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ABSTRACT

Critically ill patients are a vulnerable group at high risk of developing secondary infections. High disease severity, prolonged intensive care unit (ICU) stay, sepsis, and multiple drugs with immunosuppressive activity make these patients prone to immunoparesis and increase the risk of various opportunistic infections, including cytomegalovirus (CMV). CMV seroconversion has been reported in up to 33% of ICU patients, but its impact on patient outcomes remains a matter of debate. Even though there are guidelines regarding the management of CMV infection in immunosuppressive patients with HIV/AIDS, the need for treatment and therapeutic approaches in immunocompetent critically ill patients is still ambiguous. Even the diagnosis of CMV infection may be challenging in such patients due to non-specific symptoms and multiorgan involvement. Hence, a better understanding of the symptomatology, diagnostics, and treatment options may aid intensive care physicians in ensuring accurate diagnoses and instituting therapeutic interventions.

KEYWORDS: Cytomegalovirus; Critically ill; Immunocompetent; Intensive care unit; Virus

CORE TIP

Cytomegalovirus (CMV) reactivation in critically ill immunocompetent patients may lead to increased intensive care unit (ICU) and hospital mortality, prolonged mechanical ventilation, longer ICU stay and increased risk of secondary bacterial and fungal infections. Nevertheless, whether it is the cause of clinical deterioration or is just a marker of disease severity remains debatable. Hence, the need for any therapeutic intervention is a management

conundrum. The data extrapolated from studies on immunocompromised patients may not apply to these otherwise immunocompetent patients. This warrants future large-scale prospective studies on CMV reactivation in immunocompetent critically ill patients.

INTRODUCTION

Cytomegalovirus (CMV) infection is a known opportunistic infection in immunocompromised patients and a predictor of poor outcomes. It has been extensively studied in post-transplant patients, HIV/AIDS and neonates. Critically ill patients represent a sick cohort with risk factors like multiple comorbidities, sepsis high disease severity, prolonged ICU stay and medications with immunosuppressive effects. All these can cause immunoparesis, even in patients with no previous history of immunosuppression, making them prone to opportunistic infections.

A systematic review by Kalil et al., which included 13 studies with 1258 patients, showed that the overall rate of active CMV infection in immunocompetent patients in the ICU was 17% (95% confidence interval [CI], 11% to 24%). This review defined active CMV infection as a single positive result for viral culture, polymerase chain reaction (PCR) or CMV antigen (pp65).1 The prevalence varies depending on the test used for defining active CMV infection. In a prospective blinded study of 120 critically ill immunocompetent patients who were CMV seropositive, the CMV reactivation rate was 33% as detected by real-time PCR, indicating a high disease burden in modern ICUs.2CMV reactivation was independently associated with continued hospitalisation or death by 30 days after admission to the ICU. The rate of infection was higher in patients with severe sepsis: 32% (95% CI, 22% to 45%; $p < .0001$) and in patients with high disease severity: 32% (95% CI, 23% to 42%;

p < .0001). The overall mortality rate associated with active CMV infection was 1.93 times (95% CI, 1.29 to 2.88; p < .001) as high as that without CMV infection.1 In a meta-analysis of 18 observational studies including nearly 2400 immunocompetent patients admitted to ICUs, CMV reactivation rate was 31% (95% CI 24-39%), with the odds ratio (OR) for all-cause mortality rate with and without CMV infection being 2.16 (95% CI 1.70-2.74). However, the same study showed no effect on mortality when the analysis was limited to detecting CMV in blood.3 This raises the dilemma of CMV positivity being a marker of severe illness carrying poor prognosis rather than a direct causative factor of increased mortality.

We conducted a systematic search from the databases of PubMed, EMBASE, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and Google Scholar from all the past studies till July 2023. The search terms included major MESH terms "Cytomegalovirus", "CMV", and "Non-immunocompromised" or "Immunocompetent". Further, it was filtered for the studies published in the English language and on adult (> 18 years) humans. We manually screened the results and included the relevant literature.

PATHOPHYSIOLOGY

CMV is the most common member of the herpes virus to infect humans. It has a double-stranded linear DNA duplex containing 165 genes that encode viral proteins mimicking and interacting with human cellular proteins. After an acute or primary infection, the virus enters a latent phase, which the presence of IgG antibodies can detect. The seroprevalence of CMV IgG antibodies in women of childbearing age in India is almost 80 – 90%. In contrast, it is less than 50% in developed countries, showing a greater baseline prevalence in developing countries.4,5 During the latent phase, CMV is maintained in a latent or low production state within monocytes and dendritic cells (DC). They do not usually

express viral genes in significant numbers due to the robust CD8+ cytotoxic T lymphocyte response and T memory cells. Secondary symptomatic disease occurs due to the reactivation of latent infection during a state of decreased immunity or secondary infection with a new strain.

