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Interventions for primary (intrinsic) tracheomalacia in children

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ABSTRACT

Background

Tracheomalacia, a disorder of the large airways where the trachea is deformed or malformed during respiration, is commonly seen in tertiary paediatric practice. It is associated with a wide spectrum of respiratory symptoms from life-threatening recurrent apnoea to common respiratory symptoms such as chronic cough and wheeze. Current practice following diagnosis of tracheomalacia includes medical approaches aimed at reducing associated symptoms of tracheomalacia, ventilation modalities of continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP), and surgical approaches aimed at improving the calibre of the airway (airway stenting, aortopexy, tracheopexy).

Objectives

To evaluate the efficacy of medical and surgical therapies for children with intrinsic (primary) tracheomalacia.

Search methods

The Cochrane Airways Group searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Airways Group's Specialised Register, MEDLINE and EMBASE databases. The Cochrane Airways Group performed the latest searches in March 2012.

Selection criteria

All randomised controlled trials (RCTs) of therapies related to symptoms associated with primary or intrinsic tracheomalacia.

Data collection and analysis

Two reviewers extracted data from the included study independently and resolved disagreements by consensus.

Main results

We included one RCT that compared nebulised recombinant human deoxyribonuclease (rhDNase) with placebo in 40 children with airway malacia and a respiratory tract infection. We assessed it to be a RCT with overall low risk of bias. Data analysed in this review showed that there was no significant difference between groups for the primary outcome of proportion cough-free at two weeks (odds ratio (OR) 1.38; 95% confidence interval (CI) 0.37 to 5.14). However, the mean change in night time cough diary scores significantly favoured the placebo group (mean difference (MD) 1.00; 95% CI 0.17 to 1.83, P = 0.02). The mean change in daytime cough diary...
scores from baseline was also better in the placebo group compared to those on nebulised rhDNase, but the difference between groups was not statistically significant (MD 0.70; 95% CI -0.19 to 1.59). Other outcomes (dyspnoea, and difficulty in expectorating sputum scores, and lung function tests at two weeks also favoured placebo over nebulised rhDNase but did not reach levels of significance.

**Authors’ conclusions**

There is currently an absence of evidence to support any of the therapies currently utilised for management of intrinsic tracheomalacia. It remains inconclusive whether the use of nebulised rhDNase in children with airway malacia and a respiratory tract infection worsens recovery. It is unlikely that any RCT on surgically based management will ever be available for children with severe life-threatening illness associated with tracheomalacia. For those with less severe disease, RCTs on interventions such as antibiotics and chest physiotherapy are clearly needed. Outcomes of these RCTs should include measurements of the trachea and physiological outcomes in addition to clinical outcomes.

**PLAIN LANGUAGE SUMMARY**

**Interventions for primary (intrinsic) tracheomalacia in children**

The term malacia is derived from the Greek word ‘malakia’, meaning soft. In tracheomalacia, the walls of trachea (or windpipe) are softer than normal, which can lead to partial collapse (falling in) of the windpipe. This collapse usually happens when more air is needed, such as during exercise. The word ‘primary’ refers to tracheomalacia in which the windpipe itself is the cause of the disease, whereas secondary tracheomalacia is compressed due to some other abnormality near to the windpipe. The most common symptom of tracheomalacia is expiratory stridor (high-pitched wheezing sound). If the symptoms are severe enough, treatment such as mechanical ventilation, tracheal stenting (mesh tube inserted into windpipe to hold it open) or surgery may be needed.

We wanted to find out which out of these possible treatments was most effective. We found only one randomised controlled trial (RCT) that assessed nebulised recombinant human deoxyribonuclease (rhDNase) which helps in breaking down the mucous and has been shown to be useful in aiding airway clearance in cystic fibrosis compared to placebo (no active treatment) in children with both tracheomalacia and a concurrent respiratory infection. This trial showed no evidence of benefit in terms of the number of children who were cough-free two weeks after treatment. Also, there was less coughing reported, both during the day and at night, in the group who did not receive the intervention - however these differences were not statistically significant.

With the lack of evidence, the routine use of any therapies for intrinsic tracheomalacia cannot be recommended given the cost of nebulised rhDNase and the likely harmful effect. The decision to subject a child to any surgical or medical based therapies will have to be made on an individual basis, with careful consideration of the risk-benefit ratio for each individual situation.

It is unlikely that any RCT on surgically based management will ever be available for children with severe life-threatening illness associated with tracheomalacia. For those with less severe disease, RCTs on interventions such as antibiotics and chest physiotherapy are needed.
**SUMMARY OF FINDINGS FOR THE MAIN COMPARISON**

**Patient or population:** children with primary (intrinsic) tracheomalacia  
**Settings:** outpatient  
**Intervention:** human deoxyribonuclease  
**Control:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
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<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Human deoxyribonuclease versus placebo</td>
<td></td>
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</table>
| Clinical failure   | Number of children with no significant improvement in cough diary scores at two weeks (average of day 13 to 14)  
Follow-up: 2 weeks | 57 per 100 (33 to 87) | OR 1.38 (0.37 to 5.14) | 38 (1 study) | ⊕⊕⊕⃝⃝ Low quality¹ | These results should be interpreted with caution given there is only one study |
| Daytime cough diary scores (change from baseline)   | Follow-up: 2 weeks  
On a scale of 0 to 5, 0 being no cough and 5 means unable to perform most usual activities due to coughing | -1.7 | 0.70 higher (-0.19 to 1.59) | 38 (1 study) | ⊕⊕⃝⃝ Low quality¹ | There was no significant difference in daytime cough diary scores in two groups |
<table>
<thead>
<tr>
<th>Measure</th>
<th>Change from Baseline</th>
<th>Effect Size</th>
<th>CI</th>
<th>Quality</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night time cough diary score</td>
<td>-1.7</td>
<td>1.00 higher (0.17 to 1.83)</td>
<td>38 (1 study)</td>
<td>⊕⊕⊕⊕ Low quality²</td>
<td>Night time cough diary scores significantly favoured the placebo group</td>
</tr>
<tr>
<td>Night time VAS (change from baseline)</td>
<td>-36.7</td>
<td>23.00 higher (3.86 to 42.14)</td>
<td>38 (1 study)</td>
<td>⊕⊕⊕⊕ Low quality²</td>
<td>Night time VAS significantly favoured the placebo group</td>
</tr>
<tr>
<td>Difficulty expectorating sputum score</td>
<td>-35.6</td>
<td>0.46 higher (-0.19 to 1.11)</td>
<td>38 (1 study)</td>
<td>⊕⊕⊕⊕ Low quality²</td>
<td>The data supported the placebo but the CI is too wide</td>
</tr>
</tbody>
</table>

**Notes:**
- VAS: Visual Analog Scale
- CI: Confidence Interval
- Low quality²: Indicates low quality of evidence due to potential publication bias or other methodological issues.

