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Official publication of the American College of Chest Physicians



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Chest 2010;138;38S-43S
DOI 10.1378/chest.10-0094

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ISSN:0012-3692





Measuring Bronchitis in Airway Diseases: Clinical Implementation and Application

Airway Hyperresponsiveness in Asthma: Its Measurement and Clinical Significance

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Airway inflammation is fundamental to the cause and persistence of asthma and other airway conditions. It contributes to symptoms, variable airflow limitation, airway hyperresponsiveness, and the structural changes (remodeling) associated with asthma. However, the presence and type of airway inflammation can be difficult to detect clinically, delaying the introduction of appropriate treatment. Cellular inflammation in the airway can be accurately and reliably assessed by examining spontaneous or, when not available, induced sputum. Induced sputum cell counts are relatively noninvasive, safe, and reliable. They can accurately discriminate eosinophilic airway inflammation from noneosinophilic airway inflammation and, thus, help to guide therapy. Eosinophilic airway inflammation is steroid responsive, whereas noneosinophilic (usually neutrophilic) inflammation generally is not. Monitoring of airway inflammation using sputum cell counts helps to identify the impending loss of asthma control and, thus, the need to adjust antiinflammatory medications in patients with a variety of airway diseases, such as asthma, smoker's COPD, and chronic cough. Other noninvasive, indirect measurements of airway inflammation, such as exhaled nitric oxide, do not help to identify the cellular nature of airway inflammation associated with exacerbations of airway diseases, particularly in patients who are already on corticosteroids. Thus, although they can be a predictor of steroid responsiveness, these measures do not help to reduce asthma exacerbations when used in clinical practice. The clinical usefulness of measurements in exhaled breath condensate has not yet been established. *CHEST 2010; 138(2)(Suppl):38S–43S*

Abbreviations: LABA = long-acting β -agonist; SVC = slow vital capacity

AN INNOVATION

Progress in the diagnosis and treatment of airway diseases, such as asthma, COPD, and bronchiectasis, and of chronic cough has been made by the introduction of measurements of airway inflammation into clinical practice, especially of quantitative sputum cell

counts.^{1,2} The cell counts provide the most comprehensive, specific, and discriminative information.^{1,3,4} Although they are not available in real time, an interpreted result can be available within 24 h, in time for practical use. The new refined methods are repeatable, responsive, and valid—the qualities of good measurements.³ Normal values are well documented (Table 1).⁵ The total cell count gives a measure of the intensity of any inflammation and the differential of the type.

Quantitative sputum cell counts diagnose the bronchitis or bronchiolitis component of airway diseases, which is central to these conditions (Fig 1). The bronchitis is the primary cause of exacerbations

Manuscript received January 12, 2010; revision accepted March 15, 2010.

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Funding/Support: Dr Nair is supported by a Canada Research Chair in Airway Inflammometry. This report is based on a lecture delivered at the Inhalational Challenge Symposium held on June 27, 2009, at Hamilton, ON, Canada, which was supported by an unrestricted educational grant from Pharmaxis Ltd.

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DOI: 10.1378/chest.10-0094

Table 1—Normal Values

Sputum Cell Count	Mean	Mean + 2 SD	Median	90th Percentile
Total cells, 10 ⁶ /g	4.1	13.8	2.4	9.7
Eosinophils, %	0.4	2.2	0.0	1.1
Neutrophils, %	37.5	77.7	36.7	64.4
Macrophages, %	58.8	100	60.8	86.1
Lymphocytes, %	1.0	3.2	0.5	2.6
Metachromatic, %	0.0	0.1	0.0	0.04

Adapted from data from Belda et al.⁵

and chronic effects. The measurements do not diagnose asthma or COPD, which are primarily defined and recognized by abnormalities of airway function, or emphysema or bronchiectasis, which are defined by abnormalities of pathology and recognized by diagnostic imaging.⁶ The measurements are needed because clinical assessment of bronchitis using symptoms and spirometry is imprecise, even when performed by specialists.⁷ The measurements are especially useful when disease is difficult to control, needs treatment with high-dose inhaled steroid or prednisone, or is otherwise complex. Hence, the measurements are particularly needed by specialists in tertiary care and community practice.

