ORIGINAL ARTICLE

A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils)

H L Petsky,[1,4] C J Cates,[2] T J Lasserson,[2] A M Li,[3] C Turner,[4] J A Kynaston,[5] A B Chang[1,6]

See Editorial, p 191

► Additional material is published online only. To view this file please visit the journal online (http://throax.bmj.com/content/67/3.toc).

[1]Queensland Children's Respiratory Centre and Qld Children's Medical Research Institute, Royal Children's Hospital, Brisbane, Qld, Australia
[2]Community Health Sciences, St George's, University of London, London, UK
[3]Department of Paediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong
[4]The University of Queensland, School of Nursing & Midwifery, Qld, Australia
[5]Department of General Paediatrics, Royal Children's Hospital, Brisbane, Qld, Australia
[6]Queensland Children's Respiratory Centre and Child Health Division, Menzies School of Health Research, Darwin, NT, Australia

Correspondence to
Helen Petsky, Queensland Children's Respiratory Centre, Royal Children's Hospital, Herston, Brisbane, Queensland 4029, Australia; helen_petsky@health.qld.gov.au

Received 22 January 2010
Accepted 29 April 2010
Published Online First 11 October 2010

ABSTRACT

Asthma severity and control can be measured both subjectively and objectively. Traditionally asthma treatments have been individualised using symptoms and spirometry/peak flow. Increasingly treatment tailored in accordance with inflammatory markers (sputum eosinophil counts or fractional exhaled nitric oxide (FeNO) data) is advocated as an alternative strategy. The objective of this review was to evaluate the efficacy of tailoring asthma interventions based on inflammatory markers (sputum analysis and FeNO) in comparison with clinical symptoms (with or without spirometry/peak flow) for asthma-related outcomes in children and adults. Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and reference lists of articles were searched. The last searches were in February 2009. All randomised controlled comparisons of adjustment of asthma treatment based on sputum analysis or FeNO compared with traditional methods (primarily clinical symptoms and spirometry/peak flow) were selected. Results of searches were reviewed against predetermined criteria for inclusion. Relevant studies were selected, assessed and data extracted independently by at least two people. The trial authors were contacted for further information. Data were analysed as 'intervention received' and sensitivity analyses performed. Six (2 adults and 4 children/adolescent) studies utilising FeNO and three adult studies utilising sputum eosinophils were included. These studies had a degree of clinical heterogeneity including definition of asthma exacerbations, duration of study and variations in cut-off levels for percentage of sputum eosinophils and FeNO to alter management in each study. Adults who had treatment adjusted according to sputum eosinophils had a reduced number of exacerbations compared with the control group (52 vs 77 patients with $\geq$1 exacerbation in the study period; $p=0.0006$). There was no significant difference in exacerbations between groups for FeNO compared with controls. The daily dose of inhaled corticosteroids at the end of the study was decreased in adults whose treatment was based on FeNO in comparison with the control group (mean difference −450.03 μg, 95% CI −676.73 to −223.34; $p<0.0001$). However, children who had treatment adjusted according to FeNO had an increase in their mean daily dose of inhaled corticosteroids (mean difference 140.18 μg, 95% CI 28.94 to 251.42; $p=0.014$). It was concluded that tailoring of asthma treatment based on sputum eosinophils is effective in decreasing asthma exacerbations. However, tailoring of asthma treatment based on FeNO levels has not been shown to be effective in improving asthma outcomes in children and adults. At present, there is insufficient justification to advocate the routine use of either sputum analysis (due to technical expertise required) or FeNO in everyday clinical practice.

Key messages

What is the key question?
- What is the overall outcome of trials assessing the use of the sputum eosinophil counts and exhaled nitric oxide to tailor asthma treatment?

What is the key point?
- Treatment tailored using the sputum eosinophil count results in fewer asthma attacks than traditional management in adults with severe asthma; the overall findings with exhaled nitric oxide are negative but they are difficult to interpret because of differences in methodology.

Why read on?
- There has been considerable interest in inflammometry in asthma management and the benefits of sputum guided management in severe asthma are marked.

INTRODUCTION

Monitoring tools to assist in improving asthma control and prevention of exacerbations are two key elements in asthma guidelines.[1–3] There is no single outcome measure that can adequately assess asthma control.[4] Subjective measures usually involve a series of questions used for clinical assessment, diary cards and quality of life (QoL) questionnaires. Traditional objective methods used to monitor (but not control) asthma include spirometry/peak flow and degree of airway hyperresponsiveness (AHR).[5] Newer methods include measurement of airway inflammation such as airway cellularity in induced sputum or fractional exhaled nitric oxide (FeNO).

The inflammation in airways of people with asthma can be predominantly eosinophilic or non-eosinophilic (including neutrophilic).[6] Irrespective of the type of airway inflammation, inhaled corticosteroids (ICS) remain the major preventer treatment to control asthma symptoms in those with asthma, other than children with mild intermittent asthma.[3] However, ICS are more effective in reducing symptoms in patients with eosinophilic inflammation than those with neutrophilic inflammation.[7] Thus investigations that provide objective data on eosinophilic inflammation may be helpful in reducing exacerbations and improve asthma control. Current available techniques for clinical use are assessment of sputum cellularity and FeNO.[8]

A systematic review evaluating the efficacy of tailoring asthma interventions based on utilising sputum eosinophils or FeNO in comparison with current strategy (reliance on clinical symptoms with or without spirometry/peak flow) will be useful to guide clinical practice. Here we combine two Cochrane reviews[9 10] that address this question. The objective of this systematic review is to evaluate the efficacy of tailoring asthma interventions based on FeNO or sputum eosinophils in comparison with controls (clinical symptoms with or without spirometry/peak flow) for asthma-related outcomes in children and adults.

METHODS

Methods of the analysis and inclusion criteria were specified in advance and documented in protocols that are available alongside the original versions of these reviews in The Cochrane Library.

