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META-ANALYSIS

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MINIREVIEWS

Cytomegalovirus infection in non-immunocompromised critically ill patients: A management perspective

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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 immuneparesis 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 human immunodeficiency virus/acquired immuno deficiency syndrome, 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.

Key Words: Cytomegalovirus; Critically ill; Immunocompetent; Intensive care unit; Virus

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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.

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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, human immunodeficiency virus/acquired immunodeficiency syndrome and neonates. Critically ill patients represent a sick cohort with risk factors like multiple comorbidities, sepsis, high disease severity, prolonged intensive care unit (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 of 13 studies with 1258 critically ill immunocompetent patients showed the rate of active CMV infection to be 17% (95%CI, 11% to 24%). This review defined active CMV infection as a single positive result for polymerase chain reaction (PCR), CMV antigen (pp65) or viral culture[1]. The test used for defining active CMV infection has an impact on the prevalence. In a prospective study of 120 non-immunocompromised patients admitted in ICU who were CMV seropositive, the reactivation rate was 33% when real-time PCR was used, indicating a high disease burden in modern ICUs[2]. CMV reactivation was found to be associated with increased hospital stay or 30 d ICU mortality. Patients with severe sepsis and high disease severity had a CMV infection rate of 32% which was significantly higher to an average of 17% (P < 0.0001). Patients with active CMV infection also had a higher mortality rate with an odds ratio (OR) of 1.93 (95%CI, 1.29 to 2.88; P < 0.001)[1]. A meta-analysis which included 18 observational studies with almost 2400 immunocompetent critically ill patients, CMV reactivation rate was 31% (95%CI 24%-39%), with the 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, Reference Citation Analysis (https://www.referencecitationanalysis.com/), EMBASE 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". The results were filtered for the studies published in the English language and for adult patients (> 18 years). Studies with non-critically ill patients were also excluded. We manually screened the results and included the relevant literature.

PATHOPHYSIOLOGY

CMV is the commonest herpes viridae to infect humans. It is a double-stranded DNA virus with 165 genes which encode viral proteins that interact with host proteins. After an acute or primary infection, the virus enters a latent phase, which the presence of immunoglobulin G (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 remains latent in dendritic cells and monocytes. The cytotoxic CD8+ T lymphocyte suppress viral gene replication. 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 lead to endotoxin release and an increase in tumour necrosis factor (TNF) which can reactivate CMV[7]. Exogenously administered 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]. Leucodepleted blood products are now a norm in post-transplant patients to prevent new infections with CMV. However, a sensitivity analysis of trials done during the meta analysis by Kalil *et al*[1] study showed that the rate of active CMV infection in studies using leucodepleted blood transfusions was similar to that who did not use leucodepleted blood (19% *vs* 16%)[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. Rate of CMV infection during the first five days of ICU stay (early screening) was 1%, which increased to 21% after day 5. This review defined high severity of disease as an Acute Physiology and Chronic Health Evaluation II score above 20, Simplified Acute Physiology Score above 40 or Sequential Organ Failure Assessment score of more than 10. The rate of infection for high and low disease severity was 32% (95%CI, 23% to 42%; $P < 0.001$) and 13% (95%CI, 6% to 27%; $P < 0.0001$), respectively[1].

Limaye *et al*[2] 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 sex, ventilator at baseline and blood transfusions. The study compared CMV 7-d moving average area under the receiver operating characteristic 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 d 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]. The delay in the development of active CMV infection can be due to the time taken by 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.

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[1,2,9-14].

CMV and sepsis

Bacterial sepsis can trigger CMV infection, as proved by murine models. This reactivation could result from 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 d were monitored for CMV reactivation. Within 2 wk, 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 immunocompetent critically ill patients with sepsis due to bloodstream infection (BSI), weekly testing for CMV viraemia was performed. Twenty percent of patients developed CMV viraemia. Factors associated significantly with CMV viraemia were age ($P = 0.044$) and blood transfusions ($P = 0.022$). The primary endpoint (mortality and/or multiorgan failure) between patients with and without CMV viraemia was similar. However, patients with CMV viraemia had significantly fewer ICU-free days and fewer ventilator-free days. Patients who were in the ICU for more than 48 h before the onset of BSI had higher likelihood of developing CMV viraemia with a higher-grade of viraemia, fewer ICU-free days and ventilator-free days than those hospitalised for lesser than 48 h of BSI. Patients who developed sepsis when already in the ICU had a higher risk of CMV reactivation and worse outcomes than new ICU-bound patients, suggesting that patients with a prolonged ICU stay are more susceptible and should be considered for targeted interventions for CMV[12].

