Netherlands Journal of Critical Care
Submitted December 2019; Accepted May 2020

REVIEW

Cytomegalovirus reactivations in the critically ill

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Keywords - **cytomegalovirus reactivation, antiviral prophylaxis, ARDS**

Abstract

Cytomegalovirus (CMV) reactivation is a well-recognised complication of solid organ and stem cell transplantation, causing both direct cytopathology in various organs and indirect immunomodulating effects. However, reactivation also occurs in 14-71% of previously immunocompetent critically ill adults, and although final proof of pathogenicity in such patients is lacking, many studies show that it is independently associated with prolonged mechanical ventilation and death. Two recent RCTs indicated that both valganciclovir and ganciclovir are safe and effective in preventing CMV reactivation in plasma, yet were underpowered to detect meaningful clinical benefit. A much larger trial taking a preemptive approach is expected to report shortly. Thus, based on the available evidence, routine use of anti-CMV prophylaxis in ICU patients who were previously immunocompetent cannot be recommended at this time. However, in patients undergoing a prolonged ICU stay, viral diagnostics and treatment of CMV reactivation may be considered in cases of refractory ARDS or otherwise unexplained organ failure.

Introduction

Cytomegalovirus (CMV) is a member of the family of Herpesviridae, which are large double-stranded DNA viruses known to cause recurring infections. In case of CMV, primary infection mostly occurs during childhood or adolescence, after which the virus remains latent in the host for years. This occurs mainly in cells of the myeloid lineage (i.e., granulocytes, monocytes and dendritic cells). However, during active replication the virus may also infect other tissues, including the endothelium, lungs, liver, intestinal tract and central nervous system.[1] In the industrialised world, CMV seroprevalence increases from 50% in young adults to 90% in the elderly, but in developing countries high seroprevalence rates are found even in childhood.[2,3]

Reactivation of the virus may occur during periods of immunocompromise. In solid organ or haematopoietic stem cell recipients and patients with HIV infection, CMV infection is characterised mainly by its direct cytopathic effects on various tissues and organ systems, most commonly the lung and colon, but also including the oesophagus, liver, retina, and brain ependyma *(figure 1)*.[3]

This causes rounding of infected cells, fusion with adjacent cells to form syncytia, and the appearance of nuclear inclusion bodies, which produce the typical owl's eyes that can be observed on histopathological examination. In fact, the name of the virus is derived from the Greek words *kýtos* meaning hollow, as a cell or container, and *megálos* meaning large. In addition to its direct effects, CMV infection may also trigger various immunomodulatory responses. These include both excessive proinflammatory responses to infection as well as an increased anti-inflammatory reaction, which may render the patient susceptible to opportunistic bacterial and fungal pathogens.[4] For these reasons, antiviral prophylaxis and/or preemptive therapy have become standard practice during the management of patients who are severely immunocompromised according to classical criteria.[5,6] However, CMV reactivations also occur among other groups, including critically ill patients without prior immunodeficiency.

In this article, we report on the incidence of CMV reactivation in previously immunocompetent ICU patients, and review the latest findings regarding the attributable morbidity and mortality associated with this infection. In addition, we summarise the results of two recent intervention studies using antiviral prophylaxis in these patients.

Incidence and risk factors

The observed incidence of systemic CMV infection in various cohorts of critically ill patients without known prior

