Cochrane
Library

Cochrane Database of Systematic Reviews

Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis (Review)

Amin R, Noone PG, Ratjen F

Amin R, Noone PG, Ratjen F.

Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis.

Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD007481.

DOI: [10.1002/14651858.CD007481.pub3](https://doi.org/10.1002/14651858.CD007481.pub3).

www.cochranelibrary.com

Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis
(Review)

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	5
DISCUSSION	5
AUTHORS' CONCLUSIONS	6
ACKNOWLEDGEMENTS	6
REFERENCES	7
WHAT'S NEW	7
HISTORY	7
CONTRIBUTIONS OF AUTHORS	8
DECLARATIONS OF INTEREST	8
INDEX TERMS	8

[Intervention Review]

Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis

Reshma Amin¹, Peadar G Noone², Felix Ratjen³

¹Department of Pediatric Respiriology, The Hospital for Sick Children, Toronto, Canada. ²Department of Pulmonary & Critical Care Medicine, University of North Carolina, Chapel Hill, North Carolina, USA. ³Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada

Contact address: Reshma Amin, Department of Pediatric Respiriology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8, Canada. reshma.amin@sickkids.ca.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 4, 2015.

Citation: Amin R, Noone PG, Ratjen F. Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD007481. DOI: [10.1002/14651858.CD007481.pub3](https://doi.org/10.1002/14651858.CD007481.pub3).

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Pneumothorax is a potentially life-threatening complication for people with cystic fibrosis. Spontaneous pneumothorax is the presence of air in the pleural space and can be subdivided into first episode and recurrent. The recurrence of pneumothorax is when it occurs on the same side seven days or more after initial resolution. A pneumothorax is persistent if the air leak lasts for more than five days ([Schidlow 1993](#)). Managing spontaneous pneumothoraces is controversial and there is no standard treatment. Medical and surgical intervention are the two main categories for the treatment of recurrent pneumothoraces in people with cystic fibrosis. While surgical interventions are felt to be more effective in people without cystic fibrosis, the complications directly related to the procedure, as well as the post-operative complications make surgical interventions riskier for people with cystic fibrosis. Additionally, these interventions have the potential to make people with cystic fibrosis ineligible for lung transplantation in the future. Therefore, the benefits and side effects or disadvantages for the medical and surgical treatment of recurrent pneumothoraces in people with cystic fibrosis need to be systematically reviewed.

Objectives

To determine the clinical efficacy and safety of different treatment interventions for managing spontaneous persistent and recurrent pneumothoraces in people with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises references identified from comprehensive electronic database searches, handsearches of relevant journals and abstract books of conference proceedings.

Date of the most recent search: 29 October 2012.

Selection criteria

Randomised and quasi-randomised controlled trials which compared the use of chemical pleurodesis to surgical interventions for the treatment of persistent and recurrent pneumothoraces in CF.

Data collection and analysis

No relevant trials were identified.

Main results

No trials were included in this review

Authors' conclusions

Pneumothorax is a potentially life-threatening complication for people with cystic fibrosis and the management of spontaneous pneumothoraces remains a topic of considerable controversy. Medical and surgical intervention are the two main categories for the treatment of recurrent pneumothoraces in this population. However, it is disappointing that neither intervention has been assessed by randomised controlled trials. This systematic review identifies the need for a multicentre randomised controlled trial assessing both efficacy and possible adverse effects of the use of chemical pleurodesis versus surgical interventions for the treatment of persistent and recurrent pneumothoraces in people with cystic fibrosis.

Due to a current lack of research in this area, while searches will still be undertaken every two years, the review will only be updated if any new evidence comes to light.

PLAIN LANGUAGE SUMMARY

Chemicals for sticking the outer lung surface to surrounding membranes compared to surgery to stop air persistently collecting in the chest

Cystic fibrosis is an inherited disease which irreversibly damages the lungs. People with cystic fibrosis are prone to getting a pneumothorax. A pneumothorax is defined as the presence of air in the space between the two linings of the lungs. It can potentially kill people with cystic fibrosis because of the added stress on the heart and lungs. It can be treated by surgical and non-surgical interventions. However, although these treatments are generally effective, they are far from perfect. Certain treatments work in some people but not others. Also, the treatments do have side effects and can be dangerous for people with cystic fibrosis. Currently, physicians do not know the safest and most effective way of treating pneumothorax in people with cystic fibrosis. We did not find any randomised controlled trials that compared the surgical and non-surgical treatments for pneumothorax in people with cystic fibrosis. Therefore, more research is needed in this field. Future studies should compare the safety and efficacy of surgical and non-surgical interventions for pneumothorax in people with cystic fibrosis. There is currently no research being undertaken in this area. We will continue to search for evidence, but will not be updating the review until we find new evidence.