Patients with severe sepsis or high severity of illness scores have high levels and inflammatory markers. However, a stress response may develop compensatory anti-inflammatory response syndrome in a few patients, producing immunoparesis.6 As a result, the cytotoxic T lymphocyte-induced suppression of latent CMV is inhibited, and the virus enters the active lytic phase. Bacterial sepsis can reactivate latent CMV infection through endotoxin release by bacteria or tumour necrosis factor production.7 Exogenous catecholamine infusions used rampantly in the ICU may also contribute to stimulating the CMV reactivation.8

Another source of CMV could be blood transfusions, which are common in critically ill patients, leading to a de novo infection. The number of transfused units of packed red blood was found to be a significant risk factor (OR:1.5, CI 1.06-2.13) for CMV infection.9 Leukodepleted blood products are now a norm in post-transplant patients to prevent new infections with CMV. However, a study showed that exogenous transmission of CMV from leukodepleted blood transfusions was similar to that without it..1

Risk factors

A systematic review showed that the rate of CMV infection in mixed medico-surgical ICU patients was 8%, while the rate for primarily surgical ICUs was 23%. The cytokine storm occurring after a major surgery was suspected to be the plausible reason for this difference. For studies that screened for CMV infections before five days of ICU stay (early screening), the rate of active CMV infection was 1%, which increased to 21% after day 5. This review defined *high*

severity of disease as an Acute Physiology and Chronic Health Evaluation (APACHE II) score above 20, Simplified Acute Physiology Score (SAPS) above 40 or Sequential Organ Failure Assessment (SOFA) score of more than 10. The infection rate for high disease severity was 32% (95% CI, 23% to 42%; p < .001) and for low disease severity was 13% (95% CI, 6% to 27%; p < .0001).1

Limaye et al. conducted a prospective study in 120 CMV seropositive immunocompetent patients. CMV plasma DNAemia was assessed by thrice weekly CMV PCR. Risk factors for CMV reactivation were male gender, ventilator at baseline and blood transfusions. The study compared CMV 7-day moving average AUROC between index day (1.3) and day 30 (2.3), which showed higher values on day 30 (p < 0.0001). This indicates that patients had a higher risk of CMV reactivation after 30 days of ICU stay than on admission.2 In a prevalence study, patients who were serologically negative for CMV on admission were found to be positive on day 5 of ICU stay.1 This delay in the development of CMV infection can be explained by the time it takes for the virus to complete its lytic cycle and develop into a clinical disease. Also, most critically ill patients have a higher disease severity score on day 5 compared to admission, which shows worsening of patients with prolonged ICU stay.

[9] Patients with higher levels of inflammation are more prone to CMV reactivation. A study showed higher C-reactive protein levels at admission as a risk factor.9 Risk factors for CMV have been elaborated in table 1.

CMV and sepsis

Bacterial sepsis can trigger CMV infection, as proved by murine models. This reactivation could result from tumour necrosis factor (TNF) and nuclear factor - kß release.8 A prospective study of 25 immunocompetent CMV seropositive patients with septic shock and an ICU stay of more than 7 days was monitored for CMV reactivation. Within 2 weeks, 32% of patients showed reactivation,

with the duration of ICU stay and mechanical ventilation being higher in these patients.11 In another prospective, observational study of CMV-seropositive critically ill, otherwise non-immunosuppressed patients with sepsis due to bloodstream infection, weekly testing for CMV viraemia was performed. Outcomes were assessed at 30 days or until death/discharge from the intensive care unit (ICU). CMV viraemia developed in 20% of patients. Age (p=0.044) and blood transfusions (p=0.022) were significantly associated with CMV viraemia. There was no difference in the primary endpoint (mortality and/or multiorgan failure) between patients with and without CMV viraemia. However, CMV viraemia was associated with significantly fewer ICU-free days and fewer ventilator-free days. Patients hospitalised in the ICU for more than 48 hours prior to the onset of bloodstream infection were more likely to develop CMV viraemia, have high-grade viraemia, and have fewer ICU-free days and ventilator-free days than those admitted within 48 hours of bloodstream infection. Patients already in the ICU at the onset of sepsis had a higher risk of CMV reactivation and worse outcomes than new ICU-bound patients, suggesting that a targeted approach for interventions for CMV could be conceived towards those with a more protracted course of illness.12

CMV and mechanical ventilation

More than two decades back, Papazian et al. reported CMV as an unexpected cause of ventilator-associated pneumonia (VAP). They conducted a prospective study over a 5-year period where autopsies were performed on patients who died while they presented a clinical picture of VAP with negative microbiological cultures. In some patients who had an unexplained worsening of their respiratory status while under invasive mechanical ventilation (IMV), an open lung biopsy (OLB) was performed. Immunocompromised patients were excluded from the study. They defined ventilator-associated CMV pneumonia