CMV and mechanical ventilation

More than two decades back, Papazian *et al*[15] reported CMV as an unexpected cause of ventilator-associated pneumonia. They conducted a prospective study over 5 years where autopsies were conducted on patients who succumbed to ventilator associated pneumonia with negative microbiological cultures. Immunocompromised patients were excluded. An open lung biopsy (OLB) was performed in few patients on invasive mechanical ventilation (IMV) with unexplained worsening of their respiratory status. Ventilator-associated CMV pneumonia was defined as an IMV duration of more than seven days with histopathological signs of CMV pneumonia (basophilic or eosinophilic inclusion body with a surrounding light halo within large nuclei suggestive of owl eye appearance). A total of 26 OLBs and 60 autopsies were performed. Twenty-five cases of CMV pneumonia were identified based on the above-described criteria. Histological studies were conducted 10–40 d after ICU admission. Interestingly, no bacteria were identified in 88% of lung cultures, with CMV being the sole identified pathogen in these cases[15]. This was in the pre-PCR era when molecular testing for respiratory pathogens was unavailable.

Stéphan *et al*[16] 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. Viral cultures and PCR was used to evaluate the presence of CMV in blood and lung with 37 blood and 22 bronchoalveolar lavage (BAL) samples being examined. The tests were negative in all the 23 patients and also no CMV DNA could be amplified using PCR in blood or BAL samples indicating an absence of reactivation despite the high risk factors[16]. Hence, the dilemma of CMV being a causative pathogen or a chance finding continues.

A 5-year prospective study included 123 non-immunocompromised patients with severe acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation (ECMO). Sixty-seven patients (54%) had human simplex virus (HSV) and/or CMV reactivation (20 viral co-infection, 40 HSV alone, and 7 CMV alone). HSV reactivation was earlier than CMV [11 (6–15) *vs* 19 (13–29) d, $P < 0.01$] and both were associated with a longer IMV duration and an increased 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, including bacteraemia

Table 1 Risk factors for cytomegalovirus reactivation

Risk factors for CMV reactivation	Ref.	Statistics
High disease severity	Kalil *et al*[1]	High disease severity (APACHE > 20, SAPS > 40 or SOFA > 10) 32% *vs* low disease severity (APACHE < 20, SAPS < 40 or SOFA < 10) 13% (P < 0.0001)
	Ong *et al*[10]	Mean APACHE IV 91 (71-113) *vs* 76 (62-99) (P < 0.01)
Prolonged ICU stay	Kalil *et al*[1]	1% < 5 d *vs* 21% at > 5 d (P < 0.001)
	von Müller *et al*[11]	32% by day 14
	Limaye *et al*[2]	33% by day 12
Sepsis, septic shock	Kalil *et al*[1]	Reactivation of CMV in patients with and without septic shock: 32% *vs* 15% (P < 0.0001)
	Osawa *et al*[12]	OR 4.62 (P = 0.02)
	Ong *et al*[10]	Reactivation of CMV in patients with and without septic shock 57% *vs* 41% (P = 0.02)
Previous seropositivity	Kalil *et al*[1]	Reactivation of CMV in patients with and without previous seropositivity for CMV: 31% *vs* 7% (P < 0.0001)
Mechanical ventilation	Osawa *et al*[12]	OR: 8.5 (95%CI 1.1 to 66.5 for high-grade CMV viremia, *i.e.* CMV PCR > 1000 copies/mL)
	Limaye *et al*[2]	OR 2.5 (0.9-7.3) (P = 0.09)
Multiple blood transfusions	Frantzeskaki *et al*[9]	OR 1.50 (P = 0.02)
	Chiche *et al*[13]	OR 3.31 (P = 0.04)
	Limaye *et al*[2]	OR 9.1 (1.0-84.7) (P = 0.05)
Surgical patients	Kalil *et al*[1]	Rate of CMV reactivation in medical ICUs: 8% *vs* surgical ICUs: 23% (P < 0.001)
Steroid use	Jaber *et al*[14]	CMV reactivation in patients with and without steroid use: 55% *vs* 33% (P = 0.04)
	Chiche *et al*[13]	OR 2.26 (P = 0.08)
Renal failure	Jaber *et al*[14]	58% *vs* 33% (P = 0.02)
	Ong *et al*[10]	16% *vs* 6% (P < 0.01)
Male	Limaye *et al*[2]	OR 3.6 (P = 0.005)
Raised CRP	Frantzeskaki *et al*[9]	OR 1.01 (P = 0.02)

