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

Effective: March 1, 2024

Next Review: January 2025
Last Review: January 2024

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 components is proposed for diagnosing and managing asthma, chronic obstructive pulmonary disease, 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 one second (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.

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 well-designed comparative

studies of those managed conventionally compared with those whose management is additionally directed by test measurements. The focus of the following evidence summary is on systematic reviews (SRs) and well-designed comparative studies 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

Systematic Reviews

Bannier (2019) published a narrative review of the literature on the various markers of EBC to predict childhood asthma.[6] The authors identified a total of 30 studies, of which 20 had a cross-sectional design and 10 reported longitudinal data. The most frequently studied EBC biomarkers were cytokines (n =10), acidity (n = 9), and eicosanoids (including 8-isoprostane, cysteinyl-leukotrienes, and lipoxins: n = 9). Fourteen different analytical methods were used for measurement of the various biomarkers across these studies. Among cross-sectional studies, only one tried to create a predictive model for asthma using different EBC markers: pH, pCO2, pO2, magnesium, calcium, and urates. The diagnostic accuracy was considered only modest with a positive predictive value (PPV) of 84%, and negative predictive value (NPV) of 39%. The authors noted a high variability is found across studies in the breath condenser used, collection time, collected volume, prevention of salivary or environmental contamination, cleaning procedures, ambient air conditions, storage conditions, time between collection and analysis, and analytical methods. The authors concluded that higher quality, appropriately controlled studies are required to address each of these significant limitations.

In 2016, Aldakheel published a narrative review assessing the relationship between adult asthma and markers of oxidative stress 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 nitric oxide (NO) (n=3), hydrogen peroxide (H_2O_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 seven studies. The association between pH or NO and asthma varied between studies, and in one study, the pH in the same subjects varied by collection device. Concentrations of H_2O_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.

In 2013, Thomas conducted a SR of studies assessing the association between components of EBC and pediatric asthma.[8] 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.

Randomized Controlled Trials

No RCTs evaluating EBC for markers of asthma severity or control were identified.

Non-randomized Studies

Comparative Studies

In 2014, Keskin published a comparative study of the EBC components cysteinyl leukotrienes (Cys-LTs) and 8-IP in asthma control among 30 children.[9] 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 four 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 relationship between EBC and asthma control in a cross-sectional study of 103 children (age range, 6 to 18 years) with asthma.[10] 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 Global Initiative for Asthma (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, 7.2 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.

In 2012, Piotrowski in Poland prospectively studied adult patients with asthma.[11] The study included 27 patients with severe asthma receiving treatment (group one), 16 newly diagnosed and never-treated asthma patients (group two), and 11 health controls (group three). At baseline and at weeks four and eight, 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 one, two, and three, respectively. There was no statistically significant difference 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, FEV_1 reversibility, and scores on the ACT. In this study, 8-IP levels in EBC were not a useful marker of asthma severity.

In 2011, Liu evaluated the Severe Asthma Research Program, a multicenter study funded by NIH.[12] 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 two 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).

Non-comparative Studies

Polomska (2022) evaluated the potential of L-arginine (L-ARG) and its metabolites in serum and exhaled breath condensate (EBC) to serve as a biomarker of asthma in pediatric patients.[13] Sixty-five children (37 pediatric patients with bronchial asthma and 28 healthy control) were included in the study. No correlation between forced expiratory volume in one second (FEV1) and L-ARG or its metabolites was found, suggesting EBC concentrations of L-ARG and its metabolites are not an indicator of pediatric bronchial asthma.

Kreissl (2021) published the results of a study evaluating the predictive value of deaerated breath condensate pH (dEBC pH) for subsequent asthma risk.[14] Asthma diagnosis at school age was evaluated according to Global Initiative for Asthma recommendations in 135 children who at baseline had been classified as: (asymptomatic) atopic wheezers (n = 30), (asymptomatic) nonatopic wheezers (n = 57), allergic rhinitis only (n = 14), and healthy controls (n = 34). At school-age follow-up, all (100%) former atopic wheezers, 12 (21%) of nonatopic wheezers, two (14%) of allergic rhinitis group, and one (3%) of healthy controls had developed asthma. Among all children with baseline wheezing, baseline dEBC pH predicted asthma at follow-up with an area under the receiver operating characteristic curve (AUC) of 0.72 (sensitivity, 0.67; specificity, 0.76; at pH 7.83). The combination of pH and Capacity class (CAP) provided higher sensitivity (0.96) and negative predictive value (NPV, 0.94), and the addition of clinical information (Asthma Predictive Index, family atopy, family asthma, and inhaled corticosteroids) raised the predictive value for asthma (AUC, 0.94) sensitivity and NPV to 0.98 and 0.97, respectively.

Van Vliet (2015) 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.[15] 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 three models were 0.465, 0.543, and 0.585, respectively.

EXHALED BREATH CONDENSATE COMPONENTS AS MARKERS OF RESPIRATORY DISORDERS OTHER THAN ASTHMA

Systematic Reviews

No SRs evaluating EBC component levels as markers of respiratory disorders other than asthma were identified.

Randomized Controlled Trials

No RCTs evaluating EBC component levels as markers of respiratory disorders other than asthma were identified.

Non-randomized Studies

Hao (2019) published a comparative study of inflammatory mediators measured in EBC of patients with stable COPD and control subjects.[16] The proteins tested for were metalloproteinase-9 (MMP-9) and -12 (MMP-12), tissue inhibitor of metalloproteinase-1 (TIMP-1) and -4 (TIMP-4), and neutrophil elastase. Although no significant difference in any of the EBC protein levels was reported between COPD and control groups, the authors report higher levels of MMP-9 and -12 in the EBC of COPD smokers compared to COPD never-smokers (p=0.034 and 0.041, respectively). The authors also report that MMP-9 (r=-0.78, p<.0001) and TIMP-1 (r=-0.71, p<.0001) levels in EBC were significantly negatively correlated with pulmonary function as measured by predicted % forced expiratory volume in one minute (FEV1%pred). Although these data suggest EBC may be useful for monitoring airway inflammation, the diagnostic or prognostic value of these tests require larger, adequately controlled studies.

A 2010 comparative study by Antus evaluated EBC in 58 hospitalized patients (20 with asthma, 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers).[17] 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).[18]

EXHALED BREATH CONDENSATE-GUIDED TREATMENT DECISIONS FOR PATIENTS WITH ASTHMA OR OTHER RESPIRATORY DISORDERS

Systematic Reviews

No SRs evaluating the role of EBC tests in the management of respiratory disorders were identified.

Randomized Controlled Trials

No RCTs evaluating the role of EBC tests in the management of respiratory disorders were identified.

Non-randomized Studies

Matsunaga (2009) published a non-randomized study investigating whether components of EBC could predict response to steroid treatment in patients with asthma.[19] 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 forced expiratory volume in one second (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 clinical practice guidelines specific to the analysis of exhaled breath condensate in the diagnosis or management respiratory disorders 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.

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CODES

Codes	Number	Description
CPT	83987	pH, Exhaled breath condensate
HCPCS	None	

Date of Origin: *March 2004*