July, 5th 2011

Exhaled nitric oxide measurements

clinical application and interpretation

Children's hospital 2
Pulmonary Department

Introduction

Establishing a diagnosis is the first step in clinical management but, for diseases of the airways, a diagnostic label has its limitations.

FE NO :

- Firstly, FE NO is a good surrogate marker for eosinophilic airway inflammation
- Secondly, eosinophilic airway inflammation is steroid responsive

  Raised FE NO levels predict steroid responsiveness in patients with nonspecific respiratory symptoms.

  The use of inhaled corticosteroid (ICS) treatment in asthma results in a fall in FE NO, and there is a dose-dependent relationship between ICS and FENO.
- Thirdly, portable nitric oxide analysers are now available

  However : diagnostic role of FE NO in preschool children ?

  difficult or severe asthma.

- Given that spirometry and sputum induction cannot easily be performed in preschool children, a non-invasive measurement of airway inflammation is potentially very useful

Physiology

NO is an endogenous messenger with a diverse range of effects including non-adrenergic, non-cholinergic neurotransmission, vascular and non-vascular smooth muscle relaxation.

In pathological situations NO is a proinflammatory mediator with immunomodulatory effects.

1.eosinophilic airway inflammation

Studies confirm that FE NO measurements correlate well with airway eosinophilia in induced sputum, biopsy material, and bronchoalveolar lavage fluid, blood eosinophils

- Non specific

In the study by Brightling et al 11 patients who did not fulfil criteria for the diagnosis of asthma but who had eosinophilic bronchitis had raised FE NO levels

