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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	7
DISCUSSION	13
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	20
DATA AND ANALYSES	36
WHAT'S NEW	36
HISTORY	37
CONTRIBUTIONS OF AUTHORS	39
DECLARATIONS OF INTEREST	39
SOURCES OF SUPPORT	39
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	39
INDEX TERMS	39

Inhaled corticosteroids for cystic fibrosis

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ABSTRACT

Background

Reduction of lung inflammation is one of the goals of cystic fibrosis therapy. Inhaled corticosteroids are often used to treat children and adults with cystic fibrosis. The rationale for this is their potential to reduce lung damage arising from inflammation, as well as their effect on symptomatic wheezing. It is important to establish the current level of evidence for the risks and benefits of inhaled corticosteroids, especially in the light of their known adverse effects on growth. This is an update of a previously published review.

Objectives

To assess the effectiveness of taking regular inhaled corticosteroids, compared to not taking them, in children and adults with cystic fibrosis.

Search methods

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. We requested information from pharmaceutical companies manufacturing inhaled corticosteroids and authors of identified trials.

Date of most recent search of the Group's Trials Register: 15 August 2016.

Selection criteria

Randomised or quasi-randomised trials, published and unpublished, comparing inhaled corticosteroids to placebo or standard treatment in individuals with cystic fibrosis.

Data collection and analysis

Two independent authors assessed methodological quality and risk of bias in trials using established criteria and extracted data using standard pro formas.

Main results

The searches identified 34 citations, of which 26 (representing 13 trials) were eligible for inclusion. These 13 trials reported the use of inhaled corticosteroids in 506 people with cystic fibrosis aged between six and 55 years. One was a withdrawal trial in individuals who were already taking inhaled corticosteroids. Methodological quality and risk of bias were difficult to assess from published information. Many of the risk of bias judgements were unclear due to a lack of available information. Only two trials specified how participants

were randomised and less than half of the included trials gave details on how allocation was concealed. Trials were generally judged to have a low risk of bias from blinding, except for two which were open label or did not use a placebo. There were some concerns that a number of trials had not been published in peer-reviewed journals, but the risk of bias from this was unclear. Inclusion criteria varied between trials, as did type and duration of treatment and timing of outcome assessments. Objective measures of airway function were reported in most trials but were often incomplete. Significant benefit has not been conclusively demonstrated. Four trials systematically documented adverse effects and growth was significantly affected in one study using high doses.

Authors' conclusions

Evidence from these trials is insufficient to establish whether inhaled corticosteroids are beneficial in cystic fibrosis, but withdrawal in those already taking them has been shown to be safe. There is some evidence they may cause harm in terms of growth. It has not been established whether long-term use is beneficial in reducing lung inflammation, which should improve survival, but it is unlikely this will be proven conclusively in a randomised controlled trial.

PLAIN LANGUAGE SUMMARY

Inhaled corticosteroids for cystic fibrosis

Review question

We reviewed the evidence about the effect of inhaled corticosteroids in people with cystic fibrosis.

Background

Repeated chest infections in people with cystic fibrosis cause inflammation and damage to the lungs which, in the long term, is the most common reason for death in people with cystic fibrosis. Inhaled corticosteroids are often used to treat inflammation, but may cause some side effects. Some of these side effects are less serious, for example oral thrush, but others are more serious, such as reduced growth rate in childhood. This is an update of an earlier review.

Search date

The last search for evidence was on 15 August 2016.

Study characteristics

In this updated review, 13 trials reported the use of inhaled corticosteroids in 506 people with cystic fibrosis aged between 6 and 55 years. Three trials were in children only, four in adults only and four were mixed ages; two trials did not describe the ages of the volunteers. The lung function and severity of disease of the volunteers varied across trials and only two trials gave information about their genetic mutations. All trials took place in Europe. In 10 of the trials, all volunteers were in the same group up to the end of the trial (either a treatment group or a group receiving no treatment or a placebo (treatment that appeared the same as the steroids, but did not have any active medicine in it)), but in three trials they swapped groups halfway through the trial. In most of the trials volunteers started taking steroids or placebo at the start of the trial, but one trial was a withdrawal trial, where all volunteers were already taking steroids and half of them carried on and the rest took a placebo, in effect stopping the treatment. The trials lasted between three weeks and two years.

Key results

The clinical trials have not been able to prove that inhaled corticosteroids reduce inflammation in the lungs of people with cystic fibrosis. One trial has shown that these drugs can slow down children's growth when used in high doses. Furthermore it has been shown that under close supervision of the cystic fibrosis team, it may be safe for people who have been taking inhaled corticosteroids for some time to stop doing so.

