Cytomegalovirus (CMV) in critically-ill patients: pathogen or bystander?

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Summary

Despite broad variability in study populations, methodologies for CMV detection, and analytic methods used, multiple studies have documented frequent CMV infection in non-immunocompromised adults with critical illness due to a variety of causes. Higher rates of CMV infection in studies of seropositive patients suggest that reactivation of latent infection rather than primary infection is the main mechanism in this setting. Risk factors for CMV reactivation (other than seropositivity) have not been clearly defined and there does not appear to be a consistent association with severity of illness. Furthermore, CMV reactivation in this setting has been associated with important adverse clinical outcomes, including increased duration of mechanical ventilation, longer length of stay, and all-cause mortality. There are several biologically plausible mechanisms that could link CMV reactivation with adverse outcomes, including: direct lung injury (CMV pneumonia), amplification of inflammation systemically and within the lung, or predisposition to other nosocomial infections, but clinical data in the ICU setting are limited. Further observational studies are unlikely to significantly advance our understanding of the role of CMV in critically-ill patients. Given the significant impact of critical illness, limited current therapeutic options, the availability of generally well-tolerated antiviral options for CMV, and the clinical data supporting a possible pathogenic role for CMV, there is a strong rationale for a randomized controlled trial of CMV prevention as a novel means of improving the outcomes of critically-ill patients.

Introduction

Seroprevalence for CMV in adults ranges from 50-90% and varies with the population studied. As with all herpesviruses, primary CMV infection is followed by lifelong latency and episodes of reactivation, occasionally progressing to symptomatic disease, especially during periods of immunosuppression. With the use of sensitive molecular tools, CMV infection has been detected in previously unexpected clinical settings, including in non-immunocompromised adults with critical illness. Although reactivated infection (in seropositive patients) and primary infection (blood products) are both possible mechanisms for acquisition of CMV infection, available evidence supports reactivation of latent infection as the main mechanism in the ICU setting. Many lines of evidence suggest that CMV reactivation in critically-ill, non-immunocompromised patients might have important clinical implications, but further research, including carefully-conducted clinical trials will be required to fully understand the role of CMV in this setting. In this review we will summarize available evidence on the incidence and clinical associations of CMV infection in non-immunocompromised, critically-ill patients, describe potential mechanisms through

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which these clinical adverse outcomes could be mediated, and outline an approach to test the hypothesis that prevention of CMV reactivation in critically-ill patients might improve clinical outcomes.

How common is CMV infection in non-immunocompromised adults with critical illness and what are the risk factors?

The incidence of CMV infection in critically-ill non-immunocompromised adults has been assessed in previous studies and reviewed in a recently published meta-analysis (Table 1). In all of these studies, overtly immunocompromised patients (transplant, HIV, etc.) have specifically been excluded, since CMV reactivation and association with adverse outcomes have been previously well-documented in these populations. The included patient populations, laboratory methods used to diagnose CMV infection, and sampling frequencies varied considerably among the included studies. Important factors that influenced the rate of CMV infection included: sensitivity of the diagnostic method used (Table 2) (PCR or antigenemia vs. culture), time of screening for CMV infection after admission to the intensive care unit (ICU) (>5 days vs. less than 5 days), and baseline CMV serostatus (Table 3) [1]. The significantly higher rates of CMV infection in studies that included only seropositive patients (rather than all patients without regard to serostatus) is consistent with reactivation of latent infection rather than acquisition of primary infection as the mechanism underlying CMV infection in this setting.

The detailed quantitative virologic aspects of blood CMV reactivation in the ICU setting are illustrated by a recently published prospective study of CMV seropositive non-immunocompromised adults with a broad range of critical illness (burn, trauma, myocardial infarction, sepsis) who were monitored thrice weekly with quantitative plasma CMV PCR from the time of ICU admission until death or hospital discharge, and are shown in Table 4 and Figure 1 [3]. Data regarding CMV reactivation at other sites, particularly the lung, are more limited, but suggest that CMV reactivation in lung might occur earlier and more frequently and at greater levels than in blood [2].