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<table>
<thead>
<tr>
<th>Difficulty in expectoration and 100 would mean unable to expectorate</th>
<th>Lung function: FVC % predicted (baseline to end point)</th>
<th>Follow-up: 2 weeks</th>
<th>-8.2%</th>
<th>8.80% lower (-0.05 to 17.65)</th>
<th>27 (1 study)</th>
<th>⊕⊕⊕⊕ Low quality&lt;sup&gt;1&lt;/sup&gt;</th>
<th>The FVC % improved with placebo but worsened with rhDNase and the difference between two groups was of borderline significance</th>
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<tr>
<td>Lung function: FEV&lt;sub&gt;1&lt;/sub&gt; % predicted (baseline to end point)</td>
<td>Follow-up: 2 weeks</td>
<td>-10.8%</td>
<td>9.20% lower (-0.55 to 18.95)</td>
<td>27 (1 study)</td>
<td>⊕⊕⊕⊕ Low quality&lt;sup&gt;1&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; % at end point improved more with placebo, but the CI was too wide to be of any significance</td>
<td></td>
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*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). The assumed risk for continuous data is the mean for the placebo group and corresponding risk is the mean difference. Since there was only one study in the review, assumed risk is not expressed as a range.

CI: confidence interval; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; OR: odds ratio; rhDNase: recombinant human deoxyribonuclease; VAS: visual analogue score.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

<sup>1</sup> These results come from a single study on a small number of participants and need confirmation in other, larger studies.
BACKGROUND

Tracheomalacia is a disorder of the large airways where the trachea is deformed or malformed during respiration (Masters 2002). Tracheomalacia is commonly seen in tertiary paediatric practice (Masters 2002) and many of the children are only referred for assessment after repeated failure of therapies, which include asthma drug therapies (Gormley 1999; Thomson 2002). This large airway disorder can be classified as primary (intrinsic abnormality of the airway) or secondary (related to compression of trachea by another structure such as a mass). Primary tracheomalacia may occur in isolation, or in association with other malacia disorders (laryngomalacia and bronchomalacia), as part of a syndrome (e.g. Down's syndrome, Ehlers-Danlos syndrome), or with other congenital non-syndromic disorders (e.g. cardiac abnormalities, tracheoesophageal fistula etc.) (Austin 2003; Masters 2002). Some have classified tracheomalacia associated with other abnormalities as secondary tracheomalacia assuming that it is related to the compression effects. Embryologically, these tracheomalacia are related to a developmental abnormality with the associated condition (as opposed to because of the associated condition) (Beasley 1998) and in general do not totally resolve after correction of the associated problem (such as in tracheoesophageal fistula (Kovesi 2004) or after thoracic vascular surgery (Horvath 1992; van Son 1993). Therefore we have classified these types of tracheomalacia as primary tracheomalacia with associated abnormalities. True secondary tracheomalacia generally resolves on removal of the offending agent (such as a mediastinal mass or lymph node) and thus will not be discussed in this review.

Description of the condition

Tracheomalacia is associated with common respiratory symptoms (Masters 2009). The most common symptoms at presentation are persistent respiratory symptoms, in particular chronic cough and wheeze. These symptoms cover most of the common respiratory symptoms seen in children and thus it not surprising that diagnosis is often delayed (Gormley 1999; Masters 2002; Wood 1997). Gormley 1999 described that 75% of children with congenital tracheomalacia secondary to congenital vascular anomaly had persistent cough at presentation. As these symptoms overlap with other respiratory disorders, it is also not surprising that the diagnosis and management of tracheomalacia is often suboptimal (Gormley 1999). Other respiratory symptoms include recurrent infections and pneumonia, recurrent cyanosis, stridor, exertional dyspnoea and effort intolerance. Severe tracheomalacia may also be associated with difficult anaesthesia (Austin 2003) and increased CO2 value during flexible bronchoscopy under general anaesthesia is associated with these airway lesions (Chang 2004). Non-respiratory symptoms related to tracheomalacia have also been described and these include dysphagia (Agrawal 1999) and gastroesophageal reflux (Bibi 2001).

Tracheomalacia may be diagnosed by flexible and rigid bronchoscopy, radiological airway screening, chest computed tomography (CT) scan, magnetic resonance imaging (MRI) or tracheobronchogram. The current gold standard of diagnosing tracheomalacia is by visual assessment during bronchoscopy (Wright 2003) and flexible bronchoscopy is superior to rigid bronchoscopy for evaluation of tracheobronchomalacia (Midulla 2003). Airway screening is a rather insensitive tool for diagnosis of tracheomalacia in children (Sanchez 2012). Flexible bronchoscopy provides the best assessment for the dynamic airway changes found in tracheobronchomalacia (Midulla 2003). The other methods of diagnosis are less reliable and/or have major pitfalls. During flexible bronchoscopy, different visual descriptions of tracheomalacia have been described (Masters 2002). However the associated symptoms are similar (Masters 2002).

Description of the intervention

The respiratory symptoms attributed to tracheomalacia are most likely primarily to be related to the effect of a narrowed airway generating altered airflow. Wheeze is generated from altered flow through a narrowed tube. Misdiagnosis of asthma in children with airway malacia disorders has been well described (Finder 1997). Cough is likely related to reduction of mucociliary clearance as the compressed airway impedes clearance of secretions (Finder 1997) which sets up a bronchitic process distal to the lesion. Exactly why this occurs is unknown but the possibility of a more subtle process that involves functional abnormalities in the development of the neurovascular and airway immunological, smooth muscle and epithelial cell lines would be biologically possible, but have not been described. Thus, it is also plausible that a change in anatomical improvement (if possible) may not necessary result in symptomatic improvement.

