Editorial

New Impact Factor

Tracey Remmington, Managing Editor

The 2009 impact factor for the Cochrane Database of Systematic Reviews (CDSR) is 5.653, which describes the ratio of the number of reviews published during 2007 and 2008 (1163) to the number of citations these reviews received in 2009 (6574).

The impact factor of the Cystic Fibrosis and Genetic Disorders (CFGD) Group is 2.500 (26 publications cited 65 times).

A review published by our Group in 2007 or 2008 was cited, on average, 2.5 times in 2009.

The top ten most cited reviews from the CFGD Group contributing to the 2009 impact factor are:

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Output of the CFGD Group

98 reviews & 19 protocols will be published on Issue 1, 2011 of The Cochrane Library

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Gerard Ryan, CF Editor

Tracey Remmington & Nikki Jahnke
Managing Editors

Dr Gerard Ryan who is based in Perth in Australia has been a CF Editor with the Group since 1997. He has recently decided to resign from this position. As many of you will be aware, his input over the years has been invaluable. Not only has he been the contact editor on 18 reviews (as of November 2010), but he was also the Group’s Feedback Editor. Furthermore he is the lead author of the review ‘Inhaled antibiotics for long-term therapy in cystic fibrosis’ and also leading on the current protocol ‘Inhaled antibiotics for pulmonary exacerbations in people with cystic fibrosis’.

He will be greatly missed by the team at the Editorial Base, not only for his input into the Group, but also for his many, many humorous emails over the years!

Of course, there is no real escape from Cochrane, he is, after all, still lead author on 2 reviews……

Good luck for the future Gerard and thank you for all your hard work with the Group over the years. We’ll be keeping in touch!

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Good luck for the future Gerard and thank you for all your hard work with the Group over the years. We’ll be keeping in touch!
A major part of my role as Trial Search Co-ordinator (TSC) for the CFGD Group is to compile and maintain registers of studies that fit into the remit of our Group. Our four ‘Registers’ are essentially databases of references to randomised controlled trials (RCTs) or possible RCTs – one each for cystic fibrosis, haemoglobinopathies, coagulopathies and inborn errors of metabolism.

At approximately 13 years old, the Cystic Fibrosis Register is the oldest register. When a reference is added to the CF register, the new reference record is ‘coded’ using keywords (taken from a list designed by the group) to describe its content and the reference is then allocated a study identification number. It is, if you like, our Group equivalent of Medline MeSH terms, but a much simpler version (http://www.nlm.nih.gov/bsd/disted/mesh/mesh.html). These keywords are then used to search the CF Register to identify trials that could possibly be included in our reviews.

In order to preserve as much consistency as possible, the TSC maintains this list of keywords called the ‘Coding List’ and refers to it whenever adding keywords to a new reference record or when identifying search terms for a new review. Although the coding list has worked well in some intervention areas, other areas were quite generalised. This meant that when we ran searches for some reviews the review authors were receiving a lot of irrelevant results. At a previous Editorial Board Meeting it was decided that the CF Register needed updating and re-designing. With assistance from the Cystic Fibrosis Editors, I first of all set about reorganising the coding list so it was in a more organised format and contained up-to-date terminology. After that, I needed to convert all the existing references to the new system. The process was a long one as it entailed changing the format of the Coding List, updating over 2500 database records on the CF Register and re-labelling the papers physically stored here at the CFGD Editorial Base. A task I hope not to have to repeat!

Now we are using the new keywords to search the CF Register, we will be requesting feedback from our authors regarding their search results. There may be some older studies which are identified using the new keywords which haven’t been identified as relevant to particular reviews in the past. We will be asking for reasons why any studies identified are not included in the reviews. This information will be used to make adjustments to future searches and also aid future changes to our CF Register. We hope that the new system will benefit review authors as they should receive more precise search results, saving time, effort and allowing more time to create the high quality reviews the CFGD Group strive to produce.

Now that the CF Register has been updated, we are working on developing a more organised register for Inborn Errors of Metabolism, which at the moment is very basic. We are aware that this is a priority if we are to achieve our goal of substantially increasing the number of reviews we have in this area of our scope. I hope to report back on that project in the next 12 months.

### Two interesting articles ……


CFGD Annual Editorial Meeting

Nikki Jahnke
Asst Managing Editor

In September the CFGD Editorial Board met in Liverpool for their annual face-to-face meeting. The first part of the morning was taken up with a discussion of all of our published reviews, our published protocols and our registered titles. For each review, we discuss the last update that has been published and whether the grading for the frequency of the update schedule is still relevant. There may also be issues which arise at update stage which need to be discussed by the whole board and may inform general group policy decisions. Protocols and titles are monitored so that the Board are aware of any possible delays in the process. This allows all relevant editorial staff to stay informed of when they are likely to have to find time to deal with the draft review or draft protocol and hence facilitate the flow of the document through the editorial process. This has now become quite a time-consuming section of the meeting as we had 93 full reviews and 19 protocols to discuss.