allergic rhinitis

atopic asthma, cough

variant asthma, and eosinophilic bronchitis

Table 1 Respiratory and non-respiratory conditions in which F_ENO measurements may have a role in diagnosis

Increased F_ENO	Variable changes in F_ENO reported	Decreased F_ENO
Asthma[1 79]	Bronchiectasis[91–93]	Cystic fibrosis[91 108–110]
Late asthmatic response[80 81]	COPD[17 75 78 94–102]	Primary ciliary dyskinesia[111 112]
Allergic rhinitis[19]	Fibrosing alveolitis[103]	Pulmonary hypertension[113]
Viral infections[43 44 82]	Sarcoidosis[104]	HIV infection[114]
Hepatopulmonary syndrome[83]	Systemic sclerosis[105–107]	ARDS[115]
Liver cirrhosis[84 85]		
Acute/chronic rejection of lung transplant including bronchiolitis obliterans[86–90]		

2. Eosinophilic airway inflammation positive response to steroid treatment

Treatment with corticosteroids results in a reduction in airway eosinophilia in asthma and a simultaneous improvement in clinical parameters.

In contrast, in asthma which is not characterised by eosinophilia (at least in sputum), the response to steroids is likely to be poor

3. Raised FE NO levels predict steroid responsiveness in patients with non-specific respiratory symptoms

- Little et al have shown that the clinical benefit of increased steroid treatment in patients with asthma is greatest in patients with raised FE NO levels.
- **Smith et al**
- A similar result has been reported by Szefler et al who showed that children with high FE NO values are more likely to respond to ICS than children with lower FE NO values.

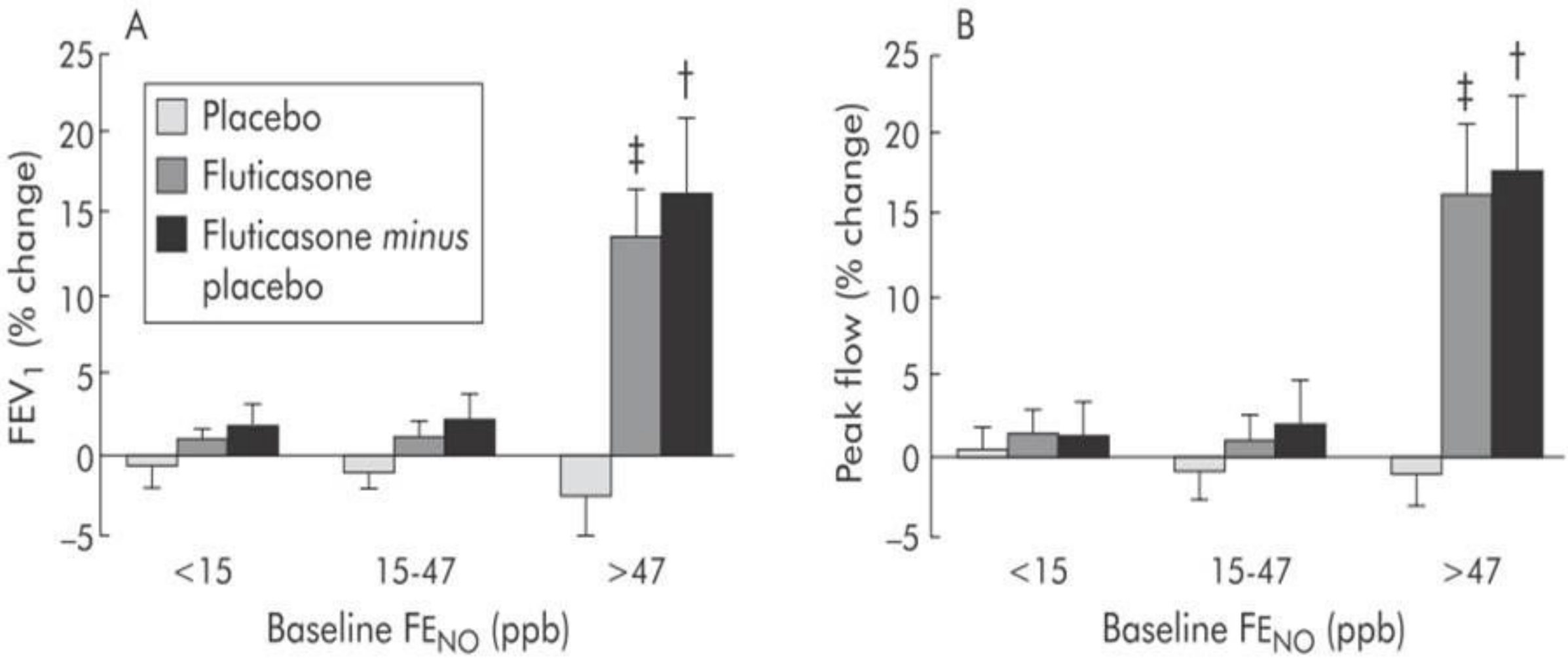
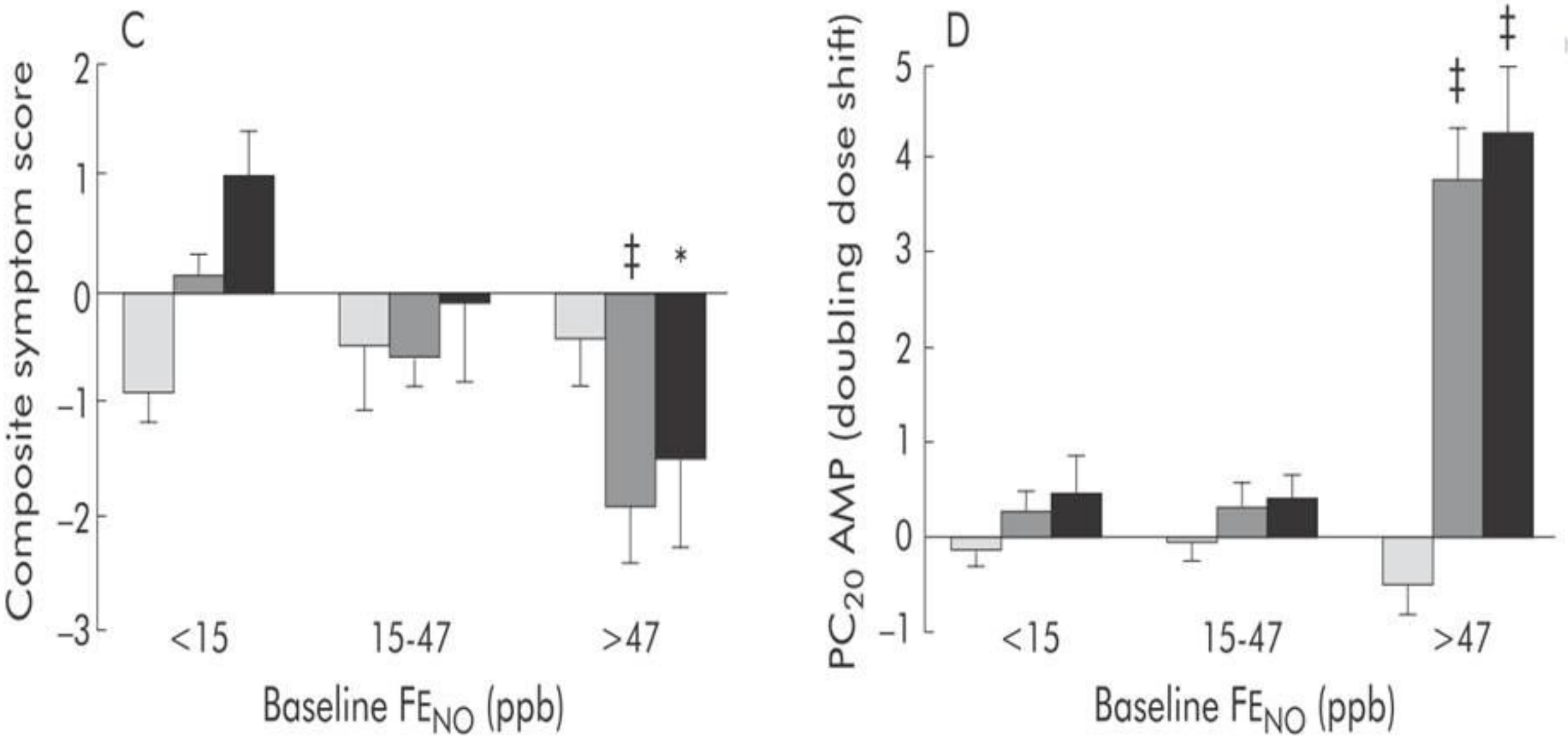


