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A patient self-collection method for longitudinal monitoring of respiratory virus infection in solid organ transplant recipients

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ABSTRACT

Background: Methods for the longitudinal study of respiratory virus infections are cumbersome and limit our understanding of the natural history of these infections in solid organ transplant (SOT) recipients.
Objectives: To assess the feasibility and patient acceptability of self-collected foam nasal swabs for detection of respiratory viruses in SOT recipients and to define the virologic and clinical course.
Study design: We prospectively monitored the course of symptomatic respiratory virus infection in 18 SOT patients (14 lung, 3 liver, and 1 kidney) using patient self-collected swabs.
Results: The initial study sample was positive in 15 patients with the following respiratory viruses: rhinovirus (6), metapneumovirus (1), coronavirus (2), respiratory syncytial virus (2), parainfluenza virus (2), and influenza A virus (2). One hundred four weekly self-collected nasal swabs were obtained, with a median of 4 samples per patient (range 1–17). Median duration of viral detection was 21 days (range 4–77 days). Additional new respiratory viruses detected during follow-up of these 15 patients included rhinovirus (3), metapneumovirus (2), coronavirus (1), respiratory syncytial virus (1), parainfluenza virus (1), and adenovirus (1). Specimen collection compliance was good; 16/18 (89%) patients collected all required specimens and 79/86 (92%) follow-up specimens were obtained within the 7 ± 3 day protocol-defined window. All participants agreed or strongly agreed that the procedure was comfortable, simple, and 13/14 (93%) were willing to participate in future studies using this procedure.
Conclusion: Self-collected nasal swabs provide a convenient, feasible, and patient-acceptable methodology for longitudinal monitoring of upper respiratory virus infection in SOT recipients.

1. Background

Respiratory virus infection (RVI) is an important complication in solid organ transplant patients, but the longitudinal virologic course of these infections has not been extensively studied, in part because of the logistical difficulties in obtaining repeated provider-collected sequential specimens [1–3]. Understanding the natural history of respiratory virus infection in this population (duration of viral infection, viral load, association with symptoms) is important for the design of future interventional studies and to assess the potential impact of RVI in the pathogenesis of clinically significant outcomes after transplantation, such as acute and chronic allograft rejection and secondary bacterial and fungal pulmonary infections. Self-collected nasal swabs have previously been shown to have comparable sensitivity to provider-obtained specimens and have been used for monitoring RVI in immunocompetent subjects, hematopoietic cell transplant recipients, and children with cystic fibrosis [4–8]. However, in these studies, self-collected respiratory samples were obtained in the clinic under observation [9,10]. Furthermore, previous studies have not assessed the feasibility or acceptability of sending patient self-collected specimens using commercially available mail systems for prospective longitudinal monitoring of RVI. Therefore, our study was designed to address, at least in part, some of these limitations and to extend the work of previous studies.

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2. Objectives

The purpose of the present study was to assess the feasibility and acceptability of sequential self-collected nasal swabs to longitudinally monitor the virologic and clinical course of upper respiratory tract viral infection in a cohort of SOT patients, and to determine the potential utility of cycle threshold (Ct) values obtained from these samples to assess changes in viral load over time.

