

Medical Policy



An Independent Licensee of the
Blue Cross and Blue Shield Association

Title: Exhaled Nitric Oxide and Exhaled Breath Condensate pH Measurement for Respiratory Disorders

Professional

Original Effective Date: October 3, 2006

Revision Date(s): June 30, 2009

Current Effective Date: June 30, 2009

Institutional

Original Effective Date: July 30, 2009

Revision Date(s):

Current Effective Date: July 30, 2009

DESCRIPTION

The National Heart, Lung, and Blood Institute, in its clinical guidelines regarding the management of asthma, offers the following definition of asthma:

"Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular: mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper responsiveness to a variety of stimuli."

Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using steroids, leukotriene inhibitors, or other anti-inflammatory drugs. Existing techniques for monitoring the status of underlying inflammation have focused on bronchoscopy, with lavage and biopsy, or analysis by induced sputum. Given the cumbersome nature of these techniques, the ongoing assessment of asthma focuses not on the status of the underlying chronic inflammation, but rather on regular assessments of respiratory parameters such as FEV-1 and peak flow. Therefore, there has been interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators. Two new strategies have been investigated, the measurement of exhaled nitric oxide and the evaluation of exhaled breath condensate. Nitric oxides an important endogenous messenger and inflammatory mediator that is widespread in the human body, functioning, for example, to regulate peripheral blood flow, platelet function, immune reactions, and neurotransmission and to mediate inflammation. In biologic tissues, nitric oxide is unstable, limiting measurement. However, in the gas phase, nitric oxide is fairly stable, permitting its measurement in exhaled air. While nitric oxide is a volatile mediator that can be measured in exhaled air, most inflammatory

mediators are not volatile and thus cannot be detected in the gas phase. Exhaled breath condensate (EBC) consists of exhaled air passed through a condensing or cooling apparatus, resulting in an accumulation of fluid. Although EBC is primarily derived from water vapor, it also contains aerosol particles or respiratory fluid droplets, which in turn contain various nonvolatile inflammatory mediators, such as cytokines, leukotrienes, oxidants, antioxidants, and various other markers of oxidative stress. The pH of EBC can also be measured. Various studies have focused on different components of EBC as inflammatory markers in respiratory disease.

The following clinical roles for measurement of NO and EBC have been investigated in the diagnosis and management of asthma:

1. Diagnosis of Asthma

The current method of asthma diagnosis focuses on the clinical history and the demonstration of reversible airflow limitation. For example, spirometry measurements may be performed before and after the administration of a short-acting bronchodilator to demonstrate the presence of reversible airflow limitation. Measurement of exhaled nitric oxide levels has been suggested as either an alternative or adjunct to spirometry.

2. Response to Anti-Inflammatory Treatment

Declining levels of exhaled nitric oxide suggest declining inflammation.

3. Monitoring Compliance of Anti-Inflammatory Treatment

Persistent elevation of exhaled nitric oxide may suggest poor compliance with long-term therapy.

4. Detection of Steroid Resistance

Steroid resistance may be reflected by persistently high nitric oxide levels despite corticosteroid treatment. Steroid resistance may be related to poor inhalation technique, inadequate dosage, overwhelming anti-inflammatory technique, or poor compliance.

5. Prediction of Exacerbation of Asthma

Currently, prediction of exacerbation of asthma is based on self-assessment of peak flow meter measurements. Increasing levels of exhaled nitric oxide may be able to predict exacerbations before the onset of clinical symptoms or changes in peak flow values.

6. Dose Optimization

There has been interest in using measurements of exhaled nitric oxide to guide dosing of anti-inflammatory medications.

Aside from asthma, the following clinical applications of nitric oxide measurement have been proposed:

1. Assessment of Chronic Cough

Chronic cough may be related to smoking, postnasal drip, gastroesophageal reflux, chronic obstructive pulmonary disease, or asthma. Elevation of exhaled nitric oxide may point to asthma as the etiology.

2. Assessment of Cystic Fibrosis

Exhaled nitric oxide appears to be decreased in patients with cystic fibrosis.

3. Rhinitis

Nasal nitric oxide (as opposed to exhaled nitric oxide) may be increased in patients with allergic rhinitis.

