Measurement of Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders

Effective: April 1, 2019

Next Review: January 2020
Last Review: March 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Measurement of exhaled breath condensate is proposed for diagnosing and managing asthma and other respiratory disorders.

MEDICAL POLICY CRITERIA

Note: This policy does not address measurement of fractional exhaled nitric oxide (FeNO) which may be considered medically necessary.

Measurement of exhaled breath condensate is considered investigational in the diagnosis and management of respiratory disorders, including but not limited to asthma, chronic obstructive pulmonary disease and chronic cough.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None
BACKGROUND

ASTHMA OVERVIEW

Asthma is characterized by airway inflammation that leads to airway obstruction and hyperresponsiveness, which in turn lead to characteristic clinical symptoms including wheezing, shortness of breath, cough, and chest tightness. 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 forced expiratory volume in 1 second (FEV1) 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.

EXHALED BREATH CONDENSATE

One proposed strategy is to evaluate the constituents in exhaled breath condensate (EBC). As an individual breathes into a mouthpiece, the exhaled air is passed through a condensing or cooling apparatus, resulting in an accumulation of fluid. The fluid is a complex matrix of potential biomarkers, not just a single component. 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 other markers of oxidative stress. There are a variety of laboratory techniques to measure the components of EBC, including such simple techniques as pH measurement and the more sophisticated gas chromatography/mass spectrometry or high-performance liquid chromatography, depending on the component of interest.

CLINICAL USES OF EBC

Analysis of EBC has been investigated in the diagnosis and management respiratory disorders, including asthma. Potential uses in management of asthma include assessing response to anti-inflammatory treatment, monitoring compliance with treatment, and predicting exacerbations. Aside from asthma, EBC analysis has also been proposed in the management of patients with chronic obstructive pulmonary disease, cystic fibrosis, allergic rhinitis, pulmonary hypertension, and primary ciliary dyskinesia.

REGULATORY STATUS

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research) and the ECoScreen EBC collection system (CareFusion, Germany) are registered with the US Food and Drug Administration (FDA) as class I devices that collect expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

EVIDENCE SUMMARY

Assessment of the clinical role of exhaled breath condensate (EBC) (when used in the management of asthma or other respiratory disorders) requires controlled studies of those
managed conventionally compared with those whose management is additionally directed by test measurements. Following is a summary of the key literature to date.

Analysis of EBC is in early development. A 2012 review by Davis noted that this is due, in part, to the fact that EBC is a matrix that contains so many potential biomarkers that research efforts have thus far been spread across numerous components.\[1\] In addition, several review articles have noted that before routine clinical use in the diagnosis and management of respiratory disorders can be considered, the following issues must be resolved:\[1-5\]

- Standardization of collection and storage techniques
- Effect of dilution of respiratory droplets by water vapor
- Effect of contamination from oral and retropharyngeal mucosa
- Variability in EBC assays for certain substances, including assay kits for the same biomarker and kit lot numbers from the same manufacturer
- Lack of a criterion standard for determining absolute concentrations of airway lining fluid nonvolatile constituents to compare with EBC
- Lack of normative values specific to each potential EBC biomarker.

**EBC Markers of Asthma Severity or Control**

In 2013, Thomas conducted a systematic review of studies assessing the association between components of EBC and pediatric asthma.\[6\] The authors identified 46 articles that measured at least one EBC marker in asthma, allergy, and atopy in children up to age 18 years. Most studies were cross-sectional, but there was wide variation in the definitions used to identify children with asthma and the collection devices and assays for EBC components. Studies reviewed evaluated multiple specific EBC components, including hydrogen ions, nitric oxide, glutathione and aldehydes, hydrogen peroxide, eicosanoids (including prostaglandins and leukotrienes), and cytokines (including interleukins in the Th2 pathway and interferon gamma). The authors noted that hydrogen ions and markers of oxidative stress, including hydrogen peroxide and oxides of nitrogen, were most consistently associated with asthma severity. Eicosanoids and cytokines demonstrated more variable results, but were frequently elevated in the EBC of patients with asthma. Overall, the authors concluded that while EBC has the potential to aid diagnosis of asthma and to evaluate inflammation in pediatric asthma, further studies on EBC collection and interpretation techniques are needed.