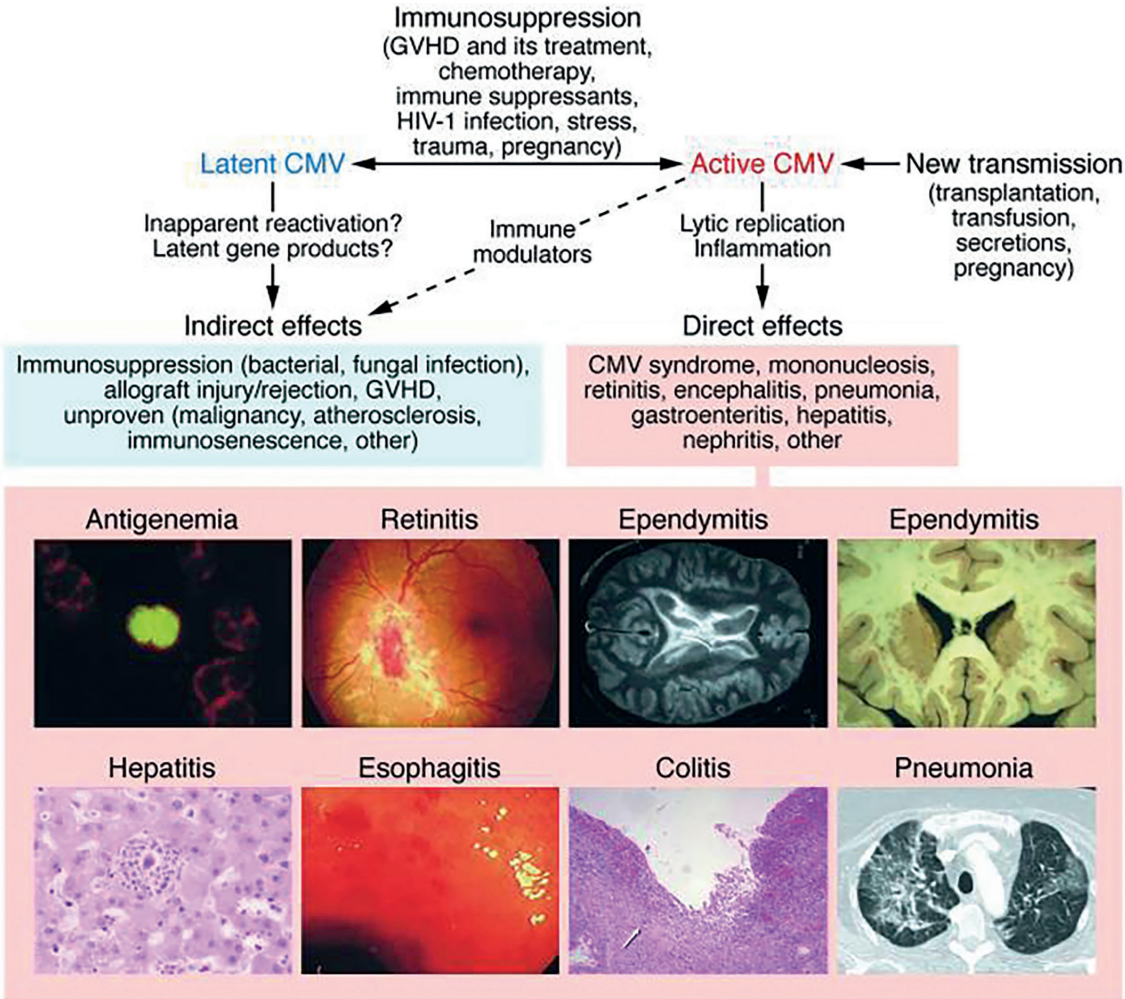

Figure 1. CMV disease mechanisms
Published with permission from original source: Boeckh M, Geballe AP. Cytomegalovirus: pathogen, paradigm, and puzzle. J Clin Invest 2011; 121:1673-80.

immunocompromise varies widely, with estimates ranging from 14% to 71% depending on serostatus *(table 1)*. Although these variations may be partly explained by the method used to diagnose viraemia (i.e., PCR versus pp65 antigen detection), they seem to be primarily related to differences in duration of mechanical ventilation and length of stay (i.e., a prolonged ICU admission is associated with both increased severity of illness and a greater time window to detect CMV reactivation). It is generally believed that the large majority of these viraemia events represent cases of viral reactivation, as primary infection in adults is rare.[7-12] In addition, there are a number of studies specifically describing local CMV reactivation in the lower respiratory tracts and colon (which can escape blood-based surveillance by PCR and the pp65 antigenaemia assay in approximately 25% of cases).

