s inflammatory response as sepsis-like acute respiratory distress syndrome (ARDS) [5].
Although CMV can be triggered by bacterial infections, it is unknown whether reactivated CMV is a real pathogen in the immune competent hosts [14]. Whether CMV produces febrile syndrome or end-organ disease directly in these patients has not been fully defined. There is no definite answer to this question of whether CMV is a real pathogen for ICU patients or it is simply a bystander [5]. Therefore, this review topic will focus on the CMV syndrome or diseases occurring in the post-sepsis status of the critically ill patient without evidence of immune suppression on admission.

**CMV Reactivation in ICU Patients**

CMV reactivation occurs frequently in critically ill immune competent patients. The incidence of CMV reactivation can reach 15-20% of ICU patients and 20-40% in CMV-seropositive ICU patients [5]. With regard to viral load, CMV viremia at any level occurred in 33% at a median of 12 days and CMV viremia greater than 1000 copies/mL occurred in 20% at a median of 26 days [1]. In a similar report by Osawa et al., CMV infection occurs in 0 to 36% of critically ill patients, mostly between 4 and 12 days after ICU admission [15]. Potential risk factors for CMV infection include sepsis, requirement of mechanical ventilation and blood transfusions [15]. CMV reactivation, defined as plasma CMV DNA viremia >500 copies/mL, occurred in 13.8% of mechanically ventilated CMV-seropositive patients at a median of day 7 post ICU admission. The total number of transfused red blood cells units and the degree of inflammation in terms of C-reactive protein levels upon ICU admission were independently associated with CMV reactivation [16]. Bravo and colleagues reported the highest prevalence of active CMV infection occurring in 46% (36 out of 78) of non-immuno suppressed critically ill patients [17].

Several previous reports demonstrated that CMV infection in critically ill non-immuno compromised patients is associated with prolonged ventilator support, higher nosocomial infections, prolonged hospital and/or ICU stay and increased mortality [1,7,8,15,18]. For example, prolonged mechanical ventilation (21 to 39 days vs. 13 to 24 days) and duration of ICU stay (33 to 69 days vs. 22 to 48 days) correlated significantly with a higher risk of CMV infection [15]. In a report of 53 critically ill non-immuno suppressed patients, of whom 13 (24.5%) presented CMV reactivation. Eleven of the 53 patients (20.7%) died during the follow-up period. Mortality was more frequent in patients with CMV reactivation (6/13, 46.1%) than those without CMV reactivation (5/40, 12.5%), reaching statistically significant difference (p=0.015) [19]. An updated meta-analysis with approximately 1,000 patients shows that active CMV infection continues to be associated with a significant higher mortality rate than that in critically ill patients without active CMV infection [20]. Therefore, CMV reactivation is a significant cause of morbidity and mortality in the immune competent CMV-seropositive critically ill patients [21].

In adequately powered cohorts of patients, active CMV infection appears to be associated with worse outcomes for mechanically ventilated ICU patients. Patients with pulmonary CMV reactivation have significantly prolonged durations of mechanical ventilation [7,8,22]. However,
Frantzeskaki and colleagues reported different results. CMV reactivation was associated with more severe of organ dysfunction, but not with a worse clinical outcome. Sequential Organ Failure Assessment scores were higher in the group with CMV reactivation compared with patients without reactivation (P<0.006). However, mortality, length of ICU stay, and duration of mechanical ventilation were similar in the 2 groups [16]. Thus there is no absolute direct proof of a negative impact of active CMV infection on the health outcomes of mechanically ventilated patients [5].

The identification of immune competent critically ill patients most at risk for developing CMV reactivation is potentially of great clinical relevance. Patients with high interleukin-10 (IL10) was reported to be marginally related to CMV reactivation (p=0.06) [16]. Furthermore, the single nucleotide polymorphisms in the genes coding for IL-10 and chemokine receptor 5 (CCR5) might be relevant to the risk of active CMV infection or the level of CMV replication within episodes, respectively. For example, IL10 C/C genotype has a trend towards a lower incidence of active CMV infection (p=0.06), whereas the CCR5 A/A genotype has high CMV DNA loads in tracheal aspirates in non-immuno suppressed critically ill patients [17]. The presence of functional CMV-specific CD8+ T lymphocyte response at intensive care unit admission may provide protection against CMV reactivation in critically ill non-immuno suppressed patients. The presence of interferon-γ (IFNγ) secreted by CMV-specific CD8+ T cells at the time of ICU admission was associated with a decreased risk of CMV reactivation [19]. In fact, CMV infection can induce dramatic CMV-specific T-cell responses. Termination of CMV reactivation is associated with an expansion of functional CMV-specific T cells. CMV-specific T-cell immunity is preserved in most critically ill patients experiencing CMV reactivation [23].

