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Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis (Review)

Elphick HE, Southern KW

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[Intervention Review]

Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis

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H.Elphick@sheffield.ac.uk, Heather.Elphick@sch.nhs.uk.**Editorial group:** Cochrane Cystic Fibrosis and Genetic Disorders Group.**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 11, 2016.**Citation:** Elphick HE, Southern KW. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD002204. DOI: [10.1002/14651858.CD002204.pub4](https://doi.org/10.1002/14651858.CD002204.pub4).

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ABSTRACT

Background

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic reaction to colonisation of the lungs with the fungus *Aspergillus fumigatus* and affects around 10% of people with cystic fibrosis. ABPA is associated with an accelerated decline in lung function. High doses of corticosteroids are the main treatment for ABPA; although the long-term benefits are not clear, their many side effects are well-documented. A group of compounds, the azoles, have activity against *Aspergillus fumigatus* and have been proposed as an alternative treatment for ABPA. Of this group, itraconazole is the most active. A separate antifungal compound, amphotericin B, has been employed in aerosolised form to treat invasive infection with *Aspergillus fumigatus*, and may have potential for the treatment of ABPA. Antifungal therapy for ABPA in cystic fibrosis needs to be evaluated. This is an update of a previously published review.

Objectives

The review aimed to test the hypotheses that antifungal interventions for the treatment of ABPA in cystic fibrosis:

1. improve clinical status compared to placebo or standard therapy (no placebo);
2. do not have unacceptable adverse effects.

If benefit was demonstrated, we aimed to assess the optimal type, duration and dose of antifungal therapy.

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.

In addition, pharmaceutical companies were approached.

Date of the most recent search of the Group's Trials Register: 29 September 2016.

Selection criteria

Published or unpublished randomised controlled trials, where antifungal treatments have been compared to either placebo or no treatment, or where different doses of the same treatment have been used in the treatment of ABPA in people with cystic fibrosis.

Data collection and analysis

Four trials were identified by the searches; none of which was judged eligible for inclusion in the review.

Main results

No completed randomised controlled trials were included.

Authors' conclusions

At present, there are no randomised controlled trials to evaluate the use of antifungal therapies for the treatment of ABPA in people with cystic fibrosis, although trials in people who do not have cystic fibrosis have shown clinical and serological evidence of improvement and a reduction in the use of corticosteroids with no increase in adverse effects. Trials with clear outcome measures are needed to properly evaluate this potentially useful treatment for cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Treatments to fight fungal infections which cause allergic bronchopulmonary aspergillosis in people with cystic fibrosis

Review question

We planned to review evidence about the effect of treatments to fight fungal infections which cause allergic bronchopulmonary aspergillosis in people with cystic fibrosis.

Background

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic lung reaction to a type of fungus (usually *Aspergillus fumigatus*) in some people with cystic fibrosis. It causes cough and wheezing and sometimes fever. If left untreated ABPA can lead to chronic lung damage. It is usually treated with a high dose of corticosteroids (also known as steroids). However, it has not been proven that corticosteroids can prevent lung function deteriorating in the long term. Also, long-term use of steroids is linked to some serious side effects. Treating the fungus which causes ABPA may be an alternative to using high doses of steroids to combat the allergic reaction. This is an update of a previously published review.

Search date

The evidence is current to: 29 September 2016.

Study characteristics

No trials were found which we could include in the review.