4. Primary Ciliary Dyskinesia

Nasal nitric oxide may be decreased in patients with primary ciliary dyskinesia.

Measurement of Nitric Oxide

The most commonly used technique for measurement of exhaled nitric oxide is chemiluminescence after reaction with ozone. Exhaled nitric oxide is typically measured during single breath exhalations. First, the subject inspires nitric oxide-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. The early studies of exhaled nitric oxide showed various levels of nitric oxide in health and disease, attributed to the lack of a standardized technique of measurement. In 1999, the American Thoracic Society published recommendations for the standardized measurement of exhaled nitric oxide.

In 2003, the U.S. Food and Drug Administration (FDA) approved for marketing the Nitric Oxide Monitoring System (NIOX) with the following indication:

"[Measurements of the fractional nitric oxide (NO) concentration in expired breath (FE-NO)] provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessments in asthma. NIOX should only be used by trained physicians, nurses and laboratory technicians. NIOX cannot be used with infants or by children approximately under the age of 4, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology."

The Breathmeter is another device used to measure exhaled nitric oxide using laser spectroscopy. The Breathmeter has not yet received FDA approval for marketing.

Collection and Measurement of Exhaled Breath Condensate (EBC)

The basic technique of collecting EBC consists of a technique to cool exhaled air and collect EBC droplets. One commercially available system, the RTube consists of a disposable polypropylene condensation chamber that is cooled by an overlying aluminum cooling sleeve. There are a variety of laboratory techniques to measure the components of EBC, including such simple techniques as pH measurement, to the more sophisticated gas chromatography/mass spectrometry or high performance liquid chromatography, depending on the component of interest.

POLICY

Measurement of exhaled or nasal nitric oxide, or collection and analysis of exhaled breath condensate, is considered **experimental / investigational** in the diagnosis and management of asthma and other respiratory disorders.

RATIONALE

Exhaled Nitric Oxide

A literature search performed on the MEDLINE database identifies a large body of published data regarding exhaled nitric oxide in asthma and other respiratory diseases. However, these studies primarily focus on exhaled nitric oxide as a research tool, exploring the underlying pathophysiology of asthma, establishment of the technical performance of the test, establishing cut-off values for normal and abnormal values in different age groups. For example, studies have shown that asthma patients have nitric oxide measurements in the range of 25–85 parts per billion (ppb) compared to control patients whose exhaled nitric oxide measurement is generally less than 20 ppb. (1, 2) Other studies have shown that levels of exhaled nitric oxide correlate with levels of other known inflammatory markers, such as airway hyper-responsiveness and sputum eosinophils. (3-6) Pulmonary function tests represent the standard method for assessment of asthma, but studies have found an inconsistent relationship between results of pulmonary function tests and exhaled nitric oxide, perhaps because changes in pulmonary function may lag behind changes in exhaled nitric oxide. (7, 8) Several studies have confirmed the expected decrease in exhaled nitric oxide levels after administration of both corticosteroids (9-12) and anti-leukotriene drugs. (13, 14)

While the cited studies demonstrate the potential role of measurements of exhaled nitric oxide in the diagnosis and management of asthma, assessment of the clinical role of this test would require controlled studies of those diagnosed and managed conventionally and those whose diagnosis and management were additionally directed by measurements of exhaled nitric oxide. No such trials were identified. Compared to asthma, the data are more limited regarding other respiratory conditions, including chronic obstructive pulmonary disease (COPD), cystic fibrosis, and primary ciliary dyskinesia.

Additional Information

In 2002, the National Asthma Education and Prevention Program of the National Heart, Lung, and Blood Institute issued its second expert panel report on guidelines for the diagnosis and management of asthma. (15) Measurements of nitric oxide were not included among its recommendations.

2005 Update

A search of the literature was performed for the period of 2003 through June 2005. The literature search revealed ongoing intense interest in exhaled nitric oxide as a biomarker for asthma. Studies have continued to explore the potential clinical applications of exhaled nitric oxide (16-19). One randomized trial was identified in which 97 patients with asthma treated with inhaled corticosteroids (fluticasone) were randomized either to a group whose care was directed by results of exhaled nitric oxygen testing or to a conventional management group based on international guidelines. (20) In the first phase of the study, the lowest dose of fluticasone was established, based either on international guidelines or exhaled nitric oxide. In the second phase, patients were maintained on this baseline dose, monitored for exacerbations either conventionally or with results of exhaled nitric oxide, with the fluticasone dose adjusted accordingly. Patients were followed up for 12 months. The primary outcome was the frequency of asthma exacerbations, and the secondary outcome was the mean daily dose of corticosteroid. While there was no difference in the frequency of asthma exacerbations between the groups, the exhaled nitric oxygen group reported a significant 40% reduction in the dosage of inhaled corticosteroid.