**CMV Reactivation in Sepsis Patients**

CMV reactivation has been linked to bacterial sepsis and likely results from inflammation stimulating the major immediate early promoter and transient impaired immunity [24]. Sepsis at admission is independently associated with active CMV infection of the CMV-seropositive ICU patients (p=0.02; odds ratio, 4.62) [25]. More interestingly, patients with nosocomial bloodstream infection were more likely to develop CMV viraemia (p=0.006), have high-grade viraemia (p=0.010), and fewer ICU-free days (p=0.018) and ventilator-free days (p=0.029) than those admitted with new bloodstream infection [26]. CMV viremia was documented in 27.5% (8/29) of the patients, a median of 7 days after the onset of sepsis due to bloodstream infection. CMV viremia is a contributor to poor outcomes in critically ill patients with sepsis [27]. In a previous study, CMV reactivation occurred in 35 of the 86 (40.7%) adult non-immuno suppressed CMV-seropositive patients with new onset of severe sepsis. Among them, CMV reactivation was independently associated with increased length of stay in the ICU and in the hospital as well as prolonged mechanical ventilation [22].

CMV infection may be a consequence of enhanced Toll like receptor (TLR) expression and responsiveness on infected macrophages. This enhanced TLR responsiveness is leaving hosts...
even more susceptible to bacterial stimulation and inflammation [28]. Hosts with coincident CMV reactivation and bacterial infections have more inflammation and immune system activation that is accompanied by an increased risk of septic shock [24]. Furthermore, the expression levels of genes encoding inflammasome-related proteins are significantly higher in the development of high grade CMV viremia in critically ill patients with sepsis than all other patients. Therefore, the host immune response by genes encoding inflammasome-related proteins is possibly involved in the pathogenesis of CMV infection [27].

**CMV Reactivation in Patients with Acute Respiratory Distress Syndrome (ARDS)**

CMV reactivation occurs frequently in patients with ARDS and has been associated with increased mortality among the subgroup with septic shock [29]. In a clinical study of open lung biopsies in ARDS patients with prolonged respiratory failure or in whom microbiological cultures remained negative, CMV pneumonia was found in 30% of cases [30]. Furthermore, of 399 immunocompetent ARDS patients, CMV reactivation occurred in 27% of CMV-seropositive patients on the median time of 8.5 days from ICU admission and 34% among those with concurrent septic shock. In addition, the proportion of patients with CMV reactivation having relatively high viral loads (at least 1000IU/mL) increased over time. CMV reactivation was associated with overall increased ICU mortality rate (31% vs. 15%; p<0.01) and a reduced successful weaning rate as well as a longer duration of mechanical ventilation (15 vs. 8 days; p<0.01). Therefore, CMV reactivation is independently associated with increased poor outcome in CMV-seropositive ARDS patients [31].

**Post Sepsis CMV Pneumonia**

Patients with CMV reactivation had a significantly higher rate of nosocomial infections, probably due to CMV-associated immune modulation that promotes bacterial super infection [5]. From our perspective, for example, prolonged colonization or delayed resolution of pneumonia caused by carbapenem-resistant Acinetobacter baumannii (CRAB) in patients with mechanical ventilation should remind physicians that concurrent CMV infection has existed in the lungs. However, it is unknown whether anti-CMV therapy may improve eradication of CRAB infection. Additional prospective trials are necessary to confirm this point.

