Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

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[Intervention Review]

Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

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ABSTRACT

Background

Asthma severity and control can be measured both subjectively and objectively. Sputum analysis for evaluation of percentage of sputum eosinophilia directly measures airway inflammation, and is one method of objectively monitoring asthma. Using sputum analysis to adjust or tailor asthma medications is potentially superior to traditional methods based on symptoms and spirometry.

Objectives

To evaluate the efficacy of tailoring asthma interventions based on sputum analysis in comparison to traditional methods (usually symptom-based with or without spirometry/peak flow) for asthma-related outcomes in children and adults.

Search methods

We searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, trials' registries, and reference lists of articles. The last search was conducted in February 2017.

Selection criteria

All randomised controlled comparisons of adjustment of asthma therapy based on sputum eosinophils compared to traditional methods (primarily clinical symptoms and spirometry/peak flow).

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. In this update, two reviewers selected relevant studies, independently assessed trial quality and extracted the data. We contacted authors for further information when relevant. We analysed data as 'treatment received' and performed sensitivity analyses.

Main results

Three new studies were added in this update, resulting in a total of six included studies (five in adults and one involving children/adolescents). These six studies were clinically and methodologically heterogeneous (use of medications, cut-off for percentage of sputum eosinophils and definition of asthma exacerbation). Of 374 participants randomised, 333 completed the trials. In the meta-analysis,

there was a significant reduction in the occurrence of any exacerbations when treatment was based on sputum eosinophil counts, compared to that based on clinical symptoms with or without lung function; pooled odds ratio (OR) was 0.57 (95% confidence interval (CI) 0.38 to 0.86). The risk of having one or more exacerbations over 16 months was 82% in the control arm and 62% (95% CI 49% to 74%) in the sputum strategy arm, resulting in a number needed to treat to benefit (NNTB) of 6 (95% CI 4 to 13).

There were also differences between the groups in the rate of exacerbation (any exacerbation per year) and severity of exacerbations defined by requirement for use of oral corticosteroids and hospitalisations: the risk of one or more hospitalisations over 16 months was 24% in controls compared to 8% (95% CI 3% to 21%) in the sputum arm. Data for clinical symptoms, quality of life and spirometry were not significantly different between groups. The mean dose of inhaled corticosteroids per day was also similar in both groups. However sputum induction was not always possible. The included studies did not record any adverse events.

One study was not blinded and thus was considered to have a high risk of bias. However, when this study was removed in a sensitivity analysis, the difference between the groups for the primary outcome (exacerbations) remained statistically significant between groups. The GRADE quality of the evidence ranged from moderate (for the outcomes 'Occurrence of any exacerbation' and 'Hospitalisation') to low (for the outcome 'Mean dose of inhaled corticosteroids per person per day') due to the inconsistency in defining exacerbations and the small number of hospital admissions.

Authors' conclusions

In this updated review, tailoring asthma interventions based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations in adults with asthma. Adults with frequent exacerbations and severe asthma may derive the greatest benefit from this additional monitoring test, although we were unable to confirm this through subgroup analysis. There is insufficient data available to assess tailoring asthma medications based on sputum eosinophilia in children.

Further robust RCTs need to be undertaken and these should include participants with different underlying asthma severities and endotypes.

PLAIN LANGUAGE SUMMARY

Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Background

Drug treatment for asthma is usually guided by various measures, such as asthma symptoms and lung function tests. In this review we wanted to find out if it was more beneficial to guide treatment according to sputum eosinophils. Eosinophils are a type of white blood cell that is increased in some forms of inflammation. The number of eosinophils in the sputum can tell us about levels of one type of inflammation in the lungs. We looked for evidence about whether measuring eosinophils in the sputum to guide asthma treatment improves asthma outcomes in children and adults.

Study characteristics

We included studies that compared adjustment of asthma medicines by counting sputum eosinophils versus usual care. To be included, the studies has to decide who would be in which group by chance. The participants all had asthma, diagnosed according to asthma guidelines.

The most recent search for studies was undertaken in February 2017.

This updated review includes six studies involving 382 people with asthma (55 children/adolescents, 327 adults). The studies varied in several ways including study duration and follow-up, sputum eosinophil counts used for adjusting medication and the way the asthma attacks were defined. Studies were between 6 and 24 months long. The age spread of participants in the studies was 12 to 48 years.

Key results

We found that guiding asthma medicines based on sputum eosinophil counts (compared to a control group) reduced the number and severity of asthma attacks in adults. In the control group where treatment was guided according to clinical symptoms, 82 participants out of 100 had at least one attack. This was reduced to 62 out of 100 in participants who had their medications guided by sputum eosinophil count. We are not certain about the effect on other measures, such as quality of life or dose of inhaled steroids needed. There is not enough data in children to assess whether using sputum eosinophil is useful.

Quality of the evidence

We are moderately confident in the evidence for any asthma attack and hospital admissions. We were concerned about the different ways the studies defined asthma attacks and the small number of hospital admissions overall, which makes it harder to detect a difference.

We are less confident in the evidence about the dose of inhaled steroids. This is because the studies used very different doses. Also, we cannot tell if the eosinophil-guided treatment reduced or increased the steroid dose overall.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Tailored interventions based on sputum eosinophils compared to tailored interventions based on clinical symptoms for asthma in adults and children

Patient or population: adults and children with asthma
Settings: hospital outpatients
Intervention: based on sputum eosinophils count
Comparison: based on clinical symptoms

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk at one year	Corresponding risk				
	Tailored interventions based on clinical symptoms	Tailored interventions based on sputum eosinophils				
Number of participants who had one or more exacerbations over the study period Follow-up: 12 to 24 months	**82 per 100**	**62 per 100** (49 to 74)	**OR 0.36** (0.21 to 0.62)	228 (3 studies)	⊕⊕⊕◯ **moderate**[1]	see Figure 1
Hospitalisations Follow-up: 12 to 24 months	**24 per 100**	**8 per 100** (3 to 21)	**OR 0.28** (0.09 to 0.84)	269 (4 studies)	⊕⊕⊕◯ **moderate**[2]	see Figure 2
Mean dose of inhaled corticosteroids per person per day (BUD equivalent mcg/day) Follow-up: 12 to 24 months		The mean dose of inhaled corticosteroids per person per day in the intervention groups was **13 mcg/day higher** (128 lower to 153 higher)		316 (4 studies)	⊕⊕◯◯ **low**[3]	

Mean daily use of oral corticosteroids per person per day Follow-up: 12 months	See comment	See comment	Not estimable	68 (1 study)	Not estimable
Yearly cost per person (USD) Follow-up: 12 months	See comment	See comment	Not estimable	68 (1 study)	Not estimable

*The basis for the **assumed risk** is the mean of the two studies with a duration of one year. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

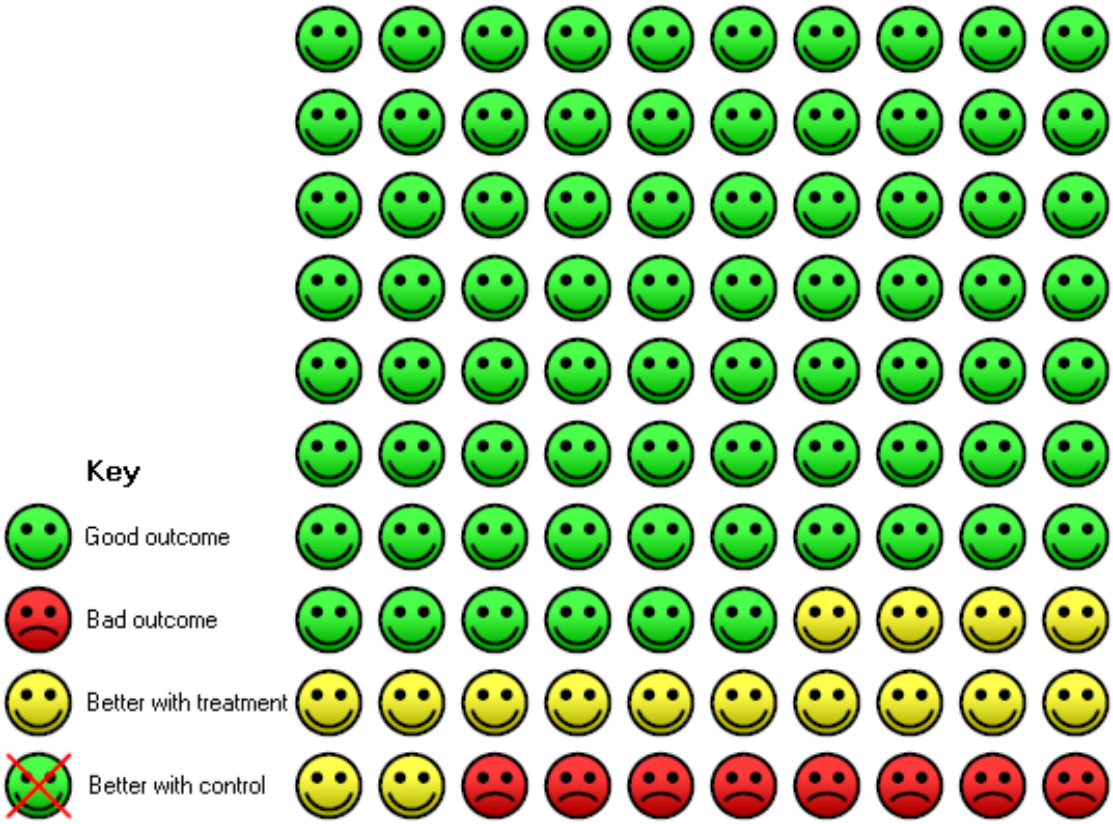
[1] One paper (Chlumsky 2006) was open labelled , but results were similar without this study. Our confidence in these results was downgraded by one point because of inconsistency in defining exacerbations

[2] One paper (Chlumsky 2006) was open labelled, but did not contribute to this outcome. Our confidence in these results was downgraded by one point because of the small number of hospitalisations

[3]The dose of inhaled steroids varied considerably within and between studies and results are compatible with both important reduction or decrease in dose of inhaled corticosteroids using sputum eosinophils.

Figure 1. In the control group 82 people out of 100 had people with one or more exacerbations over 16 months, compared to 62 (95% CI 49 to 74) out of 100 for the active treatment group.

Figure 2. In the control group 24 people out of 100 had people with one or more hospitalisations over 16 months, compared to 8 (95% CI 3 to 21) out of 100 for the active treatment group.



BACKGROUND

Description of the condition

Asthma guidelines aim to guide health practitioners in adjusting treatment for patients so as to minimise symptoms or improve asthma control, optimise lung function, and prevent acute exacerbations (BTS/SIGN 2016; GINA 2017; National Asthma Council 2014). Exacerbations are important as they cause anxiety to patients and their families and are costly to healthcare systems (Weiss 2001). Preventing exacerbations is thus an important component for maintaining ideal asthma control. The second component in asthma management is monitoring of asthma control (by subjective and objective measures) (BTS/SIGN 2016; GINA 2017; National Asthma Council 2014). Subjective measures usually involve a series of questions used for clinical assessment, diary cards and quality-of-life questionnaires. Traditional objective measures include peak flow monitoring, spirometry and degree of airway hyper-responsiveness (AHR) (Zacharasiewicz 2005). Other methods such as markers of airway inflammation (e.g. sputum eosinophils, exhaled nitric oxide levels and breath condensate markers) have been advocated for asthma monitoring. These may be more sensitive markers than subjective measures, as they directly measure airway inflammation, in comparison to traditional objective measures (Zacharasiewicz 2005).

Types of airway inflammation in people with asthma

Airway inflammation in asthma may be eosinophilic, neutrophilic or a mixture of both (Douwes 2002). Asthma management is arguably best tailored in accordance with the type of airway inflammation, as corticosteroids are more beneficial in eosinophilic inflammation (Wardlaw 2000), and inhaled corticosteroids (ICS) reduce exacerbations and improve symptoms and asthma control

(Wardlaw 2000).

Description of the intervention

There are several ways to quantify airway eosinophilic inflammation, such as determining the percentage of eosinophils in the sputum or in the bronchoalveolar lavage. Recurrent use of the latter is not feasible in clinical medicine as it is an invasive procedure (e.g. usually requiring general anaesthesia in children). Induced sputum is not invasive, it is much simpler to obtain sputum and it provides similar (but not identical) data to that of bronchoalveolar lavage. Induced sputum can be obtained by several methods including the use of nebulised hypertonic saline or mannitol (as part of a bronchial provocation testing) and chest physiotherapy techniques such as using airway clearance apparatus like the flute. The sputum obtained is then prepared and the total cell and differential cellularity determined, thereby providing the relative percentages of eosinophils, neutrophils and macrophages. Analysis of induced sputum is a reproducible method in determining airway inflammation in asthma in adults (Bacci 2002).

