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Herpesviruses in Critically Ill Patients With ARDS

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Introduction

Herpesviruses family gathers more than 100 viruses in which 8 are strictly involved in human pathogenesis. Human herpesviruses are enveloped DNA viruses with a capsid. Herpes Simplex Virus 1 and 2 (HHV1/HSV1 and HHV2/HSV2), Varicella Zoster Virus (HHV3/VZV), Epstein Barr Virus (HHV4/EBV) and Cytomegalovirus (HHV5/CMV) are among the most known in human pathology. Herpesviruses are characterized by a primo infection often occurring during childhood and associated with aspecific signs then followed by a latency period. 50–85% (Pebody, 2004; Bradley et al., 2014) of immunocompetent adults are HSV seropositive and 60–80% are CMV seropositive (Gkrania-Klotsas et al., 2013). Reactivation may occur especially in case of immunosuppression and lead to life threatening infections. The pathogenicity of herpesviruses in immunocompromised patients such as bone marrow or solid organ-transplanted or HIV, is well known. Notably, HSV and CMV can be associated with severe community acquired pneumonia potentially evolving towards acute respiratory distress syndrome (ARDS). However, intensive care unit (ICU) patients, although not immunocompromised from a classical point of view, can experience herpesviruses reactivation ranging from 5% to 64% (Luyt et al., 2014) and 15% to 45% (Papazian et al., 2016) for HSV and CMV respectively, depending on the diagnostic technic used, and occurring at different time points during the ICU stay. HSV and CMV (and more recently EBV) (**Fig. 1**) reactivations among ICU patients have been extensively focused on. They appear to be more frequently retrieved in seropositive patients, or those with septic shock and prolonged mechanical ventilation (MV) (Jaber et al., 2005). Even if the debate is still opened, it has been frequently reported that herpesviruses reactivation can alter the prognosis of critically ill patients, although a causal link remains to be proven. HSV pulmonary reactivation has been described to be associated with a longer MV duration, ICU stay and mortality (Luyt et al., 2007). CMV reactivation is also associated with a higher mortality, MV duration and ICU length of stay (Li et al., 2018). The lungs being a usual site of latency for herpesviruses, reactivation in the respiratory tractus is frequent and herpesviruses are considered as an emerging cause of ventilator associated pneumonia (VAP) (Cantan et al., 2019). They might be responsible for direct epithelial injury, favor bacterial infections, enhance local inflammation and pulmonary fibrosis, and be involved in the pathogenesis or the prolongation of ARDS, which is associated with a high mortality (Bellani et al., 2016). Considering the abundance of the data on this question and the recent publication of randomized controlled trials, we aimed to summarize the evidence available on the role of the most frequently described herpesviruses in the ICU and especially in ARDS patients, decipher the pathophysiological ways implicated, the diagnostic methods and treatments and describe their impact on the outcomes.

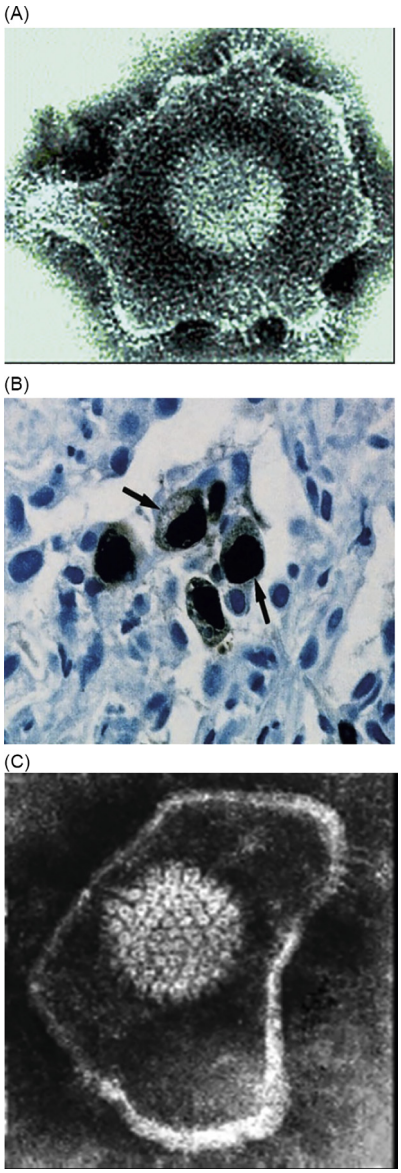

Fig. 1 (A) Herpes simplex virus 1: photography by electronic microscopy (credit: APHM, laboratory of virology). (B) CMV Photomicrograph (original magnification, 400; immunohistochemical marker for cytomegalovirus) shows positive intranuclear inclusion bodies (arrows) (credit: APHM, laboratory of virology). (C) Epstein Barr virus: photography by electronic microscopy (credit: APHM, laboratory of Virology).

HSV in ICU Patients

From Oral Reactivation to Bronchopneumonitis

In historical reports, the frequency of HSV detection in the throat of ICU patients reached 41% after surgery (Porteous et al., 1984). HSV was also isolated from the tracheobronchial secretions of a high percentage of patients, and from 30% to 71% of those with ARDS (Tuxen et al., 1982; Tuxen et al., 1987; Ong et al., 2004). A large prospective study showed that HSV was recovered from the upper and lower respiratory tract of 22% and 16% of ICU patients respectively (Bruynseels et al., 2003). When focusing on patients for whom a bronchoalveolar lavage (BAL) was performed, Linssen et al. (2008) found that HSV DNA was detected in 4.3% of samples in the community group, 15% in the non-ICU group and reached 32% of the ICU group. Patients older than 50 were more frequently concerned.

