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Cytomegalovirus reactivation in ICU patients

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Abstract *Introduction:* Approximately 20 years have passed since we reported our results of histologically proven cytomegalovirus (CMV) pneumonia in non-immunocompromised ICU patients. Even if there are more recent reports suggesting that CMV may worsen the outcomes for ICU patients, there is no definite answer to this question: is CMV a potential pathogen for ICU patients or is it simply a bystander? *Methods:* We will describe the pathophysiology of active CMV infection and the most recent insights concerning the epidemiological aspects of these reactivations. *Major findings:* Cytomegalovirus can be pathogenic by a direct organ insult (such as for the lung), by decreasing host defences against other microorganisms and/or by enhancing the body's inflammatory response (as in acute respiratory distress syndrome). The incidence of active CMV infection is dependent on the diagnostic method used. Using the most sophisticated available biological tools, the incidence can reach 15–20 % of ICU patients (20–40 % in ICU patients with positive CMV serology). In adequately powered cohorts of patients, active CMV infection appears to be associated with worse outcomes for mechanically ventilated ICU patients. *Discussion:* There is no absolute direct proof of a negative impact of active CMV infection on the health outcomes of mechanically ventilated patients. Prospective randomized trials are lacking. Future trials should examine the potential benefits for health outcomes of using antiviral treatments. Such treatments could be prophylactic, pre-emptive or used only when there is an end-organ disease. *Conclusion:* Cytomegalovirus infection may affect health outcomes for ICU patients. Additional prospective trials are necessary to confirm this hypothesis.

Keywords Cytomegalovirus · ICU ·
Mechanical ventilation · Mortality ·
Incidence · Reactivation

Introduction

Primary infection due to cytomegalovirus (CMV) is generally asymptomatic or characterized by the presence of non-specific signs and symptoms. Previous infection is confirmed by the presence of CMV-specific IgG responses. Approximately 60–80 % of immunocompetent adults are human CMV seropositive [1, 2]. Following primary

infection, CMV remains quiescent in monocytes and macrophages in multiple organs, a state defined as latency. As with other herpesviridae, this harbouring of latent CMV makes this affected population at risk for reactivation, especially during critical illness. Primary infection or reinfection with a different strain of CMV during the ICU stay is theoretically possible (blood products) but is unlikely due to leucoreduction processes. While the potential for CMV reactivation in ICU patients is now acknowledged, much controversy remains over its pathogenicity. Indeed, CMV could be pathogenic or simply an associated sign reflecting the severity of underlying disease.

Several mechanisms have been proposed to explain how CMV reactivation could cause injury. The first is a direct cytopathologic effect from the reactivated virus injuring organs that harboured the virus such as during CMV pneumonia [3–5]. The second mechanism is an immunopathological effect, in which damage to tissues is caused by the excessive immune response to the virus such as that hypothesised in ARDS patients [6]. The third mechanism is related to an alteration of patients' immune defences, rendering them more susceptible to fungal and bacterial infections [7–10]. However, CMV reactivation could only be an indicator of immune compromise and illness severity not necessitating diagnostic procedures and treatment.

Why we did this study

As with many things in medicine, our story began with an unexpected observation, which occurred during the controversy between intensive care practitioners who maintained the use of a protected specimen brush (PSB) for the diagnosis of bacteriological ventilator-associated pneumonia (VAP) and those who preferred the use of tracheal aspirates (TA) (as we did). This was the reason why we designed a study evaluating the diagnostic performance of several microbiological sampling techniques such as PSB, bronchoalveolar lavage (BAL), TA and protected telescopic catheter for the diagnosis of VAP [11]. The gold standard was lung histology and lung culture following pneumonectomy. Our work has had two major consequences. First, our surgical colleagues became convinced that performing an open-lung biopsy (OLB) was feasible at the bedside, in the ICU, in mechanically ventilated patients. It was why we started to perform OLBs at the bedside [5]. The second consequence was that our pathologist colleagues reported that in some instances they did not identify any sign of bacterial pneumonia but found typical signs of CMV pneumonia that were confirmed using specific immunological markers. After a dubitative period, we decided to

extend the use of OLBs, especially with the aim to identify authentic histological CMV pneumonia [4].