Following on from the initial session this year there was a discussion of the impact the Group’s reviews are having. As Tracey has mentioned in the editorial at the front of this newsletter, Wiley had notified us of the impact factor of both the CFGD Group and CDSR in general. We had a short discussion of how to improve our impact factor and the problems our Group will face in doing this. Firstly, we are in a niche area and nothing we can do will change this. Secondly, the publishers have chosen the journal 'Nature & Genetics' against which to measure our impact factor. However, the content of this journal is not comparable to what we publish. We have four distinct areas in our scope each of which is different. It was decided to do some research to back up this theory and also to identify journals to which we can compare our reviews. A third issue is that Wiley have just used The Cochrane Library as the only access point for the calculations. Diseases such as sickle cell are prominent in parts of the world that use other access routes to view The Cochrane Library e.g. Bireme. CD ROM access was also not included. Finally, it is a big problem that people cite the individual studies included in a review but not the review itself. It was decided to prepare a response to Wiley on this subject to allow a more realistic comparison of impact factors next year.

The Group’s annual report for the NIHR was briefly discussed. The Group had improved in ranking against the previous year.

One of our editors, Dr Kevin Southern, had applied for additional funding from The Cochrane Collaboration for a project to develop core outcome measures for CF trials. These could be incorporated into our reviews in the future. The application was unsuccessful, but it was agreed that he should seek other funding sources for this project and we should consider similar projects for future applications to The Cochrane Collaboration.

Finally, the TSC gave an update on the development of the new CF register and plans to develop and IEM register. She also gave a short presentation on the new Cochrane Register of Studies and how this would affect our Group. The Group’s statistician updated the Editorial Board on her project on outcome reporting bias in our reviews, which she was presenting at the Colloquium in Colorado. The project is about 50% completed and she hopes to finalise this in early 2011. The managing editors gave a short presentation and some informal training on the Collaboration’s Information Management System before the meeting closed.

The Group will continue to hold quarterly teleconferences and the date for the next face-to-face meeting was set for September 2011. Possible attendance at the next Colloquium in Madrid in 2011 was discussed, but not firm decisions taken.
Sapropterin dihydrochloride for phenylketonuria

Reviewers: Somaraju UR, Merrin M

Abstract

Background

Phenylketonuria results from a deficiency of the enzyme phenylalanine hydroxylase. Dietary restriction of phenylalanine keeps blood phenylalanine concentration low. Most natural foods are excluded from diet and supplements are used to supply other nutrients. Recent publications report a decrease in blood phenylalanine concentration in some patients treated with sapropterin dihydrochloride. We examined the evidence for the use of sapropterin dihydrochloride to treat phenylketonuria.

Objectives

To assess the safety and efficacy of sapropterin dihydrochloride in lowering blood phenylalanine concentration in people with phenylketonuria.

Search strategy

We identified relevant trials from the Group's Inborn Errors of Metabolism Trials Register. Last search: 07 May 2010.

We also searched ClinicalTrials.gov and Current controlled trials. Last search: 01 September 2009.

We contacted the manufacturers of the drug (BioMarin Pharmaceutical Inc.) for information regarding any unpublished trials.

Selection criteria

Randomized controlled trials comparing sapropterin with no supplementation or placebo in people with phenylketonuria due to phenylalanine hydroxylase deficiency.

Data collection & analysis

Two authors independently assessed trials and extracted outcome data.

Main results

Two placebo-controlled trials were included. One trial administered 10 mg/kg/day sapropterin in 89 children and adults with phenylketonuria whose diets were not restricted and who had previously responded to sapropterin. This trial measured change in blood phenylalanine concentration. The second trial screened 90 children (4 to 12 years) with phenylketonuria whose diet was restricted, for responsiveness to sapropterin. Forty-six responders entered the placebo-controlled part of the trial and received 20 mg/kg/day sapropterin. This trial measured change in both phenylalanine concentration and protein tolerance. Both trials reported adverse events. The trials showed an overall low risk of bias; but both are Biomarin-sponsored. One trial showed a significant lowering in blood phenylalanine concentration in the sapropterin group (10 mg/kg/day), mean difference -238.80 μmol/L (95% confidence interval -343.09 to -134.51); a second trial (20 mg/kg/day sapropterin) showed a non-significant difference, mean difference -51.90 μmol/L (95% confidence interval -197.27 to 93.47). The second trial also reported a significant increase in phenylalanine tolerance, mean difference 18.00 mg/kg/day (95% confidence interval 12.28 to 23.72) in the 20 mg/kg/day sapropterin group.