HSV reactivation occurs earlier than CMV in patients with sepsis admitted to the ICU, often during the first 10 days (Heininger et al., 2011). In many cases, HSV recovery from lower respiratory tract samples of non-immunocompromised ventilated patients corresponds to viral contamination from the mouth and/or throat but several studies have shown that histological aspects of tracheobronchitis (Tuxen et al., 1982) or bronchopneumonitis (Luyt et al., 2007) can be retrieved. In this cases, HSV is considered to be responsible for viral nosocomial pneumonia and possibly ARDS. HSV bronchopneumonitis is probably initiated by viral

reactivation in the throat (secondary to critical illness and local microtrauma caused by endotracheal and gastric tubes, and oropharyngeal cavity suctioning), followed by contamination, colonization and infection of the bronchial tree and the lung. In a study on 201 non-immunocompromised patients under MV for at least 5 days (Luyt et al., 2007), HSV reactivation in the throat was diagnosed in 109 (54%) patients. It was asymptomatic in 56% of them, whereas it was associated with herpetic ulceration of the lip or gingivostomatitis in 48 (44%). Reactivation is the first step of viral VAP, followed by tracheal colonization, and lung involvement. The mechanism leading to reactivation is probably multifactorial, including an impaired function of the immune system frequently following bacterial sepsis and called "immunoparalysis," microtrauma due to intubation and hormonal factors (Luyt et al., 2008; Hotchkiss et al., 2009; Luyt et al., 2007).

Clinical and Virological Diagnosis

Clinical symptoms of HSV reactivation with bronchopneumonitis are nonspecific, especially in ICU patients under MV. They are mainly fever, hypoxemia and purulent tracheal secretions, which can be easily confused with bacterial VAP. Oral herpetic lesions (lip ulceration or gingivostomatitis) are often associated and might be a warning sign. In ARDS patients, HSV bronchopneumonitis should be searched as the origin of ARDS especially when such signs are present or in unresolving ARDS without bacterial cause of VAP. Hemorrhagic aspect of the respiratory tractus under endoscopy can also be observed. The virological diagnosis is based on PCR in the throat and in respiratory samples. HSV detection can reflect either contamination (from mouth and/or throat for bronchial specimens) or local tracheobronchial virus excretion However, the positivity of such samples does not always mean bronchopneumonitis. Luyt et al. have described that HSV bronchopneumonitis is probable when clinical worsening, for example ARDS, is associated with positivity of lung HSV PCR and specific aspect on cytological examination of the cells in BAL or biopsy (Luyt et al., 2007). HSV-specific nuclear inclusion detection in cells recovered during BAL can diagnose parenchymal lung involvement. An easier way to diagnose HSV bronchopneumonitis could be virus-load assessment. This approach is based on the fact that the higher the virus load, the higher the incidence of HSV bronchopneumonitis. A threshold of 8×10^4 HSV copies/10^6 cells demonstrated a 81% sensitivity and 83% for diagnosing HSV bronchopneumonitis (Luyt et al., 2007). Linssen et al. reported that detection of more than 10^5 HSV-DNA copies/mL in lower respiratory material was associated with a significantly higher mortality (Linssen et al., 2008). In a recent study, a threshold of 10^5 copies/mL in BAL fluid or tracheal aspirates was considered as the cut-off between low and high load and associated with a probable invasive infection and patients prognosis (Schuierer et al., 2020).

How Does HSV Impact ICU/ARDS Patients Prognosis?

In one of the very first studies investigating the role of HSV in the ICU, Tuxen et al. (1987) showed that acyclovir was effective in preventing the high incidence of HSV in patients with ARDS but that it did not improve the severity of respiratory failure, the duration of ventilatory support or mortality. The authors concluded that routine prophylaxis of HSV was not recommended in ARDS patients. Bruynseels et al. (2003) found that the duration of stay in the ICU and in the hospital was significantly increased for patients with HSV reactivation in the throat, even when analyses were adjusted for disease severity. Mortality was also higher in those patients but this difference was due to disease severity.

Ong et al., in one of the largest studies available to date (Ong et al., 2004), detected active HSV replication in 27% of 393 ventilated ICU patients, which was associated with a nearly twofold increase in hospital mortality. Nevertheless, whether HSV replication in the lower respiratory tract has clinical consequences remains controversial.

When focusing specifically on HSV bronchopneumonitis patients, Luyt et al. (2007) found that they required longer MV, had more episodes of VAP, and a higher ICU length of stay. However, again, mortality was not different between patients with or without HSV bronchopneumonitis.

To better understand the proper negative role of HSV in ICU patients under MV, Luyt et al. (2019) designed an international randomized controlled trial (RCT) with a preemptive intravenous acyclovir administration. Patients under MV for at least 96 h who exhibited HSV oropharyngeal reactivation were enrolled. The main objective was the reduction of the duration of MV. Noteworthy, only 21 patients (9%) developed ARDS after randomization. Two-hundred and thirty-nine patients were enrolled and randomized. On day 60, there was no difference in the median number of ventilator-free days for acyclovir recipients and controls. Acyclovir was well-tolerated, without renal or neurologic adverse events, although the study was underpowered to assess major complications. Intriguingly, the authors reported a near significant decrease in mortality among patients randomized to acyclovir. On day 60, 26 (22%) acyclovir recipients and 39 (33%) controls had died (risk difference, 0.11, 95% CI −0.004 to 0.22, $P = .059$). The hazard ratio for death within 60 days post-randomization for the acyclovir group vs. controls was 0.61 (95% CI 0.37–0.99, $P = .047$). Despite this trend towards lower day-60 mortality, the number of ventilator-free days was not different between groups, implying that survivors in the acyclovir group had a longer MV. This led the authors to suppose that the prolonged duration of MV in acyclovir survivors might be due to a higher number of patients with ExtraCorporeal Membrane Oxygenation (ECMO) support and a higher percentage of patients developing ARDS after randomization. One hypothesis is that acyclovir could improve the survival of mechanically ventilated patients who reactivate HSV at the cost of a prolonged MV duration. Very recently, respiratory secretions (BAL fluid or tracheal aspirates) of patients with VAP not responding to antibiotics were tested for HSV replication by quantitative real-time PCR. ICU survival times, clinical parameters, and radiographic findings were retrospectively compared between untreated and acyclovir treated patients with high ($>10^5$ HSV copies/mL) and low (10^3–10^5 HSV copies/mL) viral load (Schuierer et al., 2020). Acyclovir improved median ICU survival and was associated with a significantly reduced hazard ratio

for ICU death in high load patients only. Moreover, circulatory (norepinephrine doses) and pulmonary oxygenation function (median PaO_2/FiO_2 ratio) of high load patients improved significantly over the course of acyclovir treatment. The authors concluded on a putative causative role for HSV in this highly selected group of patients. The retrospective design of the study and the uncertain link between HSV positivity and VAP, in the absence of histopathologic evaluation, are the mains weaknesses of this study.