Quality of the evidence

A lack of information meant we were often not able to judge if the way the trials were designed or run could have affected our confidence in the results. Only two trials gave details of how they made sure volunteers had equal chances of being in the treatment or placebo groups and only five supplied information on how they made sure the people recruiting volunteers didn't know which groups they would be going into. In most cases, we didn't think that once the trials started the volunteers or their doctors knew whether they were

getting steroids or placebo. However, we did have some concerns that five of the trials had not been published in journals, that would send the reports to experts to check for accuracy and we were not sure how this might affect our confidence in the results.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a chronic disorder, of autosomal recessive inheritance, which principally affects the respiratory tract, pancreas, gastro-intestinal tract and liver. In the respiratory tract, abnormalities result in mucus plugging of the airways and susceptibility to respiratory tract infection. This leads to neutrophil-dominated airway inflammation with consequent lung damage (bronchiectasis), and eventually respiratory failure and death. Inflammation is also important in the development of the bronchial hyperreactivity (BHR) and airway instability that may be associated with CF. Up to half of people with CF have measurable BHR, which seems unrelated to atopic status (Burdon 1980; Mitchell 1978; Tobin 1980). Although prognosis and survival continue to improve, it is the lung damage which is the single most important factor responsible for premature death. Lung damage also has implications for quality of life, and slowing of the rate of progression of lung disease is an important goal in the management of CF. The search for a suitable anti-inflammatory strategy has gone on for over two decades, but unfortunately there is still no ideal agent available (Balfour-Lynn 2007). Lung inflammation may commence very early in life (Khan 1995), and may be present even in those without clinical manifestations of lung disease (Armstrong 1995) or positive bacterial culture (Balough 1995; Konstan 1994). Although a normal inflammatory response is beneficial to host defence mechanisms, the exaggerated response seen in CF contributes to the morbidity and ultimately the mortality associated with the disease (Hilliard 2005).

Description of the intervention

Corticosteroids (glucocorticoids) are potent non-specific anti-inflammatory agents which have been widely used in a variety of inflammatory disorders. They can be administered topically or systemically, but this review is concerned only with corticosteroids given by the inhaled route.

How the intervention might work

In asthma, inhaled corticosteroids (ICS) reduce BHR and airway inflammation (Barnes 1992; Booth 1995; Djukanovic 1992; van Grunsven 1999) and lead to modest improvements in airway function (Calpin 1997). Although beneficial effects on pulmonary function, but not BHR, have been reported in chronic obstructive pulmonary disease (COPD) (Renkema 1996; Weir 1993), there is proven benefit only in certain aspects of COPD management (NICE 2004). Furthermore, a COPD biopsy study showed that three months of inhaled fluticasone did not reduce the neutrophilic inflammation, despite improvement in symptoms and exacerbation rate (Hattotuwa 2002). The rationale for their use in CF lies in observations that inflammation occurs early in the course of CF and may contribute to lung damage. The Cochrane Review of evidence for the effectiveness of oral corticosteroids in CF concluded that treatment with a prednisolone equivalent dose of 2 mg/kg on alternate days appeared to slow the progression of lung disease but was associated with a high risk of important side effects (Cheng 1999).

Corticosteroids are associated with a wide range of potential adverse effects, all of which tend to be more severe with oral or other systemic preparations (ABPI 1999). Oral administration over prolonged periods may lead to a Cushingoid appearance with redistribution of fat to the central areas of the body, obesity, muscle wasting, acne, bruising, thinning of the skin and skin striae. High doses can also precipitate or exacerbate impaired glucose metabolism. Prolonged use is associated with reduced bone mineral density and posterior subcapsular cataracts. In children, one of the most important side effects is growth suppression. There are also concerns that substantial inhibition of inflammation could impair innate immunity and make the patient more susceptible to infection (Koehler 2004).

Inhaled preparations of corticosteroids have been developed to maximise effective treatment of lung inflammation and reduce the frequency of harmful effects, but these have not been completely eliminated (Russell 2004). Systemic adverse effects occur with all ICS, although to a lesser degree than seen with oral preparations (Lipworth 1999). These appear to be related to both dose and duration of treatment. In one meta-analysis, an increased risk of adrenal suppression and bone thinning was found at daily doses above 1.5 mg (budesonide equivalent) per day (which equates to above 0.75 mg per day for fluticasone) (Lipworth 1999). Over the last decade there has been increasing concern about the potential effects of ICS on adrenal function, with several case series report-

ing symptomatic adrenal suppression including hypoglycaemia, coma and even death in asthmatic adults and children taking high (and less often standard) dose ICS (Drake 2002; Macdessi 2003; Patel 2001; Taylor 1999; Todd 1996; Todd 2002). More recently, there has been a population-based case controlled study suggesting an association of high doses for long duration may be associated with cataracts in those over 40 years old (Smeeth 2003). Other less severe adverse effects include hoarseness of voice and oral candidiasis.