The accompanying editorial by Deykin points out several limitations to this study. (21) For example, in the control group the mean dose of fluticasone after the initial titration period (567 mg/day) is nearly double the typical dose needed for asthma control. Therefore, the finding of lower fluticasone doses in patients managed with serial measurements of exhaled nitric oxide may reflect overtreatment in the control group rather than any effect of nitric oxide monitoring. The author also points out that it is unclear whether the reported results in these patients with moderate asthma can be extrapolated to those with milder or more severe asthma. Finally, Deykin questions the scientific basis of nitric oxide monitoring. For example, while corticosteroids may suppress the inflammatory activity of the airways, they also directly inhibit the enzymatic production of nitric oxide. Subsequently, a reduction in exhaled nitric oxide may also reflect exposure to corticosteroids rather than simply a reduction in inflammation. It has been concluded that the results of this trial are inadequate to permit scientific conclusions regarding the clinical role of exhaled nitric oxide in the management of patients with asthma.

In October 2005, a TEC Assessment (22) on exhaled nitric oxide monitoring as a guide to treatment decisions in chronic asthma made the following conclusions:

- The available evidence does not permit the conclusion that use of nitric oxide monitoring to guide treatment decisions in asthma leads to improved outcomes.

- The two randomized controlled trials included in the assessment, Smith (20) and Pijnenburg, (23) suggest possible benefits for nitric oxide monitoring but are not sufficient to conclude that outcomes are improved. Each study reported different benefits that have not been reproduced. Smith reported that equivalent outcomes were achieved in the nitric oxide group, with a lower overall dose of inhaled corticosteroids. Pijnenburg reported that bronchial hyper-reactivity was improved in the nitric oxide group. However, bronchial hyper-reactivity is an intermediate outcome that is not well benchmarked to true health outcomes.
- Differences in the control management strategy raise questions about the optimal management strategy to which nitric oxide monitoring should be compared.
- The 7 studies that evaluated the ability of nitric oxide to provide prognostic information that could lead to changes in management had considerable methodologic limitations and variability in study methodology that precluded synthesis of their results and definitive conclusions. (21, 24-29)

Exhaled Breath Condensate

Similar to exhaled nitric oxide, there is intense research interest in the analysis of exhaled breath condensate as a biomarker of inflammation. However, it appears from the published literature that exhaled breath condensate is at an earlier stage of development compared to exhaled nitric oxide. For example, several review articles note that before routine clinical use in the diagnosis and management of respiratory disorders can be considered the following issues must be resolved (30-33):

- Standardization of collection and storage techniques
- Effect of dilution of respiratory droplets by water vapor
- Techniques of measuring concentrations of nonvolatile substances in exhaled breath condensate; in most cases these concentrations are very low, which may be at the lower limits of detection of conventional analytic techniques
- Variability in exhaled breath condensate assays for certain substances
- Further investigation of levels of compounds in health and disease

Ultimately, controlled trials will be required to determine how evaluations of exhaled breath condensate can be used to direct patient management. The National Institute of Allergy and Infectious Disease is currently recruiting asthmatic children to a clinical trial evaluating the use of pH measurement of exhaled breath condensate in the management of asthma. (34) This trial will evaluate both asthmatic patients and normal controls with exhaled breath condensate pH, expired nitric oxide, pulmonary lung function tests, and peak flow meters over a period of a year. Neither exhaled nitric oxide nor exhaled breath condensate pH are used in the management of the patient, but the study will determine whether these measures are correlated with known parameters of disease including number of hospitalizations, absenteeism from school, number of asthma exacerbations, lost work days (if applicable), and extent of rescue medication used.