CMV: Cytomegalovirus; APACHE: Acute physiology and chronic health evaluation; SAPS: Simplified acute physiology score; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; OR: Odd's ratio, PCR: Polymerase chain reaction; CRP: C-reactive protein.

and fungemia[18,19]. It increases the proinflammatory and procoagulant states by changes in the levels of factor X, thrombin, von Willebrand factor and plasminogen inhibitor type 1. The all-cause mortality with active CMV infection is approximately twice compared to those without CMV infection[1,3,20,21]. CMV has been associated with prolonged mechanical ventilation and hospital and ICU stay[3,18,21]. Various studies with outcomes associated with CMV are elaborated in Table 2[1-3,7,9-18,22-29].

CLINICAL FEATURES

CMV presents with non-specific symptoms, affecting multiple organs making it difficult to suspect and identify in critically ill patients. Hence, the "CMV syndrome" described in post-transplant patients consists of fever, leukopenia and thrombocytopenia without other end-organ disease cannot be used to define CMV reactivation in this population[30].

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 rarely seen compared to EBV. On a peripheral blood smear examination, the two defining hematologic abnormalities associated with mononucleosis are presence of more than 50 percent lymphocytes with greater than 10 percent being atypical lymphocytes[31].

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[32]. 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%)[33]. 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