Methods and major findings of our study

During a 5-year period, autopsies were performed in patients who died while they presented a clinical picture of VAP with negative microbiological cultures (BAL, PSB, TA). In some patients who had an unexplained worsening of their respiratory status while under invasive mechanical ventilation, an OLB was performed. Immunocompromised patients were excluded from the study. We defined ventilator-associated CMV pneumonia as the association of a mechanical ventilation duration exceeding 7 days with the presence of histopathological signs of CMV pneumonia (e.g., identification of large cells with large nuclei containing a basophilic or eosinophilic inclusion surrounded by a light halo). Sixty autopsies and 26 OLBs were performed during the study period. On the basis of our criteria, 25 cases of CMV pneumonia were identified during this 5-year period (17 autopsies, 8 OLB). Histological studies were done 10–40 days following ICU admission. Interestingly, no bacteria were identified by lung cultures in 88 % of the cases ($n = 22$), with CMV being the sole identified pathogen.

Shell-vial cultures (done on BAL, blood and urine samples) were performed prior to histologies in some patients. Their sensitivity was poor, however, and failed to exceed approximately 50 %. This was before the antigenaemia and PCR era.

Concerning the reason for ICU admission, only 6 of the 25 patients were admitted following surgery for a cancer diagnosis. Four patients were admitted following a scheduled cardiac or vascular surgery, and the three remaining surgical patients had an emergent surgery for a peritonitis. Regarding the medical causes for ICU admission, five COPD patients were admitted for acute respiratory failure. A neurological cause was observed in five patients. The remaining two medical patients presented with myocarditis for the first one and with pulmonary embolism for the second one. Interestingly, 19 of these 25 patients received blood products prior to histology. At the time, leucodepletion of blood products was not as efficient as it is today, so primary infection was possible in some cases. Indeed, 5 of the 18 patients tested were IgG negative for CMV. Moreover, the potential immunomodulatory effects of a blood transfusion could have favoured CMV reactivation. This is still a matter of debate and a potential area of investigation.

The clinical pictures of these patients were diverse. Our ICU patients presented a febrile ARDS picture with a degree of hepatic dysfunction in 10 patients, an elevated

creatininaemia in 10 patients and mononucleosis in only three patients. Evidence of CMV infection of the retina was never found, and in only one case did a colonic biopsy reveal histologic hallmarks of CMV infection.

We concluded by asking an important question: Is CMV infection of the lung a clinically significant process justifying specific antiviral therapy? Approximately 20 years later, the debate remains open. We will try to depict the main advances regarding the comprehension of the mechanisms and consequences of CMV reactivation in ICU patients for the last 20 years.

Pathophysiology of CMV infection

Because many studies have reported an association between the presence of sepsis and CMV infection [12–15], some investigations have been conducted to elucidate the possible mechanisms of this association. Tumour necrosis factor (TNF) is probably involved in CMV reactivation after sepsis from a bacterial origin [13, 16]. It has been shown that TNF-α is able to directly stimulate immediate early (IE) CMV gene expression [17]. However, no clear relationship has been discovered between the severity scores recorded at admission and the risk of developing CMV infection, nor regarding production of TNF-α plasma levels and the risk of CMV reactivation. Other mechanisms might be involved in CMV reactivation. A certain degree of immune deficiency, for instance, has been reported in critically ill patients early during the ICU stay as a result of the underlying disease and/or the treatment [18, 19]. During this period, one's immune function against infection may be impaired. Studies of severely immunocompromised patients have suggested that T cell immunity is crucial in the control of CMV replication [20]. In a group of 31 CMV-seropositive non-immunosuppressed surgical and trauma ICU patients, the enumeration of CMV pp65 and immediate-early (IE)-1-specific interferon (IFN)-γ CD8$^+$ and CD4$^+$ T cells was performed by flow cytometry for intracellular cytokine staining [21]. The levels of these cells in peripheral blood have been shown to correlate with protection from active CMV infection. In that study, active CMV infection occurred in 17 out of 31 patients. Undetectable levels of pp65 and IE-1-specific IFN-γ CD8$^+$ and CD4$^+$ T cell subsets were observed in 10 patients who developed active CMV infection and in one who did not (at a median of 2 days following ICU admission). Peak CMV DNA loads in both TA and plasma were substantially higher in patients with undetectable IFN-γ T cell responses than in patients with detectable responses [21]. Taken together, these data suggest that T cell response might be involved in at least some CMV reactivation. However, in another study using different immunological methods, active