How the intervention might work

In many people with asthma, the percentage of eosinophils in induced sputum is higher than that in non-asthmatic patients (Ohnishi 1998). Neutrophilic airway inflammation has however also been described in people with asthma (Green 2002b). Thus assessing airway inflammation by quantitative measurements instead of subjective data potentially allows better tailoring of personal asthma interventions, which in turn may improve asthma control or reduce exacerbations, or both.

Why it is important to do this review

While tailoring asthma medications based on sputum eosinophilia may be helpful, undertaking induced sputum and sputum analysis is labour intensive and not widely available in non-research laboratories. Also, hypertonic saline or mannitol, used to induce sputum, may also temporarily increase asthma symptoms. Thus, a systematic review evaluating the efficacy of tailoring asthma interventions based on sputum analysis (sputum strategy, SS) in comparison with the traditional reliance primarily on clinical symptoms (CS) of asthma will be useful to help guide both physicians and patients as to whether or not undertaking this additional intervention is warranted in improving their asthma outcomes.

OBJECTIVES

To evaluate the efficacy of tailoring asthma interventions based on sputum analysis in comparison to traditional methods (usually symptom-based with or without spirometry/peak flow) for asthma-related outcomes in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing adjustment of asthma medications based on sputum analysis in comparison to traditional methods (primarily clinical symptoms with or without spirometry/peak flow).

Types of participants

Children and adults with a diagnosis of asthma in accordance to guideline-defined criteria. Exclusion criteria: eosinophilic bronchitis; asthma related to an underlying lung disease such as bronchiectasis and chronic obstructive pulmonary disease (COPD).

Types of interventions

We included studies which compared adjustment of asthma therapy based on sputum eosinophils to adjusting therapy based on clinical symptoms with or without spirometry/peak flow. Trials that included the use of other interventions were included if all participants had equal access to such interventions.

Types of outcome measures

Primary outcomes

Proportion of participants who had asthma exacerbations during follow-up.

Secondary outcomes

1. Objective measurements of asthma control (FEV_1, peak flow or airway hyper-responsiveness).
2. FeNO level.
3. Subjective symptoms as reported in Asthma Control Test or asthma-related quality of life questionnaire score.
4. Inhaled corticosteroid doses.
5. Cost analysis.

We determined the proportions of participants who failed to improve on treatment and the mean clinical improvement using the following hierarchy of assessment measures (i.e. where two or more assessment measures are reported in the same study, we used the outcome measure that is listed first in the hierarchy).

1. Hospitalisation, acute presentations to an emergency facility for asthma, frequency of exacerbations and rescue courses of oral corticosteroids.
2. Symptomatic (quality of life, Likert scale, asthma diary, visual analogue scale) - assessed by the patient (adult or child).
3. Symptomatic (quality of life, Likert scale, asthma diary, visual analogue scale) - assessed by the parents/carers.
4. Symptomatic (Likert scale, visual analogue scale) - assessed by clinicians.
5. Indices of spirometry, peak flow, airway hyperresponsiveness.
6. Beta-agonist used.

Search methods for identification of studies

Electronic searches

This is an update of a previous Cochrane Review (Petsky 2007). For this update (from November 2008 to current search), we identified trials from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, through the Cochrane Register of Studies Online (crso.cochrane.org).
2. Weekly searches of MEDLINE Ovid SP 1946 to date.
3. Weekly searches of Embase Ovid SP 1974 to date.
4. Monthly searches of PsycINFO Ovid SP.
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature).
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine).
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/), using the search strategy in Appendix 3. We searched all databases from their inception to 15 February 2017, and we imposed no restriction on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' web sites for trial information.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) on 10 March 2017.

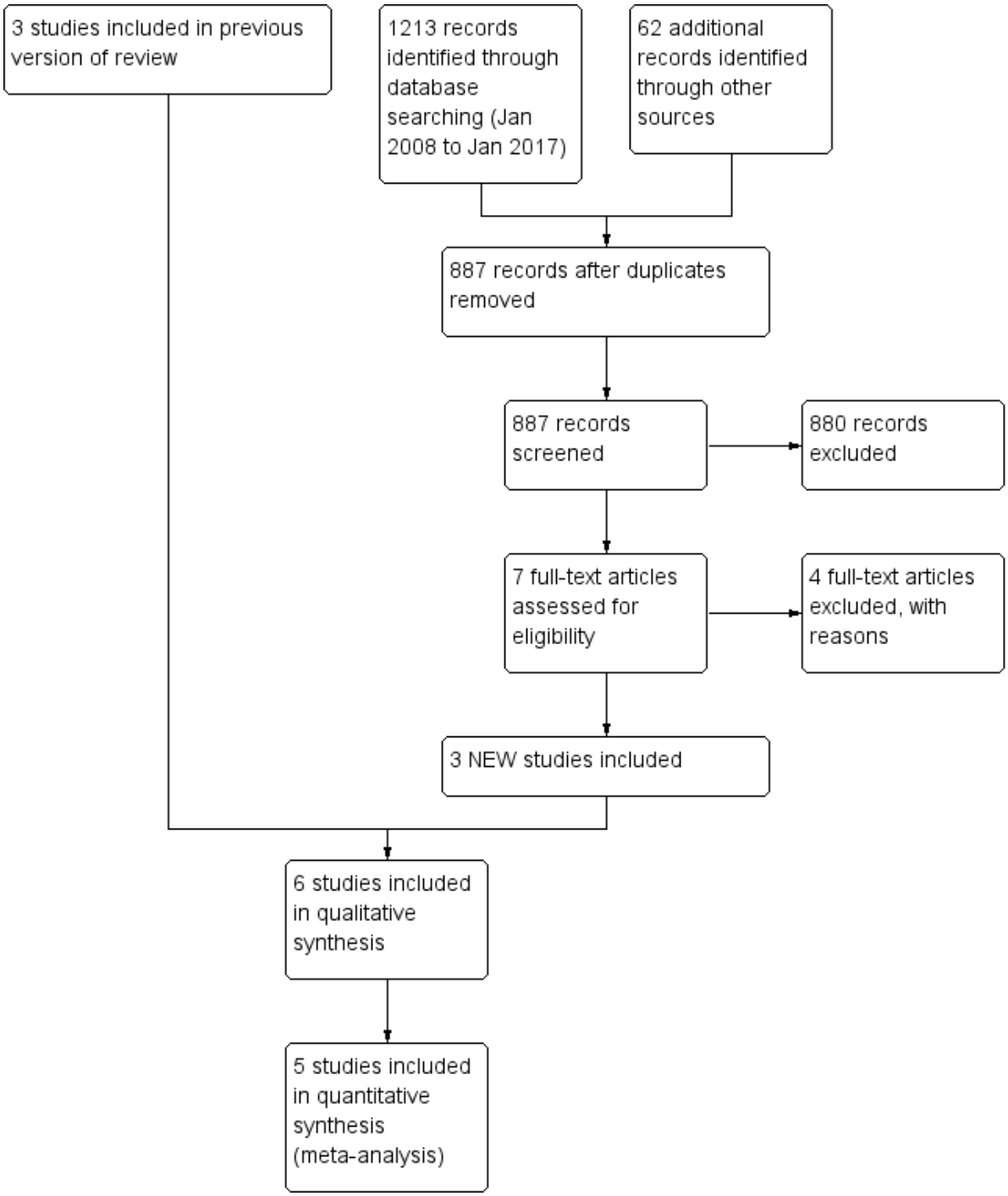
Data collection and analysis

Selection of studies

The original selection of studies were reported in the previous review (Petsky 2007).

For this update, two review authors (HP, AC) independently screened titles, abstracts and descriptors retrieved from the literature searches, to identify potential relevant trials for inclusion. We retrieved potential full text study reports/publications and two review authors (HP, AC) independently screened the full text and identified studies for inclusion, and recorded reasons for exclusion for ineligible studies. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete the PRISMA flow diagram (Figure 3) and Characteristics of excluded studies table.

Figure 3. Study flow diagram for 2008-2017 literature searches.



Data extraction and management

We reviewed trials that satisfied the inclusion criteria and recorded the following information: study setting, year of study, source of funding, patient recruitment details (including number of eligible participants), inclusion and exclusion criteria, other symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of intervention, duration of therapy, co-interventions, numbers of participants not followed up, reasons for withdrawals from study protocol (clinical, side-effects, refusal and other), details on side-effects of therapy, and whether intention-to-treat analyses were possible. We extracted data on the outcomes described previously and we double-entered data from included studies into Review Manager 5 (RevMan 5) for meta-analysis (Review Manager 2014).
Initial attempts to contact the corresponding authors in the original review were not successful (Petsky 2007). Dr Fleming provided further information and clarified some queries for Fleming 2012.

Assessment of risk of bias in included studies

We subjected studies included in the review to quality assessment and entered the results in 'Risk of bias' tables. We assessed seven components, as follows.

- Random sequence generation.
- Allocation concealment.
- Blinding of the participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We recorded each potential source of bias as high, low or unclear and provided a quote with a justification for our judgement in the 'Risk of bias' table. We then summarised the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.
When considering treatment effects, we considered the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR) and continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% confidence intervals (CI). We then entered data presented as a scale with a consistent direction of effect.
We undertook meta-analyses where it was meaningful (i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense).
We narratively described skewed data as medians and interquartile ranges.
Where multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same reported result, we halved the control group to avoid double counting.

Unit of analysis issues

For dichotomous data, we reported the proportion of participants contributing to each outcome in comparison to the total number randomised. For rate ratios of common events whereby one participant may have more than one event, we used generic inverse variance (GIV) analysis. The rate ratios were taken from the published papers and the standard errors calculated from CIs or P values published in the papers. We had planned for cross-over studies, to calculate the mean treatment differences from raw data, and variances extracted or imputed and entered as fixed-effect (GIV) outcome, to provide summary weighted differences and 95% CIs.

Dealing with missing data

We contacted investigators to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We described any heterogeneity between the study results and tested it to see if it reached statistical significance using a Chi^2 test. We planned to include the 95% CI estimated using a random-effects model whenever there were concerns about statistical heterogeneity. Heterogeneity was considered significant when the P value was less than 0.10 (Higgins 2011). We then used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we reported it and explored possible cause of prespecified subgroup analysis.

Assessment of reporting biases

We were unable to pool more than 10 trials, so did not create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We included the results from studies that met the inclusion criteria and reported the outcomes of interest in the subsequent meta-analyses. The summary weighted odds ratio and 95% confidence interval (fixed-effect model) were calculated (Review Manager 2014). For rate ratios of common events whereby one participant 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 confidence intervals or P values published in the papers. It was planned that for cross-over studies, mean treatment differences would be calculated from raw data, extracted or imputed and entered as fixed-effect GIV outcome, to provide summary weighted differences and 95% confidence intervals. For cross-over trials, it was planned that only data from the first arm were included in meta-analysis if data were combined with parallel studies (Elbourne 2002). Numbers needed to treat for an additional beneficial outcome (NNTB) were calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2008). The outcome indices were assumed to be normally distributed continuous variables so the mean difference in outcomes could be estimated (weighted mean difference). If studies reported outcomes using different measurement scales, we estimated the standardised mean difference.

Subgroup analysis and investigation of heterogeneity

We carried out the planned a priori sub-group analysis for adults versus children.

Sensitivity analysis

We planned sensitivity analyses to assess the impact of the potentially important factors on the overall outcomes.

1. Variation in the inclusion criteria.
2. Differences in the medications used in the intervention and comparison groups.
3. Analysis using random-effects model.
4. Analysis by 'treatment received'.
5. Analysis by 'intention-to-treat'.
6. Analysis by study design-parallel and crossover studies.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

See Figure 3 for study flow diagram.

For this update, the searches identified 1213 potentially relevant titles from CAGR. We identified an additional 62 titles through searches of ClinicalTrials.gov and the WHO trials portal (who.int/ictrp/en/). After assessing the abstracts, seven papers were obtained for consideration to be included into the updated review. Four papers were not relevant as treatment was not based on sputum eosinophils or non-randomised. From the searches conducted in 2014 an additional two papers (Chakir 2010; D'Silva 2008) were considered eligible but were the same participants from an already included study (Jayaram 2006). Please see our previous review for results of searches (Petsky 2007).

