Original Article

The Effect of Viral Infection on Exhaled Nitric Oxide in Children with Acute Asthma Exacerbations

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What is already known about this topic? Fraction of exhaled nitric oxide (FENO) is a tool that can be used to diagnose asthma and to predict a positive response to inhaled steroid therapy, and can help measure adherence with inhaled steroid therapy in patients with chronic asthma. Unfortunately, its utility in the management of acute asthma has not been widely studied.

What does this article add to our knowledge? This study found that in children with an acute asthma exacerbation, FENO levels are elevated compared with baseline levels. In addition, FENO levels rise to a greater extent in children who do not have a viral-induced asthma exacerbation, suggesting that eosinophilic inflammation plays more of a role in non–viral-induced asthma exacerbations. Last, prednisone was effective in reducing FENO levels to their baseline state, with the biggest reduction seen in those with viral infections.

How does this study impact current management guidelines? This study suggests that FENO is a useful marker of inflammation during an acute asthma exacerbation and that prednisone therapy improves lung function and normalizes FENO levels in children with acute asthma regardless of the underlying cause of their exacerbation.

BACKGROUND: Fraction of exhaled nitric oxide (FENO) level is used as an aid in the diagnosis and management of chronic asthma. Its role in acute asthma remains to be studied.

OBJECTIVE: To determine whether FENO levels are elevated in children with asthma exacerbations compared with baseline, and whether there is a difference in FENO levels based on PCR positive (+) (respiratory virus isolated by PCR analysis) versus PCR negative (−) (respiratory virus not isolated by PCR analysis) status.

METHODS: Children with a previous FENO level measurement while stable and who presented to an urgent care facility with an asthma exacerbation were enrolled. FENO levels, spirometry, and nasal swabs for viral PCR were obtained at the time of the exacerbation and following a course of prednisone. Data were available on 66 children. Linear mixed models were used to regress the outcomes of interest (FEV_1, FEV_1/forced vital capacity, forced expiratory flow at 25% to 75% of forced vital capacity, and natural log FENO) on detected virus (yes/no), visit (baseline, exacerbation, follow-up), and the interaction between the detected virus and visit.

RESULTS: Compared with baseline, higher FENO values and lower lung function were found at the time of an exacerbation. A respiratory virus was detected in 59% of the exacerbations. The interaction between PCR (+) and PCR (−) groups and visit on log FENO was marginally significant ($P = .07$). There was no difference in log FENO between the PCR (+) and PCR (−) groups at baseline, while higher log FENO was found in the PCR (−) group at the time of exacerbation and following prednisone ($P = .05$ and .001, respectively).

CONCLUSIONS: Higher FENO concentration in PCR (−) exacerbations suggests an eosinophilic predominance in nonviral compared with viral exacerbations. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: *Childhood asthma; Fraction of exhaled nitric oxide (FENO); Asthma exacerbations*

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Conflict of interest: J. Malka has received the device and the sensors used in the study from Aerocrine; received the reagents used in the study from Copan Diagnostics, Inc; has received consultancy and lecture fees as well as travel support from Aerocrine; and has received lecture fees and travel support from ThermoFisher. R. Covar has received research support from the National Heart, Lung, and Blood Institute, GlaxoSmithKline, and Boehringer Ingelheim. M. Gleason has received grant support from the Colorado Department of Public Health and Environment for school-centered asthma program. J. D. Spahn has received the device and sensor used in the study from Aerocrine. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
ED- emergency department
FEF_{25-75}- forced expiratory flow at 25% to 75% of forced vital capacity
FENO- fraction of exhaled nitric oxide
FVC- forced vital capacity
GC- glucocorticoid
PCR (+)- respiratory virus isolated by PCR analysis
PCR (−)- respiratory virus not isolated by PCR analysis

Asthma is a chronic inflammatory disorder most commonly associated with eosinophilic infiltration into the airways and the release of several inflammatory mediators,[1] although other phenotypes of asthma are described, that is, neutrophilic and paucigraniolocytic. Fractional exhaled nitric oxide (FENO) has been accepted as a noninvasive measure of airway inflammation that can be used in both the diagnosis and the management of asthma.[2,3] Studies have shown FENO to be as effective as beta-agonist reversibility and methacholine responsiveness in diagnosing asthma in both children and adults.[4-6] FENO levels are positively correlated with bronchial wall inflammation,[7] induced-sputum eosinophilia,[8-10] and airway hyperresponsiveness.[11-13] Increases in FENO are associated with deterioration in asthma control with poor inhaled glucocorticoid (GC) adherence,[2,11] whereas FENO levels fall in a dose-dependent manner with inhaled GC treatment.[11,12] Despite enhanced knowledge of FENO in chronic asthma, little is known regarding its role in acute asthma. In 1 of 2 recently published studies, FENO was not found to be useful in acute asthma because it could be measured only in 68% of the children presenting to the emergency department (ED) with acute asthma,[14] while in the second study, FENO failed to distinguish children requiring hospitalization from those who were discharged to home.[15] In neither study were FENO levels available at baseline, nor an attempt was made to determine what role viral infections played in FENO levels. The aims of this study were 2-fold: to determine whether the FENO level is elevated during an acute asthma exacerbation compared with baseline in children with persistent asthma and to determine the influence of viral infections on FENO levels in children presenting with an acute asthma exacerbation requiring prednisone therapy.

