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Exhaled nitric oxide levels to guide treatment for adults with asthma

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide (FeNO) in comparison to not using FeNO i.e. management based on clinical symptoms (with or without spirometry/peak flow) and/or asthma guidelines for asthma related outcomes in adults.

BACKGROUND

Asthma guidelines aim for treatment to minimize symptoms, optimise lung function and prevent acute exacerbations (BTS/SIGN 2012; GINA 2014; National Asthma Council 2014). Exacerbations cause anxiety to patients and their families, and generate large costs to health care systems (Weiss 2001) which puts stress on health care providers. Thus preventing exacerbations is 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 2012; GINA 2014; National Asthma Council 2014). Subjective measures usually involve a series of questions used for clinical assessment, diary cards and quality of life (QoL) questionnaires. Traditional objective methods include peak flow, spirometry and degree of airway hyperresponsiveness (Zacharasiewicz 2005). Newer and arguably more sensitive methods include measurement of airway inflammation such as airway cellularity in induced sputum or fractional exhaled nitric oxide (FeNO).

In asthma, inflammation can be eosinophilic or neutrophilic (Douwes 2002). Arguably, asthma management is best tailored in accordance to the type of airway inflammation, as corticosteroids is more beneficial in eosinophilic inflammation (Wardlaw 2000); inhaled corticosteroids (ICS) reduce exacerbations and improves symptoms and asthma control (Wardlaw 2000). There are several ways to quantify airway eosinophilic inflammation, such as determining the percentage of eosinophils in the sputum and FeNO. FeNO correlates with other markers of asthma e.g. eosinophilia in induced sputum (Jatakanon 1998) and bronchial reactivity in...
non-steroid treated subjects (Dupont 1998). Induced sputum and sputum analysis is labour intensive and not widely available in non-research laboratories. Hypertonic saline, used to induce sputum may also temporarily increase asthma symptoms. Thus, measures of FeNO confer some advantage over measurements of sputum eosinophils. However FeNO does not provide any data on non-eosinophilic inflammation and the equipment required to measure FeNO is relatively expensive.

**Description of the intervention**

The principle of asthma management is based on a step-up or step-down regimen of asthma medications to reduce airway inflammation, control symptoms and reduce exacerbations. Thus tailoring of asthma medications in accordance to airway eosinophilic levels may improve asthma control and/or reduce exacerbations. Induced sputum and sputum analysis is labour intensive and not widely available in non-research laboratories. Hypertonic saline, used to induce sputum may also temporarily increase asthma symptoms. Thus, measures of FeNO confer some advantage over measurements of sputum eosinophils. However it does not provide any data on non-eosinophilic inflammation and the equipment required to measure FeNO is relatively expensive. FeNO levels can be measured using commercially available analysers. These analysers vary in several ways that include methods of measurements (on-line or off-line), complexity, their set-up, calibration procedures, sampling tube design, measuring chamber and the way expiratory flow is controlled (Muller 2005). Stationary analysers measure FeNO by chemoluminescence whilst the portable FeNO analysers measure FeNO using electrochemistry.

**Objectives**

To evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide (FeNO) in comparison to not using FeNO i.e. management based on clinical symptoms (with or without spirometry/peak flow) and/or asthma guidelines for asthma related outcomes in adults.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised controlled trials (RCTs) comparing adjustment of asthma medications based on exhaled nitric oxide levels compared to those not using FeNO i.e. management based on clinical symptoms (with or without spirometry/peak flow) and/or asthma guidelines. We will include studies reported as full-text, those published as abstract only, and unpublished data.

**Types of participants**

We will include adults with a diagnosis of asthma according to a guideline defined criteria. We will exclude participants with the following co-morbidities/characteristics: eosinophilic bronchitis, asthma related to an underlying lung disease such as bronchiectasis and chronic obstructive airway disease, or diagnostic categories such as ‘cough variant asthma’ and ‘wheezy bronchitis’ where controversies exist.
Types of interventions
We will include RCTs comparing adjustment of asthma medications based on FeNO levels versus control groups where FeNO is not used to adjust asthma medications. Control group interventions may include use of clinical symptoms (with or without spirometry/peak flow) to guide adjustment of asthma medications. Trials that included the use of other interventions will be included if all participants had equal access to such interventions. We will include trials of at least 12 week's duration.