Table 2 Patient outcomes in studies in critically ill immunocompetent patients

Year of publication	Ref.	Study design	Patient population	Sample size	Prevalence of CMV (%)	Mortality rate (%) CMV positive *vs* negative	ICU stay	Ventilator duration	Other outcomes
1990	Domart *et al* [22]	Prospective, single center	Mediastinitis following cardiac surgery	115	25	55 *vs* 37 (P < 0.01)	69+/-36 *vs* 48+/-27 (P < 0.05)	ND	
1996	Stéphan *et al* [16]	Prospectivecase series, single center	Medico-surgical patients on mechanical ventilation	23	ND	52	ND	ND	
1996	Papazian *et al* [15]	Prospective single centre	Ventilator associated pneumonia	86	29	ND	ND	No difference (P > 0.05)	Severe hypoxemia CMV +/- (72 *vs* 95 mmHg, P < 0.05)
1998	Kutza *et al*[7]	Prospective longit-udinal, singles centre	Septic shock	34	32.4	ND	ND	ND	CMV active had higher TNFα, IL1ß, ALT
2006	Cook *et al*[23]	Prospective, singles centre	SICU	20		65 *vs* 33 (P = 0.006)	83.5 *vs* 36 (P < 0.03)	ND	92 *vs* 25 (P < 0.004)
2011	Heininger *et al*[24]	Prospective, singles center	Medical ICU with SAPS II > 40	56		55 *vs* 36	30 *vs* 23 (P = 0.0375)	ND	
2005	Jaber *et al*[14]	Retrospective matched case control study, single centre	Medico-surgical ICU patients	80		20 *vs* 11 (P = 0.02)	41 *vs* 31 (P = 0.04)	35 *vs* 24 (P = 0.03)	Bacteremia 15 *vs* 7 (P = 0.05)
2006	von Müller *et al*[11]	Prospective observa-tional study, single centre	Septic shock	38	18.4	57 *vs* 38 (NS)	54 *vs* 19 (P = 0.0025)	42 *vs* 16 (P = 0.0025)	
2008	Ziemann *et al* [25]	Retrospective study	Medical ICU	138	35	28.6 *vs* 10.9 (P = 0.048)	32.6 *vs* 22.1 (P < 0.001)		
2008	Limaye *et al* [2]	Prospective, multicentre	Mixed ICU	120	33	ND			
2009	Chiche *et al* [13]	Prospective study	Medical ICU on mechanical ventilator for > 2 d	242	16.1	54 *vs* 37 (P = 0.082)	32 *vs* 12 (P < 0.001)	27 *vs* 10 (P < 0.001)	Ventilator free days at 28 and 60, P < 0.001. Increased risk of bacteremia, P < 0.033, increased bacterial nosocomial pneumonia, P < 0.001
2010	Chilet *et al* [26]	Prospective observa-tional, single center	Surgical and trauma ICU	53	39.7	61 *vs* 46 (P = 0.40)	37 *vs* 11 (P = 0.01)	ND	TNF alpha, P = 0.80. CMV specific T cell response CD8+, P = 0.05. CD4, P = 0.04
2011	Heininger *et al*[24]	Prospective observa-tional study	Mixed ICU	86	40.6	37.1 *vs* 35.3, (P = 0.861)	30 *vs* 12 (P < 0.001)	22 *vs* 7.5 (P = 0.003)	
2009	Chiche *et al* [13]	Prospective, observation	Medical ICU	51	18	40 *vs* 13.3 (P = 0.21)	28 *vs* 14 (P = 0.013)	24 *vs* 8 (P = 0.019)	Bacterial VAP 40 *vs* 26.6 (P = 0.70)
2012	Coisel *et al*	Prospective study	Medical ICU	93	ND	55 *vs* 20 (P < 0.01)	25.5 *vs* 13 (P =	Bacteremia (%) 19.5 *vs* 10	VFD at 60 (d) median [IQR] 0 [0-