Figure 1 Steroid responsiveness in relation to $F_{E}NO$ measurements in patients with non-specific chronic respiratory symptoms. Mean (SE) changes from baseline in (A) forced expiratory volume in 1 second (FEV_1), (B) morning peak flow over last 7 days of treatment, (C) composite symptom score, and (D) provocative concentration of adenosine monophosphate causing a 20% fall in FEV_1 ($PC_{20}AMP$) following treatment with inhaled fluticasone 500 µg/day (minus change with placebo), stratified by baseline $F_{E}NO$ expressed as tertiles. Comparisons between tertiles were performed using one way analysis of variance with linear contrasts to identify any trend across the three tertiles; *p<0.05; †p<0.01; ‡p<0.001. Reproduced from Smith *et al*[28] with permission of the publishers.



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4. ICS treatment in asthma results in a fall in FE NO with a dose-dependent relationship between ICS and FE NO

FE NO levels tend to plateau at higher doses of ICS.

Adjustment of ICS dose Smith et al

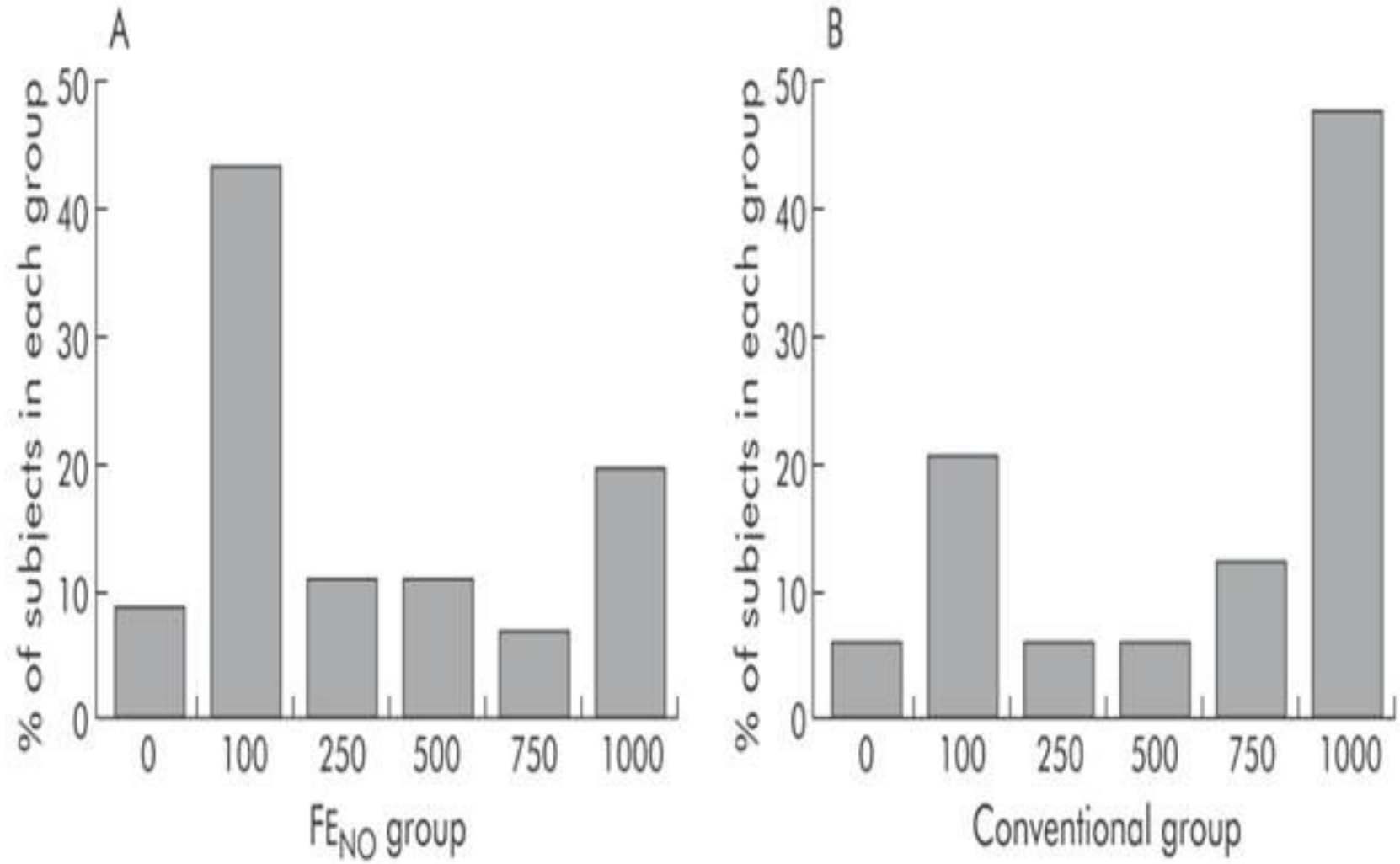

Figure 2 Profile of dose distribution for mean inhaled fluticasone requirements over 12 months in 48 patients (conventional group) whose ICS dose was adjusted using a priori guidelines and 46 patients in whom the ICS dose was adjusted on the basis of F_ENO measurements (F_ENO group; cut point equivalent to 35 ppb). There was a highly significant difference between the two groups ($p=0.008$).[138]

Titrating Steroids on Exhaled Nitric Oxide in Children with Asthma

A Randomized Controlled Trial

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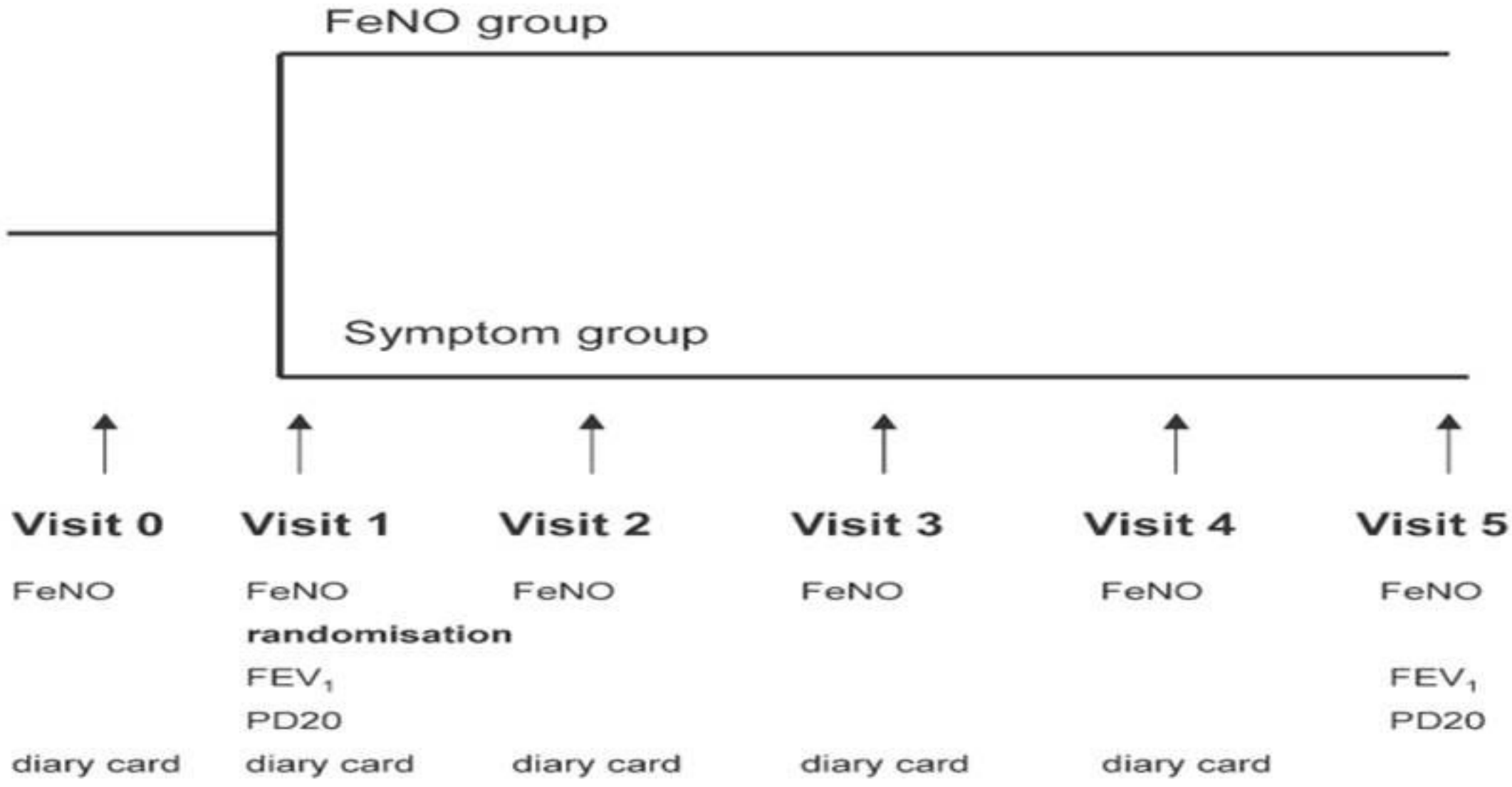

Figure 1. Study design.