Authors' conclusions

There is evidence of short-term benefit from using sapropterin in some patients with sapropterin-responsive forms of phenylketonuria; blood phenylalanine concentration is lowered and protein tolerance increased. There are no serious adverse events associated with using sapropterin in the short term. There is no evidence on the long-term effects of sapropterin and no clear evidence of effectiveness in severe phenylketonuria.
**Statins for familial hypercholesterolemia in children**

**Reviewers:** Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Strandberg T, Tonstad S, Gylling H

**Abstract**

**Background**

Familial hypercholesterolemia is one of the most common inherited metabolic diseases; the average worldwide prevalence of heterozygous familial hypercholesterolemia is about 1 in 500. Diagnosis of familial hypercholesterolemia in children is based on two measurements of low-density lipoprotein cholesterol level above 4.0 mmol/L or a DNA-based analysis. Coronary stenosis has been detected in men with familial hypercholesterolemia as young as 17 years old and in women with familial hypercholesterolemia at 25 years old. Atherosclerosis and its clinical complications occur prematurely, especially in men, thus lifelong hypolipidemic measures, started in childhood, are needed to reduce the risk of cardiovascular diseases. In children with familial hypercholesterolemia children, so far diet has been the main mode of treatment. Anion exchange resins, such as cholestyramine and colestipol, have also been found to be effective but are generally considered unpalatable and therefore poorly tolerated. Since the 1990s statin trials have been carried out among children with familial hypercholesterolemia (aged 7 to 17 years), and statins reduced their serum low-density lipoprotein cholesterol levels by 23% to 40%. The safety of statins among children is not well known even though statins seem to be safe and well-tolerated in adults.

**Objectives**

To assess the effectiveness and safety of statins in children with familial hypercholesterolemia.

**Search strategy**

Relevant trials were identified from the Group’s Inborn Errors and Metabolism Trials Register and Medline.

Date of most recent search: 11 March 2010.

**Selection criteria**

Randomized and controlled clinical trials including participants up to 18 years old comparing a statin to placebo or to diet alone.

**Data collection & analysis**

Two authors independently assessed studies for inclusion and extracted data.

**Main results**

We found 19 potentially eligible studies of which we included eight randomized placebo-controlled trials (897 participants). Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points. There was no difference between serum aspartate and alanine aminotransferase as well as creatine kinase concentrations at any time-point. The risks of myopathy and clinical adverse events were also similar in both groups. In one study simvastatin was shown to improve flow-mediated dilation of the brachial artery.

**Authors’ conclusions**

Statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. It seems to be safe in the short term but long-term safety is unknown. Children treated with statins should be carefully followed up by their pediatricians. Large long-term randomized controlled trials are needed to establish the long-term safety of statins.
Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease

Reviewers: Gøtzsche PC, Johansen HK

Abstract
Background
Alpha-1 antitrypsin deficiency is an inherited disorder that can cause lung disease. People who smoke are more seriously affected and have a greater risk of dying from the disease.

Objectives
To review the benefits and harms of augmentation therapy with alpha-1 antitrypsin in patients with alpha-1 antitrypsin deficiency and lung disease.

Search strategy
PubMed, the Cochrane Trials Register and ClinicalTrials.gov (7 January 2010), and the Cochrane Cystic Fibrosis & Genetic Disorders Group's Trials Register (13 March 2009).

Selection criteria
Randomised trials of augmentation therapy with alpha-1 antitrypsin compared with placebo or no treatment.

Data collection & analysis
The two authors independently selected trials, extracted outcome data and assessed the risk of bias.

Main results
Two trials were included (total 140 patients) that ran for two to three years. All patients were ex- or never-smokers and had genetic variants that carried a very high risk of developing chronic obstructive pulmonary disease. Mortality data were not reported. There was no information on harms in the first trial; in the second trial, serious adverse events were reported to have occurred in 10 patients in the active group and in 18 patients in the placebo group. Annual number of exacerbations and quality of life were similar in the two groups; none of the trials reported on average number of lung infections or hospital admissions. Forced expiratory volume in one second deteriorated a little more in the active group than in the placebo group (difference was -20 ml per year; 95% confidence interval -41 to 1; \( p = 0.06 \)). For carbon monoxide diffusion, the difference was -0.06 mmol/min/kPa per year (95% confidence interval -0.17 to 0.05; \( p = 0.31 \)). Lung density measured by CT scan deteriorated a little less in the active group than in the placebo group (difference 1.14 g/l; 95% confidence interval 0.14 to 2.14; \( p = 0.03 \)) over the total course of the trials.

Authors' conclusions
Augmentation therapy with alpha-1 antitrypsin cannot be recommended, in view of the lack of evidence of clinical benefit and the cost of treatment.
Deferasirox for managing transfusional overload in people with sickle cell disease

Reviewers: Meerpohl JJ, Antes G, Rücker G, Fleeman N, Niemeyer CM, Bassler D

Abstract

Background

Sickle cell disease (SCD) is a group of genetic haemoglobin disorders. Increasingly, some people with SCD develop secondary iron overload due to occasional red blood cell transfusions or are on long-term transfusion programmes for e.g. secondary stroke prevention. Iron chelation therapy can prevent long-term complications.

