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EDITORIAL

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Treating HSV and CMV reactivations in critically ill patients who are not immunocompromised: pro

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Cytomegalovirus (CMV) and herpes simplex virus-1 (HSV-1) have received increasing attention as potential pathogens in critically ill patients. Both have the ability to develop viral latency, and critically ill patients, especially those with sepsis, can develop an immunosuppressed state that might reactivate the lysogenic part of the viral life cycle [1]. The mechanisms of this immunosuppression which can contribute to viral reactivation include apoptotic depletion of CD4 and CD8 T cells, T cell exhaustion, increased T-regulatory cells, myeloid-derived suppressor cells and impaired natural killer cell function [2, 3]. However, no study has been conducted in order to analyse the impact of antiviral treatment in immunocompetent critically ill patients with HSV or CMV reactivation.

Although CMV reactivation is rare in non-selected ICU patients (2 %) [4], it is frequent in selected intensive care unit (ICU) patients, ranging from 16 to 40 % (Table 1) [4–8]. The differences in the incidences between studies are explained by their case-mix, the site of CMV reactivation (blood reactivation alone [5] or blood, leukocytes and distal airways reactivation [6, 7]), and the methodology used for CMV detection, i.e. PCR [5, 6] or virus culture [7]. Whatever the incidence of reactivation, all studies found that CMV reactivation was independently associated with morbidity (namely, prolonged duration of mechanical ventilation (MV), and prolonged ICU length of stay) [5–7], but also with mortality [5]. In a landmark study, Limaye et al. found a quantitative association such that the greater the amount of CMV reactivation, the greater the risk of continued hospitalization or death by 30 days [5]. This last point is probably important to be considered; the clinical impact of CMV reactivation is not the same in patients with low CMV–DNA plasma level as compared to those with high CMV–DNA plasma level [5, 6]. Recently, a study found that CMV pp65 and IE-1-specific IFN-γ-producing CD8(+) and CD4(+) T cells could be used for early identification of the evaluation of CMV-specific T cell immunity [9]. This hallmark in adaptive immunity has been proposed to allow an early identification of patients with high-level virus replication at risk of either having or developing an episode of active CMV infection. To date, no study has been conducted in order to analyse the impact of antiviral treatment in immunocompetent critically ill patients with CMV reactivation (Table 1).

Table 1 Main studies having evaluated HSV and/or CMV reactivation and their specific treatment in ICU patients

Reference/study type	Patients	Incidence of virus reactivation	Treatment	Mortality as a function of viral reactivation or not		Mortality in virus reactivators as a function of antiviral treatment or not	
				CMV−	CMV+	Mortality in CMV reactivators	
						Ganciclovir−	Ganciclovir+
Studies on CMV reactivation and/or infection							
Jaber et al. [4]/retrospective, case–control	237 ICU patients; 40 CMV positive matched with 40 CMV negative	40/237 (17 %) had CMV blood reactivation diagnosed by pp65 antigenemia	None	28 %[a]	50 %[a]	NA	NA
Limaye et al. [5]/prospective	120 CMV-seropositive ICU patients	39/120 (33 %) had CMV blood reactivation 24/120 (20 %) had CMV viremia >1000 copies/mL	None	CMV reactivation associated with death or continued hospitalisation by day 30 (OR 4.6, 95 %CI 2.0–10.3)		NA	NA
Chiche et al. [7]/prospective	242 ICU patients with MV >2 days	39 (16 %) had CMV reactivation: 33 (14 %) in the blood 10 (4 %) in the LRT 5 (2 %) in blood and LRT	Ganciclovir or foscarnet, not protocolised	41 %	59 %	13/21[b] (62 %)	2/18 (44 %)
Heininger et al. [6]/prospective	86 CMV-seropositive ICU patients with severe sepsis	25 (40.7 %) CMV reactivation: 10 (11.6 %) in the blood 13 (15 %) in the LRT 12 (14 %) in blood and LRT	None	35.3 %	37.1 %	NA	NA
Walton et al. [8]/prospective	356 ICU septic patients	86 (24.2 %) had CMV reactivation in the blood 33/148 tested (22.3 %) had CMV reactivation in plasma	None	Mortality rate NR, but patients with CMV detectable in plasma had increased 90-day mortality rate as compared to CMV negative patients		NA	NA