Thus, interventions for tracheomalacia include: procedures or medications that improve airway calibre (such as stents, aortopexy and continuous positive airway pressure), enhance airway clearance (such as mucoactive agents like hypertonic saline and nebulised recombinant human deoxyribonuclease (rhDNase)), short- and/or long-term antibiotics to treat and/or prevent infective exacerbations and reduce airway inflammation (such as corticosteroids).

How the intervention might work

Current practice following diagnosis of tracheomalacia includes medical approaches aimed at reducing associated symptoms of tracheomalacia and surgical approaches aimed at improving the calibre of the airway (airway stenting, aortopexy) and thus reducing associated symptoms.
Why it is important to do this review

Children with tracheomalacia often have respiratory symptoms, and it is not an uncommon disease among children (incidence of approximately 1 in 1500 to 2500 children in a study in The Netherlands) (Boogaard 2005). The interventions described above may have serious and significant adverse events. Hence, there is a need for systematic evaluation of the effects of interventions aimed at reducing the respiratory symptoms related to tracheomalacia.

OBJECTIVES

To evaluate the efficacy of medical and surgical therapies for children with intrinsic (primary) tracheomalacia.

METHODS

Criteria for considering studies for this review

Types of studies
All randomised controlled trials (RCTs) of therapies related to symptoms associated with primary or intrinsic tracheomalacia.

Types of participants
Children aged < 15 years with tracheomalacia with associated respiratory symptoms.
Exclusion criteria: secondary tracheomalacia.

Types of interventions
All randomised controlled comparisons of therapies for symptoms associated with primary or intrinsic tracheomalacia. We included trials that included the use of other medications or interventions if all participants had equal access to such medications or interventions.

Types of outcome measures

Primary outcomes
1. Proportion of participants who were not cured or not substantially improved at follow-up (clinical failure).

Secondary outcomes
1. Proportion of participants who were not cured at follow-up.
2. Proportion of participants who not substantially improved at follow-up.
3. Mean difference (MD) in number of respiratory episodes (defined by diary cards or acute respiratory illness score).
4. Proportion requiring hospitalisation for respiratory illness.
5. MD in symptoms and signs (mean improvement in clinical state).
6. Proportion developing new respiratory complications such as bronchiectasis, bronchiolitis obliterans, etc.
7. Proportion requiring acute or complicated airway intervention (prolonged intubation, tracheostomy, etc.).
8. Proportion experiencing adverse effects of the intervention (e.g. death from surgery, surgical complications, etc.).

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

1. Objective measurements of cough indices (cough frequency).
2. Symptomatic (Quality of life scale, Likert scale, visual analogue scale (VAS), level of interference of respiratory symptoms such as cough, wheeze, cyanotic events, etc. using diaries) - assessed by child.
3. Symptomatic (Quality of life scale, Likert scale, VAS, level of interference of respiratory symptoms such as cough, wheeze, cyanotic events, etc. using diaries) - assessed by the parents/carers.
4. Symptomatic (Likert scale, VAS, level of interference of respiratory symptoms such as cough, wheeze, cyanotic events, etc. using diaries) - assessed by clinicians.
5. Pulmonary function tests.
7. Relevant airway markers consistent with neutrophilic inflammation.

Search methods for identification of studies

Electronic searches
We used the following topic search strategy to identify the relevant randomised controlled trials (RCTs) listed in the electronic databases.

("tracheomalacia" OR "tracheo-malacia" OR "malacia" OR "trachea abnormalities" OR "tracheal diseases" all as (text word) or (MeSH)) AND ("child" OR "children" OR "infant" as (text word) or (MeSH)). The full search strategies are shown in Appendix 1; Appendix 2; and Appendix 3. We identified trials from the following sources.
1. The Cochrane Controlled Trials Register (CENTRAL), which includes the Cochrane Airways Review Group’s Specialised Trials Register, Issue 2 of 12, 2012.
2. MEDLINE 1946 to March 2012.

We did not impose any restriction on language of publication, or publication status. We conducted the searches in March 2012.

Searching other resources

In addition, we searched the list of references in relevant publications and wrote to authors of trials included in the review.

Data collection and analysis

Selection of studies

From the title, abstract or descriptions, two authors independently reviewed literature searches to identify potentially relevant trials for full review. We searched bibliographies and texts to identify additional studies (IBM and AC in the original review and VG and AC in this updated review. From the full-text using specific criteria, VG and AC independently selected trials for inclusion. Disagreement would have been resolved by consensus, but there was no disagreement between the two authors.

Data extraction and management

We reviewed the 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 children); inclusion and exclusion criteria; randomisation and allocation concealment method; numbers of participants randomised; blinding (masking) of participants; care providers and outcome assessors; intervention (duration and type); control; co-morbidities (all medical problems with particular attention to genetic syndromes and co-morbidities); existing respiratory problems; cointerventions; numbers of patients 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 had planned to extract data on the outcomes described previously.

We extracted information from the study for the following characteristics.

1. Type of study (description of randomisation, blinding, allocation, withdrawals).
2. Participants (N, age range).
3. Intervention (type of intervention: medical or surgical, duration of intervention, cointerventions).
4. Outcomes (primary and secondary outcomes, timing of outcome assessments, adverse outcomes).

We planned to request further information from the trial authors where required. Dr Boogaard (Boogaard 2009) kindly provided us with his raw data that enabled us to calculate the number of participants who failed to improve at the end of two weeks.

Assessment of risk of bias in included studies

We assessed risk of bias in the trials for the following seven domains using the ‘Risk of bias’ table in Review Manager 5 (RevMan 2011). The authors judged whether there was high or low risk of these biases. Where the risk was not clear, we stated as such.

1. Sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
5. Incomplete outcome data.
7. Other potential sources of biases.

Measures of treatment effect

We extracted data for each of the outcomes (where data were available) from the trial publication that fulfilled the inclusion criteria.

Unit of analysis issues

We sought to obtain data that were reported with patients (rather than events) as the unit of analysis for the primary outcomes.

Dealing with missing data

We contacted the authors for missing data. For intention-to-treat analysis, we assumed that missing values would have had poor outcomes. We planned to perform sensitivity analyses to assess how sensitive the results are to the reasonable assumptions made in regards to the missing data.

Assessment of heterogeneity

We had planned to describe and explore heterogeneity between the study results and to use the 95% CI, estimated using a random-effects model, whenever there were concerns about statistical heterogeneity.

