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Narrative review

Comparative clinical manifestations and immune effects of cytomegalovirus infections following distinct types of immunosuppression

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ABSTRACT

Background: Cytomegalovirus (CMV) infection is a well-recognised complication of solid organ and hematopoietic cell transplantation. However, CMV infection also occurs in patients with human immunodeficiency virus infection, previously immunocompetent intensive care unit patients, and individuals on immunosuppressive medications for various underlying diseases.
Objectives: This review describes the comparative effects of CMV infection in distinct types of acquired immunosuppression.
Sources: Selected peer-reviewed publications on CMV infections published until December 2021.
Content: CMV infection affects various organ systems through direct cytolytic mechanisms but may also exert indirect effects by promoting pro-inflammatory and immunosuppressive responses. This has been well studied in transplant recipients, for whom antiviral prophylaxis and pre-emptive therapy have now become standard practice. These strategies not only prevent direct CMV disease manifestations but also mitigate various immunopathological processes to reduce graft-vs.-host disease, graft rejection, and the occurrence of secondary bacterial and fungal infections. The efficacy of neither prophylactic nor pre-emptive treatment of CMV infection has been demonstrated for patients with critical illness- or medication-induced immunosuppression. Many observational studies have shown an independent association between CMV reactivation and a prolonged duration of mechanical ventilation or increased mortality in the intensive care unit. Furthermore, data suggest that CMV reactivation may increase pulmonary inflammation and prolong the duration of mechanical ventilation.
Implications: A large number of observational and experimental studies suggest attributable morbidity and mortality related to CMV infection, not only in transplant recipients and patients with human immunodeficiency virus infection but also in patients with critically illness- or medication-induced immunosuppression. Adequately powered randomised controlled trials investigating the efficacy of prophylaxis or pre-emptive treatment of CMV infection in these patients are lacking, with a notable exception for transplant recipients. **David S.Y. Ong, Clin Microbiol Infect 2022;28:1335**

Introduction

Cytomegalovirus (CMV) is a member of the family of Herpesviridae, which are large double-stranded DNA viruses [1]. Most individuals experience their primary CMV infection during childhood or adolescence, after which the virus remains latent for years

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mainly in cells of the myeloid lineage, such as granulocytes, monocytes and dendritic cells. During active infection, the virus may replicate in endothelial cells, lungs, liver, intestinal tract, and central nervous system [2]. CMV-infected cells become rounded, fuse with adjacent cells to form syncytia, and show nuclear inclusion bodies, yielding the typical appearance of the owl's eyes that can be observed during histopathological examination.

CMV reactivation from latent sites may occur during prolonged periods of impaired immunity, as following solid organ transplantation (SOT) or hematopoietic cell transplantation (HCT). CMV infection ensues when the adaptive T cell immunity of the host is unable to prevent reactivation from latent sites and/or fails to clear the virus when replication occurs [3,4]. For this reason, antiviral prophylaxis and pre-emptive therapy against CMV have become standard practices during the management of patients who have become severely immunocompromised after transplantation. These practices are well-supported by international guidelines (Table 1) [5–8]. However, routine prophylactic antiviral treatment is not recommended for all patients at risk of CMV reactivation, including patients with human immunodeficiency virus (HIV) infection [9,10].

In addition to these well-recognised populations at risk, CMV reactivations have also been observed among critically ill patients without prior immunodeficiency who require multiple days of treatment in an intensive care unit (ICU). This is most likely related to critical illness-induced immunosuppression, which is known to occur following sepsis, trauma, and other examples of prolonged illness [11,12]. Furthermore, the use of immunosuppressive agents to treat chronic immune-mediated diseases has increased over the years, which places these patients at an increased risk for CMV infection.

In this review, we address the incidence, pathophysiology and clinical manifestations of CMV infection in different groups of adult patients with acquired immunocompromise, focusing on both similarities and differences in order to gain a better understanding of its effect in these populations.

CMV infection in transplant recipients

HCT recipients are at high risk for CMV disease when no prophylactic or pre-emptive antiviral strategies are applied (Table 2) [13]. Without such treatment, detrimental effects of CMV disease occurred in 25% to 30% of patients during the first 3 months after transplant [4]. In early randomised controlled trials (RCT) that compared antiviral prophylaxis to placebo, the incidence of CMV disease was 3% in those receiving therapy as compared to 45% in those receiving placebo [14,15]. Subsequent RCTs have shown that pre-emptive treatment strategies using serial antigen- or PCR testing for CMV in plasma or whole blood were comparable to a prophylactic strategy for most outcomes [16,17]. The effectiveness of a pre-emptive approach is also supported by the latest RCTs that compared antiviral prophylaxis using letermovir, maribavir, or brincidofovir to pre-emptive treatment as standard of care; these studies found similar incidences of CMV disease among all groups [18–21].