Why it is important to do this review

In 1994, in the UK, 34% of adults with CF surveyed reported that they took inhaled steroids (Walters 1995) and this had risen to 51% in a subsequent survey conducted in 2000 (Walters 2001). National databases showed there to have been an increase in prescribing and use both in Europe and the USA. In 1994 and 1995 (snapshot data), databases of annual review returns recorded the ICS use as 36% in the UK (Koch 1997), and 26% in North America (1995 snapshot data) (Konstan 1999). Clinicians at CF centres treating children reported prescribing them to a median of 44% of children (Balfour-Lynn 1999). Data from 2001 entries showed that in the UK (CF Trust Database) 52% children and 55% adults were prescribed ICS, whilst in the USA they were given to 41% children and 48% adults (Epidemiologic Study of CF). Whilst more recent data from UK CF Trust Registry shows that in 2007, 21% children under 16 years and 23% adults were prescribed regular ICS; and North American data from the CFF registry showed that in 2005, 46% patients received ICS (Balfour-Lynn 2008). The use of ICS may be justified as a form of symptomatic prophylaxis for those with recurrent wheezing or CF asthma (Balfour-Lynn 2002), but they are also prescribed by many clinicians purely for their perceived benefit as an anti-inflammatory agent. It is therefore important to establish whether this practice is beneficial overall for patients with CF or whether their potential for harm overrides any benefit.

This version of the review is an update of previously published versions (Balfour-Lynn 2000; Balfour-Lynn 2009; Balfour-Lynn 2012; Balfour-Lynn 2014).

OBJECTIVES

The objective of this review was to assess the effectiveness of regular use of ICS when compared to not receiving ICS, in the management of people with CF. We assessed whether ICS:

1. improve lung function (including tests of lung function, bronchial hyperreactivity, exercise tolerance);
2. reduce the need for hospital admission or antibiotic treatment for respiratory exacerbations;

3. improve the well-being of people with CF (in relation to nutritional status and quality of life);
4. improve survival;
5. are associated with harmful effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-randomised controlled trials (using allocation methods such as alternate allocation to treatment and control group) were included.

Types of participants

People with CF who had been diagnosed by clinical criteria and sweat or genetic testing, or both, regardless of age or clinical severity.

Types of interventions

Any ICS administered using any inhalation device (including metered dose inhalers, dry powder inhalers, spacer devices and nebulisers) for a period of not less than two weeks, compared to either placebo or standard treatment.

Types of outcome measures

Primary outcomes

1. Objective measures of lung function
  - i) absolute change and change in % predicted of forced expiratory volume in one second (FEV₁)
  - ii) absolute change and change in % predicted of the forced vital capacity (FVC)

Secondary outcomes

1. Changes in bronchial hyperreactivity as measured by challenge with a bronchoconstricting agent such as histamine, methacholine or cold air
2. Objective or subjective improvement in exercise tolerance
3. Number of days in hospital for respiratory exacerbations
4. Number of days on intravenous antibiotics for respiratory exacerbations
5. Change in nutritional indices

- i) change in height centile
  - ii) change in weight centile
  - iii) change in body mass index or per cent predicted weight for height
  - iv) changes in growth velocity (change in cm per treatment interval)
  - v) other
- 6. Quality of life
- 7. Occurrence of any adverse effects
  - i) local effects (e.g. oral candida infections (diagnosed clinically or microbiologically), hoarseness)
  - ii) systemic effects (e.g. skin changes, diabetes mellitus, osteoporosis, Cushingoid appearance, cataract, mild or severe opportunistic infection, adrenal insufficiency (*post hoc* addition))
- 8. Survival (assessed at 6 months, 12 months and annually thereafter)

Search methods for identification of studies

Electronic searches

Relevant studies were identified from the Group's Cystic Fibrosis Trials Register using the terms: anti-inflammatory AND steroid AND (inhaled or unknown).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), 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 CF 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 Trials Register: 15 August 2016.

Searching other resources

The reference lists of all trials identified were searched. Two pharmaceutical companies manufacturing ICS preparations were contacted to identify unpublished trials. No trials were identified by one and we have not yet received a reply from the other. For a previous update, we wrote to lead authors of nine eligible trials, published only as abstracts or as full reports but with incomplete information for assessment of methodological quality or for reporting of outcomes. Replies were received from five and any information provided was incorporated.

Data collection and analysis

Selection of studies

For the update two authors (KW, IBL) independently selected trials to be included in the review. There was no disagreement between the authors as to which trials should be included.

Data extraction and management

To ensure consistency, each author independently extracted data using a standard data extraction form. The outcome measures listed above were assessed in the short term (between 2 and 12 weeks), the medium term (between 3 and 12 months) and long term (over 12 months).