Assessment of reporting biases

We had planned to identify and report on any selective reporting in the included trials. We would have tested publication bias using a funnel plot, if five or more studies were available in the review.
Data synthesis

We had planned to combine data using Review Manager 5 (RevMan 2011), with a view to using a fixed-effect mean difference (MD) (calculated as a weighted MD) for continuous data variables. If different scales were combined, we had intended to use the standardised mean difference (SMD).

For dichotomous outcome variables of each individual study, we calculated the odds ratios (ORs) using a modified intention-to-treat analysis (i.e., failure assumed if participant drops out of study). This analysis assumes that children not available for outcome assessment have not improved (and probably represents a conservative estimate of effect).

We intended to calculate a number needed to treat (benefit or harm) when possible for the different levels of risk as represented by control group event rates over a specified time period using the pooled OR and its CI using an online calculator, Visual Rx (Cates 2003). We constructed a 'Summary of findings' table according to recommendations in the Cochrane handbook of Systematic Reviews of Interventions (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We had planned an a priori subgroup analysis for:
1. age: infants (less than 12 months) or children (aged 1 to 14 years);
2. presence of congenital (cardiac, tracheoesophageal fistula) syndromes;
3. medical therapies; and
4. surgical therapies.

As there was only a single study, a subgroup analysis was not applicable.

Sensitivity analysis

We had planned sensitivity analyses to assess the impact of the following potentially important factors on the overall outcomes.
1. Variation in the inclusion criteria.
2. Differences in other medications/procedures used in the intervention and comparison groups.
3. Analysis using a random-effects model.
4. Analysis by 'treatment received' or 'intention-to-treat'.

As there was only a single study, a sensitivity analysis was not applicable.

RESULTS

Description of studies

Results of the search

The original search in 2008 did not identify any eligible studies. The Airways Group search in March 2012 identified 118 potentially relevant titles since the last update of the review (2008). After assessing the abstracts, we retrieved five papers, out of which we considered only one study for inclusion in the review as it fulfilled the study eligibility criteria.

Included studies

The single eligible study (Boogaard 2009) was conducted in children that had planned to include children aged 2 to 18 years. We included this study as children were aged 2.8 to 15.5 years. This RCT compared nebulised recombinant human deoxyribonuclease (rhDNase) with placebo in children with airway malacia and lower respiratory tract infection (LRTI). The episode of LRTI was defined by the authors as (an increase in) productive cough or dyspnoea, and/or auscultatory abnormalities on physical examination, and/or increased bronchitic markings or consolidation on a chest radiograph respiratory exacerbation. The primary outcome of this study was change in cough diary scores (week two compared to baseline) and this score was a validated scoring system (Chang 1998a). Details of the study are in Characteristics of included studies and some aspects are also described below. The authors of the study used the term airway malacia so we have used this term accordingly along with tracheomalacia.

Excluded studies

We have added one of the more recent non-controlled studies to Characteristics of excluded studies (Gallagher 2011). It was a retrospective study (hospital chart review) comparing the treatment results of ipratropium bromide in children with tracheomalacia. The authors reported that 32 out of 52 children (for whom complete data were available) diagnosed with tracheomalacia and treated with ipratropium bromide after having been referred for specialist care, had improvement in their symptoms following treatment with ipratropium bromide.

Risk of bias in included studies

Overall we assessed the sole included study (Boogaard 2009) to have a low risk of bias as detailed in the 'Risk of bias' table and summarised in Figure 1. The following 'Risk of bias' domains refer to the sole study (Boogaard 2009) included in this review.
Allocation
Randomisation was done in the pharmacy using a computer-generated blocked randomisation list prepared by a statistician. The study medication was prepared by a hospital pharmacist.

Blinding
Study medication and placebo vials had identical appearance and smell. The parents, children, pulmonologists and trial co-ordinator remained unaware of the treatment assignment.

Incomplete outcome data
The number of participants withdrawn (one in the placebo group before the study drug was given, and one in the nebulised rhDNase group after the first dose of the study drug) and those who did not fill in their cough diary scores (one in each group) were reported for both nebulised rhDNase and placebo groups.

Selective reporting
There was no suggestion that selective reporting had occurred.

Other potential sources of bias
The study was sponsored by pharmaceutical companies but reportedly they neither had influence on the design of the study, on the analysis of the study data nor in the publication of the results.

Effects of interventions
See: Summary of findings for the main comparison
Human deoxyribonuclease versus placebo for primary (intrinsic) tracheomalacia in children

Primary outcome
The primary outcome for the review was the proportion of participants who were not cured or not substantially improved at follow-up (clinical failure). Authors did not define this and hence from the raw data provided by Dr Boogaard, we calculated the number of children with clinical failure at follow-up. Based on previous published studies (Chang 1998b; Chang 2012; Marchant 2012), we defined clinical failure as less than 75% improvement in average daytime and night time cough diary scores at two weeks. We took the average of daytime and night time cough diary scores in the first two days of the study and compared it with the average of night time and daytime cough diary scores on day 13 and day 14. For one participant a cough diary score was not available for day 13 and so we used days 12 and 14 for this calculation. Another participant had daytime data missing for day 14, and so we used days 12 and 13 for this estimation. As depicted in (Analysis 1.1), 12 participants out of 21 were not cured or significantly improved at two weeks in the placebo group, compared to 11 participants out of 17 in the nebulised rhDNase group. There was no significant difference between the groups (OR 1.38; 95% CI 0.37 to 5.14; Figure 2).
Secondary outcomes

Change in cough score from baseline

Mean changes in daytime cough diary score (Analysis 1.2) from baseline was better in the placebo group compared to those on nebulised rhDNase treatment, but the difference between groups was not statistically significant (mean difference (MD) 0.70; 95% CI -0.19 to 1.59). The change in night time scores (Analysis 1.3) significantly favoured the placebo group (MD 1.00; 95% CI 0.17 to 1.83, P = 0.02; Figure 3).

There was a significant (P = 0.02) difference between groups for visual analogue scores (VAS) of night time cough (Analysis 1.5; Figure 4) favouring the placebo group (MD 23.00; 95% CI 3.86 to 42.14), but there was no significant difference between groups for daytime score (Analysis 1.4) (MD 15.70; 95% CI -3.33 to 34.73).
**Need for antibiotics**

Antibiotics were started in 5 of 17 (29%) children in the nebulised rhDNase group and in 8 of 21 (38%) children in the placebo group during the two week treatment period, (MD 9%; 95% CI -21% to 39%, P = 0.58).

