Temporal Dynamics of Nasopharyngeal and Tracheal SARS-CoV-2 Cycle Thresholds in COVID-19 Patients with Tracheostomy

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Abstract

In this study of 45 patients with COVID-19 undergoing tracheostomy, nasopharyngeal and tracheal cycle threshold (Ct) values were analyzed. Ct values rose to 37.9 by the time of tracheostomy and remained >35 postoperatively, demonstrating that persistent test positivity may not be associated with persistent transmissible virus in this population.

KEYWORDS: COVID, SARS-CoV-2, tracheostomy, PCR, cycle thresholds

Introduction

The COVID-19 pandemic resulted in a dramatic rise in tracheostomies worldwide for patients with ventilator dependency. Particularly at the start of the pandemic, much discussion surrounded the optimal technique for performing airway surgery and how to minimize transmission risk as much as possible for healthcare workers performing these aerosol-generating procedures (AGPs). Many studies have since been published on outcomes following tracheostomy in patients with COVID-19 and have supported not only its utility but also its safety for those involved in the surgery.[1–3] It is known that polymerase chain reaction (PCR) positivity after infection with SARS-CoV-2 can persist for several weeks following an initial positive test.[4] Others have studied the degree of viral aerosolization from tracheostomy and related tracheostomy care, however, the dynamics of SARS-CoV-2 viral shedding in the lower respiratory tract in a clinical setting remain poorly understood.[5]

The objectives of this pilot study are to 1) demonstrate the pattern of test positivity over time in both nasopharyngeal and tracheal aspirates in patients with COVID-19 undergoing tracheostomy and 2) determine the cycle threshold (Ct) values over time in this patient population. We hypothesized that the Ct values (a known proxy for viral load)[6] by the time of tracheostomy and during tracheostomy care postoperatively increase over time following initial diagnosis, rendering these patients unlikely to remain infectious at the time of tracheostomy.

Methods

This analysis utilized a prospective database of COVID-19 patients admitted to our institution between March and April 2020. Each patient's diagnosis was confirmed by nasopharyngeal swab RT-PCR. All included patients had respiratory failure secondary to COVID-19 and had met criteria to undergo tracheostomy as determined by an institutional protocol, as previously published.[1] To collect information on COVID-19 laboratory results, including date of test, positive or negative result, and specimen source, the electronic medical record (Eclipsys Allscripts Enterprise, Allscripts Healthcare Solutions, Inc.,

Chicago, IL) was queried. Ct values were retroactively determined from the existing qualitative positive PCR tests for a subset of the total prospective cohort for whom specimens remained available. PCR tests from tracheal aspirates were performed using various platforms detecting ORF1a, N2, and E genes. The length of viral shedding was determined by the difference from the date of last positive test (nasopharyngeal or tracheal) and the date of the first positive test (nasopharyngeal). This study was approved by the Weill Cornell Medicine Institutional Review Board.

Statistical Methods

A linear mixed effects model with a random subject intercept adjusting for first Ct measurement and time from tracheostomy date was utilized to analyze differences in Ct by location (tracheal compared to nasopharyngeal). Ninety-five percent confidence intervals were generated for all predictor estimates and statistical significance was evaluated at the 0.05 alpha level. All analyses were performed in R for Windows (version 4.0.3, 2019, Vienna, Austria).

Results

Our dataset included forty-five patients with available Ct values, including 13 females (29%) and 32 males (71%) with a median age of 67 years (IQR 56, 74). The majority of patients identified as White/Caucasian (n=22, 49%) or Other (n=13, 29%). Included patients underwent tracheostomy between April and May 2020 after a median of 23 days intubated (IQR 20, 27) and at a median of 24 days following admission (IQR 21, 31.5).

All patients were presumed positive for COVID-19 at the time of tracheostomy based on perioperative testing. The first available Ct value was obtained at a median of 25 days prior to tracheostomy (IQR -32, -20 days) and was 24 (IQR 19, 29). At the time of tracheostomy (+/- three days), the median nasopharyngeal Ct value was 37.9 (IQR 33.6, 41.4). This difference between first Ct value and Ct value at the time of tracheostomy reflected a persistent positivity for greater than three weeks. The median length of viral shedding between date of first and last positive test was 36 days (IQR 33, 48).

Following tracheostomy, subsequent nasopharyngeal Ct values increased over time (Figure 1A). The median nasopharyngeal Ct values were 35.8 (IQR 33.5, 40.4) at one week, 36.4 (IQR 33.4, 39.4) at two weeks, and 37.5 (IQR 34.7, 38.8) at three weeks following tracheostomy. Seven patients had at least one tracheal Ct value available for analysis. Contrary to the nasopharyngeal Ct values, tracheal Ct values did not consistently increase with time (Figure 1B). The median tracheal Ct values were 34.5 (IQR 32.8, 36.1) at one week, 29.4 (IQR 28.6, 30.7) at two weeks, and 33.4 (IQR 29.1, 36.6) at three weeks following tracheostomy. On average, tracheal aspirates had a Ct of 6.3 less than nasopharyngeal samples, adjusting for first Ct value and time since tracheostomy (95% CI -10, -2.5; p=0.003). When the median tracheal and nasopharyngeal Ct values at weeks one, two and three following tracheostomy were individually compared by Wilcoxon rank-sum tests, the tracheal Ct values were significantly lower at weeks two and three following tracheostomy ($p<0.0001$), but not at week one following tracheostomy ($p=0.12$). However, this analysis should be interpreted with caution due to the small sample size and potential for confounders.