CMV infection was reported in septic shock patients despite detectable levels of CMV-specific IFN-γ-producing CD4+ T cell precursors in blood, suggesting that CMV reactivation is not primarily triggered by T cell immunosuppression [22]. CMV-specific T cell immunity (CD4+) was also conserved in most critically ill surgical/trauma patients experiencing CMV reactivation [23]. In animal models [24], natural killer (NK) cells may at least partially compensate for the absence of adaptive T cell immunity. There is also some evidence of the crucial role of NK cells in keeping herpesviruses latent in humans [25]. In a recent study done in ICU patients, the function of NK cells was altered regarding INF-γ production just before the occurrence of reactivation [26]. This latter result suggests that in the context of global and major lymphopenia observed in ICU patients, dysfunction in NK cells may be involved in CMV reactivation. It has also been recently shown in non-ICU patients that CMV infections are associated with a redistribution of NK cell subsets in the peripheral blood, with expansion of unconventional "memory" NKG2C+NK cells that exhibit impaired effector functions [27]. CMV is also involved in the impaired function of dendritic cells [28]. All of these factors could explain the increase in nosocomial infections observed in patients presenting with active CMV infection [7, 9]. Regarding the pro-inflammatory properties of CMV, it has been shown in a study of upmost importance [13] that CMV can enhance the progression of post-aggressive lung fibrosis. Indeed, using a mice model of caecal ligation and puncture, Cook et al. showed that CMV reactivation was associated with a dramatic increase in lung fibrosis [13]. In summary (Fig. 1), impaired immune defences encourage CMV replication. CMV might also alter immune defences against infections (favouring the occurrence of nosocomial infections in critically ill patients) and enhance
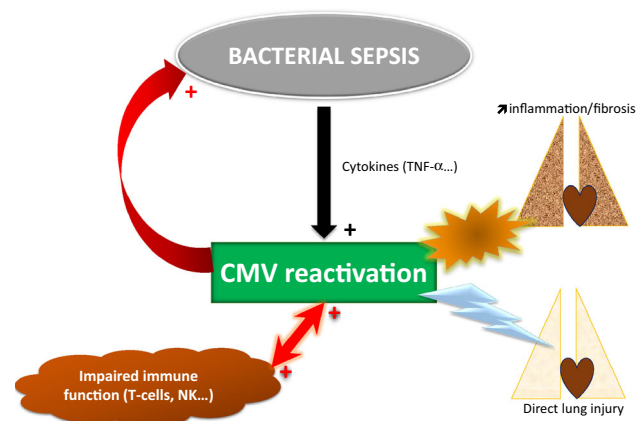

Fig. 1 Simplified representation of CMV reactivation physiopathology in ICU patients

compartmentalized pro-inflammatory responses (exacerbating lung inflammation).

Incidence, diagnosis and risk factors of CMV infection in non-immunocompromised ICU patients