HSV Reactivation Under Veno-Venous (VV)-ECMO for Severe ARDS

In a specific cohort of 123 patients under VV-ECMO for ARDS, Hraiech et al. (2019) found that HSV reactivation in throat or BAL samples reached 54% of the patients. Patients were included only if viral reactivation occurred after ECMO implantation. HSV reactivation was associated with a longer duration of MV and ECMO as compared with non-reactivated patients. In multivariate analysis, HSV reactivation remained independently associated with a longer duration of MV and hospital length of stay suggesting a pejorative role of HSV in this very specific population. Whether ECMO triggers HSV reactivation remains to be documented.

Overall, several studies and meta-analysis (Coisel et al., 2012) suggest a negative impact of HSV reactivation in critically ill patients under MV and especially during ARDS, some studies showing a higher mortality, length of MV, ICU stay and also a higher rate of nosocomial infections (**Table 1**). The exact significance of HSV reactivation is still being debated, the main RCT evaluating a preemptive treatment failing to demonstrate an improvement on duration of MV but showed a trend towards a lower mortality. The debate being still unresolved, it seems interesting to screen HSV in upper/lower respiratory samples especially in patients with sepsis and prolonged MV or unresolved ARDS with virus-load determination when the technic is available. Acyclovir treatment might be proposed for patients with ARDS and HSV signs of bronchopneumonitis and/or high load of replication in respiratory samples.

Treatment

Acyclovir is proposed to treat HSV in ICU patients and has been shown to be safe in this indication (Luyt et al., 2019). A drug regimen of 5 mg/kg/8 h during 14–21 days is usually used in subjects with a normal renal function. Acute renal failure, hepatitis, hyperbilirubinemia and skin rash are the most commonly reported adverse events (**Table 2**).

CMV in ICU Patients

Mechanisms of Reactivation

The transition from latency to viral reactivation for CMV involves a certain degree of immunosuppression, even in patients with no previous immune dysfunction. Tumor necrosis factor (TNF) is probably involved in CMV reactivation after sepsis from a bacterial origin (Cook et al., 2006a; Hummel and Abecassis, 2002). It has been shown that TNF-α is able to directly stimulate immediate early (IE) CMV gene expression. Other mechanisms might also be involved in CMV reactivation.

The term "immunoparalysis" has been used to describe the abnormalities of immune system that has been reported in critically ill patients early during the ICU stay as a result of the underlying disease and/or the treatment (Hotchkiss et al., 2013). Studies of severely immunocompromised patients have suggested that T cell immunity is crucial in the control of CMV replication (Boeckh et al., 2015).

In particular, CMV replication was shown to be higher in patients with undetectable IFN-γ T cell responses than in patients with detectable responses (Clari et al., 2013). Other data suggest the crucial role of NK cells in keeping herpesviruses latent in humans (Biron et al., 1989). In a recent study done in ICU patients, the function of NK cells was altered regarding interferon-γ production just before the occurrence of reactivation (Chiche et al., 2012). Impaired natural killer cell function with reduced interferon-γ secretion precedes the occurrence of CMV reactivation among previously immunocompetent critically ill patients. This latter results suggest that in the context of global and major lymphopenia observed in ICU patients, dysfunction in NK cells may be involved in CMV reactivation. CMV is also involved in the impaired function of dendritic cells (Avdic et al., 2014).

Frequency of CMV Reactivation Among ICU Patients

CMV reactivation in non-immunocompromised ICU patients has been largely assessed during the last three decades (Domart et al., 1990; Limaye et al., 2008; Kalil and Florescu, 2009; Coisel et al., 2012) (**Table 3**). In a meta-analysis gathering studies with heterogeneous diagnostic methods, Kalil and Florescu (2009) found that overall, about 20% of ICU patients exhibit a CMV reactivation during their ICU stay. Of course, the serological status and the diagnostic methods are determining factors. CMV reactivation is diagnosed in approximately 33% of ICU seropositive patients suffering from a large variety of critical illnesses such as sepsis, cardiac failure, burns and trauma (Limaye et al., 2008). In another large cohort of medical patients mainly under MV and presenting a septic shock, 16% developed an active CMV infection as diagnosed by positive antigenemia and/or positive rapid viral culture in BAL (Chiche et al., 2012). Apart from CMV seropositivity, severity of the disease, sepsis and septic shock, and a length of ICU stay >5 days are the main risks factors for CMV infection (Kalil and Florescu, 2009). In a match-controlled study, renal failure and steroid use were also described as risk factors (Jaber et al., 2005). CMV reactivation generally occurs later than HSV, around the

Table 1 Incidence, mortality and morbidity associated with HSV infection in non-immunocompromised ICU patients.