Deferoxamine and deferiprone have been found to be efficacious. However, questions exist about the effectiveness and safety of the new oral chelator deferasirox.

Objectives

To assess the effectiveness and safety of oral deferasirox in people with SCD and secondary iron overload.

Search strategy

We searched the Cystic Fibrosis & Genetic Disorders Group's Haemoglobinopathies Trials Register (06 April 2010).


Selection criteria

Randomised controlled trials comparing deferasirox with no therapy or placebo or with another iron chelating treatment schedule.

Data collection & analysis

Two authors independently assessed study quality and extracted data. We contacted the study author for additional information.

Main results

One study (203 people) was included comparing the efficacy and safety of deferasirox and deferoxamine after 12 months. Data were not available on mortality or end-organ damage. Using a pre-specified dosing algorithm serum ferritin reduction was similar in both groups, mean difference (MD) 375.00 µg/l in favour of deferoxamine; (95% confidence interval (CI) -106.08 to 856.08). Liver iron concentration measured by superconduction quantum interference device showed no difference for the overall group of patients adjusted for transfusion category, MD -0.20 mg Fe/g dry weight (95% CI -3.15 to 2.75).

Mild stable increases in creatine were observed more often in people treated with deferasirox, risk ratio 1.64 (95% CI 0.98 to 2.74). Abdominal pain and diarrhoea occurred significantly more often in people treated with deferasirox. Rare adverse events (less than 5% increase) were not reported; long-term adverse events could not be measured in the included study (follow-up 52 weeks). Patient satisfaction with, and convenience of treatment were significantly better with deferasirox.

Authors' conclusions

Deferasirox appears to be as effective as deferoxamine. However, only limited evidence is available assessing the efficacy regarding patient-important outcomes. The short-term safety of deferasirox seems to be acceptable, however, follow-up was too short to exclude long-term side effects and thus treatment with deferasirox cannot be judged completely safe. Future studies should assess long-term outcomes for safety and efficacy, and also evaluate rarer adverse effects.
Gene therapy for sickle cell disease

Reviewers: Olowoyeye A, Okwundu CI

Abstract

Background
Sickle cell disease encompasses a group of genetic disorders characterized by the presence of at least one hemoglobin S (Hb S) allele, and a second abnormal allele that could allow abnormal hemoglobin polymerisation leading to a symptomatic disorder.

Autosomal recessive disorders (such as sickle cell disease) are good candidates for gene therapy because a normal phenotype can be restored in diseased cells with only a single normal copy of the mutant gene.

Objectives
The objectives of this review are:
- to determine whether gene therapy can improve survival and prevent symptoms and complications associated with sickle cell disease;
- to examine the risks of gene therapy against the potential long-term gain for people with sickle cell disease.

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

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 05 March 2010.

Selection criteria
All randomised or quasi-randomised clinical trials (including any relevant phase 1, 2 or 3 trials) of gene therapy for all individuals with sickle cell disease, regardless of age or setting.

Data collection & analysis
No trials of gene therapy for sickle cell disease were found.

Main results
No trials of gene therapy for sickle cell disease were reported.

Authors' conclusions
No randomised or quasi-randomised clinical trials of gene therapy for sickle cell disease were reported. Thus, no objective conclusions or recommendations in practice can be made on gene therapy for sickle cell disease. This systematic review has identified the need for well-designed, randomised controlled trials to assess the benefits and risks of gene therapy for sickle cell disease.
Abstract

Background

Cystic fibrosis is a multi-system disease characterised by the production of thick secretions causing recurrent pulmonary infection, often with unusual bacteria. This leads to lung destruction and eventually death through respiratory failure. There are no antibiotics in development that exert a new mode of action and many of the current antibiotics are ineffective in eradicating the bacteria once chronic infection is established. Antibiotic adjuvants - therapies that act by rendering the organism more susceptible to attack by antibiotics or the host immune system, by rendering it less virulent or killing it by other means, are urgently needed.

Objectives

To determine if antibiotic adjuvants improve clinical and microbiological outcome of pulmonary infection in people with cystic fibrosis.

Search strategy

We searched the Cystic Fibrosis Trials Register which is compiled from database searches, hand searches of appropriate journals and conference proceedings.

Date of most recent search: 26 August 2010.

We also searched MEDLINE (all years) on 21 July 2010.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials of a therapy exerting an antibiotic adjuvant mechanism of action compared to placebo or no therapy for people with cystic fibrosis.

Data collection & analysis

The authors independently assessed and extracted data from identified studies.