Included studies

This updated review now includes six studies (see Characteristics of included studies): three were from our previous review (Petsky 2007); and three are new to this review (Figure 3). The six studies involved 374 randomised participants with 333 completing the trials (Cao 2007; Chlumsky 2006; Fleming 2012; Green 2002a; Jayaram 2006; Malerba 2015).

Five papers were published in English and one study in Chinese (Cao 2007), which was translated by two independent translators using a standardised extraction form.

Study design

All six studies were parallel-group studies. One was a multi-centre study (Jayaram 2006); and the other five were uni-centre studies (Cao 2007; Chlumsky 2006; Fleming 2012; Green 2002a; Malerba 2015).

Three studies were double blind (Fleming 2012; Green 2002a; Jayaram 2006); two were single blind (Cao 2007; Malerba 2015); and one had no blinding (Chlumsky 2006).

All the included studies differed in a variety of ways including the control arm, intervention arm (i.e. cut-off used for sputum eosinophil percentage used to adjust medications), definition of exacerbations and duration of study. These differences have been outlined in Table 1.

Malerba 2015 partly fulfilled the inclusion criteria but their data were not included in the meta-analyses as their intervention strategy involved adjusting the medication based on both FeNO levels and sputum eosinophil counts.

Participants

The six studies had different inclusion criteria for the participants. All studies included participants with asthma.

Five studies involved only adult patients (Cao 2007; Chlumsky 2006; Green 2002a; Jayaram 2006; Malerba 2015). There was one study that included children (Fleming 2012).

Sputum eosinophil strategy (SS)

The intervention arm in the studies, although primarily based on sputum eosinophil percentage, also differed slightly. In two studies, anti-inflammatory treatment was based on maintaining sputum eosinophil count below 3% with a minimum dose of anti-inflammatory treatment (Cao 2007; Green 2002a). In Jayaram and colleagues' study, medications were adjusted to keep sputum eosinophils to 2% or less using inhaled corticosteroids (Jayaram 2006). In Chlumsky and colleagues' study, medications were based on maintaining the sputum eosinophil count below 8% (Chlumsky 2006). The paediatric paper adjusted treatment to keep sputum eosinophils to less than 2.5% (Fleming 2012).
The intervention arm in Malerba and colleagues' study was based on maintaining FeNO levels at less than 20 ppb, in addition to keeping sputum eosinophil count below 3% (Malerba 2015).
The intervention strategies used in the various trials are further described in Table 1.

Clinical symptom strategy (CS)

Four of the six studies utilised existing asthma guidelines to adjust treatment in the control group (Cao 2007; Chlumsky 2006; Green 2002a; Jayaram 2006). One study used participant-reported symptoms (Malerba 2015). The sole paediatric study used number of major exacerbations (defined by oral corticosteroid use) and short-acting beta^2 -agonists (SABA) use in the preceding three months (Fleming 2012).
The control group strategies are described in Table 1.

Outcomes

All six studies used asthma exacerbations as their primary outcome (Cao 2007; Chlumsky 2006; Fleming 2012; Green 2002a; Jayaram 2006; Malerba 2015). However the definitions of exacerbation were different among the studies (Table 1). In addition to exacerbations, two studies included reported symptoms as the primary outcome (Fleming 2012; Malerba 2015).
The secondary outcomes also varied among the studies. Five studies used ICS doses (Cao 2007; Fleming 2012; Green 2002a; Jayaram 2006; Malerba 2015); four studies included spirometry (Cao 2007; Chlumsky 2006; Green 2002a; Malerba 2015); two studies included symptom scores (Cao 2007; Green 2002a); and two included FeNO levels (Green 2002a; Malerba 2015).
The study characteristics are described in the Characteristics of included studies table.

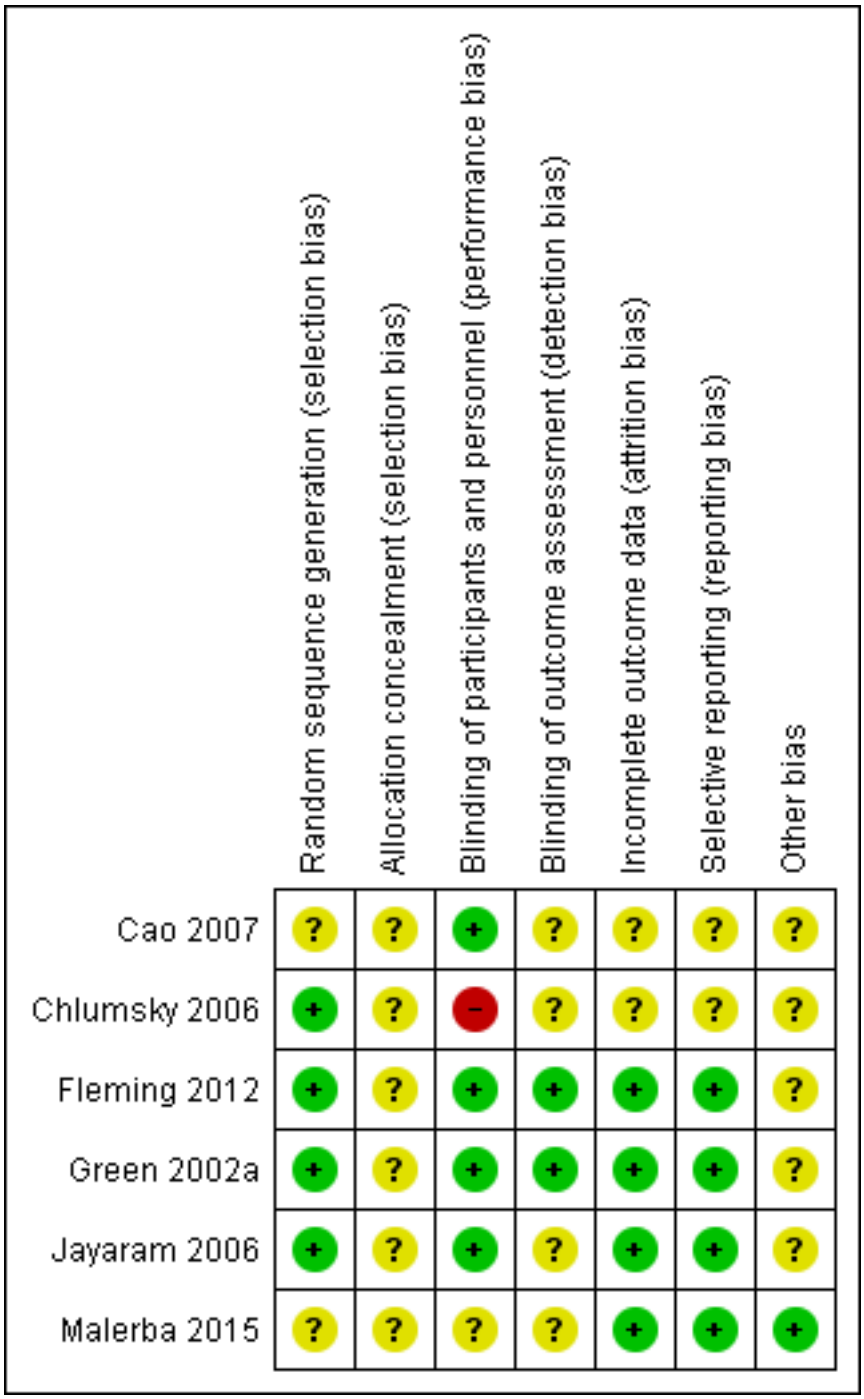
Excluded studies

We recorded the reasons for excluding 23 studies in the Characteristics of excluded studies table. The most common reason for exclusions were: treatment not adjusted according to sputum eosinophil counts (18 studies); and not an RCT (five studies).
The search in November 2008 revealed another abstract that can be included (Pinot 2008); the author was contacted for further information but this abstract was never written up in full publication.
Adverse events were not reported in any studies. We requested further information from the authors to allow data to be entered into RevMan 5 for meta-analysis. Fleming 2012 provided some raw data.

Risk of bias in included studies

The full details of risk of bias judgements are described under the 'Risk of Bias' section in the Characteristics of included studies table and summarised in Figure 4. Overall, the methodological quality of the included studies was good.

Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Three studies were double blinded (Fleming 2012; Green 2002a; Jayaram 2006); whereas one was open labelled (Chlumsky 2006); and two single blinded (Cao 2007; Malerba 2015). Allocation concealment was clearly described in one study (Green 2002a), but unclear in the other five (Cao 2007; Chlumsky 2006; Fleming 2012; Jayaram 2006; Malerba 2015). All six studies reported on the progress of all randomised participants (Cao 2007; Chlumsky 2006; Fleming 2012; Green 2002a; Jayaram 2006; Malerba 2015).

Allocation

Four studies described generation of randomisation sequence (Chlumsky 2006; Fleming 2012; Green 2002a; Jayaram 2006); it was unclear in two single-blinded studies (Cao 2007; Malerba 2015). The method of allocation concealment was adequate in one study (Green 2002a), and unclear in five studies (Cao 2007; Chlumsky 2006; Fleming 2012; Jayaram 2006; Malerba 2015).

Blinding

Risk associated with participant blinding was low when the blinding of the assessors was reported based on information provided by the authors of the studies. These included comments from the studies such as "management decisions were made by independent physician" and "decisions made by an investigator blind to identity and randomisation group of the subject".

Risk of detection bias due to inadequate blinding of outcome assessors was high in one study (Chlumsky 2006); and unclear in two studies (Cao 2007; Malerba 2015), as there was not enough information in the published article. Three double-blinded studies were assessed at low risk of bias (Fleming 2012; Green 2002a; Jayaram 2006).

Incomplete outcome data

Four studies were at low risk of attrition bias (Fleming 2012; Green 2002a; Jayaram 2006; Malerba 2015). Two studies did not report on dropouts and were therefore judged at unclear risk of attrition bias (Cao 2007; Chlumsky 2006).

Selective reporting

Reporting bias was low in four studies with all outcomes being reported (Fleming 2012; Green 2002a; Jayaram 2006; Malerba 2015). Two studies were at unclear risk of reporting bias as there was inadequate information in the published article (Cao 2007; Chlumsky 2006).

Other potential sources of bias

Another source of bias was the success of obtaining sputum at each visit. Three studies did not report the success of sputum induction at each time point (Cao 2007; Chlumsky 2006; Malerba 2015). Three studies reported their success in sputum induction: Fleming 2012 reported 85% success in sputum induction; Green 2002a reported 87%; and Jayaram 2006 reported 81% successful sputum induction.

Effects of interventions

See: **Summary of findings for the main comparison** Tailored interventions based on sputum eosinophils compared to tailored interventions based on clinical symptoms for asthma in adults and children

See: Summary of findings for the main comparison for the main comparisons.

Asthma exacerbations

All studies reported asthma exacerbations as the primary outcome (Cao 2007; Chlumsky 2006; Fleming 2012; Green 2002a; Jayaram 2006; Malerba 2015). The five adult studies described a significant reduction in asthma exacerbations in the arm that utilised treatment based on sputum eosinophils (SS) when compared to the clinical symptom (CS) arm (control arm whereby treatment was based primarily on clinical symptoms ± lung function) (Cao 2007; Chlumsky 2006; Green 2002a; Jayaram 2006; Malerba 2015). The adult studies reported a significant difference between groups in exacerbation data, with the SS group experiencing fewer exacerbations than the CS group. The paediatric study did not find a significant difference in the number of exacerbation between the strategies for the study duration (Fleming 2012). However they did see a difference with smaller number of exacerbations being experienced in the sputum strategy group within 28 days of a study visit. Some but not all data that relate to exacerbations could be combined for meta-analysis. One study utilised FeNO levels in addition to sputum eosinophil counts to adjust medications in the intervention arm, therefore data from this study were not included in the meta-analyses (Malerba 2015). Also, the definition of exacerbation of the studies differed as described in Table 1

Any exacerbation (Outcome 1)

(a) Occurrence of any exacerbations (Analysis 1.1)

Combining data from these four studies (3 adults and 1 children), the use of the symptom eosinophil strategy (SS), compared to the clinical symptom strategy (CS), significantly reduced the occurrence of any exacerbations: rate ratio was 0.57 (95% CI 0.38 to 0.86); 269 participants in four studies; P = 0.007. As there was

heterogeneity between the studies (I^2 = 51%), we used a random-effects analysis.