Year/Reference	*Study design*	*Inclusion criteria*	*Number of patients*	*HSV Detection method*	*Incidence of HSV reactivation*	*Mortality HSV +/HSV− (%)*	*Morbidity endpoints assessed*
1987 (Tuxen et al., 1987)	Double blind RCT	ARDS	45	Culture on respiratory secretions	6% acyclovir 71% control[a]	47 acyclovir 43 control	DMV
2003 (Bruynseels et al., 2003)	Prospective	Medico-surgical	764	Culture on throat or respiratory samples	22% throat 16% respiratory samples	33 vs.23[b]	ICU-LOS[b]/DMV[b]
2003 (Cook et al., 2003)	Prospective	Surgical	95	Culture in blood and respiratory samples	23%	27 vs. 26	ICU-LOS/DMV
2004 (Ong et al., 2004)	Prospective	Medico-surgical under MV	393	PCR on respiratory samples	27%	41 vs. 24[b]	NA
2007 (Engelmann et al., 2007)	Retrospective	Medico-surgical >3 days ICU stay	53	Culture, PCR and indirect immunofluorescence on respiratory samples	13%	100 vs. 18[b]	DMV[b]
2007 (Luyt et al., 2007)	Prospective	Medical MV >5 days	201	Culture and PCR on respiratory samples	54%	48 vs. 42	ICU-LOS[b]/DMV[b]/NI[b]
2008 (Linssen et al., 2008)	Retrospective	VAP suspicion	260	PCR on BAL	31%	41 vs. 20[b]	NI
2009 (De Vos et al., 2009)	Prospective	MV >2 days	105	PCR on respiratory samples	62%	35 vs. 48	DMV[b]/NI[b]
2010 (Scheithauer et al., 2010)	Prospective, case control	Suspicion of pneumonia	103	PCR on respiratory samples	NA	45 vs. 35	ICU-LOS[b]/DMV[b]/NI[b]
2010 (Smith et al., 2010)	Prospective	Patients under MV	174	PCR on respiratory samples	66%	33 vs. 32[b]	NA
2011 (Bouza et al., 2011)	Prospective	VAP	177	Culture on respiratory samples	13%	77 vs. 57	ICU-LOS[b]/DMV[b]/NI[b]
2012 (Coisel et al., 2012)	Prospective	Pneumonia	93	PCR on BAL or IgM+	24%	42 vs. 20	ICU-LOS/DMV/NI
2012 (Costa et al., 2012)	Prospective	VAP suspicion	237	PCR on respiratory samples	32%	51 vs. 27[b]	MV[b]/ICU admission[b]/Co-infection[b]
2019 (Hraiech et al., 2019)	Retrospective	Severe ARDS with VV ECMO >2 days	123	PCR on throat or BAL	49%	48 vs. 59	ICU-LOS[b]/DMV[b]/ECMOD[b]
2019 (Luyt et al., 2019)	Double blind RCT	MV >96H, HSV reactivation	239	PCR on oropharyngeal swab	NA	22 acyclovir vs. 33 placebo	ICU-LOS/DMV/NI
2020 (Schuierer et al., 2020)	Retrospective	VAP not responding to antibiotics	425	PCR on respiratory samples	30%	HR of death = 0.31, 95% (CI 0.11–0.92, $P = .03$) in high load patients with acyclovir treatment as compared with no treatment	Improved PaO_2/FiO_2, decreased norepinephrine doses over time in acyclovir treated patients with high load reactivation[b]

BAL, broncho-alveolar lavage; *DMV*, duration of mechanical ventilation; *ECMO*, extracorporeal membrane oxygenation; *ECMOD*, ECMO duration; *HR*, hazard ratio; *HSV*, Herpes Simplex Virus; *ICU-LOS*, intensive care unit length of stay; *NA*, not available; *NI*, nosocomial infections; *RCT*, randomized controlled trial.

[a] $P < .05$ between acyclovir treated patients and controls.

[b] $P < .05$ between HSV positive and HSV negative patients.

Table 2 Summary of the main antiviral treatments used for herpesviruses infections and their potential side-effects.

Drug	*Antiviral effect*	*Dose regimen and duration*	*Drug adjustment in case of renal replacement therapy*	*Side effects*
Acyclovir	HSV1/HSV2/VZV	5 mg/kg/8 h 14–21 days	5 mg/kg/12 h (5 mg/kg/24 h if estimated CrCl $<$25 mL/min)	Acute renal failure Hepatitis Hyperbilirubinemia Skin rash
Ganciclovir	CMV/HSV1/ HSV2/VZV	5 mg/kg/12 h 14–21 days	2,5 mg/kg/12 h	Leuconeutropenia Thrombocytopenia Anemia Coma Seizure Hepatitis Hyperbilirubinemia Skin rash Acute renal failure
Foscarnet	CMV/HSV1/ HSV2/VZV	Initial therapy: 60 mg/kg/8 h Maintenance treatment: 90–120 mg/kg/d Associated hydration	35 mg/Kg/8 h (initial therapy)	Acute renal failure Hypocalcemia Paresthesia Nausea, vomiting Pancreatitis
Cidofovir	CMV	Initial therapy: 5 mg/kg/week for 2 weeks Maintenance treatment: 5 mg/kg/week every twice week	Contraindication	Acute renal failure Fever, asthenia Nausea, vomiting Skin rash

CMV, Cytomegalovirus; *HSV1*, Herpes simplex virus 1; *HSV2*, Herpes simplex virus 2; *VZV*, Varicella-zoster virus; *CrCl*, creatinine clearance.

14th day of ICU stay when considering PCR in respiratory samples, and after the third week for blood samples PCR (Heininger et al., 2011).

Clinical and Virological Diagnosis

As for HSV reactivation, CMV infection often gives non-specific signs. The typical figure is represented by a patient in the 2nd-3rd week of ICU stay with moderate fever, respiratory worsening with gas exchange impairment and chest radiograph modification, and negativity of bacterial samples, hepatic cytolysis or cholestasis. In this form, diagnosis is not easy and routine PCR monitoring could be useful, especially in seropositive patients at ICU admission (Papazian et al., 2016). The clinical picture is sometimes more obvious, including de novo or persistent ARDS, hepatitis, gastritis or colitis with diarrhea (Siciliano et al., 2014), cytopenia with hemophagocytosis in myelogram. It is fundamental to highlight that there is no radiological specificity and in particular, interstitial pneumonia as it is classically described in HIV patients is very uncommon (**Fig. 2**).

