

Cough Frequency and Asthma: What Counts?



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JACI in Practice editors have done patients and providers a service with this special edition devoted to cough. Although cough is a common symptom in the respiratory practitioner's office, ideal management has remained elusive, not from lack of interest, but as the dozen plus articles show, actively evolving management paradigms.

Fukuhara et al¹ try to take advantage of emerging ambulatory monitoring technology² to look at the frequency and pattern of cough (CoFr) in a diverse group of respiratory patients and the effect of "treatment" of the underlying disease. Study subjects' diagnoses reflected a mix of asthma (73 subjects) and other diagnoses (63 subjects).

Their declared aims were to "determine whether unique features of CoFr exist in asthmatic and nonasthmatic patients, and secondly, to evaluate relationships between CoFr and the parameters of airway inflammation, airflow obstruction, and bronchial hyperresponsiveness in asthma."

In an era of precision medicine but imperfect biomarker-guided treatment, a reliably useful marker of cough activity could be of potentially great value.³ Objective measurements of cough frequency and severity could help clinicians better guide the intensity of treatment. Objective measures such as cough count, pattern, or timing would be diagnostically useful if discreet cough phenotype patterns were identified that differed enough to meaningfully enhance diagnostic precision.

Like many studies of clinical subjects, these investigators were dependent on a population available in their clinical practice. They enrolled a total of 136 coughing patients, roughly evenly divided between asthma and other disorders. Limited details were provided as to treatment selected, and why the subjects, many of whom had already received some physician-prescribed treatment, were not already better. By definition, they were on ineffective treatment before enrollment, but if fixing them was straightforward, why had it not been done already?

In this "cross-sectional observational study," subjects were recruited from the pulmonary clinic at their university hospital. This might select for more severe and difficult-to-treat disease. Selection criteria specified only a minimum of 3 weeks of cough to label their complaint as "chronic cough." This stands in contrast to American College of Chest Physicians' (ACCP) guidelines⁴ that require 8 weeks of cough to label a cough as chronic and applies the "subacute" label to patients with 3 to 8 weeks of symptom. Presumably, some subjects were labeled chronic, who were really subacute or even acute by the ACCP guideline.

Of the 73 patients with asthma evaluated, 44 were labeled newly diagnosed, whereas the remaining 29 were on treatment but "uncontrolled or partially controlled." It is unclear, but seems important, as to symptom duration, prior treatment and why such a large subset had failed earlier therapy but responded, now.

Indeed, diagnosis of asthma and therefore inclusion in the study was based on a history of "recurrent coughing, wheezing, chest tightness, and breathlessness" as well as pulmonary function, and response to methacholine or a bronchodilator. Many of these parameters were also among the outcome metrics.

Sixty-three pulmonary clinic patients, with other than asthma, were enrolled as part of the "nonasthmatic" group. There were 17 nonasthmatic diagnostic disease labels. Eleven diagnostic labels had just 2 or less subjects in their groups, whereas 12 subjects had a final diagnosis of postnasal drip, the largest group after asthma. Together with the patients with "chronic unexplained cough," 8 patients, those 20 patients with either postnasal drip or unexplained cough represented almost a third of the nonasthmatic group. There were 10 patients with nonasthmatic eosinophilic bronchitis (NAEB),⁵ a disease similar in presentation to asthma. Both asthma and eosinophilic bronchitis may be treated with inhaled steroids. In a clinical observational study of cough, distinguishing NAEB from asthma is also important, especially as it represented such a large subset.

By contrast, there was only 1 of the 136 subjects who was diagnosed with gastroesophageal reflux disease. That is a bit perplexing, as gastroesophageal reflux disease is surely a common diagnosis in the coughing population.⁶

Setting aside the above concerns, the authors collected considerable data on their diagnostic groups. This was a valuable contribution. But it also raised in some respects more questions than answers. Some findings were especially provocative, not least of which was their observation: "There were no significant differences in lung function parameters, as well as in the cough-specific questionnaires, between the asthmatic and nonasthmatic patients." Apparently, the differences between the 2 groups were most demonstrably related to CoFr.

Most remarkably, even forced expiratory volume in 1 second (FEV₁) and forced vital capacity at study enrollment were virtually the same in the asthma group as in the nonasthmatic

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group. Fractional concentration of exhaled nitric oxide (FeNO) was higher in the asthma group but by just barely a statistically significant amount,⁷ with a *P* value of .05.

A variety of comparisons were made as to response to treatment, with elegant figures illustrating change in cough frequency based on a host of variables.

There was no significant difference between the 2 groups in 24-hour CoFr and daytime CoFr. CoFr during the night was higher in sleeping patients with asthma, as was the ratio of CoFr during the night compared with during the day.

Although statistical significance was meticulously derived, in those cases where that was found, the impact of clinical significance is hard to demonstrate, noting, for example, that “differences in CoFr obtained were not influenced by the presence or absence of treatment for cough.” That makes their findings consistent with common treatment advice to focus on the cause of the cough to not just suppress symptoms.

Both groups had a meaningful drop in CoFr with disease-specific treatment. The 24-hour CoFr in patients with asthma went from a median of 21.0 to 3.5, whereas the nonasthmatic patients went from 12.0 to a median of 1.0, statistically significant *P* < .001 for both groups. Such numbers make a powerful case for treating the disease not just suppressing the cough.

Absolute reductions in CoFr after disease treatment were more significant during the day than at night, but the magnitude of beneficial effects of treating the underlying disease was far greater than statistically significant differences between day and night CoFr.

As for popular biomarkers there was no correlation between CoFr and FeNO or % predicted FEV₁. There was a “weak” but statistically significant correlation with methacholine

responsiveness⁸ and Asthma Control Test (ACT) scores. ACT scores have become a popular part of asthma management, in part driven by government and other payors.⁹

As this ambitious study illustrates, our ability to gather data can easily exceed our ability to effectively track and use it all. As we strive to improve cough and asthma care, continued focus is needed on making it count.

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