In subgroup analysis, we separated children from adult studies. In the adult-based studies (n = 3), use of the sputum strategy (compared to controls) significantly reduced the rate ratio of occurrence of exacerbations: rate ratio was 0.45 (95% CI 0.24 to 0.86), 215 participants in three studies; P = 0.02. The heterogeneity remained high with I^2 = 55%. In children there was only one study and there was no significant difference between the groups but the results numerically favoured the sputum strategy group: rate ratio was 0.75 (95% CI 0.54 to 1.04); 54 participants; P = 0.09. The test for a difference between adults and children showed no statistical significance (Chi^2 = 1.93, df = 1 (P = 0.17), I^2 = 48.1%).

(b) Number of participants who had one or more exacerbations (as defined by authors) during the study period (Analysis 1.2)

Meta-analysis from data combined from four studies showed that the number of participants experiencing any exacerbation was significantly less (P < 0.001) in the SS group than in the CS group. Pooled OR estimate effect was 0.36 (95% CI 0.21 to 0.62); 269 participants. Using the combined control event rate from the one-year studies of 82%, the NNTB for 16 months was 6 (95% CI 4 to 13); see Figure 1.

When considering the adult studies only, the SS group had significantly fewer participants experiencing one or more exacerbations compared to the CS group: OR 0.36 (95% CI 0.20 to 0.64); 215 participants in 3 studies; P < 0.001. However, the difference between the two groups in the paediatric study was not statistically significant: OR 0.39 (95% CI 0.09 to 1.71); 54 participants; P = 0.21. The test for a difference between adults and children showed no statistical significance (Chi^2 = 0.01, df = 1 (P = 0.92), I^2 = 0%).

(c) Time to first exacerbation

Four studies reported that the SS group had significantly longer time to first exacerbation compared to the CS group (Chlumsky 2006; Fleming 2012; Green 2002a; Jayaram 2006). However, the data from the studies could not be combined.

Chlumsky 2006 reported a significant difference (Chi^2 = 8.8, P = 0.003). Green 2002a reported 12 exacerbations in the BTS management group in the first month, versus one in the sputum management group.

Exacerbations classified by severity of exacerbation (Outcome 2)

(a) Number of participants requiring hospitalisation

See Analysis 1.3.

None of the participants from either arm in Jayaram 2006 or Chlumsky 2006 were hospitalised, whereas a total of seven in Green 2002a and 13 in Fleming 2012 were hospitalised. Combined data showed a difference between the groups (P = 0.02) favouring the SS group: the OR was 0.28 (95% CI 0.09 to 0.84); 269 participants in four studies. The risk of one or more hospitalisations over 16 months fell from a risk of 24% on control to 8% (95% CI 3% to 21%), giving a 16-month NNTB of 7 (95% CI 5 to 33); see Figure 2.

When considering only the adults who were hospitalised for subgroup analysis, the difference was no longer statistically significant (P = 0.08); OR 0.14 (95% CI 0.02 to 1.25); 215 participants. Likewise statistical significance was lost when considering only children, (P = 0.16): OR 0.38 (95% CI 0.10 to 1.45). The reduction in statistical power when considering subgroups of adults and children is the most likely reason for the loss of statistical significance in these subgroup findings.

(b) Number of exacerbations requiring rescue oral corticosteroids (Analysis 1.4)

The rate of exacerbations requiring treatment with rescue oral corticosteroids was significantly lower in the SS group compared to the CS group in one study (Jayaram 2006), rate ratio of 0.33 (95% CI 0.16 to 0.70); 96 participants in one study, P = 0.004.

(c) Number of mild exacerbations (Analysis 1.5)

Data on mild exacerbations were available in two studies (Fleming 2012; Jayaram 2006). As the definition of severe exacerbations (other than that defined in Analyses 1.3 and 1.4) differed between the studies it was difficult to combine this data. Combining the two studies which defined minor exacerbations similarly by loss of asthma control requiring more than four puffs extra of bronchodilators, the number of exacerbations between the groups reached borderline significance (P = 0.05) favouring SS, rate ratio of 0.82 (95% CI 0.67 to 1.00); 150 participants.

Eosinophilic exacerbations

See Analysis 1.6.

Jayaram and colleagues reported types of asthma exacerbations in each group (Jayaram 2006). Sputum could only be obtained in 39 of the 47 exacerbations in the SS group and 63 of the 79 total exacerbations in the CS group. Those exacerbations where sputum could be obtained were classified as eosinophilic or non-eosinophilic and this indicated that the overall reduction in exacerbation rate was largely due to a reduction in eosinophilic exacerbations in this study.

Exacerbations subgrouped by asthma severity

(a) Any exacerbation (risk ratio (RR)) by severity of asthma (Analysis 1.7)

Five studies did not subgroup participants by asthma severity (Cao 2007; Chlumsky 2006; Fleming 2012; Green 2002a; Malerba 2015). Jayaram and colleagues analysed data based on daily requirement for ICS and long-acting beta^2 -agonists (LABA). Asthma severity was defined based on minimum daily maintenance fluticasone (mild asthma = requiring < 250 mcg/day; moderate to severe asthma = requiring 250 mcg/day) (Jayaram 2006). Those with mild asthma (< 250 mcg/day fluticasone equivalent) showed no significant difference: RR 1.34 (95% CI 0.52 to 3.46). Those with moderate to severe asthma (= 250 mcg/day fluticasone equivalent) also showed no significant difference between groups in the RR of exacerbation, although the direction of the outcome favoured the SS group (RR 0.63, 95% CI 0.38 to 1.04). The difference between these subgroup effects was not significant (test for subgroup differences: Chi^2 1.93, df = 1, P = 0.19).

(b) Any exacerbations (RR), by use of long-acting beta^2 -agonists (LABA) (Analysis 1.8)

Green 2002a reported equal numbers of participants in both groups being treated with LABA (N = 12) but outcomes based on those on LABA were not available . Data from Jayaram 2006 did not show a significant difference between the effect on exacerbations in those taking LABA (RR 0.53, 95% CI 0.25 to 1.14) or those not on LABA (RR 1.05, 95% CI 0.62 to 1.78), (test for subgroup differences: Chi^2 2.07, df = 1, P = 0.15).

Secondary outcomes

Green 2002a reported other outcomes: exhaled nitric oxide was 48% lower in the SS group in comparison to the CS group at the end of study. The improvement in methacholine PC20 was significantly better in the SS group compared to the CS group at 6 months (doubling doses 1.0 versus −0.7, P = 0.03) and 12 months (0.2 versus −1.3, P = 0.015). However, the visual analogue symptom scores, total asthma quality of life scores, peak expiratory flow amplitude (% mean), FEV^1 after bronchodilator use and the use of rescue beta^2 -agonists did not differ significantly between the two groups in Green 2002a. Jayaram and colleagues did not report these outcomes; although asthma quality of life (QoL) assessments were undertaken, these results were not published (Jayaram 2006). Chlumsky et al's study also reported no significant difference between groups for FEV^1 change and they did not report on symptoms or QOL (Chlumsky 2006). Fleming and colleagues reported that the FeNO levels did not significantly change over the study period (Fleming 2012). Both the SS and control groups had significant improvement in FEV^1 scores when comparing z-score from end to beginning of the study. The mean (SE) difference was 0.51 (0.37) for the symptom group and 0.49 (0.34) for the sputum eosinophil group. Neither group had a significant change in their bronchodilator reversibility over the duration of the study (Fleming 2012).

Mean daily dose of corticosteroid use

(a) Inhaled corticosteroid (ICS) (Analysis 1.9)

All six studies reported no significant differences in ICS use between groups. The SD for the groups were not available in Jayaram 2006 and was imputed based on the data from Green 2002a. Forest plots showed no significant difference between the groups and a wide confidence interval. Pooled MD 12.56 mcg (95% CI −127.92 to 153.04).

(b) Oral corticosteroids (Analysis 1.10)

Only Green and colleagues reported on mean oral corticosteroids use and described no difference between the groups (mean difference of −0.40 mg, 95% CI −2.36 to 1.56) (Green 2002a). Meta-analysis was not possible.

Cost (Analysis 1.11)

Green and colleagues described estimated cost per patient per year and there was no significant difference between the groups (mean difference of −314, 95% CI −941.27 to 313.27) (Green 2002a). There were no data from other studies.

Other results

Sputum induction was not always successful: in Green's study, sputum induction was successful in 552 of 632 attempts (87%) (Green 2002a), and 102 out of a total of 126 (81%) in Jayaram and colleagues' study (Jayaram 2006). Fleming 2012, the one included paediatric paper, reported a success rate of 85% (174 occasions) with a sputum differential count success in 152 samples. Chlumsky 2006, Cao 2007 and Malerba 2015 did not report their success rate in obtaining sputum. No other adverse events were reported in the studies.

Sensitivity analyses

In the outcome of number of participants with one or more exacerbations during the study period, analyses based on 'intention to treat' (ITT) altered pooled OR only slightly from 0.49 (95% CI 0.28 to 0.87) for 'treatment received' to 0.50 (95% CI 0.28 to 0.88). The NNTB for one year changed from 6 (95% CI 4 to 13) to 7 (95% CI 4 to 35). Re-analysis of the data based on the

less conservative numbers (i.e. use of total of 102 as opposed to 96) for Jayaram and colleagues' study did not change the direction or significance of any of the outcomes (Jayaram 2006). Likewise re-analysis of data based on ITT did not alter direction or significance of effects. In the outcomes described above, significant heterogeneity was only found in subgroup comparisons and thus no sensitivity analyses were performed for this.

One study did not use blinding (Chlumsky 2006); however removing the data from this study did not alter the results of the primary outcome (exacerbations) found in the main analyses; occurrence of any exacerbation (RR 0.66, 95% CI 0.46 to 0.93; participants = 218; studies = 3), number of participants who had one of more exacerbations over the study period (OR 0.43, 95% CI 0.24 to 0.79; participants = 218; studies = 3) and exacerbations requiring hospitalisations (OR 0.28, 95% CI 0.09 to 0.84; participants = 218; studies = 3).

DISCUSSION

Summary of main results

This review consists of six RCTs involving 374 participants with 344 completing the trials. The studies varied in the sputum eosinophil levels (ranging from 2% to 8%) and algorithms used to adjust medications. The duration of the studies also differed, ranging from 6 to 24 months. We found that asthma exacerbations decreased when treatment was adjusted according to sputum eosinophil percentage. Six participants would need to have their asthma treatment adjusted by sputum eosinophil count for one participant to avoid exacerbation (95% CI 4 to 13). However, the data were robust for adult participants only as there was a single study involving children/adolescents. Also, there were no significant difference between the groups in symptoms of asthma (VAS score, QoL and beta agonist use) but this was limited by little data. All studies reported exacerbations (our review's primary outcome), but the definition varied among the studies. We were able to combine data for a maximum of four studies for the meta-analysis of the different definitions of exacerbation. The occurrence of any exacerbation was significantly lower in the group that utilised sputum eosinophil counts compared to the symptom strategy (rate ratio 0.57, 95% CI 0.38 to 0.86). Likewise, the number of participants having one or more asthma exacerbations was lower in the sputum eosinophil group (OR 0.36, 95% CI 0.21 to 0.62). The number of people with exacerbations requiring hospitalisations was significantly lower in the sputum eosinophilia strategy (OR 0.28, 95% CI 0.09 to 0.84).

There was no significant difference between groups for the mean daily dose of inhaled corticosteroids at final visit.

In the subgroup analyses, for children the reductions seen between the sputum eosinophil strategy and control strategy for occurrence of any exacerbations (RR 0.75, 95% CI 0.54 to 1.04), number of participants who had one or more episodes of asthma exacerbation (OR 0.39, 95% CI 0.09 to 1.71) or exacerbations requiring hospitalisations (OR 0.38, 95% CI 0.10 to 1.45) did not achieve statistical significance (possibly due to lack of statistical power due to small numbers).

In the sensitivity analyses, there were no changes in the primary outcomes when conducting analyses on 'intention to treat' or by removing the one study which did not have any blinding (Chlumsky 2006).

Overall completeness and applicability of evidence

This review included six studies, but the meta-analyses consisted of data from between one to five studies for the various outcomes, including our review's primary outcome. The total number of participants for the various outcomes ranged from 68 (outcomes: mean dose of oral corticosteroids per person per day and yearly cost per person) to 316 (outcome: mean daily dose of inhaled corticosteroids per person per day). Although we contacted authors of the studies, the completeness of the review was limited by availability of data.