Main results

We identified eighteen studies of which three are included that examined antibiotic adjuvant therapies, five studies are ongoing. The included studies involve the assessment of β-carotene, garlic and zinc supplementation. No therapy demonstrated a significant effect upon pulmonary function, pulmonary exacerbations or quality of life. The study of zinc supplementation reports a reduction in the requirement of oral antibiotics but not of intravenous antibiotics, an effect that is difficult to understand.

Authors' conclusions

We could not identify an antibiotic adjuvant therapy that could be recommended for the treatment of lung infection in those with cystic fibrosis. The emergence of increasingly resistant bacteria makes the reliance on antibiotics alone challenging for cystic fibrosis teams. There is a need to explore alternative strategies, such as the use of adjuvant therapies. Further research is required to provide future therapeutic options.
Percutaneous long lines for administering intravenous antibiotics in people with cystic fibrosis

Reviewers: Prayle AP, Hurley MN, Smyth AR

Abstract

Background
Percutaneous long lines (long intravenous lines) and short intravenous lines (also termed cannulae) are both used to deliver intravenous antibiotics in cystic fibrosis to treat respiratory exacerbations of the disease. The perceived advantage of a long intravenous line is a greater duration of line function, which has to be balanced against a technically more challenging insertion procedure, and the possibility of more discomfort on insertion.

Objectives
To compare long intravenous lines with short intravenous lines in people with cystic fibrosis receiving intravenous antibiotics, in terms of lifespan of the line, ease of insertion, complication rates of the line and patient satisfaction. This will help patients and clinicians choose between devices.

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

Date of most recent search: 26 August 2010.

Selection criteria
Randomised studies comparing long intravenous lines with short intravenous lines or comparing different types of long intravenous lines.

Data collection & analysis
We identified two studies, one comparing long intravenous lines with short intravenous lines, and one comparing two different types of long intravenous lines.

Main results
Two studies (67 participants) were included in the review. Based on the published reports, both studies had potential for bias in several domains. There is some evidence that long intravenous lines are superior to short intravenous lines. One study of 20 participants found that the lifespan of a long intravenous line is longer than that of a short intravenous line, and that participants preferred the long intravenous lines to short intravenous lines. A further study of 47 participants found no difference in lifespan, or participant preference when comparing two different long intravenous lines (the Hydrocath and Vygon EC). Neither study was powered to detect differences in serious complications of the devices.

Authors' conclusions
There is some evidence to support the use of long intravenous lines rather than short intravenous lines, in terms of lifespan of the line and patient satisfaction. There is no evidence to suggest that any one type of long intravenous line is superior, and currently choice of line should be determined by operator and patient preference. There are numerous devices available which are used in cystic fibrosis. Further research is required to identify clinically important differences between these devices.
Active cycle of breathing technique for cystic fibrosis

Reviewers: Robinson KA, Mckoy N, Saldanha I, Odelola OA

Abstract

Background

People with cystic fibrosis (CF) experience chronic airway infections as a result of mucus build up within the lungs. Repeated infections often cause lung damage and disease. Airway clearance therapies aim to improve mucus clearance, increase sputum production, and improve airway function. The active cycle of breathing technique (ACBT) is an airway clearance method that uses a cycle of techniques to loosen airway secretions including breathing control, thoracic expansion exercises, and the forced expiration technique.

Objectives

To compare the clinical effectiveness of ACBT with other airway clearance therapies in CF.

Search strategy

We searched the Cochrane CF Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles and reviews.

Last search: 05 August 2010.

Selection criteria

Randomised or quasi-randomised controlled clinical studies, including crossover studies, comparing ACBT with other airway clearance therapies in CF.

Data collection & analysis

Two review authors independently screened each article, abstracted data and assessed the risk of bias of each study.

Main results

Fifty-eight studies were identified of which 17 (346 participants) met the inclusion criteria. Four randomised controlled studies (98 participants) were included in the meta-analysis; three were of crossover design. The 13 remaining studies were crossover studies with inadequate reports for complete assessment.

Included studies compared ACBT to autogenic drainage, airway oscillating devices, high frequency chest compression devices, and conventional chest physiotherapy. Patient preference varied: more patients preferred autogenic drainage over ACBT, more preferred ACBT over airway oscillating devices, and more were comfortable with ACBT versus high frequency chest compression. No significant difference was seen in sputum weight between ACBT and autogenic drainage or between ACBT and airway oscillating devices. There was no significant difference in lung function and the number of pulmonary exacerbations between ACBT and ACBT plus conventional chest physiotherapy. All other outcomes were either not measured or had insufficient data for analysis.