A murine model has demonstrated post-sepsis CMV reactivation in the lungs and pathogenesis of CMV pneumonia. Mice infected with CMV were allowed to develop latent infections. Latently infected mice underwent a laparotomy with cecal ligation and puncture. Lung tissue showed reactivation of latent CMV 2 weeks later. These findings demonstrate that surgery with subsequent intra-abdominal bacterial infection reactivated CMV in the lungs of latently infected mice [32]. CMV reactivation causes abnormal tumor necrosis factor-alpha expression, and that following CMV reactivation, immune competent mice have abnormal pulmonary fibrosis. Ganciclovir blocks CMV reactivation, thus preventing abnormal tumor necrosis factor-alpha expression and pulmonary fibrosis. These data may explain a mechanism by which critically ill surgical patients
develop fibroproliferative ARDS. These data suggest that human studies using antiviral agents during critical illness are warranted [14]. For example, we present with 3 cases of post-sepsis CMV pneumonia.

Patient 1 was admitted to an ICU with dyspnea for one week and cough with fever for 3 days. The initial chest x-ray (CXR) film showed bilateral pulmonary infiltrates with mild severity (Figure 1A), which was rapidly progressive to severe consolidation of both lungs (Figure 1B). The sputum cultures yielded meticillin-resistant Staphylococcus aureus (MRSA). After appropriate antibiotic therapy with piperacillin and teicoplanin against MRSA, the general condition fluctuated with fever, unstable oxygenation and intermittent hypotension. One week later, the patient developed ARDS requiring a fraction of oxygen of 100% to maintain adequate oxygenation (Figure 1C). The patient died after 2 weeks of ICU stay. CMV DNA was identified in the sputum and blood samples one day before his death. Ganciclovir therapy was not given in time.

![Figure 1: (Patient 1). CXR series are showing progressive infiltrates over both lung fields (A and B) into ARDS pattern (C). Then, CMV DNA was positive in the sputum and blood samples.](image)

Patient 2 was admitted to an ICU due to urosepsis. The urine culture yielded Escherichia coli. After appropriate antibiotic therapy with piperacillin, the sepsis symptom was improved. The initial CXR showed bilaterally slight infiltrates (Figure 2A), which progressed to moderate infiltration (Figure 2B). Emergent hemodialysis was initiated for suspected lung edema. Meanwhile, septic shock with a white blood cell count of 28,400/μL and acute respiratory failure occurred. Antibiotics were changed to imipenen and vancomycin. However, profound shock and ARDS developed (Figure 2C). The patient died after 12 days of ICU stay. CMV DNA was identified in the sputum and blood samples 3 day before his death. Ganciclovir therapy was not given in time.
Figure 2: (Patient 2). CXR series are showing mild infiltrates (A) and moderate infiltrates over both lung fields (B) and worsening progress to ARDS pattern (C). Then, CMV DNA was positive in the sputum and blood samples.

Patient 3 with end-stage renal disease was admitted to an ICU due to lower abdominal pain by colitis. Initial CXR film showed unremarkable (Figure 3A). Nosocomial pneumonia occurred one week later (Figure 3B). The sputum culture yielded mixed flora. Meanwhile, CMV DNA was identified in the blood samples but was not found in the sputum specimens. After empirical antibiotic therapy, the pneumonia patches were resolved 10 days later (Figure 3C). However, CMV DNA was then identified in the sputum specimens. No anti-CMV therapy was given. The significant role of CMV in the pathogenesis of pneumonia remained undefined.

Figure 3: (Patient 3). CXR series are showing resolution of nosocomial pneumonia (A, B, C) probably caused by CMV infection in a patient without antiviral therapy.

According to the presented 3 cases, we highlighted that CMV diagnosis is usually delayed in clinical setting and mortality rate was high. Without confirmation of lung tissue biopsy, whether CMV was the true etiology or only a biomarker of mortality is uncertain. Currently, it is difficult to discern whether earlier management for CMV is of beneficial or not. However, the association between active CMV infection and increased illness could open new therapeutic options for patients with septic shock, especially with ARDS [33].
Post Sepsis CMV Syndrome