A number of risk factors for reactivation of herpes viruses in general, and CMV in particular, have been reported. These include blood transfusions, and the presence of severe sepsis, burn injuries or, the acute respiratory distress syndrome (ARDS).[13] In fact, a study into the diagnostic yield of open lung biopsies among patients with severe ARDS who did not show clinical improvement for ≥4 days despite negative microbiological cultures, reported histological proof of CMV-induced cytopathology (i.e., owl's eyes) in 30 of 100 cases.[14] In addition, in an experimental murine study CMV reactivation caused exacerbated and prolonged cytokine and chemokine expression in pulmonary tissue, which subsequently resulted in worsening of pulmonary fibrosis compared with control animals without CMV reactivation.[15] Of note, prophylactic use of ganciclovir was effective in preventing these effects when compared with placebo.

Morbidity and mortality associated with CMV reactivation

In most studies (listed in *table 1*) an association between the occurrence of systemic CMV reactivation and an increased risk of mortality was reported, which remained after correction for confounding covariables (although not all studies were sufficiently powered to yield this result statistically significantly).

Table 1. Observational studies of CMV reactivation in ICU patients without known prior immunocompromise

Reference (year)	ICU patient population	Detection method	Incidence	Mortality	Associated other outcomes
A. Patients with unknown CMV serostatus					
Jaber (2005) [23]	237 patients with fever >72 hours without proven bacterial or fungal infection	pp65 in blood	17%	Unknown [a]	Mechanical ventilation duration, ICU length of stay, infections
Ziemann (2008) [7]	99 patients with ICU length of stay >14 days	PCR in plasma	35%	29% vs 11% (p<0.05)	ICU length of stay
Chiche (2009) [8]	242 patients with >2 days of mechanical ventilation	pp65 in blood and viral culture in lower respiratory tract	19%	54% vs 37% (p=0.08) [b]	Mechanical ventilation duration, bacterial infections
Bordes (2011) [9]	29 severe burn patients	PCR in plasma	71%	20% vs 33% (p=0.59)	Mechanical ventilation duration, ICU length of stay
Coisel (2012) [24]	93 patients with suspected pneumonia	pp65 in blood, PCR in lower respiratory tract	24%	Unknown [a]	Mechanical ventilation duration
Walton (2014) [10]	560 patients with sepsis	PCR in plasma	24%	Unknown [c]	ICU length of stay, fungal infections
Lopez Roa (2015) [11]	150 critical heart surgery patients with ICU length of stay >3 days	PCR in plasma	17%	Adjusted OR 12.1 (95% CI 2.3-64) [d]	N.A.
B. CMV seropositive patients					
Kutza (1998) [25]	34 patients with sepsis	pp65 and PCR in blood	32%	N.A.	N.A.
Heininger (2001) [26]	56 patients with 'simplified acute physiology score' >40	PCR and viral culture in plasma and lower respiratory tract	36%	55% vs 36% (p=0.17)	ICU length of stay
Von Muller (2006) [27]	25 patients with septic shock and ICU length of stay >7 days	pp65 in blood	32%	63% vs 33% (p>0.05)	Mechanical ventilation duration, ICU length of stay
Limaye (2008) [28]	120 patients	PCR in plasma	33%	Adjusted OR 4.3 (95% CI 1.6-11.9) [a]	N.A.
Chilet (2010) [29]	53 patients with ICU length of stay >5 days	PCR in plasma and lower respiratory tract	39%	61% vs 46% (p=0.40)	ICU length of stay
Heininger (2011) [30]	86 patients with severe sepsis	PCR in plasma and lower respiratory tract	41%	Adjusted HR 0.5 (95% CI 0.2-1.2)	Mechanical ventilation duration, ICU length of stay
Chiche (2012) [31]	82 patients	pp65 in blood	27%	N.A.	N.A.
Frantzeskaki (2015) [32]	80 patients	PCR in plasma	14%	45% vs 27% (p>0.05)	Organ failure
Lopez Roa (2015) [33]	115 patients	PCR in plasma	34%	Adjusted OR 6.5 (95% CI 1.7-24.7) [a] when co-reactivation with HHV-6	N.A.
Osawa (2016) [34]	100 patients with at least one positive blood culture	PCR in plasma	20%	Adjusted OR 1.6 (95% CI 0.4-6.0) [b]	Mechanical ventilation duration, ICU length of stay
Ong (2016) [16]	271 patients with ARDS and mechanical ventilation > 4 days	PCR in plasma	27%	Adjusted SHR 2.5 (95% CI 1.3-4.7)	Mechanical ventilation duration, ICU length of stay
Ong (2017) [12]	214 patients with septic shock	PCR in plasma	27%	Adjusted SHR 3.2 (95% CI 1.4-7.1) when co-reactivation with EBV	N.A.