Eligibility, information sources, search strategy and study selection

We used the PRISMA guidelines,[11] Cochrane collaboration methodology and software (RevMan5). We searched the Cochrane Airways Group specialised register for eligible randomised controlled trials that compared adjustment of asthma medications based on sputum eosinophils or FeNO levels in comparison with clinical symptoms (with or without spirometry/peak flow) using keywords in electronic sources (Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, EMBASE) and hand searching of references as outlined in the reviews.[9 10] The latest searches were performed in February 2009. Trials that included the use of other interventions were included if all participants had equal access to such interventions.

Participant inclusion criteria were children and adults with 'classical asthma'. Exclusion criteria were: eosinophilic bronchitis, asthma related to an underlying lung disease such as bronchiectasis and chronic obstructive airway disease, or diagnostic categories such as 'cough variant asthma' and 'wheezy bronchitis' where controversies exist.

Data items

From the title, abstract or descriptors, the literature search was reviewed independently in triplicate to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, two reviewers independently selected trials for inclusion. There was no disagreement, although it was planned that disagreement would have been resolved by third-party adjudication. We extracted information from each trial on (1) study characteristics, (2) intervention type and (3) outcomes, as described in our Cochrane reviews.[9 10]

Risk of bias

Risk of bias for each study was assessed using the tool available in the RevMan software. Six components were assessed: (1) adequate sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data addressed; (5) free of selective reporting; and (6) free of other bias. Studies included in the review underwent quality assessment and were entered into a 'risk of bias' table.

Summary (outcome) measures

Primary outcomes were the number of participants who had asthma exacerbations during follow-up. Secondary outcomes were mean difference in asthma-related outcome measures, number of participants experiencing adverse effects of the interventions and number of participants experiencing complications such as requirement for medication change. The proportions of participants and the mean clinical improvement were determined using the following hierarchy of assessment measures (ie, where two or more assessment measures are reported in the same study, the outcome measure that is listed first in the hierarchy was used);

1. Hospitalisation, acute presentations to an emergency facility for asthma.
2. Rescue courses of oral corticosteroids.

Figure 1 PRISMA flow chart.