Consistent risk factors for CMV reactivation have not been identified but the rates of CMV reactivation appeared to be higher in studies that included patients with higher disease severity [1]. However, important confounding factors known to influence CMV reactivation rates (as noted above) preclude definitive conclusions. Furthermore, in a large prospective study that utilized blinded endpoints and various statistical approaches to control for confounders, the severity of illness (as assessed by APACHE II [acute physiology and chronic health evaluation] score at admission) was not associated with an increased risk for CMV reactivation [3]. Thus, although existing data are limited, CMV reactivation does not appear to be simply a marker for severity of illness in this setting.

What adverse clinical outcomes have been associated with CMV reactivation in the ICU setting?

In previously published studies, the association of CMV with various adverse clinical outcomes was assessed using a range of statistical approaches [4-14,3,15,16]. Six of eight studies that assessed all-cause mortality found an association with CMV infection, with a pooled odds ratio of 1.93 (95% confidence interval 1.29 to 2.88), p=0.001 (Table 5). Other adverse clinical outcomes associated with CMV in this setting have included: increased hospital and/or ICU length of stay, longer duration of mechanical ventilation, and increased rates of nosocomial infections as summarized in Table 6.

All of these studies had one or more important limitations, including: relatively small sample size, inclusion of only selected ICU populations, lack of quantitative CMV methods,

non-blinded assessment of clinical endpoints, or analytic issues (time-varying endpoints, limited control for confounding factors). However, the general consistency among these studies with regard to CMV reactivation rates and association with adverse clinical outcomes, along with biologically-plausible mechanisms to explain the associations (discussed below), all are consistent with a pathogenic role for CMV in this setting. We emphasize that observational studies cannot conclusively establish causality and that the data are also consistent with the possibility that CMV reactivation could be a marker (rather than a determinant) of adverse clinical outcomes. The only definitive means of differentiating between a role of CMV as a cause vs. marker for adverse clinical outcomes is by means of a randomized controlled trial of CMV prevention or treatment in this setting.

What biologically-plausible mechanism(s) could link CMV with observed adverse clinical outcomes?

CMV could potentially cause adverse clinical outcomes in ICU patients through several biologically-plausible mechanisms. Although CMV organ involvement typically has been documented in overtly immunocompromised persons, recent studies have documented CMV pneumonia in critically-ill patients without known immunocompromise [17]. Whether functional immunocompromise from critical illness alone or the inflammatory milieu within the lung of such patients could facilitate CMV pneumonia in this setting is unknown. In three studies that specifically assessed for CMV pneumonia in biopsy or autopsy lung samples from ICU patients with acute lung injury/acute respiratory distress syndrome (ARDS) and respiratory failure [18,19,5], CMV was detected by histopathology in approximately 30% of cases overall (range, 29-50%) and the sensitivity of detection was reportedly higher for histopathology than culture (10/100 [10%]) [17]. The indications for lung biopsy varied and the specific impact of CMV pneumonia was not systematically assessed in these studies, making it difficult to estimate the true incidence and clinical impact of CMV pneumonia in ICU patients with respiratory failure and/or acute lung injury. Thus, based on these limited data, direct CMV-mediated lung injury (i.e., CMV pneumonia) is an important potential mechanism through which CMV might cause adverse clinical outcomes such as longer length of stay, longer duration of mechanical ventilation, or mortality in ICU patients.