The incidence of CMV infection in non-immunocompromised ICU patients has been assessed in many studies and reviewed in some meta-analyses [29–32]. The incidence is influenced by many factors including the types of patient populations studied and their serologic status on admission, as well as the microbiological tools used to diagnose CMV and the type (blood, TA) and frequencies of sampling. Studies including only seropositive patients have generally shown higher rates of reactivation (Table 1). This is illustrated by a major study involving only seropositive patients who presented with a large variety of critical illnesses such as sepsis, cardiac failure, burns and trauma [32]. These patients were monitored three times a week using quantitative plasma CMV PCR [32]. The authors reported that one-third of the patients presented with a positive viraemia. Twenty per cent of the patients had viraemia greater than 1000 copies/mL. Interestingly, the median time to the first detection of viraemia was 12 days, with a range of 3–57 days [32]. The duration of viraemia was quite long, reaching a median of 17 days (ranging from 2 to 45 days) [32]. Using antigenaemia for the diagnosis, our group reported that the incidence of CMV reactivation was 16.1 % in non-immunocompromised mechanically ventilated ICU patients from a medical ICU [7]. It has been suggested that CMV PCR, when performed on TA, is a more sensitive technique than when performed in blood samples [15]. In this latter study, it was shown that lung reactivation was observed earlier compared with reactivation in the blood (median 14 and 24 days, respectively). Compared with herpes simplex virus (HSV) reactivation, CMV reactivation in respiratory samples exhibits a lower incidence and occurred later in the course of the ICU stay [15]. Co-infections of HSV/CMV have also been reported in as high as 27 % of CMV reactivations in a recent study [29], but there is no information regarding the potential synergistic deleterious impact of this co-infection on outcomes. In a more recent investigation, 49 % of the patients with CMV reactivation also reactivated HHV-6 [33]. The impact on outcome was synergistic between the two viruses. Indeed, the patients with co-reactivation of both HHV-6 and CMV had the greatest risk for death or continued hospitalization by day 30.

The incidence of CMV reactivation is also dependent on the method of diagnosing CMV infection. Three methods have been used: viral cultures, antigenaemia, and PCR. Culture-based techniques (conventional and shell-vial cultures) are considered outmoded because they are time-consuming and lack sensitivity. The antigenaemia assay is a technique based on direct detection of the CMV protein pp65 using monoclonal antibodies. It is sensitive, specific and quantitative. However, this technique is more labour-intensive than the PCR assays, which are now extensively used given their high sensitivity and rapid turnover time. Many diagnostic kits from different manufacturers are commercially available and sometimes PCR is performed by the hospital laboratories. However, a World Health Organization international standard was recently adopted and this allows one to use a conversion factor for expressing the results in international units per millilitre (and not in copies per millilitre). This standardization allows one to adequately compare quantitative PCR when using different diagnostic kits. It is important to underline that no specific threshold for the diagnosis has been identified in either blood or respiratory samples from ICU patients.

Concerning CMV reactivation in ICU patients, there are no specific clinical signs. It is fundamental to highlight that the clinical picture is totally different from CMV infection in HIV patients. The lung is the major organ involved in active CMV infection with end-organ disease. However, there is no radiological specificity as shown in Fig. 2 [34]. Interstitial pneumonia is very uncommon. In some instances, a discrete cholestasis or cytolysis with increased levels of hepatic enzymes are observed. Colitis is rarely observed [35], and only a few cases of retinitis have been reported. Haemophagocytic syndrome can also be associated with CMV infection [36]. In this context, bone marrow examination is useful in establishing the diagnosis.

It is truly difficult to identify associated risk factors for developing CMV reactivation other than admission to an ICU and mechanical ventilation. Active CMV infections have been reported in medical and surgical patients as well as trauma patients. Age is not recognized as a risk factor, and any evidence of an association between CMV infection and gender has been inconsistent [37]. Sepsis, blood transfusions, corticosteroids and ARDS have also been found to be associated with the risk of CMV reactivation [7, 37]. Interestingly, severity scores on ICU admission or on inclusion are generally not recognized as being associated with the occurrence of CMV reactivation except in a meta-analysis of 13 studies [7, 15, 30, 32]. This lack of association between severity scores on ICU admission and CMV reactivation suggests that factors other than severity of the underlying disease and the number and extent of organ dysfunctions are major risk factors. More studies are needed to identify factors that could predict the risk of developing a CMV reactivation. Immunologic predisposition could be responsible for CMV reactivation and warrants further study in particular.