The typical manifestations of CMV syndrome include fever, anemia, leukopenia, atypical lymphocytes, lymphocytosis, thrombocytopenia, slightly elevated transaminases, hepatosplenomegaly, acute cholestatic hepatitis, myalgia, arthralgia, pneumonitis and renal dysfunction [34-37]. In transplant recipients, fever could be the most common presenting symptom (95% of patients) [38]. Other reports showed that malaise, fever, and diarrhea were the most common symptoms [39]; and the major manifestations of CMV disease were fever of unknown origin and leukopenia [40]. Hematologic laboratory data showed anemia (64%), thrombocytopenia (47%), and leukopenia (21%) [41]. A previous report showed leukopenia (34.5%), increased serum creatinine level (34.5%), and leukocytosis (20.7%) [39]. Sometimes acute monocytosis could be found in immunocompetent patients [42]. From our perspectives, the most common CMV syndrome during post-sepsis stage in immunocompetent ICU patients with initial sepsis at admission includes unexplained thrombocytopenia, pneumonia, bloody stool and jaundice.

For immunocompetent patients admitted to an ICU due to sepsis, appropriate antibiotic therapy would generally achieve good clinical response within 3 days. The sepsis parameters of leukocytosis, leukopenia, and/or thrombocytopenia would be recovered to within normal ranges after 5 days of adequate therapy. Persistent abnormality of the inflammatory markers would indicate inadequate therapy, probably due to bacterial virulence or antibiotic resistance of the invading organisms and/or undefined source that needs to be controlled. However, emerging CMV infection should be included in a list of differential diagnosis during the post-sepsis status, which patients could experience some transient immunosuppression and CMV reactivation would be triggered. For example, we presented two cases to describe the scenarios.

Patient 4 was admitted to an ICU due to secondary peritonitis by colon perforation. After colonic resection and appropriate antibiotic therapy, the clinical symptoms were improved. Thrombocytopenia and leukocytosis became normalized in the recovery period. However, an episode of acute monocytosis up to 58% (normal range, 2-8%) was noticed (Figure 4A), followed by leukopenia with the lowest white blood cell count of 900/μL (Figure 4B). Meanwhile, CMV DNA was identified in the blood samples but was not found in the sputum specimens. Although platelet counts remained within normal values (Figure 4C), intravenous ganciclovir was given for CMV syndrome manifesting with acute monocytosis and neutropenia. The CMV syndrome was improved one week later. The patient recovered well with oral valganciclovir maintenance therapy for additional 5 weeks.
Figure 4: (Patient 4). Hematologic laboratory data are showing acute monocytosis (A) followed by leukopenia (B) in an ICU patient with CMV reactivation. The platelet counts remained within normal values. CMV DNA was positive in the blood samples.

Patient 5 was admitted to an ICU due to urinary tract infection with septic shock. Sepsis was under controlled within 5 days of antibiotic therapy. However, thrombocytopenia persisted for one week (Figure 5A), which was disproportional to hemoglobin (Hb), suggesting no relation of thrombocytopenia to blood loss (Figure 5B). The patient developed abdominal pain. Abdominal computed tomography scan revealed mild edema of whole colon, suspected colitis. CMV DNA was identified in the stool and sputum samples. The CMV viral load in blood was 95,651IU/mL. The patient had persistent lymphopenia during post-sepsis stage (Figure 5C). As palliative therapy, the patient did not receive further diagnostic test for probable CMV colitis nor receive anti-CMV therapy before death.
The presented case highlights a potential risk factor of post-sepsis lymphopenia for developing CMV infection. Pretransplant lymphopenia was suggested a novel independent predictor of CMV disease after liver transplantation [43]. Lymphopenia was also a good predictor of CMV infections among renal transplant recipients [44]. Besides, lymphopenia was one of the independent risk factors for the development of CMV GI disease in adult patients with cancer [45]. Lymphopenia was also a risk factor significantly associated with elevated CMV viral load in patients with autoimmune diseases [46].

**Figure 5**: (Patient 5). Hematologic laboratory data are showing persistent thrombocytopenia and CMV reactivation after sepsis control (A). The severity of thrombocytopenia is disproportional to hemoglobin (B). Persistent lymphopenia may be a risk factor for CMV reactivation (C). UTI: urinary tract infection; Hb: hemoglobin.
Post Sepsis CMV Gastrointestinal Diseases

CMV gastrointestinal diseases include esophagitis, gastritis, duodenitis, enteritis and colitis, which may develop after sepsis control in immunocompetent critically ill patients, for example, in patient 6 (Figure 6) and patient 7 (Figure 7).