	[27]						0.037)	(*P* = 0.009)	25] *vs* 50 [11.5-58] (*P* = 0.001). Shock (%) 77 *vs* 30 (*P* = 0.001, acute renal failure (%) 50 *vs* 16 (*P* = 0.01)
2013	Clari *et al*[28]	Prospective observational, single center study	Surgical and trauma ICU	48	0.27	8 out of 17 (reactivation of CMV) *vs* 5 out of 14 (without CMV reactivation) (*P* = 0.523)			
2016	Ong *et al*[10]	Prospective, multicenter	ARDS patients on mechanically ventilated beyond day 4	271	27	Death by day 90 46 *vs* 28 (*P* < 0.01)	16 *vs* 9 (*P* < 0.01)	15 *vs* 8 (*P* < 0.01)	
2015	Frantzeskaki *et al*[9]	Prospective, observation, multicenter	Mixed ICU, Mechanical ventilated seropositive (anti CMV IgG) positive	80	14	18 *vs* 22 (*P* > 0.05), 28 D mortality rate	32 *vs* 21 (NS)	27.5 *vs* 18 (NS)	SOFA score higher with CMV reactivation (*P* < 0.006), 28 d survival no difference
2016	Osawa *et al* [12]	Prospective, multicentre	Septic patients with BSI	100	20	20 *vs* 15 (*P* = 0.585)	27 *vs* 20 (*P* = 0.07)		VFD 15 *vs* 25 (*P* = 0.05). ICU free days 7 *vs* 18 (*P* = 0.01)
2019	Hraiech *et al* [17]	Retrospective, observational, single center	ARDS on VV ECMO, assessed for HSV and CMV	123	21.9	52 *vs* 59 (*P* = 0.58)	ICU LOS 29 *vs* 16 *P* < 0.01. Hospital LOS 44 *vs* 24 (*P* < 0.01)	34 *vs* 17.5 (*P* < 0.01)	Duration of ECMO 15 *vs* 9 (*P* < 0.01)
2021	Zhang *et al* [29]	single-center, prospective observational study	Medical ICU patients on mechanical ventialtion	71	18.3	69.2 *vs* 19 (*P* < 0.01)	ICU LOS 27 *vs* 12 (*P* < 0.01)	25 *vs* 10 (*P* < 0.01)	Hospital expenses higher in patients with CMV reactivation (*P* < 0.02)
2009	Kalil *et al*[1]	Systematic review	Included patients in ICU, 9 prospective and 4 retrospective studies	1258	17	OR: 1.93 (1.29–2.88) (*P* = 0.01)	ND	ND	ND
2009	Osawa *et al* [21]	Systematic review	13 studies, 9 prospective, 4 retrospective	ND	0-33	CMV + 29 to 100 as compared with CMV – 11 to 74 (OR: 5.7)	33 to 69 d *vs* 22 to 48 d (*P* < 0.05)	21 to 39 d *vs* 13 to 24 d (*P* < 0.05)	75% *vs* 50% (*P* = 0.04)
2017	Lachance *et al* [18]	Systematic review and meta-analysis	22 studies, randomized trials, observational studies (either retrospective or prospective), or case-control studies	2199	9–71	CMV reactivation was associated with a 2.5-fold increase in ICU mortality with low heterogeneity (10 studies, *n* = 970 patients, OR = 2.55, 95%CI = 1.87–3.47; *P* < 0.001)	MD 6.60 d, 95%CI = 3.09–10.12; *P* = 0.0002, I^2 = 79%	ICU LOS was higher in CMV positive *n* (9 studies, *n* = 973 patients, MD 8.18 d, 95%CI = 6.14–10.22; *P* < 0.001)	Increase in nosocomial infections (OR 2.37-3.2) *P* < 0.05. Most common infections being ventilator-acquired pneumonia, bacteremsia, and fungal infections
2018	Li *et al*[3]	SR and MA	18 studies, mixed population	2398	CMV infection 27; CMV reactivation 31	All cause mortality OR: 2.16 (1.7-2.74)	ICU LOS stay (MD: 12 d)	9 d	

CMV: Cytomegalovirus; APACHE: Acute physiology and chronic health evaluation; SAPS: Simplified acute physiology score; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; OR: Odd’s ratio; PCR: Polymerase chain reaction; CRP: C-reactive protein; ND: No data; TNF: Tumor necrosis factor; IL: Interleukin; SICU: Surgical intensive care unit; VAP: Ventilator associated pneumonia; VFD: Ventilator free days; VV ECMO: Veno-venous extracorporeal membrane oxygenation; HSV: Herpes simplex virus; LOS: Length of stay; SR: Systematic review; MA: Meta analysis; ARDS: acute respiratory distress syndrome; IgG: Immunoglobulin G; IQR: interquartile range; ALT: alanine aminotransferase; NS: Not significant.

[34]. However, significant hepatic dysfunction and portal vein thrombosis are relatively rare[35].

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[36-40]. Meningoencephalitis is rare but can cause long-term residual neurological deficits. The incidence of CMV-related GBS is 0.6 to 2.2 cases per 1000 cases of primary CMV infection. A prospective observational study that included 506 patients with GBS found 63 (12.4%) had primary CMV infection, as detected by immunoglobulin M antibodies with IgG avidity combined with plasma CMV PCR [41]. In a case series of 42 patients with GBS and seropositivity for recent or past CMV infection, cerebrospinal fluid (CSF) showed the presence CMV DNA by PCR in one-third of cases[42]. Antibodies to ganglioside monosialic (GM)-2 are frequently positive in CMV-associated GBS and can aid in diagnosis[15].