Table 1 Incidence, morbidity and mortality of CMV infection in non-immunocompromised ICU patients

Year/reference	ICU design	Inclusion criteria	Patients, no.	Virological diagnosis	Incidence of CMV infection, no. (%)	Morbidity end points assessed	Mortality CMV+/CMV−
1990 [41]	M-S retrospective	Mediastinis following cardiac surgery	115	Culture of blood and urine	29 (25)	H-LOS*	55 vs. 37 %
1996 [4]	M-S prospective	VAP without bacterial proven infection	86	Lung biopsy	25 (29)	NA	NA
1996 [42]	M-S prospective	Mechanical ventilation CMV seropositive	23	Culture and PCR in blood ± BAL	0 (0)	NA	NA
1998 [43]	S prospective	Sepsis	34	AG + PCR in blood twice a week	11 (32)	NA	64 vs. 74 %
1998 [44]	S retrospective	Sepsis without bacterial proven infection	142	Culture in blood ± tracheal secretions ± BAL	12 (8)	ICU-LOS	66 vs. 35 %*
2001 [45]	S prospective	SAPS II > 40, CMV seropositive	56	Culture and PCR in blood + tracheal secretions once a week	20 (35)	ICU-LOS*	55 vs. 36 %
2001 [46]	M-S prospective	±MODS	96	AG + PCR in blood	1 (1)	NA	NA
2002 [47]	M-S prospective	No specific criteria	120	PCR in blood	1 (1)	NA	NA
2003 [8]	S prospective	ICU-LOS ≥ 5 days	104	Culture in blood + tracheal secretions once a week	10 (10)	ICU-LOS*/DMV* NI*	50 vs. 27 %
2005 [9]	M-S retrospective	Fever > 72 h without proven infection	237	AG	40 (17)	ICU-LOS*/DMV*NI*	50 vs. 28 %*
2006 [48]	S prospective	Septic shock, ICU-LOS > 7 days	25	AG + culture in blood/tracheal secretions/urine twice a week for 1 week, then once a week	8 (32)	ICU-LOS*/DMV*NI*	63 vs. 35 %
2008 [32]	M-S-B prospective	TBSA > 40 %; sepsis; trauma ISS > 15; acute myocardial infarction	120	PCR in blood twice a week	39 (33)	Composite score of death or continued hospitalization by 30 days	
2008 [49]	S retrospective	ICU-LOS > 14 days	99	PCR in blood	35 (35)	ICU-LOS*	29 vs. 11 %*
2009 [7]	M prospective	Mechanical ventilation ≥ 2 days	242	AG ± BAL once a week	39 (16)	ICU-LOS*/DMV*NI*	54 vs. 37 %#
2011 [50]	B prospective	TBSA > 15 %	21	PCR in blood once to twice a week	15 (71)	ICU-LOS LVM	33 vs. 20 %
2011 [15]	M-S prospective	Severe sepsis	86	Culture of tracheal secretions + PCR in blood and tracheal secretions twice a week	35 (41)	H-LOS*/ICU-LOS*/DMV*	37 vs. 35 %
2012 [29]	M prospective	Suspicion of pneumonia	93	AG + PCR in blood + BAL	22 (24)	ICU-LOS*NI	55 vs. 20 %*
2014 [10]	M-S prospective	Sepsis	356	PCR in blood 2 to 3/week	86 (24)	ICU-LOS*NI*	day 90*
2015 [51]	M-S prospective	Mechanical ventilation, CMV seropositive	80	PCR in blood once a week	11 (14)	ICU-LOS NI	45 vs. 27 %
2015 [39]	M-S prospective	ARDS and MV > 4 days	306	PCR in blood once a week	53 (17)	NA	NA
2015 [33]	M-S prospective	CMV seropositive	115	PCR in blood twice a week	39 (34)	NA	NA

AG antigenaemia pp65, *BAL* bronchoalveolar lavage, *B* burns, *H-LOS* hospital length of stay, *ICU* intensive care unit, *ICU-LOS* ICU length of stay, *ISS* injury severity score, *DMV* duration of mechanical ventilation, *M* medical, *MODS* multiple organ dysfunction syndrome, *NA* not available, *NI* nosocomial infections, *S* surgical, *SAPS II* simplified acute physiology score II, *TBSA* total burn surface area, *VAP* ventilator-associated pneumonia

* Statistically significant (*p* < 0.05)

Not statistically significant but some CMV seropositive patients had received antiviral treatment

