Usefulness and pitfalls of exhaled NO measurements in children

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INTRODUCTION

A key feature in the pathogenesis of asthma is chronic, mostly eosinophilic, airway inflammation and anti-inflammatory agents constitute the mainstay of maintenance treatment, with inhaled corticosteroids (ICS) as first choice. The treatment of asthmatic children in most cases relies on symptoms reported by the child and/or the parents[1,2]. Yet, relationships between inflammation and symptoms, asthma control and asthma severity are complex and still unclear. The discrepancy between asthmatic symptoms and airway inflammation implies that decisions on anti-inflammatory treatment based on symptoms can be inappropriate. Therefore, there is a need for tools to assess airway inflammation and the severity of asthma, guide treatment decisions and reduce asthma morbidity. The ideal approach is not only safe, simple, noninvasive, reproducible and accurate, but also reflects control of inflammation and enables to monitor the changes induced by therapeutic interventions in individual patients.

Markers of airway inflammation can be studied by several techniques. Material may be obtained by bronchoscopy, including mucosal biopsies and bronchoalveolar lavage fluid (BALF). Bronchoscopy is invasive, unsuited for repeated use and ethical in children only if there are specific indications[3]. Indirect methods include examination of (induced) sputum, blood, urine or exhaled gases or breath condensate. Blood and urine parameters like eosinophils, ECP or EPX only weakly reflect processes in the lung. Inducing sputum production by inhalation of normal or hypertonic saline may provide sputum samples and supernatant in which cells and soluble constituents can be determined[4]. The procedure of sputum induction is feasible in 60-100 % of children aged 7 years or older, is relatively noninvasive, gives reproducible and valid results, which are responsive to clinical changes[5-7]. However, the procedure is time consuming and carries a risk of serious bronchoconstriction[7].

Exhaled breath condensate (EBC) is collected by cooling or freezing exhaled air. Various non-volatile substances have been detected in EBC. However, correlations with other indices of inflammation are still lacking and not all technical problems have been dealt with yet[8].

Exhaled nitric oxide

Since the 1990s there has been considerable interest in nitric oxide (NO), a free radical gas that forms in the airways when L-arginine is oxidized to L-citrulline[9]. Several methods to collect exhaled air and measure the fractional exhaled nitric oxide concentration (FE_{NO}) are available[10]. Online methods use an NO analyzer designed to directly sample exhaled air and offline methods analyze exhaled gas first collected in a reservoir. FE_{NO} is highly dependent on exhalation flow rate, in the sense that FE_{NO} levels drop with higher flow[11]. Standardized guidelines for the measurement of FE_{NO} in children are available[10,12]. A recent reference values study showed age-dependency in children with geometric mean going up from around 7.0 ppb at the age of 4 years to 15 ppb at the age of 14-17 years[13].

FE_{NO} is elevated in steroid-naive atopic asthma and higher FE_{NO} separates untreated asthmatics from normals with minimal overlap. Treatment with inhaled or oral steroids reduces FE_{NO} to drop in patients with asthma in a dose-dependent way[14,15]. At higher doses of ICS, the effect on FE_{NO} levels tends to plateau[16]. In atopic asthmatic adults and children, FE_{NO} correlates with eosinophils in induced sputum and with eosinophil infiltration of the airway wall[17-24]. The only biopsy study in children concerned patients with difficult asthma after treatment with oral prednisone, and showed a correlation between MBP density in biopsies as a marker of airway eosinophilia and FE_{NO}[25].

Clinical applications

As FE_{NO} is a non-invasive marker of airway inflammation and treatment of asthmatic children with ICS reduces FE_{NO}, FE_{NO} might be particularly useful in diagnosing and monitoring asthma in children.