as the association of an IMV duration exceeding seven days with the presence of histopathological signs of CMV pneumonia (e.g., identification of large cells with large nuclei containing a basophilic or eosinophilic inclusion surrounded by a light halo). Sixty autopsies and 26 OLBs were performed during the study period. Based on the above-described criteria, 25 cases of CMV pneumonia were identified. Histological studies were done 10–40 days following ICU admission. Interestingly, lung cultures identified no bacteria in 88 % of the cases (n = 22), with CMV being the sole identified pathogen.15 This was in the pre-PCR era when molecular testing for respiratory pathogens was unavailable. Stephan et al. conducted a prospective study in 23 critically ill, mechanically ventilated, non-immunocompromised patients to assess the reactivation of latent CMV in blood or lungs who were seropositive. The presence of CMV in blood and bronchoalveolar lavage (BAL) was evaluated by both viral cultures and polymerase chain reaction (PCR). Thirty-seven blood and 22 BAL samples were investigated. Viral cultures of blood and BAL were negative in all 23 non-immunocompromised, mechanically ventilated patients. Moreover, no CMV DNA could be amplified in blood or BAL samples, showing the absence of reactivation in patients despite having high risk.16 Hence, the dilemma of CMV being a causative pathogen or a chance finding continues.

16 A 5-year prospective study included 123 non-immunocompromised patients with severe acute respiratory distress syndrome (ARDS) requiring veno-venous extracorporeal membrane oxygenation (ECMO) were included. Sixty-seven patients (54%) experienced human simplex virus (HSV) and/or CMV reactivation during the ECMO course (20 viral co-infection, 40 HSV alone, and 7 CMV alone). HSV reactivation occurred earlier than CMV after the beginning of IMV [11 (6–15) versus 19 (13–29) days, $p<0.01$]. Both reactivation were associated with a longer duration of IMV and prolonged hospital and ICU stay.17 Patients on

ECMO have increased volume of distribution, increased cytokine release and added stress to the system.

Effects of CMV reactivation on critical illness

CMV is known to worsen the state of immunoparesis, thereby increasing opportunistic infections, both bacteraemia and fungemia.18,19 It induces procoagulant and proinflammatory states by its changes in factor X and thrombin generation and von Willebrand factor and plasminogen inhibitor type 1 secretion, further compromising the survival outcomes of critically ill

17 patients. The all-cause mortality rate associated with active CMV infection is approximately double compared with the rate for patients without CMV infection.1,20-22 CMV has been associated with prolonged mechanical ventilation and hospital and ICU stay.18,21,22 The various studies with outcomes associated with CMV are elaborated in table 2.

CLINICAL FEATURES

18 Identification of CMV disease in immunocompetent patients is complicated by its non-specific symptoms, multiorgan involvement and the fact that its clinical manifestations converge with those of critical illness. Hence, "CMV syndrome" described in post-transplant patients consists of fever, leukopenia and thrombocytopenia without other end-organ disease cannot be used to define in critically ill patients.32

CMV can present similarly to infective mononucleosis caused by the Ebstein-Barr virus (EBV). Fever and systemic symptoms are predominant, but cervical lymphadenopathy and tonsillitis are not as commonly seen as in EBV. Two cardinal hematologic abnormalities associated with mononucleosis are an

19 absolute lymphocytosis of more than 50 percent mononuclear cells and more than 10 percent atypical lymphocytes on a peripheral blood smear.33

Gastrointestinal manifestations include colitis, esophagitis and enteritis. Glucocorticoid use is associated with an increased risk of CMV colitis in otherwise immunocompetent adults. Diarrhoea, fever and abdominal pain are the common presenting symptoms.34 Diarrhoea is usually bloody but can present as a profuse gastrointestinal haemorrhage. On endoscopy, well-demarcated ulceration without exudate (50%) is the most common appearance, followed by ulcero-infiltrative changes (25%) and pseudo membrane formation (25%).35 Pathology findings show inflammatory colitis with classical owl eye appearance or Cowdry inclusions typical of CMV disease. CMV can also cause granulomatous hepatitis, with subclinical transaminitis being the most common finding in immunocompetent patients.36 However, significant hepatic dysfunction and portal vein thrombosis are relatively rare.37

The nervous system is the second most affected organ system in CMV infection in the immunocompetent host, leading to numerous clinical manifestations like meningoencephalitis, myelitis, Guillain-Barré syndrome (GBS), brachial plexus neuropathy, diffuse axonal peripheral neuropathy and transverse myelitis.38-42 Meningoencephalitis is rare but can cause long-term residual neurological deficits. The incidence of CMV-related GBS has been estimated to be 0.6 to 2.2 cases per 1000 cases of primary CMV infection. In a prospective study of 506 patients with GBS, 63 (12.4%) had primary CMV infection, as detected by IgM antibodies with IgG avidity combined with plasma CMV PCR.42 In a series of 42 patients with GBS and serologic evidence of recent or past CMV infection, PCR testing of the cerebrospinal fluid (CSF) demonstrated CMV DNA in approximately one-third of cases.43 Antibodies to ganglioside GM2 are frequently positive in CMV-associated GBS and can aid in diagnosis.44