Impact of CMV infection on the outcome of ICU patients

The impact of CMV infection is a matter of continuing debate. Indeed, there has been no clear demonstration of a definite relationship between the development of CMV infection and deleterious consequences regarding morbidity (duration of mechanical ventilation, duration of ICU or hospital stay) and/or mortality. For many intensivists, CMV reactivation is one of the hallmarks of the severity of an underlying disease i.e. it represents more of a symptom than an illness per se. For other intensivists, CMV is thought to be directly responsible for organ disease such as pneumonia [4, 5, 34] and colitis [35]. However, by modulating immune function and anti-inflammatory response, CMV might be responsible for the occurrence of bacterial superinfection and/or the aggravation of inflammatory processes such as ARDS. Epidemiological studies have generally documented a strong association between the occurrence of CMV reactivation and a prolonged duration of mechanical ventilation. In a matched cohort study [9], 40 antigenaemia-positive patients were matched to 40 controls. Patients with CMV had a significantly longer duration of mechanical ventilation (35 ± 27 days vs. 24 ± 20 days, respectively; $p < 0.03$) and a longer ICU stay. Interestingly, there was also a higher rate of nosocomial infections in the CMV group [9]. This important study alerted us regarding the deleterious impact of CMV infection on outcomes [9]. CMV infection might be directly responsible for an increased duration of mechanical ventilation (lung infection), which is a risk factor for the development of nosocomial infections. In addition, CMV infection might alter immune function, which would also increase the risk for acquiring nosocomial infections. However, these two mechanisms might be associated. In a series of 120 patients from medical, trauma, burn, cardiac and surgical ICUs, CMV viraemia assessed by PCR was independently associated with hospitalization or death by day 30 [32]. Furthermore, in 242 mechanically ventilated medical ICU patients [7], active CMV infection was associated with an increased duration of mechanical ventilation in survivors presenting with an active CMV infection (median 27 days) relative to controls (median 10 days). The number of ventilator-free days and alive by day 60 was also dramatically reduced when patients developed a CMV infection (median 0 days compared with 34 days for the controls) [7]. It was also reported that the rate of nosocomial infections was higher in the CMV group [7], and the difference remained even when ventilator-associated pneumonia and bacteraemia were considered separately [7]. In contrast, two recent epidemiological studies [38, 39] found no association between serological status regarding CMV and outcomes in a non-selected ICU population or in all-cause ARDS patients. However, in a particular subgroup of ARDS patients presenting with septic shock, results showed an association between the CMV serological status and the number of ventilator-free days to day 28 [39]. Other epidemiological studies and some meta-analyses have looked more specifically at the effects of CMV infection on mortality. In particular, three recent meta-analyses have suggested that there is a strong relationship between the presence of an active CMV infection and mortality, with an odds ratio of approximately 2 [29–31]. In a matched cohort study [9], in which patients were matched on age, gender, SAPS II score and reason for admission, the authors reported that ICU mortality was substantially higher in patients presenting with positive antigenaemia (50 %) compared with controls (28 %, $p < 0.02$). Mortality at day 60 was also higher in patients with a positive PCR in non-immunocompromised ICU patients (55 % vs. 20 %, $p = 0.01$) [29]. In another series of 86 patients who presented with severe sepsis, although reporting a longer duration of ICU and hospital stays and a prolonged duration of mechanical ventilation when active CMV infection was diagnosed, the authors [15] did not report any increase in mortality related to CMV.