Key results

There are some trials in people who don't have cystic fibrosis which have shown that if treatment is given to reduce the fungus, the steroid dose can be reduced with no adverse effects. However, in one cystic fibrosis centre, researchers observed that when people were given an anti-fungal treatment in addition to steroids, several of them became unable to produce enough cortisol (a hormone) in their adrenal glands in response to stress. There is not enough evidence for us to recommend the use of antifungal treatment in people with cystic fibrosis and ABPA. There should be a trial of these drugs to assess their effects in the long and the short term.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder affecting Caucasians (CF Foundation 2000). Chronic, progressive lung disease is the major cause of morbidity and shortened survival. This lung disease is characterised by a cycle of bacterial infection and lung damage (Hutchinson 1999). With increasing age, *Pseudomonas aeruginosa* is the major cause of chronic infection. However, a proportion of people with CF are also affected by allergic bronchopulmonary aspergillosis (ABPA). This is an allergic reaction to colonisation of the lungs with the fungus *Aspergillus fumigatus* (*A. fumigatus*). ABPA is associated with an accelerated decline in lung function in people with CF (Simmonds 1990). ABPA is diagnosed by a collection of clinical and laboratory criteria, including a consistent history; pulmonary infiltrates, which show as shadows on a chest X-ray (CXR); raised total serum immunoglobulin E (IgE) levels; skin test reaction to *A. fumigatus* antigen; and antibodies to *A. fumigatus* (Geller 1999). As these criteria are not specific and vary with the course of disease, a diagnosis of ABPA can be difficult to make.

The reported prevalence of ABPA in people with CF is around 10%, much higher than the non-CF population (Laufer 1984; Mroueh 1994; Simmonds 1990). Many of the findings of ABPA overlap with common manifestations of the lung disease in CF.

Description of the intervention

Currently high doses of corticosteroids are the main treatment for ABPA. However, an alternative strategy in the treatment of ABPA is to reduce or clear the lung of *A. fumigatus* colonisation by employing anti-fungal agents. A group of compounds, azoles, that can be taken orally, have activity against *A. fumigatus*.

How the intervention might work

Corticosteroids are thought to treat the inflammatory and allergic aspects of the condition. Whilst there is anecdotal evidence of impressive clinical and radiographic response to this therapy, there is little support from randomised controlled trials (RCTs) (Capewell 1989). There is evidence from uncontrolled trials for the use of corticosteroids in ABPA in the non-CF population for acute treatment of exacerbations (Rosenberg 1978; Varkey 1998); and at doses of prednisone of 7.5 mg/day they seem to inhibit the development of infiltrates (Safirstein 1973). The long-term benefits of steroids on the course of the disease, particularly in people with CF, are not clear and their many side effects are well-documented (Lai 2000).

Itraconazole is the most active of the group of compounds known as azoles (Denning 1992). A separate compound with good activity against *A. fumigatus* is amphotericin B. However, this is not absorbed orally, and when given intravenously is frequently associated with toxicity (Meunier 1991). Amphotericin has been employed in a nebulised form to treat invasive infection with *A. fumigatus* but remains very expensive (Purcell 1995).

Why it is important to do this review

Data from uncontrolled trials suggest itraconazole may be an effective additional therapy to steroids (Denning 1991; Nepomuceno 1999). The use of itraconazole for ABPA in people

without CF is evaluated in a separate Cochrane Review (Wark 2004). A randomised, double-blind trial of the use of itraconazole in ABPA in people without CF (28 treated; 27 placebo) showed that those taking itraconazole responded better than those taking a dummy treatment (placebo). This was defined by a reduction of at least 50% in corticosteroid dose and 25% in serum IgE level, along with evidence of clinical improvement with no increase in adverse events (Stevens 2000). A second randomised controlled trial of itraconazole in stable ABPA in people without CF showed a reduction in eosinophilic inflammation, serum IgE levels and exacerbations, implying that itraconazole is a useful adjunctive treatment for ABPA (Wark 2003). Whilst encouraging, these data need to be reproduced in larger trials and the specific effects of itraconazole for ABPA in CF need to be evaluated. It cannot be assumed that therapies that have demonstrated efficacy in the non-CF population will be equally efficacious and safe to use in people with CF.

This is an updated version of previously published reviews (Elphick 2000; Elphick 2012; Elphick 2014).

OBJECTIVES

The review aimed to test the hypotheses that antifungal interventions for the treatment of ABPA in CF:

1. improve clinical status compared to placebo or standard therapy (no placebo);
2. do not have unacceptable adverse effects.

If benefit was demonstrated, we aimed to assess the optimal type, duration and dose of antifungal therapy.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs, published or unpublished. Quasi-randomised (e.g. alternate allocation and stratification) controlled trials (CCTs) would have been included, if there was sufficient evidence that intervention and control groups were similar. Both short- and long-term trials were to be included, where short-term trials include those that involve treatment for up to six months and long-term trials those over six months.