In 2016, the same group of investigators published a qualitative (narrative) systematic review assessing the relations between adult asthma and oxidative stress markers and pH in EBC.\[7\] Sixteen studies met the inclusion criteria, with EBC compared between 832 patients with asthma and 556 healthy controls. In addition to measuring pH (n=6 studies), studies evaluated nitrite (n=1), nitrate (n=1), total NO (n=3), hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}, n=8), and 8-isoprostane (8-isoP, n=4). Most studies were cross-sectional (n=11) and the rest were longitudinal (n=5); one was double-blinded. A variety of EBC collecting devices were used, with a custom-made condensing device used in 7 studies. The association between pH or NO and asthma varied between studies, and in 1 study, the pH in the same subjects varied by collection device. Concentrations of H\textsubscript{2}O\textsubscript{2} and 8-isoP were significantly higher in patients with asthma in most studies. Reviewers concluded that EBC collection of oxidative stress markers is relatively robust despite variability in techniques, but to become a useful clinical tool studies are needed to evaluate the ability of EBC biomarkers to predict future asthma exacerbations and tailor asthma treatment.
Among adults, a number of studies have been published on components of EBC and their relationship with asthma severity. In 2011, Liu evaluated the Severe Asthma Research Program, a multicenter study funded by NIH. This study had the largest sample size, with 572 patients.[8] Study participants included 250 patients with severe asthma, 291 patients with nonsevere asthma, and 51 healthy controls. Samples of EBC were collected at baseline and analyzed for pH levels. Overall, the median pH of the 2 asthma groups combined (7.94) did not differ significantly from the median pH of controls (7.90; p=0.80). However, the median pH of patients with nonsevere asthma (7.90) was significantly lower than that for patients with severe asthma (8.02; p not reported).

In 2012, Piotrowski in Poland prospectively studied adult patients with asthma.[9] The study included 27 patients with severe asthma receiving treatment (group 1), 16 newly diagnosed and never-treated asthma patients (group 2), and 11 health controls (group 3). At baseline and at weeks 4 and 8, EBC was collected and patients underwent spirometry and other tests of asthma severity. Patients took all medications needed to control symptoms throughout the study. Levels of 8-isoprostane (8-IP) in breath condensate were analyzed. At baseline, the median level of 8-IP was 4.67 pg/mL, 6.93 pg/mL, and 3.80 pg/mL in groups 1, 2, and 3, respectively. There were no statistically significant differences among groups in 8-IP levels. In addition, 8-IP levels did not correlate significantly with asthma severity measures, including the number of symptom-free days, FEV1 reversibility, and scores on the ACT. In this study, 8-IP levels in EBC were not a useful marker of asthma severity.

In 2014, Keskin evaluated the relation between two EBC components, cysteinyl leukotrienes (Cys-LTs) and 8-IP, in asthma control among 30 children with asthma.[10] Included patients had a diagnosis of asthma and had been in a stable condition, free from acute exacerbations and respiratory tract infections for the two months prior to the EBC evaluation. Asthma control was evaluated with the childhood ACT and by pediatric allergists. Of the entire group, 19 subjects had mild persistent asthma, while 11 had moderate persistent asthma. EBC 8-IP levels were higher in those with moderate persistent asthma (114.0 pg/mL) than in those with mild persistent asthma (52 pg/mL; p=0.05), and higher in those with more than 4 exacerbations per year (114 pg/mL) than in those who had 1 to 4 exacerbations per year (52 pg/mL; p<0.05). Cys-LTs levels were not significantly associated with asthma exacerbation frequency or asthma severity.