The lung involvement by CMV may be less conspicuous in critically ill patients, especially if they were intubated for other reasons. For CMV positivity in

bronchoalveolar lavage, discrimination between a causal or associative relationship is challenging because the diagnosis depends on the quality of the respiratory sample, pathologist skills, and variation of the diagnostic test. The gold standard diagnostic test is lung biopsy, which may not always be feasible in critically ill patients.45 Pericarditis and myocarditis have been described in immunocompetent patients with acute CMV infection; however, it is difficult to establish direct causality as it needs invasive endomyocardial biopsy. In an autopsy study of 40 patients with fatal myocarditis, CMV DNA was isolated in 15 patients. In 67% of the patients for whom PCR was positive for CMV, in situ hybridisation revealed viral DNA in cardiomyocytes.46

Haematological manifestations include mild to moderate haemolytic anaemia, thrombocytopenia, pancytopenia and disseminated intravascular coagulation. Laboratory investigations may show false positivity for cold agglutinins, rheumatoid factor and antinuclear antibodies.47,48

Venous thrombosis with or without associated pulmonary embolism has been reported in case reports and small case series of immunocompetent patients with acute CMV infection. While the lower extremity deep vein thrombosis may be attributed to prolonged immobilisation in the ICU, the development of venous thrombosis at unusual sites such as the portal vein, internal jugular vein, splanchnic vein, and mesenteric veins suggests that CMV may have a procoagulant effect.49 Other rarer manifestations of CMV are cystitis, nephritis and retinitis.50,51

DIAGNOSIS

PCR is the most common test and can be used on serum, CSF and tissue samples. While qualitative PCR can be used to diagnose reactivation of infection, a quantitative test helps to determine the CMV DNA viral load.

Recently, the FDA has approved the Aptima CMV Quant Assay for quantitative testing of CMV. It is an in-vitro nucleic acid amplification test in human EDTA plasma on the fully automated Panther system. The intended use is to aid in managing solid organ transplant patients and hematopoietic stem cell transplant patients. In patients receiving anti-CMV therapy, serial DNA measurements can be used to assess viral response to treatment. The Aptima CMV Quant Assay results must be interpreted within the context of all relevant clinical and laboratory findings. However, it is not intended for use as a screening assay for the presence of CMV in blood or blood products.52 Nevertheless, this test's lack of widespread availability makes the CMV viral load test the only viable alternative. The CMV viral load tests are considered laboratory-developed tests (LDTs) that an individual laboratory validates to the standard of the laboratory inspecting agencies. Without a standardised test across laboratories, each laboratory and its clinicians must establish the local population's viral load cut-off values considered significant or correlate with disease. A multicentre study across 33 laboratories in the United States, Europe and Canada showed that the variability in viral load values for individual samples ranged from 2.0 log10 copies/ml to 4.3 log10 copies/ml. This means 100,000 copies/ml can be reported as 100 copies/ml from a different laboratory (3 log10 difference).53 Hence, clinicians cannot compare results from two different laboratories. This poses a significant challenge in developing guidelines for managing CMV infection based on viral load cut-offs. There is significant heterogeneity in the type of tests used and threshold cut-offs used to define CMV DNAemia across various studies, as shown in table 3.

On the day treatment for CMV is initiated, a baseline sample for quantitative test needs to be collected, followed by weekly monitoring throughout the therapy. This is because the half-life of CMV DNA in plasma is 3 – 8 days.54

Therapy needs to be continued till viral load values are undetectable. The chances of resistant strains are higher if there is an increase in viral load after an initial drop, no decrease in viral load after two weeks of therapy and if there is a plateau in the rate of decline. Such patients should be considered for evaluating the resistant strain by sequencing the UL97 and/or UL54 genes. However, this recommendation applies to post-transplant patients, and its generalisability to critically ill immunocompetent patients is questionable.55 Most of the studies in these patients take a breakpoint of 500-1000 U/ml as a significant titre to begin therapy.

CMV DNA by PCR in BAL is a sensitive test to detect CMV in the respiratory tract. However, a prospective study of immunocompromised patients by Berengua et al. showed that only 34% of BAL samples positive for CMV by quantitative (qPCR) were also positive by culture. The probability for isolation of CMV by culture was 4.3% for a viral load cut-off of < 200 IU/ml and 100% for a viral load cut-off of > 900 IU/ml. Vergara et al. conducted a prospective observational cohort study of consecutive adult patients admitted to two ICUs within 24 hours of admission to the Emergency Department. The study included both immunocompromised and immunocompetent patients. On testing for CMV in BAL, results were positive in 35 out of 133 ICU patients (26%), with 29% of the patients who tested positive for CMV in BAL being immunocompetent. Immunosuppression was associated with a positive CMV result (p=0.017), mainly related to systemic corticosteroid use (p=0.002). The detection of CMV in BAL was associated with a more extended hospital stay (p=0.017) and higher mortality (p=0.024). Another prospective study by Boeckh et al., in patients who had undergone haematopoietic stem cell transplant, found higher median viral loads in patients with CMV pneumonia. The control cohorts were divided into three groups. First were patients with radiological pneumonia but negative

for standard virologic testing for CMV, second were patients with idiopathic pneumonia syndrome, and last was a cohort of asymptomatic patients. The study group included patients positive on standard CMV testing, shell culture or direct fluorescence assay (DFA). This study found a threshold of > 500 IU/ml to differentiate between true CMV pneumonia and pulmonary shedding. A 500 IU/ml cut-off for BAL CMV is reasonable when associated with a relevant clinical picture. However, studies specific to immunocompetent critically ill patients are needed before we define a definite cut-off.