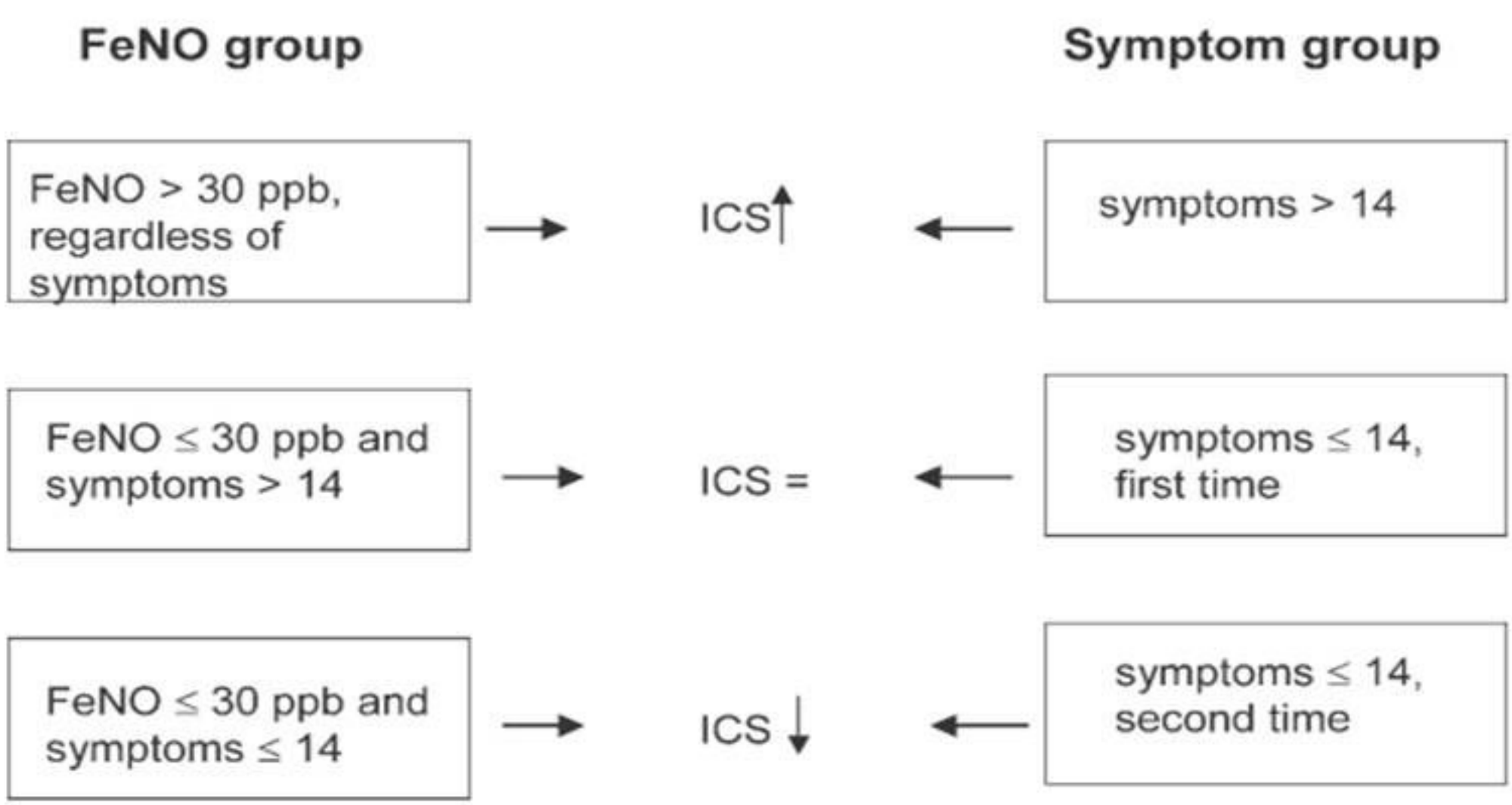

Figure 2. Treatment algorithm. ICS = inhaled corticosteroids.

Symptom Scores

Symptom scores were obtained from diary cards (20). Mean daily symptom scores (dyspnea, wheezing, cough; daytime and nighttime, each scored 0–3), the use of □ -2 agonists and the percentage of symptom free days were calculated over the 2 weeks preceding each visit

DIAGNOSING AIRWAYS DISEASE

1. Asthma

FE NO offers advantages as well as limitations as a "test for asthma"

- In adults, FE NO measurements are helpful in discriminating asthma from non-asthma

Dupont et al, FE NO levels were highly predictive of asthma with a sensitivity and specificity of 85% and 90%

Smith et al, similar sensitivity (88%) and specificity (79%)

- Predictive values were almost identical to those obtained using induced sputum cell counts

Interestingly, the combination of a raised FE NO (.33 ppb) and abnormal spirometry (FEV1 80% predicted) provides even greater sensitivity (94%) and specificity (93%) for the diagnosis of asthma

- Normal values do not exclude the diagnosis of asthma.

This highlights further the fact that the asthma phenotype is heterogeneous

2. Non-specific respiratory symptoms

FE NO measurements have a wider role in assessing patients with undiagnosed chronic respiratory symptoms

It includes **eosinophilic bronchitis, cough variant asthma**, post-viral bronchial hyperresponsiveness, postnasal drip and other ENT problems, gastro-oesophageal reflux disease, vocal cord dysfunction, primary hyperventilation syndrome, and COPD. In children, recurrent wheezy bronchitis, cystic fibrosis, congenital abnormalities of the airways or lungs, and primary ciliary dyskinesia also need to be considered

In children

- standard online technique to offline tidal breathing. Exhaled air was collected offline in a bag during tidal breathing without flow control

- FE NO performed poorly in distinguishing between asthma and non-asthma symptoms, the same issues are encountered. Baraldi et al studied a group of 13 young children with recurrent wheeze and compared their FE NO values with those of nine healthy controls and six children with a first episode of wheezing.

- During an acute episode, FE NO was significantly higher in those with recurrent wheeze than in controls, while in children with their first episode of wheezing FE NO levels did not differ from normal children.

These data are in keeping with those of Ratjen et al who measured peak FE NO values online in mixed exhaled air (from mouth and nose).

3. Chronic obstructive pulmonary disease (COPD)

- FE NO levels are inconsistent in patients with COPD
- Perhaps the most important question is not whether the diagnostic label is accurate, but whether the response to anti-inflammatory treatment can be predicted

Zietkowski et al showed that the increase in post-bronchodilator FEV1 after 2 months of open label treatment with inhaled budesonide 800 mg/day was strongly correlated ($r = 0.73$, $p = 0.0003$) with baseline FE NO levels in 19 ex-smoking patients with COPD

FE NO MEASUREMENTS IN THE MANAGEMENT OF CHRONIC ASTHMA

Predicting exacerbations

Peak flow measurements have been used to fulfil this role, but with limited success because changes in peak flow largely coincide with deteriorating symptoms rather than precede them.

the prognostic value of FE NO measurements to predict deteriorating asthma appears limited.

changes in sputum eosinophils were superior to FE NO measurements in predicting loss of control.

Predicting the outcome of ICS withdrawal in stable asthma

- Zacharasiewicz et al the negative predictive value of sputum eosinophils (at a cut point of 0%) was 100%

A negative predictive value of 92% was obtained for FE NO at a cut point of 22 ppb or less

Pijnenburg et al reported that, following steroid withdrawal in currently asymptomatic children, FE NO levels 2 and 4 weeks later were highly predictive of relapse during the subsequent 24 weeks of follow up, with a cut point for FE NO of 49 ppb providing best predictive accuracy

we can conclude that sputum eosinophil counts (.1%) probably offer superior prognostic accuracy when evaluating whether or not patients require ongoing ICS treatment.

Furthermore, in circumstances where induced sputum cannot be obtained (in the majority of centres and in young children), a high FE NO level (.50 ppb) is likely to predict asthma relapse and a low FE NO level (,20 ppb in children, 25 ppb in adults) is likely to predict asthma stability if measured at least 4 weeks after ICS treatment is reduced/withdrawn in a currently asymptomatic patient.

The outcome in those with an intermediate result (FE NO 20–50 ppb) is less certain.

In a study by Pijnenburg et al comprising 85 children with atopic asthma, the cut point for FE NO levels was similar at 30 ppb; there was no difference in cumulative ICS use between the FE NO and control groups.

However, in the FE NO group there was a significant reduction in the severity of AHR, with a concomitant (but, for reasons of study size, non-significant) reduction in exacerbations requiring oral prednisone.

Thus, data to date suggest that dose reduction is a fairly achievable objective. However, in patients with persistently high FE NO levels (.50 ppb), it remains to be determined whether increasing the dose of ICS further will prove to be successful.

Until further studies have been completed, it seems prudent to put the emphasis on dose reduction when FE NO levels are low (,25 ppb). Only if asthma is poorly controlled and issues of poor compliance and/or poor inhaler technique have been addressed should high FE NO levels prompt an increase in ICS dose.