Among the different organ systems in which CMV disease can manifest, pneumonitis has been most frequently observed. Its reported occurrence was 15% in untreated CMV seropositive HCT recipients after engraftment [22], but this has decreased substantially to 2% to 6% following the introduction of antiviral prophylaxis and pre-emptive therapy [21,23]. Signs and symptoms of CMV pneumonitis are non-specific and may include new pulmonary infiltrates on imaging, worsening hypoxia, and tachy-dyspnoea [24]. Patients who developed CMV pneumonitis had an up to 70% overall mortality within 6 months and 63% of deaths were attributed to CMV pneumonitis, but fortunately survival rates have improved dramatically since then because of both the arrival of antiviral treatment and general improvements in transplantation practices [25]. In SOT recipients, the incidence of pneumonitis is more variable and depends on both the type of organ transplant and the occurrence of donor-recipient CMV serostatus mismatch [4]. Without antiviral prophylaxis, CMV disease (i.e., not limited to

Table 1
Overview of existing international guidelines for CMV prophylaxis and/or pre-emptive antiviral treatment

Guideline	Patient group	Recommendation
European Conference on Infections in Leukaemia (2017) - Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation [5].	HCT	Letermovir as prophylaxis in CMV seropositive recipients. (Val)ganciclovir as first-line pre-emptive treatment (at least 2 wk), followed by optional maintenance therapy.
American Society for Transplantation and Cellular Therapy (2021) - Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation [6].	HCT	Prophylactic and pre-emptive strategies should be viewed as complementary and not mutually exclusive. Letermovir as prophylaxis during 100 d in CMV seropositive recipients. (Val)ganciclovir as first-line pre-emptive treatment in CMV D+/R- during induction phase (2 wk), followed by maintenance phase (i.e., secondary prophylaxis).
Transplantation Society International CMV Consensus Group (2018) - The management of cytomegalovirus in solid organ transplantation [7].	SOT	Antiviral prophylaxis should start within 10 d after transplantation for a duration of 3 to 6 mo. (Val)ganciclovir most commonly used. Pre-emptive therapy is an equal alternative strategy to prophylaxis for kidney, liver, intermediate risk CMV D-/R+ pancreas, intermediate risk CMV D-/R+ islets. (Val)ganciclovir as pre-emptive therapy for D-/R-.
American Society of Transplantation (2019) - Cytomegalovirus in solid organ transplant recipients guidelines [8].	SOT	Antiviral prophylaxis is preferred when CMV D+ and started within the first 10 d after transplantation. (Val)ganciclovir as prophylaxis during 3 to 6 mo for kidney, pancreas, kidney-pancreas, liver, intestinal, and composite tissue allograft recipients. For lung or heart-lung transplant recipients, 6 to 12 mo. For kidney recipients, high-dose valaciclovir is an alternative to ganciclovir. (Val) ganciclovir as pre-emptive treatment is an alternative to prophylactic treatment in CMV D-/R+ kidney, liver, and pancreas recipients.
German and Austrian AIDS societies (2013) - Guidelines on therapy and prophylaxis of opportunistic infections in HIV-infected patients [9].	HIV	Routine primary prophylaxis is not recommended. Ganciclovir prophylaxis for CMV retinitis with a CD4 T cell count of <50 cells/microL is effective, but this is usually too toxic. Secondary prophylaxis with valganciclovir after about 3 wk of acute therapy and after lesions have formed scars, at least 6 mo of maintenance therapy and immune reconstitution at a CD4 T cell count of 100 to 150 cells/microL.
Canadian consensus guidelines for the management of cytomegalovirus disease in HIV/AIDS (2004) [10].	HIV	No routine primary prophylaxis. Secondary prophylaxis or maintenance therapy for CMV retinitis.

Abbreviations: CMV, cytomegalovirus; D, donor; HCT, hematopoietic cell transplantation; HIV, human immunodeficiency virus; R, recipient; SOT, solid organ transplantation.

Table 2
Direct and indirect effects of CMV infection following distinct types of immunosuppression