The incidence of CMV reactivation also depends on the diagnosis method. Three technics have been used: viral cultures, antigenemia, and PCR. Culture-based techniques are considered outmoded because they are time-consuming and lack sensitivity. When analyzing only the studies that evaluated CMV infections by PCR/antigen in patients with positive CMV serology and $\geq$5 days in ICU, Kalil and Florescu (2009) found that the rate of active CMV infection increased to 36% as compared to 21% when including former studies based on culture diagnosis. The antigenemia 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 progressively replaced by PCR assays, given their high sensitivity and rapid turnover time. Quantitative PCR has been used to evaluate the severity of infection. Limaye et al. (2008) showed that a plasma CMV load $>$1000 copies/mL occurred in 20% of seropositive patients. This population had a much higher risk for death or prolonged ICU stay by day-30 as compared to patients negative for CMV, whereas this risk was not so pronounced in patients with CMV reactivation at any level. At the moment, no specific threshold for the diagnosis can be proposed in either blood or respiratory samples. Some authors suggested that CMV PCR, when performed on respiratory samples, is a more sensitive technic than when performed in plasma (Heininger et al., 2011).

The Role of CMV in ICU/ARDS Patients Prognosis (Fig. 3)

Several meta-analysis found that all-cause mortality was higher in ICU patients developing a CMV infection during their stay. In a meta-analysis on 13 studies with a total of 1258 patients, the mortality rate associated with active CMV infection was 1.93 times as high as that for patients without infection (Kalil and Florescu, 2009). A more recent meta-analysis (Li et al., 2018) on 18 studies involving 2398 immunocompetent patients admitted to the ICU reported that for CMV seropositive patients, the odds ratio for mortality in patients with CMV reactivation as compared with patients without CMV reactivation was 1.72. Patients with CMV infection required significantly longer MV and duration of ICU stay than patients without CMV infection. However, when analysis was

Table 3 Incidence, mortality and morbidity associated with CMV infection in non-immunocompromised ICU patients.

Year/Reference	*Study design*	*Inclusion criteria*	*Number of patients*	*CMV Detection method*	*Incidence of CMV reactivation (%)*	*Mortality CMV+/CMV −(%)*	*Morbidity endpoints assessed*
1990 (Domart et al., 1990)	Retrospective	Mediastinitis after cardiac surgery	115	Culture of blood and urine	25	55 vs. 37	Higher LOS in CMV+ patients
1998 (Kutza et al., 1998)	Prospective	Sepsis	34	Antigenemia + PCR in blood	32	64 vs. 74	NA
1998 (Cook et al., 1998)	Retrospective	Sepsis	142	Culture in blood or BAL	8	66 vs. 35[a]	ICU-LOS
2001 (Heininger et al., 2001)	Prospective	SAPS II <40, CMV seropositive	56	Culture and PCR in blood/ tracheal secretions	35	55 vs. 36	ICU-LOS[a]
2003 (Cook et al., 2003)	Prospective	ICU-LOS >5 days	104	Culture in blood and tracheal secretions	10	50 vs. 27	ICU-LOS[a]/DMV[a]/ NI[a]
2005 (Jaber et al., 2005)	Retrospective, case control	Fever >72 h without proven infection	237	Antigenemia	17	50 vs. 28[a]	ICU-LOS[a]/DMV[a]/ NI[a]
2006 (von Müller et al., 2006)	Prospective	Septic shock	25	Antigenemia + culture in blood/tracheal secretions/ urine	32	63 vs. 35	ICU-LOS[a]/DMV[a]/ NI[a]
2008 (Limaye et al., 2008)	Prospective	Burn, trauma and sepsis	120	PCR in blood	33	adjusted odds ratio 4.3 (95% CI, 1.6–11.9) for continued hospitalization or death by 30 days	
2008 (Ziemann et al., 2008)	Retrospective	ICU-LOS >14 days	99	PCR in blood	35	29 vs. 11[a]	ICU-LOS[a]
2009 (Chiche et al., 2009)	Prospective	MV >2 days	242	AG ± BAL culture	16	54 vs. 37[a]	ICU-LOS[a]/DMV[a]/ NI[a]
2011 (Bordes et al., 2011)	Prospective	Burns	21	PCR in blood	71	33 vs. 20	ICU-LOS/DMV
2011 (Heininger et al., 2011)	Prospective	Sepsis	86	Culture or PCR in blood and tracheal secretions	41	37 vs. 35	H-LOS[a]/ICU-LOS[a]/DMV[a]
2012 (Coisel et al., 2012)	Prospective	Pneumonia	93	Antigenemia + PCR in blood	24	55 vs. 20[a]	ICU-LOS[a]/NI
2014 (Bravo et al., 2014)	Prospective	Surgical ICU	78	PCR in blood and low respiratory tract and saliva	46	56 vs. 36	ICU LOS[a]/DMV[a]
2015 (Frantzeskaki et al., 2015)	Prospective	MV CMV seropositive	80	PCR in blood	14	45 vs. 27	ICU-LOS/NI
2016 (Cook et al., 2006b)	Prospective	ARDS MV >4 days	271	PCR in blood	27	31 vs. 15[a]	DMV[a]
2017 (Forel et al., 2014)	Prospective	Septic shock and ICU LOS >4 days	399	PCR in blood	27	33 vs. 23[a]	NA
2017 (Hraiech et al., 2017)	Open-label RCT	CMV seropositive >24 h MV	124	PCR in blood, urine, throat, lung	27 control 0.02 valganciclovir[b] 0.06 valacyclovir[b]	15.9 control 41.2 valacyclovir[b] 21.7 valganciclovir	Organ failure free-days, ICU LOS
2017 (Cowley et al., 2017)	Double blind RCT	CMV seropositive >24 h MV	156	PCR in blood, BAL and throat	10/84 (12) ganciclovir[b] 28/72 (39) control	15 placebo 12 Ganciclovir	VFD[a] ICU-LOS/DMV/NI
2019 (Hraiech et al., 2019)	Retrospective	Severe ARDS with VV ECMO >2 days	123	PCR in blood or BAL or AG	22	52 vs. 59	ICU-LOS[a]/DMV[a]/ ECMOD[a]

ARDS, acute respiratory distress syndrome; *BAL*, broncho-alveolar lavage; *DMV*, duration of mechanical ventilation; *ECMO*, extracorporeal membrane oxygenation; *ECMOD*, ECMO duration; *HR*, hazard ratio; *HSV*, Herpes Simplex Virus; *ICU-LOS*, intensive care unit length of stay; *LOS*, length of stay; *NA*, not available; *NI*, nosocomial infections; *RCT*, randomized controlled trial; *VFD*, ventilator-free days and alive at day 28.