Critical illness secondary to trauma or sepsis frequently leads to the complication of acute lung injury (ALI) or its more severe form, ARDS. Acute lung injury/ARDS are associated with high rates of morbidity and mortality despite current standards of ICU care. Dysregulated inflammation is thought to play a major role in the pathogenesis of ALI/ARDS [20]. Two specific inflammatory mediators (IL-6, IL-8) have been shown to be elevated in blood and/or bronchoalveolar lavage fluid (BAL) of patients with ALI/ARDS, and higher levels either at onset or during the course of illness are associated with worse outcomes [21-24]. Furthermore, the intervention of lung protective ventilation in ALI/ARDS, which has been shown to improve mortality in randomized controlled trials, is associated with reductions in levels of IL-6 and IL-8, suggesting that these cytokines either are integrally involved or are potentially useful biomarkers in this clinical setting [23]. Importantly, CMV has been linked to both of these cytokines both *in vitro* and *in vivo* [25-33]. Local reactivation of CMV within the lung appears to be common in ICU patients [2], and could therefore provide a mechanistic link between CMV and dysregulated inflammation within the lungs of patients with ALI/ARDS. Based on the relatively later onset of CMV reactivation compared to the onset of acute lung injury/ARDS, it is more plausible that CMV might exacerbate or prolong rather than initiate the process of ALI/ARDS. Thus, CMV could potentially worsen clinical outcomes (lung injury, duration of mechanical ventilation) through upregulation of these key cytokines (or other inflammatory mediators) in the lungs of patients with critical illness and ALI/ARDS.

Another potential mechanism through which CMV could contribute to worse clinical outcomes in ICU patients is through its immunomodulatory properties [34]. A number of studies in immunocompromised populations (solid organ and hematopoietic cell transplant recipients) have linked CMV with an increased risk for subsequent bacterial, fungal or other opportunistic infections, and nosocomial infections have been associated with longer lengths of stay and increased mortality [35-41]. Consistent with this hypothesis are the findings of prior studies that reported an increased rate of nosocomial infections (the majority of which were ventilator-associated pneumonias) in ICU patients with CMV reactivation [12,13,16].

Although there are multiple plausible mechanisms for a pathogenic role of CMV in ICU patients, much of the data are extrapolated from other clinical settings, and thus their applicability in non-immunocompromised patients remains unproven. Thorough investigation into the specific mechanisms by which CMV mediates adverse clinical outcomes should be an important component of future clinical trials of CMV prevention in the ICU setting.

What should be the next steps to further define the relationship between CMV and adverse outcomes in patients with critical illness?

As discussed earlier, given the inherent difficulty in ascertaining causality from prior observational studies, additional data from observational studies is unlikely to significantly advance our understanding of the role of CMV in ICU patients. Rather, given the existing large body of evidence demonstrating frequent CMV reactivation and association with adverse clinical outcomes in critically-ill patients, biologically-plausible mechanisms through which CMV could mediate these outcomes, and the urgent clinical need for new treatment options, a controlled trial of CMV prevention in ICU patients is warranted and should be the next appropriate step. Since the association of CMV with adverse outcomes is far from proven, and because robust data on the potential effect size and appropriate endpoints are not yet available, an initial phase II pilot study using a randomized controlled trial design would be more appropriate than proceeding directly to a large-scale phase III efficacy trial.

Based on currently available data, the most appropriate study populations for initial clinical trials should include adult CMV seropositive patients with either sepsis or pneumonia-associated ALI/ARDS. These populations are known to have high morbidity and mortality despite current state of the art ICU care and represent those in whom previous studies have documented high rates of CMV reactivation [1]. Furthermore, these are populations in whom specific biomarkers (IL-6, IL-8) have been shown to be associated with important clinical endpoints [21-24], thereby providing rational surrogate endpoints for initial "proof of concept" clinical trials.

The choice of antiviral drug and appropriate strategy for employing antiviral drug requires careful consideration. Among currently available options, ganciclovir is favored over alternative agents based on its potent activity against CMV, availability of intravenous and oral formulations (via valganciclovir), and better efficacy vs. comparators in previous clinical trials [42-46]. The two major approaches for CMV prevention that have been used in immunocompromised patient populations are antiviral prophylaxis (antiviral drug given to all patients at risk for CMV infection/reactivation) and preemptive therapy (antiviral drug given only to patients with early laboratory evidence of CMV infection). At least for initial clinical trials, there is a stronger rationale for the approach of antiviral prophylaxis over preemptive therapy. Although preemptive therapy and prophylaxis appear to both be effective for prevention of symptomatic CMV infection (i.e., CMV disease), there are emerging data suggesting that antiviral prophylaxis might have a greater beneficial effect on other CMV-associated effects [47-50], such as those hypothesized to be responsible for the

