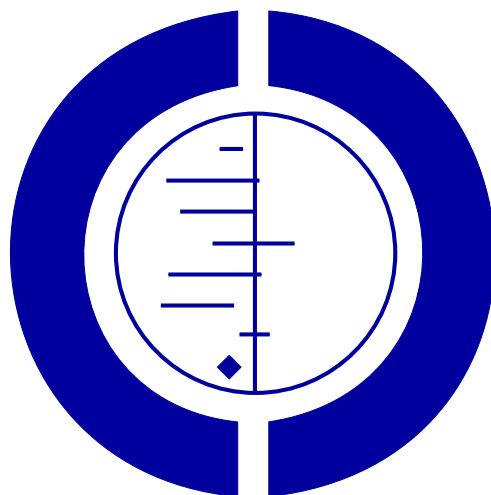


Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis (Review)

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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.

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 strategy

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: May 2006.

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Published or unpublished randomised controlled trials, where antifungal treatments have been compared to either placebo or no treatment, or where different doses of the same treatment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

No completed randomised controlled trials were identified.

Main results

No completed randomised controlled trials were identified.

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

PLAIN LANGUAGE SUMMARY

Allergic bronchopulmonary aspergillosis (ABPA) contributes to progressive damage of the airways in about 10% of people with cystic fibrosis

Standard therapy for ABPA is high dose corticosteroids, although these drugs have not been shown to prevent long-term deterioration in lung function and chronic use is associated with serious side effects. An alternative treatment strategy for ABPA is reducing the fungus *Aspergillus fumigatus* using antifungal agents, which may reduce the need for high doses of steroids. This review aimed to identify randomised controlled trials (RCTs) evaluating the use of antifungal therapies for treatment of ABPA in cystic fibrosis. No completed trials were identified. RCTs with clear outcome measures are needed to properly evaluate this potentially useful treatment for cystic fibrosis.

BACKGROUND

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.

Corticosteroids, in high doses, are the main treatment for ABPA because they 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).

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*. Of this group, itraconazole is the most active (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).

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.

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.

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 intervention

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.

Outcome data were grouped into those measured at one, three, six, twelve months and annually thereafter. If the outcome data were recorded at other time periods, then consideration was given to examining these as well.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Cystic Fibrosis and Genetic Disorders Group methods used in reviews.

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the terms: azoles OR amphotericin OR itraconazole OR ambisone OR imidazole OR triazole OR ketoconazole.

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*), 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 Cystic Fibrosis and Genetic Disorders Group Module.

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.

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: May 2006.

METHODS OF THE REVIEW

The two authors (HEE and KWS) planned to independently select the trials to be included in the review. Each author was to assess the methodological quality of each trial based on a method described by Schulz (Schulz 1995). In particular, authors would examine details of the randomisation method, allocation concealment, whether the trial was blinded, whether intention-to-treat analysis was possible from the available data and if the number of participants lost to follow up or subsequently excluded from the trial was recorded. 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.

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 we plan 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).

In order to allow an intention-to-treat analysis, authors will 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. The authors aimed to test for heterogeneity between trial results using a standard chi-squared test. They 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.

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

DESCRIPTION OF STUDIES

No trials were identified for this review.

METHODOLOGICAL QUALITY

No trials were identified for this review.

RESULTS

No trials were identified for this review.

DISCUSSION

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.

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

NOTES

Please see related review:

Wark P, Wilson AJ, Gibson PG. Azoles for allergic bronchopulmonary aspergillosis (Cochrane Review). In: The Cochrane Library, Issue 4, 2002. Oxford: Update Software Ltd.

Information on previous updates

Review updated: August 2005

A search of the Group's Cystic Fibrosis Trials Register found no new trials eligible for inclusion in this review.

Review updated: June 2004

A search of the Group's trials register found no new trials eligible for inclusion in this review.

Review updated: June 2003

A search of the Group's trials register found no new trials eligible for inclusion in this review.

Review updated: April 2002

A search of the Group's trials register found no new trials eligible for inclusion in this review.

POTENTIAL CONFLICT OF INTEREST

None known.

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GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS**Medical Subject Headings (MeSH)**

Antifungal Agents [*therapeutic use]; Aspergillosis, Allergic Bronchopulmonary [*drug therapy]; Cystic Fibrosis [*complications]; Randomized Controlled Trials

MeSH check words

Adult; Child; Humans

COVER SHEET

Title	Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis
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Contribution of author(s)	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.
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Date new studies found and included/excluded	Information not supplied by author
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