**Other scores**

Boogaard 2009 also described VAS for daytime dyspnoea, night time dyspnoea (Analysis 1.6), and for difficulty in expectorating sputum (Analysis 1.7). These outcomes all improved significantly in both the nebulised rhDNase and placebo groups during the treatment period; the difference between the nebulised rhDNase and placebo favoured the placebo group, but these differences were not statistically significant.

**Lung function**

The forced vital capacity (FVC) percentage predicted improved significantly in the placebo group but worsened in the nebulised rhDNase group (Analysis 1.8; Figure 5). The difference between the groups was at borderline significance (MD 8.80; 95% CI -0.05 to 17.80, P = 0.05). The forced expiratory volume in one second (FEV1) percentage predicted also improved (Analysis 1.9) in the placebo group as compared to the nebulised rhDNase group, but there was no significant difference between the groups (MD 9.20; CI -0.55 to 18.95, P = 0.06; Figure 6).

**DISCUSSION**

**Summary of main results**

This review update is limited to a single study eligible for inclusion. Nebulised recombinant human deoxyribonuclease (rhDNase) did not improve and likely worsened respiratory symptoms when used during lower respiratory tract infections (LRTIs) in children with airway malacia. The data from this review were different to that published in the paper as we did not adjust for baseline imbalance. The children in the nebulised rhDNase group were symptomatic for seven days as compared to three days for placebo. Also, at baseline the placebo group showed lower lung function, and higher visual analogue scores (VAS) for night time cough and night time dyspnoea than did the nebulised rhDNase group. There were no other significant differences between groups at baseline. Hence, we did not adjust for baseline. The likely harm from nebulised rhDNase which was found in our review, was not evident in the published paper after adjusting for baseline (Boogaard 2009).

Boogaard 2009 postulated that dynamic airway collapse during coughing in children with airway malacia results in airway obstruc-
tion and impaired mucociliary clearance, and expected a beneficial effect of nebulised rhDNase during LRTIs. However, we found the reverse. There are several possible explanations for the lack of beneficial effect of nebulised rhDNase in this study compared to that for children with cystic fibrosis (CF). One reason is the difference between the physical characteristics of mucus produced in children with CF (in CF large polymers predominate in the airway secretions; these polymers include deoxyribonucleic acid (DNA), filamentous actin, proteoglycans, and bio films, which in combination with bacteria and inflammatory cells constitute sputum) and children with primary tracheomalacia (Voynow 2009). The mucous produced in children with airway malacia is likely similar to normal children. Unlike children with CF; the reduced mucous clearance in children with airway malacia is likely related to airway mechanics. The quality of sputum can be measured by different properties like dynamic viscoelasticity, wettability, cohesiveity, interfacial (surface) tension, solids composition, Interleukin 8 and DNA content (Rubin 2007). The rheologic properties that favour mucociliary clearance appear to hinder cough clearance and vice versa (Rogers 2006). Thus the use of nebulised rhDNase that alters sputum cohesiveness can impair airway clearance. This review highlights the fact that some of the interventions (like nebulised rhDNase) advocated by some for use in children with primary tracheomalacia are not efficacious or even potentially harmful. The non-beneficial and likely harmful effect of nebulised rhDNase we found in our review is similar to that described in the detrimental effect of nebulised rhDNase when used in adults with non-CF bronchiectasis (Crockett 2001).

Overall completeness and applicability of evidence

For determining the primary outcome in our review, we averaged the scores over the first two days (for baseline) and the last two days (for final score). This was done as there is a day to day variability in cough diary cards and thus taking an average at the start and at the end (as done in our various studies on cough such as Chang 2010 and Marchant 2012) is arguably more robust. Furthermore, when we used only the first and last day’s data, the difference in results of clinical failure remained statistically insignificant. The single study on nebulised rhDNase cannot be applied to the effect of other mucolytics for airway malacia. This review has highlighted the fact that, although there are many medical and surgical therapies being used for the management of children with tracheomalacia, there remains a paucity in high quality data to support any single intervention. Although the review has shown that nebulised rhDNase is not useful as a medical therapy in children with airway malacia, this review is not a meta-analysis of different types of treatment options for tracheomalacia as there are no published RCTs. This review highlights the need to provide evidence based answers to this query.

Quality of the evidence

There is only a single study in this review and hence quality of evidence is substantially limited.

Potential biases in the review process

The Cochrane Airways Group conducted an extensive search for RCTs in children with airway malacia. Two authors independently screened the searches and identified one study for inclusion. We identified the study itself as having overall low risk of bias. We have contacted the original investigators who kindly provided the raw data for calculation of clinical failure.

Agreements and disagreements with other studies or reviews

There are numerous cohort descriptive studies with varying numbers of patients that reported on a variety of interventions (mainly surgical) to increase the airway calibre. Most of these children managed surgically had presumably the severe end of the clinical spectrum, with life-threatening apnoea episodes. These cohort studies (see Characteristics of excluded studies) have highlighted the importance of interventions in terms of clinical improvement. However these surgical procedures (tracheopexy, aortopexy and/or stenting) are not universally successful and have associated morbidity and mortality (Valerie 2005). Continuous positive airway pressure (CPAP) alters forced expiratory flow in infants, but the authors did not describe clinical correlates (Davis 1998). There are no studies that quantitatively defined severity, either anatomically or clinically. Also, when tracheomalacia is associated with a vascular compression, surgical correction of the vascular compression alleviates major respiratory symptoms in most (68%) but not in a significant number of children (Benjamin 1976; Bonnard 2003). Physiological measurement studies of lung function have shown short-term benefits in function in lung mechanics and improvement in spirometric parameters for selective children managed with surgical intervention (Zinman 1995) and CPAP (Davis 1998). However there are no quantitative assessments of severity of the tracheomalacia at the entry or end point. Interpretation of lung function may be limited unless paired (pre- and post-intervention) data are obtained, as children with these airway abnormalities may have reduced lung growth (Agrawal 1999). At the mild end of the spectrum there are no studies that have assessed the disease impact, assessed the management of intercurrent respiratory illness or symptoms associated with tracheomalacia, nor supported any treatment for it.

