Discovering symptom clustering patterns during a pulmonary exacerbation in people with cystic fibrosis

E. Gill1, C. Goss2,3, S. Sagel4, J. Zuniga1.

1School of Nursing, University of Texas at Austin, Austin, TX; 2Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA; 3Division of Pulmonary and Sleep Medicine, Department of Pediatrics, University of Colorado, Denver, CO; 4Department of Pediatrics, Children’s Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, CO

Background: Pulmonary exacerbations (PEs) in people with cystic fibrosis (CF) are characterized by worsening symptoms, and more research is needed to understand how symptoms group together during PEx. A symptom cluster is defined as co-occurrence of two or more related symptoms. Symptom clusters in chronic obstructive pulmonary disease are associated with greater health care use and mortality. Symptom clusters have not been systematically studied in CF. The purpose of this study was to identify distinct symptom clustering patterns during a CF PEx.

Methods: This study (N = 120) was a secondary, longitudinal analysis. Children aged 10 and older and adults being treated with intravenous (IV) antibiotics for a CF PEx were enrolled from six Cystic Fibrosis Foundation–accredited centers across the United States. The CF Respiratory Symptom Diary (CFRSD), a valid, reliable tool, was used to measure eight symptoms associated with greater health care use and mortality. Symptom clusters are characterized by worsening symptoms, and more research is needed to understand how symptoms group together during PEx. A symptom cluster is defined as co-occurrence of two or more related symptoms. Symptom clusters in chronic obstructive pulmonary disease are associated with greater health care use and mortality. Symptom clusters have not been systematically studied in CF. The purpose of this study was to identify distinct symptom clustering patterns during a CF PEx.

Results: Symptoms measured using the CFRSD were found to be significantly clustered based on symptom severity on days 1 (n = 72) and 7 (n = 79) of a PEx. On day 1, cluster 1 (n = 42) was low symptom severity, mean symptom burden was 6.6 ± 2.9, and cluster 2 (n = 30) was high symptom severity, mean symptom burden 14.3 ± 2.7. Figure 1 is a visual representation of day 1 clusters. Cluster 2 had significantly higher symptom scores on all eight symptoms than cluster 1 except the symptom assessing fevers (p = 0.29). There were significant differences in age and days spent in the hospital: Cluster 1 mean age was 21.0, and days spent was 23.9; cluster 2 mean age was 26.7, and days spent was 41.6. There were no differences between clusters 1 and 2 on day 1 percentage predicted forced expiratory volume in 1 second (FEV1), lung clearance index (LCI), and inflammatory markers (EBC). LCI and functional residual capacity (FRC) were measured according to sulfur hexafluoride multiple-breath washout (MBW) using the Innocor LCI. At least two acceptable LCI and FRC values were recorded. EBC samples were collected using the R-Tube method. EBC metabolites were analyzed using liquid chromatography coupled with high-resolution mass spectrometry covering 472 validated metabolites and detection of novel molecules using data-dependent ion fragmentation. Methionine sulfoxide, a metabolite associated with inflammation in early CF bronchoalveolar lavage, was used to test our hypothesis that it is high in people with CRMS who progress to CF. Other EBC metabolites were used for untargeted analysis to assess risk for progression to CF diagnosis.

Conclusions: Symptoms cluster significantly based on severity on days 1 and 7 of a PEx in people with CF. There was not a significant difference in lung function between clusters 1 and 2 on day 1, suggesting that higher symptom burden is not associated with worsening lung disease severity. On day 1, participants grouped into cluster 2 spent significantly more days in the hospital than those in cluster 1, suggesting that people with higher symptom burden may be at greater risk of spending more days in the hospital. The findings that symptoms improved significantly between days 1 and 7 suggest that symptoms are sensitive to IV antibiotic therapy.
the CRMS and CF groups ($p = 0.32$). Similarly, there was insufficient evidence to conclude that mean percentage predicted (FEV$_1$pp) differed between the CRMS (102.2 ± 6.4%) and CF (96.6 ± 11.6%) groups ($p = 0.23$).

Conclusions: There were no significant differences in LCI or FEV$_1$pp between the CF and CRMS groups, although we identified one child with CRMS with an abnormal LCI, suggesting the potential utility of MBW to stratify children with CRMS at risk of developing CF. Ongoing EBC analysis and correlation with lung function tests may be an additional way to assess lower airway inflammation in children with CRMS and risk of progression to CF.

Acknowledgements: This work was supported by a Warshaw Fellows Research Grant.