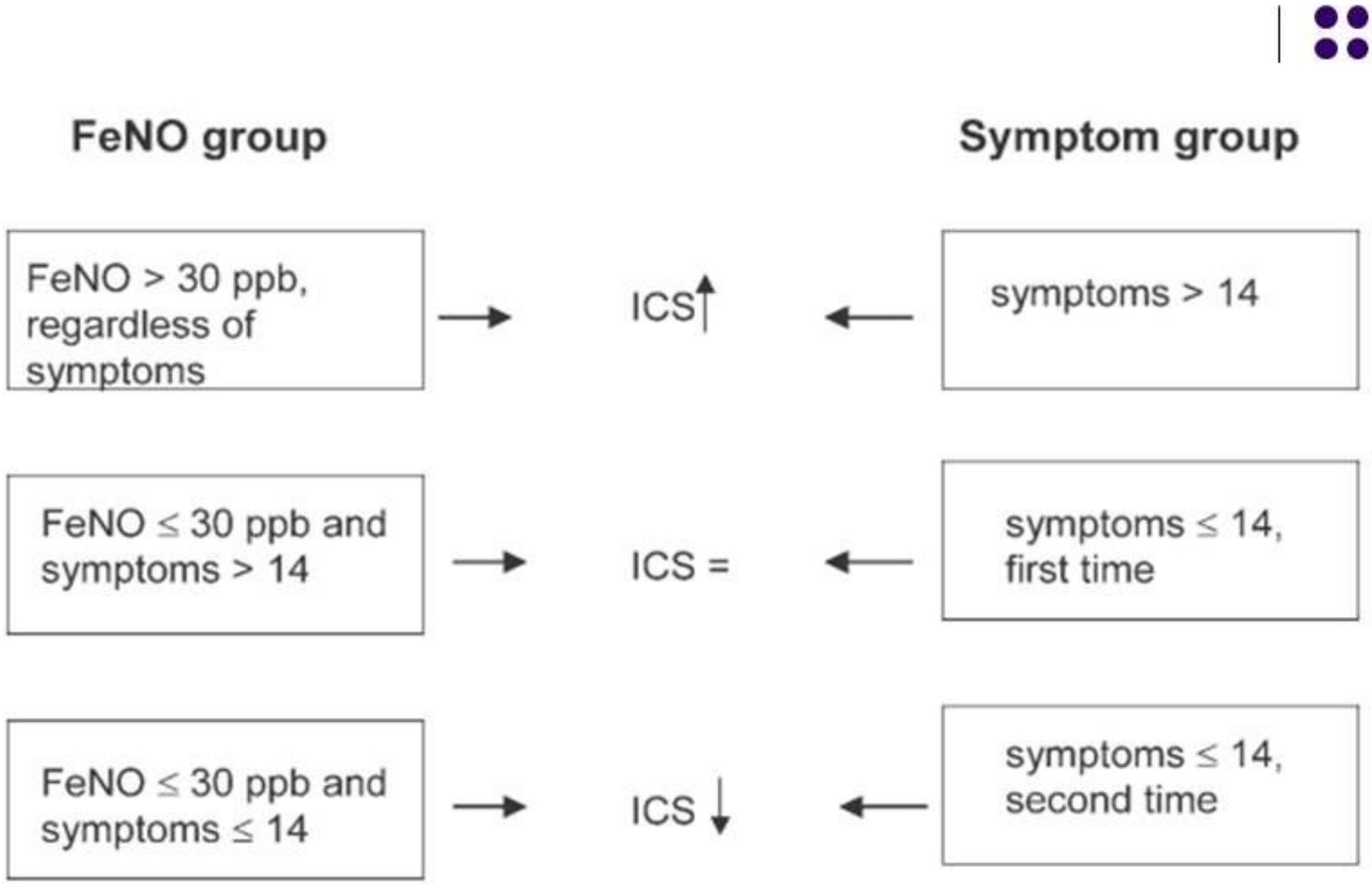

Figure 2. Treatment algorithm. ICS = inhaled corticosteroids.

MEASURING AND INTERPRETING FE NO

Table 2 F_ENO levels as an aid to diagnosis of chronic respiratory symptoms

F_ENO (ppb)	Range	Eosinophilic airway inflammation	Interpretation (as an aid to diagnosis of chronic respiratory symptoms)	
			Adults	Children
5 10 15 20 25	Low (<20 ppb if 12 years or younger; <25 ppb for adults)	Unlikely	Consider: Neutrophilic asthma Anxiety/hyperventilation Vocal cord dysfunction Rhinosinusitis Gastro-oesophageal reflux Cardiac disease	Consider: Wheezy bronchitis Gastro-oesophageal reflux ENT disorders Cystic fibrosis Primary ciliary dyskinesia (F_ENO <5 ppb), (check nasal NO) Congenital abnormalities, e.g. airway malacia Other immunodeficiencies
30 35 40 45	Intermediate	Present but mild	Interpretation based on clinical presentation	Interpretation based on clinical presentation
50 55 60 65 Higher levels	High	Significant	Consider: Atopic asthma *if the history is appropriate.* If FEV_1 <80% predicted, diagnosis of asthma is very likely Eosinophilic bronchitis Churg-Strauss syndrome A positive response to a trial of inhaled or oral steroid is likely. In ex-smokers with COPD this may also be true	If combined with any objective evidence of reversible airway obstruction, asthma is very likely and a positive response to a trial of inhaled or oral steroids is likely

F_ENO (ppb)	Range	Eosinophilic airway inflammation	Interpretation (as an aid in the management of asthma)	
			Adults	Children
5 10 15 20 25	Low	Unlikely	If *symptomatic*, review diagnosis Neutrophilic asthma Anxiety/hyperventilation Vocal cord dysfunction Rhinosinusitis Gastro-oesophageal reflux	If *symptomatic*, review diagnosis Consider also: Wheezy bronchitis Cystic fibrosis Congenital abnormalities, e.g. airway malacia Primary ciliary dyskinesia
			If *asymptomatic* and taking ICS: Implies good compliance with treatment. Reduce dose or, in case of low ICS dose, even withdraw ICS altogether	If *asymptomatic* and taking ICS: as for adults
30 35 40	Intermediate	Present but mild	If *symptomatic*, consider: Infection as reason for worsening High levels of allergen exposure Adding in other therapy apart from ICS (e.g. long acting β agonist) Consider ICS dose increase	If *symptomatic* (besides considerations in adults), consider: Possible inadequate ICS treatment (1) check compliance (2) check for poor inhaler technique and consider metered dose inhaler and spacer if patient is currently using a dry powder device
			If *asymptomatic* No change in ICS dose if patient is stable	If *asymptomatic*: as for adults

45 50 55 60 65 Higher levels	High (or rise of 60% or more since previous measurement)	Significant	If *symptomatic*, consider: Inadequate ICS treatment: (1) check compliance (2) check for poor inhaler technique (3) inadequate ICS dose Continuous high level allergen exposure Imminent exacerbation or relapse depending on history of individual patient. More likely if ICS dose is zero Steroid resistance (rare) If *asymptomatic* No change in ICS dose if patient is stable	If *symptomatic* (besides considerations in adults) consider: Metered dose inhaler and spacer if patient is currently using a dry powder device If *asymptomatic*: as for adults

parts per billion (ppb)

Figure 1. Portable nitric oxide analyzer.

