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Discordant SARS-CoV-2 Detection in the Nasopharynx versus Trachea for Patients with Tracheostomies

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Running title: SARS-CoV-2 tests in tracheostomized patients

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Abstract

Objective – Patients with tracheostomies have an anatomically altered connection between their upper and lower airways that could impact SARS-CoV-2 testing. Our goal was to evaluate for discordance in SARS-CoV-2 detection in hospitalized patients with COVID-19 and tracheostomies based on the site analyzed.

Methods – This single-institution study evaluated hospitalized patients with COVID-19 who had tracheostomies placed during their treatment. We analyzed SARS-CoV-2 RNA nucleic acid amplification test (NAAT) results after tracheostomy. All included patients had nasopharyngeal (NP) and tracheal (TR) samples taken within a 48-hour period, allowing us to characterize rate of test concordance.

Results – Forty-five patients met our inclusion criteria. Thirty-two (71.1%) patients had entirely concordant results after tracheostomy. However, 13 (28.9%) patients had at least one set of discordant results, the majority of which were NP negative and TR positive. There were no statistically significant differences in demographic or clinical variables, including time to tracheostomy and time to testing, among patients with concordant versus discordant SARS-CoV-2 results.

Conclusion – This represents the first study to examine SARS-CoV-2 RNA NAAT concordance between NP and TR sites in hospitalized patients with COVID-19 and tracheostomies. One-third of patients demonstrated discordant testing when NP and TR specimens were collected within a 48-hour time period. Thus, patients with tracheostomies may have a higher false negative rate if only one site is assessed for SARS-CoV-2. We recommend analyzing samples from both the nasopharynx and trachea for these patients until more prospective data exists.

Keywords: SARS-CoV-2, COVID-19, tracheostomy, nasopharyngeal, detection

Level of evidence: IV

Introduction

As of late December 2020, the COVID-19 pandemic has afflicted greater than 79 million people across the globe, with over 1.7 million deaths.[1] Approximately 5% of patients have required admission to an intensive care unit (ICU) with prolonged periods of endotracheal intubation and mechanical ventilation.[2,3] In certain patients, early tracheostomy provides significant benefit by reducing sedation, duration of ventilatory support and ICU stay, and rates of intubation-induced laryngotracheal injury.[4,5] However, tracheostomy in patients with COVID-19 has major clinical implications for risk of viral transmission to healthcare providers and other patients.[6] This has led to a spirited global debate about best practices and special considerations for perioperative care of patients with COVID-19 and tracheostomies.[7,8]

Nucleic acid amplification tests (NAAT) for detection of SARS-CoV-2 RNA in upper respiratory tract samples (i.e. nasal cavity, nasopharynx, or oropharynx) have become the current gold-standard for diagnosis and monitoring of COVID-19 infection.[9,10] This is due to high test sensitivity and specificity as well as ease, safety, and reliability of specimen collection.[10] Though more difficult to collect, NAATs of lower respiratory tract samples are associated with lower false negative test rates. [11] These include tracheal aspirate, bronchoalveolar lavage, and sputum samples. Clinicians have also seen variable SARS-CoV-2 shedding depending on anatomic site and time point of sampling.[12,13]

Patients with tracheostomies placed during their COVID-19 disease course have an anatomically-altered connection between their upper and lower airways that could theoretically impact the detection of SARS-CoV-2. Multiple case reports have shown discordant detection of SARS-CoV-2 in the nasopharynx versus trachea for patients with a history of laryngectomy.[14,15] On the contrary, a recent prospective cohort study of 15 patients with tracheostomies either with or without underlying COVID-19 (experimental versus control groups) reported greater than 90% correlation between nasopharyngeal (NP) and tracheal (TR) samples for their patients.[16] In this manner, there exists conflicting information in the literature regarding SARS-CoV-2 detection at different anatomic sites for patients with tracheostomies or laryngectomy stomas.

Indeed, stronger data on concordance of SARS-CoV-2 RNA NAATs on upper and lower airway samples in patients with COVID-19 and tracheostomies is needed to guide isolation precautions and optimal post-tracheostomy care. Therefore, we sought to evaluate the concordance rate of SARS-CoV-2 NAATs for NP versus TR samples in a single institution cohort of hospitalized patients with COVID-19 and tracheostomies placed during their hospital course. This study does not include patients with pre-existing tracheostomies or laryngectomy stomas as there was only one patient in this cohort, and these patients represent a unique sub-population with potential for different viral kinetics and testing patterns.

