MAYO CLINIC

ORIGINAL ARTICLE

The Diagnostic Accuracy of Fractional Exhaled Nitric Oxide Testing in Asthma: A Systematic Review and Meta-analyses

Zhen Wang, PhD; Paolo T. Pianosi, MD; Karina A. Keogh, MD; Feras Zaiem, MD; Mouaz Alsawas, MD, MSc; Fares Alahdab, MD; Jehad Almasri, MD; Khaled Mohammed, MBBCh; Laura Larrea-Mantilla, MD; Wigdan Farah, MBBS; Lubna Daraz, PhD; Patricia Barrionuevo, MD; Allison S. Morrow, BA; Larry J. Prokop, MLS; and Mohammad Hassan Murad, MD, MPH

Abstract

Objective: To evaluate the diagnostic accuracy of fractional exhaled nitric oxide (FeNO) measurement in individuals with suspected asthma.

Methods: We searched MEDLINE, EMBASE, PsycINFO, Cochrane databases, and SciVerse Scopus from the databases' inception through April 4, 2017, for studies that enrolled patients aged 5 years and older with suspected asthma and evaluated FeNO diagnostic accuracy. Independent reviewers selected studies and extracted data. We used the symmetric hierarchical summary receiver operating characteristic models to estimate test performance.

Results: We included 43 studies with a total of 13,747 patients. In adults, using FeNO cutoffs of less than 20, 20 to 29, 30 to 39, and 40 or more parts per billion, FeNO testing had sensitivities of 0.80, 0.69, 0.53, and 0.41, respectively, and specificities of 0.64, 0.78, 0.85, and 0.93, respectively. In children, using FeNO cutoffs of less than 20 and 20 to 29 parts per billion, FeNO testing had sensitivities of 0.78 and 0.61, respectively, and specificities of 0.79 and 0.89, respectively. Depending on the FeNO cutoff, the posttest odds of having asthma with a positive FeNO test result increased by 2.80- to 7.00-fold. Diagnostic accuracy was modestly better in corticosteroid-naive asthmatics, children, and nonsmokers than in the overall population.

Conclusion: Fractional exhaled nitric oxide measurement has moderate accuracy to diagnose asthma in individuals aged 5 years and older. Test performance may be modestly better in corticosteroid-naive asthmatics, children, and nonsmokers than in the general population with suspected asthma.

Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) Identifier: CRD42016047887

 ■ Mayo Clin Proc. 2017;■■(■):1-8

Asthma is a chronic inflammatory disorder of the airways characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.[1] It is estimated that 24.6 million Americans had asthma in 2015.[2]

Diagnosing asthma is challenging. The common symptoms, such as shortness of breath, wheezing, and cough, are relatively nonspecific. Various tests, including bronchodilator response and positive results on bronchial challenge, may be used by clinicians to aid in the diagnosis of asthma in the appropriate clinical context. However, the diagnosis remains clinical, based on compatible symptoms and evidence of reversible airway obstruction; no single criterion standard diagnostic test exists. More recently, fractional exhaled nitric oxide (FeNO) concentration has been added to the list of tests that clinicians may use to diagnose asthma. Thus, the objective of this systematic review was to evaluate the diagnostic accuracy of FeNO concentration in individuals

From the Mayo Clinic Evidence-based Practice Center, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (Z.W., F.Z., M.A., F.A., J.A., K.M., L.L.-M., W.F., L.D., P.B., A.S.M., M.H.M.), Division of Health Care Policy and Research, Department of Health Sciences Research

Affiliations continued at the end of this article.

aged 5 years and older with suspected asthma.

METHODS

The reporting of this systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[3] We developed the study protocol with input from clinical and research experts and professional organizations. The study protocol is registered in the International Prospective Register of Systematic reviews (PROSPERO Identifier: CRD42016047887).

Data Sources and Searches

We conducted a comprehensive literature search of 6 databases, including Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and SciVerse Scopus from the databases' inception to April 4, 2017. We searched relevant systematic reviews and conducted reference mining of relevant publications to identify additional literature. We searched gray literature through all of the following: US Food and Drug Administration device registration studies, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency, Agency for Healthcare Research and Quality Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. An experienced medical librarian (L.J.P.), with input from the study investigators, developed and executed the search strategy (Supplemental Appendix, available online at http://www.mayoclinicproceedings.org). An independent librarian reviewed the search strategy.

Study Selection

We included randomized clinical trials and observational studies that (1) enrolled patients aged 5 years and older with suspected asthma, (2) compared FeNO testing (diagnostic test) to standard diagnostic testing of asthma by health care professionals based on history, clinical course, or other diagnostic tests (clinical diagnosis, bronchodilator response, and positive results on bronchial challenge) (reference test), and (3) reported FeNO diagnostic accuracy. We excluded studies with mixed populations (eg, patients with asthma and chronic obstructive lung disease) without reporting separate results for individuals with asthma. We also excluded surveys, narrative reviews, editorials, letters, or errata, qualitative research, in vitro studies, and animal studies. We did not restrict study location, publication time, or language.

Independent reviewers working in pairs screened the titles and abstracts of all citations and then the full text of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. If they did not reach consensus, a third reviewer was added to resolve the difference.

Data Extraction and Quality Assessment

We developed a pilot-tested standardized data extraction form at the beginning of the study. The following information was extracted: author, study design, inclusion and exclusion criteria, patient characteristics, characteristics of FeNO test and reference tests, diagnostic accuracy measures (reported as true-positives, true-negatives, false-positives, and false-negatives), and related FeNO cutoff values. We used the QUADAS-2 instrument to evaluate risk of bias of the included studies.[4] Data extraction and quality assessment were completed by pairs of independent reviewers.

Main Outcome Measures

The outcomes of interest were diagnostic accuracy measures, including sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR).

Data Synthesis and Analysis

We categorized FeNO cutoff values as less than 20, 20 to 29, 30 to 39, and 40 or more parts per billion (ppb). Analyses were conducted by age group (less than 18 years vs 18 years or older) as well as overall. We extracted true-positives, true-negatives, false-positives, and false-negatives from the included studies for each FeNO cutoff value and reference test. If multiple cutoffs within the same category were reported from the same study, we selected the one with the highest DOR. The DOR is a single indicator of diagnostic performance that facilitates comparison across tests. It was defined as the ratio of the odds of positivity in