Types of outcome measures

Primary outcomes
Asthma exacerbations during follow-up. Defined as:
1. Number of subjects who had one or more exacerbations over the study period
2. Number of exacerbations per 52 weeks (exacerbation rate)
3. Severe exacerbations requiring oral corticosteroids
4. Severe exacerbation requiring hospitalisations

Secondary outcomes
1. Objective measurements of asthma control (FEV1, peak flow, airway hyper-responsiveness)
2. FeNO level
3. Symptoms of asthma as reported in asthma quality of life score
4. Inhaled corticosteroid dose at final visit

Reporting one of more of the outcomes listed here in the trial is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches
We will identify trials from the Cochrane Airways Group’s Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2. We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Data collection and analysis

Selection of studies
Two authors (HP, KK) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as ‘retrieved’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. We will retrieve the full-text study reports/publication and two review authors (HP, KK) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (AC). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and ‘Characteristics of excluded studies’ table.

Data extraction and management
We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (HP) will extract study characteristics from included studies. We will extract the following study characteristics.
1. Methods: study design, total duration of study, details of any ‘run in’ period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (HP, KK) will independently extract outcome data from included studies from 2014 searches. We will note in the ‘Characteristics of included studies’ table if outcome data was not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (AC). One review author...
(HP) will transfer data into the Review Manager (RevMan) file. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (KK) will spot-check study characteristics for accuracy against the trial report.

**Assessment of risk of bias in included studies**

Two review authors (HP, KK) will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (AC). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

**Assessment of bias in conducting the systematic review**

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

**Measures of treatment effect**

We will analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We will enter data presented as a scale with a consistent direction of effect. We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will narratively describe skewed data reported as medians and interquartile ranges.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

**Unit of analysis issues**

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

**Dealing with missing data**

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

**Assessment of heterogeneity**

Any heterogeneity between study results will be described and tested to see if it reaches statistical significance using a chi-squared test. The 95% confidence interval estimated using a random effect model will be included whenever there are concerns about statistical heterogeneity. Heterogeneity is considered significant when the P value is less than 0.10 (Higgins 2011). We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by pre-specified subgroup analysis.

**Assessment of reporting biases**

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

**Data synthesis**

The results from studies that meet the inclusion criteria and reported any of the outcomes of interest will be included in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed effects model) will be calculated using Review Manager (RevMan). For rate ratios of common events...
whereby one participants may have more than one event, GIV will be utilised. The rate ratios will be taken from the published papers and the standard errors calculated from confidence intervals or P values published in the papers. For cross-over studies, mean treatment differences will be calculated from raw data, and variances extracted or imputed and entered as fixed effects generic inverse variance (GIV), to provide summary weighted differences and 95% confidence intervals. Numbers needed to treat (NNT) will be calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2008). The outcome indices will be assumed to be normally distributed continuous variables so the mean difference in outcomes could be estimated. If studies report outcomes using different measurement scales, the standardised mean difference will be estimated.

**Summary of findings (SoF) table**

We will create a ‘Summary of findings’ table using the following outcomes:
1. Number of participants who had one or more exacerbations over the study period,
2. Number of exacerbations per 52 weeks,
3. ICS dose at final visit.

The SoF table in the previous combined review (Petsky 2009) will be amended to reflect new data and restricted to the inclusion criteria. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the pre-specified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (GRADEpro). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid reader’s understanding of the review where necessary.