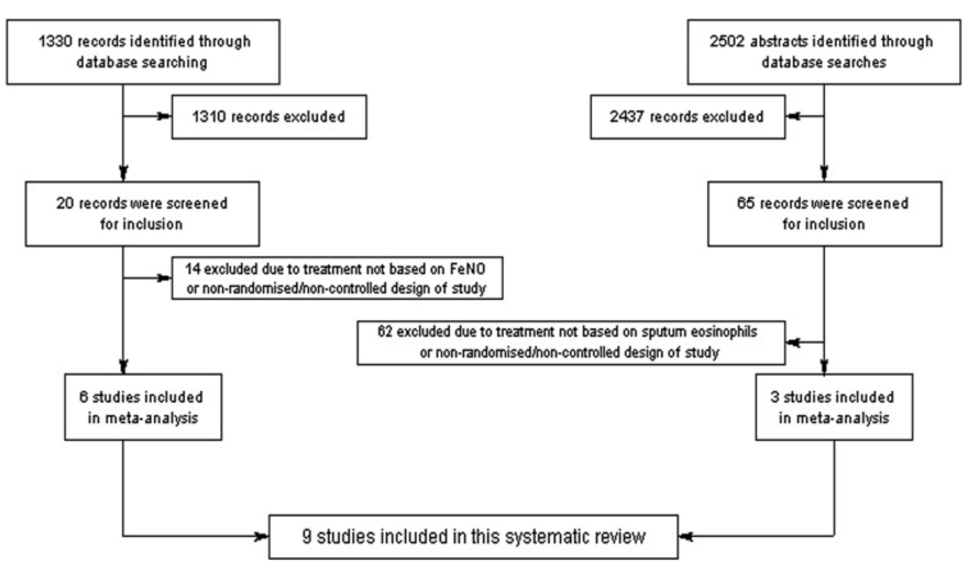


Table 1 Characteristics of included studies

Study	Sample size	Participant age	Description of intervention and control arms	Primary outcome and definition of exacerbation	Duration
Chlumsky 2006[14]	55 randomised Eosinophil strategy, n=30 Standard strategy, n=25	Eosinophil strategy: mean age 42 (SD 19), 13 males Standard strategy: mean age 48 (SD 16)	Standard strategy arm: treatment decisions were based on morning PEF variation, frequency of daytime symptoms or SABA use/week, frequency of night time symptoms or SABA/week. Eosinophil strategy: treatment decisions were based on the same as the standard strategy arm plus sputum eosinophils as a % of total cell count	Primary outcome: rate of asthma exacerbations Secondary outcomes: FEV_1, postbronchodilator FEV_1 and FEV_1/inspiratory vital capacity ratio. Exacerbation: a doubling of the frequency of symptoms or number of puffs of rescue salbutamol or a reduction in morning PEF by ≥30% on at least two consecutive days or two of the aforementioned or all three.	Participants were assessed every 3 months for 18 months
deJongste 2009[21]	151 children randomised FeNO group, n=75 Symptom group, n=72	FeNO group: mean age 11.6 (SD 2.6), 46 males. Symptom group: mean age 11.8 (SD 4.3), 54 males	All participants scored asthma symptoms in an electronic diary over 30 weeks. The FeNO group received a portable nitric oxide analyser. Data were transmitted daily to centres, patients were phoned every 3 weeks and their steroid dose was adapted according to FeNO and symptoms (FeNO group) or according to symptoms (symptom group).	Primary outcome: proportion of symptom-free days over the last 12 study weeks. Secondary outcomes: cumulative symptom scores, ICS dose as budesonide equivalent, FEV_1 and reversibility, FeNO 0.05, prednisone courses, emergency visits, hospitalisations for asthma and PACQLQ scores. Exacerbation: emergency visit, hospitalisation or prednisolone course	Children were seen at 3, 12, 21 and 30 weeks for examination, assessment of FeNO, spirometry before and after salbutamol and recording of adverse events. Study concluded at 30 week visit.
Fritsch 2006[16]	52 patients entered the study. FeNO group n=22 Control group n=25	FeNO group: mean age 11.3 (SD 3.4), 14 males. Control group: mean age 12.1 (SD 2.8), 14 males.	FeNO group: treatment was based on symptoms, β-agonists use, lung function and FeNO. Control group: treatment based on symptoms, β-agonists and lung function only.	Primary outcome: FEV_1 Secondary outcomes: no. of exacerbations, MEF 50% predicted, better symptom control, less SABAs and ICS dose. Exacerbation defined by 4 parameters: oral steroid courses, and/or off-scheduled visit because of asthma symptoms over the past 4 weeks, and/or increase of asthma symptoms from a symptom score 0 or 1 to a symptom score 2 and/or decline of FEV_1 (litres) >10% compared with the previous visit.	Visits were at 6, 12, 18 and 24 weeks after 4 week run-in.
Green 2002[15]	74 randomised Sputum management group, n=37 BTS management group, n=37	Sputum management group: median age 50, range 19–73, 19 males. BTS management group: median age 47, range 20–75, 21 males.	Sputum management group: anti-inflammatory treatment was based on maintenance of sputum eosinophil count <3% with a minimum dose of anti-inflammatory treatment. BTS management group: treatment decisions were based on traditional assessments of symptoms, PEF and use of β_2-agonists.	1. No. of severe asthma exacerbations 2. Control of eosinophilic airway inflammation measured by the induced sputum eosinophil count 3. Exhaled nitric oxide concentrations 4. Symptom scores (0–3 for daytime and night time symptoms) 5. Total asthma quality of life scores 6. Peak flow amplitude as a proportion of the mean 7. FEV_1 8. Changes from baseline of methacholine PC20 9. Drug use 10. Admissions for asthma 11. Severe exacerbations defined as a decrease in morning PEF to >30% below baseline value on 2 consecutive days, or deterioration in symptoms needing rescue course of oral corticosteroid.	Study duration was for 12 months with visits at months 1, 2, 3, 4, 6, 8, 10 and 12.
Jayaram 2006[22]	117 randomised Sputum strategy group, n=50 Clinical strategy group, n=52	Sputum strategy group: mean age 46 (SD 13.8), 15 males Clinical strategy group mean age 43.5 (SD 13.9), 15 males	Sputum strategy: dose of inhaled steroid was guided solely by induced sputum eosinophils to keep <2%. Spirometry was used to identify clinical control, exacerbations and other treatment. Clinical strategy: guided by symptoms	1. RR reduction for the first exacerbation 2. The length of time without exacerbations 3. Type and severity of exacerbations 4. The usefulness of monitoring sputum cell counts in relation to the overall serverity of asthma. Defined by the minimum dose of ICS to maintain control 5. The cumulative dose of ICS needed in Phase 2 adjusted for its duration. Exacerbation: Loss of symptomatic control requiring increased use of SABAs by 4 extra puffs per day for a minimum of 48 h, or by nocturnal symptoms, or early morning wakening due to respiratory symptoms ≥2 in 1 week. Severe exacerbations were defined as requiring rescue courses of oral prednisone as defined by the investigator.	2 year study duration with monthly visits in Phase 1 until control maintained with minimum treatment (variable duration) or at exacerbations Phase 2: 3 monthly visits or at exacerbations