Authors' conclusions

There is insufficient evidence to support or reject the use of ACBT over any other airway clearance therapy. Four studies, with four different comparators, found that ACBT was comparable to other therapies in outcomes such as patient preference, lung function, sputum weight, oxygen saturation, and number of pulmonary exacerbations. Longer-term studies are needed to more adequately assess the effects of ACBT on outcomes important for patients such as quality of life and patient preference.
Antioxidant micronutrients for lung disease in cystic fibrosis

Reviewers: Shamseer L, Adams D, Brown N, Johnson JA, Vohra S

Abstract

Background
Airway infection leads to progressive damage of the lungs in cystic fibrosis (CF), partly due to oxidative stress. Supplementation of antioxidant micronutrients (vitamin E, vitamin C, β-carotene and selenium) may help maintain an oxidant-antioxidant balance. Current literature suggests a relationship between oxidative status and lung function.

Objectives
To synthesize existing knowledge of the effect of vitamin C, vitamin E, β-carotene and selenium in CF lung disease.

Search strategy
The Cochrane CF and Genetic Disorders Group CF Trials Register, PubMed, CINAHL and AMED were searched using detailed search strategies. We contacted authors of included studies and checked reference lists of these studies for additional, potentially relevant studies.

Last search of CF Trials Register: 09 September 2010.

Selection criteria
Randomized controlled trials and quasi-randomized controlled trials of people with CF with explicitly stated diagnostic criteria, comparing vitamin E, vitamin C, β-carotene and selenium (individually or in combination) to placebo or standard care.

Data collection & analysis
Two authors independently selected trials, extracted data and assessed risk of bias. We contacted trialists to obtain missing information. Primary outcomes are lung function and quality of life; secondary outcomes are oxidative stress, inflammation, body mass index, days on antibiotics and adverse events during supplementation. If meta-analysed, studies were subgrouped according to combined or single antioxidant supplementation.

Main results
Four randomized controlled trials and one quasi-randomized controlled trial were included; only three trials (87 participants) presented data suitable for analysis. Based on two trials, there was no significant improvement in lung function; one trial indicated significant improvement in quality of life favouring control, mean difference -0.06 points on the quality of well-being scale (95% confidence interval -0.12 to -0.01). Based on two trials, selenium-dependent glutathione peroxidase enzyme significantly improved in favour of combined supplementation, mean difference 1.60 units per gram of haemoglobin (95% CI 0.30 to 2.90) and selenium supplementation, mean difference 10.20 units per gram of haemoglobin (95% CI 2.22 to 18.18). All plasma antioxidant levels, except vitamin C, significantly improved with supplementation.

Authors’ conclusions
There appears to be conflicting evidence regarding the clinical effectiveness of antioxidant supplementation in CF. Based on the evidence, antioxidants appear to decrease quality of life and oxidative stress; however, few trials contributed data towards analysis. Further trials examining clinically important outcomes and elucidation of a clear biological pathway of oxidative stress in CF are necessary before a firm conclusion regarding effects of antioxidants supplementation can be drawn.
Abstract

Background
Cystic fibrosis is a genetic disorder which can lead to multiorgan dysfunction. Malabsorption of fat and fat-soluble vitamins (A, D, E, K) may occur and can cause subclinical deficiencies of some of these vitamins. Vitamin K is known to play an important role in both blood coagulation and bone formation. Supplementation with vitamin K appears to be one way of addressing the deficiency, but there is very limited agreement on the appropriate dose and frequency of use of these supplements.

Objectives
To assess the effects of vitamin K supplementation in people with cystic fibrosis and to determine the optimal dose and route of administration of vitamin K for both routine and therapeutic use.

Search strategy
We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Most recent search: 15 April 2010.

Selection criteria
Randomised and quasi-randomised controlled trials of all preparations of vitamin K used as a supplement compared to either no supplementation (or placebo) at any dose or route and for any duration, in children or adults diagnosed with cystic fibrosis (by sweat test or genetic testing).

Data collection & analysis
Two authors independently screened papers, extracted trial details and assessed their risk of bias.

Main results
Two trials (total of 32 participants) were included in the review and were assessed as having a moderate risk of bias. One was a dose-ranging parallel group trial; and the other had a cross-over design, but no separate data were reported for the first intervention period. Neither of the trials addressed any of the primary outcomes (coagulation, bone formation and quality of life). Both trials reported the restoration of serum vitamin K and undercarboxylated osteocalcin levels to the normal range after one month of daily supplementation with 1 mg of vitamin K.