Types of participants

Children and adults with defined CF, diagnosed clinically and by sweat or genetic testing, including all ages and all degrees of severity, who also have ABPA diagnosed by clearly defined clinical and laboratory criteria.

Types of interventions

Antifungal treatments which have been compared to either placebo or no treatment, or where different doses of the same treatment have been used for treating ABPA in people with CF. Such trials would have been included if the only difference between the groups was use of antifungal treatment or a comparison of different antifungal regimens.

The major interventions were:

1. oral azoles;
2. nebulised amphotericin.

If any other antifungal interventions were studied, these would also be considered.

Types of outcome measures

Primary outcomes

1. Rate of reduction of steroid dosage
2. Clinical improvement
 - a. improvement in symptoms, e.g. wheeze
 - b. improvement in chest X-ray (CXR) scores
 - c. improvement in spirometric lung function e.g. forced expiratory volume at one second (FEV₁) and forced vital capacity (FVC)
 - d. nutritional status, e.g. weight gain, body mass index (this outcome measure may be complicated by the confounding influence of steroid reduction on weight)
3. Time to next exacerbation or acute ABPA episode

Secondary outcomes

1. Laboratory evidence of improvement in ABPA
 - a. reduction in serum IgE and IgG to *A. fumigatus*
 - b. reduction in peripheral eosinophil count
 - c. reduction in total serum IgE
 - d. reduction in the frequency of isolation of *A. fumigatus* in respiratory culture
2. Quality of life assessments
3. Adverse events, in particular: liver function abnormalities; peripheral neuropathy (azoles); nephrotoxicity; and arrhythmias (amphotericin)

Outcomes were considered short-term if they were measured at the end of the treatment period, unless the treatment period was for six months or more, in which case outcomes were then considered long-term. Outcomes were also considered long-term if it was more than three months between the end of the treatment and the measure.

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the term: allergic bronchopulmonary aspergillosis.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*), weekly 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 [Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 29 September 2016.

For future searches, we will look for the specific agents itraconazole and voriconazole.

Searching other resources

In addition, principal investigators known to work in the field and previous authors were contacted for unpublished or follow-up data.

Pharmaceutical companies who manufacture antifungal agents, were also approached.

Data collection and analysis

Selection of studies

The two authors (HEE and KWS) planned to independently select the trials to be included in the review.

Data extraction and management

Each author planned to independently extract data using standard data acquisition forms. If disagreement arose on the suitability of a trial for inclusion in the review or on its quality, the authors planned to reach a consensus by discussion.

The authors planned to group outcome data into those measured at one, three, six, twelve months and annually thereafter. They also planned to consider examining outcome data reported at other time periods.

Assessment of risk of bias in included studies

Each author planned to assess the risk of bias for each trial using the Cochrane Risk of Bias tool as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In particular the authors planned to assess the following as leading to a high, unclear or low risk of bias:

- Allocation (both generation of sequence and its concealment)
- Blinding (of clinicians, participants and outcome assessors)
- Incomplete outcome data
- Selective reporting
- Any other potential sources of bias

If there was any disagreement on these judgements, the authors planned to reach a consensus by discussion.

Measures of treatment effect

For continuous outcomes, the authors planned to record either the mean change from baseline for each group or mean post treatment/ intervention values and the standard deviation or standard error for each group.

For binary outcome measures they planned to calculate a pooled estimate of the treatment effect for each outcome across trials, (the odds of an outcome among treatment allocated participants to the corresponding odds among controls).

For any time-to-event outcomes included in the review, the authors planned to obtain a mixture of logrank and Cox model estimates from the trials; they will combine all results using the generic

inverse variance method, since they will be able to convert the logrank estimates into log hazard ratios and standard errors as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

In order to allow an intention-to-treat analysis, authors planned to seek data on the number of participants by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Assessment of heterogeneity

The authors aimed to test for heterogeneity between trial results using a standard chi-squared test and the I^2 statistic where the following ranges and judgements will apply:

- 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.

