Feasibility and Reliability of Home-based Spirometry Telemonitoring in Allogeneic Hematopoietic Cell Transplant Recipients

Ajay Sheshadri\textsuperscript{1}, Amin Alousi\textsuperscript{2}, Lara Bashoura\textsuperscript{1}, Karen Stolar\textsuperscript{2}, Shiva Baghaie\textsuperscript{1}, Muhammad H. Arain\textsuperscript{1}, Laila Noor\textsuperscript{1}, Amulya Balagani\textsuperscript{1}, Akash Jain\textsuperscript{1}, David Blanco\textsuperscript{1}, Abel Ortiz\textsuperscript{1}, Susan K. Peterson\textsuperscript{3}, Renee Langhals\textsuperscript{4}, Michael Taylor\textsuperscript{4}, Alex Stenzler\textsuperscript{4}, Rohtesh S. Mehta\textsuperscript{2}, Uday R. Popat\textsuperscript{2}, Chitra Hosing\textsuperscript{2}, Gabriela Rondon\textsuperscript{2}, Fan Shen\textsuperscript{4}, Liang Li\textsuperscript{4}, Guang-Shing Cheng\textsuperscript{6}, David E. Ost\textsuperscript{1}, Richard E. Champlin\textsuperscript{2}, Burton F. Dickey\textsuperscript{1}

Departments of \textsuperscript{1}Pulmonary Medicine, \textsuperscript{2}Stem Cell Transplantation and Cellular Therapy, \textsuperscript{3}Behavioral Science, and \textsuperscript{4}Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas; \textsuperscript{5}Monitored Therapeutics, Incorporated, Dublin, Ohio; \textsuperscript{6}Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington.

\textbf{Address correspondence to}: Ajay Sheshadri, MD, MSCI, Department of Pulmonary Medicine, Unit 1462, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: (713) 563-1987; Fax: (713) 794-4922; E-mail: asheshadri@mdanderson.org

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Morbidity and mortality from bronchiolitis obliterans syndrome (BOS) remain unacceptably high after allogeneic hematopoietic cell transplantation (A-HCT) (1). Prompt diagnosis may improve outcomes (2). Adherence to home-based spirometry (HS) in lung allograft recipients is high, supporting the feasibility of BOS surveillance (3-6). Low adherence to HS has been a barrier to implementation after A-HCT (7-10), possibly due to psychosocial burnout and fatigue (11, 12). The goal of this pilot study was to: 1) determine the feasibility and validity of HS real-time telemonitoring in A-HCT recipients; 2) determine factors associated with adherence to HS; and 3) determine the variability of HS among participants without acute illness.

Methods

We consented and enrolled adult A-HCT recipients at around 100 days post-transplantation between October 2016 and June 2018 at a single transplant center, excluding those who had pneumonia within 4 weeks of screening. The MD Anderson Institutional Review Board approved the study (2015-0990). Participants received a Bluetooth®-compatible home spirometer (GoSpiro, Monitored Therapeutics Inc., Dublin, OH), which instantaneously transmits data to a cloud-based portal for review by patients and clinicians. Participants were trained in HS immediately following clinic-based spirometry (CS) and instructed to perform three maneuvers/session up to thrice weekly for 9 months, with the goal of recording at least one high-quality session/week. Week 1 measurements were used for training. Baseline FEV₁ was defined as mean FEV₁ in weeks 2-3. We defined adherence as recording at least one session during a Sunday-Saturday period. One week of non-adherence resulted in phone call and/or email reminders. All measurements were assessed for technical acceptability (13). FEV₁
measurements that declined >10% from baseline values generated a daily email alarm to the study team. Declines in FEV\textsubscript{1} of 10-19% sustained over two consecutive weeks, or >20% declines in FEV\textsubscript{1} at any time and confirmed within 24 hours, triggered a clinical evaluation.

