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Major Article

Case-control study evaluating risk factors for SARS-CoV-2 outbreak amongst healthcare personnel at a tertiary care center

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A B S T R A C T

Background: Despite several outbreaks of SARS-CoV-2 amongst healthcare personnel (HCP) exposed to COVID-19 patients globally, risk factors for transmission remain poorly understood.

Methods: We conducted an outbreak investigation and case-control study to evaluate SARS-CoV-2 transmission risk in an outbreak among HCP at an academic medical center in California that was confirmed by whole genome sequencing.

Results: A total of 7/9 cases and 93/182 controls completed a voluntary survey about risk factors. Compared to controls, cases reported significantly more patient contact time. Cases were also significantly more likely to have performed airway procedures on the index patient, particularly placing the patient on high flow nasal cannula, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP) (OR = 11.6; 95% CI = 1.7 –132.1).

Discussion: This study highlights the risk of nosocomial infection of SARS-CoV-2 from patients who become infectious midway into their hospitalization. Our findings also reinforce the importance of patient contact time and aerosol-generating procedures as key risk factors for HCP infection with SARS-CoV-2.

Conclusions: Re-testing patients for SARS-CoV-2 after admission in suspicious cases and using N95 masks for all aerosol-generating procedures regardless of initial patient SARS-CoV-2 test results can help reduce the risk of SARS-COV-2 transmission to HCP.

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BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first documented to cause hospital outbreaks amongst healthcare personnel (HCP) early in the course of the pandemic.[1] HCP are at higher risk of SARS-CoV-2 infection due to close contact with infected patients and increased exposure to their respiratory droplets.[2,3] In addition, inadequate supply of personal protective equipment (PPE) may have exacerbated HCP's risk when caring for patients with coronavirus disease 2019 (COVID-19).[4]

There have been several reports of increased SARS-CoV-2 infections among HCP worldwide since the beginning of the pandemic.[5−8] In a large prospective cohort study of over 2 million community individuals and nearly 100,000 HCP in the UK and USA, HCP were found to have a 3.4 times increased risk of SARS-CoV-2 infection compared to the general population.[6] Several SARS-CoV-2 outbreaks amongst healthcare workers have also been reported and directly linked to a single index patient, often a patient with a delayed diagnosis of COVID-19 due to negative tests early in the hospital course.[8−13] Although these outbreaks are often relatively small, they provide critical information about risk factors for nosocomial transmission and can help guide infection control practices.

The CDC stratifies the risk of COVID-19 transmission to HCP by duration or type of exposure. A prolonged exposure is defined as any cumulative exposure to SARS-CoV-2 infected patients or visitors for greater than 15 minutes in a 24-hour period. However, risk factors like exposure in confined spaces or performing an aerosol-generating procedure (AGP) are considered high risk for transmission regardless of exposure time.[14] HCP spend a variable amount of time in patients' rooms depending on their jobs and departments. A study in the UK showed increased rates of COVID-19 amongst doctors and nurses working in emergency medicine and critical care.[15] In the US, nursing staff have been shown to have higher COVID-19 rates and associated hospitalizations compared to other HCP; other clinical HCP also had higher rates compared to non-clinical support and infrastructure personnel.[7,16]

Although our understanding of COVID-19 hospital outbreaks and infection control measures have improved dramatically since the start of the pandemic, healthcare worker outbreaks continue to occur and the risk of SARS-CoV-2 infection for HCP exposed to various types of AGPs remains unclear. Evidence about the risks associated with exposure to AGPs performed on patients with COVID-19 who didn't require intubation is particularly lacking. Better understanding of risk factors for SARS-CoV-2 transmission, particularly in non-intubated patients, is critical to formulating infection control policies to prevent nosocomial transmission and protect HCP.

We conducted an outbreak investigation and case-control study of nosocomial SARS-CoV-2 transmission amongst HCP that occurred in a well-resourced academic medical center that was found to originate in a non-intubated patient transferred from an outside hospital. We evaluated risk factors for transmission including work type, PPE use, participation in various AGPs and non-aerosol generating procedures (non-AGPs), and duration of time spent with the patient.