In contrast, although the fraction of exhaled nitric oxide is easier and immediately available, it is not as valid or discriminative and has a range in normal individuals.⁸ It does not directly measure bronchitis, correlate with airway eosinophilia in patients with severe prednisone-dependent asthma,⁹ or reduce the frequency of exacerbations when incorporated into clinical practice.¹⁰ Other measurements in the exhaled breath, including temperature and pH, although they can help to predict exacerbations, are not yet evaluated enough for clinical practice.¹¹

THE TEST

At present, the test is a hospital procedure. In patients with symptoms, sputum can often, with encouragement, be produced spontaneously. Only a small amount, selected from the expectorate of sputum plus saliva, is needed. When a spontaneous sample cannot be obtained, sputum can usually be induced in the pulmonary function laboratory by a technologist with an aerosol of normal or hypertonic saline.^{3,12,13} Saline is a potential bronchoconstrictive stimulus; therefore, pretreatment with an inhaled β -agonist, such as salbutamol 200 μ g, is given, and the FEV₁ is monitored for safety. An ultrasonic nebulizer delivering about 0.9 mL/min provides optimum success with minimal side effects. We use the Universal III ultrasonic nebulizer (Methapharm Inc; Brantford, ON, Canada), which is not yet approved

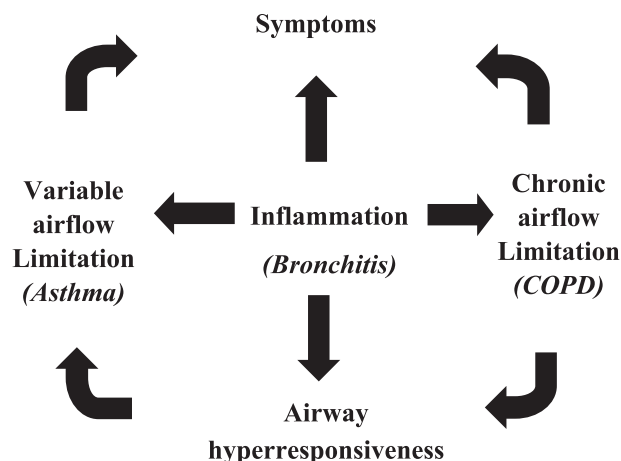


FIGURE 1. Quantitative sputum cell counts diagnose the bronchitis or bronchiolitis component of airway diseases, which is central to these conditions.

for use in the United States. The procedure can be safely performed and is usually successful, even in patients with an exacerbation of asthma¹⁴ or with severe chronic airflow limitation.¹⁵

In clinical practice, the examination of the sputum needs a certified technologist trained in the examination of cell counts; it is a laboratory medicine procedure. The specimen can be held in the refrigerator for up to 8 h without alteration of the counts.¹⁶ The cell counts involve selection of a limited amount (0.1–0.3 g) of sputum from saliva using an inverted microscope, treatment of the weighed sample with dithiothreitol and buffered saline, and filtering to give a homogeneous suspension of cells.^{12,13} An Accu-filter sputum processing kit simplifies the procedure and provides a detailed evaluated protocol, which standardizes it. Total cell count and cell viability (with trypan blue) are determined in a hemocytometer, and a 400 differential cell count is obtained from Wright-stained cytopins. Regular quality control is essential for the standardization of methods and reliability of counts. Normal values have a narrow range, particularly for eosinophils (Table 1). With a trained technologist, the results of sputum examination can be available in about 1.5 h, involving 1 h of technologist time. This is only about 15 min longer than cell counts performed on other body fluids. Interpreted reports can be sent out within 24 h, which is a suitable time frame for clinical decisions to be made.

ITS USE AND INTERPRETATION

Sputum cell counts have a number of uses (Table 2), three of which are illustrated by the case studies that follow. In general, we recommend examining cell counts as often as they are required to optimize the maintenance

Table 2—Indications for the Test

Asthma that is not showing adequate response to usual therapy.
Exacerbations of asthma to decide on appropriate therapy.
COPD to decide if inhaled corticosteroid is needed or to detect an infection.
Exacerbations of COPD to decide whether antibiotic or corticosteroids are needed.
Cough that is not showing adequate response to usual therapy.
Identification of eosinophilic or neutrophilic bronchitis as part of evaluation of occupational "asthma" or "bronchitis."

treatment dose of corticosteroids and at the time of exacerbations. On average, a patient may require two to three tests a year.

Case Study 1

A 30-year-old woman was referred for reassessment of her asthma because she had daily symptoms of cough and wheeze that were not controlled on inhaled budesonide 400 µg bid. She required treatment with salbutamol two to three puffs daily. Her FEV₁ and slow vital capacity (SVC) were 2.0 L and 3.4 L (68% and 80% predicted, respectively). The FEV₁ improved to 2.5 L after inhaling 200 µg of salbutamol, confirming the presence of asthma. Most guidelines would recommend the addition of a long-acting β-agonist (LABA) to her current dose of corticosteroid.¹⁷ However, we assessed airway inflammation by measuring sputum cell counts. The total cell count was 22 million cells/g (normal < 9.7 million cells/g) of which 88% were neutrophils (normal < 64.4%) and 5% were eosinophils (normal < 2%). This indicates a combined infective and eosinophilic bronchitis. She was treated with an antibiotic, and her corticosteroid was increased to budesonide 800 µg bid. Two weeks later, she no longer required daily salbutamol, her FEV₁ had improved to 2.6 L presalbutamol, and sputum total cell counts were normal.