Authors’ Conclusions

Interventions for primary (intrinsic) tracheomalacia in children (Review)

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Implications for practice

Based on a single randomised trial, it is not possible to make meaningful recommendations for the routine use of any therapies for intrinsic tracheomalacia. Results of a single trial show that nebulised rhDNase appears not to be efficacious and likely harmful when used during a respiratory exacerbation. The decision to subject a child to surgical and/or medical based therapies will have to be made on an individual basis, with careful consideration of the risk-benefit ratio for each individual situation.

Implications for research

It is unlikely that any RCT on surgery for children with life-threatening illness associated with tracheomalacia will ever be available. For those with less severe disease, RCTs on interventions currently used by many respiratory physicians such as early use of antibiotics and chest physiotherapy are clearly needed. Other possible interventions include different mucolytics (such as hypertonic saline) and anti-inflammatories such as corticosteroids. Such trials should be parallel double-blind studies and outcomes should include correlation with measurements of the trachea and physiological based measurements in addition to clinical outcomes.

ACKNOWLEDGEMENTS

We thank Toby Lasserson and Chris Cates from the Airways Group for their advice, supportive role and comments to the protocol and review. For the update we also thank Emma Welsh for her support. We are also very grateful to Elizabeth Stovold for performing the relevant searches over many years and for obtaining the articles.

REFERENCES

References to studies included in this review

Boogaard 2009 [published data only]

References to studies excluded from this review

Abdel-Rahman 2002 [published data only]

Corbally 1993 [published data only]

Davis 1998 [published data only]

Filler 1993 [published data only]

Gallagher 2011 [published data only]

McCarthy 1997 [published data only]

Nicolai 2001 [published data only]

Vazquez-Jimenez 2001 [published data only]

Vinograd 1994 [published data only]

Additional references

Agrawal 1999

Austin 2003
Interventions for primary (intrinsic) tracheomalacia in children (Review)

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Beasley 1998

Benjamin 1976

Bibi 2001

Bonnard 2003

Boogaard 2005

Cates 2003 [Computer program]

Chang 1998a

Chang 1998b

Chang 2004

Chang 2010

Chang 2012

Crockett 2001

Finder 1997

Gormley 1999

Higgins 2011

Horvath 1992

Kovesi 2004

Marchant 2012

Masters 2002

Masters 2009

Midulla 2003

RevMan 2011 [Computer program]

Rogers 2006
Rubin 2007

Sanchez 2012

Thomson 2002

Valerie 2005

van Son 1993

Voynow 2009

Wood 1997

Wright 2003

Zinman 1995

References to other published versions of this review

Masters 2005

* Indicates the major publication for the study
## CHARACTERISTICS OF STUDIES

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

**Boogaard 2009**

| **Methods** | • Prospective, double-blind, parallel group randomised controlled study  
• Compared effect of inhaled rhDNase with placebo on respiratory symptoms, the need for antibiotics, and lung function  
• Outpatient setting in Erasmus MC-Sophia Children's Hospital and Amphia Hospital, Breda between September 2005 and March 2008  
• Children already diagnosed with malacia according to accepted guidelines (described in the study)  
• Children with airway malacia and recurrent LRTIs from outpatient department, were instructed to contact the hospital when they developed symptoms suggestive of a LRTI  
• Patients were recruited by paediatric pulmonologists at the outpatient department within 2 days of this contact  
• Allocation sequence executed by the study co-ordinator based on the randomisation schedule prepared by the study statistician  
• The decision for investigations was up to the paediatric pulmonologist  
• Patients were re-evaluated by a paediatric pulmonologist after 1 (visit 2) and 2 weeks (visit 3)  
• The study co-ordinator contacted parents by telephone after 3 weeks |
| **Participants** | • 49 children screened for inclusion  
• 5 did not have LRTI and 4 needed antibiotics  
• 22 were assigned to the placebo group and 18 to the rhDNase group (total 40)  
• 21 children received placebo and 17 children received rhDNase (20 females out of 38); one withdrawal in each group  
• Mean age in placebo group was 6.0 and 6.7 years in the rhDNase group. Inclusion criteria: children aged 2 to 18 years with airway malacia and symptoms of LRTI  
• Baseline demographic characteristics did not differ between the treatment groups  
• Exclusion criteria: need for antibiotics at initial presentation, chronic cardiopulmonary disease and neuromuscular disease |
| **Interventions** | • 2.5 mg of rhDNase (2.5ml solution of 1 mg/ml rhDNase) or 2.5 mg placebo (2.5ml sodium chloride 0.9%), twice daily for 2 weeks  
• Study medication was administered with a Sidestream jet nebuliser using a PortaNeb Compressor  
• The first dose of study medication was administered in the outpatient department |
| **Outcomes** | Primary outcomes: change in symptom severity from baseline to second week of treatment, assessed with a cough diary score  
Secondary outcomes:  
• need for an antibiotic course during the two-week treatment period  
• cough scores  
• severity of dyspnoea  
• ease of expectorating sputum  
• lung function |
### Boogaard 2009  *(Continued)*

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random sequence generation (selection bias)</strong></td>
<td>Low risk</td>
<td>Randomisation done in the pharmacy using a computer-generated blocked randomisation list prepared by statistician</td>
</tr>
<tr>
<td><strong>Allocation concealment (selection bias)</strong></td>
<td>Low risk</td>
<td>The study medication was prepared by hospital pharmacist and rhDNase and placebo vials had identical appearance and smell</td>
</tr>
<tr>
<td><strong>Blinding of participants and personnel (performance bias)</strong></td>
<td>Low risk</td>
<td>Throughout the study, parents, children, pulmonologists and trial co-ordinator remained unaware of the treatment assignment</td>
</tr>
<tr>
<td><strong>Blinding of outcome assessment (detection bias)</strong></td>
<td>Unclear risk</td>
<td>Both subjects and researchers were blinded to the outcomes measured but blinding by statistical team was not mentioned</td>
</tr>
<tr>
<td><strong>Incomplete outcome data (attrition bias)</strong></td>
<td>Low risk</td>
<td>No study data was available for one child from each group as they did not take the study medication or withdrew after randomisation</td>
</tr>
<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td>Low risk</td>
<td>No evidence of selective reporting found</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Unclear risk</td>
<td>Study funded by pharmaceutical companies but the companies did not have influence on the design of the study, analysis of the study data or writing of the manuscript</td>
</tr>
</tbody>
</table>

