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Response to letter "Study conclude that routinely monitoring of sputum viral load in severe COVID-19 patients may be beneficial for development of infection control guidelines and prediction of prognosis

van Wezel, Esther M.; Boef, Anna G. C.; Buter, Coretta Van Leer

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Response to letter “Study conclude that routinely monitoring of sputum viral load in severe COVID-19 patients may be beneficial for development of infection control guidelines and prediction of prognosis: We are not sure!”



We thank Honore et al. for their critical review of our manuscript “Viral load dynamics in intubated patients with COVID-19 admitted to the intensive care unit”. We would like to take the opportunity to respond to the concerns raised: 1. That sputum viral load in severe COVID-19 patients may not be an appropriate criterion for infection control guidelines 2. That suggesting prognosis could be related to SARS-CoV-2 RNA clearance from sputum could be misleading. The authors state that only bronchoalveolar lavage (BAL) samples should be used for guidance of infection control guidelines and prognosis.

1. Infection control guidelines

Honore et al. state “that telling us that sputum may be beneficial for development of infection control guidelines is not through” (true? thorough?) “and could mislead the clinician. The only way to detect nosocomial infection is BAL and nothing else”.

First, test-based infection control strategies in Dutch and international guidelines advise that isolation can be discontinued when a patient has improvement in symptoms, has no fever and negative results of a molecular viral assay from at least two consecutive respiratory specimens collected ≥ 24 h apart. These guidelines are mainly based on nasopharyngeal and sputum samples [1–3].

The reason we conclude that routine monitoring of sputum samples in patients with severe COVID-19 patients can be beneficial for infection control guidelines is that it is more cautious than discontinuing isolation measures based on (few) nasopharyngeal samples only. Sputum SARS-CoV-2 RNA levels were initially higher than nasopharyngeal SARS-CoV-2 levels in our study, concurrent sputum and nasopharyngeal samples sometimes showed discrepant results, and 20% of patients showed a relapsing pattern in nasopharyngeal samples [4]. A negative/weak-positive SARS-CoV-2 PCR test from nasopharyngeal swab only or sputum only and/or at a single time point may therefore be insufficient to discontinue isolation measures in severely ill COVID-19 patients. However, it is unknown whether the prolonged detection of SARS-CoV-2 indicates the presence of viable virus and whether a relapsing pattern may indicate the presence of viable virus, as viral culture was not performed in our study.

We agree with Honore et al. that it would be very interesting to also study BAL samples of patients, as in literature this has been shown to be more sensitive than other respiratory samples. Of course, it would also be very interesting to study BAL samples in patients with a relapsing pattern. Patients with initial high Ct values in sputum or nasopharyngeal samples and with a sudden decrease in Ct values may have had

stable and low Ct values in BAL samples. One of the studies cited by Honore et al. concludes that BAL may be considered as a complementary tool to noninvasive microbiological tests in selected patients with COVID-19-associated ARDS [5]. In the cohort we studied BAL was not routinely performed and therefore BAL samples were only available for a few selected patients. We have not included these samples in our analysis, because we believe this would have caused a bias in the analysis.

If a BAL sample is obtained for clinical reasons (e.g. secondary respiratory deterioration after initial improvement), we agree that the result of the BAL SARS-CoV-2 PCR should be taken into consideration when deciding whether isolation measures can be lifted. However, we would consider obtaining a BAL sample solely for infection prevention purposes inappropriately invasive. In intubated patients for whom there is no indication for BAL, a sputum sample can be easily obtained (and is routinely obtained twice weekly for bacteriological and fungal screening in our centre). In these patients, we consider the sputum SARS-CoV-2 PCR to be an important addition to nasopharyngeal SARS-CoV-2 PCRs.

2. Trend towards better survival in patients with early clearance from the sputum

As can be seen in the results section of our manuscript (Fig. 4C) survival was 100% in the 9 patients with early negative sputum samples. As mentioned in the discussion this is an observation in a small cohort and it was not statistically significant. Therefore, we wrote in the discussion that this trend needs to be investigated in larger prospective studies [4]. Honore et al. state “...it is difficult to imagine that viral load of the sputum specimen is closely related to prognosis as it is less sensitive than BAL samples. It stand to reason that negative nasopharyngeal and sputum samples does not mean (even far from) that BAL samples should be negative. In some way, establishing a prognosis upon a negative nasopharyngeal and sputum samples might mislead the clinician as the BAL might still be positive and could push the clinicians to reduce the therapy levels whereas virus and RNA could still be found in the BAL while negative sputum.”

As mentioned previously BAL was not routinely performed in our study cohort. As stated by Honore et al. BAL samples have been shown to be more sensitive than sputum samples. Wang et al. studied a total of 1070 specimens collected from 205 patients with COVID-19. Bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%) [6]. In this study BAL may have only been performed in patients with a clinically severe condition or with specific indications, because only in a small group of patients BAL samples were analyzed. It would be interesting to compare BAL PCR results to sputum PCR results in patients for whom BAL samples were available.

We by no means intend to suggest that based on the trend observed in our study clinicians should reduce therapy levels in patients with negative sputum sample SARS-CoV-2 PCRs. Many other factors can influence survival and reduction in therapy levels should certainly not be based on negative molecular testing only (on sputum or BAL samples

for that matter). However, we would suggest that in further studies investigating prognosis in patients with severe COVID-19, sputum and -if available- BAL SARS-CoV-2 RNA levels should be included as potential prognostic factors.

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Declarations of Competing Interest

None.

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Esther M. van Wezel

Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

Anna G.C. Boef

Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

*Corresponding author.

E-mail address: a.g.c.boef@umcg.nl

Coretta Van Leer Buter

Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.