[a] $P < .05$ between CMV positive and CMV negative patients.

[b] $P < .05$ as compared with control.

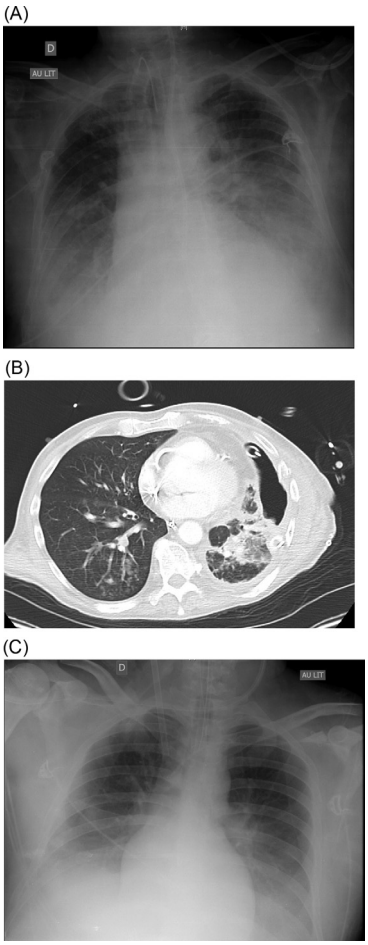

Fig. 2 The radiological (chest radiographs and scans) patterns of HSV and CMV reactivation among ICU patients. (A) A 69 old man with suspicion of VAP with fever, gaz exchange worsening and chest radiograph infiltrates. BAL found no bacteria only positive CMV PCR. (B) A 62 years old man with history of bacterial pleuro-pneumonia and suspicion of VAP. CT scan found bilateral bronchiolar micronodules evocating pneumonia. Bacteriological culture of BAL performed without antibiotics was sterile. CMV PCR in blood and BAL was positive. (C) A 36 years old man with severe ARDS under VV-ECMO, fever and gaz exchange worsening. BAL culture found *S. aureus* and *K. pneumonia* but also throat, blood and BAL HSV reactivation and liver cytolysis.

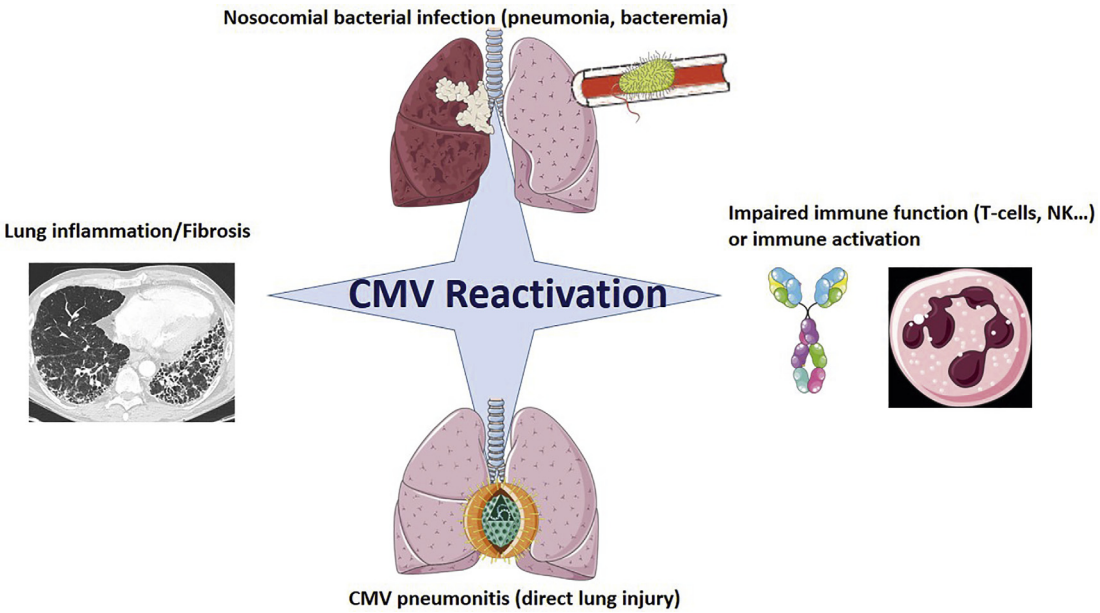

Fig. 3 The pathophysiological mechanisms by which CMV could alter the prognosis of ICU patients.