	Immunocompromised following HCT/SOT	HIV-induced immunosuppression	Critical illness-induced immunosuppression	Medication-induced immunosuppression
Cytopathological effects	Large amount of clinical data showing different presentations of CMV disease in an era before antiviral treatment was standard care [4,13,22]. Good historical evidence regarding reduction of CMV disease after routine implementation of antiviral prophylaxis and pre-emptive treatment strategies [14–23,25].	Significant amount of clinical data showing especially CMV retinitis, and to a lesser extent gastrointestinal disease [36,37]. Multiple RCTs showing that initiation of systemic anti-CMV treatment during early phase of retinitis reduces mortality and retinitis progression [40].	One observational study with histopathological proven CMV pulmonary disease in previously immunocompetent ICU patients [74]. Several case reports of CMV colitis [75–77].	One observational study and some case reports showing more CMV retinitis and other CMV disease following (certain combinations of) immunosuppressive treatment [81,89].
Pro-inflammatory effects	Pneumonitis reflects both lytic infection as well as immunopathological response [1,22,33,100,101]. Graft-vs.-host disease, graft rejection, and the development of atherosclerosis after transplant are assumed to (partially) be the result of pro-inflammatory effects triggered by CMV [13,29,30]. Reduced incidence of acute graft rejections following antiviral treatment [31,32].	In one RCT among HIV-infected individuals with incomplete CD4+ T cell recovery, valganciclovir significantly reduced CD8 activation in comparison to placebo [43].	In an animal RCT study, antiviral treatment is effective in inhibiting pro-inflammatory responses and the development of pulmonary fibrosis [78]. Suggestive finding in human RCT that antiviral treatment may reduce mechanical ventilation by reducing CMV reactivation that can endorse pulmonary inflammation [68].	Low-quality evidence of potential benefit of antiviral treatment to reduce ulcerative colitis progression requiring colectomy in patients with steroid-refractory ulcerative colitis [87].
Immunosuppressive effects	In RCTs, the antiviral treatment arms have lower incidences of secondary bacterial and/or fungal infections in comparison to the placebo arms [31,34].	In observational studies, CMV infection in the absence of end-organ disease is associated with accelerated development of AIDS, but analyses not adjusted for potential confounders [40,44].	Two observational studies showing more opportunistic bacterial and fungal infections in patients with CMV reactivation in comparison to no reactivation, but analyses not adjusted for potential confounders [62,67].	One observational study showing more bacterial and fungal infections in patients with CMV reactivation, but analysis not adjusted for potential confounders [91].

Abbreviations: CMV, cytomegalovirus; HCT, hematopoietic stem cell transplantation; HIV, human immunodeficiency virus; ICU, intensive care unit; RCT, randomised controlled trial; SOT, solid organ transplantation.

pneumonitis) occurs in 8%, 29%, 25%, 50%, 22%, and 39% of kidney, liver, heart, pancreas/kidney-pancreas, human small bowel, and heart-lung transplantation recipients, respectively [26].

CMV gastrointestinal tract involvement in immunocompromised patients usually presents with gastroenteritis. Endoscopy may show macroscopically apparent mucosal inflammation, erosion, and/or bleeding at any location throughout the gastrointestinal tract. CMV infection is one of the possible causes of clinically manifest gastrointestinal disease in HCT recipients, particularly in those with graft-vs.-host disease [4,27].

CMV involvement in other organ systems is rare, and may include hepatitis, pancreatitis, myocarditis, nephritis, retinitis, encephalitis, peripheral neuropathy, and polyradiculoneuritis [1,28].

Allograft rejection may be triggered by the indirect effects of CMV infection [13]. CMV infection can upregulate adhesion molecules on vascular endothelial cells and involve their ligands on leucocytes, which may facilitate a host immune response against both the allograft and CMV, resulting in the recruitment of inflammatory effectors such as chemokines and cytokines [29,30]. Moreover, an increased expression of MHC class II on multiple cell types also contributes to graft rejection, because recognition of nonself MHC antigens is the major determinant of allograft rejection [29]. In patients with SOT, the incidence of biopsy-confirmed acute graft rejections after renal transplantation was significantly reduced by valaciclovir in the CMV seropositive donor and CMV seronegative recipient subgroup of patients in an RCT [31], and valganciclovir improved graft function in patients with CMV-associated late-acute rejection [32]. Atherosclerosis in heart transplantation patients, which is believed to be the consequence of inflammation and monocyte activation, could also be reduced by prophylactic ganciclovir administration post transplantation [33].

In addition to pro-inflammatory effects, CMV infection may render the patient susceptible to bacterial and fungal pathogens, as demonstrated by higher rates of opportunistic infections in the placebo group compared to the antiviral treatment group in several RCTs [31,34]. However, it should be noted that opposite the potential benefits of preventing CMV reactivation, longer courses of (val)ganciclovir treatment may pose a risk of bone marrow suppression, rendering the patient yet more susceptible to infections by opportunistic pathogens [35].