BACKGROUND

Description of the condition

A spontaneous pneumothorax is defined as "the presence of air in the pleural space" (Tschopp 2006). Spontaneous pneumothorax can be subdivided into first episode and recurrent. The recurrence of a pneumothorax is defined as one that occurs on the same side seven days after a pneumothorax has resolved (Flume 2005). A pneumothorax can be defined as persistent if the air leak is ongoing for more than five days (Schidlow 1993). Spontaneous pneumothoraces are mainly caused by the rupture of subpleural air collections (blebs) through the visceral pleura. Pneumothorax may be iatrogenic (i.e. caused by medical intervention), for example, due to a central line insertion, or due to the barotrauma of mechanical ventilation (Schidlow 1993).

Pneumothorax is a potentially life-threatening complication for people with cystic fibrosis (CF) given the added cardiopulmonary compromise. Pneumothoraces increase the risk for death in people with CF; 48.6% of individuals with a pneumothorax died as compared to 12.2% of individuals without a pneumothorax for the years 1990 to 1999 according to the Cystic Fibrosis Foundation (CFF) registry data (Cystic Fibrosis Foundation 2002). The reported annual incidence of a pneumothorax is 0.64%; there was no evidence of a yearly increase over time (Flume 2005). Approximately, 3.4% of all people with CF will develop a pneumothorax (Flume 2005). The median (range) age at the time of the first pneumothorax was 21 years (0 to 61 years) (Flume 2005). Pneumothoraces are more prevalent among adults and the incidence increases proportionally with age and disease severity (Flume 2005; Schidlow 1993). The proportion of pneumothoraces that occur in individuals younger than 18 years of age is 27.6% versus 72.4% occurring in individuals older than 18 years of age (Flume 2005). The CFF registry data in the United States of America reports forced expiratory volume at one second (FEV₁) of less than 40% predicted in 75% of people with CF who develop a pneumothorax (Cystic Fibrosis Foundation 2002). Flume reported a steep increase in the number of pneumothoraces once the FEV₁ dropped below 50% predicted (Flume 2005).

Description of the intervention

The management of spontaneous pneumothoraces remains a topic of considerable controversy and treatments vary from observation to aggressive intervention (Tschopp 2006). This review will discuss the treatment of spontaneous persistent and recurrent pneumothoraces.

Medical and surgical intervention are the two main categories for the treatment of recurrent pneumothoraces in people with CF. Pleurodesis is a procedure that cause the pleura (the membranes around the lungs) to stick together. Medical intervention consists of chemical pleurodesis using agents such as quinacrine, silver nitrate, talc or tetracycline derivatives. These agents are administered via a chest tube. The choice of sclerosing agent, ideal dose and technique for administration (i.e. with or without patient rotation) remains variable among clinicians. Limitations to the procedure of sclerosant instillation include prolonged pleural drainage and unequal deposition resulting in incomplete pleurodesis (Aelony 1995; Colt 1994). In addition, although talc has been reported as the most efficient agent for pleurodesis, it is known to result in more systemic inflammation and is a relative contraindication for

lung transplantation in people with CF (Aelony 1995; Bresticker 1993; Colt 1997; Flume 2005; Tschopp 2006). Hence, there is still no consensus on which agent to use for these individuals.

Surgical intervention primarily includes open thoracotomy versus video assisted thorascopic surgery (VATS) for pleurodesis, pleurectomy and resection, electrocautery or laser ablation of a bleb or bullae. Surgical pleurodesis includes pleural abrasion as well as chemical, laser or electrocautery pleurodesis (Tschopp 2006).

How the intervention might work

Medical intervention consisting of chemical pleurodesis induces an inflammatory reaction resulting in adherence of the parietal and visceral pleura to prevent pneumothorax occurring again.