limited to detection in blood, CMV infection without antiviral drug treatment or reactivation was not significantly associated with higher mortality. In patients with CMV infection and a VAP suspicion, mortality at day 60 was higher as compared with control patients. This difference remained significant after adjusting for age, SAPS II score on admission and SOFA score on the day of diagnosis (Coisel et al., 2012) . Furthermore, in 242 mechanically ventilated medical ICU patients (Chiche et al., 2009), active CMV infection was associated with an increased duration of MV in survivors presenting with an active CMV infection relative to controls. The number of ventilator free days and alive by day 60 was also dramatically reduced when patients developed a CMV infection. In the same study, the incidence of VAP as well as the occurrence of other nosocomial infections was higher in CMV positive patients. Two other studies reported an increased risk of nosocomial bacteremia during the ICU stay (Jaber et al., 2005; Coisel et al., 2012). Of course, the increased duration of MV might be a confounder. However, it is possible that CMV reactivation plays an immunosuppressive role, leading to an enhanced susceptibility towards bacterial infection. This has been suggested in a mice model of CMV reactivation triggered by ceacal-ligation and puncture (CLP), in which CMV positive mice developed abscessing form of staphylococcal pneumonia after exposure to *Staphylococcus aureus* whereas CMV negative mice had cleared bacteria from lungs within 5 days (Hraiech et al., 2017). Despite these results, two recently published studies failed to demonstrate an efficacy of CMV treatment. In a single-center, open-label, randomized, controlled clinical trial on CMV-seropositive patients undergoing MV for at least 24 h (Cowley et al., 2017), an anti-CMV prophylaxis with valacyclovir or low-dose valganciclovir reduced the rate of reactivation but the valacyclovir arm was halted prematurely because of higher mortality. Valganciclovir did not reduce mortality. The rate of reactivation in the control group was of 27%. This study shows the limit of the prophylactic treatment strategy in which ¾ of the patients are unnecessarily treated, with the risk of developing adverse events.

In a double-blind, randomized, placebo-controlled trial (Limaye et al., 2017), Limaye et al. included 156 seropositive mechanically ventilated patients (mainly sepsis), to assess change in IL-6 at day 14, according to treatment with IV ganciclovir or placebo, considering that ganciclovir would decrease the inflammation induced by CMV reactivation. The primary outcome was not different between groups. However, in prespecified exploratory analyses among the sepsis subset (88% of the enrolled cohorts), there were several improved outcomes in the ganciclovir arm, including a higher number of ventilator-free days, shorter duration of MV, and higher PaO_2/FiO_2 ratio among ventilated patients. In addition, a post hoc exploratory analysis among patients with sepsis who survived through day 28 showed a significantly shorter duration of MV in the ganciclovir arm (4 vs. 6.5 median days, $P = .006$).

CMV and ARDS

CMV reactivation and ARDS share tight links. CMV pneumonia has been described as a frequent cause of persistent ARDS. Papazian et al. unexpectedly found histological signs of CMV pneumonia in 25/86 ARDS patient's surgical biopsies after more than 7 days of MV (**Fig. 1**). CMV was the only pathogen in most of time (Papazian et al., 1996). This work was the reason for performing a larger series of 100 open lung biopsies in ARDS in which 30 were positive for CMV infection (Papazian et al., 2007). Noteworthy, CVM and lung fibrosis were associated in four cases. It is probable that CMV enhances the progression of post-aggressive lung fibrosis because of its pro-inflammatory properties. This has been demonstrated in a mouse model of CLP inducing CMV reactivation. Three weeks after the surgical trigger, CMV reactivated mice had a much higher risk of lung fibrosis which was reversed in animals treated with ganciclovir (Cook et al., 2006b). In a large cohort of 399 patients with ARDS who required MV for more than 4 days, Ong et al. (2016) demonstrated that seropositive patients with CMV reactivation had both a longer duration of MV and higher mortality as compared to subjects without reactivation. The population-attributable fraction of ICU mortality due to CMV reactivation was estimated at 23% by day 30, meaning an absolute mortality difference of 4.4%. The authors concluded that CMV reactivation was independently associated with increased case fatality in immunocompetent ARDS patients who are CMV seropositive. In severe ARDS patients requiring VV-ECMO (Hraiech et al., 2019), CMV reactivation either in blood or BAL occurred in 40% of patients. CMV was most often combined with HSV reactivation. Patients with CMV reactivation had a prolonged duration of MV and ICU length of stay as compared with patients with no herpesviruses reactivation.

CMV Treatment

Pending the results of the ongoing and future trials, the use of a curative antiviral treatment should be considered when there is a CMV reactivation (positive antigenaemia and/or PCR) associated with clinical signs of infection (for example persistent ARDS) meaning CMV end-organ disease (**Fig. 4**) especially when risk factors are present. Pre-emptive treatment (CMV reactivation without clinical signs of infection) is currently under analyze and the result of a RCT should be soon known (NCT02152358). When CMV PCR is positive without any clinical signs, unless viral load is very high (greater than 10,000 copies/mL), trends in viral load may be more useful than a given value (Papazian et al., 2016; Forel et al., 2014). Ganciclovir, 5 mg/kg twice daily, during 14–21 days is the first line treatment when necessary. The main side-effects are hematological and renal toxicity. Foscarnet or cidofovir can be an alternative in case of occurrence of cytopenia but are associated with greater risk of renal failure (**Table 2**).

HSV and CMV Co-reactivation

Co-infections of HSV/CMV have also been reported in as high as 27% of CMV reactivations (Coisel et al., 2012). In severe ARDS patients undergoing VV-ECMO, HSV/CMV co-reactivation occurred in 30% of cases and was associated with worse outcomes