**Figure 6**: (Patient 6). Panendoscopic study is showing diffuse ulceration of esophagus (A) and gastric diffuse ulcers with bleeding (B). CMV DNA was detected in the blood and gastric juice samples. The CMV antigenemia was 2 positive cells per 200,000 polymorphonuclear leukocytes.

**Figure 7**: (Patient 7). Panendoscopic study is showing bleeding at a small duodenal ulcer of second portion (A). Transarterial embolization is performing at inferior pancreaticoduodenal artery (B), of which a branch is showing extravasation (arrow). A blood CMV viral load was 135,000IU/mL, indicating CMV duodenitis.

CMV esophagitis is rarely highlighted in critically ill patients. The most common lesions could be well-circumscribed ulcers, usually located in the middle to distal parts of the esophagus, diffuse ulcers of whole esophagus (Figure 6A) and pseudomembranous lesions of the esophagus [47]. Duodenal ulcer due to CMV infection is quite infrequent in clinical practice. Early diagnosis of CMV duodenitis could be considered for the unusual recurrence of duodenal ulcer bleeding even
after placement of hemoclips, transcatheater arterial embolization and surgical duodenorrhaphy in patients on chronic steroid use [48]. In similar, intestinal bleeding due to CMV ileitis may not be easily controlled only by transcatheater arterial embolization and/or segmental bowel resection but without appropriate antiviral therapy [49,50]. CMV ileitis is rarely reported in the literature, but could still occur in the immunocompetent patients [50-52]. CMV ileitis could cause massive gastrointestinal bleeding in a patient following operation for terminal ileum perforation in a patient at the recovery stage of severe dengue fever [50].

Patients of the CMV colitis may manifest with bloody or watery diarrhea [18,53,54]. CMV colitis is potentially life-threatening if severe complications occur, such as sepsis secondary to colitis, massive colorectal bleeding, toxic megacolon, and colonic perforation [9]. CMV colitis coexisting with Clostridium difficile infection (CDI) may occur in patients post sepsis control [55]. The CDI colitis usually presents with watery diarrhea, however, CMV colitis commonly presents with bloody stool. Treatment failure of fecal microbiota transplant for pseudomembranous colitis may be due to coexistent CMV colitis in critically ill patients [56].

For example, patient 8 is a liver cirrhosis patient who has received antibiotic therapy for spontaneous bacterial peritonitis. Then the patient had bloody stool passage, for which initial colonoscopy revealed ischemic colitis of sigmoid colon (Figure 8A). Two weeks later, bloody stool recurred. CMV DNA was detected in the stool and blood samples. The CMV antigenemia assay showed 4 positive cells per 200,000 polymorphonuclear leukocytes. Three weeks later, colonoscopy found extensive ulceration (Figure 8B) and tissue biopsy revealed nuclear inclusion bodies which were demonstrated by CMV using immunohistochemical staining, characteristic of CMV colitis. In a previous report, diagnosis of CMV colitis was initially missed as mimicking ischemic colitis in an immunocompetent man [57]. The mucosal ulceration probably is due to an ischemic process resulting from narrowing of capillary lumens by swollen endothelial cells affected by CMV infection [58].

**Figure 8:** (Patient 8). Initial colonoscopy is showing sigmoid ischemic colitis (A). Followed-up colonoscopy is revealing extensive ulceration (B) and CMV colitis was demonstrated by tissue biopsy (not shown).
**Post Sepsis CMV-associated Haemophagocytic Lymphohistiocytosis**

Haemophagocytic lymphohistiocytosis (HLH) is an immunopathological syndrome of ineffective multisystem inflammatory response and cytokine dysregulation, of which secondary HLH could be associated with CMV infection [59,60]. The HLH disease is defined by the HLH-2004 criteria, requiring five of eight findings. These criteria include: (1) the presence of fever, (2) splenomegaly, (3) cytopenias affecting greater than or equal to two of three lineages in the peripheral blood, (4) hypertriglyceridemia (≥265mg/dL), (5) hemophagocytosis in the bone marrow, spleen, or lymph nodes, (6) soluble CD25>2400U/mL, (7) low or absent natural killer cell (NK-cell) activity, and (8) ferritin≥500μg/L [61].