Theoretically the use of sputum to guide asthma therapy may result in significant differences in doses of oral or ICS. This meta-analysis found that there was no significant differences in the amount of corticosteroids (inhaled or oral) used between the two groups. Also, Green 2002a reported that the annual cost was not significantly more expensive in the SS group compared to the CS group. In contrast to the favourable data in the outcome of exacerbations that support the use of sputum to guide asthma therapies, there was a lack of difference between the groups in symptoms of asthma (VAS score, QoL and beta agonist use). While exacerbations are an important outcome, arguably subjective measures of asthma control are also important.

Asthma is a heterogeneous condition, and there is increasing appreciation of non-eosinophilic asthma (Seys 2017) and overlap syndromes (with COPD) (Karampitsakos 2016). The data from this review is unlikely to be applicable to those who have non-eosinophilic asthma, overlap syndromes, or exacerbations that are non-eosinophilic asthma. Thus, although this meta-analysis that has shown that monitoring airway inflammation through eosinophils in induced sputum is useful in reducing exacerbations in adults, it is arguable that it cannot be universally advocated. However, in people with frequent exacerbations it is likely that this intervention is useful.

None of the studies used the new biologic compounds (e.g. anti-interleukin-5) that is efficacious for severe eosinophilic asthma in adults (Robinson 2017).

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

to exhaled nitric oxide) and is not always successful. Also, it can be very difficult to obtain satisfactory samples in young children. Lastly this review is limited in children as there was only one small study that included children (Fleming 2012).

Quality of the evidence

We summarised the evidence for the three main outcomes related to exacerbations and ICS dose in the 'Summary of findings' table. Overall, we judged the quality of evidence to be moderate for exacerbations (due to inconsistency of definition of an exacerbation) and hospitalisations (due to the small number of events). One study was a non-blinded trial but removing this study did not alter the results of the primary outcomes (Chlumsky 2006).
The quality of the evidence for the outcome of ICS dose per person per day at the end of the study was low. We downgraded this outcome by one for imprecision and one for lack of blinding in one study. The dose of inhaled steroids varied considerably within and between studies.

Potential biases in the review process

We are unaware of any bias in the review process. We used a comprehensive search strategy and adhered to the protocol. Two review authors (HP, AC) independently assessed the risk of bias. We contacted the corresponding authors of all the studies for raw data to include in the meta-analysis. AC and the review editor (Christopher Cates) independently checked the data extraction, 'Risk of bias' assessment, and downgrading decisions for the 'Summary of findings' table in order to minimise the risk of bias in the review process.
The inclusion of Malerba 2015 in the meta-analyses would have introduced bias, as the strategy used included FeNO in addition to sputum eosinophil counts.

Agreements and disagreements with other studies or reviews

This is an update of a previous Cochrane Review (Petsky 2007) and has been strengthened by the addition of three RCTs (Cao 2007; Fleming 2012; Malerba 2015). The findings of both Cochrane Reviews are in agreement, with fewer asthma exacerbations occurring in the group that had their asthma treatment adjusted based on sputum eosinophil percentage.
A recent literature review (Seys 2017) concluded that monitoring eosinophilic inflammation using sputum cell counts is helpful to monitor asthma severity, control and progression of disease.

AUTHORS' CONCLUSIONS

Implications for practice

The results from this review suggests that tailoring asthma interventions based on sputum eosinophils instead of primarily on clinical symptoms with or without spirometry/peak flow decreases frequency and severity of asthma exacerbations, especially eosinophilic exacerbations in adults. However, as data for clinical symptoms, QoL and spirometry were not different between groups, the value of the intervention in all settings is less clear at this time. Nevertheless, the findings of this review support the addition of sputum eosinophil measurement to traditional strategies to tailor asthma interventions in adult patients. Adults with frequent exacerbations and severe asthma may derive the greatest benefit from this additional monitoring test, although we were unable to confirm this through subgroup analysis. Studies using newer biologic compounds for eosinophilic diseases did not fulfil the inclusion criteria and hence this review cannot be extrapolated to these agents (e.g. anti-interleukin-5), Also, as data on children was restricted to a single study with no significant difference between groups for any outcomes, there is insufficient data for or against tailoring asthma medications based on sputum eosinophilia in children.

Implications for research

Further RCTs with groups stratified by asthma severity and type of airway inflammation (eosinophilic or neutrophilic) are required. The trials need to include children as well as adults. The design of future RCTs should preferably be multi-centre studies and include other objective measures of asthma including exhaled nitric oxide in addition to the sputum analysis and traditional outcomes of spirometry and peak flow. Subjective outcome measures should also be determined including scores for asthma control and quality of life. Analysis of costs and possible adverse events of inhaled and oral corticosteroids would also provide additional important information. New RCTs should also report the success rate of sputum induction/differential cell count and adverse events associated with sputum induction.

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Chris Cates was the Editor for this review and commented critically on the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cao 2007

Methods	Randomised controlled, parallel-group trial comparing a strategy of minimising induced sputum eosinophil count with standard clinical guidelines
Participants	41 adults with asthma were randomised. Sputum eosinophil group N = 20, mean age 41 (SD 2), 11 males, 9 females. Standard guidelines group N = 21, mean age 43 (SD 4) , 11 males, 10 females Visiting the Peking University Third Hospital as an outpatient Inclusion criteria: persistent asthma undergoing inhaled corticosteroid treatment for more than 2 months Exclusion criteria: patients with intermittent asthma. Unclear as to how many patients withdrew after randomisation
Interventions	Participants had a 2-week run-in period and then were followed up for 6 months, with assessments attended at the end of months 2, 4 and 6 Sputum eosinophil group had treatment adjusted based on their sputum eosinophil count Standard clinical guidelines group had treatment adjusted based on asthma symptom score and use of short-acting beta$_2$ -agonist use
Outcomes	Primary outcome: total number of acute exacerbations Secondary outcomes: beta$_2$ -agonist use, symptom score, PEF variability, FEV$_1$ %, ICS use and sputum eosinophil ratio
Notes	Article published in Chinese and funded by the Capital Medical Development Foundation (No. 2002-3004)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random number table but unsure who conducted the generation.
Allocation concealment (selection bias)	Unclear risk	No information about concealment was reported in the article
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators were blinded but unclear if the participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The attending physician adjusted on sputum eosinophil count and blinded to symptoms and pulmonary functions

Cao 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information in published article.
Selective reporting (reporting bias)	Unclear risk	Insufficient information in published article.
Other bias	Unclear risk	Unsure of the success in inducing sputum.

Chlumsky 2006

Methods	An open, prospective, randomised, parallel-group trial comparing standard strategy of asthma severity assessment (standard strategy) with a strategy based on reducing the number of sputum eosinophils (EOS strategy) over a period of 18 months Participants were stratified by dose of inhaled steroids, treatment with systemic steroids and add-on therapy with inhaled long-acting beta$_2$ -agonists and theophyllines Decisions in EOS strategy were made by an independent physician who was blinded to the participants' clinical data and telephoned the participants within one week after a study visit There were 4 dropouts (all in standard strategy); 2 withdrew for protocol violation and 2 were lost to follow-up Participants were assessed every 3 months for 18 months.
Participants	55 participants were randomised. Standard strategy N = 21, mean age 48 (SD 16), 6 males, 15 females. EOS strategy N = 30, mean age 42 (SD 19), 13 males, 17 females. Visiting an outpatients department. Inclusion criteria: FEV$_1$ 31% to 110% predicted, daily dose of inhaled corticosteroid 800 to 6400 mcg budesonide or equivalent, diagnosis of asthma confirmed with bronchodilator response greater than 15% after 200 mcg salbutamol and/or diurnal peak expiratory flow variation of > 20% on at least 4 of 14-day run-in period. Exclusion criteria: current smokers and no upper respiratory tract infections within a month preceding the study
Interventions	Participants were run in for 2 weeks and then attended outpatients in the morning at 3-monthly intervals for the 18 months Standard strategy arm: treatment decisions were based on morning PEF variation, frequency of daytime symptoms or short-acting beta$_2$ -agonists (SABA) use/week, frequency of night time symptoms or SABA/week. EOS strategy: treatment decisions were based on the same as the standard strategy arm plus sputum eosinophils % of total cell count
Outcomes	Primary outcome: rate of asthma exacerbations. Secondary outcomes: FEV$_1$; post bronchodilator FEV$_1$; and FEV$_1$ /inspiratory vital capacity ratio
Notes	The study was funded by an Internal Grant Agency of the Ministry of Health of the Czech Republic (Grant No. 5866/3)

Chlumsky 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Independent investigator using a computer program.
Allocation concealment (selection bias)	Unclear risk	Insufficient information of concealment in published article
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label, therefore participants and investigators were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	An independent physician who was blinded to the participants' clinical information made decisions for the EOS strategy; however for the standard strategy the dose was adjusted by the investigators
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided in published article.
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided in published article.
Other bias	Unclear risk	Nil information provided on success of inducing sputum.

Fleming 2012

Methods	Randomised, double-blind, parallel study comparing asthma management based on the differential sputum eosinophil count with conventional management Neither the physicians nor the participants were aware of which group they were randomised to There were 6 dropouts including 1 with uncontrolled asthma during follow-up Study duration was 12 months with 5 study visits.
Participants	55 children randomised from 65 invited to participate. Inflammatory management group n = 27: median age 13.4 (range 11 to 15.8), 16 males, 11 females. Symptom management group n = 28: median age 12.6 (range 10.2 to 14.7), 13 males, 15 females Attending outpatient clinic at the Royal Brompton Hospital, UK Inclusion criteria: children with severe asthma diagnosed by a paediatric respiratory physician and requiring steps 4 or 5 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines (≥ 500 mcg fluticasone propionate/day or equivalent plus a long-acting beta agonist plus a trial of leukotriene receptor antagonist) Exclusion criteria: currently prescribed an immunomodulatory steroid-sparing agent or a continuous infusion of subcutaneous terbutaline, or had received intramuscular

Fleming 2012 (*Continued*)

	triamcinolone in the previous 3 months or had another significant chronic respiratory or medical condition
Interventions	Outpatient visits were at baseline, months 3, 6, 9, 12. Symptom management group: treatment decisions made on the number of major exacerbations (defined as those needing treatment with high-dose oral corticosteroids (> 20 mg/day) for ≥ 2 days in the preceding 3 months) and short-acting beta$_2$ -agonists use (daytime and nighttime) in the preceding 2 weeks Inflammatory management group: treatment decisions were based on the differential sputum eosinophil count (performed by an investigator blinded to the identity, clinical status and randomisation group of the participant) to keep level below 2.5%
Outcomes	Primary outcome: rate of major exacerbations and asthma control as assessed by symptom-free days and SABA use Secondary outcome: daily dose of ICS prescribed over the course of the study
Notes	The study was funded by a grant from the British Lung Foundation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generated by an independent statistician using random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information of concealment in published article
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded, i.e. physician and participant (child and parent)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator conducting the sputum analysis was blinded to the participant's identity, clinical status and randomisation group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis completed on intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the text.
Other bias	Unclear risk	Sputum induction was successful on 174 (85%) occasions; 152 of these had sputum differential cell count obtained. FeNO was used to determine management on 27 occasions in inflammatory management group

Green 2002a

Methods	Randomised, double-blind, parallel study comparing asthma management based on British Thoracic Society (BTS group) asthma guidelines or by normalising sputum eosinophil count (Sputum management group). Participants were stratified by number of oral corticosteroids used in the previous 12 months, the baseline-induced sputum eosinophil count and baseline methacholine PC20 Neither the physicians nor the participants were aware of which group they were randomised to or the treatment protocol. At completion of the study each participant was asked to guess which group they were in There were 14 dropouts, 8 during run-in and 6 during follow-up The study ran for 12 months and the participants were assessed 9 times
Participants	74 adults randomised from 82 recruited participants. Sputum management group n = 37: median age 50, range 19 to 73, 19 males, 18 females. BTS management group n = 37: median age 47, range 20 to 75, 21 males, 16 females. Attending one of 3 specialists clinics at Glenfield Hospital, Leicester, UK Inclusion: diagnosis of asthma and needed hospital follow-up. Exclusion: current smokers, had a history of smoking more than 15 packs/year, clinically important comorbidity, poor compliance, inadequately controlled aggravating factors e.g. rhinitis or GOR, had severe asthma exacerbation within 4 weeks of entry
Interventions	Outpatient visits were at baseline, month 1, 2, 3, 4, 6, 8, 10, 12. BTS management group: treatment decisions were based on traditional assessments of symptoms, peak expiratory flow and use of beta$_2$ -agonists. Sputum management group: anti-inflammatory treatment was based on maintenance of sputum eosinophil count below 3% with a minimum dose of anti-inflammatory treatment
Outcomes	1. Number 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 to 3 for daytime and nighttime 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.
Notes	Funding by a grant from Trent NHS Regional Research Scheme.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by independent individual with method of minimisation

Green 2002a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information in published article.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, i.e. physician and participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Management decisions were made by an independent individual who was unaware of clinical characteristics of the participant, and who recorded separate treatment plans to be followed depending on whether the participant's asthma was controlled well or poorly
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis by intention to treat and extrapolated for the 12-month period
Selective reporting (reporting bias)	Low risk	All outcomes reported in the published article.
Other bias	Unclear risk	Sputum induction successful in 552 of 632 attempts (87%).