OR = odds ratio; HR = hazard ratio; SHR = subdistribution hazard ratio; CI = confidence interval.
a Multivariable model not presented in published article; b In some CMV seropositive patients ganciclovir treatment was initiated during ICU admission; c Mortality numbers not presented in published article; d Composite endpoint: Prolonged hospital length of stay or mortality.

In the largest of these, published by us in 2016, we used marginal structural models to adjust for the evolution of disease severity up until the onset of viral reactivation and a multistate model to calculate the attributable mortality associated with these events.[16] Based on these mathematical models, we estimated that in ARDS patients (who were mechanically ventilated for ≥4 days) case fatality due to CMV infection was 4.4% (95% CI 1.1%-7.9%) by day 30 in the ICU. Moreover, in another study CMV reactivation was associated with more secondary fungal and opportunistic bacterial infections.[10]

Randomised studies using valganciclovir or ganciclovir

Until now, two randomised controlled phase II trials have assessed prophylactic use of valganciclovir or ganciclovir in ICU patients *(table 2)*.[17,18] As these drugs have been associated with bone marrow toxicity, which could possibly harm already

Table 2. Overview of randomised controlled trials in CMV-seropositive ICU patients

Study	Intervention	ICU patient population	Primary outcome measure	CMV reactivation	Main findings
GRAIL trial NCT01335932	(Val)ganciclovir vs placebo (prophylaxis)	156 patients with sepsis, trauma or ARDS	Change in IL-6 level from day 1 to day 14	12% vs 39% (p<0.001	- No significant change in IL-6 - More ventilator-free days in (val) ganciclovir group - No difference in adverse effects between ganciclovir versus placebo
CCCC trial NCT01503918	Valacyclovir vs valganciclovir vs placebo (prophylaxis)	124 patients who are mechanically ventilated >1 day	Time to first reactivation of CMV in blood	6% vs 3% vs 35% (p<0.001)	- Effective suppression of CMV reactivation by valganciclovir and valacyclovir - Higher mortality in valacyclovir group - No difference in adverse effects between valganciclovir versus placebo
PTH trial NCT02152358	Ganciclovir vs placebo (preemptive)	240 patients who are mechanically ventilated >4 days	Ventilator-free days at day 60	Results not yet available	Results expected in Q4 2020

vulnerable ICU patients, these trials were primarily focused on estimating the effectiveness of a prophylactic strategy for the prevention of CMV reactivation, assessing the safety of the antiviral drugs used in critically ill patients, and studying the feasibility of future phase III trials. These studies were thus underpowered to detect differences in patient-centred outcomes.