Current situation regarding the pathogenicity of CMV

At the present time, there is no definitive proof of CMV pathogenicity. Arguments suggesting that CMV is pathogenic have come from epidemiological studies and from reports on specific subsets of ICU patients such as ARDS patients who exhibited histological and immunological hallmarks of CMV pneumonia or colitis. Twenty years later, we are still waiting for randomised controlled trials designed to test whether specific antiviral therapies can decrease morbidity and/or mortality. To the best our knowledge, three prospective studies are ongoing that are evaluating a prophylactic or pre-emptive treatment with ganciclovir/valganciclovir/acyclovir. However, only one of these randomised controlled trials aims to evaluate the effectiveness of an antiviral therapy in improving outcomes. Indeed, the main objective of the PTH study (Pre-emptive Treatment for Herpesviridae) is to show that ganciclovir can increase the number of days alive and free of mechanical ventilation to day 60 in patients presenting a reactivation evaluated by blood CMV PCR (NCT02152358). Only non-immunocompromised patients receiving at least 96 h of mechanical ventilation are included. In the CCCC study (Cytomegalovirus Control in Critical Care), seropositive patients receiving at least 24 h of mechanical ventilation are included (NCT01503918). Time-to-reactivation of CMV is the main object of analysis. In the GRAIL study (Study of Ganciclovir/Valganciclovir for Prevention of
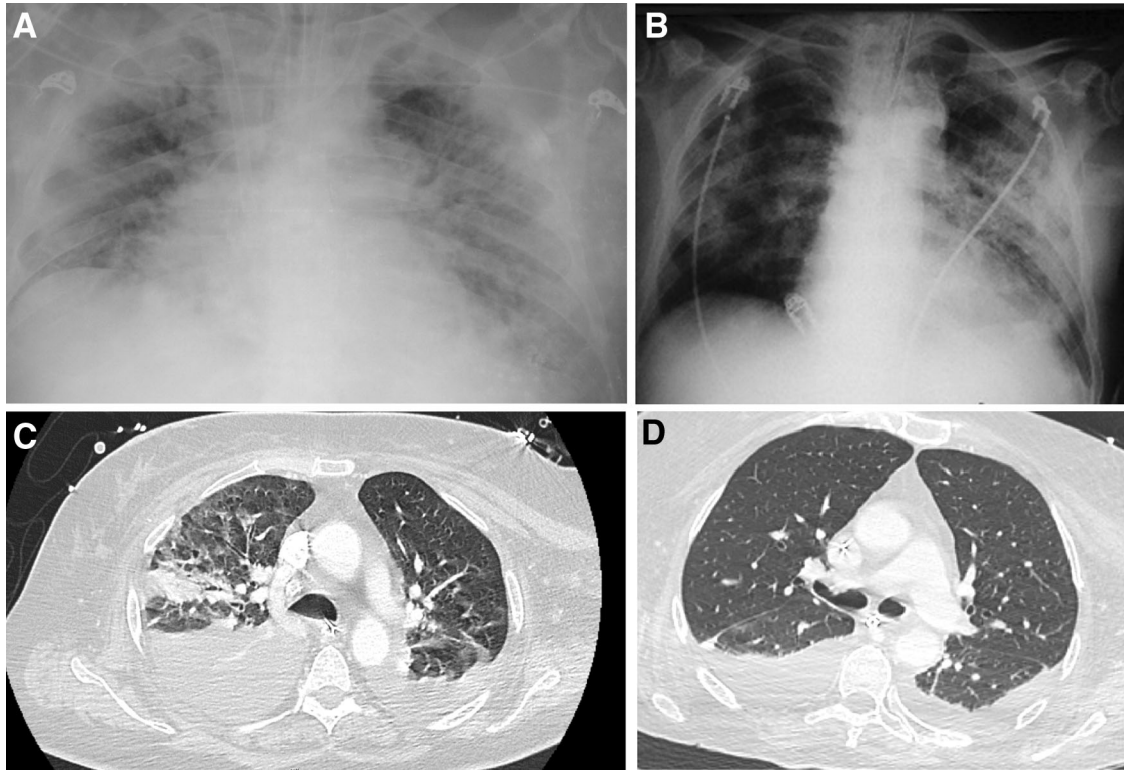
Fig. 2 Lung radiological aspects associated with CMV reactivation. **a** Interstitial and alveolar infiltrates in an ARDS patient under veno-venous ECMO with a positive PCR (BAL and blood). **b** Predominantly left lung infiltrates in a patient with histological signs of CMV pneumonia. **c** Pleural effusion, alveolar condensation and ground-glass opacifications of the right upper lobe in a patient with a positive PCR (BAL and blood). **d** Bilateral pleural effusion without lung infiltrates in a patient with a positive PCR (BAL and blood). There was no clinical sign of active CMV infection

Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure), CMV-seropositive ALI/ARDS patients with severe sepsis or trauma (NCT01335932) are included. The main objective is to study the course of interleukin-6. However, even if the interventional studies show negative results, an etiologic role of CMV is not excluded. Indeed, observed clinical study end points will be influenced by both the effectiveness of the antiviral drug to prevent or to treat CMV reactivation as well as by any negative side effects caused by the antiviral drugs. Furthermore, especially in the trials testing prophylactic treatment, about 60–80 % of the patients will be unnecessarily exposed to antiviral treatment, as CMV does not reactivate in the majority of patients even without receiving prophylaxis. The likelihood of a successful prophylactic approach will largely depend on the ability to improve the selection of patients who are going to reactivate CMV during their ICU stay.