3. Study design

Potential participants were identified from real-time databases of SOT recipients who had laboratory-confirmed respiratory virus infection during their routine clinical care at the University of Washington Medical Center in Seattle, Washington. After written informed consent, participants were taught the self-collection procedure by a research coordinator and assessed for competency (demonstration of the procedure back to the coordinator). Participants were provided study kits, instructions, and pre-addressed/pre-paid overnight FedEx shipping mailers (FedEx, Inc., Memphis, TN), and instructed to collect specimens every 7 ± 3 days until two consecutive specimens were negative. The requirement for two negative specimens was included to ensure that a positive result near the PCR assay threshold was not missed. The duration of the viral infection episode was defined as the amount of time from the date of clinical diagnosis (laboratory-confirmed) to the date of the first of two consecutive negative study swab PCR results. A new episode was defined as the detection of a new viral pathogen (different than the initial virus) for which the patient was being serially monitored. The study kits were as previously described, using sterile polyurethane foam swabs with a custom-shaped tip (Puritan Medical Products Co., LLC; no. 25-1805 1PF SC2 Arrow) [4]. Participants sent the swabs at ambient temperature in sterile 15 mL centrifuge tubes (Bio Express, Inc., Kaysville, UT). Participants completed a survey about the tolerability of the procedure and a symptom survey at the time of each specimen collection. Symptom surveys were used to generate a weekly symptom score for each patient based on the presence of common upper respiratory and associated systemic symptoms. The specific upper respiratory symptoms assessed were: rhinorrhea, sinus congestion, post-nasal drip, shortness of breath, cough, wheezing/chest tightness, sputum, sore throat, sneezing, watery eyes, ear ache, and hoarseness. The systemic symptoms included: subjective fever, headache, muscle ache, and diarrhea. The total symptom score was the sum of all reported symptoms for each weekly symptom survey. The maximum possible score was 16. Study staff either scheduled a weekly pick-up at the patient's home through FedEx or the participant delivered the mailer to a FedEx shipping drop box. Once received at the central PCR laboratory, specimens were processed within 24 h and tested using real time PCR assays as previously described [11–16]. Samples were considered positive if the PCR amplification plot crossed the threshold at less than 40 cycles (cycle threshold [Ct] < 40). Quality of specimens was assessed by amplification of human beta-globin DNA (forward primer TGAAGGCTCATGGCAAGAAA, probe TCCAGGTGAGCCAGGCCATCACTA, reverse primer GCTCACTCAGTGTGGCAAAGG) using nucleic acid extracted from the sample previously tested for RVI. The Fred Hutchinson Cancer Research Center Institutional Review Board approved this study.

4. Results

4.1. Patients and specimens

Eighteen SOT patients were enrolled: 14 lung, 3 liver, and 1 kidney transplant recipients. The median age was 61 years (mean 54, range 24–69) and included 7 women and 11 men. The median time from transplantation was 2.7 years (mean 4.4 years, range 8 days-14 years). Specimens were sent from locations ranging from 0.8 to 175 miles from the transplant center. The transit time from self-collection of the sample to arrival at the laboratory (available for 75/86 [87%] follow-up samples) was a median of 25.1 h, range 17.5–84.3 h. In these samples, rates of respiratory virus positivity did not differ between swabs whose transit time was less than 24 h (18/30, 60%) and those with a transit time greater than 24 h (29/45, 64.4%). All specimens had detectable beta-globin DNA, ranging from 56 to 1.5e5 copies/10 μL of specimen (median 6.9e3). There was no correlation between sample positivity for RV and amount of beta-globin present (measured by PCR Ct values/10 μL of sample) (Fig. 1). The beta-globin mean $\log_{10}$ copies/10 μL of specimen of RV positive samples (3.71) was similar to that of negative samples (3.75, $p = 0.78$). All participants had clinically ordered, laboratory-confirmed, upper or lower RVI by either culture (1/18; 6%) or PCR (17/18; 94%), from either bronchoalveolar lavage (11/18; 61%), nasopharyngeal swab (6/18; 33%), or nasal wash (1/18; 6%).

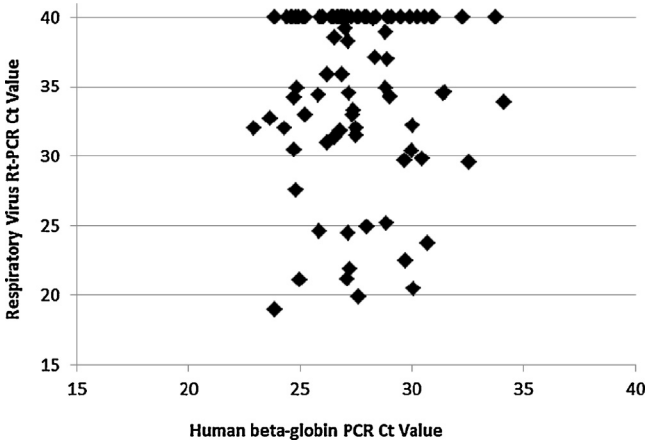

Fig. 1. Relationship between human beta-globin and respiratory virus cycle times.