Table 1. Summary of studies investigating exhaled nitric oxide as a tool for monitoring asthma.

Study	Design	Population	Duration	Intervention	Courses of oral steroids	Change in ICS dose	Comment	Ref.
Smith *et al.*	Single-blind, parallel group	97 adults with mild–moderate asthma	12 months, after 12-month optimization phase	Control: conventional measures of asthma control Intervention: FE_{NO} < 15* ppb	22 in the FE_{NO} group and 29 in the control (p = 0.60)	40% lower in intervention group (p = 0.003)	Too many factors for uptitrating steroids in the control group	[37]
Pijnenburg *et al.*	Single-blind, parallel group	85 children with atopic asthma	12 months	Control: control of symptoms Intervention: control of symptoms and FE_{NO} < 30 ppb	Eight courses of prednisolone in intervention and 18 in control (p = 0.6)	Cumulative dose over five visits of 4407 µg in intervention, 4332 µg in control	Underpowered study	[29]
Shaw *et al.*	Single-blind, parallel group	118 adults with a primary care diagnosis of asthma	12 months	Control: control of symptoms Intervention: FE_{NO} < 26 ppb	0.42 severe exacerbations/patient/year in control and 0.33 in intervention (p = 0.4)	12% higher in intervention group (p = 0.4)	Underpowered study	[34]
Szefler *et al.*	Multicenter, randomized, double-blind, parallel-group study	546 adherent adolescent and young adult persistent asthmatics	46 weeks	Control: control of symptoms and maintenance of lung function Intervention: addition of maintaining a normal FE_{NO} (<20)	32.1% of FE_{NO} group and 42% of control had ≥one course oral steroids (p = 0.01)	Patients in the NO group received higher doses of ICS. Difference 119 µg per day (p = 0.001)	Used FE_{NO} as adjunct rather than distinct entity	[35]
de Jongste *et al.*	Prospective, open-label, randomized, multicenter, parallel group	151 children with atopic asthma	30 weeks	Control: control of symptoms Intervention: control of symptoms and telemonitoring of FE_{NO} (<60)	Nine exacerbations requiring oral steroids in the FE_{NO} group, 12 in control, not significant	Reduction in ICS use in both groups, no difference between groups	Underpowered, used FE_{NO} as an adjunct	[36]

*Measured at 250 ml/s.
FE_{NO}: Exhaled nitric oxide; ICS: Inhaled corticosteroid; ppb: Parts per billion.

References

Pediatric Pulmonology 46:627–631 (2011)

— Original Articles —

Can We Use Portable Nitric Oxide Analyzer in Young Children?

Satu Kalliola, MD,* Pekka Malmberg, MD, PhD, Tuija Rito, RN, Anna S. Pelkonen, MD, PhD, and Mika J. Mäkelä, MD, PhD

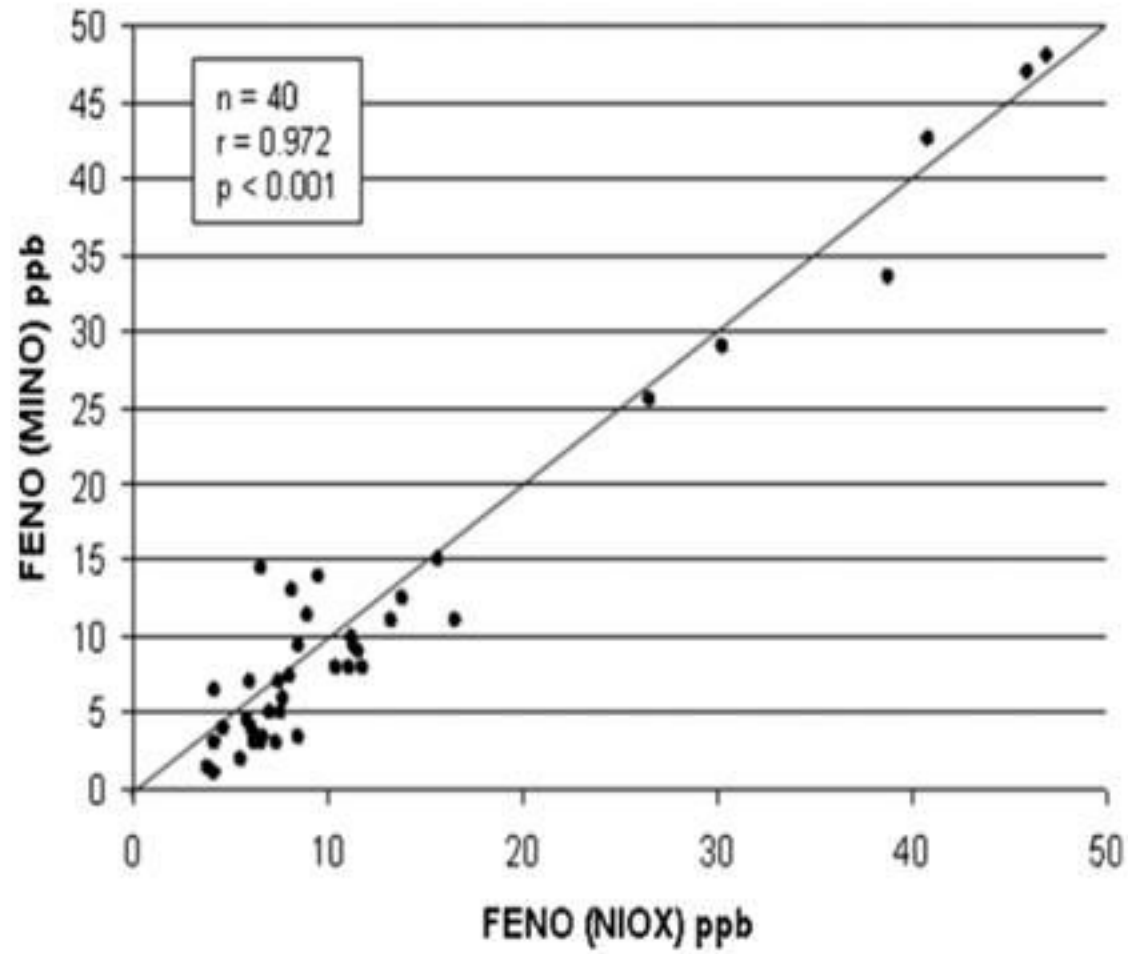

Fig. 2. The relationship of FENO measured with the conventional analyzer NIOX and NIOX MINO, and the line of identity.