Each participant was expected to have three CS measurements - enrollment, 3 months and 9 months. Patient data was censored upon death, cancer relapse, or loss of contact with the study team for over one month. Mean HS measurements in the week before and after CS were compared to CS measurements using Bland-Altman analyses with limits of agreement and 95% confidence intervals (CIs). We used generalized linear mixed models with random intercept and random slope of time to analyze adherence. Linear mixed models were fitted to repeated measurements of HS FEV\textsubscript{1} with a fixed effect of time and a random intercept. Intra-class correlation (ICC) was calculated to assess the longitudinal HS reliability, and 95% CIs for ICC were calculated with bootstrap. In addition, we calculated the average of within-subject coefficients of variation (CoV) across all participants, with 95% bootstrap CI. All statistical analyses were performed in R Version 3.5.2.

**Results**

Figure 1 shows our cohort selection (n=51). The median age of the final cohort was 55 years (interquartile range 41-64); 34 (66.7%) participants were female, and 47 (92.2%) participants were non-Hispanic white. The most common malignancy was acute myeloid leukemia (49%); other malignancies requiring A-HCT included acute lymphoblastic leukemia (n=4), chronic lymphocytic leukemia (n=4), chronic myeloid leukemia (n=4), lymphoma (n=6), multiple myeloma (n=3), and myelofibrosis (n=2). 39 (76.5%) participants experienced acute graft-
versus-host disease (GVHD) after A-HCT. Most participants had normal predicted lung function at baseline, and none experienced chronic dyspnea or cough at the time of enrollment, though one participant with normal baseline lung function subsequently developed intermittent asthma (14). Asymptomatic mild (n=3) and moderate (n=1) airflow obstruction were noted in a few participants, and one participant had mild restriction attributed to weakness, which resolved after A-HCT. Participants performed a mean of 3.4±3.5 acceptable measurements/week. Weekly adherence to HS was 69%. 75% of all loops met ATS/ERS technical criteria, and 94% of patient-weeks with measurements had at least one technically acceptable measurement. The primary reasons for missed sessions were non-adherence (403 patient-weeks), technical issues (85 patient-weeks), and health-related issues, such as hospitalization or acute outpatient illness (56 patient-weeks). Acute GVHD was associated with lower adherence (OR 0.37, 95% CI 0.13-1.02, p=0.05). We did not identify an association between chronic GVHD and adherence in this cohort (OR 0.85, 95% CI 0.3-2.2, p=0.71). The probability of performing one session/week dropped by 6% per week during the study (p=0.008).

The ICC of repeated measurements, after adjusting for time effects, was 0.85 (95% CI 0.75-0.91), indicating that only 15% of measurement variability was due to within-patient variation. The within-subject CoV for longitudinal FEV₁ was 8% (95% CI 6.6%-9.5%). Similarly, adjusted ICC for FVC was 0.86 (95% CI 0.78-0.91) and the CoV was 7.3% (6.2-8.4%). We performed Bland-Altman analyses comparing HS to CS (Figure 2). HS FEV₁ measurements systematically underestimated CS FEV₁ by 0.33 L (95% CI -0.45 L to -0.22 L). Similarly, HS FVC
measurements systematically underestimated CS FVC by -0.29 L (95% CI -0.42 to -0.17 L, Figure 3).

In a representative month during which 23 participants were concurrently being monitored, we spent 7 hours in total to remind non-adherent participants or provide technical assistance. Fourteen participants experienced significant pulmonary declines during the study. Of these, eight were due to poor spirometric technique and were easily identified and corrected remotely. The remainder had clinically confirmed pulmonary impairment, but no participants developed BOS during the study period.

Discussion

Because symptoms of BOS are often insidious until pulmonary impairment is extensive (15), HS is an attractive quantitative screening tool for A-HCT recipients. Adherence was acceptable among participating subjects, and most participants completed the study. Participants achieved acceptable technical proficiency without extensive study team involvement. Agreement with CS was acceptable, though HS slightly underestimated, and day-to-day variability in measurements was minor. Importantly, HS did not result in unnecessary testing or interventions.