Other available tests are assays based on pp65 antigen in leukocytes. This is a less standard, labour-intensive manual procedure. As it detects antigens in human leukocytes, its sensitivity is poor in neutropenic patients. Tissue cultures are invasive, time-consuming and challenging to perform. However, histopathology examination remains the gold standard test to confirm end-organ disease in cases of pneumonia and colitis.

Serological tests are of limited benefit in highly endemic regions. The diagnosis of primary infection is ascertained when seroconversion is documented by the
35 appearance of virus-specific immunoglobulin G (IgG) in the serum of a previously seronegative patient. Such an approach is feasible only when high-risk patients are identified and prospectively monitored, which may need to be more cost-effective. A study comparing the clinical outcomes between CMV seropositive and CMV seronegative critically ill, non-immunocompromised patients could not demonstrate an independent association between the CMV serostatus and ICU mortality. Secondary endpoints like time to alive, discharge
36 from ICU or hospital, weaning from mechanical ventilation, and the need for renal replacement therapy were also comparable in both groups. Hence, merely testing for seropositivity is not recommended.55

PROPHYLAXIS AND PRE-EMPTIVE THERAPY

The use of prophylaxis in high-risk critically ill patients may seem attractive because the treatment cost is significantly less than weekly surveillance of CMV. However, most patients in the ICU have risk factors for CMV. Hence, universal prophylaxis for all such patients exposes already critical patients to potentially toxic medications. Suboptimal antiviral therapy may also induce resistant CMV strains. The advantage of pre-emptive therapy is that it explicitly targets only patients with laboratory evidence of active CMV infection. This minimises the number of patients who are exposed to antiviral drugs. Currently, the drug of choice for pre-emptive therapy is Ganciclovir (GCV).

Cowley et al. conducted a single centre open-label randomised controlled trial (RCT), Cytomegalovirus Control in Critical Care (CCCC-trial), enrolling 124 non-immunosuppressed, seropositive for CMV and mechanically ventilated patients. The patients were randomised 1:1:1 to Valacyclovir, Valganciclovir (450 mg daily), or no treatment. They found a significantly lower hazard of CMV reactivation in the blood in antiviral treatment groups vs control (HR = 0.14; 95% CI 0.04 to 0.5), which was the primary outcome. However, the valacyclovir arm was prematurely terminated because of an increase in mortality rate. There were no differences in biomarkers (IL-6, TNFα) between different arms at days 14 and 28 and no differences in renal impairment or need for platelet transfusions. No neutropenia or GM-CSF use was also reported.59

In a phase II trial by Limaye et al., Ganciclovir/valganciclovir was used to prevent CMV reactivation in the acute injury of the lung (GRAIL study). Nearly 160 CMV-seropositive immunocompetent patients with critical illness due to sepsis or trauma were included. Patients were randomly assigned to receive prophylaxis with intravenous (IV) Ganciclovir for five days, followed by IV Ganciclovir or oral Valganciclovir, or to receive a placebo. Antiviral prophylaxis was associated with a reduced incidence of CMV reactivation (12 vs 39%).

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However, there was no difference between the groups in interleukin (IL)-6 levels (the primary outcome), nor were there differences in the incidence of secondary bacteraemia or fungemia or ICU length of stay. IL-6, a proinflammatory cytokine, was chosen as the primary endpoint because it has been associated with increased mortality in ICU patients. Ganciclovir group (sepsis subset) had higher ventilator-free days (difference of 3 median days, 95% CI 0 to 4, P = .03), trend for fewer mechanical ventilation days (difference of -1 median days, 95% CI -4 to 0, P = .06) and higher PaO2:FiO2 ratio during the first seven days of ventilation. However, the mortality rate was comparable in both arms.60

Given the small size of the current studies and the absence of any mortality benefit, universal prophylaxis for all immunocompetent critically ill patients cannot be recommended. A phase 3 trial (GRAIL 3 study) is underway with the target of randomly enrolling 500 acute respiratory failure patients to receive IV Ganciclovir or placebo.61 This may shed more light on the therapeutic approach to managing these patients.