association with adverse clinical outcomes in ICU patients. Importantly, in a murine model of sepsis-induced CMV reactivation, early (prophylactic) administration of high dose ganciclovir was significantly more effective in preventing both CMV reactivation and subsequent pulmonary fibrosis than a delayed (i.e., treatment) approach [51] (Figure 2). Also, from a logistical standpoint, few clinical laboratories have the capability of providing real-time results for a large multicenter trial without significant delays in instituting antiviral drug. This might be particularly relevant in the ICU setting where a prior study has demonstrated an apparent dose effect of CMV with adverse outcomes [3]. Since in a preemptive approach antiviral drug would not be started (after some delay) until some degree of viral replication had already occurred, this could potentially minimize the effect size seen in the active drug arm if a preemptive strategy were used. These potential disadvantages of a preemptive therapy approach must be carefully weighed against the likely higher risk for toxicity, cost and potential for resistance with the use of a prophylactic strategy.

Since the ability of a pilot study to assess the impact on true clinical endpoints is limited, the incorporation of a surrogate endpoint (biomarker) should be strongly considered, with the use of various clinical events (mortality, length of stay, duration of mechanical ventilation, safety) as secondary endpoints. Although a single consensus biomarker for trials of acute lung injury has not been well-defined, IL-6 and IL-8 have previously been hypothesized to be important in the pathogenesis of ALI/ARDS, shown to be important in predicting clinical outcomes in ICU patients, and have also been linked to CMV *in vitro* and *in vivo* [25-33]. Furthermore, current interventional clinical trials in patients with acute lung injury/ARDS have used these cytokines as primary endpoints [NCT00351533, NCT00559130]. Thus, levels of these cytokines (or changes over time) are appropriate to consider as surrogate endpoints for initial "proof of concept" pilot studies of CMV prevention in the ICU setting.

Acknowledgments

ABBREVIATIONS

ALI	acute lung injury
ARDS	acute respiratory distress syndrome
BAL	bronchoalveolar lavage fluid
ICU	Intensive care unit

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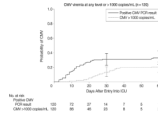
Figure 1.
Cumulative incidence of CMV viremia in CMV seropositive, non-immunocompromised adults in the ICU [3].
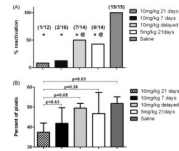
Figure 2.
Impact of different ganciclovir regimens on reactivation of CMV (A) and pulmonary fibrosis (B) in a murine model of CMV reactivation and lung injury induced by cecal ligation and puncture [51].

Table 1

Rates of CMV infection in non-immunocompromised adults in the ICU. Adapted from Reference [1].

Reference	Incidence	95% CI
11	1 / 120	0.00 – 0.06
9	1 / 96	0.00 – 0.07
6	1 / 24	0.00 – 0.26
8	12 / 142	0.05 – 0.14
5	8 / 86	0.05 – 0.18
12	10 / 104	0.05 – 0.17
13	40 / 237	0.13 – 0.22
4	29 / 115	0.18 – 0.34
14	8 / 25	0.17 – 0.52
7	11 / 34	0.19 – 0.50
3	39 / 120	0.25 – 0.41
15	35 / 99	0.27 – 0.45
10	20 / 56	0.24 – 0.49
Pooled	**215 / 1258 (17%)**	**0.11 – 0.24**

Table 2

Rates of CMV infection in non-immunocompromised adults in the ICU according to diagnostic method. Adapted from Reference [1].