Reference/study type	Patients	Incidence of virus reactivation	Treatment	Mortality as a function of viral reactivation or not		Mortality in virus reactivators as a function of antiviral treatment or not	
				HSV−	HSV+	Mortality in HSV reactivators	
						Aciclovir−	Aciclovir+
Studies on HSV reactivation and/or infection							
Tuxen et al. [15]/RCT	43 ICU patients randomised to receive aciclovir or placebo	1/17 (6 %) aciclovir group 15/21 (71 %) placebo group	Aciclovir 5 mg/kg tid or placebo	NR	NR	9/21 (43 %)	8/17 (47 %)
Bruynseels et al. [10]/prospective	764 ICU patients (ventilated or not)	169 (22 %) in the throat 58/361 (16 %) in the LRT	None	23 %[a]	33 %[a]	NA	NA
Ong et al. [11]/prospective	393 ICU mechanically ventilated patients	106 (27 %) in the throat and/or in the LRT	None	24.4 %[a]	40.6 %[a]	NA	NA
Luyt et al. [12]/prospective	201 patients with MV > 4 days	109 (54 %) in the throat 129 (64 %) in the LRT 42 (21 %) with HSV BPn	Aciclovir (10 mg/kg tid) in 19 patients with HSV BPn	40 %[c]	44 %[c]	13/23 (57 %)[d]	7/19 (37 %)[d]

Table 1 continued

Reference/study type	Patients	Incidence of virus reactivation	Treatment	Mortality as a function of viral reactivation or not		Mortality in virus reactivators as a function of antiviral treatment or not	
				HSV−	HSV+	Mortality in HSV reactivators	
						Aciclovir−	Aciclovir+
Linssen et al. [13]/retrospective	260 ICU patients	82 (31 %) in the LRT	None	23 %[a]	61 %[a]	NA	NA
Walton et al. [8]/prospective	560 ICU septic patients	76/538 (14 %) in the blood	None	NR	NR	NA	NA
Traen et al. [21]/retrospective	212 ICU patients with HSV reactivation	NA	Aciclovir, not protocolised	NA	NA	28/85 (33 %)[e] (48 %)[a,f]	10/21 28/77 (36 %)[e] 6/29 (21 %)[a,f]

CMV cytomegalovirus, *ICU* intensive care unit, *HSV* herpes simplex virus, *RCT* randomised controlled trial, *LRT* lower respiratory tract, *MV* mechanical ventilation, *BPn* bronchopneumonitis, *NR* not reported, *NA* not applicable

[a] $p < 0.05$ for between groups comparison

[b] One patient received foscarnet

[c] Mortality rates for the 138 patients who had HSV reactivation (throat and/or lower respiratory tract) and the 63 who had no HSV reactivation

[d] Mortality rates in patients with HSV bronchopneumonitis receiving or not aciclovir

[e] Patients with HSV reactivation detected in one of the following sample: oropharyngeal swab, nasopharyngeal aspirate, tracheal aspirate or bronchial aspirate

[f] Patients with HSV reactivation in the bronchoalveolar lavage fluid only

HSV-1 reactivation in the oropharynx is frequent in ICU patients, ranging from 22 to 54 % (Table 1) [10–12]. Although this reactivation is asymptomatic in the vast majority of patients, some of them can develop oral–labial lesions or gingivostomatitis [12]. This oropharyngeal reactivation can be followed by contamination of the lower respiratory tract (HSV-1 can be recovered from distal airways of 19–64 % of patients) [10–12]. In some patients, a true HSV bronchopneumonitis (defined as clinical signs of pneumonia, viral detection in the distal airways and cytological/histological confirmation of lung involvement) can develop: in an observational study performed in patients ventilated ≥5 days, Luyt et al. [12] found that 24 % of them developed HSV bronchopneumonitis. Oropharyngeal HSV-1 reactivation, HSV-1 lung carriage and HSV bronchopneumonitis are associated with poor outcome (longer duration of MV, higher rate of bacterial ventilator-associated pneumonia and/or higher mortality rate) in observational studies [10, 12, 13]. Unfortunately, no strong data exist on the efficacy of a specific antiviral treatment (Table 1): most observational studies found no positive effect of aciclovir on outcome [12, 14], and the only randomized controlled trial investigating the efficacy of aciclovir as a prophylactic treatment was underpowered to detect a beneficial effect [15].