METHODS

Index patient

A 72-year-old female with a pertinent past medical history of atrial fibrillation on amiodarone and rivaroxaban, chronic obstructive pulmonary disease requiring oxygen at baseline, and remote history of lung cancer status post radiation was transferred to an academic medical center for a carotid endarterectomy after being diagnosed with a left middle cerebral artery stroke at an outside facility. She was admitted to the intensive care unit in a 214 square foot private room with excellent ventilation (approximately 20 air changes per hour). She had a negative nasopharyngeal SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test from the referring hospital on the day of transfer and another negative nasopharyngeal SARS-CoV-2 RT-PCR upon arrival to our hospital. On hospital day (HD) 3, she developed acute hypoxic respiratory failure; diagnostic work-up included a chest CT which revealed bilateral patchy ground glass and consolidative opacities and a negative nasopharyngeal viral respiratory pathogen PCR panel on HD4 which did not include SARS-CoV-2. Alternative etiologies were considered, and the patient was started on prednisone 60 mg daily for presumed amiodarone-induced lung toxicity. She required increasing oxygen support and received high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP). Due to clinical deterioration, she had a repeat nasopharyngeal SARS-CoV-2 PCR test on HD 12 which was positive.

Outbreak investigation and study design

We performed a case-control study as part of an outbreak investigation conducted by the Infection Prevention and Control Department (IPCD). This quality improvement project was reviewed and deemed exempt by the Stanford University School of Medicine Panel on Human Subjects in Medical Research.

All exposed HCP were tested for SARS-CoV-2 by RT-PCR by occupational health and were invited to complete a voluntary survey to characterize their exposure to the index patient. All individuals with a negative RT-PCR test who completed the survey and reported at least one day working with the index patient were included in the final analysis as controls. Survey data were directly entered by the employees into REDCap data management tool.[17,18] The survey asked questions regarding demographic and work characteristics, COVID-19 symptoms, PPE use, care activities, and time spent with the patient. Potential demographic and work predictors of cases were assessed in univariate analysis by Fisher's exact test, linear regression, and ordinal regression where appropriate. Multivariable analysis was not performed due to the small sample size. Instead, given that most cases were nurses or therapists, a secondary restricted analysis was performed including only individuals who fell into occupational categories that contained at least one case. All data were analyzed using RStudio version 1.1.456.

Sequencing methods

Whole genome sequencing was performed on samples from the index patient and all positive HCP. A multiplex PCR based technology developed at Stanford Genome Technology Center was used to perform the whole genome sequencing.[19,20] A total of 62 PCR amplicons of ~540bp were designed to cover the entire SARS-COV-2 genome from position 46 to 29793 (NC_045512) (manuscript under preparation). The samples were pooled and sequenced on MiSeq. The SNP analysis was performed using MiSeq Reporter and an in-house software. Nextclade (https://clades.nextstrain.org) and GISAID EpiCoV (https://www.epicov.org) were then used to track the origin of this strain and assign it to its corresponding clade.[21]

RESULTS

Outbreak investigation results

On the patient's HD 11, IPCD was notified of 3 HCP who worked on the same unit with positive nasopharyngeal SARS-CoV-2 RT-PCR tests. Of these 3 HCP, 1 was also in contact with another HCP from the same unit outside of work. On HD 12, the index patient was retested because of worsening clinical condition. After this result was

Figure: Outbreak Investigation

Hospital Day	1	2	3	4	5	6	7	8	9	10	11	12	-	-	-
Index Patient Testing	NEG			T*								T			
Oxygen requirement	Nasal Cannula + Nightly CPAP		BiPAP	Nasal Cannula + Nightly CPAP		BiPAP	High Flow Nasal Cannula				BiPAP				
					Nebulizer Treatment										
Healthcare Personnel (Cases)															
1				P	U	U		S	T						
2	U			P	U		S		T						
3		U	P	P	P			P	T						
4				U	U	P			S	T					
5			U	U	U	U			U	U	U			S	T
6			U										S	T	
7		U	P	P				U		S P			T		
8			U	P	P	P					U	S	T		
9		U	P	P	U	U			S U	T					

Abbreviations: NEG = negative SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure.

