Exhaled nitric oxide in the diagnosis of childhood asthma

A small but important piece of the clinical jigsaw

Although asthma is the most common chronic disease of childhood, it remains a clinical diagnosis. Common symptoms include recurrent wheezing, cough, difficulty in breathing, and chest tightness, but no agreed “gold standard” definition exists. Improvements in symptoms and lung function seen after adequate treatment often provide retrospective confirmation of the diagnosis.

Accurate diagnosis of asthma in children may be difficult but is vital for two reasons. Firstly, a correct diagnosis is essential for the institution of guideline based treatment, which may involve specialist referral; this is needed to avoid the morbidity and rarely mortality associated with poorly controlled disease. Secondly, the exclusion of asthma prevents potential harm from inappropriate anti-asthma treatment and may highlight other crucial diagnoses such as cystic fibrosis.

Asthma is a heterogeneous disease, and data from large population based studies have informed the concept of different patterns or “phenotypes” in children who wheeze. Importantly, preschool children who wheeze only when they have viral respiratory tract infections form a discrete and largely self-resolving group in which wheeze is independent of allergic sensitisation. Wheeze associated with multiple triggers and allergic sensitisation, recognised as the “classic” atopic asthma phenotype, is responsible for most clinically important disease in school aged children but may also be relevant in younger life.

Eosinophilic airway inflammation is the dominant pathology in atopic asthma, and anti-inflammatory drugs are the maintenance treatment of choice. However, only a weak correlation exists between airway inflammation and conventional measures of disease status, such as lung function or symptoms. This raises the important question: is it better to assess a child on the basis of improvement of symptoms or lung function or a reduction in inflammation, or even a combination of these?

Some studies in adults with asthma show that treatment aimed at normalisation of sputum eosinophils reduces exacerbations without the need to increase anti-inflammatory drugs. Any extrapolation to children should be done with caution, but it makes sense to try to measure some aspect of airway inflammation to aid clinical decision making. Such a test or “inflammometer” should ideally be non-invasive, safe, practical, reproducible, accurate, and cost effective.

Airway eosinophils can be measured in children with the aid of bronchoscopy, so that bronchoalveolar lavage or endobronchial biopsy can be performed, or by the induction of sputum using nebulised saline. Bronchoscopy is invasive and normally requires a general anaesthetic. Induction of sputum requires cooperation from the child and support from laboratory staff. Sputum induction may also provoke substantial bronchoconstriction, and cells from the proximal airway are likely to predominate. Nonetheless, the cytology of airway samples may provide evidence of eosinophilic or neutrophilic inflammation that can usefully guide treatment.

Nitric oxide is formed in the airways by a reaction catalysed by nitric oxide synthases. The expression of inducible nitric oxide synthases is increased in inflammation, and the fractional concentration of exhaled nitric oxide (FeNO) is raised in atopic asthma. FeNO has therefore been shown to be a useful marker of the degree of airway inflammation and can be used to monitor disease activity and response to treatment.

### Best values for fractional concentration of exhaled nitric oxide, sputum eosinophils, and forced expiratory volume in one second

<table>
<thead>
<tr>
<th>Test</th>
<th>Cut off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>19 ppb</td>
<td>86</td>
<td>89</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>Sputum eosinophils</td>
<td>2.7%</td>
<td>85</td>
<td>89</td>
<td>92</td>
<td>81</td>
</tr>
<tr>
<td>FeNO + eosinophils</td>
<td>19 ppb + 3%</td>
<td>87</td>
<td>89</td>
<td>92</td>
<td>81</td>
</tr>
<tr>
<td>FEV₁</td>
<td>80%</td>
<td>52</td>
<td>72</td>
<td>75</td>
<td>48</td>
</tr>
</tbody>
</table>

FeNO= fractional concentration of exhaled nitric oxide; FEV₁ = forced expiratory volume in one second; ppb = parts per billion.
Attracted a great deal of attention as a potential non-invasive measure of airway inflammation in childhood asthma.\textsuperscript{3} In children with atopic asthma, this measure correlates best with eosinophil counts in steroid naive children in sputum or bronchoalveolar lavage but less well with mucosal eosinophils in endobronchial biopsies.\textsuperscript{9, 9} Importantly, several non-disease factors such as diet, age, race, time of day, and repeatability affect the measurements.\textsuperscript{7} Also, FeNO is raised in children with atopy, irrespective of the presence or absence of asthma.\textsuperscript{9} This suggests that complex interassociations exist between FeNO, eosinophils, and clinical asthma.\textsuperscript{3} However, high FeNO in the presence of symptoms of asthma is suggestive of steroid responsive eosinophilic inflammation.\textsuperscript{3}

A recent study measured FeNO and the percentage of eosinophils in induced sputum, in addition to carrying out spirometry, in 150 consecutive white children with a mean age of 12 years, who were referred to a respiratory clinic for evaluation of possible asthma.\textsuperscript{10} Children with eczema or allergic rhinitis were included, but those with other “systemic manifestations of atopy,” such as food allergy, were excluded. After 18 months of follow-up, 69 children were diagnosed retrospectively by conventional criteria (two or more wheezing episodes documented by a doctor; dyspnoea or cough relieved by bronchodilators; bronchodilator reversibility or variability in lung function over time with or without controller drugs but blind to FeNO and sputum eosinophil results) as having steroid naive asthma, 37 as having asthma already being treated with inhaled corticosteroids, and 44 as not having asthma. The specificity, positive predictive value, and negative predictive value of FeNO and sputum eosinophils depended on the cut-off values used but compared favourably to forced expiratory volume in one second (FEV\textsubscript{1}) as having steroid naive asthma, as having asthma already being treated with inhaled corticosteroids, and as not having asthma. The sensitivity, specificity, positive predictive value, and negative predictive value of FeNO and sputum eosinophils depended on the cut-off values used but compared favourably to forced expiratory volume in one second (table). However, application of the best cut-off levels placed 10.6% of children with asthma in an inconclusive “borderline” category. This study was performed in a selected population with a specific measure of airway inflammation in childhood asthma.

Advocates for the use of FeNO in childhood asthma argue that the context is crucial, with clinical usefulness being greatest in the specialist clinic.\textsuperscript{7} FeNO should be viewed as complementary to conventional history taking, examination, spirometry, and measures of bronchial liability. The history, clinical assessment during an acute episode, and response to anti-asthma treatment are arguably the most valuable criteria in reaching a diagnosis. If several components of the picture are not suggestive then the probability of asthma is reduced. FeNO seems to represent a small but important piece of this clinical jigsaw.

Other possible niches for FeNO include assessment of control, compliance, or the appropriate timing of a reduction in inhaled corticosteroids.\textsuperscript{11, 11} Crucially, however, well conducted trials of adding the measurement of FeNO to evidence based management of asthma in children and adults have been disappointing, and “getting the basics right” remains paramount in childhood asthma.\textsuperscript{12}

7 Bush A, Eber E. The value of FeNO measurement in asthma management: the motion for Yes, it’s NO—or, the wrong end of the stick! \textit{Paediatr Respir Rev} 2006;9:127-31.