Discussion

Ct values for nasopharyngeal and tracheal aspirates in patients with COVID-19 undergoing tracheostomy have not been previously well-studied. Results from our pilot study show that patients may test persistently positive in both upper and lower respiratory tract specimens for greater than one month, which is slightly longer than the average time noted in a recent meta-analysis.[7] However, our viral shedding time may be longer than others since all of our patients were inpatients with critical COVID-19 illness and therefore represented the severest of cases. Although other variables (i.e., time from symptom onset) may account for risk of COVID-19 transmission, a Ct value >30 is generally thought to be associated with a low risk of transmission.[8–10] Ct values from nasopharyngeal samples were approximately 24 at the time of admission, rose to 37.9 by the time of tracheostomy at our institution, and remained >35 in the weeks postoperatively. Tracheal Ct values were more variable and slightly lower than nasopharyngeal samples at similar time points, but for the most part exceeded 30 in the weeks

following tracheostomy suggesting low viral load in the lower respiratory tract. The reduced and more variable tracheal Ct values may also have been related to random variation due to the small sample size of patients with tracheal aspirates. A larger sample of tracheal aspirate data would allow for more robust comparison with that from the nasopharynx.

It should be noted that a limitation to this study is the use of Ct values as a surrogate for viral load. Additionally, our institution used a variety of testing platforms with different genes analyzed, which may have affected the results. Some Ct values were not available or calculated despite a positive test being recorded, which also limited our dataset. Although viral culture is a better measure of infectivity, multiple studies have documented the correlation between Ct values and isolation of replication competent virus in culture.[11] Additionally, qualitative PCR tests are widely used across institutions and therefore this study utilizing Ct values as a surrogate can be valuable from a clinical perspective.

Future directions include longitudinal, high-powered studies examining the association between persistent positivity/Ct values and patient characteristics such as comorbid conditions, symptom severity, and recovery time. These factors are becoming particularly important with the rise of new viral strains such as the Delta and Omicron variants.

Conclusions

Our pilot findings suggest that persistent test positivity in both the upper and lower respiratory tract in patients with COVID-19 undergoing tracheostomy is unlikely to be associated with persistent infectious virus. These data support a low risk of SARS-CoV-2 transmission to healthcare workers performing tracheostomy in patients with COVID-19-related respiratory failure, and reinforce the safety of current personal protective equipment recommendations for AGPs including tracheostomy care. Although Ct values from tracheal aspirates may be more variable and slightly lower compared to those from the nasopharynx, the degree of potential infectivity in patients with COVID-19 decreases over time and many persistently positive patients are unlikely to remain highly infectious.

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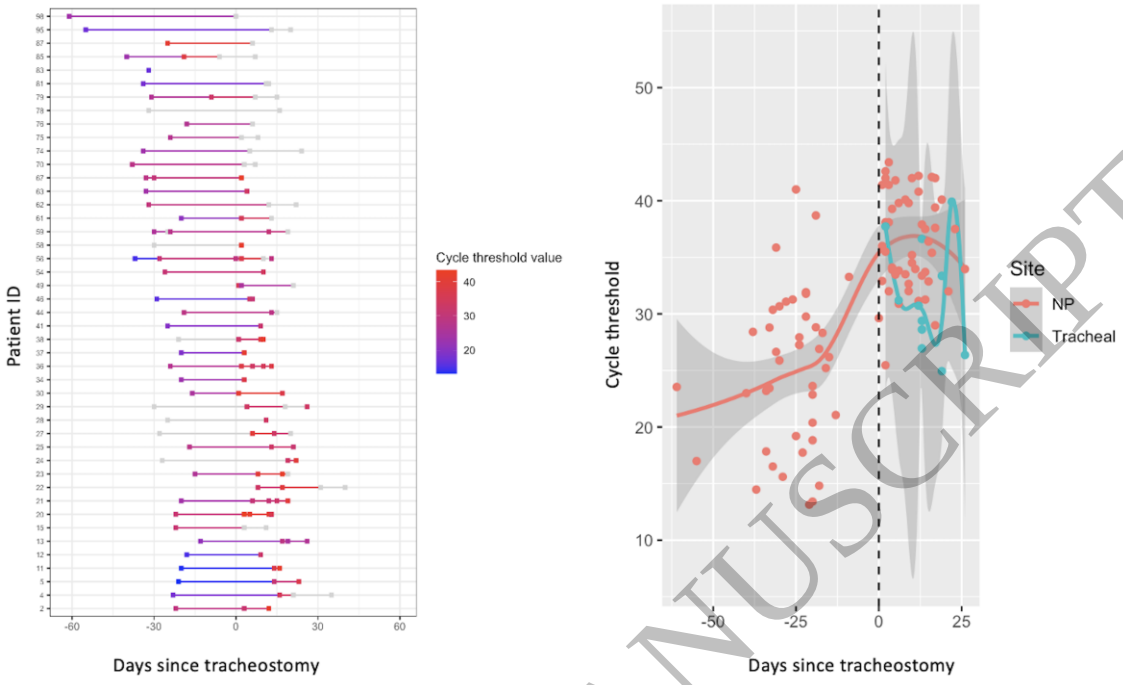

Figure 1: A) Cycle threshold timelines by patient across both nasopharyngeal and tracheal samples. Cycle threshold values are color coded; grey indicates missing time or level. **B)** Cycle threshold value plotted against the number of days since tracheostomy. The date of tracheostomy is indicated by day zero. The pink line indicates nasopharyngeal swabs and the blue line indicates tracheal swabs.