Jayaram 2006

Methods	Randomised, double-blind, parallel-group, effectiveness study. It was a multicentre study over a 2-year period. Stratified by duration of the asthmatic symptoms (≤ 20 years or > 20 years), ICS dose (equivalent to fluticasone ≤ 500 or > 500 mcg/day) and FEV_1 (≤ 70% or > 70% predicted) Participants blinded to sputum cell counts. Physicians blinded to sputum cell count in clinical strategy group Dropouts: 15 dropouts including 5 who were excluded due to protocol violations by investigator
Participants	117 randomised out of 140 approached. Clinical strategy group n = 52; mean age 43.5 (SD 13.9), 15 males, 37 females. Sputum strategy group n = 50; mean age 46 (SD 13.8), 15 males, 35 females. Attending 1 of 3 Canadian or 1 Brazilian chest clinic. Inclusion criteria: symptoms of asthma for a minimum of a year. Exclusion criteria: not mentioned.
Interventions	Clinical strategy: guided by symptoms and strategy. Sputum strategy: dose of inhaled steroid was guided solely by induced sputum eosinophils to keep < 2%. Spirometry and symptoms were used to identify clinical control, exacerbations and other treatment

Jayaram 2006 (*Continued*)

Outcomes	1. Relative risk 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 severity of asthma. Defined by the minimum dose of inhaled steroid to maintain control. 5. The cumulative dose of inhaled steroid needed in Phase 2 adjusted for its duration
Notes	The study was supported by a Canadian Institutes of Health Research Clinical Trials Grant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised off-site in blocks of 4.
Allocation concealment (selection bias)	Unclear risk	Information not available in published article.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physician and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	In the control strategy the investigators were blinded to the sputum cell counts but no blinding for outcomes in the sputum strategy
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported as planned.
Selective reporting (reporting bias)	Low risk	Adjudicator researcher used, blinded to treatment arms.
Other bias	Unclear risk	Sputum induction successful in 81% of attempts.

Malerba 2015

Methods	Randomised, single-blind, parallel study comparing a group of participants whose asthma treatment was based on FeNO and sputum eosinophil counts versus a group whose treatment was based on clinical score Study duration was 24 months with 6 outpatient visits, at month 0, 3, 6, 12, 18 and 24 The study personnel assessing outcome measures were blinded. The participants were not blinded

Participants	28 adults with confirmed diagnosis of asthma (confirmed by positive response to methacholine challenge) randomised from 40 screened Clinical strategy: n = 14; mean age 46.7 years (SD 30.1), 6 males, 8 females Sputum strategy: n = 14; mean age 45.2 years (SD 31.2), 5 males, 9 females Inclusion criteria: aged 18 to 70 years with mild to moderate asthma, sputum eosinophil cell counts > 3%. All were on maintenance ICS with or without LABA Exclusion criteria: previous respiratory tract infection in the previous 6 weeks, oral corticosteroids in the previous 4 weeks, co-morbidities of hepatic, cardiovascular, neurologic, respiratory diseases such as bronchiectasis, cystic fibrosis, COPD or respiratory failure. Participants could not be on angiotensin-converting enzyme inhibitors or beta-blockers or anti-depressants
Interventions	Clinical strategy: treatment was adjusted based on symptom score, use of beta$_2$ -agonists and night symptoms Sputum strategy: treatment was adjusted based on FeNO level, sputum eosinophil count, symptom score, use of beta$_2$ -agonists and night symptoms
Outcomes	Primary outcome: asthma exacerbations combined with changes in symptom score at end of study Secondary outcomes: mean values of PD$_{20}$, FEV$_1$, FEV$_1$ /FVC ratio, FeNO, sputum eosinophil cell counts and variations in ICS dose
Notes	Study funded by the University of Brescia. Authors state they have no conflicts of interest to disclose

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation schedule" used to assign participants but unclear on the method. Block randomisation with 1:1 allocation
Allocation concealment (selection bias)	Unclear risk	"Principal investigator enrolled participants and assigned to study groups" with no description of allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States single blind with the "person assessing outcome measures were blinded", participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States single blind with the "person assessing outcome measures were blinded" but unclear who did the eosinophil counts
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants finished the study and authors report "no missing data"

Malerba 2015 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcome measures were reported in published paper.
Other bias	Low risk	Nil noted.

BTS: British Thoracic Society; FeNO: fractional exhaled nitric oxide; FEV_1 : forced expiratory volume in 1 second; GOR: gastro-oesophageal reflux; ICS: inhaled corticosteroids; N: number; PEF: peak expiratory flow; SABA: short-acting beta-agonist; SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aldridge 2002	Randomised, placebo-controlled, cross-over study of terbutaline and budesonide, comparing the changes in eosinophil counts and ECP in induced sputum and blood. Excluded as treatment was not adjusted according to sputum eosinophil counts
Almosawi 2008	Non-randomised, nor treatment based on sputum eosinophil counts. Observational study to determine the relationship between sputum eosinophil markers and asthma severity and prognosis in atopic and non-atopic patients in United Arab Emirates
Foresi 2005	Randomised, double-blind, parallel study treating one group with fluticasone propionate 1000 mcg/day and then reducing to 200 mcg/day in comparison to a fixed dose of fluticasone 200 mcg/day in the control of bronchial hyper-responsiveness to methacholine and eosinophilic inflammation. Excluded as treatment was not adjusted using sputum eosinophils
Gauvreau 2005	Excluded as treatment was not adjusted according to sputum eosinophils. Randomised, double-blind, cross-over study of ciclesonide versus placebo after allergen challenge
Giannini 2000	Excluded as treatment not adjusted according to sputum eosinophil counts. Randomised, double-blind, placebo-controlled study of beclomethasone dipropionate versus placebo
Gibson 2001	Randomised, double-blind, placebo-controlled, cross-over trial of single dose of budesonide 2400 mcg versus placebo and effect on sputum eosinophils and mast cells in adults with asthma. Excluded as treatment was not based on sputum eosinophil count
Griese 2000	Non-RCT nor treatment based on sputum eosinophil count. Prospective study to assess exhaled nitric oxide in comparison to clinical symptoms, treatment adjusted using clinical symptoms
Jatakanon 1997	Randomised, double-blind, cross-over study of budesonide versus placebo. Excluded as treatment not based on eosinophil count

(*Continued*)

Jatakanon 1998	Excluded as treatment not based on sputum eosinophils. Randomised into two double-blind, placebo-controlled studies (1 was parallel study involving 3 groups receiving either budesonide 100 mcg/day, budesonide 400 mcg/day or placebo; the second was a cross-over randomised to receive budesonide 1600 mcg or placebo)
Leigh 2000	Excluded as treatment not adjusted based on sputum eosinophils. RCT of budesonide versus placebo in patients with mild to moderate asthma who had non-eosinophilic airway inflammation
Lonnkvist 2001	Treatment not adjusted according to sputum eosinophil. RCT of budesonide versus placebo in children with mild to moderate asthma. Investigated the effect of withdrawing inhaled budesonide on eosinophil count in blood and eosinophil proteins in serum and urine, and the relationship between these markers and symptoms of asthma
Malerba 2008	Excluded as non-RCT but prospective observational study. Anti-inflammatory therapy was adjusted according to FeNO and sputum eosinophil values
McKinlay 2011a	Treatment not adjusting according to sputum eosinophil counts. RCT to evaluate the usefulness of inflammatory surrogates (adenosine monophosphate) in determining step-down therapy in asthma
McKinlay 2011b	Treatment not adjusted according to sputum eosinophil counts. RCT where patients were treated according to BTS guidelines or mannitol challenge
Meijer 2002	Excluded as treatment not adjusted according to sputum eosinophils. Randomised to either prednisolone 30 mg/day, fluticasone propionate 2000 mcg/day or fluticasone propionate 500 mcg/day for 2 weeks
Nocker 2000	Randomised parallel group study to evaluate the usefulness of induced sputum as an alternative to bronchoalveolar lavage. Excluded as treatment not adjusted according to sputum eosinophils
Prehn 2000	Excluded as randomised to serum eosinophil cationic protein levels. A pilot study of 21 asthmatic children, allocated to receive budesonide 200 mcg twice daily if ECP between 15 to 30 mcg/L or budesonide 400 mcg twice daily if ECP > 30 mcg/L
Smith 2005	Randomised, single-blind, placebo-controlled trial adjusting corticosteroids based on exhaled nitric oxide versus conventional guidelines. Excluded as treatment not based on sputum eosinophil count
Sosa 2004	Non-RCT, literature review about sputum induction to explore airway inflammation in asthma
Van Rensen 1999	Excluded as treatment not based on sputum eosinophil count. Randomised, double-blind, placebo-controlled parallel study to compare the changes in non-invasive markers (airway hyper-responsiveness, sputum eosinophils and exhaled nitric oxide) after treatment with inhaled glucocorticosteroids
Wark 2003	Non-randomised nor treatment adjusted based on sputum eosinophil count. Review article looking at the techniques of sputum induction, exhaled gas measurements and blood or serum measures as noninvasive measures of eosinophilic inflammation
Wilson 2000	Non-RCT. Cross-sectional study of children to determine the feasibility of sputum induction, repeatability of sputum eosinophil counts and the correlation to asthma symptoms

(*Continued*)

Zacharasiewicz 2005	Non-RCT. Prospective, observational study in children using non-invasive measures (exhaled nitric oxide, induced sputum and exhaled breath condensate) to monitor airway inflammation to result in optimal treatment
Zubovic 2003	RCT using serum eosinophil cationic protein (ECP). Excluded as not using sputum eosinophil. One group was treated with disodium cromoglycate and the other corticosteroid flunisolide to assess the success of anti-inflammatory treatment by measuring the level of ECP and FEV

Characteristics of ongoing studies *[ordered by study ID]*

Pinot 2008

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Awaiting publication

DATA AND ANALYSES

Comparison 1. Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Occurrence of any exacerbation	4	269	Rate Ratio (Random, 95% CI)	0.57 [0.38, 0.86]
1.1 Adults	3	215	Rate Ratio (Random, 95% CI)	0.45 [0.24, 0.86]
1.2 Children	1	54	Rate Ratio (Random, 95% CI)	0.75 [0.54, 1.04]
2 Number of participants who had one or more exacerbations over the study period	4	269	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.21, 0.62]
2.1 Adult	3	215	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.20, 0.64]
2.2 Children	1	54	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.09, 1.71]
3 Number of participants with exacerbations regarding hospitalisations over the study period	4	269	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.09, 0.84]
3.1 Adult	3	215	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.25]
3.2 Children	1	54	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.10, 1.45]
4 Number of severe exacerbations requiring oral corticosteroids	1		Rate Ratio (Fixed, 95% CI)	Totals not selected
5 MIld exacerbations over study period	2	150	Rate Ratio (Fixed, 95% CI)	0.82 [0.67, 1.00]
6 Eosinophilic v Noneosinophilic exacerbations	1		Risk Ratio (Fixed, 95% CI)	Subtotals only
6.1 Eosinophilic Exacerbations	1	2	Risk Ratio (Fixed, 95% CI)	0.28 [0.10, 0.76]
6.2 Noneosinophilic Exacerbations	1	2	Risk Ratio (Fixed, 95% CI)	1.07 [0.62, 1.85]
7 Exacerbations subgrouped by asthma severity: Mild vs Severe	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
7.1 Very mild to mild asthma	1	2	Rate Ratio (Fixed, 95% CI)	1.34 [0.52, 3.43]
7.2 Moderate to severe asthma	1	2	Rate Ratio (Fixed, 95% CI)	0.63 [0.38, 1.04]
8 Exacerbations subgrouped by asthma severity: Use of LABA	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
8.1 On LABA	1	2	Rate Ratio (Fixed, 95% CI)	0.53 [0.25, 1.14]
8.2 Not on LABA	1	2	Rate Ratio (Fixed, 95% CI)	1.05 [0.62, 1.78]
9 Mean dose of inhaled corticosteroids per person per day (Bud equiv)	5	316	Mean Difference (Fixed, 95% CI)	12.56 [-127.92, 153.04]
9.1 Adults	4	262	Mean Difference (Fixed, 95% CI)	0.67 [-154.39, 155.73]
9.2 Children	1	54	Mean Difference (Fixed, 95% CI)	67.0 [-264.81, 398.81]
10 Mean dose of oral corticosteroids per person per day	1		Mean Difference (Fixed, 95% CI)	Totals not selected