We recognise that the importance of the observed value of I^2 depends on (i) the magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2).

Subgroup analysis and investigation of heterogeneity

The authors planned to analyse different antifungal treatments separately, e.g. oral azoles separately from nebulised amphotericin B.

Sensitivity analysis

The authors planned to make an overall analysis with and without quasi-randomised trials, to ensure that these did not bias the final result. The authors also planned to perform a sensitivity analysis based on the methodological quality of the trials.

Where trials included participants with ABPA, both with and without CF, the authors intended to attempt a separate analysis for those with CF and ABPA. Where this could not be done, the results would not be included in the meta-analysis, but would be described. The impact of these trials would then be assessed by sensitivity analysis. People with non-CF ABPA are the subject of another Cochrane Review (Wark 2004), where they will be dealt with similarly.

RESULTS

Description of studies

No trials were identified for inclusion in this review.

Results of the search

Four trials were identified in the searches for this review (Aaron 2012; Cohen-Cymerknoh 2008; Novartis 2008; Proesmans 2010). All trials have now been excluded.

Excluded studies

One excluded trial considered the treatment of sputum colonised with *A. fumigatus*, not ABPA (Aaron 2012). A second trial investigated different types of steroids and not antifungal therapies (Cohen-Cymerknoh 2008). The intervention in the Novartis trial was not relevant (anti IgE therapy) (Novartis 2008). The fourth trial was a non-randomised trial (Proesmans 2010).

Risk of bias in included studies

No trials were included in this review.

Effects of interventions

No trials were included in this review.

DISCUSSION

At present, there are no RCTs to evaluate the use of antifungal therapies for the treatment of ABPA in people with CF.

Allergic bronchopulmonary aspergillosis is an important complication of CF, contributing to worsened morbidity and leading to progressive deterioration in lung function. Most of the findings of ABPA overlap with common manifestations of the lung disease in CF, which makes the diagnosis complicated. Whilst there is anecdotal evidence of response to corticosteroid therapy, there is no support from RCTs in CF. The long-term benefits of steroids on the course of the disease, particularly in people with CF, are not clear and their many side effects are well-documented. Consequently, treatment with antifungal agents may be advantageous over treatment with corticosteroids alone, and may lead to the ability to reduce the doses of steroid therapy. Two RCTs of itraconazole in ABPA in people without CF have shown a reduction in corticosteroid dose and eosinophilic inflammation, along with clinical and serological evidence of improvement with no increase in adverse events. A number of uncontrolled trials and case reports have also documented that the use of itraconazole in ABPA is advantageous. However, a recent report of suppression of adrenal glucocorticoid synthesis observed a potential adverse effect in 11 out of 25 people with CF treated with both itraconazole and budesonide. The likely pathogenesis is that an itraconazole caused an increase in systemic budesonide concentration due to inhibited metabolism, leading to suppressed adrenocorticotrophic hormone (ACTH) secretion (Skov 2002). The presence of adrenal insufficiency would be an important adverse effect to identify as an outcome measure in future trials.

Trials with clear outcome measures are needed to properly evaluate this potentially useful treatment for CF.

AUTHORS' CONCLUSIONS

Implications for practice

There are no published data available to recommend the use of antifungal therapies for ABPA in people with CF. Use of these drugs in people with CF remains experimental and RCTs evaluating both efficacy and safety are needed.

Implications for research

This systematic review has identified the need for a well-designed, adequately-powered, multicentre, randomised controlled trial to

assess the efficacy and possible adverse effects of antifungal therapies for ABPA in people with CF. Outcome measures, such as pulmonary function, should be clearly stated and multicentre trials should be co-ordinated so that maximum power is available to achieve a clear result. Trials should look at the effects on both acute exacerbations and chronic outcome measures and therefore cross-over trials would not be suitable. The adjuvant role of antifungals with corticosteroids should be investigated, including the effects on reduction of corticosteroid dose and the potential for serious adverse effects, including adrenal suppression. It cannot

be assumed that therapies that have demonstrated efficacy in the non-CF population will be equally efficacious and safe to use in people with CF and therefore these two groups should be studied separately.