The WISE trial is a withdrawal study and all participants had been on steroids for a number of years before these were withdrawn. The other studies present data from the start of treatment with steroids. The review authors decided that the data from the withdrawal study should be presented on a different graph to the data from the other studies since the populations in the placebo arms of the studies are heterogeneous and that there may possibly be carry over effect which will tend to reduce the difference.

Assessment of risk of bias in included studies

We used the criteria for assessing risk of bias as provided in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We asked if the six domains listed below were considered to be adequate. There were three possible responses, 'yes', 'no' or 'unclear'. 'Yes' indicated a low risk of bias, and 'no' indicated high risk of bias. If insufficient detail was reported the judgement was 'unclear' risk of bias. We assessed the new studies included in the updated review and we reassessed the studies already included in the old review using the new criteria.

Sequence generation

'Yes', if the allocation sequence was generated using techniques such as a random number table; a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice.

'No', if the allocation sequence was generated using techniques such as odd or even date of birth; date (or day) of admission; hospital or clinic record number.

'Unclear', if there was insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.

Allocation concealment

'Yes', if the allocation concealment used methods such as central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of

identical appearance; sequentially numbered, opaque, sealed envelopes.

'No', if the participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on; using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number.

'Unclear', if there was insufficient information to permit judgement of 'Yes' or 'No'. This was usually the case if the method of concealment was not described or not described in sufficient detail to allow a definite judgement for example if the use of assignment envelopes was described, but it remained unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding

'Yes', if there was no blinding, but the review authors judged that the outcome and the outcome measurement was not likely to be influenced by lack of blinding; blinding of participants and key study personnel was ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

'No', if there was no blinding or incomplete blinding, and the outcome or outcome measurement was likely to be influenced by lack of blinding; blinding of key study participants and personnel was attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

'Unclear', if there was insufficient information to permit judgement of 'Yes' or 'No' or the study did not address this outcome.

Incomplete data assessment

'Yes', if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to true outcome; missing outcome data was balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; missing data were imputed using appropriate methods.

'No', if reason for missing outcome data were likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to induce clinically relevant bias in

intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes was enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.

'Unclear', if there was insufficient reporting of attrition or exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized were not stated, no reasons for missing data were provided); the study did not address this outcome.

Selective outcome reporting

'Yes', if the study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review were reported in the pre-specified way; the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified.

'No', if not all of the study's pre-specified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods or subsets of the data (e.g. sub scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study.

'Unclear', if there was insufficient information to permit judgement of 'Yes' or 'No'.

Other sources of bias

'Yes', if the study appeared to be free of other sources of bias.

'No', if there was at least one important risk of bias. For example, the study had a potential source of bias related to the specific study design used; or stopped early due to some data-dependent process (including a formal-stopping rule); or had extreme baseline imbalance; or has been claimed to have been fraudulent; or had some other problem.

'Unclear', if there was either: insufficient information to assess whether an important risk of bias existed; or insufficient rationale or evidence that an identified problem would introduce bias.

Measures of treatment effect

The statistical analysis proposed, included calculation of a pooled estimate of treatment effect for each dichotomous outcome across all studies (odds of outcome in participants allocated to receive treatment compared with odds of outcome in participants allocated to control group); and calculation of a pooled estimate of

treatment effect for each continuous outcome across all studies in the form of a mean difference (MD). For continuous variables, the authors recorded mean absolute change from baseline for each group, or mean post-treatment values and standard deviation for each group.

Unit of analysis issues

Elbourne discusses methods for meta-analysing cross-over trials (Elbourne 2002). The methods discussed rely on the data that are reported within the primary paper. The method that has been adopted within this review uses data from the first period only, ignoring the second period data. If results of the first period only were not available, the results of the trial were described in the text.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors sought data on the number of participants with each outcome event listed above, by allocated treatment group, irrespective of whether the participant complied with treatment or was later excluded from treatment or follow up.

The authors also contacted the study investigators for clarification of information in their publications or additional data where necessary.

Assessment of heterogeneity

If indicated, the authors examined heterogeneity between trial results using a standard chi-squared test. The authors also assessed the degree of heterogeneity between trials using the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across studies that are due to heterogeneity rather than by chance; the values of I^2 lie between 0% and 100%, and can be simply categorized so that heterogeneity is low when I^2 has a value of 25%, moderate if I^2 has a value of 50%, and high when I^2 has a value of 75% (Higgins 2003).