LRTI: lower respiratory tract infection  
rhDNase: recombinant human deoxyribonuclease
### Characteristics of excluded studies  
**[ordered by study ID]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Rahman 2002</td>
<td>Non-controlled study. Authors reported on effect of aortopexy on 16 infants and children with tracheomalacia. No intraoperative or postoperative mortality occurred and 13 (81%) had permanent relief of symptoms</td>
</tr>
<tr>
<td>Corbally 1993</td>
<td>Non-controlled study. Authors reported on 48 patients with repaired congenital oesophageal anomaly who underwent aortopexy for significant tracheomalacia. Indications for aortopexy included recurrent apnoea/cyanosis, near fatal episodes, recurrent respiratory distress and infection and worsening stridor. Aortopexy cured near fatal episodes in all patients and resulted in improvement of airway obstruction in 95%. The procedure failed in 2 patients due to unrecognised bronchomalacia and phrenic nerve palsy</td>
</tr>
<tr>
<td>Davis 1998</td>
<td>Non-controlled study. Continuous positive airway pressure (CPAP) was used to minimise airway collapse in infants with tracheomalacia. Forced expiratory flows increased with CPAP use</td>
</tr>
<tr>
<td>Filler 1993</td>
<td>Non-controlled study. The authors reported on their five-year experience of inserting the Palmaz stent into infants and children who had a variety of major airway obstructions, including tracheomalacia in eight children. Granulation tissue developed over the stents in five of eight cases. Obstructing granulations were removed by scraping or balloon compression in three and resulted in earlier than the planned removal in two</td>
</tr>
<tr>
<td>Gallagher 2011</td>
<td>Non-controlled study. Authors retrospectively reviewed charts of 52 children with tracheomalacia and treated with ipratropium bromide after having been referred for specialist care. Mild tracheomalacia was diagnosed in 34 (65.3%) children while moderate tracheomalacia was seen in 18 (34.7%). Overall 32 (61.5%) children had improvement in their symptoms following treatment with ipratropium bromide</td>
</tr>
<tr>
<td>McCarthy 1997</td>
<td>Non-controlled study. Twenty-four infants and children with various causes of airway obstruction including tracheomalacia. Hospital mortality was 8.7%, 19 (79.2%) patients were alive and symptom-free. The single most important predictor of mortality was the presence of associated cardiac anomalies</td>
</tr>
<tr>
<td>Nicolai 2001</td>
<td>Non-controlled study. Authors reported on 7 children with extreme structural central airway obstruction (six were mechanically ventilated). All patients showed marked improvement of their respiratory obstruction; six were weaned at least temporarily from ventilation. Three children are well and at home</td>
</tr>
<tr>
<td>Vazquez-Jimenez 2001</td>
<td>Non-controlled study. Authors reported on 29 children operated for tracheomalacia associated with oesophageal atresia. No early nor late mortality occurred. Surgery associated morbidity: reversible lesion of the phrenic nerve was observed in two patients, a pneumothorax in three, and secondary wound healing in one. In all but one patient symptoms improved markedly or disappeared within days or within the first three months postoperatively. An increased susceptibility to respiratory infections was observed in long-term follow-up of children</td>
</tr>
<tr>
<td>Vinograd 1994</td>
<td>Non-controlled study. Authors reported on surgical management (aortopexy) of 54 children with airway problems, of whom 20 had tracheomalacia. No operative deaths occurred</td>
</tr>
</tbody>
</table>
### DATA AND ANALYSES

**Comparison 1. Human deoxyribonuclease versus placebo**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>1 Clinical failure (Number of children with no significant improvement in cough scores at two weeks)</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
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<tr>
<td>2 Daytime cough diary scores (change from baseline)</td>
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<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
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<tr>
<td>3 Night time cough diary score (change from baseline)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4 Daytime visual analogue score (change from baseline)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5 Night time visual analogue score (change from baseline)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6 Night time dyspnoea score (change from baseline)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>7 Difficulty expectorating sputum score (change from baseline)</td>
<td>1</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8 Lung function: FVC % predicted</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9 Lung function: FEV1 % predicted</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 1 Clinical failure (Number of children with no significant improvement in cough scores at two weeks).**

Review: Interventions for primary (intrinsic) tracheomalacia in children

Comparison: 1 Human deoxyribonuclease versus placebo

Outcome: 1 Clinical failure (Number of children with no significant improvement in cough scores at two weeks)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>rhDNase n/N</th>
<th>Placebo n/N</th>
<th>Odds Ratio M-H (Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boogaard 2009</td>
<td>11/17</td>
<td>12/21</td>
<td>1.38 [0.37, 5.14]</td>
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</tbody>
</table>
### Analysis 1.2. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 2 Daytime cough diary scores (change from baseline).

Review: Interventions for primary (intrinsic) tracheomalacia in children

Comparison: 1 Human deoxyribonuclease versus placebo

Outcome: 2 Daytime cough diary scores (change from baseline)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<th>Mean Difference</th>
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<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Boogaard 2009</td>
<td>17</td>
<td>-1 (1.6)</td>
<td>21</td>
<td>-1.7 (1.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.70 [ -0.19, 1.59 ]</td>
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</table>

### Analysis 1.3. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 3 Night time cough diary score (change from baseline).

Review: Interventions for primary (intrinsic) tracheomalacia in children

Comparison: 1 Human deoxyribonuclease versus placebo

Outcome: 3 Night time cough diary score (change from baseline)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<td>Mean(SD)</td>
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<tr>
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<td>17</td>
<td>-0.7 (1.1)</td>
<td>21</td>
<td>-1.7 (1.5)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00 [ 0.17, 1.83 ]</td>
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### Analysis 1.4. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 4 Daytime visual analogue score (change from baseline).

**Review:** Interventions for primary (intrinsic) tracheomalacia in children  
**Comparison:** 1 Human deoxyribonuclease versus placebo  
**Outcome:** 4 Daytime visual analogue score (change from baseline)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>rDNase</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference 95% CI</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Boogaard 2009</td>
<td>17</td>
<td>-16.2 (36.4)</td>
<td>21</td>
<td>-31.9 (18.5)</td>
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</table>

### Analysis 1.5. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 5 Night time visual analogue score (change from baseline).