However, the benefit of a pre-emptive treatment (started based on seropositivity) is doubtful. The exact mechanisms of CMV reactivation are still not clear, and CMV reactivation could instead be a surrogate marker of primary disease severity. Therefore, giving antiviral drugs to these patients should be considered cautiously in terms of the benefit-risk ratio. A retrospective cohort study evaluating non-immunocompromised adult patients with CMV reactivation included 136 patients with CMV DNAemia, comprising 66 Ganciclovir-treated (48.5%) and 70 non-treated (51.5%) patients. Primary and secondary endpoints, including 30-month survival (28.0 vs 38.9%, respectively) and 12-month survival (40.3% vs 49.2%), were not statistically different between the Ganciclovir-treated and non-treated groups. In the multivariate analyses, Ganciclovir treatment was not associated with 30-month survival (HR

1.307, 95% CI 0.759–2.251) and 12-month survival (HR 1.533, 95% CI 0.895–2.624).62 Pre-emptive treatment based on CMV PCR copies was not beneficial. This was further substantiated by Papazain et al. through a double-blind, placebo-controlled RCT involving 19 ICUs in France to assess the effectiveness of pre-emptive antiviral therapy in mechanically ventilated patients. Seventy-six adults who had been mechanically ventilated for at least 96 h, expected to remain on mechanical ventilation for ≥ 48 h and exhibiting reactivation of CMV in blood were randomised to receive Ganciclovir 5 mg/kg bid for 14 days or a matching placebo. No significant difference was seen in ventilator-free days from randomisation to day 60 or 60-day mortality rate. However, no significant side effects like leukopenia or rise in creatinine were seen in the Ganciclovir arm. The trial was stopped for futility based on the results of an interim analysis. The sub-distribution hazard ratio for being alive and weaned from mechanical ventilation at day 60 for patients receiving Ganciclovir (N=39) compared with control patients (N=37) was 1.14 (95% CI from 0.63 to 2.06; P=0.66). This trial showed no benefit in treating cases pre-emptively.63

Treatment

Antiviral treatment is mandatory in case reactivation is associated with clinical CMV disease. It is reasonable that treatment for evident CMV replication (blood or BAL with significant viral load or antigen titre) is not indicated unless it is associated with lung infiltrates and at least two factors (prolonged mechanical ventilation, absence of a bacterial diagnosis for infiltrate, leukopenia, haemophagocytosis, high liver enzymes, hyperbilirubinemia, fever, or diarrhoea) which if found points for CMV being a probable pathogen invading multiple organs and not only a bystander or innocent viral shedding.64

The duration of treatment should be individualised. According to the third international consensus guidelines on the management of CMV in solid organ

transplantation, the duration of therapy for CMV infection is determined by the fulfilment of the criteria below:

47 1. Till CMV PCR or antigenemia becomes undetectable. Eradication of CMV DNAemia is defined as below LLOQ on 1 highly sensitive assay (LLOQ < 200 IU/mL) or lack of detection on two consecutive less sensitive assays. Using highly sensitive assays, a completely undetectable viral load may not always be achievable.

2. Clinical evidence of the disease has resolved.

3. At least 2 – 3 weeks of therapy.65

48 DNAemia may not accurately reflect the clinical disease status in all patients.

49 Therefore, longer courses of treatment may be needed in treating tissue-invasive gastrointestinal disease, pneumonitis in lung transplant recipients, and central nervous system or retinal disease. Secondary prophylaxis, defined as continuing prophylactic doses after discontinuing treatment dosing, is not associated with fewer relapses after suppression of CMV DNA and is not routinely recommended. The available therapeutic options for treating CMV are summarised in Table 4.

CONCLUSIONS

CMV reactivation is prevalent in up to one-third of critical patients in the modern ICUs. The most common risk factors for CMV reactivation are previous seropositivity, higher disease severity, sepsis and septic shock and prolonged ICU stay. CMV reactivation may be associated with increased ICU and hospital mortality, prolonged mechanical ventilation, longer ICU stay and increased risk of secondary bacterial and fungal infections. There are a few challenges in treating CMV reactivation, as most of the studies in this field are observational.

The 2 RCTs, the CCC study59 and GRAIL study60, did not show any mortality benefit by treating CMV pre-emptively.

Further, the breakpoints to initiate therapy for pre-emptive treatment still need to be defined, and studies have considerable heterogeneity. Whenever the decision is made to treat, Ganciclovir remains the drug of choice. The patient monitoring using CMV DNA levels therapy is extrapolated from protocols from immunocompromised patients, especially solid organ transplant patients. This warrants validation from prospective studies in immunocompetent critically ill patients. Lastly, appropriate treatment duration and the role of secondary prophylaxis in patients who continue to be critically ill even after completing an anti-CMV regimen need to be investigated.

1.	*Critically ill patients are a vulnerable group at*	Part 2: pressure ulcer assessment: implementation and revision of CALCULATE	Originality
2.	*the overall rate of active CMV infection in*	Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit*	Originality
3.	*The rate of infection was higher in patients with severe sepsis: 32% (95% CI, 22% to 45%; p < .0001) and in patients with high disease severity: 32% (95% CI, 23% to 42%; p < .0001). The overall mortality rate associated with active*	Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit — Research Nebraska https://experts.nebraska.edu/en/publications/prevalence-and-mortality-associated-with-cytomegalovirus-infectio	Originality
4.	*infection was 1.93 times (95% CI, 1.29 to 2.88; p < .001) as high as that without*	Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit — Research Nebraska https://experts.nebraska.edu/en/publications/prevalence-and-mortality-associated-with-cytomegalovirus-infectio	Originality
5.	*CMV is the most common member of the herpes virus to infect humans.*	Cytomegalovirus infection in immunocompetent critically ill adults: literature review	Originality
6.	*CMV is maintained in a latent or low production state within monocytes and dendritic cells (DC). They do not usually express viral genes in significant*	Cytomegalovirus infection in immunocompetent critically ill adults: literature review | Annals of Intensive Care | Full Text https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-016-0207-8	Originality
7.	*The number of transfused units of packed red blood*	Role of interventional radiology in pregnancy complicated by	Originality