Our study shows the high longitudinal reproducibility of HS measurements in A-HCT recipients, similar longitudinal FVC measurements in idiopathic pulmonary fibrosis (16, 17). Furthermore, the average within-subject CoV of FEV$_1$ was 8%, similar to CS (18). Based on our data, we propose that significant pulmonary impairment could reasonably be defined by confirmed 10% declines in FEV$_1$ from baseline values.
Our study has some weaknesses. Only 25% of screened patients participated in the study. We observed that acute GVHD was associated with lower adherence to HS. Frailty, as a global indicator of impaired health reserve, is common after A-HCT (19, 20), especially in patients with GVHD (21), and is associated with increased fatigue, impaired quality of life, and lower adherence to healthy behaviors (22, 23). Increasing frailty may synergize with acute illnesses like acute GVHD to negatively impact adherence, but this requires further study. We did not identify BOS within 9 months of A-HCT. Because BOS typically manifests 12-18 months after transplantation, screening may be more efficient if started later in the course of transplantation (10, 24). Alternatively, targeting A-HCT recipients at high risk for BOS, such as those with recent viral lower respiratory infection (25) or active chronic GVHD (26), may be fruitful. Furthermore, the duration of monitoring should continue to three years post-transplantation to capture most at-risk A-HCT recipients (27). In conclusion, we show the feasibility of monitoring A-HCT recipients for BOS with HS telemonitoring.
References


**Figure Legends**

**Figure 1.** Enrollment flowchart.

**Figure 2.** Bland-Altman plots showing agreement between HS and CS FEV$_1$ measurements or a) all timepoints, b) baseline, c) month 3, and d) month 9. The x-axis shows the mean of HS and CS measurements, while the y-axis shows the difference between HS and CS measurements. Negative y-axis values indicate underestimation by HS. The large blue dotted line represents mean bias and small dark blue dotted lines indicate 95% confidence intervals around the mean bias. The light blue dashed line indicates upper and lower limits of agreement with 95% confidence intervals around the limits indicated by small light blue dotted lines.

**Figure 3.** Bland-Altman plots showing agreement between HS and CS FVC measurements or a) all timepoints, b) baseline, c) month 3, and d) month 9. The x-axis shows the mean of HS and CS measurements, while the y-axis shows the difference between HS and CS measurements. Negative y-axis values indicate underestimation by HS. The large blue dotted line represents mean bias and small dark blue dotted lines indicate 95% confidence intervals around the mean bias. The light blue dashed line indicates upper and lower limits of agreement with 95% confidence intervals around the limits indicated by small light blue dotted lines.
Enrollment flowchart.

208 A-HCT recipients screened between October 2016 and June 2018

123 did not consent to study
- Pre-existing medical or social burden (30)
- Not English-speaking or difficulty following instructions (5)
- Acute health-related issues (3)
- Establishing care elsewhere (3)
- No reason given (82)

82 A-HCT recipients consented to the study protocol

31 subjects did not meet the run-in phase by generating a baseline FEV₁ value
- Withdrew consent (20)
- Technical issues precluding participation (7)
- Cancer relapse (4)

51 A-HCT recipients performed the study protocol and were included in the final analyses
Bland-Altman plots showing agreement between HS and CS FEV1 measurements or a) all timepoints, b) baseline, c) month 3, and d) month 9. The x-axis shows the mean of HS and CS measurements, while the y-axis shows the difference between HS and CS measurements. Negative y-axis values indicate underestimation by HS. The large blue dotted line represent mean bias and small dark blue dotted lines indicate 95% confidence intervals around the mean bias. The light blue dashed line indicates upper and lower limits of agreement with 95% confidence intervals around the limits indicated by small light blue dotted lines.
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