4.2. Longitudinal monitoring of upper respiratory virus infection

A total of 104 sequential self-collected respiratory samples were obtained from 18 participants. The median number of samples collected per participant was 4 (mean 6, range 1–17). The initial study swab was negative in 3 patients (17%) and these patients were therefore not included in longitudinal monitoring. Six patients (33%) had only one positive study swab (the initial swab), and 6 patients (33%) had a second viral episode (a new virus detected during monitoring of the initial viral infection). Median time from the initial positive clinical test to enrollment was 5 days (mean 5, range 0–13 days). Twenty-four RVI episodes were identified in 15 patients. The most common respiratory virus was rhinovirus (37%), followed by respiratory syncytial virus (12.5%), the human coronaviruses (12.5%), parainfluenza viruses (12.5%), and human metapneumovirus (12.5%) (Table 1). Patients with more than one RVI episode have each RVI listed separately in Table 1 in the order they occurred post-transplantation (e.g. RV-13 had three separate RVI episodes: First a rhinovirus infection that resolved after 68 days, then an adenovirus infection that lasted at least 48 days before the patient was lost to follow-up, and lastly a second rhinovirus episode, distinct from the first, that lasted at least 8 days before being lost to follow-up. Table 1 also shows the number of days between the date of clinical diagnosis to date of the first self-collected specimen for each virus.

Table 1
Pooled summary of respiratory virus infections.

Patient	Virus	Time to first study sample	Duration of episode
RV-01	Rhinovirus	7 days	15 days
RV-02	Rhinovirus	12 days	19 days
RV-03	Rhinovirus	13 days	28 days
RV-04	Coronavirus	5 days	33 days
	Rhinovirus	0 days	77 days
	RSV	0 days	11 days
RV-05	PIV 2	3 days	14 days
RV-06	Influenza A	1 day	4 days
RV-07	RSV	0 days	Lost to follow-up
RV-08	Influenza A	1 day	28 days
	Coronavirus	0 days	22 days
	Rhinovirus	0 days	71 days
RV-09	PIV 3	5 days	26 days
	MPV	0 days	43 days
RV-10	RSV	7 days	12 days
RV-11	MPV	7 days	21 days
RV-12	Rhinovirus	2 days	37 days
RV-13	Rhinovirus	6 days	68 days
	Adenovirus	0 days	>48 days[a]
	Rhinovirus	0 days	≥8 days[a]
RV-14	Coronavirus	5 days	14 days
	PIV 2	0 days	6 days
RV-15	Rhinovirus	3 days	17 days
	MPV	0 days	22 days

[a] Patient was lost to follow up.

Mean baseline symptom score was 8.5 (median 8, range 5–12). Among the 9 participants who were initially diagnosed with lower tract infection by bronchoalveolar lavage (BAL), all had the same virus concomitantly detected in the upper respiratory tract from patient self-collected specimens.

Fig. 2 shows sequential Ct values over time for the initial viral episode and a secondary viral episode for two representative patients. The data for all of the patients is included in Supplemental Fig. 1A, B, and C. The median duration of the initial viral episode for the entire cohort was 20 days (range 4–77 days). Pooled values for the duration of the viral episode are shown in Table 2. We documented a viral episode lasting at least 14 days in 12 (86%) of the 14 patients followed for at least two weeks. Interestingly, 6/15 (40%) patients had 9 new respiratory viruses detected during follow-up monitoring (i.e. a new virus was identified in specimens during sequential monitoring of a different initial viral episode). The virologic course of new viral episodes (i.e. viral detections of a new virus in patients with a prior viral episode) are shown separately in Supplemental Fig. 1C. In these patients, we were able to identify the onset of infection since previous monitoring for the new virus was negative. Overall, for both initial and secondary viral episodes, there was a sequential increase in Ct value over time, indicating a reduction in viral load during the course of infection.

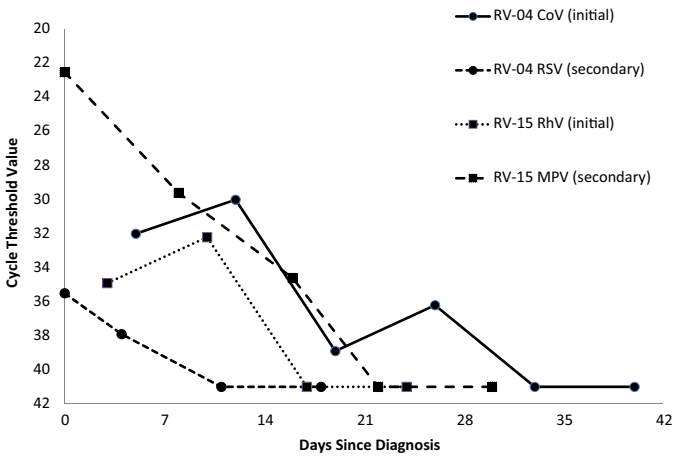

Fig. 2. Initial and secondary viral episodes in two patients. *Note*: negative samples were assigned a Ct value of 41 (assay threshold of detection).