During pleural abrasion, surgical interventions mechanically induce an inflammatory reaction by abrasion of the pleura with gauze under direct vision. A pleurectomy removes the parietal pleura resulting in pulmonary adherence to the chest wall preventing further pneumothoraces. Resection, electrocautery and laser ablation are targeted therapies for the etiology of the air leak.

Why it is important to do this review

The most recent review of the treatment of pneumothoraces for people with CF was published by Flume in 2005 (Flume 2005). However, to date there has not yet been a systematic review of the literature to determine the efficacy and safety of the various interventions for the management of either spontaneous primary or recurrent pneumothoraces in people with CF.

While surgical interventions are felt to be more effective in people without CF, the complications directly related to the procedure, as well as the post-operative complications make surgical interventions riskier for people with CF. In addition, these interventions have the potential to make people with CF ineligible for lung transplantation in the future. As such, the benefits and side effects or disadvantages for the medical and surgical treatment of recurrent pneumothoraces in people with CF needs to be reviewed.

OBJECTIVES

To determine the clinical efficacy and safety of different treatment interventions for the management of spontaneous persistent and recurrent pneumothoraces in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and quasi-randomized controlled trials.

Types of participants

Children and adults diagnosed with CF as defined by two or more clinical features of CF and a documented sweat chloride greater than 60 milliequivalent per liter (mEq/L) by quantitative pilocarpine iontophoresis test or a genotype showing two well-characterized disease causing mutations. Participants have also been diagnosed with either spontaneous persistent (if the air leak is ongoing for more than five days) or spontaneous recurrent pneumothorax

(occurring more than seven days since radiographic resolution of a previous pneumothorax).

Types of interventions

We compared chemical pleurodesis with surgical interventions for the treatment of persistent and recurrent pneumothoraces in CF.

Chemical pleurodesis uses quinidine, silver nitrate, talc or tetracycline derivatives.

Surgical intervention includes open thoracotomy or video assisted thoroscopic surgery (VATS) for pleurodesis, pleurectomy, resection, electrocautery and laser ablation of a bleb or bullae.

Types of outcome measures

Primary outcomes

1. Recurrence of pneumothorax
2. Mortality
3. Quality of life

Secondary outcomes

1. Length of hospital stay
2. Time to radiographic resolution
3. Pulmonary function tests
 - a. forced expiratory volume at one second (FEV₁) (liters per second or per cent predicted)
 - b. forced vital capacity (FVC) (liters per second or per cent predicted)
4. Successful lung transplantation in the future
5. Adverse events
 - a. mild or moderate
 - b. severe or life-threatening

Search methods for identification of studies

Electronic searches

We searched the Group's Cystic Fibrosis Trials Register for relevant studies using the term: pneumothorax.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of last search: 29 October 2012.

Searching other resources

We did not identify any review articles and bibliographies from this process, but if we do so in the future, these will be reviewed for additional citations and controlled trials. As of January 2009,

The Therapeutics Development Network and the European Cystic Fibrosis Society are not currently planning any future studies.

Data collection and analysis

We were unable to identify any studies which were potentially eligible for inclusion in this review. If, in future updates of this review, we are able to include any studies, we plan to collect and analyse the data as follows.

Selection of studies

Three authors will independently review all identified articles for possible inclusion in this review. If disagreement arises on the suitability of a trial for inclusion in the review or on its quality, a consensus will be reached by discussion.

Data extraction and management

Three authors will independently review all the data. We will use a data abstraction form provided by the Cochrane Cystic Fibrosis and Genetic Disorders Review Group and modified for the purpose of data collection for this review.

Unless otherwise stated, we will report outcomes at the following time periods outlined below. Two of the measures are short-term outcomes and we will measure these in days (time to radiographic resolution and length of hospital stay). We will group these data into the following categories: up to one week, one to two weeks, two to four weeks, and then greater than four weeks.

Likewise for the remaining long-term outcomes, we plan to group outcome data into the following categories: one month, up to three months, up to six months, up to twelve months and then annually thereafter.

If outcome data is recorded at other time periods, then we will consider examining these as well.

The authors will undertake a meta-analysis comparing chemical pleurodesis versus surgical intervention.