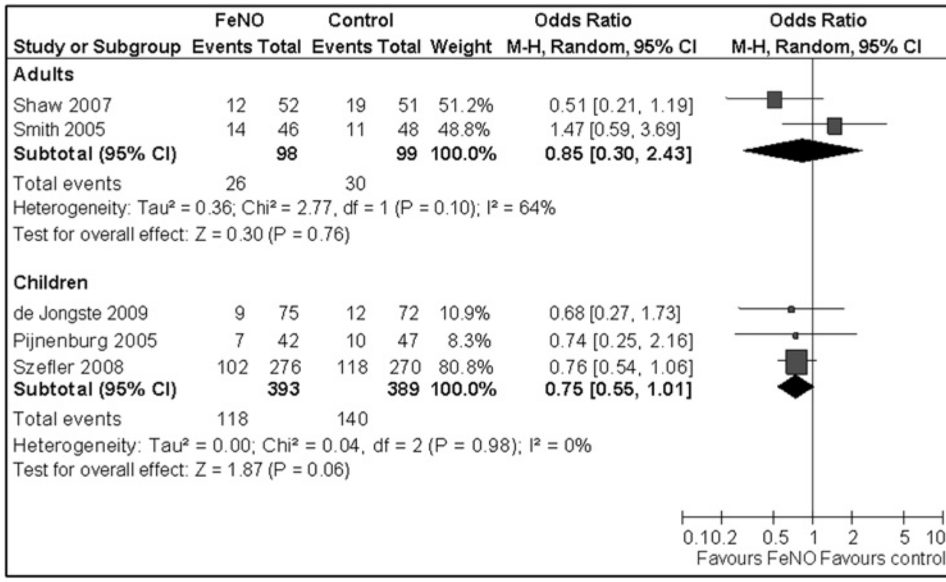
Continued

Table 1 Continued

Study	Sample size	Participant age	Description of intervention and control arms	Primary outcome and definition of exacerbation	Duration
Pijnenburg 2005[17]	89 children randomised. FeNO group, n=39 Symptom group, n=46	FeNO group: median age 11.9 (SD 2.9), 25 males. Symptom groupK mean age 12.6 (SD 2.8), 30 males.	FeNO group: FeNO-guided ICS dosing according to predetermined algorithm. Symptom group: symptom scores influenced ICS dosing.	Primary outcome: cumulative steroid dose (sum of mean daily steroid doses of visits 1−5) Secondary outcomes: mean daily symptom score, mean daily number of bronchodilator doses taken, percentage of symptom-free days during the last 4 weeks of the study, number of oral prednisolone courses during the study and provocative dose of methacholine causing a 20% fall in FEV_1 (PD20), FVC, FEV_1 and MEF25 during final visit. Exacerbation: deterioration in symptoms requiring oral prednisone course.	Study duration was 12 months with 3 monthly visits.
Shaw 2007[19]	118 adults were randomised. FeNO group, n=58 Control group, n=60.	FeNO group: median age 50 (range 20−75), 27 males. Control group: median age 52 (range 24−81), 27 males.	FeNO group: FeNO >26 ppb, ICS was increased. If FeNO <16 ppb or <26 ppb on 2 separate occasions, treatment was decreased. In control group treatment was doubled if JACS >1.57 and treatment halved if JACS <1.57 for 2 consecutive months.	Primary outcome: Number of exacerbations Secondary outcomes: total inhaled corticosteroid dose. Exacerbation: an increase in symptoms requiring oral steroids or antibiotics	Study duration was 12 months with participants being send at baseline, 2 weeks, months 1, 2, 3, 4, 6, 8, 10 and 12.
Smith 2005[18]	97 patients randomised from 110 patients recruited.	n=46 in FeNO group achieved optimal dose in Phase 1 and n=28 achieved optimal dose in control group. Mean age of randomised patients was 44.8 (range 12−73), 41 males.	Phase 1: run-in period was for 6 weeks, after 2 weeks fluticasone 750 µg/day was commenced. Visits were every 4 weeks until optimal dose was achieved. FeNO group: adjustment of dose of ICS was based soley to keep FeNO <15 ppb at 250 ml/s. Control group: dose adjustment based on asthma symptoms, night time waking, bronchodilator use, variation in PEF rate and FEV_1. Phase 2: visits every 2 months with upward adjustments made as per Phase 1 but no downward adjustments would be made from optimal dose.	Primary outcome: frequency of exacerbation Secondary outcome: mean daily dose of inhaled corticosteroids A minor exacerbation was defined as a daily asthma score of ≥2 on ≥2 consecutive days, whereas a major exacerbation was a daily asthma score of ≥3 on ≥2 consecutive days.	2 phase study, with phase 1 varying in duration (3−12 months) depending when optimal dose was deemed to have been achieved. During phase 2 (12 months) optimal dose from Phase 1 was continued and treatment stepped up if asthma control was lost.
Szefler 2008[20]	546 participants randomised from 780 patients screened. FeNO group n=276. Control group n=270	FeNO group: mean age 14.4, 146 males. Control group: mean age 14.4, 142 males.	FeNO group: standard treatment modified on the basis of measurements of FeNO Control group: standard treatment based on the guidelines of NAEPP.	Primary outcome: no. of days with asthma symptoms. Secondary outcomes: admission to hospital, unscheduled visits to emergency departments or clinics, prednisone courses for asthma, asthma exacerbations, days of wheeze, days of interference with activities, nights of sleep disruption, days of school or work missed, and days of interruption of guardian's activities. Exacerbation: combination of admissions to hospital, unscheduled visits and oral prednisone.	The study duration was 46 weeks with visits every 6−8 weeks.

BTS, British Thoracic Society; FeNO, fractional expired nitric oxide; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; JACS, Juniper Asthma Control Score; MEF, maximal expiratory flow; NAEPP, National Asthma Education and Prevention Program; PACQLQ, Paediatric Asthma Caregiver's Quality of Life Questionnaire; PEF, peak expiratory flow; SABA, short-acting β-agonist.

Figure 2 Number of subjects who had ≥1 exacerbation over the study period (fractional exhaled nitric oxide (FeNO)).



3. Symptomatic (QoL, Likert scale, asthma diary, visual analogue scale)—assessed by the patient (adult or child).
4. Symptomatic (QoL, Likert scale, asthma diary, visual analogue scale)—assessed by the parents/carers.
5. Symptomatic (Likert scale, visual analogue scale)—assessed by clinicians.
6. Indices of spirometry, peak flow, AHR.
7. β-Agonist used.

In addition, dose of ICS used was also analysed as a post hoc analysis.

Methods of analysis

The results from studies that met the inclusion criteria and reported any of the outcomes of interest were included in the subsequent meta-analyses. All data were double entered (HP and AC) and triple checked (CC). For the dichotomous outcome variables of each individual study, relative and absolute risk reductions were calculated using a modified intention-to-treat analysis when the outcome event is a beneficial event. When the event is non-beneficial (such as exacerbation), 'treatment received' analysis was utilised. The summary weighted RR and 95% CI (fixed effect model) were calculated (Cochrane statistical package, RevMan 5.0). For rate ratios of common events whereby one subject may have more than one event, generic inverse variance (GIV) was utilised. The rate ratios were taken from the published papers and the standard errors were calculated from CIs or p values published in the papers. Number needed to treat (NNT) was calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator.[12] If studies reported outcomes using different measurement scales, the standardised mean difference was estimated. Any heterogeneity between the study results was described and tested to see if it reached statistical significance using a χ^2 test. The 95% CI estimated using a random effects model was included whenever there were concerns about statistical heterogeneity. Heterogeneity was considered significant when the p value is <0.10.[13] An a priori subgroup analysis was planned for adults versus children.

RESULTS

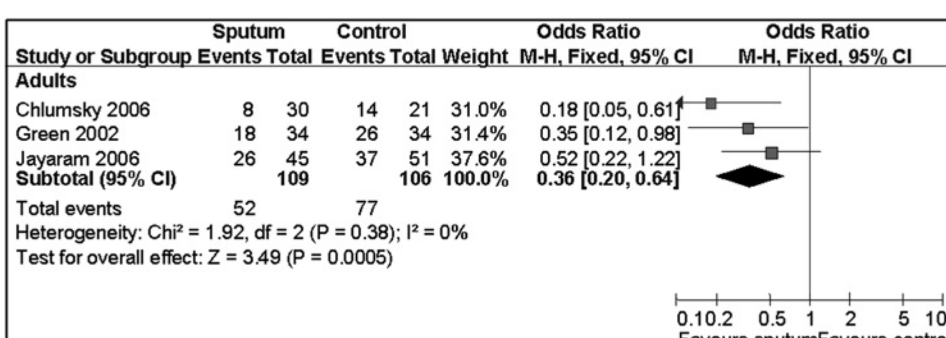
Study selection and study characteristics

The searches identified 1330 FeNO-based studies and 2502 sputum studies (figure 1). After screening 20 and 65 papers, respectively, 6 and 3, respectively, fulfilled the inclusion criteria (figure 1) for the interventions. The nine studies (3 adult studies utilising sputum eosinophils, 6 studies utilising FeNO—2 adults, 4 children) involved 1299 participants, with 1231 completing.