The lung involvement by CMV is less conspicuous in critically ill patients, especially if they had any other concurrent pulmonary pathology. For BAL samples it is difficult to differentiate between a casual association with CMV positivity from a true infection. This is because the diagnosis depends on the quality of the BAL sample, the skillset of the pathologist and choice of diagnostic test. The gold standard diagnostic test is lung biopsy, which may not always be feasible in critically ill patients[15]. CMV has been known to cause pericarditis and myocarditis in immunocompetent patients, however, it is difficult to establish direct causality as it needs invasive endomyocardial biopsy. In a study of 40 patients with fatal myocarditis undergoing autopsy, CMV DNA was detected in 15 patients. In 67% of the patients for whom PCR was positive for CMV, *in situ* hybridisation revealed viral DNA in cardiomyocytes[43].

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[44,45].

Venous thrombosis including pulmonary embolism has been reported in immunocompetent patients with acute CMV infection. Deep vein thrombosis in lower limbs is a known complication of prolonged immobilisation in the ICU. However, development of thrombosis at unusual sites like internal jugular vein, portal vein, splanchnic vein, and mesenteric veins suggests an underlying procoagulant effect of CMV[46]. Other rarer manifestations of CMV are cystitis, nephritis and retinitis[47,48].

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 performed on the fully automated Panther system. The indicated use is for solid organ and hematopoietic stem cell transplant patients. By performing serial DNA levels, it can also be used to assess the response to treatment in those receiving anti-CMV therapy. However, the Aptima CMV Quant Assay results should be interpreted with consideration to relevant clinical and laboratory findings. It has not been designed to serve as a screening assay for the presence of CMV in blood or blood products[49].

Nevertheless, this test's lack of widespread availability makes the CMV viral load test the only viable alternative. Laboratory-developed tests are tests developed or used by individual laboratory after validating them to the standard of the laboratory inspecting agencies. In the absence of standardised test across laboratories, each laboratory should establish independent cut off values as per the local population's viral load. A multicentre study that included 33 laboratories across United States, Europe and Canada demonstrated that for an individual sample the test variability ranged from 2.0 Log10 copies/mL to 4.3 Log10 copies/mL. This means 100000 copies/mL can be reported as 100 copies/mL from a different laboratory (3 Log10 difference)[50]. 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[10,12,15,17,30,51].

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 due to CMV DNA having a half-life of 3–8 d in the plasma[52]. 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 cases should be evaluated for resistant strains done by sequencing UL54 and/or UL97 genes. However, this recommendation applies to post-transplant patients, and its generalisability to critically ill immunocompetent patients is questionable[53]. 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*[54] 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[54]. Vergara *et al*[55] conducted a prospective observational study of adult patients admitted to two ICUs within 24 h of presentation to the Department of Emergency. The study included both immunocompromised and immunocompetent patients. CMV in BAL, was detected in 35 of 133 ICU patients (26%), out of which 29% were immunocompetent. Factors significantly associated with positive CMV BAL test were immunosuppression (P = 0.017) and use of systemic corticosteroids (P = 0.002). CMV positivity was also associated with prolonged hospital stay (P = 0.017) and increased mortality rate (P = 0.024)[55]. Another prospective

Table 3 Polymerase chain reaction tests for cytomegalovirus and the cut offs used in various studies

Ref.	Test	Threshold copies/ml	Threshold as per IU/mL
Papazian *et al*[15]	PCR		500 IU/mL whole blood
Park *et al*[51]	RT-PCR	> 270 copies/mL in whole blood	
Hraiech *et al*[17]	PCR	Copy number > 500/mL CMV	"High reactivation" for viral loads greater than or equal to 1000 IU/mL or "low reactivation" for viral loads of 100-999 IU/mL
Zhang *et al*[29]	PCR	Copies > 500/mL	
Osawa *et al*[12]		Copies > 500 copies/mL	
Ong *et al*[10]			100 IU/mL

CMV: Cytomegalovirus; IU: International units; RT- PCR: Reverse transcription polymerase chain reaction.

study by Boeckh *et al*[56], 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. This study found a threshold of > 500 IU/mL to differentiate between true CMV pneumonia and pulmonary shedding[56]. 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 appearance of virus-specific 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 alive, rate of discharge from ICU or hospital, weaning rates and the requirement for renal replacement therapy were also comparable in both groups. Hence, merely testing for seropositivity is not recommended[53].