Assessment of reporting biases

Reports of all the included studies were checked to see that all the stated outcomes were reported and the results are presented in the 'Risk of bias table' in [Characteristics of included studies](#)

Data synthesis

The authors have analysed the data using a fixed-effect model. If, in future updates of this review, they are able to combine data and establish a moderate or high degree of heterogeneity between trials, they will analyse the combined data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If there are a sufficient number of trials included in a future update and heterogeneity is identified, the authors plan to investigate this by undertaking subgroup analyses comparing age, atopy with non-atopy, baseline lung function and individuals infected with *Pseudomonas aeruginosa* with those not infected with *Pseudomonas aeruginosa*. It is unlikely, however, that this will be possible.

Sensitivity analysis

If appropriate, the authors planned to undertake a sensitivity analysis by allocation method (quasi-randomised versus randomised).

RESULTS

Description of studies

Results of the search

The searches identified 34 citations, of which 26 referred to 13 trials meeting the inclusion criteria for this review ([Austrian Trial 1995](#); [Belgian Trial 2007](#); [Canadian Trial 1997](#); [CF WISE 2006](#); [Danish Trial 1983](#); [Danish Trial 1997](#); [Dutch Trial 1995](#); [German Trial 1999](#); [Irish Trial 1995](#); [Swiss Trial 1996](#); [Turkish Trial 2008](#); [UK Trial 1996](#); [UK Trial 1997](#)).

Seven citations referred to four trials, all of which were excluded ([Australia Trial 2000](#); [Bessaci 2008](#); [USA Trial 1996](#); [USA Trial 1998](#)). The final citation referred to a trial which is currently listed in [Studies awaiting classification](#) until the methods of the trial can be clarified with the investigators ([Kapustina 2008](#)).

Included studies

Full reports have been published for both Danish trials ([Danish Trial 1983](#); [Danish Trial 1997](#)), the Dutch and Swiss trials ([Dutch Trial 1995](#); [Swiss Trial 1996](#)), two UK trials ([CF WISE 2006](#); [UK Trial 1997](#)), the German trial ([German Trial 1999](#)) and the Belgian trial ([Belgian Trial 2007](#)). There are five trials reported in abstracts or conference proceedings only ([Austrian Trial 1995](#); [Canadian Trial 1997](#); [Irish Trial 1995](#); [Turkish Trial 2008](#); [UK Trial 1996](#)).

Trial Design

Ten trials were parallel in design ([Austrian Trial 1995](#); [Belgian Trial 2007](#); [Canadian Trial 1997](#); [CF WISE 2006](#); [Danish Trial 1983](#); [Danish Trial 1997](#); [German Trial 1999](#); [Swiss Trial 1996](#); [Turkish Trial 2008](#); [UK Trial 1996](#);) and three were cross-over in design

(Dutch Trial 1995; Irish Trial 1995; UK Trial 1997). One trial was a withdrawal trial in which participants who were already taking inhaled fluticasone were randomised to continue fluticasone or start placebo (CF WISE 2006). All trials were placebo-controlled, with the exception of two (German Trial 1999; Swiss Trial 1996). Eleven trials were based in a single centre (Austrian Trial 1995; Canadian Trial 1997; Danish Trial 1983; Danish Trial 1997; Dutch Trial 1995; German Trial 1999; Irish Trial 1995; Swiss Trial 1996; Turkish Trial 2008; UK Trial 1996; UK Trial 1997) and two were multicenter (Belgian Trial 2007; CF WISE 2006). Overall they randomised between 7 and 171 participants per trial; collectively they randomised 506 participants. Ten trials reported sex distribution: in these trials, 49.6% (206 out of 415) of participants randomised were male.

Participants

Three trials were specifically in children (Canadian Trial 1997; UK Trial 1997; Belgian Trial 2007), four trials included both children and adults (CF WISE 2006; Danish Trial 1983; Danish Trial 1997; Swiss Trial 1996) and four enrolled only adults (Dutch Trial 1995; German Trial 1999; Irish Trial 1995; UK Trial 1996). In the remaining two trials it was not explicitly stated whether children or adults or both were enrolled; although one was conducted in a paediatric department (Austrian Trial 1995) and the other stated the mean age of participants as 10.5 years old (Turkish Trial 2008). Participant eligibility was based on clinical diagnosis of CF, usually with confirmation by sweat test. Two trials reported genotype distribution (CF WISE 2006; UK Trial 1997). Eligibility according to severity of pulmonary involvement varied between the trials. Acute pulmonary exacerbation was an entry criterion in the Austrian trial (Austrian Trial 1995); chronic *Pseudomonas aeruginosa* lung infection in both Danish trials (Danish Trial 1983; Danish Trial 1997); moderate to severe bronchial obstruction (FEV₁ less than 55% predicted) in the Swiss trial (Swiss Trial 1996); 'mild disease' (mean FEV₁ 85% predicted) in the Irish trial (Irish Trial 1995); 'established pulmonary disease' in the 1996 UK trial (UK Trial 1996); and 'stable' disease in the German trial (German Trial 1999). In the Belgian trial participants had mild to moderate lung disease and FEV₁ had to be at least 60% predicted (Belgian Trial 2007). In the withdrawal trial, FEV₁ had to be greater than or equal to 40% predicted and participants had to have been taking ICS for more than three months (CF WISE 2006). Where exclusion criteria were stated, these generally included recent treatment with oral or ICS and allergic bronchopulmonary aspergillosis. Two trials excluded people with asthma but not those with atopy (Danish Trial 1997; UK Trial 1997).