Of the nine studies included (table 1), six were unicentre studies[14–19] and three were multicentred.[20–22] Four studies were in children or adolescents,[16 17 20 21] four with adult patients[19] and one combining adolescents and adults.[18] We classified studies into children/adolescent studies based on the mean age reported as opposed to the entry criteria. Four studies were double blind, parallel groups[17 20] whereas five were single blind, parallel groups.[16 18 19 21] All nine papers were published in English.

There was a degree a clinical heterogeneity between studies as summarised in table 1. Most variation related to the definition of

Figure 3 Number of subject who had ≥1 exacerbation over the study period (sputum eosinophils (SpEos)).



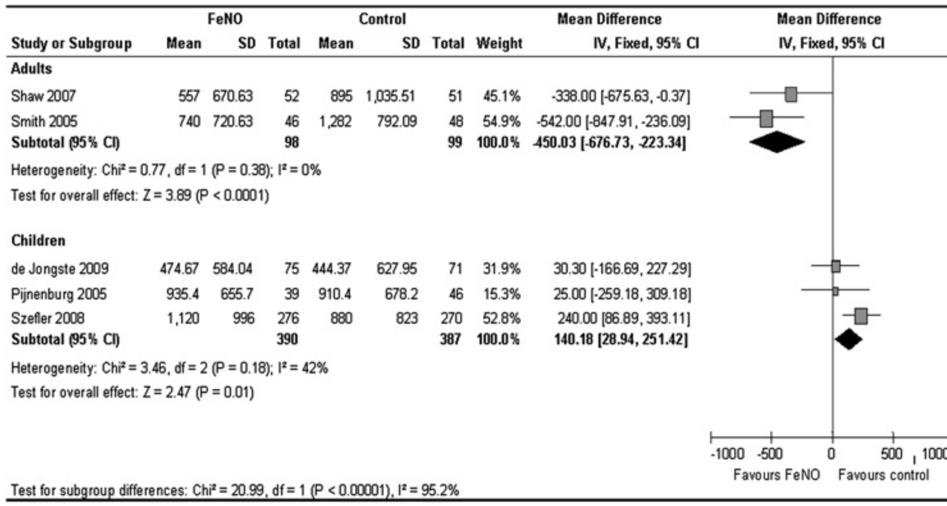


Figure 4 Inhaled corticosteroid dose at final visit (fractional exhaled nitric oxide (FeNO)).

an asthma exacerbation and the cut-off utilised for adjusting treatments. Although asthma exacerbations were an outcome measure in all papers, they differed in how they were defined, ranging from unscheduled emergency visits[21 20] to defining an exacerbation using diary card data.[18] Although there was variation in how exacerbations were defined, all included studies uniformly managed exacerbations with rescue oral steroids. Algorithms for adjustment of medications differed between studies and the cut-off values to step-up and step-down also varied across the FeNO studies (range from 20[16 20 21] to 35[18]), and the sputum eosinophil percentages (range from 2[22] to 8[14]).

Outcomes and synthesis of results

Primary (Exacerbations)

In FeNO-based adult studies (figure 2), the number of participants with exacerbations in the group with treatment adjusted according to FeNO was similar to the control group; 26 with exacerbations vs 30, respectively (p=0.763), OR 0.85 (95% CI 0.30 to 2.43). The number of children who had exacerbations in the FeNO-based group was not significantly different in the control group (102 vs 118, respectively, p=0.062), OR 0.75 (95% CI 0.55 to 1.01) (figure 2).

In contrast, in the sputum-based meta-analysis (figure 3) significantly fewer adults in the group that utilised sputum eosinophil count had asthma exacerbations compared with the control group (52 vs 77; p=0.0006), OR 0.36 (95% CI 0.20 to 0.64). NNT for benefit was 6 (95% CI 4–32) over 52 weeks.

Secondary outcomes

ICS dose

For FeNO-based studies, meta-analysis of adult studies was opposite to that of paediatric studies (figure 4). Adults who had treatment adjusted according to FeNO had a significantly lower dose of ICS at the end of the study period (figure 4) than those in the control group (mean difference between groups was −450.03 μg budesonide equivalent; 95% CI −676.73 to −223.34; p<0.0001). However, Shaw[19] also reported an 11% increase in the total amount of ICS used during the study (95% CI −15% to 37%). In paediatric studies, the group who had treatment adjusted according to FeNO (figure 4) had significantly higher doses of ICS at the end of the study compared with the control group (mean difference 140.18, 95% CI 28.94 to 251.42; p=0.014).

All three studies that utilised sputum eosinophils to adjust treatment reported no differences in doses of ICS used between groups (figure 5). The SDs for the groups were not available in Jayaram's paper and were estimated based on the data from Green's paper. Mean dose of ICS per person per day between groups was non-significant; weighted mean difference was 78.99, 95% CI −90.13 to 248.11; p=0.157.

Symptom scores

Symptom scores did not differ between groups for FeNO-based studies in both adults and children (figure 6). In adults, the mean difference was −0.10, 95% CI −0.33 to 0.12; p=0.372. In children, the mean difference was 0.13, 95% CI −0.32 to 0.57; p=0.577. For the sputum-based studies, the two studies that reported on symptom scores also described no difference in symptoms scores between groups.[14 15]

Sensitivity analyses

There were insufficient data reported from the individual studies to include other secondary outcomes (forced expiratory volume in 1 s (FEV_1). AHR, rescue β-agonist use, QoL) for meta-analysis. FEV_1 was an outcome in all nine studies; eight studies[14 15 18 19 21] described no difference between the participants who had treatment adjusted to inflammatory markers in comparison with the control group.