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, leading to minimal exposure to antiviral drugs. Ganciclovir (GCV) is the drug of choice for pre-emptive therapy for CMV.

Cowley *et al*[57] conducted a single centre open-label randomised controlled trial (RCT), CMV Control in Critical Care (CCCC-trial), enrolling 124 non-immunosuppressed, seropositive for CMV and mechanically ventilated patients. The patients were randomised into three cohorts of 1:1:1 to Valacyclovir, Valganciclovir (450 mg per day) and no treatment. The primary outcome was CMV reactivation which was significantly lower in treatment groups *vs* control [Hazard ratio (HR) = 0.14; 95%CI 0.04 to 0.5]. However, the valacyclovir arm was prematurely terminated because of an increase in mortality rate. There were no differences between different arms in the levels of biomarkers [interleukin (IL)-6, TNFα] measured at days 14 and 28. Other secondary outcome measure like renal dysfunction or rate of platelet transfusions were not significant. Neutropenia or GM-CSF use was also not reported[57].

In a phase II trial by Limaye *et al*[58], GCV/valganciclovir was used to prevent CMV reactivation in the acute injury of the lung (GRAIL study). This study included nearly 160 non-immunocompromised, CMV seropositive, critically ill patients admitted with sepsis or trauma. Patients were randomised to receive prophylaxis with intravenous (IV) GCV for five days, followed by IV GCV or oral Valganciclovir, or to receive a placebo. Patients who received antiviral prophylaxis had decreased CMV reactivation as compared to the placebo arm (12% *vs* 39%). However, the primary outcome of IL-6 levels was not significantly different between both arms, nor were there any differences in the incidence of secondary infections including both bacteraemia or fungemia or the length of ICU stay. IL-6 is a proinflammatory cytokine, that was chosen as the primary outcome because increased levels have been shown to be associated with increased mortality. The sepsis subset of GCV group had higher ventilator-free days (difference of median: 3 d, $P = 0.03$), had fewer mechanical ventilation days (difference of median: 1 d, $P = 0.06$) and a higher PaO_2:FiO_2 ratio during the initial week of ventilation. However, the mortality rate was comparable in both arms[58].

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 GCV or placebo[59]. 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 that included 136 adult non-immunocompromised patients with CMV DNAemia, had a cohort group of 66 GCV-treated patients (48.5%) and control group of 70 non-treated (51.5%) patients. There was no statistically significant difference for primary and secondary outcomes of 30-month survival (28.0% *vs* 38.9%) and 12-mo survival (40.3% *vs* 49.2%) respectively. In the subsequent multivariate analyses, GCV treatment was not associated with greater 30-mo survival (HR 1.307, 95%CI 0.759–2.251) and 12-mo survival (HR 1.533, 95%CI 0.895–2.624)[54]. Pre-emptive treatment based on CMV PCR copies was not beneficial. This was further substantiated by Papazian *et al*[60] 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 on mechanical ventilation for at least 96 h, expected to remain so for ≥ 48 h and positive for CMV in blood were randomised to receive IV GCV at a dose of 5 mg/kg bid for 14 d ($n = 39$) or a matching placebo ($n = 37$). No significant difference was seen in ventilator-free days from randomisation to day 60 or 60-d mortality rate. However, no significant side effects like leukopenia or rise in creatinine were seen in the GCV arm. Based on the results of an interim analysis, the trial was stopped for futility. The sub-distribution hazard ratio for being alive and weaned from mechanical ventilation at day 60 was not significant (1.14, 95%CI of 0.63 to 2.06; $P = 0.66$). This trial showed no benefit in treating cases pre-emptively[60].

Treatment

Antiviral treatment is mandatory incase reactivation is associated with clinical CMV disease. It is reasonable that treatment for only significant CMV replication (blood or BAL) is not indicated unless it is associated with relevant clinical feature including lung infiltrates and at least two factors: Prolonged IMV, fever, diarrhoea, absence of bacterial diagnosis for the infiltrate, leukopenia, haemophagocytosis, hepatitis or hyperbilirubinemia. This points for CMV being a probable pathogen causing multiple organ dysfunction and not just a bystander or viral shedding[61].