		placenta accreta spectrum disorder: systematic review and meta-analysis https://ricerca.unich.it/handle/11564/706807	
8.	*an Acute Physiology and Chronic Health Evaluation (APACHE II) score*	Comparison of Various Scoring Systems and Biochemical Markers in Predicting the Outcome in Acute Pancreatitis — University of Texas Southwestern Medical Center https://utsouthwestern.elsevierpure.com/en/publications/comparison-of-various-scoring-systems-and-biochemical-markers-in-	Originality
9.	*Patients with higher levels of inflammation are more*	Biomarkers and electroconvulsive therapy in late-life depression	Originality
10.	*of CMV-seropositive critically ill, otherwise non-immunosuppressed patients with sepsis due to bloodstream infection, weekly testing for CMV viraemia was performed. Outcomes were assessed at 30 days or until death/discharge from the intensive care unit (ICU). CMV viraemia developed in 20*	Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk and better outcomes in new versus already hospitalised intensive care unit admissions	Originality
11.	*patients. Age (p=0.044) and blood transfusions (p=0.022) were significantly associated with CMV viraemia. There was no difference in the primary endpoint (mortality and/or*	Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk and better outcomes in new versus already hospitalised intensive care unit admissions	Originality
12.	*However, CMV viraemia was associated with significantly fewer ICU-free days*	Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk and better outcomes in new versus already hospitalised intensive care unit admissions	Originality
13.	*Patients hospitalised in the ICU for more than 48 hours prior to the onset of*	Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk	Originality

	bloodstream infection were more likely to develop CMV viraemia,	and better outcomes in new versus already hospitalised intensive care unit admissions	
14.	*Patients already in the ICU at the onset of sepsis had*	Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk and better outcomes in new versus already hospitalised intensive care unit admissions	Originality
15.	*higher risk of CMV reactivation and worse outcomes than new ICU-bound patients, suggesting that a targeted approach for interventions for CMV could*	Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk and better outcomes in new versus already hospitalised intensive care unit admissions	Originality
16.	*with severe acute respiratory distress syndrome (ARDS) requiring veno-venous extracorporeal membrane oxygenation*	Massive Lung Abscess Due To Streptococcus Intermidius In An Immunocompetent Patient	Originality
17.	*active CMV infection is approximately double compared with the rate for patients without CMV infection.*	Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit*	Originality
18.	*Identification of CMV disease in immunocompetent patients is complicated by its non-specific symptoms, multiorgan involvement and the fact that its clinical manifestations converge with those of*	Cytomegalovirus infection in immunocompetent critically ill adults: literature review | Annals of Intensive Care | Full Text https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-016-0207-8	Originality
19.	*more than 50 percent mononuclear cells and more than 10 percent atypical lymphocytes*	Clinical manifestations and treatment of Epstein-Barr virus infection https://www.medilib.ir/uptodate/show/8283	Originality
20.	*Glucocorticoid use is associated with an increased risk of*	Corticosteroid Is Associated with Both Hip Fracture and Fracture-Unrelated Arthropathy	Originality

21.	*discrimination between a causal or associative relationship is challenging because the diagnosis depends on*	Cytomegalovirus infection in immunocompetent critically ill adults: literature review | Annals of Intensive Care | Full Text https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-016-0207-8	Originality
22.	*quality of the respiratory sample, pathologist skills, and variation of the diagnostic test.*	Cytomegalovirus infection in immunocompetent critically ill adults: literature review | Annals of Intensive Care | Full Text https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-016-0207-8	Originality
23.	*however, it is difficult to establish direct causality*	Epidemiological assessment of the factors associated with antimicrobial use in French free-range broilers | BMC Veterinary Research | Full Text https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-019-1970-1	Originality
24.	*In 67% of the patients for whom PCR was positive for*	http://keywen.com/en/VIRAL	Originality
25.	*Venous thrombosis with or without associated pulmonary embolism has been reported in case reports and small case series of*	Spontaneous splenic rupture and multiple lung embolisms due to cytomegalovirus infection: a case report and review of the literature	Originality
26.	*the development of venous thrombosis at unusual sites such as the*	56 – Does the risk for VTE increase after COVID – 19 vaccination? – ICM Philly https://icmphilly.com/vte-56-does-the-risk-for-vte-increase-after-covid-19-vaccination/	Originality
27.	*It is an in-vitro nucleic acid amplification test*	A protocol for feasibility of plasma based GeneXpert platform and Dried Blood Spot (DBS) based Abbott platform for HIV-1 viral load testing among the people	Originality

