

EDITORIAL



Herpes simplex virus and cytomegalovirus lung reactivations in severe COVID-19 patients: to treat or not to treat? That is (still) the question

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Patients developing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requiring mechanical ventilation (MV) are prone to develop nosocomial infections, either bacterial or fungal, as well as viral infections [1–4]. Among viral nosocomial infections, reactivation of latent viruses, namely Orthoherpesviridae members, is among the most frequent [4].

In this issue of Intensive Care Medicine, Boers et al. evaluated the incidence and impact of cytomegalovirus (CMV) and herpes simplex virus (HSV) lung reactivation in mechanically ventilated patients suffering from coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) and evaluated the impact of antiviral treatment against HSV on outcomes [5]. They found that in a cohort of 194 COVID-19 patients, 6% of the 156 CMV-seropositive patients had CMV lung reactivation $>10^4$ copies/ml, without impact on mortality, duration of MV, or length of stay in the intensive care unit (ICU). Among the 172 HSV-seropositive positive cases, 37% had HSV lung reactivation of $>10^4$ copies/ml. Compared to patients without HSV lung reactivation, those with HSV lung reactivation had a higher rate of lower respiratory tract bacterial infection, duration of MV, ICU length of stay, and lower ventilator-free days on day 28, but similar ICU and hospital mortality rates. The authors sought to assess the effect of reactivation

on outcomes by comparing viral load kinetics over time and its correlation with mortality among individuals with HSV lung reactivation. They found that in patients who did not receive antiviral treatment, the HSV load increased as long as MV persisted and was associated with increased mortality, whereas in patients who received antiviral treatment, the HSV load decreased during treatment and was not associated with mortality. Furthermore, the authors investigated, in a subset of patients, the levels of blood and alveolar inflammation by examining the dosage of various cytokines at both sites. They discovered that alveolar inflammation increased following HSV reactivation as opposed to patients without HSV reactivation. Conversely, plasma cytokine levels were found to be similar.

The results of this study are significant and warrant comments for proper interpretation. First, among the two most common Orthoherpesviridae that may reactivate in ICU patients, namely CMV and HSV, CMV lung reactivation seems to be very rare and without clinical impact, whereas HSV lung reactivation is frequent, as previously demonstrated [4]. However, CMV seems to reactivate more frequently in the blood than in the lungs of ICU patients with or without COVID-19 [6, 7]. Second, although the rate of HSV reactivation is high in the present study, it corresponds to previously published rates in patients requiring prolonged MV with or without COVID-19 [4, 8–10]. Hence, it appears that, in contrast to the suggestion that COVID-19 may be a cause of secondary viral reactivation, it is actually the condition of the patient (i.e., prolonged mechanical ventilation and ICU-induced immunoparalysis) that may increase the

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likelihood of HSV lung reactivation. Similarly, the relationship between HSV lung reactivation and secondary bacterial infections remains an open question, and it is unclear whether such a relationship exists, and if so, what form it might take. Third, the relationship between CMV and HSV reactivation and patient outcomes has not yet been clearly established. Although most studies found a relationship between HSV or CMV reactivation and outcomes, the causality of this relationship is still a matter of concern, and this study does not provide new data on this particular point. Finally, the most important question is related to antiviral treatment. Few studies have evaluated the impact of antiviral treatment on HSV reactivation or infection in ICU patients. An old study performed on 38 ARDS patients demonstrated a beneficial effect of prophylactic acyclovir on HSV reactivation but failed to demonstrate any beneficial effect of this treatment on mortality or MV duration [11]. More recently, Luyt et al. randomised 238 patients to receive, in a double-blind manner, pre-emptive acyclovir or placebo during 14 days in patients with oropharyngeal HSV reactivation [12]. Although patients who received acyclovir had an absolute 11% reduction in the 60-day mortality rate as compared to those who received placebo, the number of ventilator-free days at day 60 (the primary endpoint) was similar between groups. These two trials explored prophylactic and pre-emptive approaches, respectively, and no randomised controlled study has evaluated acyclovir in patients with HSV lung reactivation/infection. Only a meta-analysis of observational studies showed a beneficial effect of acyclovir on mortality in these patients [13], but with limitations inherent to the design of the included studies. Therefore, to date, no strong data exists regarding the usefulness of acyclovir in ICU patients. A randomised controlled trial evaluating acyclovir in mechanically ventilated patients with HSV lung reactivation is currently recruiting (NCT06134492) and will perhaps help to answer this difficult question. To date, no study has evaluated the effect of anti-CMV treatment on CMV lung reactivation. Only 2 randomized placebo-controlled studies evaluated the impact of prophylactic ganciclovir in CMV-seropositive patients, and although CMV blood reactivation was less frequent in patients receiving ganciclovir as compared to those receiving placebo, this didn't translate into better outcomes [14, 15].

Unfortunately, the present study did not directly explore the effect of antiviral treatment in patients with HSV lung reactivation. Indeed, the authors showed that in patients not receiving antiviral treatment, HSV viral load dynamics were associated with increased mortality, whereas in patients receiving acyclovir, HSV viral load dynamics were not associated with increased mortality [5]. These data provide only indirect answers on the

usefulness of acyclovir in these patients, since confounding factors were not considered. Moreover, crude or adjusted mortality rates of patients with or without acyclovir were not given by the authors, and it could have been interesting to directly investigate the impact of antiviral treatment on outcome.

In summary, this study confirms that in mechanically ventilated ICU patients with COVID-19, CMV lung reactivation is rare and HSV lung reactivation is frequent, but unfortunately, it does not provide any new data on the potential usefulness of acyclovir in patients with HSV lung reactivation. Without strong data from randomised control trials, no recommendation regarding antiviral treatment of HSV lung reactivations can be provided to clinicians.

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Declarations

Conflicts of interest

C-EL received lecture fees from Merck, Aerogen and AdvanzPharma, and grant from Eumedica and Merck, all outside the submitted work. MG has no conflict of interest to declare in relationship to this manuscript. PP received lecture fees from Merck and Pfizer, outside the submitted work.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 8 July 2024 Accepted: 12 July 2024

Published: 24 July 2024

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