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Asthma Diagnosis without Aerosol-Generating Procedures (Spirometry): Evidence for and Beyond the COVID-19 Pandemic



Hannu Kankaanranta, MD, PhD^{a,b,c}, Lauri Lehtimäki, MD, PhD^{c,d}, and Leena E. Tuomisto, MD, PhD^b Gothenburg, Sweden; and Seinäjoki and Tampere, Finland

Evaluation of bronchial obstruction and its reversibility by spirometry forms the basis of current asthma diagnosis.¹ However, performing spirometry may produce aerosols, which may transmit coronavirus disease-19 (COVID-19) infection, because inhalation of virus-laden aerosols is the primary mode of transmission.² Virus-laden aerosols (<100 μm) are exhaled and transported to the environment through expiratory activities or cough. An uninfected person may inhale these aerosols, and thus a new infection may be initiated. Aerosols can remain in the air for hours and travel beyond 1 to 2 m from a COVID-19–infected person.² Therefore, the recommendation has been to avoid performing spirometry if possible, to prevent transmission of the disease to other patients or staff. Use of spirometry during the COVID-19 pandemic has often been limited to urgent diagnostics or to assess lung function status for interventional procedures or surgery.³ These recommendations exclude most patients with asthma from undergoing spirometry during the COVID-19 pandemic, which raises problems with regard to asthma diagnosis and follow-up for these patients.

In a single-center, real-life study published in this issue of the *Journal*, Drake and coworkers⁴ evaluated alternative diagnostic

pathways when aerosol-generating procedures (AGPs) such as spirometry cannot be used or are unavailable. The results support using other tests to diagnose asthma in the absence of spirometry and provide evidence related to asthma diagnosis with implications far beyond the COVID-19 pandemic. They included 65 adults with clinical suspicion of asthma who were naive to asthma diagnosis and steroid therapy.⁴ Clinical history, physical examination, spirometry with bronchodilator reversibility, home peak flow (PEF) monitoring, and bronchial challenges were performed; FeNO and blood eosinophils were measured; and response to steroid therapy was evaluated.⁴ Asthma diagnosis was confirmed in 36 patients and refuted in 24 by an expert panel evaluation; five patients could not be classified. The expert panel evaluation included clinical information, all available pretreatment objective evidence, and improvement in these tests and symptoms after inhaled corticosteroid treatment. Different algorithms were tested, including data from non–aerosol producing (non-AGP) measurements (wheeze present on auscultation and blood eosinophilia) and home PEF variability. The recommended algorithm is considered positive if one of the following is found: wheeze present on auscultation, blood eosinophils of 0.40×10^9 cells/L or greater, or 3 days or more of greater than 20% variability in home PEF.⁴ The authors evaluated various cut points and test combinations, but this algorithm performed best for ruling in asthma. Combining clinical suspicion of asthma with at least one positive non-AGP test or PEF monitoring, the algorithm had a sensitivity of 55%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 60% for asthma.⁴ This algorithm had a comparable discriminative ability to the established Global Initiative for Asthma and National Institute for Health Care and Excellence guidelines to rule in asthma in this study population. In practice, this means that this algorithm could help diagnose every second patient, and treatment could begin without the need to perform spirometry.

This diagnostic tool is especially important during the COVID-19 pandemic, when spirometry may be unavailable owing to infection control. Furthermore, this algorithm can be beneficial when access to spirometry is limited because of a lack of resources (eg, in primary care or developing countries). However, every second patient with asthma will not be captured with this tool, and AGPs will still be needed in these cases.

If asthma is diagnosed using this algorithm and treatment is started, does the patient need to be evaluated by spirometry at a later stage? This algorithm is intended to be used to rule in asthma in adults.⁴ Adult-onset asthma is a chronic disease, remission is rare (<5% to 10%), and most patients do not achieve asthma control.⁵ Thus, patients who do not achieve

^aKrefting Research Centre, Institute of Medicine, Department of Internal Medicine and Clinical Nutrition, University of Gothenburg, Gothenburg, Sweden

^bDepartment of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

^cFaculty of Medicine and Health Technology, Tampere University, Tampere, Finland

^dAllergy Centre, Tampere University Hospital, Tampere, Finland

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Corresponding author: Hannu Kankaanranta, MD, PhD, Krefting Research Centre, Institute of Medicine, University of Gothenburg, Box 424, SE-405 30, Gothenburg, Sweden. E-mail: hannu.kankaanranta@tuni.fi.

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asthma control despite adequate treatment should be evaluated by spirometry.