Materials and Methods

This was a single-institution cohort study with retrospective data collection from March through December 2020. Our primary outcome of interest was the concordance rate of SARS-CoV-2 RNA NAATs from NP versus TR samples in hospitalized COVID-19 patients with tracheostomies. Patients who were admitted with COVID-19 infection and had tracheal NAAT testing for SARS-CoV-2 were identified with the Electronic Medical Record Search Engine (EMERSE).[17] Identified subject charts were reviewed for inclusion criteria. Inclusion criteria were as follows: 1) adults at least 18 years of age; 2) confirmed COVID-19 infection on hospital admission by positive NAAT on NP swab specimen; 3) tracheostomy placed after admission by percutaneous or open surgical technique; and 4) at least one set of post-tracheostomy NP and TR specimens obtained within a 48-hour period. The 48-hour period was chosen based on high concordance of repeat testing within this window and practice guidelines for SARS-CoV-2 re-testing in patients with high clinical suspicion for COVID-19 but initial negative tests.[9,10] Clinical documentation was reviewed to collect demographic information and pertinent clinical variables such as comorbidities. This study was determined to be exempt after review by the University of Michigan Institutional Review Board.

All NAATs were done by the University of Michigan Department of Pathology Laboratories. NP and TR specimens were run on one of three real-time, RT-PCR platforms. These included the Abbott m2000 SARS-CoV-2 assay, Abbott Alinity SARS-CoV-2 assay, or the DiaSorin Molecular Simplexa COVID-19 assay. All assays have been approved for routine clinical use under the U.S. Food and Drug Administration's Emergency Use Authorization. Our institution's protocol for de-escalating isolation precautions for hospitalized patients with COVID-19 and tracheostomies has evolved over the course of the pandemic. Presently, de-escalation of "special pathogens precautions" requires either: 1) two negative NP swabs collected greater than 24 hours apart plus one negative TR specimen; or 2) two negative TR specimens collected greater than 24 hours apart plus one negative NP swab.[18] This framework contextualizes the SARS-CoV-2 testing patterns after tracheostomy in our population.

Statistical analyses were completed with SPSS (IBM). Fisher's exact tests and Wilcoxon rank-sum tests were used to compare categorical and continuous variables, respectively. *P* values less than 0.05 were considered statistically significant.

Results

We identified 63 patients treated at the University of Michigan between March and December 2020 with COVID-19 and tracheostomies. Eighteen of 63 (28.6%) patients were excluded due to lack of at least one set of NP and TR specimens obtained within a 48-hour period. Thus, our final patient cohort included 45 patients. Out of these 45 patients, 32 had entirely concordant results between their NP and TR tests post-tracheostomy. The other 13 patients had at least one set of discordant results. There were no statistically significant differences in patient demographics nor other important clinical variables among patients with concordant versus discordant tests (Table 1).

In the 32 patients with concordant NP and TR results, a total of 122 SARS-CoV-2 RNA NAATs (median [range] of 3.5 [2 – 7] tests per patient) were run post-tracheostomy. Out of these 122 tests there were 36 sets of NP and TR specimens to analyze. The median (range) time to tracheostomy (measured from date of initial positive SARS-CoV-2 test) in this cohort was 22 (5 – 47) days. The time from initial positive SARS-CoV-2 test to collection of the first set of NP and TR specimens showed a median of 33 days with a range of 5 – 78 days (Table 1). Of the 36 sets of NP and TR results, 30 (83.3%) were concordant negative and six (16.7%) were concordant positive (Supplemental Figure 1). A single patient with concordant negative NP and TR results had a positive NP swab one day after.