Case Study 2

An 86-year-old man was referred by a cardiologist with a diagnosis of severe COPD, severe coronary artery disease, type 1 diabetes, and obesity. His respiratory symptoms were cough, sputum, dyspnea on minimal exertion, and orthopnea. Previous heart failure was controlled, and his respiratory treatment was salbutamol/ ipratropium two puffs qid. His FEV₁ and SVC after salbutamol were 0.68 L and 1.33 L (predicted 2.84 L and 3.81 L), confirming severe airflow limitation. Guidelines recommend that he be given tiotropium or a LABA and later an inhaled corticosteroid.¹⁸ He could not produce sputum spontaneously, so this was carefully induced with an aerosol of normal saline without causing bronchoconstriction. The sputum was mucoid and showed a modest

eosinophilic bronchitis (4.2%). He was treated with a short course of prednisone. His symptoms improved and his FEV₁/SVC increased to 1.4 and 2.67 L. Subsequently, sputum cell counts were used to guide the minimum treatment to maintain the best results; this was identified as budesonide 400 µg bid and budesonide/formoterol fumarate dihydrate 200 µg bid. During the next year, he had one exacerbation, which sputum cell counts identified as being due to an infective bronchitis. This was treated with an antibiotic successfully without alteration of his other treatment.

Case Study 3

A 42-year-old woman who had never smoked presented with a cough of 8 years. Results of physical examination, spirometry, methacholine inhalation test, bronchoscopy, and a high-resolution chest CT scan were normal. Sputum was induced and showed normal cell counts, excluding eosinophilic or infective bronchitis as a cause. She thus did not require treatment with inhaled corticosteroids or antibiotics. The lipid-laden macrophage index was 40 (normal < 7.0), suggesting aspiration of gastric contents as a cause of cough.¹⁹ Esophageal manometry and 24-h ambulatory esophageal pH monitoring and impedance studies confirmed the diagnosis of a nonacid reflux, and the patient's cough improved significantly after a laparoscopic fundoplication.

INTERPRETATION

These case studies illustrate that there are different types of bronchitis (eosinophilic, neutrophilic, combined eosinophilic and neutrophilic, or paucigranulocytic) and that knowing what is present guides treatment (Table 3). An eosinophilic bronchitis is characterized by an increase in percent of eosinophils usually with a total cell count within the normal range. Sputum eosinophilia (particularly of 3% or more) or the presence of moderate-to-many eosinophil-free

Table 3—Treatment Titration Based on Cell Counts

Eosinophilic bronchitis
> 3%: increase inhaled/ingested steroids even if asthma is clinically controlled
2-3%: increase inhaled/ingested steroids if symptomatic
1-2%: leave current dose of inhaled/ingested steroid unchanged
< 1%: consider decreasing dose of inhaled/ingested steroid
Neutrophilic bronchitis
TCC > 25 × 10 ⁶ /g, N > 80%: antibiotics
TCC 10-25 × 10 ⁶ /g, N > 80%: consider antibiotics
TCC < 10 × 10 ⁶ /g, N = 65%-80%: antibiotics not necessary
Recheck sputum cell counts 4-6 weeks after a treatment change
Add LABA after controlling bronchitis if the patient continues to have symptomatic variable airflow obstruction
LABA = long-acting β-agonist; N = neutrophils; TCC = total cell count.

granules predicts benefit from added/increased corticosteroid treatment in asthma,^{20,21} as well as in COPD^{22,23} or chronic cough.^{24,25} However, there is a gray area between 1% to 3% when clinical benefit can occur in some patients. It is advisable not to reduce the dose of antiinflammatory therapy if the sputum eosinophils are in this range even if the patients are asymptomatic.²⁶ Sputum neutrophils are much more variable because they are influenced by many airborne stimuli. When only the percentage is increased the clinical significance is uncertain. A neutrophilic bronchitis with an increased total cell count can be arbitrarily graded as mild if the total count is >9.7 but <20 million cells/g (mL) in sputum selected from saliva, moderate if 20 to <50 million cells/g, and intense if 50 million/g or more, and suggests infection. Current evidence suggests that the infective bronchitis of viral origin is generally milder as judged by the total cell count and neutrophils of <80%, whereas bacterial bronchitis can be more intense and have a percentage of >80^{27,28}; however, this requires further validation with studies that combine traditional culture and molecular methods to identify bacterial and viral infection. At present, there is no evidence that stimuli other than bacterial infections or smoker's bronchitis²⁹ can elevate the total cell count in sputum when this is expressed as 10⁶/g of selected sputum, but one might expect this to happen when intense inflammation is caused by noxious stimuli, as in endotoxin exposure or reactive airways dysfunction syndromes. When there is a persistent or recurrent intense neutrophilia, bronchiectasis with infective bronchitis should be suspected.^{30,31} Neutrophilic bronchitis and paucigranulocytic cell counts, with a normal total and differential counts, suggests there will be no benefit from corticosteroid³² or antibiotic treatment.