METHODS

Study design

In this prospective cross-sectional study, informed consent was obtained from the parent or guardian and assent was obtained from the child when appropriate. The study was reviewed and approved by the National Jewish Health Institutional Review Board. The study was performed at the National Jewish Health Urgent Care Clinic from June 2010 to May 2011. A total of 70 participants aged 7 to 18 years were enrolled. We chose this age group because children of this age can perform adequate spirometry and exhaled nitric oxide measurements.

All patients who presented to the Urgent Care Clinic at National Jewish Health for an acute asthma exacerbation and who had undergone spirometry and FENO measurements within the last 6 months when clinically stable (visit 1) were approached to participate in the study (Figure 1). Patients who could not perform either spirometry or FENO measurements at the time of the exacerbation were ineligible as were patients who were on or had been treated with prednisone within 1 week before the urgent care visit. Children with a history of lung disease other than asthma and patients with a history of vocal cord dysfunction were also excluded from participating in the study. Once consent and assent were obtained, participants completed a clinical questionnaire, spirometry, and FENO measurement and had a nasal swab obtained for viral PCR (visit 2). Urgent care physicians independently directed treatment and determined the participants' dispositions. The treating physicians were not study investigators and the decision to treat with prednisone was at the discretion of the treating physician using treatment algorithms based on the National Asthma Education and Prevention Program guidelines.[16] Participants who were discharged home were instructed to continue usual controller medications, to take albuterol at a frequency directed by the urgent care physician, and to complete a 5- to 7-day course of oral prednisone (2 mg/kg/d; maximum daily dose 60 mg). All discharged participants were also scheduled for follow-up 1 week later (visit 3). At the follow-up visit, all participants underwent spirometry and had FENO levels measured.

Lung function measurement

All participants underwent spirometry with at least 3 acceptable maneuvers. The three highest forced vital capacity (FVC) and FEV_1 values were recorded according to the American Thoracic Society Guidelines[17] using a Jaeger MasterScreen Pneumo running JLab 5.20 software (Erich Jaeger, Inc, Wurzburg, Germany). The data for FEV_1, FVC, and forced expiratory flow at 25% to 75% of forced vital capacity (FEF_{25-75}) were expressed as % predicted using the NHANES III reference values.[18]

FENO level measurement

The FENO level was obtained after spirometry, and before the administration of short-acting beta-agonist therapy. The FENO level was measured using the online technique recommended by the American Thoracic Society with the Niox Mino system (Aerocrine AB, Stockholm, Sweden).[19] This technique uses a resistive device that provides a constant low expiratory flow rate and vellum closure. The combination of vellum closure and low flow rate ensures accurate measurement of pulmonary-derived exhaled NO levels and excludes contamination from nasal NO. Participants exhale to their residual volume, insert the mouthpiece, inhale to total lung capacity, and then exhale for 10 seconds at a steady rate of 50 mL/s. Visual incentives provide feedback for flow rate compliance. The end point of measurement occurred when a plateau for 4 seconds was observed. Only 1 measurement was obtained because the repeatability of FENO obtained with the Niox Mino is very high.[20]

Viral PCR measurement

Nasopharyngeal swabs were collected using Copan flocked swabs (Copan Diagnostics, Inc, Murrieta, Calif) placed in Universal Transport Medium. These samples were extracted using the Quigen MinElute Virus Kit (Quiagen, Inc, Valencia, Calif) and tested for the presence of respiratory viral nucleic acid using the Quigen ResPlex II v2.0 Kit. This kit can detect the following respiratory viruses: respiratory syncytial virus, influenza A virus, influenza B virus, rhinovirus/enterovirus, parainfluenza virus, human metapneumoviruses A and B, coxackievirus/echovirus, adenovirus, coronavirus, and bocavirus.

Statistical analysis

Comparisons between PCR (+) (respiratory virus isolated by PCR analysis) and PCR (−) (respiratory virus not isolated by PCR analysis) groups at baseline and at the time of an exacerbation were evaluated using independent sample *t* tests (for normally distributed continuous variables), or Wilcoxon rank-sum tests (for variables that were not normally distributed), and using either χ^2 tests or the