2006 Update

A literature search was performed for the period of June 2005 through October 2006. No new studies were identified that would alter the conclusions of the policy statements to date. No additional clinical trials were identified in which use of these markers were used to adjust treatment decisions. While research efforts continue, the clinical utility of these measures is not currently known. In addition, studies also report factors that may influence the reliability of these results. (35, 36) In a study of 17 patients with asthma, Belda and colleagues concluded that measure of nitric oxide was not helpful in predicting loss of asthma control during corticosteroid withdrawal. (37) A study of exhaled breath condensate concluded that the findings did not correlate with results from bronchoalveolar lavage. (38)

2007 Update

The policy was updated with a literature search using MEDLINE from October 2006 through June 2007. Shaw and colleagues randomized 118 participants with asthma to a single-blind trial of corticosteroid therapy based on either exhaled nitric oxide measurements (n = 58) or British Thoracic Society guidelines (n = 60). (39) During the 12-month study, the primary outcome was the number of severe asthma exacerbations. The estimated mean exacerbation frequency was 0.33 per patient per year in the experimental group and 0.42 in the control group (p = 0.43). Overall the experimental group used 11% more inhaled corticosteroid, although the final daily dose of inhaled corticosteroid was lower in the nitric oxide directed group (557 vs. 895 mug, p = 0.028). The authors concluded that the asthma treatment strategy based on the measurement of exhaled nitric oxide did not result in a large reduction in asthma exacerbations or in the total amount of inhaled corticosteroid therapy used during the 12-month study when compared with current asthma care.

Fritsch and colleagues reported on a prospective, randomized, single-blind study to examine whether the inclusion of repeated exhaled nitrous oxide (FeNO) measurements into asthma monitoring leads to an improvement in asthma outcome. (40) Forty-seven children with mild to moderate asthma were allocated to an NO group (n = 22) and to a control group (n = 25) for 5 visits performed at 6-week intervals. In the FeNO group, therapy was based on symptoms, beta-agonist use, lung function, and FeNO whereas in the control group, the FeNO results were not obtained. Frequency of respiratory symptoms, beta-agonist use, FEV-1-percent of predicted and the frequency of exacerbations were similar between groups. Patients in the FeNO group received higher doses of inhaled corticosteroids and had significantly higher mean expiratory flow (as a percent of predicted) was 68.5% in the control group and 83.2% in the FENO group. The authors concluded that a therapy regimen aimed at lowering FeNO in children with asthma showed improved parameters of small airway function, but was not able to improve clinical markers of asthma control.

Finally, Gelb reported on the use of combining FeNO and FEV-1 in predicting asthma exacerbations among 44 non-smoking adults (average age 51 years) with stable asthma

during a subsequent 18-month period. This study reported that having FeNO below 28 ppb and FEV-1 above 76% predicted a probability of 0% among the 9 patients who met both criteria. (41)

These studies add to the existing literature, but the relationship between use of these assays and improvements in patient outcomes is uncertain. The policy statement(s) are unchanged.

None of the literature identified during the update adds important new information to the existing literature on the use of exhaled breath condensates.

2008 Update

The policy was updated with a literature review using MEDLINE in September 2008. One new randomized trial of using exhaled nitric oxide measurement in clinical care was identified. In this study, Szeffler and colleagues randomly assigned 546 eligible participants (inner-city adolescents and young adults) who adhered to treatment during a run-in period to 46 weeks of either standard treatment, based on the guidelines of the National Asthma Education and Prevention Program (NAEPP), or standard treatment modified on the basis of measurements of fraction of exhaled NO. (42) The primary outcome was the number of days with asthma symptoms. During the 46-week treatment period, the mean number of days with asthma symptoms did not differ between the treatment groups (1.93 in the NO monitoring group vs. 1.89 in the control group; difference 0.04 [-0.22 to 0.29], $p=0.78$). Other symptoms, pulmonary function, and asthma exacerbations did not differ between groups. Patients in the NO monitoring group received higher doses of inhaled corticosteroids (difference 119 mug per day, $p=0.001$) than controls. Adverse events did not differ between treatment groups. The authors concluded that conventional asthma management resulted in good control of symptoms in most participants and that the addition of a fraction of exhaled NO as an indicator of control of asthma resulted in higher doses of inhaled corticosteroids without clinically important improvements in symptomatic control. A Cochrane review from 2008 identified 4 trials using exhaled NO in the care of patients with asthma. (43) The reviewers noted that the approach to tailoring the dose of inhaled corticosteroids based on exhaled NO in comparison to clinical symptoms was carried out in different ways in the 4 studies, and the results show only modest differences. The report concluded that the role of utilizing exhaled NO to tailor the dose of inhaled corticosteroids is currently uncertain.