*The index patient tested negative for SARS-CoV-2 on HD1. She tested positive on HD12 and on retrospective testing of a HD4 viral respiratory panel swab.

The index patient was admitted from an outside hospital on Hospital Day (HD) 1 requiring oxygen by nasal cannula and nightly CPAP. She continued to decline over the next week, initiating intermittent BiPAP on HD3 and nebulizer treatments on HD5. She ultimately died on HD12.

All healthcare personnel working on the unit during the patient's stay were tested for SARS-CoV-2 by RT-PCR. Those who tested positive are included in the table above with days they worked on the unit, worked directly with the index patient, developed COVID-19 symptoms, and tested positive indicated above. Case #3 had unclear symptom onset. Cases #5 & 6 were float personnel so specific days they worked with the index patient are unknown.

LEGEND	
U	Worked in outbreak Unit
P	Worked with index Patient
S	Symptomatic
T	Tested positive
NEG	Tested negative

Fig 1. Outbreak investigation.

available, the index patient's previous (non-SARS-CoV-2) viral respiratory sample that was collected on HD 4 was tested for SARS-CoV-2 which was then detected. Seven additional patients on the unit at the same time as the index patient were tested and all 7 were negative.

The exposure window was defined as the patient's entire 12-day hospitalization. A total of 191 HCP were identified as potentially exposed and were evaluated by the occupational health department. HCP were tested twice within 14 days of the last exposure. Of the 191 HCP, 9 ultimately tested positive for SARS-CoV-2. The timing of the patient's clinical course in relation to the work schedule, symptom development, and testing of HCP cases was mapped in the outbreak investigation (Fig 1).

Whole Genome Sequencing

Whole genomic sequencing was performed on available samples from the index patient and 7 of the 9 HCP. A total of 12 SNPs were found and shared among all 8 samples. This showed 100% similarity amongst SARS-CoV-2 strains of the index patient and 7 HCP cases. In comparison, the frequency of these SNPs ranged from 0.005% to 87.5% when searched across 96,303 SARS-CoV-2 sequences from the GESS whole genome sequencing database for the U.S. as of May 7th, 2021 (Table 1). The strain identified in this cluster of cases was identified as belonging to Nextstrain clade 20A and traced back to a likely importation from Europe in March 2020.

Demographic and work characteristics

In total, 7/9 (77.8%) of cases and 93/182 (51.1%) of controls responded to the survey. The mean age was 37 years old and 37% of respondents were men. *Cases:* Of the 7 cases, there were 4 nurses, 1 nursing assistant, 1 respiratory/speech therapist, and 1 physical therapist. All of the 7 cases reported having COVID-19 symptoms, compared to 15/93 (16%) of the controls; fatigue and anosmia were the two symptoms reported by every case. *Controls:* Of the 6 controls who reported additional SARS-CoV-2 testing at an outside facility, none had a positive test result. Only 7 individuals reported having an immunocompromising condition, all of whom were controls. *PPE use:* No one reported a breach in PPE and everyone reported using a procedure mask 100% of the time. Of the 7 cases, 6 reported never wearing an N95 but 5 of those 6 reported wearing protective goggles/face shield and mask 100% of the time. *Univariate analysis:* There were no significant differences in demographic characteristics or PPE practices between cases and controls. (Table 2)

Patient care activities

A total of 5/7 (71.4%) of cases performed any AGP compared to only 19/93 (20.4%) of controls (OR = 9.44; 95%CI = 1.42 –106.44) (Table 3). Several aerosolizing and non-aerosolizing procedures were found to be significantly higher in cases than controls. Given that