In immunocompromised patients, notably transplant patients, treating HSV or CMV infection (curative treatment) and CMV prophylactic treatment are not disputable [16]. Moreover, treating CMV reactivation in such patients (those with allogenic bone marrow transplantation, organ transplant, AIDS-related low CD4 infections, etc.) is also obvious. If treatment of a clinically apparent infection with HSV or CMV (curative treatment) in immunocompetent critically ill patients is not controversial, the treatment of infra-clinical viral reactivation (pre-emptive treatment) is widely debated. However, several data support this strategy for CMV reactivation. Firstly, CMV reactivation is associated with excess mortality and morbidity in critically ill patients [5–7]. Secondly, CMV reactivation may lead to pneumonia [17, 18]. Lastly, in a mice model of CMV reactivation, Cook et al. [19] showed that ganciclovir blocks CMV reactivation and prevents prolonged pulmonary inflammation and lung fibrosis. As for CMV, several data support the need for treating HSV reactivation. Firstly, HSV lung carriage can be associated with HSV bronchopneumonitis (and histologic bronchial lesions). These lesions alter the epithelial barrier and may pave the way for bacterial infection. Secondly, the higher the viral load in the distal airways, the poorer the outcome [12, 13], which is in favour of virus pathogenicity [20]. Thirdly, some specific mechanisms of adaptative immunity (overexpression of Herpes Virus Entry Mediator) in ICU septic patients favour the entry of HSV in lung cells [2]. Lastly, Traen et al. [21]

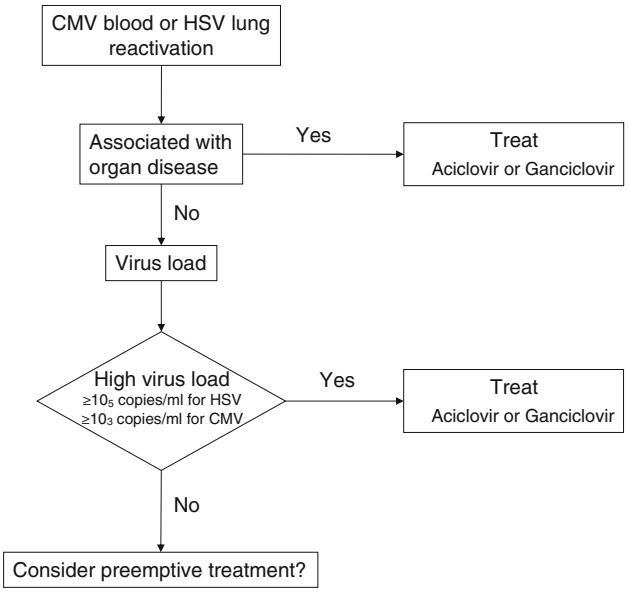

Fig. 1 Therapeutic approach of CMV or HSV reactivation in ICU, nonimunocompromised patients. *CMV* cytomegalovirus, *HSV* herpes simplex virus

recently showed, in a retrospective study, that the treatment by aciclovir of patients with positive HSV-1 culture in their respiratory tract was positively linked to in-hospital and ICU-mortality reduction.

Thus, we think that preventing HSV or CMV disease by a prophylactic or preemptive treatment of their respective reactivation may improve outcome of ICU patients. Because ganciclovir and aciclovir are associated with potential severe side-effects (leucopenia, thrombocytopenia and acute renal failure, respectively), universal prophylactic treatment for all ICU patients is not reasonable (and probably not cost-effective). A population-focused prophylaxis, targeting a population at risk for virus reactivation, is a possible alternative and is currently under clinical investigation for CMV (Cytomegalovirus Control in Critical Care, NCT01503918, and Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure, NCT01335932). Another way could be to give a specific antiviral treatment in a pre-emptive strategy only in patients with virus reactivation, but early in the course of viral infection, before the appearance of virus-induced disease. To our mind, it is questionable only for patients with low virus-load reactivation; those with high virus load have clearly higher morbidity and/or mortality than others [4, 5, 11, 12], and should be treated, whatever the virus (CMV or HSV) (Fig. 1). Moreover, whatever the viral load, the association with clinical signs is in favour of the antiviral treatment. The use of modern sensitive and specific diagnostic techniques for detecting virus at a low level (PCR) allows a strategy targeting patients with low-level viral reactivation, which is the objective of an ongoing multicenter French study (Preemptive Treatment of Herpesviridae, NCT02152358).

In conclusion, CMV and HSV reactivations are frequent in ICU patients, mostly in patients with prolonged MV, and are associated with increased morbidity and/or mortality. These reactivations may lead to true viral disease (HSV bronchopneumonitis, CMV pneumonia) or CMV-induced immunosuppression [22], all these conditions being known to increase duration of MV, thus potentially increasing the risk of bacterial VAP and death. Although no randomised controlled trial exists on the efficacy of a specific antiviral treatment in this setting, and most observational studies on the topic are not interpretable because of lack of standardized protocol, treating patients with CMV- or HSV-specific disease is not questionable, as well as those with high viral load reactivation (Fig. 1), whereas an early, preemptive treatment of virus reactivation (patients with low viral load) could improve outcome remains to be determined.

Conflicts of interest J.M.F., I.M.L. and C.E.L. have no conflicts of interest related to this work.

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