A total of 71 SARS-CoV-2 RNA NAATs (median [range] of 5 [3 – 8] tests per patient) were run post-tracheostomy in the 13 patients with discordant NP and TR results. This included 9 NP specimens only, 10 TR specimens only, and 26 sets of NP and TR specimens. The median (range) time to tracheostomy and time to specimen collection (as measured from initial positive SARS-CoV2 test to first set of NP/TR specimens) in this cohort was 20 (5 – 27) and 32 (25 – 57) days, respectively (Table 1). Out of the 26 sets of NP and TR specimens in this group, 19 were discordant. Five of these were NP positive and TR negative while the other 14 were NP negative and TR positive (Figure 1). Of particular interest is patient 4 whose initial pair of tests was NP positive and TR negative but subsequently had two sets that were NP negative and TR positive. There were five patients that had concordant NP and TR negative samples after their initial discordant results. This would indicate that they had effectively cleared SARS-CoV-2 from their system.

Discussion

Characterization of SARS-CoV-2 viral load kinetics and shedding by anatomic site and time point of illness has been a primary goal of global research efforts during the COVID-19 pandemic.[19,20] Such parameters dictate duration of infectivity, risk of viral transmission and guide hospital testing and isolation protocols.[21] The most contemporary evidence suggests that viral shedding in the upper and lower respiratory tracts peaks during the first week of illness, though can be quite prolonged (i.e. more than 60 days).[22] Various factors have been posited to correlate with duration of viral shedding, including symptomatic (versus asymptomatic) and febrile COVID-19 illness,[23] older age,[22] and time from symptom onset to hospital admission.[24]

At present, there are conflicting data on the superiority of upper versus lower respiratory tract SARS-CoV-2 RNA NAATs in most patient populations and settings.[9] In hospitalized patients with COVID-19, the Infectious Disease Society of America (IDSA) Practice Guidelines recommend an initial NP swab that, if negative, is followed by testing of tracheal aspirate to minimize false negative results.[10] The IDSA noted a particular need for comparative studies assessing the accuracy and concordance of upper versus lower respiratory tract SARS-CoV-2 RNA NAATs for patients in whom these samples were collected simultaneously. In the few published case series with this framework, test concordance and accuracy was quite high.[13,25]

The optimal testing strategy for hospitalized patients with tracheostomies due to COVID-19 remains unclear. To de-escalate special pathogens precautions in hospitalized patients with COVID-19 and tracheostomies, our institution requires either: 1) two negative NP swabs collected greater than 24 hours apart plus one negative TR specimen; or 2) two negative TR specimens collected greater than 24 hours apart plus one negative NP swab.[18] This testing framework allowed us to analyze the concordance rate of nearly simultaneous (i.e. within 48 hours) NP and TR tests in our population. The majority of patients (n = 32, 70%) in our cohort had concordant positive or negative NP and TR results (Supplemental Figure 1).

Importantly, almost 30% of patients had at least one set of discordant NP and TR results after tracheostomy. The majority of discordant tests showed negative NP but positive TR specimens, frequently leading to repeat testing, prior to de-escalating special pathogens precautions (Figure 1). These results are consistent with studies showing persistent viral replication and shedding in the lower respiratory tract after clearance of virus from the nasal cavity and nasopharynx.[26,27] Four patients had discordant results showing positive NP but negative TR specimens. It is possible that inadequate sampling may have contributed to this discordance. Only one of these patients (Figure 1, patient 4**)** later had a repeat TR specimen that was positive.

Two additional patients in the discordant cohort had an interesting pattern to their results. Patient 7 had an initial pair of concordant NP and TR negative samples, but their subsequent set showed discordant results with NP positive and TR negative. It is difficult to say what led to this discordance, but it could be the result of an initial false negative test. Patient 12 was initially NP positive and TR positive followed by NP negative and TR positive, indicating persistence of detectable virus solely in the trachea.

SARS-CoV-2 viral load kinetics and shedding by anatomic site is likely variable among individual patients and influenced by factors such as age, severity of illness, and duration of symptoms. Our study suggests that patients with tracheostomies placed during their COVID-19 illness may have higher rates of discordant NP and TR test results than most populations. In certain patients, this may be due to the tracheostomy tube effectively separating the upper and lower airways. However, insufficient sampling, assay characteristics, and time to sampling may also be contributing factors.