		living with HIV attending ART centers in India	
28.	*in human EDTA plasma on the fully automated Panther system. The*	Premarket Approval (PMA) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P210029	Originality
29.	*transplant patients and hematopoietic stem cell transplant patients. In patients receiving anti-CMV therapy, serial DNA measurements can be used to assess viral response to treatment. The*	Premarket Approval (PMA) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P210029	Originality
30.	*must be interpreted within the context of all relevant clinical and laboratory findings.*	Premarket Approval (PMA) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P210029	Originality
31.	*is not intended for use as a screening assay for the presence of CMV in blood or blood products.*	Premarket Approval (PMA) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P210029	Originality
32.	*a prospective observational cohort study of consecutive adult patients admitted to two ICUs within 24 hours of admission to the Emergency Department.*	Detection of human cytomegalovirus in bronchoalveolar lavage of intensive care unit patients	Originality
33.	*testing for CMV in BAL, results were positive in 35 out of 133 ICU patients*	Detection of human cytomegalovirus in bronchoalveolar lavage of intensive care unit patients	Originality
34.	*The detection of CMV in BAL was associated*	Detection of human cytomegalovirus in bronchoalveolar lavage of intensive care unit patients	Originality
35.	*immunoglobulin G (IgG) in the serum of a*	Rocket Immunoelectrophoresis- Objectives, Principle, Procedure, Results, Uses https://stemcelldaily.com/rocket-immunoelectrophoresis-	Originality

		objectives-principle-procedure-results-uses/	
36.	*weaning from mechanical ventilation, and the need for renal replacement therapy were also comparable in*	Cytomegalovirus serostatus and outcome in nonimmunocompromised critically ill patients*	Originality
37.	*Patients were randomly assigned to receive prophylaxis with*	Intravenous and Oral Itraconazole versus Intravenous and Oral Fluconazole for Long-Term Antifungal Prophylaxis in Allogeneic Hematopoietic Stem-Cell Transplant Recipients: A Multicenter, Randomized Trial	Originality
38.	*PaO2:FiO2 ratio during the first seven days of*	Geriatrics | Free Full-Text | Pitfalls of Early Systemic Corticosteroids Home Therapy in Older Patients with COVID-19 Pneumonia https://www.mdpi.com/2308-3417/7/1/21	Originality
39.	*A retrospective cohort study evaluating non-immunocompromised adult patients with CMV reactivation*	Impact of antiviral treatment on long-term prognosis in non-immunocompromised patients with CMV reactivation	Originality
40.	*survival (40.3% vs 49.2%), were not statistically different between the Ganciclovir-treated and non-treated groups. In the multivariate analyses, Ganciclovir treatment was not associated with*	Impact of antiviral treatment on long-term prognosis in non-immunocompromised patients with CMV reactivation	Originality
41.	*who had been mechanically ventilated for at least 96 h, expected to remain on mechanical ventilation for ≥ 48 h and*	Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation	Originality
42.	*to receive Ganciclovir 5 mg/kg bid for 14 days*	Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation	Originality
43.	*The trial was stopped for futility based on the results of an interim analysis.*	Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation	Originality

44.	*hazard ratio for being alive and weaned from mechanical ventilation at day 60 for patients receiving Ganciclovir (N=39) compared with control patients (N=37) was 1.14 (95% CI from 0.63 to 2.06; P=0.66*	Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation	Originality
45.	*is not indicated unless it is associated with lung infiltrates and at least two factors (prolonged mechanical ventilation, absence of*	Cytomegalovirus infection in immunocompetent critically ill adults: literature review | Annals of Intensive Care | Full Text https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-016-0207-8	Originality
46.	*pathogen invading multiple organs and not only a bystander or innocent viral shedding.*	Cytomegalovirus infection in immunocompetent critically ill adults: literature review | Annals of Intensive Care | Full Text https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-016-0207-8	Originality
47.	*Eradication of CMV DNAemia is defined as below LLOQ on 1 highly sensitive assay (LLOQ < 200 IU/mL*	The Third International Consensus Guidelines on the Manageme... : Transplantation https://journals.lww.com/transplantjournal/Fulltext/2018/06000/The_Third_International_Consensus_Guidelines_on.13.aspx	Originality
48.	*DNAemia may not accurately reflect the clinical disease status in all*	The Third International Consensus Guidelines on the Manageme... : Transplantation https://journals.lww.com/transplantjournal/Fulltext/2018/06000/The_Third_International_Consensus_Guidelines_on.13.aspx	Originality
49.	*tissue-invasive gastrointestinal disease, pneumonitis in lung transplant recipients, and central nervous system or retinal disease. Secondary prophylaxis, defined as continuing prophylactic doses after discontinuing treatment dosing, is not associated*	The Third International Consensus Guidelines on the Manageme... : Transplantation https://journals.lww.com/transplantjournal/Fulltext/2018/06000/The_Third_International_Consensus_Guidelines_on.13.aspx	Originality

with fewer relapses after suppression of CMV DNA