CMV associated HLH could occur in an immunocompetent adult following sepsis control. Diagnosis of CMV associated HLH may be delayed as the syndrome mimicking ongoing sepsis, septic shock, and multiple organ dysfunction [62]. Physicians should raise awareness of checking serum ferritin in critically ill patients who remain a sepsis like syndrome even after adequate control of the sepsis, in order to early recognize the development of CMV associated HLH [59]. A higher cutoff value of ferritin level may have improved utility in the diagnosis of secondary HLH in the critical care setting [63].

Intravenous ganciclovir therapy significantly decreases the CMV viral load and benefit does exist in the presence of a CMV organ disease, but it might fail to improve the HLH syndrome [60]. HLH-2004 confirms that a majority of patients may be rescued by the combination therapy with etoposide and dexamethasone [64].

**Diagnosis of CMV Reactivation**

With advances in monitoring and detection methods, CMV reactivation could be detected not only limited in the immunocompromised patients, but also in the immunocompetent patients with critical illness. The pp65 antigen is a sensitive and specific diagnostic method. Positive antigenemia diagnosed 85% of 39 patients with active CMV infections among 242 ICU patients [8]. The polymerase chain reaction (PCR) as applied to CMV DNA detection should provide a valuable tool for rapid, reliable diagnosis of infection, thereby allowing prompt treatment. This semi-quantitative PCR technique should allow rapid diagnosis of systemic infection and provide a reliable means of monitoring clearance of CMV from blood during drug therapy [65]. The degree of viral replication or viremia was strongly associated with progression to CMV disease (risk ratio, 8.8 and 51.5 among patients with virus loads <2860 and >2860copies/10\(^6\) peripheral blood leukocytes, respectively) after liver transplantation [66]. Real-time PCR is more sensitive and specific for earlier detection than pp65 antigen test and it is a more reliable marker to monitor the clearance of CMV viremia, which is recognized as a contributor to poor outcomes in critically ill patients with sepsis [27].

Analysis of respiratory specimens is imperative for an optimal monitoring of CMV reactivation in the lung. Among 53 CMV-seropositive patients in a surgical and trauma intensive care unit, CMV
reactivation occurred in 39.7% of patients (23% had CMV DNA detected only in tracheal aspirates, allowed an earlier diagnosis in 28% of patients). Peak CMV DNA levels were significantly higher in tracheal aspirates than in plasma (p=0.02). Clearance of CMV DNAemia preceded that of CMV DNA in tracheal aspirates in some episodes [23]. Further, in a murine model, CMV DNA could be detected in broncholaveolar lavage (BAL) at all time-points during acute CMV infection, becoming undetectable in all mice during latency, thereby it could be detected again during bacterial sepsis, peaking 3 weeks after onset, supporting the use of BAL PCR for the diagnosis of CMV replication in immune competent hosts [67]. In addition, CMV analyses of body fluids and biopsies are more sensitive. Biliary CMV DNA levels measured with real-time PCR could reveal occult CMV cholangitis [68]. For example, we here present a case of occult CMV cholangitis post sepsis.

Patient 9 had chronic hepatitis C with early cirrhosis, and experienced fever, jaundice, worsening thrombocytopenia, progressive leukocytosis and elevated C-reactive protein. The echo of abdomen revealed distended gallbladder with stones, suspected acute cholecystitis. In addition to antibiotic therapy, percutaneous transhepatic gallbladder drainage was inserted, but the bile culture yielded no growth of bacteria. Then the patient developed hepatic encephalopathy with continuous worsening of jaundice. CMV DNA was detected by PCR in the bile sample and blood CMV viral load revealed 1,598IU/mL, indicating occult CMV cholangitis as one of the etiologies of hepatic failure (Figure 9).