Table 2
Pooled summary of respiratory virus infections.

Virus (pooled)	*N* (%)	Median duration (days)	Range (days)
Rhinovirus	9(37.5)	32.5[a]	15–77
RSV	3(12.5)	11.5[b]	11–12
Coronavirus	3(12.5)	22	14–33
PIV	3(12.5)	14	6–26
MPV	3(12.5)	22	21–43
Influenza A	2(8.3)	16	4–28
Adenovirus	1(4.2)	>48[c]	>48

[a] Includes only 8 infections.
[b] Includes only 2 infections.
[c] Patient was lost to follow up.

Supplementary Fig. 1A–C related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcv.2014.10.021.

Fig. 3 shows the averaged change from baseline in the patient-reported symptom score for the initial viral episode over time. The apparent increase in symptom score at four weeks corresponds to the onset of symptomatic secondary viral episodes in a subset of the study population.

4.3. Compliance and acceptability of specimen collection

Seventy-nine (92%) of 86 follow-up specimens were collected by participants within the protocol-defined window period of 7 ± 3 days for each sample. Sixteen (89%) of the participants collected all of the protocol-specified samples. All 14 study participants who completed a survey agreed or strongly agreed that the procedure was comfortable, simple, and not messy. Thirteen (93%) of 14 participants agreed or strongly agreed that the instructions were easy to follow and expressed an interest in participating in future studies using this method.

5. Discussion

We have applied a simple, patient-acceptable, and feasible self-collection method to facilitate longitudinal monitoring of upper RVI. Using this sensitive method [4], we confirmed the results of prior studies that used provider-collected swabs, and demonstrated that the duration of viral shedding varies substantially and can be prolonged [17]. In our study, the duration of viral infection from the initial clinically obtained positive test was greater than 2 weeks in the majority (86%) of patients followed for at least two weeks. The high rate of concomitantly positive nasal swab samples associated with positive lower respiratory tract samples is consistent with the hypothesis that the majority of lower tract infection represents progression of infection from the upper respiratory tract. Thus, the use of this self-collection methodology could be useful for understanding the pathogenesis of progression from upper to lower tract infection, since it would allow for the determination of the precise timing of upper tract infection in relation to lower tract disease. However, the presence of lower tract infection without concomitant upper tract infection has been reported for influenza A(H1N1)pdm2009 and other viruses, and might be related to sensitivity or sampling issues [18,19].

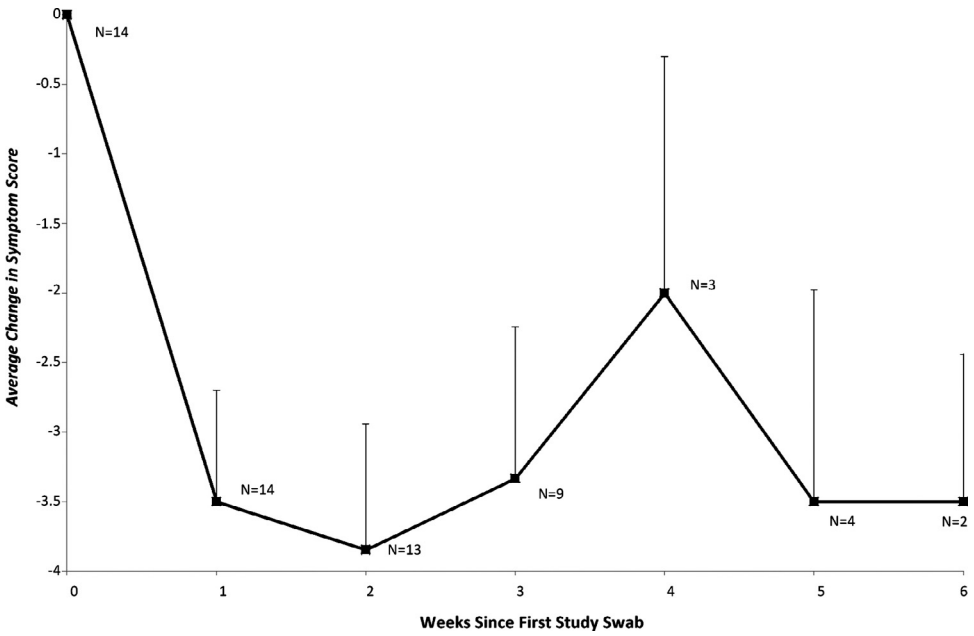

Fig. 3. Average change in symptom score from baseline. *Note*: weekly samples were collected within the specified 7 ± 3 day window. Only initial viral episodes from patients with more than 1 study sample were included.