ACKNOWLEDGEMENTS

The authors would like to thank the referees, particularly Dr P Wark, for their useful comments and suggestions.

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Cohen-Cymerknoh 2008 {published data only}

Cohen-Cymerknoh M, Blau H, Shoseyov D, Efrati O, Armoni S, Kerem E. Intravenous methylprednisolone pulse therapy vs. oral prednisone for allergic bronchopulmonary aspergillosis (ABPA) in CF [abstract]. *Journal of Cystic Fibrosis* 2008;**7**(Suppl 2):S58.

Novartis 2008 {published data only}

Novartis. An exploratory study to assess multiple doses of Omalizumab in patients with cystic fibrosis complicated by acute bronchopulmonary aspergillosis (ABPA). Clinicaltrials.gov (www.clinicaltrials.gov) (accessed 21/01/2013) 2008: ClinicalTrials.gov Identifier: NCT00787917. [CFGD Register: PI264; CRS: 5500100000010742]

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aaron 2012	Treatment of sputum colonised with <i>A. fumigatus</i> , not ABPA.
Cohen-Cymberknob 2008	Comparison of different types of steroids, not antifungals.
Novartis 2008	Not a relevant intervention, anti IgE therapy for ABPA.
Proesmans 2010	Non-randomised study.

A. fumigatus: *Aspergillus fumigatus*

ABPA: allergic bronchopulmonary aspergillosis

WHAT'S NEW

Date	Event	Description
29 September 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in the review.
29 September 2016	New citation required but conclusions have not changed	Since no new data have been added to this review, our conclusions remain the same.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 4, 2000

Date	Event	Description
20 November 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Trials Register identified two new references, both of which have been excluded (Aaron 2012 ; Novartis 2008). The Plain Language Summary has been redrafted in line with new Group guidance.
20 November 2014	New citation required but conclusions have not changed	As no new studies have been included in this update of the review, our conclusions remain the same.
9 May 2012	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in this review. The Proesmans study has now been moved from Awaiting Classification to Excluded Studies following contact with the author of the study (Proesmans 2010).
9 May 2012	New citation required but conclusions have not changed	This review has been updated.
30 March 2010	New search has been performed	Two studies were newly identified; one is listed as Awaiting Classification (Proesmans 2009), and the other has been excluded (Cohen-Cymerknoh 2008). Itraconazole and voriconazole have been added as therapeutic agents to be included in future searches and updates.
31 March 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register found no new trials eligible for inclusion in this review.
20 March 2008	Amended	Converted to new review format.
20 August 2007	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register found no new trials eligible for inclusion in this review. The plain language summary has been re-drafted in light of the current guidance from The Cochrane Collaboration.
17 August 2006	New search has been performed	New search, no new studies found.
14 August 2005	New search has been performed	New search, no new studies found.
28 June 2004	New search has been performed	New search, no new studies found.
30 June 2003	New search has been performed	New search, no new studies found.
30 July 2002	New search has been performed	New search, no new studies found.
30 June 2001	New search has been performed	New search, no new studies found.

Date	Event	Description
18 August 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Dr Southern conceived the review and contributed towards the writing of the protocol and review.

Dr Elphick drafted the protocol and review. Dr Elphick completed the updates of the review and acts as guarantor of the review.

DECLARATIONS OF INTEREST

Dr Heather Elphick declares no known potential conflict of interest.

Dr Kevin Southern declares no known potential conflict of interest.

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- No sources of support supplied

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NOTES

Please see related review:

Wark PAB, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD001108. DOI: 10.1002/14651858.CD001108.pub2.

INDEX TERMS

Medical Subject Headings (MeSH)

**Aspergillus fumigatus* [drug effects]; Antifungal Agents [*therapeutic use]; Aspergillosis, Allergic Bronchopulmonary [*drug therapy]; Cystic Fibrosis [*complications]

MeSH check words

Adult; Child; Humans