	Viral Culture			Viral DNA or Antigen		
Reference	Incidence	95% CI	Reference	Incidence	98% CI
8	12 / 142	0.05 – 0.14	11	1 / 20	0.00 – 0.06
5	8 / 86	0.05 – 0.18	9	1 / 96	0.00 – 0.07
12	10 / 104	0.05 – 0.17	6	1 / 24	0.00 – 0.26
4	29 / 115	0.18 – 0.34	13	40 / 237	0.13 – 0.22
			14	8 / 25	0.17 – 0.52
			7	11 / 34	0.19 – 0.50
			3	39 / 120	0.25 – 0.41
			15	35 / 99	0.27 – 0.45
			10	20 / 56	0.24 – 0.49
Pooled	**59 / 447 (13%)**	**0.06 – 0.22**	**Pooled**	**156 / 811 (19%)**	**0.13 – 0.31**

Table 3

Rates of CMV infection in non-immunocompromised adults in the ICU according to baseline CMV serology. Adapted from Reference [1].

	Active CMV Infection Rate by CMV Serology					
	Not Reported			Reported		
Reference	Incidence	95% CI	Reference	Incidence	95%	
11	1 / 120	0.00-0.06	6	1 / 24	0.00-0.26	
9	1 / 96	0.00-0.07	12	10 / 76	0.07-0.23	
8	12 / 142	0.05-0.14	14	8 / 25	0.17-0.52	
5	8 / 86	0.05-0.18	7	11 / 34	0.19-0.50	
13	40 / 237	0.13-0.22	3	39 / 120	0.25-0.41	
			4	8 / 22	0.19-0.58	
			10	20 / 56	0.24-0.49	
			15	23 / 41	0.41-0.70	
Pooled	**62 / 681 (9%)**	**0.03-0.14**	**Pooled**	**120 / 398 (30%)**	**0.22-0.42**	

Table 4

Rates of CMV infection in non –immunocompromised adults in the ICU as assessed by PCR [3].

CMV Variable	Overall (n = 120)	Burn ICU (n = 20)	Cardiac ICU (n = 20)	Medical ICU (n = 40)	Trauma ICU (n = 40)
CMV viremia at any level, No. (%)	39 (33)	11 (55)	3 (15)	10 (25)	15 (38)
CMV viremia at >1000 copies/mL, No. (%)	24 (20)	9 (45)	1 (5)	6 (15)	8 (20)
CMV viremia at >10000 copies/mL, No. (%)	11 (9)	4 (20)	0	4 (10)	3 (8)
Maximum CMV load, median (range), $\log_{10}$ PCR copies	3.3 (1.8-5.5)	3.9 (2.5-5.5)	2.4 (1.8-3.7)	3.4 (2.3-4.8)	3.1 (2.1-4.5)
Days to first detectable CMV viremia, median (range)	12 (3-57)	19 (7-57)	15 (9-21)	8 (3-13)	11 (3-21)
Duration of viremia, median (range), d	17 (2-45)	20 (4-45)	4 (2-17)	18 (4-38)	14 (2-32)

Table 5

Association of CMV infection with mortality in non-immunocompromised adults in the ICU. Adapted from Reference [1].

	Deaths / Total		
References	**Active CMV Infection**	**No Active CMV Infection**	**P-Value**
15	10 / 35	7 / 64	0.031
13	20 / 40	11 / 40	0.041
4	16 / 29	31 / 86	0.073
12	5 / 10	25 / 94	0.132
3	1 / 39	9 / 81	0.146
10	11 / 20	13 / 36	0.174
14	5 / 8	6 / 17	0.209
7	7 / 11	17 / 23	0.540
Pooled	**75 / 192 (39%)**	**119 / 441 (27%)**	**0.001**

Table 6

Adverse clinical outcomes associated with CMV infection in non-immunocompromised adults in the ICU.

Adverse Outcome	References
All-cause mortality	4,8,10,12,13,14,15,16
Increased length of hospital and/or ICU stay	4,13,12,16,10,14,3,15
Increased duration of mechanical ventilation	12,13,16,14,15
Increased nosocomial infections	12,13,16