CMV infection in HIV patients

CMV disease once was one of the most frequent opportunistic infections associated with HIV, occurring in 20% to 40% of patients with the acquired immune deficiency syndrome (AIDS) during the 1980s and early 1990s [36]. CMV seropositive patients with CD4 counts less than 50 cells per microliter were at the highest risk. Retinitis was the most common manifestation of CMV-related end-organ disease in these patients [37], which might be related to damage to the blood-retina barrier due to HIV, facilitating viral access to the eye [38,39]. However, the incidence of CMV disease has declined tremendously since the introduction of highly active antiretroviral therapy (HAART), which suppresses HIV replication and restores immunity [40]. Among those patients with profound immunodeficiency despite HAART, the continued use of HAART and systemic anti-CMV treatment reduces the risk of mortality by 65% [38]. Systemic anti-CMV treatment is independently associated

Table 3
Overview of studies on CMV reactivation in previously immunocompetent critically ill patients

Reference (y)	ICU patient population	Detection method: incidence	Mortality (CMV reactivation vs. no reactivation)	Associated other outcomes
A. Observational studies in patients with unknown CMV serostatus				
Jaber et al. (2005) [45]	237 patients with fever >72 hours without proven bacterial or fungal infection	pp65 in blood: 17%	Unknown [a]	Increased mechanical ventilation duration, ICU length of stay, and number of infections
Ziemann et al. (2008) [46]	99 patients with ICU length of stay >14 d	PCR in plasma: 35%	29% vs. 11% ($p < 0.05$)	Increased ICU length of stay
Chiche et al. (2009) [57]	242 patients with >2 d of mechanical ventilation	pp65 in blood and viral culture in lower respiratory tract: 19%	54% vs. 37% ($p = 0.08$) [b]	Increased mechanical ventilation duration, and bacterial infections
Bordes et al. (2011) [60]	29 severe burn patients	PCR in plasma: 71%	20% vs. 33% ($p = 0.59$)	Increased mechanical ventilation duration, and ICU length of stay
Coisel et al. (2012) [61]	93 patients with suspected pneumonia	pp65 in blood, PCR in lower respiratory tract: 24%	Unknown [a]	Increased mechanical ventilation duration
Walton et al. (2014) [62]	560 patients with sepsis	PCR in plasma: 24%	Unknown [c]	Increased ICU length of stay, and numbers of fungal infections
Roa et al. (2015) [63]	150 critical heart surgery patients with ICU length of stay >3 d	PCR in plasma: 17%	Adjusted OR 12.1 (95% CI, 2.3–64) [d]	N.A.
B. Observational studies in CMV seropositive patients				
Kutza et al. (1998) [64]	34 patients with sepsis	pp65 and PCR in blood: 32%	NA	NA
Heininger et al. (2001) [65]	56 patients with 'simplified acute physiology score' >40	PCR and viral culture in plasma and lower respiratory tract: 36%	55% vs. 36% ($p = 0.17$)	Increased ICU length of stay
Von Müller et al. (2006) [66]	25 patients with septic shock and ICU length of stay >7 d	pp65 in blood: 32%	63% vs. 33% ($p > 0.05$)	Increased mechanical ventilation duration, and ICU length of stay
Limaye et al. (2008) [47]	120 patients	PCR in plasma: 33%	Adjusted OR 4.3 (95% CI, 1.6–11.9) [a]	NA
Chilet et al. (2010) [48]	53 patients with ICU length of stay >5 d	PCR in plasma and lower respiratory tract: 39%	61% vs. 46% ($p = 0.40$)	Increased ICU length of stay
Heininger et al. (2011) [49]	86 patients with severe sepsis	PCR in plasma and lower respiratory tract: 41%	Adjusted HR 0.5 (95% CI, 0.2–1.2)	Increased mechanical ventilation duration, and ICU length of stay
Chiche et al. (2012) [50]	82 patients	pp65 in blood: 27%	40% vs. 13% ($p = 0.21$)	Increased mechanical ventilation duration, and ICU length of stay
Bravo et al. (2014) [51]	78 patients	PCR in plasma, lower respiratory tract or saliva: 46%	55.6% vs. 35.7% ($p = 0.11$)	Increased mechanical ventilation duration, and ICU length of stay
Frantzeskaki et al. (2015) [52]	80 patients	PCR in plasma: 14%	45% vs. 27% ($p > 0.05$)	Increased organ failure
Roa et al. (2015) [53]	115 patients	PCR in plasma: 34%	Adjusted OR 6.5 (95% CI, 1.7–24.7) [a] when co-reactivation with HHV-6	NA
Osawa et al. (2016) [54]	100 patients with at least one positive blood culture	PCR in plasma: 20%	Adjusted OR 1.6 (95% CI, 0.4–6.0) [b]	Increased mechanical ventilation duration, and ICU length of stay
Ong et al. (2016) [55]	271 patients with ARDS and mechanical ventilation >4 d	PCR in plasma: 27%	Adjusted SHR 2.5 (95% CI, 1.3–4.7)	Increased mechanical ventilation duration, and ICU length of stay
Ong et al. (2017) [56]	214 patients with septic shock	PCR in plasma: 27%	Adjusted SHR 3.2 (95% CI, 1.4–7.1) when co-reactivation with EBV	NA
Hraiech et al. (2019) [58]	123 patients with severe ARDS requiring extracorporeal membrane oxygenation	PCR in blood and lower respiratory tract: 22%	71% vs. 59% [b] (non-significant)	Increased mechanical ventilation duration
Zhang et al. (2021) [59]	71 patients with mechanical ventilation	PCR in plasma: 18%	90-d all-cause mortality 69% vs. 19% ($p < 0.01$)	Increased mechanical ventilation duration, and ICU length of stay
C. Observational studies in COVID-19 patients				
Naendrup et al. (2021) [71]	117 patients with severe COVID-19	PCR in whole blood: 9%	50% vs. 50% [b]	NA
Simonnet et al. (2021) [72]	34 patients with COVID-19	PCR in whole blood: 15%	20% vs. 17% [b]	27 d vs. 12 d ($p = 0.11$)
Niitsu et al. (2021) [73]	26 patients with COVID-19 and mechanical ventilation >1 wk	pp65 in blood: 23%	33% vs. 0%	Increased mechanical ventilation duration, and bacterial/fungal infections
D. Randomised controlled trials in CMV seropositive patients				
Limaye et al., 2017 [68]	156 patients with sepsis, trauma or ARDS	PCR in plasma: 12% in (val) ganciclovir vs. 39% in placebo group ($p < 0.001$) [as prophylaxis]	More ventilator-free days in (val) ganciclovir group	No significant change in IL-6 from day 1 to day 14; no difference in adverse effects between ganciclovir vs. placebo