Interventions

Beclomethasone was given for periods of between four and twenty-two weeks in four trials (Austrian Trial 1995; Danish Trial 1983;

Irish Trial 1995; Swiss Trial 1996); budesonide for six weeks and six months in two trials (Danish Trial 1997; Dutch Trial 1995); and fluticasone for periods of between three weeks and two years in four trials (Belgian Trial 2007; Canadian Trial 1997; German Trial 1999; UK Trial 1996); in one trial the active treatment was budesonide, but duration of treatment was not specified (Turkish Trial 2008).

In four trials, the active treatment was inhaled beclomethasone, given via metered dose inhaler with or without a spacer device (Austrian Trial 1995; Danish Trial 1983; Irish Trial 1995; Swiss Trial 1996). The daily dosage schedule was 1500 mcg except in the Danish trial, where it was 400 mcg (Danish Trial 1983). Duration of active treatment assessed ranged from four to twenty-two weeks. In two trials, the active treatment was budesonide, total daily dose 1600 mcg given as dry powder for six months (Danish Trial 1997) or by metered dose inhaler for six weeks (Dutch Trial 1995).

In the remaining trials, the active intervention was fluticasone propionate given as 1000 mcg daily by metered dose inhaler with a spacer device for 22 days (German Trial 1999) or for one year (Belgian Trial 2007; Canadian Trial 1997) or for two years (UK Trial 1996) or as 800 mcg daily as a dry powder for six weeks (UK Trial 1997).

In the withdrawal trial there was a two-month period in which participants either continued to take fluticasone propionate via a spacer device or were switched to an equivalent dose of fluticasone propionate if they were already taking budesonide or beclomethasone dipropionate (CF WISE 2006). After the two-month period they were then randomised to continue taking to fluticasone propionate or start a placebo.

With the exception of the Swiss trial (Swiss Trial 1996), all treatment was given on an outpatient basis.

Outcomes

Lung function measurements were a specified outcome in 11 trials, but were not reported in two (Canadian Trial 1997; Irish Trial 1995). Following communication with the authors of the Canadian trial, data on FEV₁ have been provided (Canadian Trial 1997). Two cross-over trials reported FEV₁ and FVC (Dutch Trial 1995; UK Trial 1997). The Dutch trial reported mean absolute FEV₁ and FVC but without the standard deviations (SDs) for each treatment period (Dutch Trial 1995). The 1997 UK trial reported the mean per cent predicted FEV₁ and FVC with 95% confidence intervals (CI) for each treatment period (UK Trial 1997). In further communication with the author of the latter trial, data (SDs) have been provided for FEV₁ and FVC and have been updated in the relevant graphs. In the Swiss trial, FEV₁ and FVC were reported as mean change in per cent predicted but without SDs (Swiss Trial 1996). In the 1983 Danish trial, the median and range at baseline and after treatment were reported for these lung function data (Danish Trial 1983). In the 1996 UK trial, FEV₁ and FVC were reported as absolute means and SDs at baseline, 6

months and 24 months (UK Trial 1996); and in the 1997 Danish trial, as absolute change from baseline but without SDs at three and six months (Danish Trial 1997); whereas, in the German trial they were reported as mean per cent predicted and SD at baseline and after 21 days treatment (German Trial 1999). The CF-WISE trial reported mean % predicted FEV₁ and FVC at baseline, two, four and six months and mean % change in % predicted FEV₁ and FVC at the same time points. In the de Boeck trial, mean % predicted FEV₁ were reported at baseline, 6 and 12 months pre- and 20 minutes post-salbutamol (bronchodilator) as a measure of bronchial lability (Belgian Trial 2007). Mean change in % predicted FEV₁ post-salbutamol and % predicted FVC were also reported.

Bronchial reactivity was assessed in four trials: by histamine challenge alone (Dutch Trial 1995); histamine challenge or exercise test (Danish Trial 1997); or by methacholine challenge (Irish Trial 1995, Turkish Trial 2008). In the Dutch cross-over trial, results were expressed as mean log PC20 and as geometric mean PC20 at baseline and after budesonide, but no data were reported for the placebo treatment period (Dutch Trial 1995). In the 1997 Danish trial, data were expressed as mean change in histamine dose steps from baseline within each group, but without SDs, and as mean difference in mean change in histamine dose steps with 95% CI between groups (Danish Trial 1997). Data were not reported in either the Irish or the Turkish trials (Irish Trial 1995; Turkish Trial 2008).