11 Yearly cost per person (USD)	1	Mean Difference (IV, Fixed, 95% CI)		Totals not selected

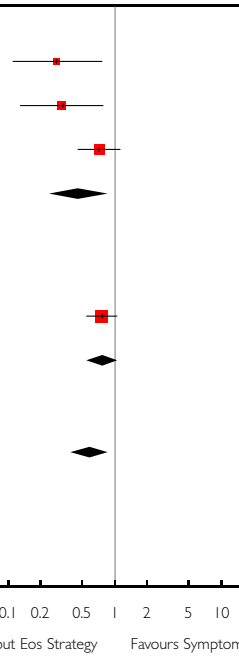
Analysis 1.1. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 1 Occurrence of any exacerbation.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 1 Occurrence of any exacerbation

Study or subgroup	Sputum Eos Strategy N	Symptom Strategy N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
1 Adults						
Chlumsky 2006	30	21	-1.266 (0.5)		13.2 %	0.28 [0.11, 0.75]
Green 2002a	34	34	-1.136 (0.45)		15.4 %	0.32 [0.13, 0.78]
Jayaram 2006	45	51	-0.343 (0.23)		32.2 %	0.71 [0.45, 1.11]
Subtotal (95% CI)	**109**	**106**			**60.7 %**	**0.45 [0.24, 0.86]**
Heterogeneity: Tau^2 = 0.18; Chi^2 = 4.43, df = 2 (P = 0.11); I^2 =55%						
Test for overall effect: Z = 2.43 (P = 0.015)						
2 Children						
Fleming 2012	28	26	-0.2877 (0.1676)		39.3 %	0.75 [0.54, 1.04]
Subtotal (95% CI)	**28**	**26**			**39.3 %**	**0.75 [0.54, 1.04]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.72 (P = 0.086)						
Total (95% CI)	**137**	**132**			**100.0 %**	**0.57 [0.38, 0.86]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 6.12, df = 3 (P = 0.11); I^2 =51%						
Test for overall effect: Z = 2.69 (P = 0.0071)						
Test for subgroup differences: Chi^2 = 1.93, df = 1 (P = 0.17), I^2 =48%						



Analysis 1.2. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 2 Number of participants who had one or more exacerbations over the study period.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 2 Number of participants who had one or more exacerbations over the study period

Study or subgroup	Sputum Eos Strategy n/N	Symptom Strategy n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Adult					
Chlumsky 2006	8/30	14/21		26.9 %	0.18 [0.05, 0.61]
Green 2002a (1)	18/34	26/34		27.2 %	0.35 [0.12, 0.98]
Jayaram 2006	26/45	37/51		32.6 %	0.52 [0.22, 1.22]
Subtotal (95% CI)	**109**	**106**		**86.7 %**	**0.36 [0.20, 0.64]**
Total events: 52 (Sputum Eos Strategy), 77 (Symptom Strategy)					
Heterogeneity: Chi^2 = 1.92, df = 2 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 3.49 (P = 0.00048)					
2 Children					
Fleming 2012	21/28	23/26		13.3 %	0.39 [0.09, 1.71]
Subtotal (95% CI)	**28**	**26**		**13.3 %**	**0.39 [0.09, 1.71]**
Total events: 21 (Sputum Eos Strategy), 23 (Symptom Strategy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
Total (95% CI)	**137**	**132**		**100.0 %**	**0.36 [0.21, 0.62]**
Total events: 73 (Sputum Eos Strategy), 100 (Symptom Strategy)					
Heterogeneity: Chi^2 = 1.93, df = 3 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 3.70 (P = 0.00022)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 =0.0%					

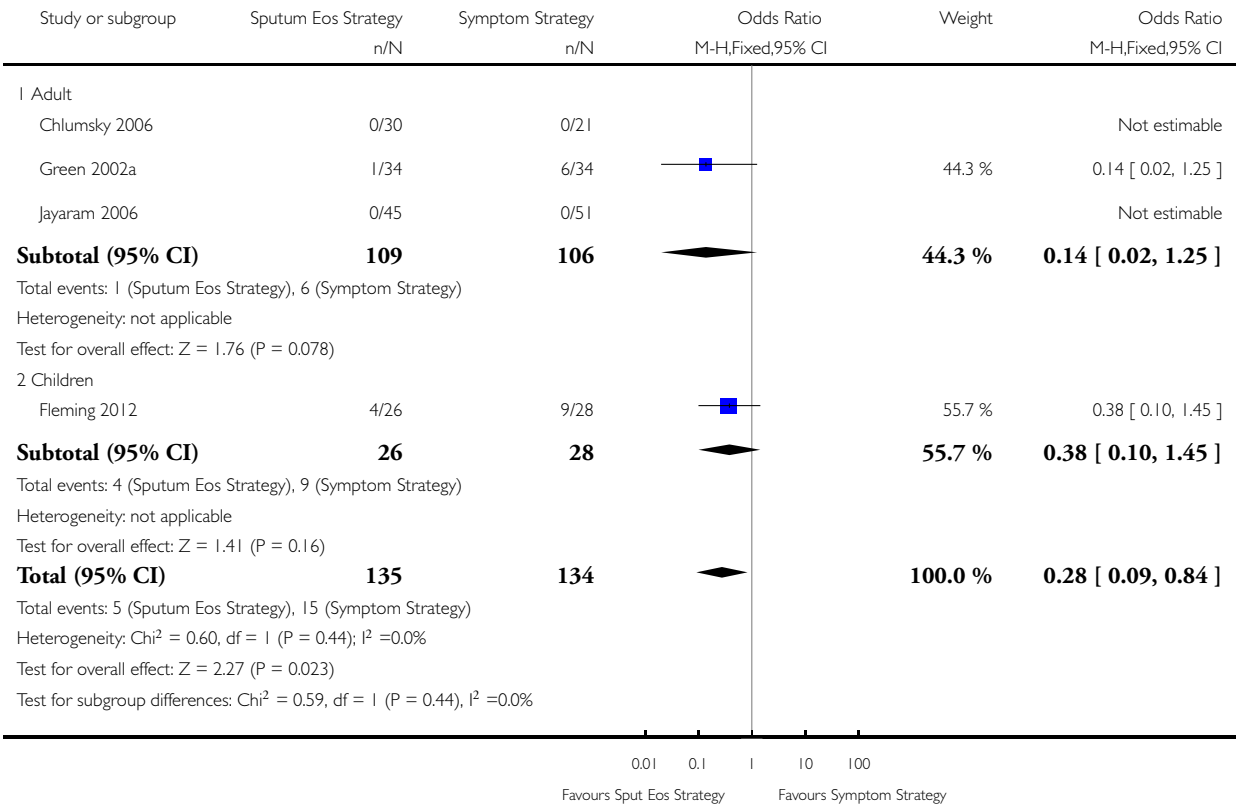
(1) p=0.058

Analysis 1.3. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 3 Number of participants with exacerbations regarding hospitalisations over the study period.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 3 Number of participants with exacerbations regarding hospitalisations over the study period



Analysis 1.4. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 4 Number of severe exacerbations requiring oral corticosteroids.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 4 Number of severe exacerbations requiring oral corticosteroids

Study or subgroup	Sputum Eos Strategy N	Symptom Strategy N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Rate Ratio IV,Fixed,95% CI
Jayaram 2006	45	51	-1.1 (0.38)		0.33 [0.16, 0.70]

Analysis 1.5. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 5 MIld exacerbations over study period.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

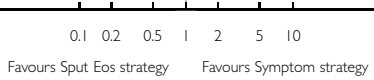
Outcome: 5 MIld exacerbations over study period

Study or subgroup	Sputum Eos Strategy N	Symptom Strategy N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
Fleming 2012	26	28	-0.2357 (0.265)		14.7 %	0.79 [0.47, 1.33]
Jayaram 2006	45	51	-0.19 (0.11)		85.3 %	0.83 [0.67, 1.03]
Total (95% CI)	**71**	**79**			**100.0 %**	**0.82 [0.67, 1.00]**

Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 1.94 (P = 0.053)

Test for subgroup differences: Not applicable

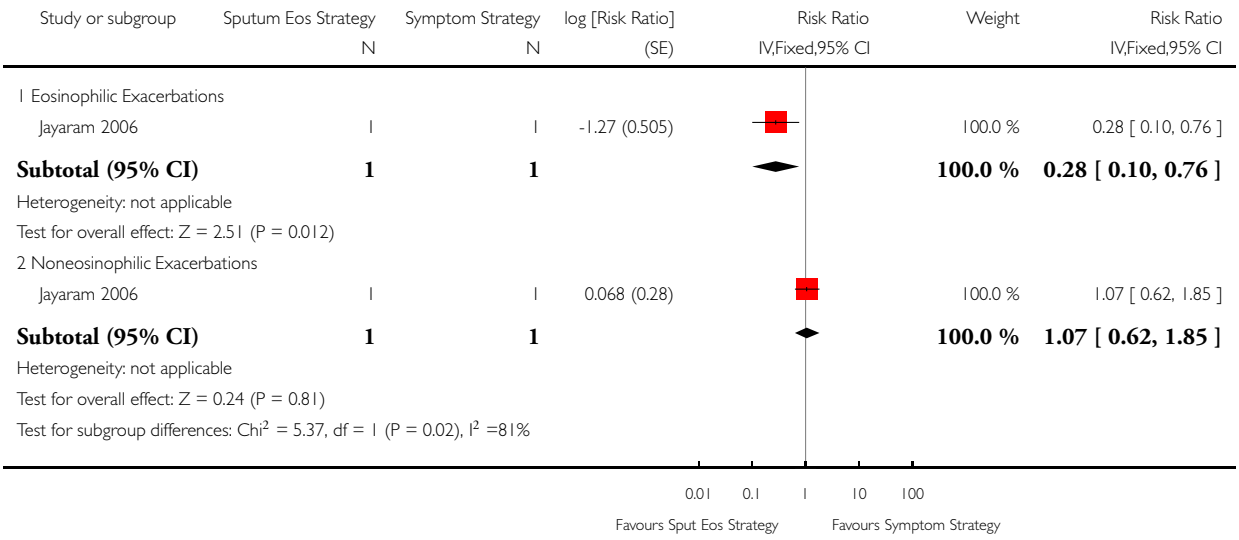


Analysis 1.6. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 6 Eosinophilic v Noneosinophilic exacerbations.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 6 Eosinophilic v Noneosinophilic exacerbations