Assessment of risk of bias in included studies

We will assess the studies for the risk of bias and will generate risk of bias tables. In particular, we will assess for limitations in the design and implementation of the study, directness of evidence, heterogeneity or inconsistency of the results, precision of effect estimates and risk of publication bias.

Measures of treatment effect

For binary outcomes, we will analyze the data according to an intention-to-treat analysis. We will calculate a pooled estimate of the treatment effect for each outcome across the studies. We will use odds ratios (OR) and risk ratios (RR) and 95% confidence intervals (CIs).

For continuous outcomes, we will record a mean change from baseline to post-treatment and standard deviation for each group. We will calculate a pooled estimate of the treatment effect across studies by calculating the mean difference (MD) and 95% CIs if appropriate.

We will summarize time to radiographic resolution analysis graphically by Kaplan-Meier curves and report the treatment

effect as a hazard ratio with 95% CIs. We will define an event as radiographic resolution of the pneumothorax. We will censor participants from the analysis if they die, are medically unstable to continue in the trial or if they move away and are no longer able to be followed at each of the respective CF centers. We will estimate the relative risk of radiographic resolution for each treatment intervention using Cox regression analysis.

Unit of analysis issues

If trials have a cross-over design we will carry out the analysis according to Elbourne using the results from the paired analysis (Elbourne 2002). If this is not possible then the cross-over trial will be described narratively assuming that the data has been more appropriately analysed in the primary paper.

Dealing with missing data

We will perform an intention-to-treat analysis. If there are missing data, the review authors will contact the trial authors using open-ended questions. Where standard deviations are not provided in the publications and individual patient data are not available, we will estimate the standard deviation using the formula suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We will test for heterogeneity between study results using the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across studies that are caused by heterogeneity rather than by chance (Higgins 2003). We will use the following cutoffs for the I^2 statistic:

- 0 to 40%: might not be important;
- 30 to 60%: may represent moderate heterogeneity;
- 50 to 90%: may represent substantial heterogeneity;
- 75 to 100%: considerable heterogeneity.

Assessment of reporting biases

We will use a funnel plot to look for possible sources of bias as indicated by asymmetry. If we find asymmetry, we will explore heterogeneity (see below). We will also consider whether there has been multiple publication of studies. We aim to minimise publication bias by contacting the respective companies for any missing data from the trials. Also, we will assess trial reports to determine if the selective reporting of outcomes has occurred (outcome reporting bias) by comparing trial protocols to publications when available or comparing the methods section of the publication to the results section. If we suspect selective reporting of outcomes we will contact trialists to further assess the measurement and analysis of the outcomes.

Data synthesis

Depending on the results of our assessment of heterogeneity, we will use a fixed-effect model for a low degree of heterogeneity, i.e. if the I^2 statistic is up to 40%, and a random-effects analysis for a moderate or high degree of heterogeneity, i.e. if the I^2 statistic is over 40%.

Subgroup analysis and investigation of heterogeneity

If we identify significant heterogeneity using the I^2 statistic (Higgins 2003), we will investigate this using the following tools.

We will check the data to ensure they are correct. We will explore heterogeneity by conducting subgroup analyses. These will include a comparison of the various chemical pleurodesis agents such as talc, quinidine, silver nitrate and tetracycline derivatives. Similarly, we will use a subgroup analysis to compare the various surgical interventions to one another. These include open thoracotomy versus video assisted thorascopic surgery (VATS) for pleurodesis, pleurectomy and resection, electrocautery or laser ablation of a bleb or bullae. We will investigate heterogeneity by changing the effect measure and by performing a sensitivity analysis both with and without a potential outlier study. If we are still unable to explain the heterogeneity, we will employ a random-effects model.

Sensitivity analysis

We plan the following sensitivity analyses: performing the analysis both with and without quasi-randomized trials; including and then excluding trials with high risks of bias; analysing the data using a random-effects model and a fixed-effects model; analysing the data imputing a reasonable range of values for missing data; and analysing the data both with and without outlier studies. We will also conduct a sensitivity analysis including and excluding studies that have been published more than once and for parallel and cross-over trials will be performed.

RESULTS

Description of studies

No studies were identified for inclusion in this review.

Risk of bias in included studies

No studies were identified for inclusion in this review.

Effects of interventions

No studies were identified for inclusion in this review.