Finally, as only one ongoing randomised controlled trial (PTH) evaluates if CMV treatment is able to improve the outcome, there is the need for additional interventional trials designed to assess if CMV is pathogenic for ICU patients. While waiting for the results of these studies, a screening of CMV reactivation using repeated PCR should focus on mechanically ventilated patients seropositive for CMV on admission. Additional studies are also needed to identify which specific ICU patients have the highest risk for developing active CMV infections.

If the results of the ongoing and future studies suggest that CMV is pathogenic, future trials should investigate the mechanisms causing CMV pathogenicity (direct, indirect or both) and the predisposing immunologic conditions associated with the development of a CMV reactivation. Indeed, one can easily imagine that immune-active drugs could be effective in decreasing the incidence of reactivation and/or the immune system alterations related to CMV reactivation.

To treat or not to treat?

Pending the results of the ongoing and future trials, we recommend the use of a curative antiviral treatment (principally ganciclovir) when there is a CMV reactivation (positive antigenaemia and/or PCR) associated with clinical signs of infection (primarily lung infiltrates) and
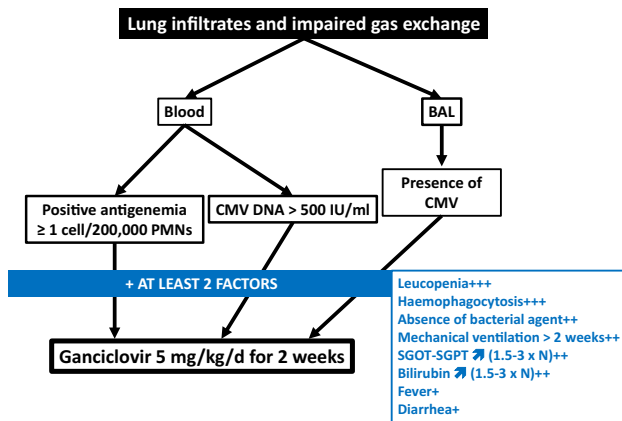
Fig. 3 Criteria for starting ganciclovir in ICU patients with unexplained lung infiltrates and impairment of gas exchange

the presence of risk factors (Fig. 3). Pre-emptive treatment (CMV reactivation without clinical signs of infection) could be discussed in certain circumstances following an assessment of the risk–benefit balance (patients with impaired host defences) [40]. In this context, unless viral load is very high (greater than 10,000 copies/mL), trends in viral load may be more useful than a given value.

There are few antiviral drugs currently available for use against CMV. All of these therapies are associated with side effects, which can worsen the outcomes for ICU patients. The toxicities of ganciclovir, foscarnet and cidofovir are well known. Ganciclovir's toxicity is mainly related to its haematological side effects (mainly neutropenia, thrombocytopenia and sometimes anaemia). The toxicity of foscarnet is essentially renal. Some disturbances to electrolytes have also been observed in patients receiving foscarnet (regular monitoring of calcium, magnesium, phosphate and potassium is required). Nephrotoxicity is also a significant side effect when using cidofovir. Ganciclovir so far appears to be the least toxic and is currently the leading choice among these agents. The oral formulation of valganciclovir precludes its early use during critical illness when many patients have ileus and unreliable intestinal absorption. By targeting the DNA polymerase, all of these drugs can cause the emergence of drug-resistant strains.

Conclusions

Active CMV infection is observed in 15–20 % of ICU patients (20–40 % in ICU patients with positive CMV serology). Although observed in epidemiological studies, there is no definite proof that CMV worsens the outcome of mechanically ventilated patients. Prospective randomized trials are needed to elucidate this point further.

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