Table 3 (*continued*)

Reference (y)	ICU patient population	Detection method: incidence	Mortality (CMV reactivation vs. no reactivation)	Associated other outcomes
Cowley et al., 2017 [69]	124 patients who are mechanically ventilated >1 d	PCR in blood: 6% in valacyclovir vs. 3% in valganciclovir vs. 35% in placebo ($p < 0.001$) (as prophylaxis)	Not powered to assess clinical endpoints	Effective suppression of CMV reactivation by valganciclovir and valacyclovir; no difference in adverse effects between valganciclovir vs. placebo
Papazian et al., 2021 [70]	76 patients with CMV reactivation who are mechanically ventilated >4 d	Ganciclovir vs placebo (as pre-emptive treatment)	Study prematurely terminated because of low inclusion rate; not powered to assess clinical endpoints	No difference in adverse effects between ganciclovir vs. placebo

Overview of studies on CMV reactivation as detected by PCR or pp65.
Abbreviations: ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HR, hazard ratio; ICU, intensive care unit; NA, not available; SHR, subdistribution hazard ratio.
[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 was prolonged hospital length of stay or mortality.

with a 28% lower mortality rate in patients with AIDS and CMV retinitis after adjustment for confounding by HAART and other variables [38]. Multiple RCTs have demonstrated that systemic anti-CMV treatment effectively reduced mortality and progression of CMV retinitis [40].

Although ganciclovir prophylaxis is effective for preventing CMV retinitis in patients with HIV, this strategy is usually considered too toxic relative to its potential benefit [9]. Because of the much lower rate of retinitis cases following HAART [40], CMV prophylaxis is now considered redundant. However, in contrast to primary prophylaxis, maintenance therapy (i.e., dose-reduced secondary prophylaxis) following initial high-dose induction treatment for CMV retinitis is still recommended until immune reconstitution has been achieved or discontinuation is inevitable because of the side effects [9,10]. Furthermore, unless full immune recovery has been established, CMV relapse may occur after discontinuation of anti-CMV therapy. Nevertheless, it is important to consider that prolonged treatment may increase the risk of the development of resistant CMV strains [36].

Gastrointestinal disease is the second most frequent manifestation of CMV disease [36]. In particular, HIV patients may present with symptoms of odynophagia or dysphagia that often are initially ascribed to Candida esophagitis but later appear to be related to CMV esophagitis. The colon is the most affected part of the lower gastrointestinal tract. Accompanying symptoms may include diarrhoea, gastrointestinal bleeding, abdominal pain and fever, while during coloscopy a wide spectrum of findings can be observed, ranging from no visibly apparent colitis to deep ulcers. CMV adrenalitis has also been reported in up to 84% of autopsies performed on patients with AIDS and CMV infection [41]. However, the reason behind the observed tropism of the adrenal gland remains unknown. CMV disease manifestations in other organs, such as hepatitis, encephalitis, and polyradiculoneuritis are rare in HIV patients [37].

Moreover, in patients without CMV end-organ disease, detection of CMV in blood by PCR was associated with death also after correction for CD4 count and HIV load in multivariable models, which could point towards indirect effects caused by CMV infection [42]. In a small RCT including HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral treatment, valganciclovir-treated patients had significantly greater reductions in CD8 activation in comparison to placebo-treated patients during 3 months of follow-up [43]. This suggests that CMV replication causes significant immune activation. Although a clear understanding regarding the effect of CMV on AIDS progression is lacking, observational studies showed that CMV infection in the absence of end-organ disease was also associated with accelerated development of AIDS [40,44]. However, pre-emptive treatment of asymptomatic CMV viremia in patients receiving HAART has not been studied in RCTs.