Table 1
Whole genome sequencing (WGS) of the index patient and HCP cases

Region	SNP	% of US Cases
non-coding region	C241T	87.3%
ORF1a: synonymous	C3037T	87.4%
ORF1b: P314L	C14408T	87.3%
ORF1b: synonymous	C15660T	0.016%
ORF1b: A1643V	C18395T	0.258%
ORF1b: synonymous	A20268G	10.2%
ORF1b: A2431V	C20759T	0.44%
S protein: D614G	A23403G	87.5%
S protein: synonymous	T24076C	3.02%
N protein: S194L	C28854T	10.2%
N protein: M210I	G28903T	0.366%
non-coding region	G29778T	0.005%

Abbreviations: WGS, whole genome sequencing; HCP, healthcare personnel; SNP, single nucleotide polymorphism; US, United States; ORF, open reading frame.
The index patient and all 7 HCP cases included in the case-control study underwent whole genome sequencing. 12 SNPs across coding and non-coding regions were identified and were identical across all 8 cases. These SNPs were searched for in the GESS WGS database across 96,303 samples available from the U.S. as of 7 May 2021. The percentage of SARS-CoV-2 sequences across the U.S. with a matching SNP ranged from 0.005% to 87.5% (column 3). Notably, 5 SNPs were found in less than 0.5% of samples as highlighted in bold. One non-coding SNP was only found in 5 out of the 96,303 (0.005%) other samples in the database. This is highly supportive of these cases being linked.

Table 2
Demographic and work characteristics

	Cases (N = 7) N (%)	Controls (N = 93) N (%)	Odds Ratio	95% CI
Demographics				
Age - mean years (SD); mean difference	37.000 (6.733)	36.925 (9.962)	0.08	(-7.00 −6.00)
Female	5 (71.4%)	57 (61.3%)	1.50	(0.23 −16.59)
Immunocompromising condition reported	0 (0.0%)	7 (7.5%)	0.00	(0 −10.58)
Healthcare Role				
- Nurse*	4 (57.1%)	25 (26.9%)	3.57	(0.56 −26.12)
- Physician / advanced practice practitioner	0 (0.0%)	19 (20.4%)		
- Medical or nurse assistant	1 (14.3%)	14 (15.1%)		
- Respiratory therapist / Speech therapist	1 (14.3%)	11 (11.8%)		
- Physical or occupational therapist	1 (14.3%)	4 (4.3%)		
- Manager/social worker/ patient coordinator	0 (0.0%)	6 (6.5%)		
- Patient technician	0 (0.0%)	6 (6.5%)		
- Phlebotomist	0 (0.0%)	4 (4.3%)		
- Food service / environmental service worker	0 (0.0%)	4 (4.3%)		
Contact with other HCP				
- Yes (contact tested positive)*	1 (14.3%)	1 (1.1%)	14.27	(0.17 −1201.18)
- Yes (contact tested negative)	2 (28.6%)	2 (2.2%)		
- Yes (contact with unknown test results)	0 (0.0%)	4 (4.3%)		
- None	4 (57.1%)	86 (92.5%)		
PPE practices with index patient				
No breaches in PPE	7 (100.0%)	93 (100.0%)	-	-
Procedure mask	7 (100.0%)	93 (100.0%)	-	-
N95				
- All the time*	1 (14.3%)	11 (12.8%)	0.81	(0.08 −40.35)
- More than half the time	0 (0.0%)	4 (4.7%)		
- Less than half the time	0 (0.0%)	10 (11.6%)		
- None of the time	6 (85.7%)	61 (70.9%)		
- No response	0	7		
Gloves				
- All the time*	6 (85.7%)	70 (77.8%)	0.51	(0.01 −4.56)
- More than half the time	1 (14.3%)	5 (5.6%)		
- Less than half the time	0 (0.0%)	6 (6.7%)		
- None of the time	0 (0.0%)	9 (10.0%)		
- No response	0	3		
Gown				
- All the time*	1 (14.3%)	12 (14.1%)	0.89	(0.09 −44.25)
- More than half the time	0 (0.0%)	4 (4.7%)		
- Less than half the time	0 (0.0%)	11 (12.9%)		
- None of the time	6 (85.7%)	58 (68.2%)		
- No response	0	8		

