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Research Brief

Prolonged severe acute respiratory coronavirus virus 2 (SARS-CoV-2) viral shedding in lower-respiratory specimens of critically ill patients does not correlate with nasopharyngeal swab results

Daniel M. Brailita MD[1], Allison M. Cushman-Vokoun MD, PhD[2], Macy G. Wood PhD[2], Ann M. Crowley BS MB(ASCP)CM[2], Sharleen A. Rapp BS MB(ASCP)CM[2], Paul D. Fey PhD[2], Mark E. Rupp MD[1] and Angela L. Hewlett MD, MS[1]

[1]Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, Nebraska and [2]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska

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Early in the COVID-19 pandemic, our institution adopted a conservative approach for patients admitted with COVID-19 illness, maintaining isolation precautions for a total of 21 days from date of initial positive polymerase chain reaction (PCR) assay, unless test-based criteria for exiting isolation (2 negative PCR tests separated by >24 hours) was met. The COVID-19 infectious diseases team (COVID ID) evaluates patients who meet time-based criteria for discontinuation of isolation but are severely immunocompromised or remain critically ill, to provide expert consultation and to assist with decision making regarding duration of isolation.

Reports of prolonged viral shedding in severely immunosuppressed patients are available.[1–3] There are also concerns regarding prolonged viral shedding in patients who remain critically ill, particularly because many of these patients remain intubated or undergo other aerosol-generating procedures.[4–6] At our center, the COVID ID physician assesses patients who are 21 days from their initial positive test for clinical improvement and typically recommends repeat PCR testing of respiratory specimens in patients who remain critically ill.[7] In patients with positive PCR results, the cycle threshold value (Ct) is evaluated to make a better-informed determination on whether isolation can safely be discontinued. Generally, Ct ≥ 30 has been associated with the inability to recover viable SARS-CoV-2 virus.[8,9] A nasopharyngeal (NP) swab is the typical specimen for SARS-CoV-2 PCR; however, concerns have surfaced regarding the continued risk for viral replication in the lower respiratory tract in patients who remain critically ill and whether tracheal aspirates should be utilized in lieu of NP swabs.

Factors that increase the risk of nosocomial transmission of respiratory viruses include high community incidence rates, high viral load, greater symptoms when viral loads are high, proximity between people, duration of exposure, lack of maskings, and poor ventilation.[10] Because continued viral shedding in the lower respiratory tract could represent continued risk for transmission and nosocomial outbreaks, we evaluated the correlation of Ct values from NP swabs and tracheal aspirates in critically ill patients who remain intubated or on assisted ventilation at least 21 days from their initial positive SARS-CoV-2 PCR as a quality improvement initiative to determine the utility of PCR of tracheal aspirates and to assist with decision making regarding discontinuation of isolation.

This analysis was performed on a small series of patients admitted to critical care units at University of Nebraska Medical Center/Nebraska Medical between October and December 2021. At that time, the δ (delta) variant (B.1.617.2) accounted for >99% of COVID-19 hospital admissions. Patients who had surpassed 21 days since their initial positive SARS-CoV-2 PCR but remained intubated or on assisted ventilation were evaluated by the COVID ID team according to routine protocol. Paired NP swabs and tracheal aspirates were collected for SARS-CoV-2 PCR. Tracheal aspirates were extracted on the KingFisher Flex Purification System (ThermoFisher, Waltham, MA) using the MagMAX Viral/Pathogen II (MVP II) nucleic acid isolation kit (ThermoFisher). Because of viscosity issues, samples were extracted in triplicate, using a 400-µL input volume and a 50-µL elution volume for each replicate. The extracted RNA was used for the detection of SARS CoV-2 RNA using a reverse-transcription, real-time PCR assay on the Applied Biosystems QuantStudio Dx Real-Time Instrument (ThermoFisher). The NP swabs in viral transport media were spun in a vortexer to mix the sample, then placed in aliquots (ie, 750 µL) in a second tube and loaded directly onto the Roche Cobas 6800 system (Roche Molecular Systems, Branchburg, NJ) for extraction and amplification using the SARS-CoV-2 assay. The Roche SARS-CoV-2 assay includes 2 targets for the qualitative detection of SARS-CoV-2: the *orf1a* gene, which is specific for SARS-CoV-2, and the *E* gene, a pansarbecovirus target.

We found a significant discrepancy between Ct values from NP swabs and tracheal aspirates in some patients, and our discordant results on paired NP and tracheal aspirate specimens (obtained within 24 hours of each other) are shown in Table 1.

Although sufficient evidence indicates that immunosuppressed individuals may shed SARS-CoV-2 for extended periods, critical illness may also result in prolonged viral shedding. Our results demonstrate that Ct values from lower-respiratory-tract specimens

Author for correspondence: Dr. Daniel Brailita, E-mail: dabrailita@unmc.edu

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Table 1. SARS-COV-2 PCR Results From Paired Tracheal Aspirate (TA) and Nasopharyngeal (NP) Specimens

Patient	Days from Symptom Onset to TA	Days from Initial SARS-CoV-2 Positive PCR to TA	TA Collection Date	TA Cycle Threshold (*E* gene)	NP Swab Collection Date	NP Swab Result and Cycle Threshold (*ORF1a*/*E* gene)
1	25	24	10/31/21	Positive (24)	10/31/21	Positive (35/36)
1	30	29	11/05/21	Positive (27)	11/05/21	Positive (35/36)
2	22	21	11/03/21	Positive (19)	11/03/21	Negative (n/a)
3	22	22	11/04/21	Positive (29)	11/03/21	Positive (32/35)
4	25	24	11/26/21	Positive (17)	11/26/21	Positive (25/26)

in patients who remain intubated or critically ill at day 21 from initial positive PCR may be low enough to be consistent with active viral replication, and these results do not necessarily correlate with results from NP swabs. This finding is concerning because nosocomial transmission of COVID-19 could occur as a result of discontinuing isolation in patients who continue to undergo aerosol-generating procedures and as a result of management of secretions by healthcare workers.

We recognize the limitations of our study related to very small sample size, the potential difference in Ct values from use of different types of samples and laboratory platforms, and the lack of viral cultures to confirm active viral replication. Furthermore, this evaluation was performed during the SARS-CoV-2 δ (delta) variant wave, and it may not be applicable to the SARS-CoV-2 (omicron) variant (B.1.1.529) or subsequent lineages. Despite these limitations, the discrepancy in Ct values in this small series was compelling enough for our institution to continue our practice of reviewing all critically ill, intubated patients at day 21 from initial positive PCR and to obtain tracheal aspirates to inform decisions regarding the need for continued isolation in the inpatient setting.

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