Several limitations and restrictions should be considered. First, the number of patients was small ($n = 65$).⁴ The results need to be confirmed in larger studies, meaning that sensitivity and specificity estimates may change. Furthermore, the asthma patients included were relatively young adults; individuals with longer smoking histories, other lung diseases, and other significant diseases were excluded.⁴ Thus, the algorithm may not be accurate for older adults (aged >50 to 60 years), in whom chronic obstructive pulmonary disease (COPD), obesity, and cardiac and other diseases are much more common. For example, wheezing is common in COPD and thus may not be a useful predictor in all cases. Furthermore, the patients in this study often had a T2-high asthma profile (83%; elevated eosinophils, allergic sensitization, high FeNO, high variability in lung function, and good response to therapy).⁴ In contrast, older individuals presenting with new asthma may have T2-low type asthma inflammation (low eosinophils, low FeNO, no allergy, and poor response to therapy).⁶ Thus, application of this algorithm in T2-low asthma may lead to lower sensitivity and higher false-negative rates than reported here. Therefore, this algorithm is unsuitable for adults with a low clinical probability of asthma, for those with a significant smoking history, for differentiating asthma from COPD, for patients in whom alternative diagnoses are likely, or for diagnosing children. However, this proposed algorithm is meant to rule in asthma in patients with clinical suspicion of asthma instead of ruling it out, and it allows for early initiation of treatment in positive cases without performing AGPs.

Evaluating diagnostic pathways and tests in asthma may seem trivial. Everyone knows them, and they are written in the guidelines. But what do we really know about the diagnostic performance of the test we use so often? We evaluated the evidence behind the commonly used bronchodilator response Δ FEV₁ of 12% or greater and 200 mL or greater to diagnose asthma in adults.⁷ We searched for bronchodilator response studies including therapy-naïve patients with symptoms typical of asthma, in which asthma was confirmed by other objective means and diagnosis was evaluated by a clinician or a panel of experts. We were unable to find any such studies,⁷ so the sensitivity and specificity of currently used main diagnostic criteria for asthma remain unknown. A similar lack of evidence has been described in children.⁸ Recently, in therapy-naïve patients with new adult-onset asthma, the overall sensitivity of Δ FEV₁ of 12% and greater and 200 mL or greater as a diagnostic criterion was reported to be as low as 35.6%, although it was somewhat higher in patients with airflow obstruction (55.9%; pre-bronchodilator FEV₁/FVC <0.70).⁹ Furthermore, another recent study in steroid-naïve patients evaluated the relationship between hyperreactivity to methacholine and salbutamol reversibility and showed poor concordance between these tests.¹⁰ The proportion of patients fulfilling Δ FEV₁ of 12% or greater and

200 mL or greater was low (20%). Furthermore, there was no correlation between a provocative concentration of methacholine causing a fall in FEV₁ of 20% and the magnitude of salbutamol reversibility.¹⁰ These results clearly show that further rigorous evaluations of diagnostic algorithms for asthma are needed.

Drake and colleagues⁴ suggest that among subjects with clinical suspicion of asthma, at least one positive test out of the following rules in asthma: wheeze present on auscultation, blood eosinophils of 0.40×10^9 cells/L or greater, or 3 days or more of greater than 20% variability in home PEF. This algorithm will help to identify every second patient with asthma without the need to perform spirometry.⁴ Although this tool is not suitable for all patients, it can help identify asthma patients and start their treatment during the COVID-19 pandemic, when access to spirometry is restricted. In addition, this tool is valuable for contexts in which spirometry is unavailable or prohibitively expensive. Furthermore, it is one of the first serious attempts to provide an objectively evaluated diagnostic algorithm for asthma. Thus, its application in asthma diagnostics will be valuable long after the COVID-19 pandemic has passed.

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REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Accessed June 28, 2021. <http://www.ginasthma.org>
2. Wang CC, Prather KA, Sznitman J, Jimenez JL, Lakdawala SS, Tufekci Z, et al. Airborne transmission of respiratory viruses. *Science* 2021;373:eabd9149.
3. Halpin DMG, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, et al. Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2021;203:24-36.
4. Drake S, Wang R, Healy L, Roberts SA, Murray CS, Simpson A, et al. Diagnosing asthma with and without aerosol generating procedures. *J Allergy Clin Immunol Pract*. 2021;9:4243-51.
5. Tuomisto LE, Ilmarinen P, Niemelä O, Haanpää J, Kankaanranta T, Kankaanranta H. A 12-year prognosis of adult-onset asthma: Seinäjoki Adult Asthma Study. *Respir Med* 2016;117:223-9.
6. Fitzpatrick AM, Chipps BE, Holguin F, Woodruff PG. T2-“low” asthma: overview and management strategies. *J Allergy Clin Immunol Pract* 2020;8:452-63.
7. Tuomisto LE, Ilmarinen P, Lehtimäki L, Tommola M, Kankaanranta H. Immediate bronchodilatation response in FEV₁ as a diagnostic criterion of adult-onset asthma. *Eur Respir J* 2019;53:1800904.
8. Hopp RJ, Pasha MA. A literature review of the evidence that a 12% improvement is an appropriate cut-off for children. *J Asthma* 2016;53:413-8.
9. Tuomisto LE, Ilmarinen P, Lehtimäki L, Niemelä O, Tommola M, Kankaanranta H. Clinical value of the immediate bronchodilator response for diagnosing asthma in steroid-naïve adults. *ERJ Open Res* 2021. In press.
10. Louis R, Bougard N, Guissard F, Paulus V, Henket M, Schleich F. Bronchodilatation test with inhaled salbutamol versus bronchial methacholine challenge to make an asthma diagnosis: do they provide the same information? *J Allergy Clin Immunol Pract* 2020;8:618-25.