DISCUSSION

Despite the high prevalence of spontaneous persistent and recurrent pneumothoraces in people with CF, there are no randomized controlled trials to systematically evaluate their management. Limitations to the procedure of sclerosant instillation include prolonged pleural drainage and unequal deposition resulting in incomplete pleurodesis (Aelony 1995; Colt 1994). While surgical interventions are felt to be more effective in people without CF, the complications directly related to the procedure, as well as the post-operative complications make surgical interventions riskier for individuals with CF. As such, the benefits and side effects or disadvantages for the medical and surgical treatment of recurrent pneumothoraces in people with CF needs to be clarified. Therefore, a multi-centered randomized controlled trial to explore the optimal management of spontaneous and persistent pneumothoraces in people with CF will provide useful information for both clinicians and individuals with CF.

AUTHORS' CONCLUSIONS

Implications for practice

Several clinical trials have been performed to evaluate the use of medical and surgical interventions for spontaneous persistent and recurrent pneumothoraces in people without CF. However, it is difficult to apply the results of these trials to individuals with CF as there are significant differences between the patient populations.

Conclusions cannot be made regarding the clinical efficacy and safety of various treatment interventions for the management of spontaneous persistent and recurrent pneumothoraces in people with CF. Clinicians must balance the potential efficacy of the intervention against the possible risk for complications for each patient on a case by case basis.

Due to a current lack of research in this area, while searches will still be undertaken every two years, the review will only be updated if any new evidence comes to light.

Implications for research

There is a need for a multi-centre, randomized controlled trial to assess the efficacy and safety of medical and surgical interventions for the management of spontaneous persistent and recurrent pneumothoraces in people with CF. The primary outcome most relevant to patients is recurrence of pneumothorax. The most important secondary outcome measures are length of hospital stay and adverse events. The trial should be powered based on a quality of life calculation.

ACKNOWLEDGEMENTS

The authors would like to thank Nikki Jahnke for all of her help and guidance.

REFERENCES

Additional references

Aelony 1995

Aelony Y. Talc pleurodesis. Talc slurry versus talc poudrage. *Chest* 1995;**108**(1):289.

Bresticker 1993

Bresticker MA, Oba J, LoCicero J. Optimal pleurodesis: a comparative study. *Annals of Thoracic Surgery* 1993;**55**(2):364-6.

Colt 1994

Colt H, Dumon JF. Development of a disposable spray canister for talc pleurodesis. A preliminary report. *Chest* 1994;**106**(6):1776-80.

Colt 1997

Colt HG, Russack V, Chiu Y, Konopka RG, Chiles PG, Pedersen CA, et al. A comparison of thorascopic talc insufflation, slurry and mechanical abrasion pleurodesis. *Chest* 1997;**111**(2):442-8.

Cystic Fibrosis Foundation 2002

Cystic Fibrosis Foundation. Patient registry 2001: annual data report. Cystic Fibrosis Foundation 2002.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Woithington HV, Vail A. Meta-analysis involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):1902-9.

Flume 2005

Flume PA, Strange C, Ye X, Ebeling M, Hulsey T, Clark LL. Pneumothorax in cystic fibrosis. *Chest* 2005;**128**(2):720-8. [PUBMED: 16100160]

WHAT'S NEW

Date	Event	Description
13 April 2015	Amended	Contact details updated.
5 December 2012	Review declared as stable	Due to a current lack of research in this area, it has been agreed between the review authors and the CFGD Editorial Board, that while searches will still regularly (every two years) be run by the Group's Trials Search Co-ordinator, the review will only be updated if any new evidence comes to light.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 2, 2009

Date	Event	Description
30 October 2012	New search has been performed	A search of the Group's Cystic Fibrosis register did not identify any new references for this review.

Date	Event	Description
30 October 2012	New citation required but conclusions have not changed	No new studies or data were added to this review at this update, hence the conclusions remain the same.
8 November 2010	New search has been performed	A search of the Group's CF register did not identify any new references for this review.

CONTRIBUTIONS OF AUTHORS

R Amin drafted the protocol and full review with comments from F Ratjen and P Noone.

R Amin acts as guarantor for the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Cystic Fibrosis [*complications]; Pleurodesis [*methods]; Pneumothorax [etiology] [surgery] [*therapy]; Recurrence

MeSH check words

Humans