Abbreviations: CI, Confidence Interval; SD, Standard Deviation; HCP, Healthcare personnel; PPE, Personal protective equipment
Cases included all potentially exposed HCP who tested positive for SARS-CoV-2 by RT-PCR. Controls included potentially exposed HCP who tested negative for SARS-CoV-2 twice within 14 days after their last exposure.
*Categorical variables were collapsed into binary variables for univariate analysis using Fisher's exact test. Odds ratios compare the indicated group to all other groups in the category. None of the univariate analyses above were significant.

several of these activities are common procedures for certain work categories like nurses and nursing assistants, a secondary analysis was performed restricted to only those work categories which included at least one case (eg nurse, nursing assistant, respiratory/speech therapist, and physical therapist). Activities that were significantly higher in cases in both the primary and restricted analyses included: placing the patient on HFNC/CPAP/BiPAP, performing suctioning, being present during suctioning, and adjusting oxygen mask/tubing.

Amount of time spent with the patient

All of the cases spent at least 2 days with the index patient compared to only 37/93 (39.8%) of controls (Table 4). Similarly, 6/7 (85.7%) of cases had at least 3 patient contacts per day compared to only 31/93 (33.3%) of controls. In ordinal regression analysis, cases spent significantly more time with the index patient across all time measurements compared to controls. In a secondary analysis restricted to only individuals in work categories including at least one case, the total number of days with the index patient, longest single contact with the patient, and time with the patient during an AGP remained significantly higher amongst cases.

DISCUSSION

After exposure to an index patient with a delayed COVID-19 diagnosis, 9 of 191 exposed HCP tested positive for SARS-CoV-2. The index patient tested negative on admission and standard infection control measures were taken throughout her hospital stay. Compared to controls, positive HCP cases were more likely to report more direct patient contact time, performing AGPs (particularly placing the patient on HFNC/CPAP/BiPAP), and being involved in non-AGPs like adjusting oxygen, performing or being present during suctioning.

Our study reinforces the risk of SARS-CoV-2 transmission to HCP due to delayed diagnosis of COVID-19 cases. Delayed or missed diagnosis of COVID-19, often due to alternative diagnoses or limited testing capabilities or initial negative tests, has been linked to nosocomial transmission and hospital outbreaks among HCP in multiple settings. In the Solano County outbreak in February 2020, the lack of readily available SARS-CoV-2 testing and the low clinical suspicion of community transmission led to the delayed diagnosis of the

