Effective Health Care Program

The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management

Evidence Summary

Objectives and Rationale for the Review

This report summarizes a systematic review on "The Clinical Utility of Fractional Exhaled Nitric Oxide in Asthma Management". This was one of the 6 high priority topics within asthma identified by an NHLBI Advisory Council Asthma Expert Working group.[1]

Background

The diagnosis of asthma is a clinical diagnosis and is challenging without a criterion standard test. Fractional exhaled nitric oxide (FeNO) testing has been suggested as a diagnostic test for asthma. It has also been studied as a tool that aids in selecting asthma treatments, predicting response to therapy (e.g., inhaled corticosteroids) and for monitoring the response to therapy. In young children with recurrent wheezing, FeNO may predict the ones who are likely to be diagnosed with asthma later in childhood.

Data Sources

We conducted a comprehensive literature search of six databases from the inception of the databases to April 4, 2017: MEDLINE® In-Process & Other Non-Indexed Citations, MEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic

Purpose of Review

To assess the role of measuring the fractional concentration of exhaled nitric oxide (FeNO) in the diagnosis, treatment and monitoring of asthma.

Key Messages

- Depending on the FeNO cutoff, the likelihood of having asthma in people ages 5 years and older increases by 2.8 to 7.0 times given a positive FeNO test result.

- FeNO is modestly more accurate in diagnosing steroid-naïve asthmatics, children (ages 5-18), and nonsmokers than other patients suspected to have asthma.

- FeNO results can predict which patients will respond to inhaled corticosteroid therapy.

- Using FeNO to manage long-term control medications including dose titration, weaning, and monitoring of adherence, reduces the frequency of exacerbations.

- There is insufficient evidence supporting the use of FeNO in children (ages 0-4) for predicting a future diagnosis of asthma.

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Reviews, and SciVerse Scopus. The systematic review protocol is available in the full report.

Results

We found 175 studies that met the eligibility criteria for inclusion in this review.

KQ 1.a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?

Key Points

- The diagnostic accuracy of FeNO for the diagnosis of asthma varies with the FeNO level used for diagnosis. Sensitivity and specificity per cutoff were: <20 ppb (0.79, 0.72), 20-30 ppb (0.64, 0.81), 30-40 ppb (0.53, 0.84), ≥40 ppb (0.41, 0.94). (SOE: Moderate).

- Depending on the FeNO cutoff, the posttest odds of having asthma given a positive FeNO test result increased by 2.80 to 7.00 fold. (SOE: Moderate).

- Diagnostic accuracy is likely higher in nonsmokers, in children and in steroid-naïve asthmatics.

KQ 1.b: What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma ages 5 and older?

Key Points

- In adults (ages >18) and children (ages 5 -18), FeNO level is weakly associated with asthma control (as measured by the ACQ and ACT).This association can be further attenuated in those who smoke, pregnant or are on ICS. (SOE: Low)

- In adults (ages >18) and children (ages 5 -18), FeNO levels have a weak association with the risk of subsequent and prior exacerbations. (SOE: Low) The association between FeNO levels and exacerbation risk is likely stronger in individuals (ages>5 years) with atopy. (SOE: Low)

- In adults (ages >18) and children (ages 5 -18) with acute asthma exacerbations, FeNO levels do not correlate with exacerbation severity and were poorly reproducible. (SOE: Low)

- In children (ages 5 - 12) and adolescents (ages 13 - 18), FeNO levels were inversely associated with adherence to asthma medications (mainly ICS). (SOE: Low)

KQ 1.c: What is the clinical utility of FeNO measurements to select medication options (including steroids) for individuals ages 5 and older?

Key Points

- In adults (ages of >18 years) and children (ages of 5-18 years), using asthma management algorithms that incorporate FeNO testing reduced the risk of exacerbations (SOE: High), and possibly the risk of exacerbations requiring oral steroids (SOE: Moderate), but did not affect other outcomes such as hospitalization, quality of life, asthma control, or FEV1% predicted.

- FeNO testing can identify patients who are more likely to respond to inhaled corticosteroids (SOE: Low).

KQ 1.d: What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 and older?

Key Points

- FeNO levels are reduced when patients with asthma take inhaled corticosteroids, leukotriene receptor antagonists or omalizumab. FeNO levels are not reduced when patients with asthma take long acting beta agonists.

- FeNO predicts exacerbations in patients undergoing ICS reduction or withdrawal, but FeNO alone is likely insufficient and its ability to predict exacerbations can be substantially enhanced by clinical measures (e.g. ACT).

KQ 1.e. In children ages 0-4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at age 5 and above?

Key Points

- It is unclear whether FeNO testing in children at ages 0-4 years with symptoms suggestive of asthma can predict a future asthma diagnosis (SOE: insufficient).

Limitations

For several of the key questions (KQ 1.b-e), studies were quite heterogeneous in terms of design, population, control tests, control strategies, and outcome measures. For the diagnostic accuracy question (KQ 1.a), the main challenge relates to the lack of true gold standard for diagnosis.

Applicability

The current literature reports on patients and settings similar to contemporary clinical practice. Clinicians considering FeNO as an adjunct to diagnose asthma should expect a fair number of false negatives and an even a larger number of false positives and should be aware of pretest odds (prevalence).

Suggestions for Future Research

- Studies with explicit asthma diagnostic criteria and better stratification according to asthma phenotype are needed to identify populations who may benefit from serial FeNO measurement.

- Studies of FeNO-based medication titration are needed and should focus on symptomatic patients with previously documented elevated FeNO. Studies evaluating disease activity and outcomes should use validated measures of activity and well defined outcomes.

- The role of serial FeNO measurements in children ages 0-5 year who develop illness associated with wheezing remains unclear. Cohort studies of such infants with follow up into later years of childhood and adolescence are needed to establish if persistently elevated levels correlate with increased risk of ultimate asthma diagnosis.

Conclusions

FeNO has moderate accuracy to diagnose asthma in people ages 5 years and older. Test performance is modestly better in steroid-naïve asthmatics, children, and nonsmokers than the general population with suspected asthma. Algorithms that include FeNO measurements can help in monitoring response to anti-inflammatory or long-term control medications, including dose titration, weaning, or treatment adherence. At this time, there is insufficient evidence supporting the measurement of FeNO in children under the age of 5 as a means for predicting a future diagnosis of asthma.

References

1. National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group. Needs Assessment Report for Potential Update of the Expert Panel Report-3 (2007): Guidelines for the Diagnosis and Management of Asthma. 2015. https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/Asthma-Needs-Assessment-Report.pdf. Accessed July 18, 2016.

Full Report