The duration of treatment should be individualised. According to the third international consensus 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:

(1) Till CMV PCR or antigenemia becomes undetectable. Eradication of CMV is defined as below lower limit of quantification (LLOQ) on atleast one highly sensitive assay (LLOQ < 200 IU/mL) or two negative consecutive less sensitive assays. A completely undetectable viral load may not always be achievable when highly sensitive assays are used;

(2) Clinical evidence of the disease has resolved;

and (3) At least 2–3 wk of therapy[62].

CMV DNAemia does not accurately reflect the severity of clinical disease in all patients. Therefore, longer duration of treatment is essential in invasive diseases like pneumonitis in lung transplant recipients, tissue-invasive gastrointestinal disease and retinal or central nervous system infections. Secondary prophylaxis is not associated with fewer relapses after suppression of CMV DNA and is not routinely recommended in critically ill population. The available therapeutic options for treating CMV are summarised in Table 4[63-65].

CONCLUSION

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 CCCC study[57] and GRAIL study[58], 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, GCV 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.

Table 4 Therapeutic options for cytomegalovirus

No.	Drug	Mechanism	Dose	Salient features	Adverse effects
1	Ganciclovir[1][63]	Nucleoside analog, needs intracellular phosphorylation to inhibit DNA polymerase, hence can develop resistance	5 mg/kg iv q12h	Preferable in life threatening disease, very high viral load and when there is a concern for inadequate gastrointestinal absorption	Severe neutropenia may become a therapy limiting adverse effect in up to 32% patients. May respond to G-CSF or GM-CSF
2	Valganciclovir[1]	Prodrug of ganciclovir	900 mg po q12h	Oral bioavailability is equivalent to iv ganciclovir, once-daily dosing and reduced risk of development of resistance	Neutropenia, thrombocytopenia, anemia, acute renal failure
3	Foscarnet or Phosphonoformate[1]	Does not require intracellular phosphorylation and therefore, retains activity against most GCV-resistant strains of CMV	90 mg/kg iv q12h	Intravenous PFA may be used under conditions of failure of GCV treatment, GCV resistance or excessive side effects such as leukopenia	PFA is nephrotoxic in 1/3rd patients, which limits its use in many critically ill patients
4	Cidofovir[1]	Acts directly on DNA polymerase	5 mg/kg iv once weekly	May be used as an alternative to PFA in case of GCV resistance. FDA approved only for CMV retinitis in HIV	Nephrotoxic on proximal tubular cells (Fanconi like syndrome). Pre-hydration and probenecid before the dose
5	Maribavir[1][64] (Livtencity, Takeda)	Inhibition of human CMV encoded kinase pUL97: Required for viral replication	400 mg po q12h	Used in resistance to GCV, PFA, CDV	No renal or hepatic dose adjustment required. It can cause nausea, vomiting, diarrhea and neutropenia
6	Letermovir[1][65] (Prevymis, Merck)	CMV viral terminase inhibitor	480 mg q24h po or iv	FDA approval for post HSCT and post renal transplant prophylaxis	Nausea, diarrhoea, vomiting, oedema. Various drug interactions requiring dose adjustments
7	Hyperimmune serum	Passive immune prophylaxis	400 U/kg on day 1, 4 and 8 and then 200 U/kg on day 12 and 16	As salvage therapy in severe recurrent CMV infections	High cost and heterogeneity of the preparation. Infusion related adverse effects like fever, shivering, rash

[1]United States Food and Drug Administration approved for treatment of cytomegalovirus in immunocompromised patients.
CMV: Cytomegalovirus; G-CSF: Granulocyte colony stimulation factor; GM-CSF: Granulocyte macrophage colony stimulation factor; GCV: Ganciclovir; CDV: Cidofovir; PFA: Phosphonoformate; DNA: Deoxy ribonucleic acid; FDA: Food and drug administration; HSCT: Hematopoietic stem cell transplantation; DNA: Deoxyribose nucleic acid; HIV: Human immunodeficiency virus; iv: Intravenous; po: Per oral.

FOOTNOTES

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