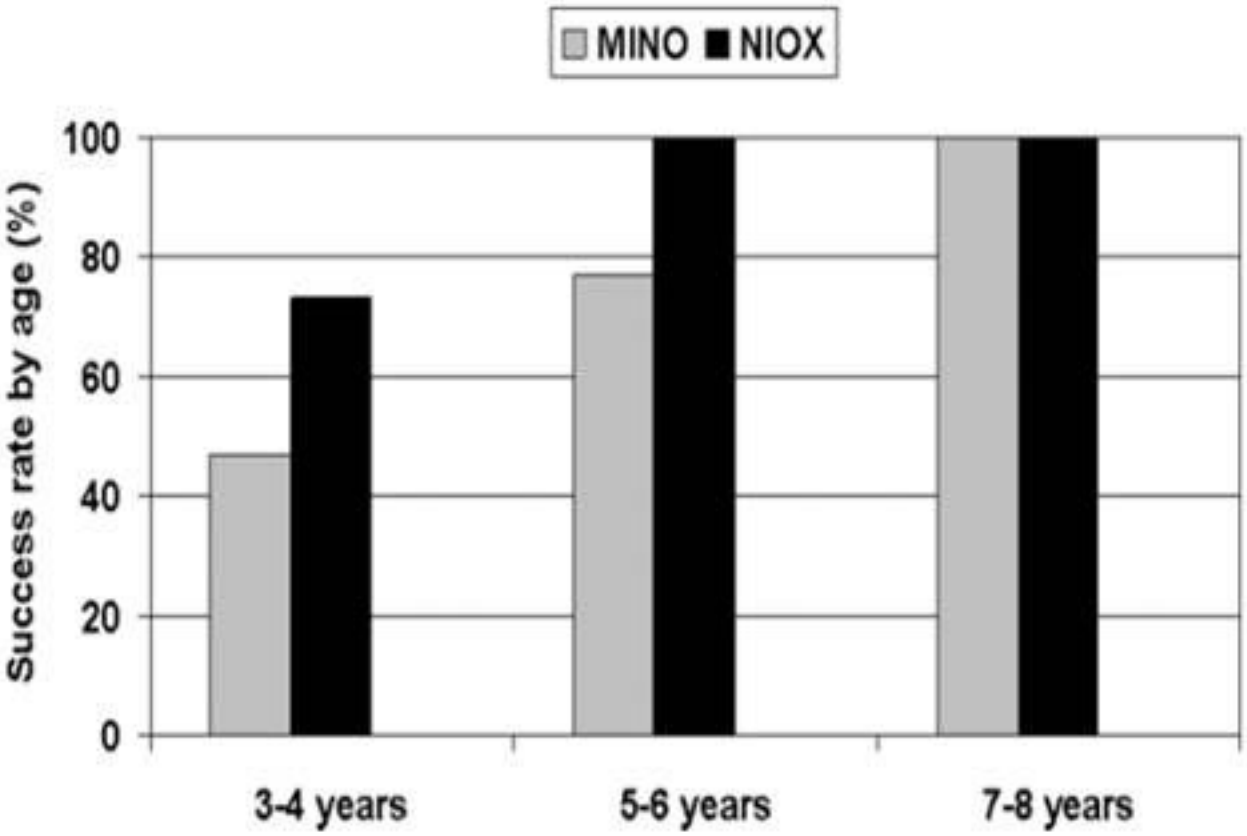

Fig. 1. Success rate by different age groups (%) in the sample of the healthy (n = 27) and asthmatic (n = 28) young children, by using portable NIOX MINO (MINO) and stationary device (NIOX).

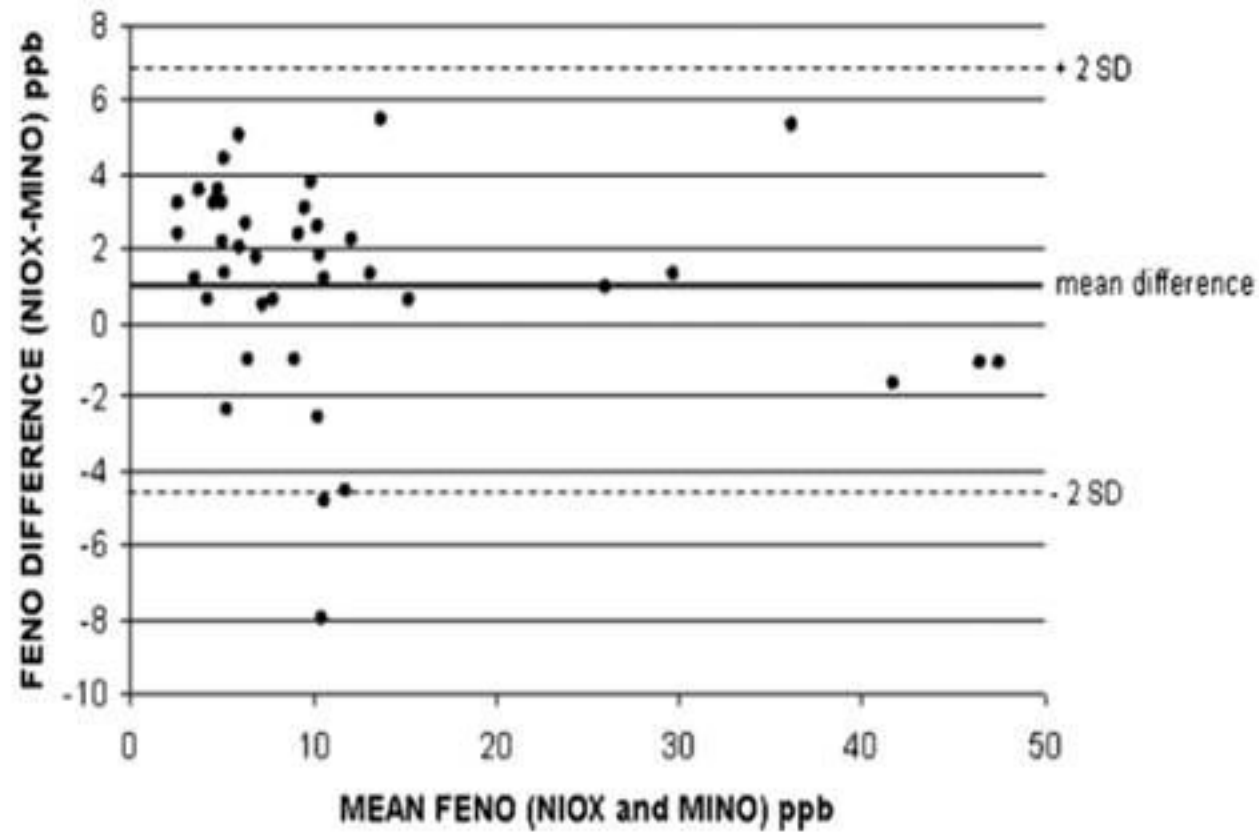

Fig. 3. Bland–Altman plot of the difference between NIOX and NIOX MINO against the mean FENO measured with both devices including the line of mean difference ± 2 SD.