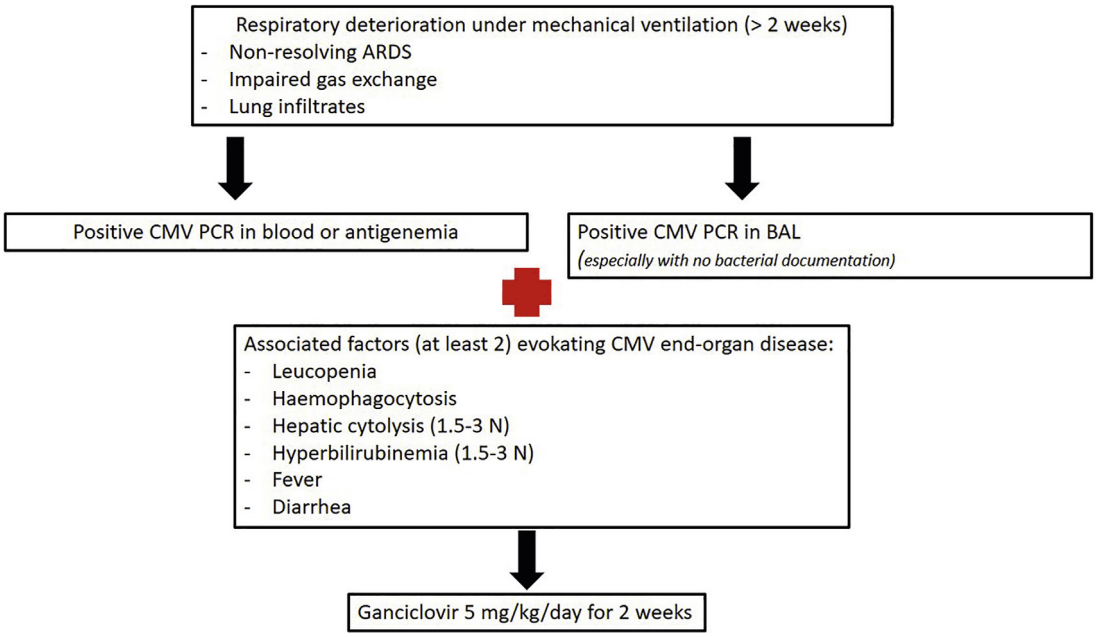

Fig. 4 A propositional algorithm for the treatment of CMV reactivation with end-organ disease signs in ARDS patients.

(Hraiech et al., 2019). Co-reactivation patients had a longer duration of MV and ICU stay as compared to HSV or CMV alone and non-reactivated patients. They also had a longer ECMO duration and hospital length of stay.

EBV and HHV-6

Besides HSV and CMV, other herpesviruses have been recently described in ICU patients. Their significance is not yet well understood.

EBV was found to be frequently retrieved in BAL and blood of ICU non-immunocompromised patients. In 329 patients with septic shock, Ong et al. described 157 (48%) EBV detection in the blood with an association with a higher mortality in reactivated patients (Ong et al., 2017). In a prospective observational study including 90 patients (Libert et al., 2015) with an ICU stay of ≥ 5 -days, EBV was the most frequently reactivated herpesvirus (68%), before HSV and CMV. Co-reactivation with either HSV or CMV was frequent. An association between EBV reactivation and a higher mortality, length of MV and ICU stay as compared with non-EBV reactivated patients was found. Patients with two or more herpesviruses reactivation, whatever the subtype (EBV, CMV, or HSV), had longer duration of MV or ICU stay. In a series of 54 patients (Bonizzoli et al., 2016) admitted in ICU with a diagnosis of ARDS, without a known microbiological causative agent, EBV was detected in 23 of 54 patients (43%) in respiratory samples (BAL or throat sample), either as a single infection or as mixed infection (with HSV or CMV).

Overall, the role of EBV reactivation in ICU and specifically in ARDS patients is not yet clearly defined and a specific treatment against EBV premature.

It has also been reported that 49% of the patients with CMV reactivation also reactivated HHV-6 (Lopez Roa et al., 2015). 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.

Discussion and Conclusion

Herpesviruses pathogenicity were first reported in transplant recipients, and they have been increasingly documented in critically ill patients since then. HSV and CMV reactivations are frequent in ICU patients and associated with mortality, prolonged MV and ICU stay in several observational studies and meta-analysis. An association with bacterial sepsis has also been reported, in animal and clinical studies. In ARDS patients, herpesviruses reactivation go hand in hand with an impaired prognosis and may prolong ECMO duration. However, a statistical association does not necessarily mean a causal link. Randomized controlled trials published to date have not permitted to know if herpesviruses are simple bystanders, witnesses of the severity of the disease or real pathogens (Schildermans and De Vlieger, 2020). In some cases, they are associated with a true disease; but sometimes, the relationship between viral reactivation and symptoms is not established. In these later cases, whereas a specific antiviral treatment may improve outcomes remains to be determined. To date, neither prophylactic acyclovir to prevent HSV reactivation nor prophylactic ganciclovir to prevent CMV reactivation can be recommended (Cantan et al., 2019). Preemptive treatment with acyclovir in patients with

oropharyngeal HSV did not impact MV duration although the difference of mortality between groups was disturbing (Luyt et al., 2019). Moreover, two interventional studies have shown negative results and one was even stopped early because of higher mortality in patients who received antiviral treatment (Cowley et al., 2017; Limaye et al., 2017). The second study showed an increase in ventilator-free days at day 28 in patients with sepsis. Although this was a secondary endpoint in a subgroup, it warrants further research. Preemptive treatment of CMV reactivation with ganciclovir is under investigation (PTH [Preemptive Treatment for Herpesviridae] study, Clinical Trials no NCT02152358). Curative treatment of HSV bronchopneumonitis or CMV lung disease is based on expert opinions in patients with either cytological/histological proofs of lung involvement, high viral load, or specific clinical and biological patterns suggestive of CMV (Papazian et al., 2016; Cantan et al., 2019). Considering the pulmonary tropism of herpesviruses and the role of HSV in bronchopneumonitis and CMV in lung fibrosis, reactivation should be investigated in unresolving or worsening ARDS, rather by PCR in BAL.

In the light of what previous studies learned to us, some question persist and research perspectives should aim to:

- Better scope the patients susceptible to have a reactivation and in whom it could be deleterious (seropositive, under prolonged VM, with sepsis and/or ARDS).
- Better define reactivation from a virological point of view (blood, throat, lung samples? threshold of PCR? Use of quantitative real time PCR?)
- Determine the place of tests assessing marker of upcoming reactivation (IFNγ production by CMV-specific T lymphocytes upon exposure to CMV-antigens) (Castón et al., 2016).
- Assess the efficacy of curative treatment, in patients with reactivation and one or more signs evocating end organ disease, especially ARDS.
- Precise the role of "emerging" herpesviruses such as EBV and HHV6.

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