Hospital admissions and antibiotic usage were specified as outcomes in the Dutch trial, but no data were reported (Dutch Trial 1995). Overall antibiotic usage was reported in the 1996 UK trial, but not by treatment group (UK Trial 1996). Data regarding patient days in hospital and patient days on antibiotics were provided for the previous update by the Canadian investigators (Canadian Trial 1997). In the CF-WISE withdrawal trial, the primary outcome reported was the time to first respiratory exacerbation. Secondary outcomes reported were the number of participants who had unplanned courses of oral or intravenous antibiotics and the median number of courses required per participant. The number of individuals requiring rescue bronchodilator and the median number of doses per participant were also reported (CF WISE 2006). The de Boeck trial reported the mean number of respiratory exacerbations between groups and reported Brasfield chest X-ray scores (median and quartiles) at baseline, six and twelve months (Belgian Trial 2007).

Symptoms were specified as outcomes in four trials (Dutch Trial 1995; German Trial 1999; UK Trial 1996; UK Trial 1997). The incidence of *P. aeruginosa* positive respiratory cultures were recorded in two trials (Belgian Trial 2007; CF WISE 2006).

Clinical status and nutritional indices were specified as outcomes in the Canadian trial but have not been reported to date (Canadian Trial 1997). Change in longitudinal growth (height) was recorded at baseline then at three monthly intervals during the treatment duration of one year and then for a further one year after discon-

tinuation (and for up to two years in a subgroup of participants) in the Belgian trial (Belgian Trial 2007). In the CF-WISE withdrawal trial, height was measured at the start and end of the trial in the paediatric participants (CF WISE 2006). The review authors were provided with these data. The UK trial assessed well-being and appetite using a visual analogue scale (UK Trial 1997); but formal measurement of quality of life was not attempted in any trial.

Number of deaths was reported in one trial (CF WISE 2006); but no other information on survival was reported in any other trial. Specific adverse effects were recorded in five trials (Belgian Trial 2007; Canadian Trial 1997; CF WISE 2006; Danish Trial 1997; UK Trial 1997). In two trials, adverse effects were reported as not differing significantly or not occurring but no details were provided (Dutch Trial 1995; UK Trial 1996). In the remaining trials no comment about adverse effects was made.

Sputum or serum markers of inflammation were measured in six trials (Austrian Trial 1995; Danish Trial 1983; German Trial 1999; Irish Trial 1995; UK Trial 1997; Turkish Trial 2008), serum IgG and HbA1C were recorded at baseline, 6 and 12 months in one trial (Belgian Trial 2007) and oxidative status as measured by plasma malondialdehyde in one trial (Turkish Trial 2008) - but these are not specified outcomes for this review.

Adherence to treatment was monitored and reported in the two trials using fluticasone delivered by Diskhalers (Danish Trial 1997; UK Trial 1997).

Excluded studies

Four trials (seven citations) were excluded (Australia Trial 2000; Bessaci 2008; USA Trial 1996; USA Trial 1998). Two citations referring to one trial from the USA were identified, but this trial was deemed ineligible, as the outcomes reported were not specified as outcomes for this review (USA Trial 1998). A further two citations related to an observational study from the USA which did not meet the inclusion criteria as treatment had not been allocated on a random basis (USA Trial 1996). Published details for the trial referred to in the third citation were insufficient to determine whether treatments were allocated by random or quasi-random methods (Australia Trial 2000) and further details could not be obtained from the authors, therefore this trial was excluded. Two references identified relate to a trial of seretide (which contains an inhaled steroid) plus salmeterol which is not a steroid (Bessaci 2008). Since this trial does not consider an ICS alone, it can not be included.

Risk of bias in included studies

For the 2008 update, in order to establish a risk of bias for the included trials, two authors (KW, IBL) independently assessed methodological quality using criteria suggested by Schulz (Schulz

1995). Concealment of allocation and method used to generate the random sequence were assigned to one of three categories: adequate, unclear or inadequate which related to a low, unclear or high risk of bias respectively. The reported intention-to-treat analysis was defined as complete, when less than 15% of participants were excluded, or incomplete when more than 15% were excluded from the final analysis, where the risk of bias increased as the number of participants excluded from the final analysis increased. Reporting of double blinding was recorded as either present or absent; the absence of blinding was considered to lead to a high risk of bias. Minor differences between the two authors in determining adequacy of random sequence generation in one trial and concealment of allocation in two trials were resolved by discussion, as were differences in assessing the completeness of intention-to-treat analysis in two trials. Assessments were otherwise concordant. For a previous update, authors were contacted and asked to clarify methodological issues, including randomisation method and steps undertaken to ensure concealment of allocation. Account has been taken of relevant information received.