CMV infection in critically ill patients

Risk factors for CMV reactivation in critically ill patients include the presence of severe sepsis, burn injuries, and the acute respiratory distress syndrome (ARDS) [45–66]. Before the coronavirus disease 2019 (COVID-19) pandemic, the observed incidence of CMV reactivation in blood varied between 14% to 46% after 1 to 2 weeks in the ICU among CMV seropositive patients without known prior immune impairments (Table 3). Many observational studies have shown an association between CMV viremia and an increased risk of mortality in these patients, which remained after controlling for possible confounding covariables [47,53,55,56,63]. In the largest study to date, complex statistical models were used to calculate the attributable mortality associated with CMV viremia [55]. It was estimated that mortality caused by CMV reactivation is approximately 4.4% by day 30 in ARDS patients who are mechanically ventilated for $\geq$4 days in the ICU [55]. In another study in patients with septic shock, concurrent CMV and Epstein-Barr virus reactivation also remained independently associated with increased mortality, even after elaborate adjustment for confounders, time-dependent bias, and competing risks [56]. Furthermore, patients with sepsis and other critical illnesses who experience systemic CMV reactivation are more likely to develop secondary bacterial and fungal infections [62,67]. However, the causality between CMV reactivation and the development of these opportunistic infections remains to be proven.

In contrast to transplant recipients, prophylaxis and pre-emptive antiviral treatment are not part of standard practice in the ICU. However, two phase II trials testing (val)ganciclovir prophylaxis in critically ill patients showed that this drug was highly effective in preventing CMV reactivation in blood, without causing adverse effects, including the development of neutropenia [68,69]. Furthermore, an increased number of ventilator-free days was observed in patients receiving ganciclovir in one of these trials [68], lending support to the hypothesis that prevention of CMV reactivation could mitigate a pro-inflammatory reaction in the lungs. Unfortunately, both trials were underpowered to assess differences in mortality between treated and untreated patients. A third RCT tested a pre-emptive ganciclovir strategy in patients with at least four days of mechanical ventilation who developed CMV

reactivation in whole blood during ICU stay [70]. Unfortunately, this study was stopped prematurely because of low enrolment rates, eventually including no more than 39 patients receiving ganciclovir vs. 37 receiving placebos. The resulting lack of statistical power precludes any recommendation in favour of or against the pre-emptive use of ganciclovir.

During the recent pandemic, CMV reactivation has been reported in 9% to 23% of critically ill patients with COVID-19 in three small observational studies [71–73]. The majority of these subjects were subsequently treated with ganciclovir. Across these three studies, observed mortality was 19% (3 out of 16) in patients receiving ganciclovir vs. 100% (6 patients) among those on no antiviral treatment. However, this finding should be carefully interpreted as these studies were small and highly prone to bias/confounding.

Evidence for direct cytopathologic effects of CMV infection that occurs because of critical illness-induced immunosuppression is scarce. A study evaluating the diagnostic yield of open lung biopsy in a highly-selected subgroup of severe ARDS patients, who did not show clinical improvement for at least four days despite negative microbiologic cultures, reported histological proof of CMV-induced cytopathology (i.e., owl's eyes) in 30 of 100 cases [74]. Furthermore, several histology-proven cases of CMV colitis have been reported among critically ill patients who were not previously immunocompromised [75–77]. Gastrointestinal bleeding and diarrhoea were the most frequently observed clinical manifestations in these patients, although most had severe other infections and/or shock, which could alternatively have caused these symptoms.

Experimental evidence for pro-inflammatory effects of CMV reactivation is primarily derived from animal models mimicking critical illness. For example, in a murine ARDS model, an exacerbated and prolonged cytokine and chemokine expression was observed in pulmonary tissue of animals with CMV infection compared to controls without CMV reactivation, which subsequently resulted in increased pulmonary fibrosis [78]. In those with CMV reactivation, prophylactic use of ganciclovir was effective in preventing these effects when compared to animals receiving placebo. In humans, the effects of viral reactivation on pro-inflammatory and anti-inflammatory cytokine responses have been investigated in a matched cohort study, showing increased IP-10 and decreased IL-1RA plasma concentrations on days 3, 7, and 10 after first CMV detection in patients with sepsis [79]. However, because of limited statistical power, these effects could not be assessed with certainty.