In our cohort of patients, time to specimen collection and testing patterns overall were quite variable. The reason for this heterogeneity is multifactorial though attributable at least in part to individualized clinical-decision making and enhanced understanding of viral shedding patterns as the COVID-19 pandemic has progressed. A recent study suggested that live, infectious virions are unlikely to persist in either the upper or lower airways past day nine of COVID-19 illness.[22] This raises the question of necessity and utility of additional SARS-CoV-2 testing after tracheostomy to guide isolation precautions. Until more definitive data is available however, evidence-based and institution-dependent protocols for SARS-CoV-2 testing for hospitalized patients should be closely followed.

There are important limitations to this study. First, this was performed in a retrospective manner. As this pandemic continues it will be important to evaluate this type of data in an organized, prospective fashion for more definitive information. Another limitation for this study is that we did not analyze patients who had pre-existing tracheostomies or laryngectomy stomas. These patients represent a unique patient population with special considerations for COVID-19 diagnostics, viral transmissibility, and risk of severe pulmonary sequelae.[14,28,29] We only identified one patient with a pre-existing tracheostomy, and to maintain a uniform cohort in this study they were ultimately excluded from our final analysis. Indeed this patient population requires further analysis to determine if SARS-CoV-2 is detected differently at NP versus TR sites as we have shown in the present study.

Based on our comprehensive analysis that included all hospitalized COVID-19 patients that underwent tracheostomy at our tertiary care academic medical center between March and December of 2020, we determined that almost one-third of patients had discordant SARS-CoV-2 detection in the nasopharynx versus trachea after tracheostomy. This high percentage of discordant results has important implications to all healthcare personnel as we need to have a high degree of confidence before removing special pathogens precautions for patients to reduce the spread of this virus and slow the progression of

the pandemic. Thus, we recommend routinely testing both NP and TR sites for patients with COVID-19 and tracheostomies. Moreover, we would extrapolate this data to patients with pre-existing tracheostomies and laryngectomy stomas and recommend sending NP and TR specimens for these patients until more specific data is available.

Conclusion

To our knowledge, this is the first study to examine SARS-CoV-2 RNA NAAT concordance between nasopharyngeal and tracheal sites in hospitalized patients with COVID-19 and tracheostomies. We saw a fairly high rate of discordant testing (28.9% of patients) when nasopharyngeal and tracheal specimens were collected within a 48-hour period. We conclude that patients with tracheostomies may have a higher false negative rate if only one site is assessed for SARS-CoV-2. Our data supports analyzing samples from both the nasopharynx and trachea for these patients until more prospective data exists.

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Table and Figure Captions

Table 1. Comparison of patients with COVID-19 and concordant versus discordant nasopharyngeal and tracheal test results after tracheostomy. Data presented as median (range) or n (%). Abbreviations: y, years; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; d, days; ICU, intensive care unit.

[a] Time from initial positive SARS-CoV-2 test result to tracheostomy

[b] Time from initial positive SARS-CoV-2 test result to collection of first set of NP and TR specimens

Figure 1. SARS-CoV-2 NAAT results after tracheostomy in patients with COVID-19 and discordant nasopharyngeal (NP) and tracheal (TR) results, by individual patient.

Supplemental Figure 1. SARS-CoV-2 NAAT results after tracheostomy in patients with COVID-19 and concordant nasopharyngeal (NP) and tracheal (TR) results, by individual

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To: Andrew Stein

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Subject: Notice of Exemption for [HUM00190341]

SUBMISSION INFORMATION:
Title: SARS-CoV2 Detection in Nasopharyngeal versus Tracheal Swabs for Patients with Tracheostomies and Laryngectomies
Full Study Title (if applicable): SARS-CoV2 Detection in Nasopharyngeal versus Tracheal Swabs for Patients with Tracheostomies and Laryngectomies
Study eResearch ID: HUM00190341
Date of this Notification from IRB: 10/28/2020
Date of IRB Exempt Determination: 10/28/2020
UM Federalwide Assurance: FWA00004969 (For the current FWA expiration date, please visit the UM HRPP Webpage)
OHRP IRB Registration Number(s):

Additional Supporting Documents:

IRB EXEMPTION STATUS:
The IRBMED has reviewed the study referenced above and determined that, as currently described, it is exempt from ongoing IRB review, per the following exemption category:

EXEMPTION 4(iii) at 45 CFR 46.104(d):

Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(iii)The research involves only information collection and analysis involving the investigator's use of **identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E**, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b)

Note that the study is considered exempt as long as any changes to the use of human subjects (including their data) remain within the scope of the exemption category above. Any proposed changes that may exceed the scope of this category, or the approval conditions of any other non-IRB reviewing committees, must be submitted as an amendment through eResearch.

