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

Carl M. Preiksaitis[a], Jane M. Kuypers[b,e], Cynthia E. Fisher[a], Angela P. Campbell[c,d,e,1], Keith R. Jerome[b,e], Meei-Li Huang[b,e], Michael Boeckh[a,e], Ajit P. Limaye[a,*]

[a] Department of Medicine, University of Washington, Seattle, WA, United States
[b] Department of Laboratory Medicine, University of Washington, Seattle, WA, United States
[c] Department of Pediatrics, University of Washington, Seattle, WA, United States
[d] Seattle Children's Hospital, Seattle, WA, United States
[e] Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, United States

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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.

* Corresponding author at: University of Washington, Box 356174, 1959 NE Pacific St, Seattle, WA 98195-6174. Tel.: +1 2065981041.
E-mail address: limaye@uw.edu (A.P. Limaye).
[1] Present address: Centers for Disease Control and Prevention, Atlanta, GA, United States.

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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%).

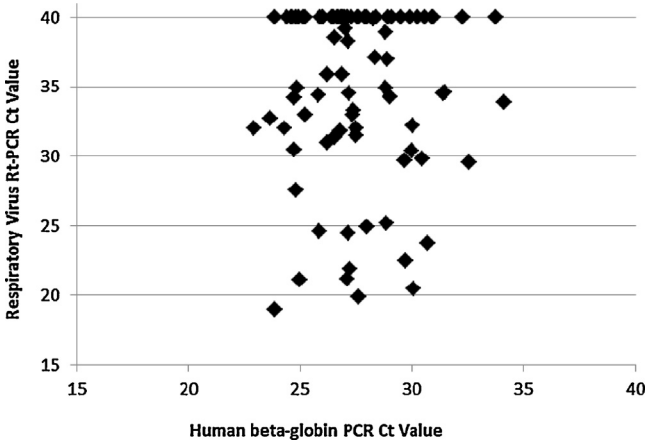

Fig. 1. Relationship between human beta-globin and respiratory virus cycle times.

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.