Results from the sensitivity analyses did not alter direction or non-significance of primary outcomes (exacerbations) but

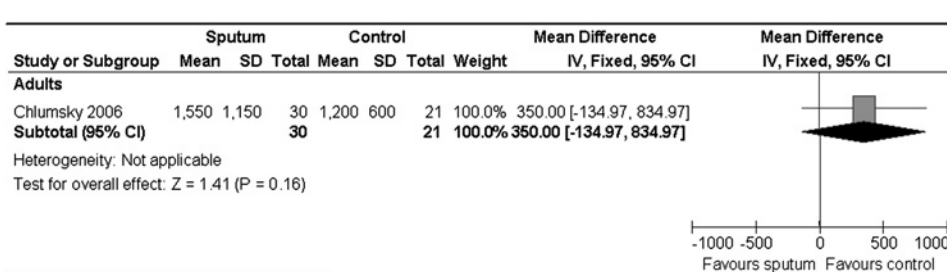
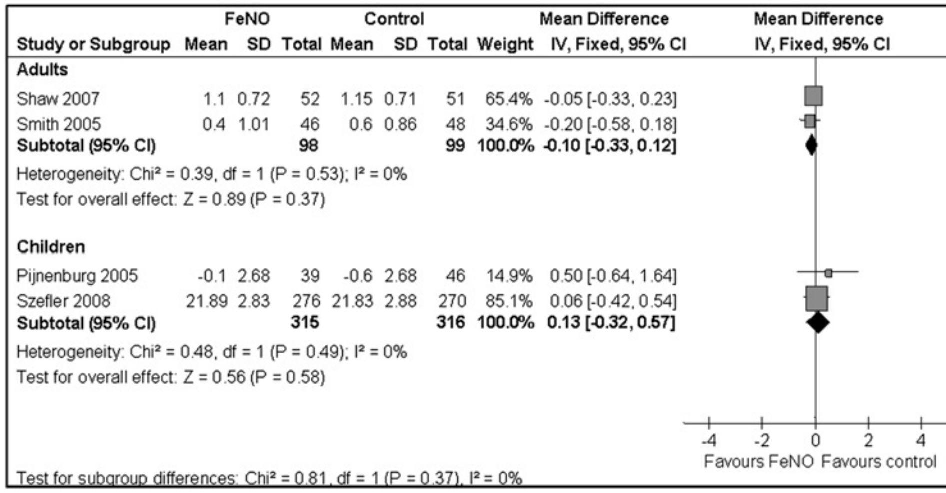


Figure 5 Mean dose of inhaled corticosteroid per person per day (sputum eosinophils (SpEos)).

Figure 6 Symptom score (fractional exhaled nitric oxide (FeNO)).



changed the final ICS dose in the paediatric studies from favouring controls to a non-significant difference between groups (see supplementary file online).

Risk of bias in individual studies

The risk of bias table (table 2) shows that four studies[15 17 19 22] were considered moderate to high quality, but in all studies there were insufficient details about either allocation concealment and/or adequacy of blinding. One study[14] was open labelled while another[21] was single blinded.

For the FeNO-based papers, the quality of evidence using the GRADE approach surmises that of the four outcomes assessed, three were of moderate quality and one (ICS dose in children) was low quality due to one study[21] being single blinded and a high final daily dose of ICS in another study[20] (table 3). For sputum-based studies, GRADE assessment shows that the quality of both outcomes was low (exacerbation) and very low (ICS dose) due to the lack of blinding in one study[14] and the high daily doses of ICS at the end of the study in two studies[14 15] (table 4).

Table 2 Risk of bias summary of included studies

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Chlumsky 2006	+	?	−	?	?	?
de Jongste 2009	?	?	−	?	?	−
Fritsch 2006	?	?	?	?	−	−
Green 2002	+	?	+	+	+	?
Jayaram 2006	+	?	+	+	+	?
Pijnenburg 2005	?	?	+	+	+	?
Shaw 2007	?	+	+	+	?	+
Smith 2005	?	?	+	+	?	?
Szefler 2008	+	+	+	?	?	−

DISCUSSION

In this meta-analysis, we combined data from our Cochrane reviews[9 10] that evaluated the efficacy of tailoring asthma interventions based on FeNO or sputum eosinophils in comparison with controls (clinical symptoms with or without spirometry/peak flow) for asthma-related outcomes in children and adults. Based on nine studies in 1299 adults and children (1231 completed), we found that the number of adults who had an exacerbation (as defined by the author) was significantly lower in the group in which ICS was tailored based on sputum eosinophilia compared with the control group (ie, managed with the usual traditional methods, based primarily on clinical symptoms). In contrast there was no significant difference between groups when ICS was tailored based on FeNO. In children/adolescents there was a non-significant trend favouring the FeNO strategy in a number of participants with one or more exacerbations, but this was at the expense of higher levels of ICS. In adults, the FeNO-based strategy enabled a reduction in the final (but not the overall) daily dose of ICS. For both FeNO- and sputum-based strategies, there was no difference between groups for all secondary outcomes (FEV_1, symptom scores, AHR and β_2-agonist use).

Tailoring medications based on FeNO has been advocated in an editorial[23] and is now relatively widely used in some countries where a rebate for its use is available. This meta-analysis has shown that the benefits of utilising an FeNO-based strategy (as opposed to a standard strategy based on clinical symptoms and simple tests such as FEV_1) is at best modest and could potentially be harmful with increased ICS use in children. There was no significant difference between the two strategies in both adult and paediatric studies in the primary outcome of exacerbation when utilising FeNO. The only significant beneficial difference found between groups was the final daily dose of ICS