Also in 2014, Navratil evaluated the relation between EBC and asthma control in a cross-sectional study of 103 children (age range, 6-18 years) with asthma.[11] Subjects were enrolled from a single clinic, had an established asthma diagnosis, and were on stable dosage of their asthma treatment. Patients were considered to have controlled (n=50 [48.5%]) or uncontrolled asthma (n=53 [52.5%]) based on GINA guidelines. Controlled and uncontrolled asthmatics differed significantly in EBC urates (uncontrolled median EBC urate, 10 µmol/L vs controlled median EBC urate, 45 µmol/L; p<0.001); EBC pH (uncontrolled mean pH, 7.33 vs controlled mean pH, 7.33; p=0.002); and EBC temperature (uncontrolled mean EBT, 34.26°C vs controlled mean EBT, 33.9°C; p=0.014). In addition, EBC urate concentration was significantly associated with time from last exacerbation (p<0.001), ACT results (p<0.001), and short-acting bronchodilator use (p<0.001) within the entire cohort.

Van Vliet evaluated whether the combination of fractional exhaled nitric oxide (FeNO) and EBC inflammatory markers (including interleukin [IL] 1α, IL-5, IL-6, IL-8, IL-13, IL-17 and tumor necrosis factor α) predicted asthma exacerbations in a cohort of 102 children ages 6 to 18 years.[12] Ninety-six subjects were included in the analysis. The authors generated three
predictive models for asthma exacerbations based on EBC components and clinical factors, using a k-nearest neighbor algorithm. The areas under the ROC curves for the 3 models were 0.465, 0.543, and 0.585, respectively.

**EBC Components as Markers of Respiratory Disorders Other Than Asthma**

There is little published literature on EBC levels in patients with respiratory disorders other than asthma. A 2010 study by Antus evaluated EBC in 58 hospitalized patients (20 with asthma, 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers). EBC pH was significantly lower in patients with asthma exacerbations (all nonsmokers) at hospital admission (6.2) than in nonsmoking controls (6.4; p<0.001). EBC pH in asthma patients increased during the hospital stay and was similar to that of nonsmoking controls at discharge. Contrary to investigators’ expectations, EBC pH values in ex-smoking COPD patients (n=17) did not differ significantly from nonsmoking controls, either at hospital admission or at discharge. Similarly, pH values in EBC samples from smoking COPD patients (n=21) at admission and discharge did not differ significantly from smoking controls.

Other small studies have reported on the feasibility of using EBC in the diagnosis or recognition of other respiratory conditions, including radiation pneumonitis after stereotactic ablative radiotherapy (N=26).

**EBC-Guided Treatment Decisions for Patients with Asthma or Other Respiratory Disorders**

No controlled studies were identified evaluating the role of EBC tests in the management of asthma or other respiratory disorders. Uncontrolled studies include a 2009 case series investigating whether components of EBC could predict response to steroid treatment in patients with asthma. Eighteen steroid-naive asthma patients were included; EBC collection, spirometry, and methacholine challenge were performed before and 12 weeks after ICS therapy (equivalent daily dose of fluticasone propionate 400 µg). Among the molecules in EBC examined, higher IL-4 and RANTES (regulated on activation normal T cell expressed and secreted) levels and lower 10-IP levels at baseline correlated with an improvement in FEV1. The study had a small sample size, was uncontrolled, and did not address whether EBC measurement could improve patient management or health outcomes.

**PRACTICE GUIDELINE SUMMARY**

No practice guidelines specific to the analysis of exhaled breath condensate were identified.

**SUMMARY**

More research is needed to know if or how well measurement of exhaled breath condensate works for the diagnosis and management of asthma and other respiratory disorders. No clinical guidelines based on research recommend exhaled breath condensate measurement for people with respiratory disorders. Therefore, the use of exhaled breath condensate tests for the diagnosis and management of respiratory disorders, including but not limited to asthma, is considered investigational.
References


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