Although the methodology used in the present study was not quantitative, Ct values from the RT-PCR assays might provide an estimation of viral load. For most infections, sequential Ct values showed a pattern of increase over time (Fig. 2, Supplemental Fig. 1), consistent with sequential decreases in viral load. Furthermore, increases in Ct values were concomitantly associated with reductions in the average patient-reported symptom burden (Fig. 3). PCR Ct values obtained by testing the standardized self-collection specimens described in the present study could potentially be used as a general indicator of viral load changes over time. Future studies should systematically assess the variability of Ct values using this methodology, to confirm that the observed changes in Ct values are greater than those explained by specimen collection and assay variability. Furthermore, it would be of interest to determine whether changes in Ct values reliably are associated with resolution of clinical symptoms. If verified in larger studies, use of semi-quantitation of respiratory virus load with the described methodology could potentially provide a patient-acceptable and useful means of assessing response to therapies such as new antiviral agents or reductions in immunosuppression.

There were several interesting and unexpected findings in this study that likely resulted from the ability of this methodology to facilitate frequent and longitudinal monitoring of a cohort of immunosuppressed patients at risk for acquiring RVI. First, we detected 9 additional respiratory viruses (i.e. new viral episodes) in 6 (40%) of 15 patients during the course of monitoring of their initial RVI. The majority (7 of 9) of these new viral episodes were asymptomatic by symptom surveys and all were in lung transplant recipients. This high level of asymptomatic infection is consistent with the findings of Bridevaux et al., suggesting that asymptomatic RVI is relatively common in lung transplant recipients. Furthermore, both asymptomatic and symptomatic RVI have been hypothesized to contribute to persistent lung injury and possibly long term chronic lung allograft dysfunction [10,20–25]. It remains to be determined whether these subclinical infections carry similar risks as symptomatic infections for post-transplant complications, such as development of bronchiolitis obliterans syndrome or restrictive allograft syndrome. Future prospective studies using the methodology described here are needed to clarify this important issue. Interestingly, we found an apparent increase in duration of rhinovirus infection as compared to other respiratory infections (Table 1). While this could be related to specific host or viral factors, given the small numbers this finding should be interpreted cautiously and future larger studies should verify this preliminary and interesting finding, and include specific assessment of possible mechanisms.

There were several strengths of the present study. We used a prospective study design, a set of highly sensitive and previously well-validated PCR assays, and had high compliance rates with monitoring. One limitation was the relatively small number of patients assessed. The generalizability of our findings should be confirmed in other populations, since our study included selected patients who had the cognitive and physical capabilities of performing the self-collection procedure. This approach might not be applicable to more ill patients or those with significant cognitive or physical impairments. Additionally, due to our experience that patients have difficulty collecting throat swabs and concerns about adherence and acceptability (e.g. gagging or choking with oral/throat swabs), for this study we focused on nasal swab self-collection only. This may have under-detected viruses that can be easier to isolate on throat swabs, such as adenovirus.

In summary, we have described the application of a patient self-collection method combined with sensitive RT-PCR for longitudinal monitoring of upper respiratory viral infection in solid organ transplant recipients. By extending the results of previous studies to include prospective weekly monitoring using patient self-collected nasal swabs sent to a central lab using commercially available overnight ambient temperature shipping protocols, we demonstrate a feasible, convenient, and patient-acceptable methodology for longitudinal monitoring of RVI in SOT patients. Knowledge of PCR Ct values in specimens collected over time will be useful in future natural history and interventional studies for monitoring the virologic course of RVI in immunosuppressed patients and other populations. Such methodology could also potentially be used to facilitate self-testing for diagnosis of upper RVI in immunosuppressed patients without ready access to medical facilities.

Funding

None.

Competing interests

None declared.

Ethical approval

This study was approved by the University of Washington Human Subjects Division and written informed consent was obtained from each participant.

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