Authors' conclusions
Evidence from randomised controlled trials on the benefits of routine vitamin K supplementation for people with CF is currently weak and limited to two small trials of short duration. However, no harm was found and until further evidence is available, the present recommendations should be adhered to.
### 2011 Timetable for Cochrane Workshops

#### Australasian Cochrane Centre
For more information see: [http://www.cochrane.org/tags/events/workshops/asia-pacific-region-workshops](http://www.cochrane.org/tags/events/workshops/asia-pacific-region-workshops)

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#### Canadian Cochrane Centre
For more information see: [http://www.cochrane.org/tags/events/workshops/north-american-region-workshops](http://www.cochrane.org/tags/events/workshops/north-american-region-workshops)

#### Dutch Cochrane Centre

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<tr>
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#### Iberoamerican Cochrane Centre
For more information see: [http://www.cochrane.es/](http://www.cochrane.es/)

#### Nordic Cochrane Centre
For more information see: [http://www.cochrane.dk/courses/index.htm](http://www.cochrane.dk/courses/index.htm)

#### South African Cochrane Centre
For more information see: [http://www.mrc.ac.za/cochrane/project.htm](http://www.mrc.ac.za/cochrane/project.htm)

#### US Cochrane Centre

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#### UK Cochrane Centre

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#### Asia-Pacific Region Workshops
For more information see: [http://www.cochrane.org/tags/events/workshops/asia-pacific-region-workshops](http://www.cochrane.org/tags/events/workshops/asia-pacific-region-workshops)
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Cochrane Cystic Fibrosis and Genetic Disorders Review Group
**- Contact Details -**

Please photocopy, complete and return the following section if:

- Your contact details have changed & you wish to be kept informed about the Cystic Fibrosis and Genetic Disorders Group
- You are not on our mailing list and you would like to receive information about the Group in the future
- You would like to be removed from the Group’s mailing list

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**Proposed contribution to Cystic Fibrosis and Genetic Disorders Group, if any (e.g. undertaking a review (give interested area), hand searching, refereeing, etc):**

I would like to receive future postal mailings: Yes / No
Trial Registers

The register of randomised controlled trials (RCTs) for cystic fibrosis contains 1806 references to 1078 RCTs. This is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (updated each new issue), 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.

The haemoglobinopathies register holds 610 references to 320 trials, the coagulopathies register has 276 references to 191 trials, and there are also 144 references for phenylketonuria and 658 references for hyperlipoproteinemia (subsets on the inborn errors of metabolism register). As well as the electronic searching described above the following are searched for trials to include in the genetic disorders registers: the journals: Haemophilia and the Journal of Inherited Metabolic Disease; and the proceedings of the European Haematology Association conference; the American Society of Hematology conference; the Caribbean Health Research Council Meetings; the National Sickle Cell Disease Program Annual Meeting; the European Haematology Association conference; the American Society of Hematology conference; and the Society for the Study of Inborn Errors of Metabolism conference.
Cystic fibrosis reviews
Active cycle of breathing technique for cystic fibrosis
Antibiotic adjuvant therapy for pulmonary infection in cystic fibrosis
Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis
Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis
Anti-inflammatory drugs and analgesics for managing symptoms in people with cystic fibrosis -related arthritis
Antioxidant micronutrients for inflammation and oxidation in cystic fibrosis lung disease
Bisphosphonates for osteoporosis in people with cystic fibrosis
Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis
Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis
Combination antimicrobial susceptibility testing for acute exacerbations in chronic infection of *Pseudomonas aeruginosa* in cystic fibrosis
Conventional chest physiotherapy compared to any form of chest physiotherapy for cystic fibrosis
Disease modifying anti-rheumatic drugs in people with cystic fibrosis -related arthritis
Dornase alfa for cystic fibrosis
Drug therapies for reducing gastric acidity in cystic fibrosis
Duration of IV antibiotic therapy for people with cystic fibrosis
Elective versus symptomatic intravenous antibiotic therapy for cystic fibrosis
Enteral tube feeding for cystic fibrosis
Home intravenous antibiotics for cystic fibrosis
Inhaled bronchodilators for cystic fibrosis
Inhaled corticosteroids for cystic fibrosis
Inspiratory muscle training for cystic fibrosis
Insulin and oral agents for managing cystic fibrosis-related diabetes
Macrolide antibiotics for cystic fibrosis
Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis
Nebulised anti-*Pseudomonas* antibiotic therapy for cystic fibrosis
Nebulised hypertonic saline for cystic fibrosis
Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis
Newborn screening for cystic fibrosis
Non-invasive ventilation for cystic fibrosis
Omega-3 fatty acids for cystic fibrosis
Once daily versus multiple daily dosing with intravenous aminoglycosides for cystic fibrosis
Oral anti-*Pseudomonas* antibiotics for cystic fibrosis
Oral calorie supplements for cystic fibrosis
Oral non-steroidal anti-inflammatory drugs for cystic fibrosis
Oral steroids for cystic fibrosis
Oscillating devices for airway clearance in people with CF
Oxygen therapy for cystic fibrosis
Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis
PEP physiotherapy for airway clearance in cystic fibrosis
Percutaneous long lines for administering intravenous antibiotics in people with cystic fibrosis
Physical training for cystic fibrosis
Prophylactic anti-*Staphylococcal* antibiotics for cystic fibrosis
Psychological interventions for people with cystic fibrosis and their families
Singing for children and adults with cystic fibrosis
Single versus combination intravenous antibiotic therapy for people with cystic fibrosis
Sodium channel blockers for cystic fibrosis
Topical cystic fibrosis transmembrane conductance regulator gene replacement for cystic fibrosis-related lung disease
Totally implantable vascular access devices for cystic fibrosis
Ursodeoxycholic acid for cystic fibrosis -related liver disease
Vaccines for preventing infection with *Pseudomonas aeruginosa* in people with cystic fibrosis
Vaccines for preventing influenza in people with cystic fibrosis
Vitamin A supplementation for CF
Vitamin D supplementation for cystic fibrosis
Vitamin K supplementation for cystic fibrosis