Table 3
Patient care activities

		All survey participants			Restricted to job categories with cases		
	Cases (N = 7) N (%)	Controls (N = 93) N (%)	Odds Ratio	95% CI	Controls (N = 54) N (%)	Odds Ratio	95% CI
Airway procedures							
Performed AGP							
Placed on HFNC/CPAP/BiPAP	5 (71.4%)	16 (17.2%)	11.60	(1.72 −132.08)	14 (25.9%)	6.87	(0.99 −79.76)
Gave nebulizer treatment	1 (14.3%)	6 (6.5%)	2.39	(0.05 −25.84)	6 (11.1%)	1.33	(0.02 −14.5)
Performed endoscopy	0 (0.0%)	2 (2.2%)	0.00	(0.00 −74.88)	-	-	-
Performed any AGP	5 (71.4%)	19 (20.4%)	9.44	(1.42 −106.44)	17 (31.5%)	5.28	(0.77 −60.75)
Present during AGP							
Present while HFNC/CPAP/BiPAP was on the patient	5 (71.4%)	38 (40.9%)	3.57	(0.55 −39.37)	24 (44.4%)	3.07	(0.45 −34.91)
Present during nebulizer treatment	4 (57.1%)	15 (16.1%)	6.74	(1.03 −50.85)	12 (22.2%)	4.52	(0.67 −35.28)
Present during endoscopic procedure	0 (0.0%)	7 (7.5%)	0.00	(0 −10.58)	2 (3.7%)	0.00	(0 −43.32)
Present during any AGP	5 (71.4%)	43 (46.2%)	2.88	(0.44 −31.66)	27 (50.0%)	2.46	(0.36 −28.02)
Other airway procedures							
Performed suctioning	3 (42.9%)	3 (3.2%)	20.64	(2.12 −213.66)	3 (5.6%)	11.74	(1.19 −122.43)
Present during suctioning	4 (57.1%)	14 (15.1%)	7.30	(1.11 −55.34)	8 (14.8%)	7.29	(1.03 −59.86)
Adjust oxygen mask/tubing	7 (100.0%)	34 (36.6%)	Inf	(2.3 −Inf)	29 (53.7%)	Inf	(1.1 −Inf)
Moving/touching patient							
Check vital signs	7 (100.0%)	37 (39.8%)	Inf	(2.02 −Inf)	36 (66.7%)	Inf	(0.63 −Inf)
Perform a history and/or physical exam	4 (57.1%)	35 (37.6%)	2.19	(0.35 −15.85)	20 (37.0%)	2.24	(0.34 −16.84)
Administer medications	5 (71.4%)	21 (22.6%)	8.34	(1.26 −93.58)	21 (38.9%)	3.84	(0.57 −43.82)
Perform blood draw or IV insertion	1 (14.3%)	9 (9.7%)	1.55	(0.03 −15.28)	4 (7.4%)	2.05	(0.04 −26.1)
Bathe the patient	6 (85.7%)	29 (31.2%)	12.91	(1.47 −616.19)	29 (53.7%)	5.06	(0.56 −246.94)
Position the patient	6 (85.7%)	45 (48.4%)	6.30	(0.72 −299.94)	38 (70.4%)	2.49	(0.27 −123.29)
Assist in patient exercises/walking	4 (57.1%)	21 (22.6%)	4.48	(0.7 −33.04)	21 (38.9%)	2.07	(0.32 −15.58)
Cleaning							
Empty bedpan	5 (71.4%)	21 (22.6%)	8.34	(1.26 −93.58)	21 (38.9%)	3.84	(0.57 −43.82)
Change linens	5 (71.4%)	29 (31.2%)	5.41	(0.83 −60.05)	28 (51.9%)	2.29	(0.34- −26.05)
Empty the trash	2 (28.6%)	8 (8.6%)	4.15	(0.34 −31.15)	5 (9.3%)	3.79	(0.29 −32.68)
Clean the patient's room	2 (28.6%)	16 (17.2%)	1.91	(0.17 −13.01)	13 (24.1%)	1.26	(0.11 −8.88)

Abbreviations: CI, Confidence Interval; AGP, aerosol generating procedure; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure; BiPAP, Bilevel positive airway pressure.
Univariate analysis was performed using Fisher's exact test. Primary analysis of the relationship between case status and patient care activities was performed including all survey respondents. A secondary restricted analysis was performed which included only individuals in a healthcare role that had as least one case. Significant results are indicated in bold. There was significant overlap in many activities. Notably, all the individuals who performed suctioning also placed the patient on HFNC/CPAP/BiPAP. All individuals who performed a particular procedure were also included as present during that procedure. 1 case reported being present during suctioning but did not perform suctioning and reported no AGP exposures.