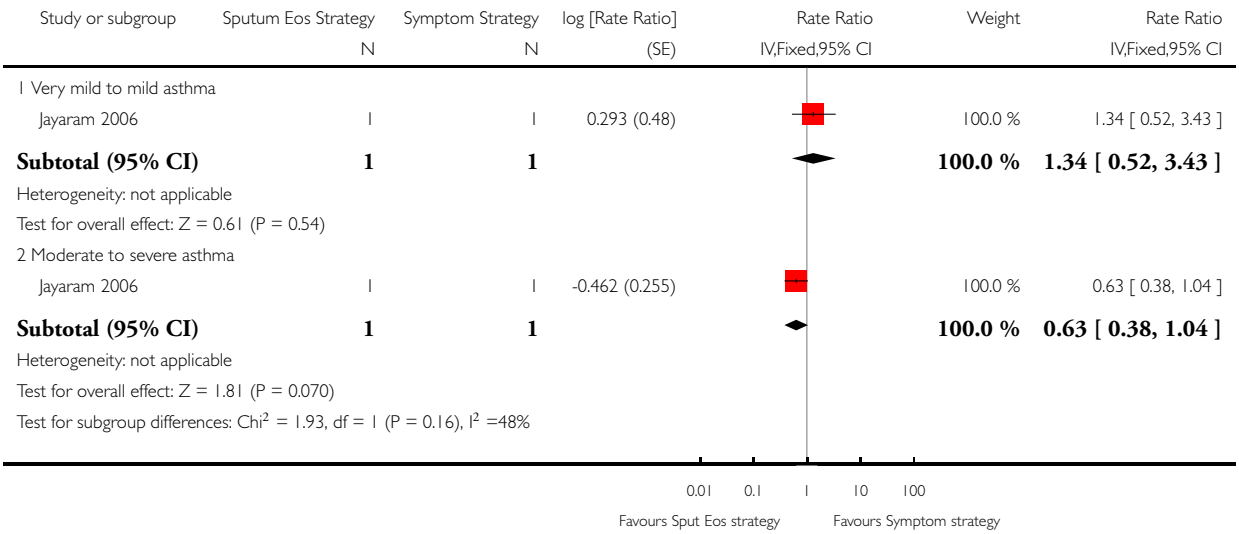


Analysis 1.7. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 7 Exacerbations subgrouped by asthma severity: Mild vs Severe.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 7 Exacerbations subgrouped by asthma severity: Mild vs Severe

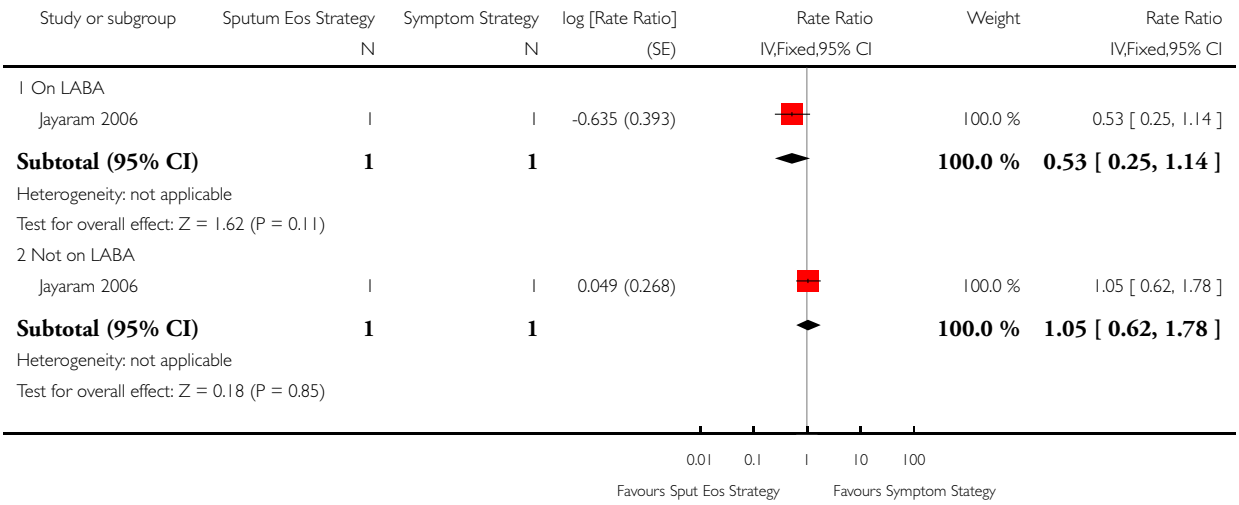


Analysis 1.8. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 8 Exacerbations subgrouped by asthma severity: Use of LABA.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 8 Exacerbations subgrouped by asthma severity: Use of LABA



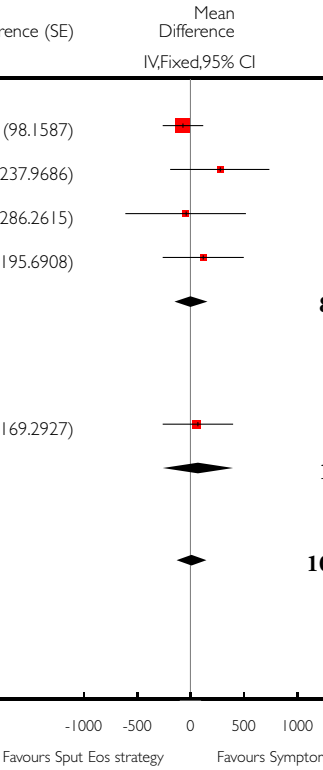
Analysis 1.9. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 9 Mean dose of inhaled corticosteroids per person per day (Bud equiv).

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 9 Mean dose of inhaled corticosteroids per person per day (Bud equiv)

Study or subgroup	Sputum Eos Strategy N	Symptom Strategy N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults						
Cao 2007	20	21	-71 (98.1587)		53.3 %	-71.00 [-263.39, 121.39]
Chlumsky 2006	30	21	277 (237.9686)		9.1 %	277.00 [-189.41, 743.41]
Green 2002a	34	34	-45 (286.2615)		6.3 %	-45.00 [-606.06, 516.06]
Jayaram 2006 (1)	50	52	120 (195.6908)		13.4 %	120.00 [-263.55, 503.55]
Subtotal (95% CI)	**134**	**128**			**82.1 %**	**0.67 [-154.39, 155.73]**
Heterogeneity: Chi^2 = 2.28, df = 3 (P = 0.52); I^2 =0.0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
2 Children						
Fleming 2012 (2)	26	28	67 (169.2927)		17.9 %	67.00 [-264.81, 398.81]
Subtotal (95% CI)	**26**	**28**			**17.9 %**	**67.00 [-264.81, 398.81]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
Total (95% CI)	**160**	**156**			**100.0 %**	**12.56 [-127.92, 153.04]**
Heterogeneity: Chi^2 = 2.40, df = 4 (P = 0.66); I^2 =0.0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi^2 = 0.13, df = 1 (P = 0.72), I^2 =0.0%						



(1) Mean and SD reported as FP, therefore doubled to make Bud equiv

(2) Data obtained from author, Mean and SD given as FP, therefore doubled to make Bud equiv

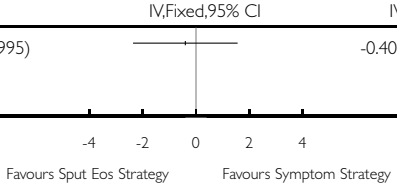
Analysis 1.10. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 10 Mean dose of oral corticosteroids per person per day.

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 10 Mean dose of oral corticosteroids per person per day

Study or subgroup	Sput Eos Strategy N	Symptom Strategy N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Green 2002a	34	34	-0.4 (0.9995)		-0.40 [-2.36, 1.56]



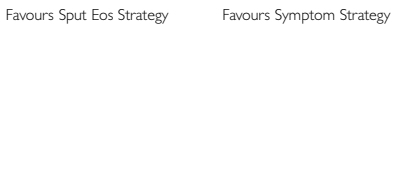
Analysis 1.11. Comparison 1 Asthma treatment tailored on sputum esoinophils versus symptoms, Outcome 11 Yearly cost per person (USD).

Review: Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Comparison: 1 Asthma treatment tailored on sputum esoinophils versus symptoms

Outcome: 11 Yearly cost per person (USD)

Study or subgroup	Sputum Eos Strategy N	Mean(SD)	Symptom Strategy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Green 2002a	34	2768 (1096.22)	34	3082 (1510.22)		-314.00 [-941.27, 313.27]



ADDITIONAL TABLES

Table 1. Included studies definitions

Study	Exacerbation definition	Sputum eosinophil cut-off (%)	Control arm	Study duration (months)
Cao 2007	Unknown	Decrease ICS < 1 Keep same 1 to 3 Increase ICS > 3	"Standard clinical guidelines"	6
Chlumsky 2006	Doubling of the frequency of symptoms and/or number of puffs of rescue salbutamol and/or reduction in morning PEF by 30% or more on at least 2 consecutive days. A decrease in FEV_1 by > 30% at any study visit	Decrease ICS ≤ 3 Keep same 4 to 8 Increase ICS ≥ 8	GINA guidelines	18
Fleming 2012	Minor exacerbation: use of bronchodilators > 5 times/week (excl. routine or pre-exercise) Major exacerbation: deterioration requiring high-dose OCS (≥ 20 mg/day) for at least 2 days	Decrease ICS < 0.1 (or FeNO < 22 ppb) Keep same 0.1 to 2.5 (or FeNO 22 to 30 ppb) Increase ICS > 2.5 (or FeNO > 30 ppb)	Based on number of major exacerbations in preceding 3 months and SABA use in preceding 2 weeks	12
Green 2002	Severe exacerbations: decrease in morning PEF > 30% on 2 or more consecutive days, or deterioration in symptoms needing OCS	Decrease ICS < 1 Keep same 1 to 3 Increase ICS > 3	BTS guidelines	12
Jayaram 2006	Worsening of symptoms requiring increased use of SABA by ≥ 4 puffs/day for a minimum of 48 hours, or early morning wakening due to respiratory symptoms > 2 times/week, with or without reduction in FEV_1 of at least 20% Severe exacerbation: course of OCS as determined by study investigator	Decrease ICS ≤ 2 Increase ICS ≥ 2	Canadian Asthma Consensus Group Guidelines	24

Table 1. Included studies definitions (*Continued*)

Malerba 2015	Moderate exacerbation: requiring an unscheduled visit with a course of OCS Severe exacerbation: hospital admission and requiring > 3 days OCS	Sputum eosinophil (%) & FeNO (ppb) Decrease ICS < 2% & ≤ 10 pbb Keep same 2% to 3% & 11 to 20 ppb Increase ICS > 3% & ≥ 20 ppb	Symptom scores, use of SABA and night time symptoms	24

FeNO: exhaled nitric oxide; FEV_1 : forced expiratory volume in one second; ICS: inhaled corticosteroids; OCS: oral corticosteroids; PEF: peak expiratory flow; ppb: parts per billion

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.

8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search Strategies

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Sputum
#6 MeSH DESCRIPTOR Mucus
#7 phlegm*
#8 sputum*:ti,ab
#9 mucus*:ti,ab
#10 eosinophil*
#11 MeSH DESCRIPTOR Eosinophils
#12 airway* NEXT inflam*:ti,ab
#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 #4 and #13
[In search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, asthma]

Appendix 3. Search strategy to identify relevant trials from ClinicalTrials.gov and WHO trials portal

"sputum eosinophils" AND "asthma" AND "clinical trials"

WHAT'S NEW

Last assessed as up-to-date: 15 February 2017.

Date	Event	Description
15 February 2017	New citation required but conclusions have not changed	More data has been added to the review but the conclusions remain unchanged
15 February 2017	New search has been performed	Updated to latest template. Searched and three new studies added (Cao 2007; Fleming 2012; Malerba 2015). Change of authorship. Many sections of the review redrafted

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 2, 2007

Date	Event	Description
24 December 2009	New search has been performed	Searched for 2009 and inclusion of Risk of Bias and Summary of Findings Tables. 1 study added to Ongoing studies
11 May 2009	Amended	Corrected data
12 December 2008	New search has been performed	2008 Searches and edited
1 September 2008	Amended	Converted to new review format.
21 November 2007	New search has been performed	New studies sought but none found
2 February 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For this updated review: HP and AC selected studies from search, and conducted data extraction, data analysis, and writing of review.

Original review: all participated in selection of studies. HP and AC extracted data, performed analysis and wrote review. AL reviewed the manuscript In the previous review (Petsky 2007), AL, AK, CT reviewed manuscript.

DECLARATIONS OF INTEREST

HP: none known

AL: none known

AC: none known

SOURCES OF SUPPORT

Internal sources

- Children's Hospital Foundation, Australia.

Support for research group via Program Grant for AC & HP

External sources

- Australian Cochrane Airways Group Scholarship 2006, Australia.
- National Health Medical Research Council, Australia.

Support for AC and HP (post doctoral fellowship through CRE)

- Asthma Australia, Australia.

Early Career Fellowship for HP

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

February 2017: The original protocol was written in 2006; since this time Cochrane methodology has become more rigorous. Therefore this updated review has considered these changes and adapted as necessary. The primary and secondary outcomes were changed for this update to be more specific.

INDEX TERMS

Medical Subject Headings (MeSH)

*Eosinophils; Adrenal Cortex Hormones [therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy; pathology]; Leukocyte Count; Randomized Controlled Trials as Topic; Sputum [*cytology]

MeSH check words

Adult; Child; Humans