**Subgroup analysis and investigation of heterogeneity**

Subgroup analysis is planned for:

1. Basis for adjustment of ICS in the control group (guideline driven monitoring versus non-guideline driven)
2. Use of spirometry or peak flow as an adjunctive monitoring tool for adjustment of medications (versus non-use of spirometry or peak flow)
3. Baseline ICS dose at commencement of intervention (low-medium [<800 mcg/day budesonide equivalent] versus high dose [800 mcg/day or more budesonide equivalent])
4. FeNO cut-offs for adjustment of medications (≤ 20 ppb vs. > 20 ppb)
5. FeNO cut-offs, based on presence of atopy

**Sensitivity analysis**

We plan to carry out the following sensitivity analyses.

1. Sensitivity analysis excluding studies with a high risk of bias based on the ‘Risk of bias’ assessment. Studies that do not have adequate allocation concealment and sequence generation will be removed.
2. Variation in the inclusion criteria. Studies that included adults not receiving ICS at recruitment will removed.
3. Differences in the medications used in the intervention and comparison group. Studies that adjusted medications only for one arm will be removed.
4. Analysis used random effects model
5. Analysis by “strategy received”. Studies with hierarchy management protocols that only considered use of steroids for each step (i.e. without consideration for using montelukast and/or LABA at any point) will be removed.

**ACKNOWLEDGEMENTS**

We thank Elizabeth Stovold for conducting the relevant searches.

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

The background and methods section of this protocol is based on a standard template used by Cochrane Airways Group.

**REFERENCES**

**Additional references**

**BTS/SIGN 2012**

**Cates 2008 [Computer program]**
Dr Christopher Cates. Visual Rx. Online NNT Calculator.

Dr Christopher Cates, 2008.

**Douwes 2002**

**Dupont 1998**
GINA 2014

GRADEpro [Computer program]

Higgins 2011

Jatakanon 1998

Muller 2005

National Asthma Council 2014

Review Manager (RevMan) [Computer program]

Wardlaw 2000

Weiss 2001
Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *Journal of Allergy and Clinical Immunology* 2001; 107:3–8.

Zacharasiewicz 2005

References to other published versions of this review

Petsky 2009

* Indicates the major publication for the study

APPENDICES

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

Electronic searches: core databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Frequency of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL (<em>the Cochrane Library</em>)</td>
<td>Monthly</td>
</tr>
<tr>
<td>MEDLINE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>Embase (Ovid)</td>
<td>Weekly</td>
</tr>
</tbody>
</table>
Hand-searches: core respiratory conference abstracts

<table>
<thead>
<tr>
<th>Conference</th>
<th>Years searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Allergy, Asthma and Immunology (AAAAI)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>American Thoracic Society (ATS)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>Asia Pacific Society of Respirology (APSR)</td>
<td>2004 onwards</td>
</tr>
<tr>
<td>British Thoracic Society Winter Meeting (BTS)</td>
<td>2000 onwards</td>
</tr>
<tr>
<td>Chest Meeting</td>
<td>2003 onwards</td>
</tr>
<tr>
<td>International Primary Care Respiratory Group Congress (IPCRG)</td>
<td>2002 onwards</td>
</tr>
<tr>
<td>Thoracic Society of Australia and New Zealand (TSANZ)</td>
<td>1999 onwards</td>
</tr>
</tbody>
</table>

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 strategy to identify relevant trials from the CAGR**

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Nitric Oxide
#6 nitric* NEXT oxide*
#7 FeNO
#8 eNO
#9 "airway inflammation"
#10 "exhaled NO"
#11 biomarker*:ti,ab
#12 #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 #4 and #12

[Note: in search line #1, MISC1 denotes the field in which the reference has been coded for condition, in this case, asthma]

**Contributions of Authors**

Written by HP and AC. KK, JAK and CT reviewed the protocol.
DECLARATIONS OF INTEREST

Some of the authors (HP, AC, JAK, CT) have conducted a RCT on this subject.

KK: none known

SOURCES OF SUPPORT

Internal sources

- Children's Hospital Foundation, Australia.
  Support for research team which AC & HP belong

External sources

- National Health and Medical Research Council, Australia.
  Support for AC and post doctoral fellowship for HP through a Centre of Research Excellence