None of the other publications identified during the literature search, for either exhaled nitric oxide or exhaled breath condensate, were studies that would address the clinical utility of this test in practice.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

95012 Nitric oxide expired gas determination
 0064T Spectroscopy, expired gas analysis (eg, nitric oxide/carbon dioxide test)
 0140T* Exhaled breath condensate pH

A variety of substances have been analyzed in a collected sample of exhaled breath condensate, including but not limited to leukotrienes, cytokines, and other substances reflecting oxidative stress. *0140T would not apply to this expanded analysis of exhaled breath condensate. It is likely that specific CPT codes describing the underlying laboratory technique for analysis would be used.

REVISIONS

06-30-2009	Policy added to the bcbsks.com web site. No policy changes were made.
------------	---

REFERENCES

1. Baraldi E, Scollo M, Zaramella C et al. A simple flow-driven method for online measurement of exhaled NO starting at the age of 4 to 5 years. *Am J Respir Crit Care Med* 2000; 162(5):1828-32.
2. Kharitonov SA, Gonio F, Kelly C et al. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. *Eur Respir J* 2003; 21(3):433-48.
3. Salmone CM, Roberts AM, Brown NJ et al. Exhaled nitric oxide measurements in a population sample of young adults. *Am J Respir Crit Care Med* 1999; 159(3):911-6.
4. Dupont LJ, Rochette F, Demedts MG et al. Exhaled nitric oxide correlates with airway hyperresponsiveness in steroid-naïve patients with mild asthma. *Am J Respir Crit Care Med* 1998; 157(3 pt 1):894-8.
5. Jatakanon A, Lim S, Kharitonov SA et al. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax* 1998; 53(2):91-85.
6. Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000; 161(1):64-72.
7. Stirling RG, Kharitonov SA, Campbell D et al. Increase in exhaled nitric oxide levels in patients with difficult asthma and correlation with symptoms and disease severity despite treatment with oral and inhaled corticosteroids. *Thorax* 1998; 53(12):1030-4.
8. Sippel JM, Holden WE, Tilles SA et al. Exhaled nitric oxide levels correlate with measures of disease control in asthma. *J Allergy Clin Immunol* 2000; 106(4):645-50.
9. Lim S, Jatakanon A, John M et al. Effect of inhaled budesonide on lung function and airway inflammation. Assessment by various inflammatory markers in mild asthma. *Am J Respir Crit Care Med* 1999; 159(1):22-30.

