Exhaled nitric oxide levels to guide treatment for children with asthma (Protocol)

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[Intervention Protocol]

Exhaled nitric oxide levels to guide treatment for children 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 medications based on exhaled nitric oxide (FeNO) for asthma related outcomes in children. We will compare this with not using FeNO i.e. management based on clinical symptoms (with or without spirometry/peak flow) and/or asthma guidelines.

BACKGROUND

Description of the condition

Asthma is one of the most common chronic diseases in children. Acute flare-ups (exacerbations) are common in children with asthma and some require more intensive treatment in hospital. Hospitalisations for asthma account for 12 to 21% (Anderson 2007; Akinbami 2009) of hospitalisations worldwide (Gupta 2006). Thus prevention of exacerbations, particularly severe exacerbations, is one goal of good asthma management. The second component in asthma management is monitoring of asthma control (by subjective and objective measures) (BTS/SIGN 2014; 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).

Airway inflammation associated with asthma 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 in-

flammation, 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).

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. Obtaining induced sputum samples and sputum analysis is labour intensive and not widely available in most routine clinical settings. Hypertonic saline, used to induce sputum may also temporarily increase asthma symptoms (such as wheeze, cough and chest tightness) and sputum is not always successfully obtained in young children. Thus, measures of FeNO confer some advantage over measurements of sputum eosinophils. However, assessment of FeNO levels do 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). The stationary analysers measure FeNO by chemoluminescence whilst the portable FeNO analysers measure FeNO using electrochemistry.

How the intervention might work

As FeNO is reflective of airway eosinophilia in some circumstances, FeNO can be considered as a biomarker. For asthma, FeNO levels can be potentially used in children with asthma to:

- monitor airway eosinophilia
- verify the adherence to ICS, and
- predict upcoming asthma exacerbations.

Reduction of airway inflammation improves symptoms and asthma control (Wardlaw 2000). Hence, the use of FeNO levels to tailor asthma medications in children with asthma may improve asthma control and/or reduce exacerbations.

Why it is important to do this review

A previous Cochrane Review analysed adults and children together (Petsky 2009). Given the clinical heterogeneity between children and adults, rather than update that review, we plan to undertake separate reviews for children and adults, this protocol focuses on children and there will be a similar systematic review that includes only adult participants.

A systematic review evaluating the efficacy of tailoring asthma interventions based on FeNO levels will be useful to guide clinical practice in children with asthma. Using FeNO routinely in clinical practice adds to the burden of asthma care and resource utilisation. On the other hand, routine use of FeNO to guide use of asthma medications may improve asthma control and reduce exacerbations and hospitalisations related to asthma.

OBJECTIVES

To evaluate the efficacy of tailoring asthma medications based on exhaled nitric oxide (FeNO) for asthma related outcomes in children. We will compare this with not using FeNO i.e. management based on clinical symptoms (with or without spirometry/peak flow) and/or asthma guidelines.

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 (FeNO) levels in comparison to those not using FeNO i.e. management based on clinical symptoms (with or without spirometry/peak flow) and/or current asthma guidelines.

Types of participants

We will include children/adolescents 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 pulmonary disease (COPD), or diagnostic categories such as 'cough variant asthma' and 'wheezy bronchitis'.

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 includes 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 weeks duration.

Types of outcome measures

Primary outcomes

Asthma exacerbations during follow-up. Defined as:

1. Number of participants 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 (FEV_1, 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. We will include studies reported as full-text, those published as abstract only, and unpublished data.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

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 'retrieve' (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. A second review author (KK) will spot-check study characteristics for accuracy against the trial report. 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 current search. 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.

Assessment of risk of bias in included studies

Two review authors (HP, KK) will independently assess risk of bias for each new 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.
4. Blinding of outcome assessment.
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.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations form 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 (MD) or standardised mean difference (SMD). 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 analysis (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. 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 (95%CI).

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 the study results will be described and tested to see if it reaches statistical significance using a chi-squared test. The 95%CI estimated using a random effects model will be included whenever there are concerns about statistical heterogeneity. Heterogeneity is considered significant when the P value is < 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 prespecified 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%CI (fixed effects model) will be calculated Review Manager (RevMan). For rate ratios of common events whereby one subject

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 CIs 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 GIV outcome, to provide summary weighted differences and 95%CI. 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 MD in outcomes could be estimated. If studies report outcomes using different measurement scales, the SMD 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 ($\leq$ 20 ppb versus > 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 children 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.

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

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* *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

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

Hand-searches: 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 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

HP, AC, JAK, CT: Have conducted a RCT on this topic which will be included in the review.

KK: none known

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Internal sources

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