CMV infection in patients receiving immunosuppressive therapy for (chronic) diseases

Patients receiving immunosuppressive therapy for (chronic) diseases could also be considered immunocompromised. In contrast to HCT patients, CMV reactivation in patients with haematological malignancies who are treated with immune- and/or chemotherapy or received autologous transplantation has not been extensively studied [80]. Lower rates of CMV diseases were observed in these patients, while short-term mortality rates are relatively high because of the underlying haematological diseases. However, patients receiving high-dose steroids, irradiation, purine analogues (e.g., fludarabine), alemtuzumab, or phosphoinositide 3-kinases inhibitors (e.g., idelalisib) are at an increased risk of developing CMV infection [80]. Cases of CMV retinitis have been reported in 4% of patients who received combination therapy of rituximab and fludarabine in comparison to 0% of those who received only rituximab [81]. The risk for CMV reactivation was ten times higher in patients who received alemtuzumab and chemotherapy for chronic lymphocytic leukemia in comparison to only chemotherapy [82]. Moreover, symptomatic CMV infections (i.e., symptoms and signs compatible with CMV infection but without (proven) end-organ involvement for which antiviral treatment was mostly started by the treating physician) occurred in 16% of patients who received alemtuzumab compared to 0% in those who received chlorambucil [83]. As idelalisib treatment is associated with an increased risk of CMV reactivation, monitoring for CMV infection is recommended during the course of therapy among CMV-seropositive patients or in the presence of clinically suspected CMV disease [84]. Bortezomib, a proteasome inhibitor, was associated with CMV reactivation at an incidence of 8% in autologous stem cell transplantation patients with multiple myeloma as compared to 1% in those who received vincristine, doxorubicin, and dexamethasone [85].

Moreover, the availability of many biological agents has led to significant improvement in the treatment of chronic immune-mediated diseases, such as chronic inflammatory bowel diseases (IBD), rheumatic diseases, and multiple sclerosis. However, the use of these agents might also increase the risk of CMV reactivation, especially when therapy affects T cell responses.

In one observational study, CMV reactivation could be detected in 30% of patients with steroid-refractory ulcerative colitis [86]. According to a meta-analysis, antiviral treatment seems beneficial by reducing the need for colectomy for this specific patient population, although findings were derived from low-quality observational studies because of the lack of RCTs that evaluated antiviral treatment [87]. The use of corticosteroids or thiopurines was associated with an increased risk of CMV reactivation in IBD patients, whereas tumor necrosis factor (TNF)-α antagonists, such as infliximab, were not associated [88]. Disseminated CMV infection occurred rarely in patients with Crohn's disease who received TNF-α antagonists [89]. The exact role of CMV in exacerbations of IBD is uncertain and the clinical significance of a positive CMV by PCR in the bowel in the absence of supportive histology or immunohistochemistry remains to be further unravelled [90].

In a retrospective cohort study, CMV reactivation was reported in 40% of patients with rheumatic diseases who received glucocorticoids or an increase in dosage for new-onset or relapsed rheumatic diseases [91]. Although higher mortality and more bacterial and fungal infections were observed in these patients with CMV reactivation, it remains to be determined whether CMV reactivation is directly associated with increased mortality or is merely a surrogate marker of overall immunosuppression. In patients with multiple sclerosis, CMV reactivation occurred in 51% of those receiving the anti-CD52 monoclonal antibody, alemtuzumab, in comparison to only 6% of those receiving the anti-CD20 agents, ocrelizumab or rituximab [92].

Comparison between different patient groups

Direct cytopathological effects of CMV reactivation, as evidenced by end-organ disease in transplant recipients or patients with AIDS during the pre-HAART era, are only occasionally observed in patients with critical illness or medication-induced immunosuppression. This difference could be related to the shorter duration of immune impairment during critical illness or the lower intensity of immune impairment caused by chronic medication use that occurs in the latter groups, respectively. Indeed, overt CMV disease is usually not observed until weeks to months after HCT or SOT [28,39], whereas the length of stay in an ICU is typically much shorter.

Documentation of CMV invasion of tissues in the affected organs is required to establish a definite diagnosis of CMV end-organ disease. Yet, in clinical practice, biopsies to obtain histopathological evidence are infrequently performed. CMV viremia, as determined