---

Oxygen-enhanced magnetic resonance imaging and multiple-breath washout with or without short extension as novel functional assessments of cystic fibrosis lung health

C. Short$^{1,2,3}$, T. Semple$^{1,2}$, M. Abkhir$^{1,2,3}$, M. Tibiletti$^{4,3}$, M. Rosenthal$^{1}$, S. Farley$^{1,2}$, G. Parker$^{1,2,4,6}$, J. Davies$^{1,2,3,5}$, Royal Brompton and Harefield Hospitals, Guys and St Thomas’ Trust, London, UK; 2National Heart and Lung Institute, Imperial College London, London, UK; 3European Cystic Fibrosis Society, Lung Clearance Index Core Facility, London, UK; 4Bioxyl Ltd, Manchester, UK; 5Department of Pediatric Respiratory Medicine, Royal Brompton Hospital, Guys and St. Thomas’s NHS Foundation Trust; 6Centre for Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College London, London, UK

Background: Poor sensitivity of spirometry and forced expiratory volume in 1 second (FEV$_1$) means that the gold standard for lung function testing in cystic fibrosis (CF) is suboptimal. The lung clearance index (LCI$_{2.5}$) derived from multiple-breath washout (MBW) is considered a good alternative but also has limitations. We recently developed an extension to MBW (MBW$_{ShX}$) to capture signal from previously overlooked under- and upper airway disease, which, although any MBW (LCP$_{2.5}$) will lack spatial information. Oxygen-enhanced magnetic resonance imaging (OE-MRI) provides a functional assessment of the lung on a spatial level, without the use of hyperpolarized gas or ionizing radiation. The parameter reported here, R$_2^{*}$ enhancement, originates from the influence on the proton MRI signal of oxygen in the airways and dissolved within alveolar water and capillary blood. It thus represents a surrogate outcome combining ventilation, gas exchange, and perfusion, with lower enhancement indicative of worse disease. We are conducting a longitudinal study to establish clinimetrics of these techniques; early cross-sectional data are reported here.

Methods: Twenty people with CF underwent spirometry, MBW$_{ShX}$ (EcoMedics Exhalizer D, Spiroware software 3.3.1), and OE-MRI on one day. MBW$_{ShX}$ protocol: After the standard MBW end of test, subjects performed a slow vital capacity (VC), followed by tidal breathing until end-of-test criteria were re-met. Quantification of UVLU is calculated by change in percentage of nitrogen resulting from the SVC, standardized for lung size. LCI$_{2.5}$ (LCI$_{2.5}$ + UVLU) is a measure of global lung health, whereas UVLU is a standalone marker. The MRI protocol consisted of a dynamic series of multislice two-dimensional dual-echo radio frequency–spoiled T$_1$-fast field echo sequences acquired with a temporal resolution of approximately 1.5 seconds during free breathing using a Siemens Aera 1.5 T scanner. The initial 60 acquisitions were obtained with medical air; the gas supply was then switched to 100% oxygen for 150 acquisitions and then returned to medical air for a final 150 acquisitions. Dynamic quantitative R$_2^{*}$ maps were calculated, and the lung parenchyma, excluding central major vasculature, was manually segmented. Normally distributed parameters are presented as mean ± SD and nonparametric parameters as median (range). Pearson (R) and Spearman ($r$) tests were used to assess correlations. $p < 0.05$ was considered significant.

Results: All 20 participants completed MBW$_{ShX}$ and the OE-MRI protocol. Subjects were aged $13 ± 5.3$, with FEV$_1$pp of 92.2 ± 12.3%, predicted forced vital capacity (FVCpp) of 98.8 ± 11.2%, LCI$_{2.5}$ of 7.5 (6.3–15.6), LCI$_{ShX}$ of 9.0 (6.1–31.0), and UVLU of 1.2 (–0.3–15.3). R$_2^{*}$ enhancement (0.087 ± 0.017/ms) did not correlate with FEV$_1$pp or FVCpp, but significant correlations were seen with LCI$_{2.5}$ (R = –0.47, $p < 0.05$), LCI$_{ShX}$ ($r = –0.64, p < 0.01$), and UVLU ($r = –0.67, p < 0.001$).

Conclusions: OE-MRI is feasible and tolerated by children as young as 7. Unlike spirometric values, LCI$_{2.5}$ correlated significantly with OE-MRI R$_2^{*}$, again highlighting the superior sensitivity of MBW over FEV$_1$ in mild to moderate CF lung disease. Novel MBW$_{ShX}$ values also performed well; correlations with OE-MRI were numerically greater than with LCI$_{2.5}$ although at this stage, we are not powered for statistical comparison. This ongoing project will assess short- and long-term repeatability of these novel assays, create a normative range, assess spatial heterogeneity, and optimize MBW and OE-MRI parameters for use as future clinical and research outcomes.

Acknowledgements: This project was funded by Cystic Fibrosis Foundation Grant ID – 0208A120.

Reference