Although an exemption determination eliminates the need for ongoing IRB review and approval, you still have an obligation to understand and abide by generally accepted principles of responsible and ethical conduct of research. Examples of these principles can be found in the Belmont Report as well as in guidance from professional societies and scientific organizations.

HIPAA REVIEW:
The IRB has reviewed the project referenced above and has granted a Waiver of HIPAA Authorization. The IRB has determined that the proposed project conforms with applicable regulations and policies. This project must be conducted in accordance with the description and information provided in the application and associated documents.

Note: This project is regulated under the HIPAA Privacy Rule, which requires you to account for certain disclosures of Protected Health Information (PHI).

SUBMITTING AMENDMENTS VIA eRESEARCH:
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ACCESSING EXEMPT STUDIES IN eRESEARCH:
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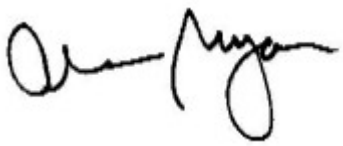
You will receive an annual message reminding you of your responsibilities to manage this research application. Terminate the application once you only hold or are analyzing deidentified data, or the research has ended.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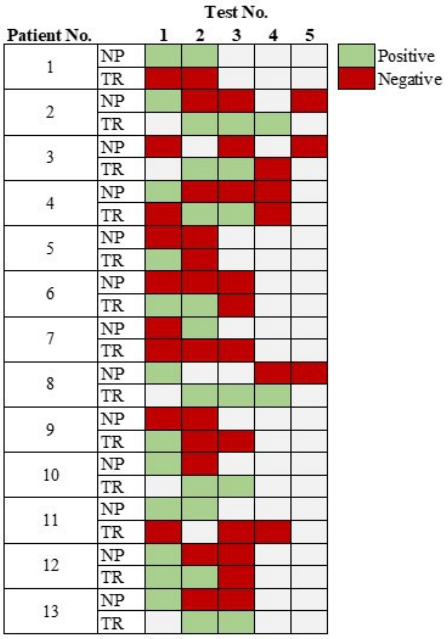
	All Patients (n = 45)	Concordant Results (n = 32)	Discordant Results (n = 13)	*p* Value
Age, y	53.7 (24.6 – 89.8)	57.3 (25.0 – 89.8)	47.6 (24.6 – 70.7)	0.12
Sex				0.88
Male	25 (55.6)	18 (56.3)	7 (53.8)	
Female	20 (44.4)	14 (43.7)	6 (46.2)	
Race				0.75
African American	18 (40.0)	13 (40.6)	5 (38.5)	
Caucasian	26 (57.8)	18 (56.3)	8 (61.5)	
Other/Unknown	1 (2.2)	1 (3.1)	0 (0)	
BMI, kg/m^2	33.2 (20.5 – 53.1)	32.3 (20.5 – 47.2)	34.3 (26.2 – 53.1)	0.14
Comorbidities				
Asthma/COPD	15 (33.3)	10 (31.3)	7 (53.8)	0.16
Coronary Artery Disease	6 (13.3)	4 (12.5)	2 (15.4)	0.80
Diabetes	17 (37.8)	11 (34.4)	6 (46.2)	0.46
Hypertension	25 (55.6)	20 (62.5)	5 (38.5)	0.14
Time to Tracheostomy, d[a]	22 (5 – 47)	22 (5 – 47)	20 (5 – 27)	0.54
Time to Specimen Collection, d[b]	33 (5 – 78)	33 (5 – 78)	32 (15 – 60)	0.73
Duration ICU Stay, d	36 (9 – 156)	41 (9 – 156)	33 (25 – 57)	0.12
Duration Hospital Stay, d	56 (22 – 170)	56 (22 – 170)	57 (30 – 114)	0.67



LARY_29617_SARS-CoV Figure 1 wo PreExisting Trach.jpg