FE_{NO} in the diagnosis of asthma

FE_{NO} may play a role as a diagnostic tool in epidemiological studies or in selected patients with respiratory symptoms. In unselected patients FE_{NO} performed rather poorly in distinguishing asthma and non-asthma[26-28]. Contrastingly, in a *selected* group of 96 young children with asthmatic symptoms or history, FE_{NO} discriminated between probable asthma or healthy control with 86% sensitivity and 92% specificity[29]. Narang et al. found negative and positive predictive values of 80 and 100%, respectively, for FE_{NO} as a predictor of asthma[30].

FE_{NO} measurements also may have a role in the differential diagnosis of non-specific chronic respiratory symptoms, especially in young children in whom respiratory complaints are extremely common.

Predicting the response to steroids

One study, in adults and children, examined if elevated FE_{NO} levels can predict steroid responsiveness in patients with non-specific respiratory symptoms[31]. FE_{NO} appeared a much better predictor than spirometry, bronchodilator response and airway hyperresponsiveness (AHR) measurements.

In a study set up to characterize the within-subject responses to fluticasone and montelukast, children with elevated FE_{NO} values were more likely to respond to fluticasone than to montelukast[32,33].

Predicting exacerbations and asthma relapse

Overall, there is limited evidence that FE_{NO} may have prognostic value to predict deteriorating asthma in children[34,35]. Fritsch et al, found a sensitivity of 80% and specificity of 60% for predicting exacerbations at a cut-off point of 22.9 ppb[34]. A second study suggested that FE_{NO} levels rose during the pollen season in sensitized patients before an exacerbation occurred although this did not reach significance[35]. With the advent of home monitoring programs, the inclusion of daily FE_{NO} measurements may prove to be beneficial in anticipating deteriorating asthma.

TABLE 1. **Possible applications of FE_{NO} measurements in paediatric asthma**

Screening for asthma in epidemiological studies
Diagnosis of eosinophilic airway inflammation
Predicting response to steroids
Evaluation of response to:
Steroids (inhaled or systemic)
Leukotriene receptor antagonists (LTRA)
Other
Selection of treatment modalities additional to ICS (e.g. LABA or LTRA)
Predicting asthma exacerbations
Predicting asthma relapse after clinical remission
Adherence check
Dose titration of ICS

Following steroid withdrawal, FE_{NO} levels in currently asymptomatic children 2 and 4 weeks later were highly predictive of relapse during the subsequent 24 weeks. A cut-off point for FE_{NO} of 49 ppb provided the best predictive accuracy[36].

Reducing ICS in stable asthmatic children

Zacharasiewicz *et al.* performed a study in 40 children with stable asthma eligible for steroid reduction[37]. They halved ICS doses every 8 weeks and found a negative predictive value of 92% for FE_{NO} at a cut-off point of 22 ppb or less.

Adjustment of inhaled corticosteroid dose

Three randomized controlled trials have used FE_{NO} measurements to guide long-term treatment with ICS[34,38,39]. In the first paediatric study, 85 allergic asthmatic children on ICS were included and randomly allocated to 2 groups. In the FE_{NO} group (n = 39) treatment decisions were made on both FE_{NO} and symptoms, in the symptom group (n = 46) on symptoms only. The FE_{NO} group showed a significant reduction in the severity of AHR, with a concomitant (but non-significant) reduction in exacerbations requiring oral prednisone. Cumulative ICS use did not differ between the two groups[39].

In a dose titration study in 47 asthmatic children, patients were randomized to a control group in which therapy was based on symptoms, beta-agonist use and lung function, or a FE_{NO} group where FE_{NO} was used additionally to guide treatment. After 6 months children in the FE_{NO} group had higher MEF_{50}% predicted, however at the cost of higher ICS doses[34]. Smith et al followed 94 adult asthmatics who completed a dose titration phase and then for 12 months were assigned to either treatment on the basis of FE_{NO} measurements or the conventional guidelines[38]. In this study a 40% reduction in ICS dose requirements was achieved in the FE_{NO} group, without difference in the rate of asthma exacerbations between groups. The full range of possible applications of FE_{NO} measurements is summarized in table 1.

What are the pitfalls of FE_{NO} measurements?