index patient and 3 PCR-confirmed HCP cases out of 121 exposed.[22] In another case in Boston, 44 HCP were exposed (with 2 attributable HCP cases) to a patient who presented with abdominal pain and shortness of breath who was initially diagnosed with cholecystitis and only tested and diagnosed with COVID-19 on HD 13 after developing acute respiratory failure; the patient was retrospectively thought to have undiagnosed infection on admission.[11] In the aforementioned cases, HCP had unprotected exposures to the index case yet resulted in fewer cases compared to our outbreak in which all HCP were wearing masks at all times and frequently also wearing eye protection. One key difference may be the different stages of infection in the index patients. Our index patient had a negative PCR on admission but developed new progressive respiratory symptoms between HD 3 to 6. This timing suggests that our index patient was infected in the community, was in the incubation period of her infection on HD 1 and likely became most infectious around HD 3 to 6, when the SARS-CoV-2 viral load in upper respiratory tract is thought to be highest.[23] This is also consistent with the timing of patient contact with cases: all 7 cases with direct patient contact took care of the patient on at least one of the days between HD 3 to 6, with 6 cases taking care of the patient on HD 4.

A significant challenge in evaluating nosocomial transmission risk is the small number of cases that result from an exposure. Having survey responses from only 7 cases does limit the power of our study and our ability to perform multivariable analyses. However, compared to other outbreaks as described above, we did have a relatively large number of both cases and exposed controls which allowed for both a univariate analysis and a restricted sub-analysis to evaluate risk factors. Another critical concern in any outbreak investigation is determining the relationship between the index and secondary cases. The timeline of HCP cases in relation to the patient's testing and clinical course is consistent with the patient being the index case. Furthermore, a major strength of this study is the corroborating molecular evidence that these cases were all related. Whole genome sequencing is being increasingly used as an important epidemiologic method to investigate SARS-CoV-2 outbreaks including healthcare facility transmission events[12,13] and provides very strong evidence that this cluster of cases is due to a single outbreak. However, we could not rule out the possibility of HCP to HCP transmission after exposure to the index patient.

Although power was limited by the small number of cases, our study did identify several key risk factors for transmission. Our study clearly demonstrated a higher risk of transmission with increased time spent in contact with the index patient. This is consistent with other studies showing higher HCP nosocomial infection risk with increased duration of exposure to suspected and confirmed COVID-19 cases.[24,25] Our findings also add to the evidence regarding increased risk of AGPs. Several AGPs such as bronchoscopy, tracheostomy, cardiopulmonary resuscitation, and pre-intubation ventilation are generally thought to be high risk for SARS-CoV-2 transmission.[26] There is less demonstrated risk associated with other AGPs such as administering nebulizer treatments or manipulating non-invasive ventilation or high flow nasal canula.[27,28] In our study, placing the patient on HFNC/CPAP/BiPAP was significantly associated with risk of transmission. The other AGPs evaluated in our study (eg performing endoscopy and giving nebulizer treatments) were not significantly

Table 4
Self-reported amount of time spent caring for the patient

		All survey participants			Restricted to job categories with cases		
	Cases (N = 7) N (%)	Controls (N = 93) N (%)	Odds Ratio*	95% CI*	Controls (N = 54) N (%)	Odds Ratio*	95% CI*
Total # of days with patient			5.01	(1.39 −18.9)		5.37	(1.37 −22.51)
- 1 day	0 (0.0%)	56 (60.2%)			31 (57.4%)		
- 2-3 days	5 (71.4%)	22 (23.7%)			15 (27.8%)		
- 4-5 days	1 (14.3%)	10 (10.8%)			5 (9.3%)		
->6 days	1 (14.3%)	5 (5.4%)			3 (5.6%)		
Total amount of time with patient			4.56	(1.22 −17.14)		3.09	(0.79 −12.16)
- <30 minutes	1 (14.3%)	43 (46.2%)			18 (33.3%)		
- 30 to 60 minutes	0 (0.0%)	25 (26.9%)			17 (31.5%)		
- 1 to 5 hours	5 (71.4%)	15 (16.1%)			11 (20.4%)		
- 5 to 10 hours	1 (14.3%)	7 (7.5%)			5 (9.3%)		
- > 10 hours	0 (0.0%)	3 (3.2%)			3 (5.6%)		
# of patient contacts per day			7.78	(1.95 −34.30)		3.86	(0.95 −17.32)
- 1-2 times	1 (14.3%)	62 (66.7%)			26 (48.1%)		
- 3-4 times	1 (14.3%)	13 (14.0%)			10 (18.5%)		
- 5-6 times	1 (14.3%)	4 (4.3%)			4 (7.4%)		
- 7-8 times	1 (14.3%)	3 (3.2%)			3 (5.6%)		
- >8 times	3 (42.9%)	11 (11.8%)			11 (20.4%)		
Longest single contact with patient			14.35	(3.14 −77.70)		17.49	(3.16 −146.78)
- <15 minutes	0 (0.0%)	36 (38.7%)			17 (31.5%)		
- 15-30 minutes	1 (14.3%)	32 (34.4%)			21 (38.9%)		
- 30-60 minutes	4 (57.1%)	22 (23.7%)			15 (27.8%)		
- >60 minutes	2 (28.6%)	3 (3.2%)			1 (1.9%)		
Time with patient during an aerosol generating procedure			6.56	(1.55 −30.18)		5.83	(1.30 −29.30)
- Zero	0 (0.0%)	27 (29.0%)			14 (25.9%)		
- <15 minutes	2 (28.6%)	28 (30.1%)			15 (27.8%)		
- 15-30 minutes	1 (14.3%)	23 (24.7%)			15 (27.8%)		
- 30-60 minutes	2 (28.6%)	11 (11.8%)			8 (14.8%)		
- >60 minutes	2 (28.6%)	4 (4.3%)			2 (3.7%)		