Table 3 Grade assessment of FeNO-based papers

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intervention based on clinical symptoms	**Tailored intervention based on FeNO**				
Number of subjects who had one or more exacerbations over the study period in adults Follow-up: 52 weeks	**30 per 100**	**27 per 100** (12 to 51)	**OR 0.85** (0.3 to 2.43)	197 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
Number of subjects who had one or more exacerbations over the study period in children and adolescents Follow-up: 26-52 weeks	**36 per 100**	**30 per 100** (24 to 36)	**OR 0.75** (0.55 to 1.01)	782 (3 studies)	⊕⊕⊕⊖ **moderate**[2,3,4]	
ICS dose at final visit in adults mcg/day Follow-up: 52 weeks	The mean ics dose at final visit in adults in the control groups was **1088 mcg/day (budesonide equivalent)**	The mean ICS dose at final visit in adults in the intervention groups was **450 lower** (677 to 223 lower)		197 (2 studies)	⊕⊕⊕⊖ **moderate**[5]	
ICS dose at final visit in children and adolescents mcg/day Follow-up: 26-52 weeks	The mean ics dose at final visit in children and adolescents in the control groups was **804 mcg/day (budesonide equivalent)**	The mean ICS dose at final visit in children and adolescents in the intervention groups was **140 higher** (29 to 251 higher)		777 (3 studies)	⊕⊕⊖⊖ **low**[3,6,7]	

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.
*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
1 CIs are wide and include clinically important benefit and harm.
2 One study (deJongste 2008) design was open label which may have introduced bias.
3 Studies reported technical difficulties with FeNO analyses as reported in risk of bias table.
4 Medication increased prior to commencement of study.
5 In one study the overall dose of ICS was higher with FeNO-based interventions even though the final ICS dose was lower.
6 One study presented in these results was single blinded with the intervention arm analysing FeNO only.
7 Final ICS doses were quite varied, with one study having particularly high doses.
FeNO, fractional expired nitric oxide; ICS, inhaled corticosteroid.

in adults. However, this finding is limited as this was a post hoc analysis.

The primary outcome chosen was exacerbation, an important outcome as this affects the patient's QoL and the extent to which the patient can carry out their activities of daily life.[4] Arguably this is the most important outcome in studies on efficacy of interventions for asthma control. Our meta-analysis has shown that in contrast to the non-beneficial effect of FeNO on rate of exacerbation, tailoring treatment based on sputum eosinophils decreased the number of exacerbations experienced by this group of adults.

In contrast to the favourable data in the outcome of exacerbations that support the use of sputum to guide asthma treatments in adults, there was no significant difference between the groups for both sputum- and FeNO-based strategies in other asthma outcomes (FEV_1, QoL and β_2-agonist use). While exacerbations are an important outcome, arguably subjective measures of asthma control are also important. Thus, although our findings demonstrate that monitoring airway inflammation through eosinophils in induced sputum is useful in reducing exacerbations, it is debatable whether it should be universally advocated. Furthermore, sputum analysis is restricted to laboratories with specific expertise in inducing and analysing sputum. Obtaining and analysing sputum is relatively time consuming (when compared with FeNO) and is not always successful, particularly in young children. Nevertheless, use of sputum induction to guide asthma treatment is most likely to be beneficial in adults with severe asthma and those with frequent exacerbations.

The FeNO-based studies need to be considered in light of several issues. First, none of the six included studies utilising FeNO considered presence or severity of atopy in their algorithm of management, although some but not all subjects were atopic. Raised FeNO in children has been associated with atopy with or without respiratory symptoms.[24] Shaw and colleagues[19] reported that some of their participants were atopic (62% in the FeNO group, 70% in the control group). Smith *et al*[18] did not describe whether their subjects were atopic or not. 'Atopic asthma' was an inclusion criterion for Pijnenburg *et al*[25] as

Table 4 Grade assessment of sputum eosinophil-based papers

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Tailored interventions based on clincal symptoms	**Tailored interventions based on sputum eosinophils**				
Number of subjects who had one or more exacerbations over the study period	**726 per 1000**	**488 per 1000** (346 to 629)	**OR 0.36** (0.2 to 0.64)	215 (3 studies)	⊕⊕⊖⊖ **low**[1]	
Mean dose of inhaled corticosteroids per person per day		The mean Mean dose of inhaled corticosteroids per person per day in the intervention groups was **78.99 higher** (90.13 lower to 248.11 higher)		221 (3 studies)	⊕⊖⊖⊖ **very low**[1,2]	

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
1 One paper (Chlumsky) was open labelled with no blinding.
2 Two studies (Chlumsky and Green) had significantly higher doses of ICS overall.
ICS, inhaled corticosteroid.

defined as RAST (radioallergosorbent test) class 2 or higher for at least one airborne allergen ever. Similarly, all children in the study of Fritsch *et al*[16] had an inclusion criterion of positive skin prick test or RAST.

Secondly, the cut-offs of FeNO utilised for stepping up or down treatment differed between studies (range 15–30 ppb). The subjects of the study of Pijnenburg *et al*[17] (paediatric study) had the highest mean daily dose of ICS and subjects in this study also had quite high FeNO at the final visit (∼25.5 pbb in the FeNO group, 36.7 in the controls). Disconcertingly, use of the FeNO strategy did not result in a lower FeNO level at the end of the trial. Smith *et al*[18] mentioned that their 15 ppb threshold is equivalent to 35 ppb at a slower 50 ml/s flow rate. There is no evidence-based algorithm to adjust treatment in relation to FeNO levels (or indeed to sputum eosinophils levels). There are differences in guidelines (such as GINA[1], BTS[2], NAC[3]) with respect to when and how to step-up and step-down asthma treatments. Arguably the algorithm should provide a result sufficiently different from clinical decision making in order for there to be any benefit.[26]

The difference in results of using sputum eosinophils (beneficial for exacerbations) versus FeNO (not beneficial) is likely to be because FeNO levels do not necessarily reflect sputum eosinophil density, particularly in non-steroid-naïve patients.[27 28] Also, consideration of cost is important for the universal use of FeNO in health systems. FeNO measurements require a nitric oxide analyser that needs maintenance and/or calibration. Nitric oxide analysers are relatively expensive, and adding FeNO as a monitoring tool adds not only cost but also another layer of complexity in asthma care. Analysers were only approved by the US Food and Drug Administration for clinical monitoring of anti-inflammatory treatment in 2003.[29] As reported in the risk of bias table (table 2), accurate FeNO measurements at each visit could not be obtained, due either to a faulty analyser[21] or to technical issues.[16] Also, many aspects need to be considered when analysing FeNO; this includes the timing of spirometry (transiently reduces FeNO), food and beverage, circadian rhythm, smoking history, ambient nitric oxide and exercise.[29]

Limitations of the review

This systematic review is limited to nine studies with 1231 subjects completing the trials. While the studies share some common issues, there are also significant differences, notably the definition of asthma exacerbation, how the decision to prescribe oral steroids was made, the different cut-off levels for FeNO and sputum eosinophils, the control strategies and how medications were adjusted.