Guidelines for asthma fail to emphasize the frequent occurrence of infections. Unless the patient is asked to cough sputum in the clinic (an uncommon practice), and this is frankly purulent, infection can be easily missed and inappropriate treatment given. Case 1 shows an instance in which guidelines would have incorrectly advocated adding LABA or prednisone. However, cautious interpretation is needed here since an infective neutrophilia can mask an eosinophilia.³³ Therefore, if symptoms do not resolve, it is important to recheck sputum cell counts after the neutrophilia has been treated.

Case 2 illustrates how sputum cell counts can also be used to monitor treatment and identify the minimum dose of corticosteroid needed to control the eosinophilic bronchitis. In patients treated with inhaled steroid or with prednisone, absent eosinophils suggest that the steroid treatment might be excessive and can be reduced. When the dose is adjusted to

keep sputum eosinophils less than 2% or 3%, eosinophilic exacerbations are reduced without the need for increased steroid treatment in both asthma³⁴ and COPD.³⁵ Such monitoring does not reduce noneosinophilic exacerbations. These might be reduced by treatment with a LABA when needed to control symptomatic variable airflow limitation,³⁴ but this requires validation. This use of the test to monitor treatment is cost effective.³⁶

Case 3 draws attention to the use of sputum cell counts in the investigation and treatment of chronic cough. This symptom in patients with a normal chest radiograph is common and arises from a number of causes.³⁷ The cause in 10% to 15% of patients referred to a tertiary care center is an eosinophilic bronchitis that responds to corticosteroid treatment. Although most respond to inhaled steroid, some require additional prednisone. A few have a previously unrecognized infective bronchitis. Case 3 had no bronchitis, but the result was still useful to focus the investigation and treatment on other causes, such as gastroesophageal reflux.

AVAILABILITY AND MISCONCEPTIONS

Quantitative sputum cell counts have been slow to be introduced widely into specialist clinical practice for a number of reasons, which include absence of funding, a perception that the procedure is complex or time consuming, that the results are not in real time, and prejudice that the counts are not needed. There are several misconceptions (Table 4). However, cell counts are now included in guidance documents.^{17,18,37,38} They are available for clinical practice in Hamilton,

Table 4—Common Misconceptions

Misconceptions	Comments
Sputum always needs to be induced.	Spontaneous sputum is just as good.
Sputum cell counts help diagnose asthma.	Cell counts do not diagnose asthma or COPD. They identify the presence and type of bronchitis.
Sputum examination is all about eosinophilia.	The total cell count and the proportion of neutrophils provide useful information about infective bronchitis.
In clinical practice, single examination is sufficient to manage patients.	The type of bronchitis changes depending on the cause of exacerbation. Hence sputum should be examined at each exacerbation.
Sputum examination is a complicated procedure.	It is a simple procedure that can be done in a core laboratory, but it needs dedicated technologists.
Specialists do not need sputum cell counts to optimize treatment.	This may hold true but will lead to considerable mistreatment.

Quebec City, Montreal, Calgary, and Edmonton with current funding through research income, hospital budget, or worker compensation. However, their use should now be more widespread in specialist practice and the cell counts should be a test of laboratory medicine and funded by hospital budgets. The Ontario Medical Association has approved billing fees for sputum induction and examination, but these still need government insurance approval. In the future, automation of cell counts will make the process simpler to implement and more widely available.

CONCLUSION

Measurements of airway inflammation are needed to validate the bronchitic component of airway diseases and to guide treatment, particularly when symptoms are difficult to control or the disease is moderate, severe, or complex.³⁹ Quantitative sputum cell counts provide the most comprehensive, specific, valid, and discriminative information and need to be made widely available for specialists in respiratory and allergy.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Drs Nair and Hargreave are listed on an international patent for a sputum filtration device.

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DOI 10.1378/chest.10-0094

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