First, the dose titration studies cited here used a single cut-off level for FE_{NO} to prompt either an increase or a decrease in ICS dose. Two cut-points defining three management choices – i.e. increase, no change or decrease in dose – may be more effective. Second, the "one size fits all" approach used in these studies may not be appropriate in regular clinical practice. Group mean data may not always be helpful in determining clinical relevant changes in individual patients. An alternative method of dealing with FE_{NO} in individual patients might be using "personal best values" as baseline or target FE_{NO} levels.

Third, the studies applied substantially different criteria to guide ICS dose adjustment in the control groups.

TABLE 2.

FE_{NO} (ppb)	Range	Eosinophilic airway inflammation	Interpretation	
			ICS naive	ICS treated
< 5	Low	Unlikely	Consider: PCD, CF	
5-25	Normal	Unlikely	Consider: – wheezy bronchitis – ENT disorders – gastro-oesophageal reflux – neutrophilic asthma – congenital abnormalities – immunodeficiencies – sinusitis – vocal cord dysfunction – anxiety/hyperventilation	IF SYMPTOMATIC: Review diagnosis (see steroid naive) IF ASYMPTOMATIC: Implies good adherence to treatment. Reduce dose, or in case of low ICS, withdraw ICS
25-35	Intermediate	Present, but mild	Consider ICS, consider viral infection	IF SYMPTOMATIC, consider: – infection – ongoing allergen exposure – poor adherence – poor inhaler technique – MDI plus spacer instead of DPI – adding LABA or LTRA – increasing ICS dose IF ASYMPTOMATIC: No change in ICS if patient is stable
> 35	High	Significant	Asthma is very likely, positive response to ICS is likely	IF SYMPTOMATIC: see intermediate values. PLUS: – imminent exacerbation or relapse (FE_{NO} > 50 ppb) – steroid resistance (rare) IF ASYMPTOMATIC: No change in ICS if patient is stable

PCD: primary ciliary dyskinesia; DPI: dry powder inhaler; LTRA: leukotriene receptor antagonist; ENT: ear nose throat; CF:cystic fibrosis; MDI: metered dose inhaler; LABA: long acting β_2-agonist.

Cut-points will significantly determine the outcome in any dose-adjustment strategy.

An important and as yet unresolved issue is whether FE_{NO} measurements should be used for both upwards and downwards ICS dose titration. Clearly, the withdrawal of unnecessary ICS treatment or reducing excessive doses is an important goal of FE_{NO} monitoring. However, for patients with persistently high FE_{NO}, it is as yet unknown whether increasing the dose of ICS is justified, particularly if a patient is asymptomatic.

Most of the studies on the utility of FE_{NO} measurements in asthma management concerned allergic patients and to date, insufficient data are available on the utility of FE_{NO} in non-atopic asthmatic patients. And as follow up is limited in most studies using FE_{NO} in the management of asthma, we can only speculate on the longer term benefits of titrating steroids on FE_{NO}.

Last, frequent monitoring of FE_{NO} at home is a promising development, as it could help prevent exacerbations of asthma by adjusting the steroid dose as soon as baseline FE_{NO} is increasing. Reversely, a dose decrease in periods of suppressed inflammation may prevent overdosing.

A practical approach

An algorithm for interpreting FE_{NO} results in paediatric practice is presented in table 2. As asthma is a disease with a wide range of phenotypes and the response of ICS on FE_{NO} is heterogeneous, this algorithm has to be used with caution[40].

Conclusions

Despite the pitfalls mentioned, the use of FE_{NO} measurements in asthmatic children enables us to administer ICS more effectively and more efficiently. FE_{NO} provides us with a practical tool to distinguish patients who will benefit from ICS from those who will not, and patients who require additional therapy from those whose medication dose could feasibly be reduced.

As an "inflammometer", FE_{NO} provides the clinician with hitherto unavailable information regarding the nature of underlying airway inflammation, thus complementing conventional physiological testing, including the measurement of AHR.

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