Sensitivity analyses was done post hoc where the study of Szefler *et al*[20] was excluded from the meta-analysis, as study design was slightly different because traditional asthma measures were part of both groups. While the non-significant difference between groups for the primary outcome was upheld, that for the final ICS that favoured controls became non-significant.

CONCLUSION

The studies included in this review highlight the difficulties involved in tailoring the dose of ICS based on inflammatory markers (FeNO and sputum eosinophils), instead of primarily on clinical symptoms. Tailoring of asthma treatment based on sputum is effective in decreasing asthma exacerbations in adults. However, tailoring of asthma treatment based on FeNO levels has not been shown to be effective in improving asthma outcomes in children and adults. At present, despite their popularity, there is insufficient evidence to advocate their use in routine clinical practice.

Further randomised controlled trials in both adults and children are required. A priori pragmatic issues of clinical practice such as high versus low doses of ICS and, to a lesser extent, eosinophilic versus non-eosinophilic asthma should be considered with costs analysis for each subgroup. Future randomised controlled trials should preferably be parallel multicentre studies and include outcomes of exacerbations, subjective measures (such as scores for asthma control and QoL) as well as objective measures (FEV_1, etc.). It is likely that a clear algorithm based on outcomes rather than a single cut-off is required.[26] Analysis of costs and possible adverse events of inhaled and oral corticosteroids would also provide additional important information.

Funding Australian Cochrane Airways Group and Royal Children's Hospital Foundation. AC is supported by an NHMRC Practitioner Fellowship (grant no. 545216).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. GINA Report, Global Strategy for Asthma Management and Prevention, 2008. http://www.ginasthma.com/GuidelinesResources.asp (accesssed Nov 2009).
2. *Asthma Management Handbook*. Australia, Melbourne: National Asthma Council, 2006. http://www.nationalasthma.org.au/cms/index.php (accessed Nov 2009).
3. **British Thoracic Society Scottish Intercollegiate Guidelines Network.** British guideline on the management of asthma. *Thorax* 2008;**63**(Suppl 4:iv):1—121.
4. **Reddel HK,** Taylor DR, Bateman ED, *et al*. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations; standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;**180**:59—99.
5. **Zacharasiewicz A,** Wilson N, Lex C, *et al*. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005;**171**:1077—82.
6. **Douwes J,** Gibson P, Pekkanen J, *et al*. Non-eosinophilic asthma: importance and possible mechanisms. *Thorax* 2002;**57**:643—8.
7. **Berry M,** Morgan A, Shaw D, *et al*. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. *Thorax* 2007;**62**:1043—9.
8. **Wark PA,** Gibson PG. Clinical usefulness of inflammatory markers in asthma. *Am J Respir Med* 2003;**2**:11—19.
9. **Petsky H,** Kynaston J, Turner C, *et al*. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* 2007;(2):CD005603.
10. **Petsky HL,** Cates CJ, Li AM, *et al*. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* 2009;(2):CD006340.
11. **Liberati A,** Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Br Med J* 2009;**339**:b2700.
12. Visual Rx. Online NNT calculator [program]. 3 version, 2008.
13. **Higgins JP,** Green S, eds. *Analysing and Presenting Results*. Chichester, UK: John Wiley & Sons Ltd, updated, M2005.
14. **Chlumsky J,** Striz I, Terl M, *et al*. Strategy aimed at reduction of sputum eosinophils decreases exacerbation rate in patients with asthma. *J Int Med Res* 2006;**34**:129—39.
15. **Green RH,** Brightling CE, McKenna S, *et al*. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;**360**:1715—21.
16. **Fritsch M,** Uxa S, Horak F Jr, *et al*. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol* 2006;**41**:855—62.
17. **Pijnenburg M,** Bakker E, Hop W, *et al*. Titrating steriods on exhaled nitric oxide in children with asthma: a randomised controlled trial. *Am J Respir Crit Care Med* 2005;**172**:831—6.
18. **Smith AD,** Cowan JO, Brassett KP, *et al*. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;**352**:2163—73.
19. **Shaw D,** Perry MA, Thomas M, *et al*. The use of exhaled nitric oxide to guide asthma management. *Am J Respir Crit Care Med* 2007;**176**:231—7.
20. **Szefler SJ,** Mitchell H, Sorkness CA, *et al*. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008;**372**:1065—72.
21. **de Jongste JC,** Carraro S, Hop WC, *et al*. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009;**179**:93—7.
22. **Jayaram L,** Pizzichini MM, Cook RJ, *et al*. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;**27**:483—94.
23. **Szefler S.** Facing the challenges of childhood asthma: what changes are necessary? *J Allergy Clin Immunol* 2005;**115**:685—8.
24. **Franklin PJ,** Turner SW, Le Souef PN, *et al*. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003;**58**:1048—52.
25. **Pijnenburg M,** Hofhuis W, Hop W, *et al*. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2004;**60**:215—18.
26. **Gibson PG.** Using fractional exhaled nitric oxide to guide asthma therapy: design and methodlogical issues for ASthma ALgorithm studies. *Clin Exp Allergy* 2009;**39**:478—90.
27. **Leuppi JD,** Salome CM, Jenkins CR, *et al*. Markers of airway inflammation and airway hyperresponsiveness in patients with well-controlled asthma. *Eur Respir J* 2001;**18**:444—50.
28. **Lim S,** Jatakanon A, John M, *et al*. Effect of inhaled budesonide on lung function and airway inflammation. Assessment by various inflammatory markers in mild asthma. *Am J Respir Crit Care Med* 1999;**159**:22—30.
29. **American Thoracic Society.** ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;**171**:912—30.