by PCR testing of blood, usually precedes end-organ disease [13]. The viral load has thus been used as a surrogate endpoint in clinical studies and as a biomarker for the development of CMV disease [93]. Of note, HCT recipients may develop end-organ disease at lower viral loads as compared to SOT recipients [39]. Furthermore, two studies showed that high peak CMV viremia in HCT recipients is significantly associated with decreased overall survival [94,95]. However, it remains to be established what thresholds of viral load in plasma can be used to distinguish between clinically important infection and mere reactivation, and how viral loads in plasma and the respiratory tract are correlated with each other. Among HCT recipients, one study suggested that a CMV DNA load threshold of 500 IU/mL in bronchoalveolar lavage fluid provided good positive and negative predictive values for CMV pneumonitis [96]. Another study showed that a CMV DNA load below 1210 IU/mL in bronchoalveolar lavage fluid samples unlikely reflects CMV pneumonitis, whereas the detection of >500 IU/mL was independently associated with pneumonia-attributable mortality in HCT recipients with clinical and radiological signs of pneumonia (i.e., bacterial, viral, fungal, mixed) [97]. Certain thresholds also appear to exist for lung transplant recipients, in which high viral loads in bronchoalveolar lavage fluid were strongly associated with clinically apparent pneumonitis [98,99]. Nevertheless, it remains challenging to standardise bronchoalveolar lavage fluid sampling, as well as to differentiate between true CMV pneumonitis and mere pulmonary CMV DNA shedding. Observed viral loads in critically ill patients are generally lower than have been reported in transplant recipients. During the first 2 weeks following ICU admission, CMV loads in plasma mostly remain below 1000 IU/mL, with levels exceeding 1000 IU/mL not occurring until after 4 weeks [55]. The harmful effects of CMV infection in critically ill patients are thus presumably more limited. However, it should be noted that general awareness of CMV disease in critically ill patients is much lower than in transplant recipients and that many cases may thus remain undiagnosed. Because of the complex nature of the ICU environment and the multifactorial aetiology of critical illness, it is quite easy to erroneously attribute incompletely understood clinical deterioration to a multitude of other causes.

The indirect effects of CMV are important to consider as well in addition to tissue-invasive disease. CMV infection may trigger various immunomodulatory responses, including pro-inflammatory effects characterised by increased levels of acute phase proteins and type 1 cytokines, such as interleukin-18, interferon-inducible protein-10, and interferon-gamma [100]. Furthermore, during CMV pneumonitis, the detrimental effects are not only ascribed to lytic infection but also to an immunopathologic reaction [1,22,101]. A first hypothesis is that the presence of CD4+ T lymphocytes is crucial in this response, which could explain why CMV pneumonitis occurs only rarely in patients with HIV infection having low CD4+ counts, as there is a lack of adequate T cell responses to drive inflammation [22]. Another hypothesis suggests that the pathogenesis of CMV pneumonitis is based on uncontrolled viral replication in the lungs due to inadequate numbers of CD8+ cells, allowing the local release of several pro-inflammatory mediators such as TNF-α [101]. Although neither hypothesis has been robustly verified, it is likely that lung damage is caused by a combination of direct lytic infection and amplified pro-inflammatory response.

The immunomodulating effects of CMV and the ability to evade the immune system are not surprising [39]. CMV-specific T cells account for 10% of total CD4+ and CD8+ T cells in CMV seropositive adults, which far exceeds other pathogen-specific T cells [102]. Similarly, CMV also modulates the expansion and differentiation of adaptive subsets of NK cells [103]. In healthy monozygotic twins who were discordant regarding their CMV serostatus, more than half of immunological parameters, such as effector CD8+ and γδ T cells, were different [104]. The ability of CMV to modulate immunity is also supported by the observation of increased mortality and morbidity in patients with viremia but without organ manifestation of CMV disease [105,106].

Impaired T cell immunity can increase the likelihood of CMV reactivation and its subsequent immunological effects. If the immune system cannot sufficiently control CMV replication, CMV disease may eventually develop even in less severely immunocompromised patients. Nevertheless, not all immunocompromised patients are homogenous, and a more adequate risk stratification is needed for the prediction of CMV infections in patients that could benefit the most from frequent CMV surveillance and subsequent antiviral treatment to avoid serious clinical outcomes.

Conclusions and future implications

CMV infection may exert detrimental effects through a combination of cytolytic, pro-inflammatory, and immunosuppressive mechanisms. This notion is most strongly supported by data from patients who are prolonged and severely immunocompromised, such as occur after HCT or SOT. Antiviral therapy directed to CMV infection has proven to be effective in reducing end-organ disease and mortality in these subjects. Similarly, in patients with AIDS, systemic antiviral treatment of CMV retinitis is effective in reducing the progression of organ disease and mortality. There is also data derived from a large number of clinical and experimental studies suggesting there is attributable mortality related to CMV reactivation in critically ill patients who were previously immunocompetent. Three RCTs testing antiviral prophylaxis and/or pre-emptive treatment suggest that (val)ganciclovir use in critically ill patients is both safe and effective in preventing CMV reactivation and the possible effect of antiviral treatment in reducing the duration of mechanical ventilation. However, much larger RCTs are necessary to assess the effect of antiviral treatment on relevant patient-centred endpoints. Considering the evidence, pre-emptive antiviral treatment in ICU patients with CMV reactivation should currently be considered only in specific situations, such as cases of prolonged respiratory failure without obvious (other) etiological cause. Furthermore, patients with steroid-refractory ulcerative colitis or patients receiving particular biological agents, including fludarabine, alemtuzumab, idelalisib, or bortezomib, may be at increased risk for CMV infections. Large prospective observational studies investigating the incidence of CMV infections and RCTs addressing the effect of antiviral therapy in these specific patient populations are needed.

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The authors have nothing to disclose.

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