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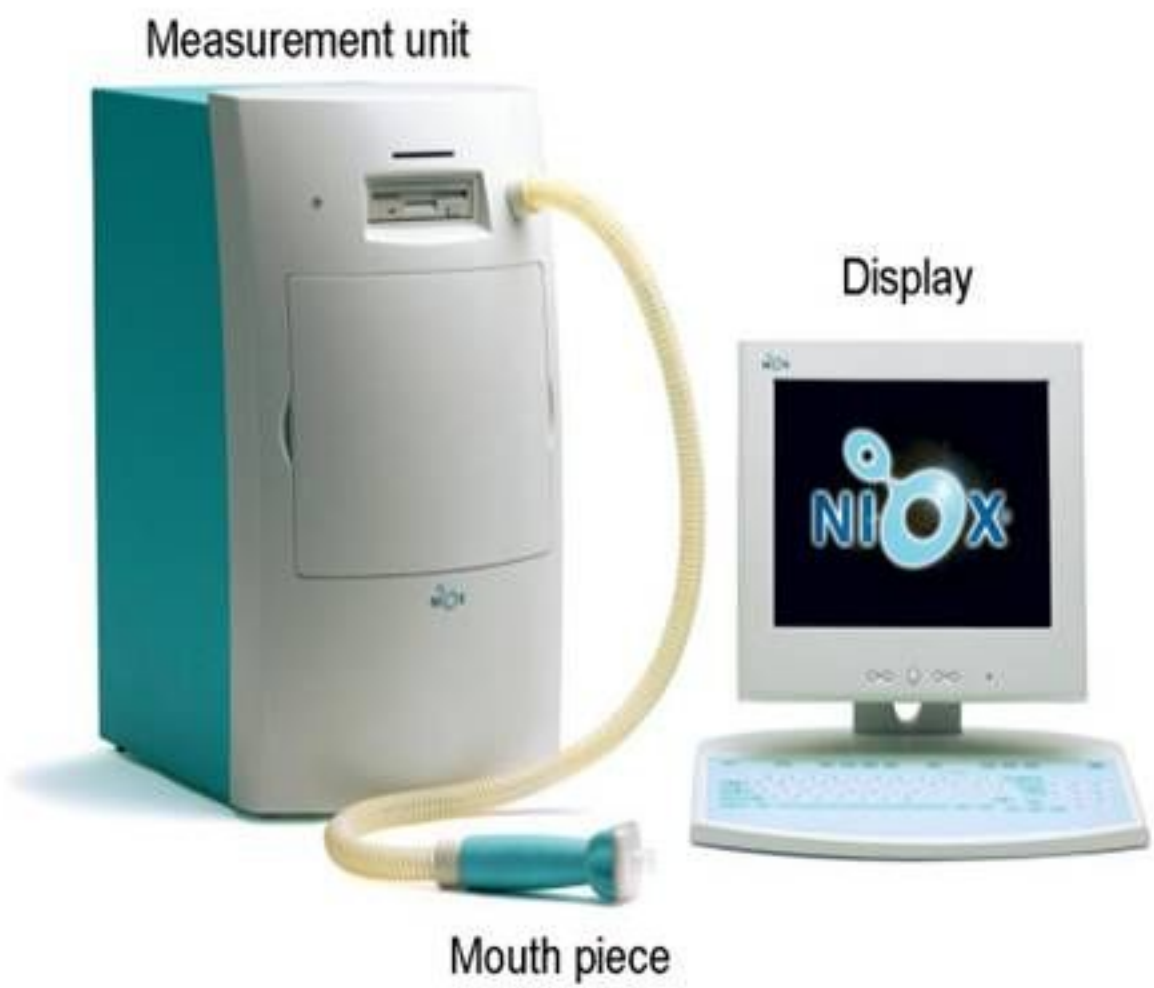
Measurement unit
Display
Mouth piece

B


Mouth piece
Display
Measurement unit

CHEST

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CHEST ONLINE

Effects of Montelukast Treatment and Withdrawal on Fractional Exhaled Nitric Oxide and Lung Function in Children With Asthma*

Paolo Montuschi, Chiara Mondino, Pierluigi Koch, Giovanni Ciabattoni, Peter J. Barnes and Giuseppe Baviera

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Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma

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Table 1. Criteria for Adjustment of the Dose of Inhaled Corticosteroid in the Two Study Groups.*

Group	Asthma Controlled?†	
	Yes	No
Control‡		
Asthma symptoms§	Present ≤2 days/wk (24-hr scores of 1 of 5 not counted)	Present >2 days/wk with 24-hr asthma score ≥2 of 5
Nighttime waking (nights/wk)	≤1	>1
Bronchodilator use	≤4 Occasions/wk and on ≤2 days/wk	>4 Occasions/wk or on >2 days/wk
Variation in PEFR (amplitude % of mean, previous 7 days)‡	≤20	>20
FEV_1 (% of baseline)	≥90	<90
Exhaled nitric oxide		
F_{ENO} (ppb at 250 ml/second)	<15	≥15

* PEFR denotes peak expiratory flow rate, FEV_1 forced expiratory volume in one second, and ppb parts per billion.

† For asthma to be considered controlled, a yes answer was required in each of the five categories for the control group; for asthma to be considered uncontrolled, a no answer was required in at least one category.

‡ Data were obtained from patient diaries for seven days before the study visit.

§ Asthma symptoms were given a score of 0 to 5, with 5 being the most severe.

Urinary leukotriene E_4/exhaled nitric oxide ratio and montelukast response in childhood asthma

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tent and reproducible predictors of preferential montelukast response.

Enzyme immunoassays have been shown to be a sensitive method for measurement of LTE_4 values. The immunoassay used in this report has also been used in a number of other pediatric asthma reports.[6,21-24] It uses enrichment methods to purify the urine and increase assay specificity. Despite these improvements, the LTE_4 immunoassay used in this study is labor intensive and sometimes produces higher readings, suggesting poorer specificity than obtained with solid-phase extraction and reverse-phase HPLC.[7] Although multiple repeated biomarker measurements for each subject were not performed in the CLIC study and PACT, Rabinovitch et al[6,23] have previously reported that daily changes in LTE_4 values were associated with individual changes in FEV_1 or rescue medication use. Unpublished observations by these authors using these repeated-measures data found moderate but not excellent intraclass correlations for LTE_4 values measured by means of immunoassay. These observations indicate the need for a more precise LTE_4 assay, repeated LTE_4 measurements, or both to maximize precision and minimize measurement error, which might produce estimates biased toward the null. Because the LTE_4/FE_{NO} ratio was consistently associated with differential montelukast response despite the immunoassay limitations, these study population using the meta-analytic approach, this translates into 3.3 doubling doses or greater to achieve at least a 1-ACD per week difference in the montelukast-FP response.

In summary, LTE_4/FE_{NO} ratios were associated with a greater FEV_1 and ACD response to montelukast than FP therapy in analysis of 2 randomized studies of 318 schoolchildren with mild-to-moderate asthma. Children with LTE_4/FE_{NO} ratios at or greater than the 75th percentile were younger and more likely to be female and exhibited lower levels of atopic markers and bronchial hyperreactivity. Although clinical guidelines support the use of ICS therapy as first-line controller therapy in patients with mild-to-moderate persistent childhood asthma, measurement of LTE_4/FE_{NO} ratios might be useful in identifying individual children who achieve a greater improvement in FEV_1 and ACDs with an LTRA compared with an ICS.

Clinical implications: In children with mild-to-moderate asthma, the LTE_4/FE_{NO} ratio is associated with a better response to montelukast compared with fluticasone therapy.

REFERENCES

1. National Asthma Education and Prevention Program. Expert panel report 3: guide-