10. Van Rensen EL, Straathof KC, Veselic-Charvat MA et al. Effect of inhaled steroids on airway hyper-responsiveness, sputum eosinophils and exhaled nitric oxide levels in patients with asthma. *Thorax* 1999; 54(5):403-8.
11. Kharitonov SA, Donnelly LE, Montuschi P et al. Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. *Thorax* 2002; 57(10):889-96.
12. Jones SL, Herbison P, Cowan JO et al. Exhaled NO and assessment of anti-inflammatory effects of inhaled steroid: dose-response relationship. *Eur Respir J* 2002; 20(3):601-8.
13. Bisgaard H, Loland L, Oj JA. NO in exhaled air of asthmatic children is reduced by the leukotriene receptor antagonist montelukast. *Am J Respir Crit Care Med* 1999; 160(4):1227-31.
14. Bratton DL, Lanz MJ, Miyazawa N et al. Exhaled nitric oxide before and after montelukast sodium therapy in school-age children with chronic asthma: a preliminary study. *Pediatr Pulmonol* 1999; 28(6):402-7.
15. National Asthma Education and Prevention Program. Expert Panel Report: guidelines for the diagnosis and management of asthma update on selected topics-2002. *J Allergy Clin Immunol* 2002; 110(5 suppl):S141-219.
16. Delgado-Corcoran C, Kissoon N, Murphy SP et al. Exhaled nitric oxide reflects asthma severity and asthma control. *Pediatr Crit Care Med* 2004; 5(1):48-52.
17. Meyts I, Proesmans M, De Boeck K. Exhaled nitric oxide corresponds with office evaluation of asthma control. *Pediatric Pulmonol* 2003; 36(4):283-9.
18. Malmberg LP. Exhaled nitric oxide in childhood asthma - time to use inflammometry rather than spirometry? *J Asthma* 2004; 41(5):511-20.
19. Zeidler MR, Kleerup EC, Tashkin DP. Exhaled nitric oxide in the assessment of asthma. *Curr Opin Pulm Med* 2004; 10(1):31-6.
20. Smith AD, Cowan JO, Brassett KP et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005; 352(21):2163-73.
21. Deykin A. Targeting biologic markers in asthma - is exhaled nitric oxide the bull's-eye? *N Engl J Med* 2005; 352(21):2233-5.
22. 2005 TEC Assessments; Tab 17.
23. Pijnenburg MW, Bakker EM, De Jongste JC et al. Titrating steroids on exhaled nitric oxide in asthmatic children: a randomized controlled trial. *Am J Respir Crit Care Med* 2005; 172(7):831-6.
24. Gill M, Walker S, Khan A. Exhaled nitric oxide levels during acute asthma exacerbation. *Acad Emerg Med* 2005; 12(7):579-86.
25. Zacharasiewicz A, Wilson N, Lex C et al. Clinical use of noninvasive measures of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005; 171(10):1077-82.
26. Pijnenburg MW, Hofhuis W, Hop WC et al. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005; 60(3):215-8.
27. Prieto L, Bruno L, Gutierrez V et al. Airway responsiveness to adenosine 5'-monophosphate and exhaled nitric oxide measurements: predictive value as markers for reducing the dose of inhaled corticosteroids in asthmatic subjects. *Chest* 2003; 124(4):1325-33.
28. Jones SL, Kittelson J, Cowan JO et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med* 2001; 164(5):738-43.

29. Leuppi JD, Salome CM, Jenkins CR et al. Predictive markers of asthma exacerbation during stepwise reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001; 163(2):406-12.
30. Liu J, Thomas PS. Exhaled breath condensate as a method of sampling airway nitric oxide and other markers of inflammation. *Med Sci Monitor* 2005; 11(8):MT53-62.
31. Hunt J. Exhaled breath condensate: an evolving tool for noninvasive evaluation of lung disease. *J Allergy Clin Immunol* 2002; 110(1):28-34.
32. Effros RM, Su J, Casaburi R et al. Utility of exhaled breath condensates in chronic obstructive pulmonary disease: a critical review. *Curr Opin Pulm Med* 2005; 11(2):135-9.
33. Rosias PP, Dompeling E, Hendriks HJ et al. Exhaled breath condensate in children: pearls and pitfalls. *Pediatr Allergy Immunol* 2004; 15(1):14-9.
34. www.clinicaltrials.gov/ct/gui/show/NCT00078208
35. Gaston B, Kelly R, Urban P et al. Buffering airway acid decreases exhaled nitric oxide in asthma. *J Allergy Clin Immunol* 2006; 118(4):817-22.
36. Belda J, Parameswaran K, Lemiere C et al. Predictors of loss of asthma control induced by corticosteroid withdrawal. *Can Respir J* 2006; 13(3):129-33.
37. Nguyen TA, Woo-Park J, Hess M et al. Assaying all of the nitrogen oxides in breath modifies the interpretation of exhaled nitric oxide. *Vascul Pharmacol* 2005; 43(6):379-84.
38. Jackson AS, Sandrini A, Campbell C et al. Comparison of biomarkers in exhaled breath condensate and broncho-alveolar lavage. *Am J Respir Crit Care Med* 2006; 175(3):222-7.
39. Shaw DE, Berry MA, Thomas M et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; 176(3):231-7.
40. Fritsch M, Uxa S, Horak F Jr et al. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol* 2006; 41(9):855-62.
41. Gelb AF, Flynn Taylor C, Shinar CM et al. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. *Chest* 2006; 129(6):1492-9.
42. Szeffler SJ, Mitchell H, Sorkness CA et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008; 372(9643):1065-72.
43. Petsky HL, Cates CJ, Li AM et al. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* 2008 Apr 16; (2):CD006340.