**Review:** Interventions for primary (intrinsic) tracheomalacia in children  
**Comparison:** 1 Human deoxyribonuclease versus placebo  
**Outcome:** 5 Night time visual analogue score (change from baseline)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>rDNase</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Boogaard 2009</td>
<td>17</td>
<td>-13.7 (30.6)</td>
<td>21</td>
<td>-36.7 (29.1)</td>
</tr>
</tbody>
</table>
**Analysis 1.6. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 6 Night time dyspnoea score (change from baseline).**

Review: Interventions for primary (intrinsic) tracheomalacia in children

Comparison: 1 Human deoxyribonuclease versus placebo

Outcome: 6 Night time dyspnoea score (change from baseline)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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<td>Mean(SD)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
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<td></td>
</tr>
<tr>
<td>IV,Fixed,95% CI</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boogaard 2009</td>
<td>17</td>
<td>-7.1 (18.5)</td>
<td>21</td>
<td>-19 (29.1)</td>
</tr>
</tbody>
</table>

**Analysis 1.7. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 7 Difficulty expectorating sputum score (change from baseline).**

Review: Interventions for primary (intrinsic) tracheomalacia in children

Comparison: 1 Human deoxyribonuclease versus placebo

Outcome: 7 Difficulty expectorating sputum score (change from baseline)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>rhDNase</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>IV,Fixed,95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boogaard 2009</td>
<td>17</td>
<td>-20.8 (29.8)</td>
<td>21</td>
<td>-35.6 (33.1)</td>
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</table>
### Analysis 1.8. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 8 Lung function: FVC % predicted.

Review: Interventions for primary (intrinsic) tracheomalacia in children

Comparison: 1 Human deoxyribonuclease versus placebo

Outcome: 8 Lung function: FVC % predicted

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>rhDNase</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Boogaard 2009</td>
<td>14</td>
<td>0.6 (13.8)</td>
<td>13</td>
<td>-8.2 (9.4)</td>
</tr>
</tbody>
</table>

### Analysis 1.9. Comparison 1 Human deoxyribonuclease versus placebo, Outcome 9 Lung function: FEV1 % predicted.

Review: Interventions for primary (intrinsic) tracheomalacia in children

Comparison: 1 Human deoxyribonuclease versus placebo

Outcome: 9 Lung function: FEV1 % predicted

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>rhDNase</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Boogaard 2009</td>
<td>14</td>
<td>-1.6 (14.1)</td>
<td>13</td>
<td>-10.8 (11.7)</td>
</tr>
</tbody>
</table>
A P P E N D I C E S

Appendix 1. CENTRAL search strategy (the Cochrane Library)

#1 MeSH descriptor Tracheal Diseases explode all trees with qualifiers: DT, SU, TH
#2 MeSH descriptor Trachea explode all trees with qualifiers: AB, SU
#3 MeSH descriptor Bronchi explode all trees with qualifiers: AB, SU
#4 tracheomalac*
#5 tracheo-malac*
#6 trache* near malac*
#7 malacia*
#8 trache* near abnormal*
#9(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

Appendix 2. MEDLINE search strategy (Ovid)

Topic search
1. tracheomalacia$.mp.
2. tracheo-malac$.mp.
3. (trache$ adj5 malac$).mp.
4. malacia$.mp.
5. exp Tracheal Diseases/dt, su, th [Drug Therapy, Surgery, Therapy]
6. exp TRACHEA/ab, su [Abnormalities, Surgery]
7. exp BRONCHI/ab [Abnormalities]
8. (trache$ adj5 abnormal$).mp.
9. or/1-8
10. ADOLESCENT/ or exp CHILD/ or exp INFANT/ or exp PEDIATRICS/
11. (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre-school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).mp.
12. 10 or 11
13. 9 and 12

RCT filter
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
Appendix 3. EMBASE search strategy (Ovid)

Topic search
1. tracheomalac$.mp.
2. tracheo-malac$.mp.
3. (trache$ adj5 malac$).mp.
4. malacia$.mp.
5. (trache$ adj5 abnormal$).mp.
6. exp TRACHEOMALACIA/
7. or/1-6
8. exp pediatrics/
9. exp CHILD/ or exp INFANT/ or exp ADOLESCENT/
10. (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).mp.
11. 8 or 9 or 10
12. 7 and 11

RCT filter
1. Randomized Controlled Trial/
2. randomisation/
3. Controlled Study/
4. Clinical Trial/
5. controlled clinical trial/
6. Double Blind Procedure/
7. Single Blind Procedure/
8. Crossover Procedure/
9. or/1-8
10. (clonica$ adj3 trial$).mp.
11. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).mp.
12. exp Placebo/
13. placebo$.mp.
14. random$.mp.
15. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).mp.
16. (crossover$ or cross-over$).mp.
17. or/10-16
18. 9 or 17
19. exp ANIMAL/
20. Nonhuman/
21. Human/
22. 19 or 20
23. 22 not 21
24. 18 not 23

WHAT’S NEW
Last assessed as up-to-date: 8 March 2012.
### Date | Event | Description
--- | --- | ---
8 March 2012 | New citation required and conclusions have changed | One randomised controlled trial (RCT) identified and added to the review. We added a summary of findings table and updated the text including the plain language summary and background.
8 March 2012 | New search has been performed | New literature search run

### HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 4, 2005

### Date | Event | Description
--- | --- | ---
7 April 2008 | Amended | Converted to new review format.
25 July 2005 | New citation required and conclusions have changed | Substantive amendment

### CONTRIBUTIONS OF AUTHORS

IBM: formulation and writing of protocol.
AC: initiation, formulation and writing of protocol, review and selection of studies from the search, data extraction and writing and updating the review.
VG: updated the review, entered data in the updated review and contacted the original investigator of the included study for raw data.

### DECLARATIONS OF INTEREST

None known.
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• Centre of Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children, Australia.
  NHMRC grant number 1040830

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
The inclusion criteria was children under 15 years old with tracheomalacia, but we included a trial in which the oldest child enrolled was 15.5 years (Boogaard 2009).

INDEX TERMS

Medical Subject Headings (MeSH)
Administration, Inhalation; Cough [drug therapy]; Deoxyribonucleases [*administration & dosage]; Dyspnea [drug therapy]; Randomized Controlled Trials as Topic; Tracheomalacia [*drug therapy]

MeSH check words
Adolescent; Child; Child, Preschool; Humans