In one study, prophylactic use of ganciclovir (2 dd 5 mg/kg IV for 5 days) in CMV-seropositive patients with sepsis, trauma or ARDS (n=84) was compared with placebo (n=72).[17] Prophylaxis was indeed effective in preventing CMV reactivation, with 12% of patients in the ganciclovir arm versus 39% of subjects in the placebo arm developing viraemia while in the ICU (p<0.001). Of note, this may even be an underestimation of the true efficacy of prophylaxis, as screening for CMV seropositivity —which was a prerequisite for trial inclusion— was performed in a centralised microbiological laboratory. The approximately three days that were necessary to transport samples to this external facility and await results inevitably led to a delayed start of prophylaxis in many patients, which may have contributed to the finding that in 6% of patients CMV reactivation was already present at the time of randomisation. Importantly, the investigators did not find a difference in the number of reported adverse effects between groups, and no single patient developed neutropenia. Although there was no overall reduction in plasma IL-6 levels by day 14 (which was the primary endpoint of the trial), an increased number of ventilator-free days was observed in patients receiving ganciclovir, which lends some support to the hypothesis that prevention of CMV reactivation could mitigate a pro-inflammatory reaction in the lungs.

The other CMV prevention trial included three study arms, with 34 patients receiving high-dose valacyclovir (4 dd 2000 mg orally), 46 patients receiving low-dose valganciclovir (1 dd 450 mg orally), and 44 receiving placebo.[18] Of note, if patients were unable to receive enteral medications, these drugs could be substituted by acyclovir 3 dd 10 mg/kg IV or ganciclovir 1 dd 2.5 mg/kg IV, respectively. The valacyclovir arm was dropped prematurely because of an unexpected increase in mortality observed during interim analysis, yet valganciclovir was highly effective in preventing CMV reactivation in plasma (from 35% to 3%). The reason for the observed mortality excess remains elusive however -and may in fact have been a chance finding- as other safety endpoints did not differ between groups. In particular, the occurrence of renal impairment and bone marrow suppression (both potential adverse effects of the study drugs) were comparable, although the study was underpowered to identify small differences.

A third study, the Preemptive Treatment of Herpesviridae (PTH) trial (NCT02152358), recently reported (overall) negative results regarding acyclovir treatment of herpes simplex virus oropharyngeal reactivation in patients receiving more than four days of mechanical ventilation.[19,20] However, this randomised controlled trial (RCT) also included a randomisation arm investigating the preemptive use of ganciclovir in subjects who had developed CMV viral loads >500 IU/ml in their blood, for which the results are still pending. As primary study endpoint, a ventilator-free day construct was used which reflects a composite of both duration of mechanical ventilation and mortality. This is clearly a relevant outcome measure from the patient perspective, yet it is important to realise that despite its multicentre design, the trial will only be able to detect relatively large outcome differences (i.e., with 120 patients to be included in each study group, it is powered to detect a reduction of ≥8 ventilator-free days).

Implications for clinical practice and further research

When considering the implications of CMV reactivation in critically ill patients, it is important to differentiate between two distinct questions: (1) Does viral reactivation cause clinical deterioration? (or is this rather an innocent bystander phenomenon that merely reflects underlying immunity?); and (2) Is prophylactic or preemptive antiviral treatment effective in reducing morbidity and mortality in ICU patients? As CMV reactivation cannot be randomised to occur amongst patients,

only experiments using animal models and epidemiological research using large observational databases can address the first aetiological question. However, the second question concerns the efficacy of antiviral treatment in clinical practice, and this can be tested by RCTs. Although the findings of such trials may provide clues regarding the underlying causality question, an aetiological association between the occurrence of CMV reactivation and poor outcome cannot be excluded when no difference is observed between treated and control patients. After all, the observed clinical endpoints are the combined result of both the effectiveness of antiviral prophylaxis or preemptive therapy, and the adverse effects caused by this treatment. Therefore, it is possible that interventions directed against systemic CMV reactivation may not lead to a detectable clinical benefit, while the virus is still causally linked to poor outcome in a pathophysiological sense.