![Figure 9:](image)

**Figure 9:** (Patient 9). Laboratory data are showing thrombocytopenia, leukocytosis, and elevated total bilirubin, CRP, and ammonia. CRP: C-reactive protein
To confirm the presence of CMV disease should be based on the demonstration of CMV from the suspected organ/tissue by histopathological evaluation of biopsy. CMV produces typical cytopathic effects of cytomegaly containing intranuclear inclusions and of which are usually associated with clusters of intracytoplasmic inclusions. The sensitivity of histopathologic CMV diagnosis could be increased by immunohistochemistry staining using monoclonal antibodies and in situ DNA hybridization on the biopsied tissue [3]. For example, routine tissue biopsy staining might not be able to find CMV inside, that physicians should need to request further immunohistochemistry methods specific for CMV staining.

Patient 10 was a 64-year-old diabetic man admitted to an ICU due to acute respiratory and renal failure that we have previously reported in the literature [69]. The patient developed nosocomial pneumonia by Acinetobacter baumannii and received appropriate antibiotic therapy. One month later, as delayed resolution of pneumonia, CMV DNA was identified in the sputum and blood samples. A lung biopsy initially diagnosed organizing pneumonia but did not identify CMV infection, which was then demonstrated in immunohistochemistry staining requested by clinical physicians. Although anti-CMV therapy was given, the patient died in septic shock due to an episode of catheter-associated enterococcal bloodstream infection. This report presents scenarios that nosocomial pneumonia could trigger CMV pneumonia in a mechanically ventilated ICU patient, who would become more vulnerable to other bacterial sepsis.

**Anti-CMV Therapy**

Several drugs are available to treat CMV infections. Using anti-CMV therapy to improve outcome is possible in patients with acute CMV infections. Ganciclovir and valganciclovir have been the first-line antiviral therapies for the treatment of immunocompromised patients, while foscarnet and cidofovir are reserved mainly for treatment of ganciclovir-resistant cytomegalovirus infections [18]. Cost advantages of the oral route of drug therapy administration over the intravenous route for managing CMV disease should be mentioned. The overall costs usually are lower for the oral route of administration than for the intravenous route. Other advantages of the oral route include greater safety and convenience, which may improve patient adherence and quality of life. Valganciclovir, the oral prodrug of ganciclovir, the oral route of administration is more cost-effective than the intravenous route for ganciclovir. Evidence suggests that oral maintenance therapy is usually cost-effective, safer, and more convenient than intravenous therapy in the management of CMV diseases [70].

There are limited data of anti-CMV therapies as a prophylactic agent of non-immunocompromised critical illness patients. Among CMV-seropositive adults with critical illness due to sepsis or trauma, CMV reactivation in plasma was significantly lower in the ganciclovir group (12% vs. 39%); absolute risk difference, -27 (95% CI, -40 to -14), p<0.001. The ganciclovir group had more median ventilator-free days in both the intention-to-treat group and in the sepsis subgroup than in the placebo group (23 days vs. 20 days, p=0.05; and 23 days vs. 20 days, p=0.03, respectively).
However, there were no significant differences between the ganciclovir and placebo groups in duration of mechanical ventilation (5 days vs. 6 days, p=0.16), incidence of secondary bacteremia or fungemia (15% vs. 15%, p=0.67), ICU length of stay (8 days vs 8 days, p=0.76), or mortality (12% vs. 15%, p=0.54). The current data does not support routine clinical use of ganciclovir as a prophylactic agent in critically ill patients with sepsis [71].

**CONCLUSION**

CMV syndrome may occur following sepsis in a critically ill patient without immunosuppression before or on ICU admission, even though sepsis has been well controlled. Physicians should be alert to the development of CMV syndrome, which would not be status of ongoing sepsis in the patients with sepsis at ICU admission. There is epidemiological linkage between CMV reactivation and poor outcome of critically ill patients, but there is no definite answer as to whether CMV is a real pathogen or simply a bystander for ICU patients. Unexplained thrombocytopenia, pneumonia, bloody stool, and jaundice are the most common post-sepsis CMV syndromes or diseases. Ganciclovir or valganciclovir may decrease CMV syndromes but there is no definite proof that anti-CMV therapy could improve health outcome. Antiviral treatment could be started when there is an end-organ disease or pre-emptive based on positive antigenaemia and/or CMV DNA testing only when life-threatening events exist, such as ARDS or massive gastrointestinal bleeding. Further prospective randomized trials are needed to elucidate this hypothesis.

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