Abbreviation: CI, Confidence Interval.
Primary analysis of the relationship between case status and patient care activities was performed including all survey respondents. A secondary restricted analysis was performed which included only individuals in a healthcare role that had at least one case. Significant results are indicated in bold.
*Univariate analysis for amount of time spent with the index patient was performed using ordinal logistic regression.

associated with transmission, however the power of this analysis was severely limited as very few people performed these procedures in either group.

Curiously, performing or being present during suctioning and adjusting oxygen were also activities statistically significantly associated with cases in both the full and restricted analyses. However, there are several possible explanations for this. First, suctioning is an activity that occurs quite frequently and may be a proxy for increased time spent with the patient. Additionally, there is significant overlap among patient care responsibilities that involve the airway, which is particularly true for the small number of cases. Amongst cases, 3 of the 4 (75%) individuals who were present during suctioning also performed suctioning and placed the patient on BiPAP/CPAP/HFNC. Given the limited sample size and substantial overlap of activities and time, it is unclear whether these other airway procedures truly pose an increased risk above and beyond the risk attributed to AGPs. Nevertheless, it is possible that there is an increased risk associated with these other airway procedures that place HCP in close contact with airway secretions for extended periods of time. This would be most likely in a critically ill, non-intubated patient in which suctioning occurs in an open system (unlike in intubated patients where suctioning occurs in a closed system). Therefore, it is possible that in non-intubated patients, suctioning or other airway procedures that are not classified as strictly AGPs may in fact be an important, underappreciated mode of SARS-CoV-2 transmission.

In response to this outbreak, we implemented some major changes to minimize risk of transmission. Prior to this outbreak, the universal hospital protocol included universal procedure masks and eye protection in all patient encounters. Prior to CDC changing its recommendations,[14] a new protocol was implemented in our hospital requiring N95 masks for all contact with a patient undergoing intermittent or continuous AGPs even with negative SARS-CoV-2 testing on admission. This case also reinforced the importance of repeated SARS-CoV-2 re-testing after admission in suspicious cases. Our hospital laboratory also updated test codes so that it was not possible to order the respiratory virus panel without also testing for SARS-CoV-2.

CONCLUSIONS

Our study underlines the risk of HCP transmission due to unidentified COVID-19 cases. It also highlights that patients who are admitted during the incubation period with a negative PCR test on admission may in fact be particularly high risk because they may become most infectious during their hospitalization. Finally, our study demonstrates that prolonged contact and placement or manipulation of HFNC/CPAP/BiPAP are a key risk factors for transmission.

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