**Cochrane Cystic Fibrosis and Genetic Disorders Review Group**
Cystic fibrosis protocols
- Appetite stimulants for people with cystic fibrosis
- Inhaled antibiotics for pulmonary exacerbations in people with cystic fibrosis
- Inhaled mannitol for cystic fibrosis
- Nebuliser devices for drug delivery in cystic fibrosis
- Pancreatic enzyme replacement therapy for people with cystic fibrosis
- Pneumococcal vaccines for cystic fibrosis
- Recombinant growth hormone therapy for children and young adults with cystic fibrosis
- Self-management education for cystic fibrosis
- Timing of dornase alfa inhalation for cystic fibrosis
- Timing of hypertonic saline inhalation in cystic fibrosis
- Topical nasal steroids for treating nasal polyposis in people with cystic fibrosis

Haemoglobinopathy reviews
- Antibiotics for treating acute chest syndrome in people with sickle cell disease
- Antibiotics for treating community acquired pneumonia in people with sickle cell disease
- Blood transfusion for osteomyelitis in people with sickle cell disease
- Blood transfusion for acute chest syndrome in people with sickle cell disease
- Blood transfusion for preventing stroke in people with sickle cell disease
- Deferasirox for iron chelation in people with transfusion-dependent sickle cell disease
- Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia
- Drugs for preventing red blood cell dehydration in people with sickle cell disease
- Fluid replacement therapy for acute episodes of pain in people with sickle cell disease
- Gene therapy for sickle cell disease
- Hematopoietic stem cell transplantation for children with sickle cell disease
- Hydroxyurea for sickle cell disease
- Inhaled bronchodilators for acute chest syndrome in people with sickle cell disease
- Inhaled nitric oxide for treating acute chest syndrome in people with sickle cell disease
- Neonatal screening for sickle cell disease
- Oral deferiprone for iron chelation in people with thalassaemia
- Phytomedicines (medicines derived from plants) for sickle cell disease
- Piracetam for reducing the incidence of sickle cell disease crises
- Pneumococcal vaccines for sickle cell disease
- Preoperative blood transfusions for sickle cell disease
- Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease
- Psychological therapies to sickle cell disease and pain
- Psychological therapies for thalassaemia
- Splenectomy versus conservative management for acute sequestration crises in people with sickle cell disease
- Treatment for avascular necrosis of bone in people with sickle cell disease
- Treatments for priapism in boys and men with sickle cell disease
- Vaccines for preventing invasive salmonella infections in people with sickle cell disease

Haemoglobinopathy protocols
- Deferasirox for iron chelation in people with transfusion-dependent thalassaemia
- Interventions for treating leg ulcers in people with sickle cell disease
- Regular long-term red blood cell transfusions for chronic chest complications in sickle cell disease
- Stem cell transplantation for people with beta thalassaemia major
Coagulopathy reviews
Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B
Recombinant Factor VIIa concentrate versus plasma derived concentrates for the acute treatment of Haemophilia A & inhibitors

Inborn errors of metabolism reviews
Bisphosphonate therapy for osteogenesis imperfecta
Carnitine supplementation for the treatment of inborn errors of metabolism
Dietary interventions for phenylketonuria
Dietary treatment for familial hypercholesterolaemia
Enzyme replacement therapy for Fabry disease
Hematopoietic stem cell transplantation for Gaucher disease
Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease
Protein substitute for children and adults with phenylketonuria
Recombinant growth hormone therapy for X-linked hypophosphatemia in children
Sapropterin dihydrochloride for phenylketonuria
Statins for familial hypercholesterolemia in children
Tyrosine supplementation in phenylketonuria

Inborn errors of metabolism protocols
Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome)
Newborn screening for homocystinuria

Orphan reviews
Dietary advice for illness-related malnutrition in adults
Embolisation therapy for pulmonary arteriovenous malformations
Oral protein calorie supplementation for children with chronic disease

Orphan protocols
Proanthocyanidin supplements for the treatment of chronic disorders
Surgical interventions for treating pectus excavatum