A prophylactic strategy targets all CMV-seropositive patients who are considered to be at risk for reactivation based on the presence of simple clinical criteria. This has the advantage that, after initial serological screening, no further periodical monitoring of CMV plasma loads by quantitative PCR is required. Moreover, antiviral drugs are initiated early (i.e. before reactivation occurs), which likely benefits the effectiveness of such approach. However, 60-75% of patients admitted to an ICU ultimately will not develop CMV viraemia even without prophylaxis,[7-12] and these patients would thus unnecessarily be exposed to potential drug toxicity. In contrast, a preemptive strategy does not target patients until viraemia is first detected in blood (or alternatively in the lower respiratory tract). As a result, no patients are exposed to valganciclovir or ganciclovir unnecessarily. However, a potential disadvantage of this approach is that the delayed start of antiviral treatment may reduce its overall efficacy (i.e., both with regard to controlling the virus and preventing subsequent organ injury). Of note, the cost-effectiveness of either strategy (which involves a trade-off between expenditures for antiviral medications and those for repeated viral screening by PCR) has yet to be determined.

Both phase II trials (discussed above) have shown that prophylaxis with valganciclovir or ganciclovir can be effectively used to prevent systemic CMV reactivation in critically ill patients, and that the adverse effects associated with this approach are limited. However, both trials also have failed to detect clinically meaningful outcome differences between treated and untreated subjects (although neither study was primarily designed to do so). The logical next step is thus to proceed with the assessment of antiviral strategies in much larger phase III trials that are adequately powered on patient-centred endpoints. Previously, we estimated that such a prophylactic intervention trial would require at least 570 patients per study arm to show an absolute outcome difference of 5% (when targeting a combination of mortality and duration of mechanical ventilation), and a comparable required number of patients was estimated by others.[21,22] Unfortunately, the PTH trial that is currently underway in France does not meet these criteria by large (with only 120 subjects scheduled for enrolment per group). Indeed, the largest challenge for any study on antiviral treatment is its required sample size. For instance, when choosing the prophylactic approach, patient selection based on clinical risk factors only (e.g., prolonged mechanical ventilation in a setting of ARDS or sepsis) would result in an absolute reactivation risk of 40% at most amongst CMV seropositive patients in the ICU *(table 1)*. The required sample size would substantially decrease if biomarkers were to be identified that could somewhat adequately predict in which patients CMV reactivation will occur, and in whom the most detrimental effects are to be expected, as this would enable the trial to target specific subgroups to maximise treatment effect. However, until novel methods for better patient selection become possible, a preemptive approach to CMV reactivation seems to be most rational. For this, molecular diagnostics would need to be performed at least twice per week, which also requires optimised logistics.

Many physicians are sceptical about the pathogenicity of CMV reactivation in patients who would not be labelled 'immunocompromised' according to classical criteria - particularly if virus loads are relatively low. They thus consider systemic herpesvirus reactivation mainly as a marker of decreased immunity that is related to the underlying severity of illness rather than an independent cause of poor outcome. As a result, CMV loads are rarely requested in the ICU. Nevertheless, based on accumulating evidence from epidemiological studies reporting an independent association between CMV viraemia and morbidity in previously immunocompetent ICU patients, it is important to perform further studies that can improve our understanding of the pathophysiology of herpesvirus reactivation and its potential aetiological consequences. Examples of pertinent study questions revolve around determining (1) the thresholds of viral load in plasma that can distinguish between clinically important and irrelevant reactivation, and (2) the differences between systemic and local CMV reactivation (e.g., in the lower respiratory tract or gut only). Until a better understanding of these issues is obtained, we recommend to simultaneously test for CMV reactivation by PCR in plasma as well as samples obtained from the target organ (e.g., respiratory secretions).

Conclusion and recommendations

Although final proof of CMV-induced pathogenicity is currently lacking in critically ill patients who were previously immunocompetent, a large number of clinical studies (as well as a few experimental ones) suggest the existence of attributable morbidity and mortality related to systemic CMV reactivation in this setting. Until the results of large phase III RCTs become available, neither routine prophylaxis nor preemptive treatment

using valganciclovir or ganciclovir can be recommended. However, in specific situations in the ICU, such as cases of prolonged respiratory failure due to unexplained ARDS (i.e., where conventional bacteriological and other diagnostics have remained negative), the possibility of CMV reactivation should be considered.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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