Allocation

The method used to generate the random sequence was clearly mentioned in three trials, which we judged to have a low risk of bias: the German trial, which used a random number row to determine the intervention for the first participant, and then used alternation to determine the groups for the remaining participants (German Trial 1999); the CF WISE trial, which used randomisation by permuted blocks of four (CF WISE 2006); and the Belgian trial, which used random numbers (Belgian Trial 2007). The method of randomisation in the other trials is unclear and not stated in the trial reports. These other trials therefore have an unclear risk of bias.

Concealment of allocation was deemed to be adequate in six trials, which therefore had a low risk of bias: in one trial it was stated that treatment codes were not broken before clean file was declared by the data manager (Danish Trial 1997); in the Dutch trial treatment and placebo were given by blinded metered dose inhalers supplied by pharmaceutical company (Dutch Trial 1995); and in the CF WISE trial allocation was carried out independently over the telephone from the Clinical Trials & Evaluation Unit of Royal Brompton Hospital to the trial centre (CF WISE 2006). Trialists supplied information from three trials where sealed envelopes were used, therefore the risk of bias in these trials was low (Canadian Trial 1997; Irish Trial 1995; UK Trial 1997). Concealment of allocation was deemed to be inadequate in the German trial which used a method of alternation allowing the trial investigators to foresee to which group the next participant would be assigned; this trial was judged to have a risk of bias (German Trial 1999). The remaining trials did not discuss allocation concealment and were judged to have an unclear risk of bias.

Blinding

Nine trials were described as double-blind and judged to have a low risk of bias (Austrian Trial 1995; Belgian Trial 2007; Canadian Trial 1997; CF WISE 2006; Danish Trial 1983; Danish Trial 1997; Dutch Trial 1995; Irish Trial 1995; UK Trial 1997). In one trial there was an unclear risk of bias as blinding was not discussed (Turkish Trial 2008). In the two remaining trials there was a risk of bias; one trial was described as open label (German Trial 1999) and in the other trial there was no placebo arm (Swiss Trial 1996). Details of the methods used are listed in the 'Risk of bias tables' in the [Characteristics of included studies](#).

Incomplete outcome data

In three trials an intention-to-treat analysis was based on all participants (CF WISE 2006; Danish Trial 1997; Irish Trial 1995); in two trials less than 15% of participants were excluded (Belgian Trial 2007; UK Trial 1997); in two trials more than 15% of participants were excluded but reasons were given for their exclusion and the numbers were equal across groups (Danish Trial 1983; UK Trial 1996). These trials therefore have a low risk of bias. Reasons for exclusion included clinical deterioration, failure to take treatment or failure to attend for the follow-up assessments. In the remainder of the trials this could not be judged from the information available, and these were judged to have an unclear risk of bias.

Selective reporting

We examined the published papers and identified the following instances of selective reporting which could be a potential source of bias. Hospital admissions and antibiotic usage were specified as outcomes in the Dutch trial, but no data were reported (Dutch Trial 1995). Clinical status and nutritional indices were specified as outcomes in the Canadian trial but have not been reported to date (Canadian Trial 1997). FVC was recorded, but not reported, in the 1996 UK trial (UK Trial 1996). Although participants in the 1996 UK trial kept a symptom diary card, data were not reported (UK Trial 1996).

Other potential sources of bias

The Canadian trial was halted prematurely making it difficult to draw any conclusions (Canadian Trial 1997). A number of trials have never been published in peer-reviewed journals (Austrian Trial 1995; Canadian Trial 1997; Irish Trial 1995; Turkish Trial 2008; UK Trial 1996). The Dutch trial was of cross-over design, but did not describe any washout period; we have judged this trial to have an unclear risk of bias.

Effects of interventions

We were unable to undertake pooled analyses of any treatment outcome partly because reports differed in the way data were summarised and partly because some data needed for the analysis, for example SDs or standard errors (SEs), were not available from the published reports. As stated above, data from the CF WISE trial are presented, but results from this trial were not pooled with other trials because the trial was a withdrawal trial (CF WISE 2006). There were also differences between trials in the outcomes reported, so that for some variables, only a single trial result could be reported. The results are presented by outcome in the order in which they appear in the aims of the review. Within each outcome, data are discussed separately for parallel and cross-over trials but sequenced by short-, medium- and long-term outcomes as specified in the [Methods](#) section.

Primary outcome

1. Objective measures of lung function

a. Forced expiratory volume in one second (FEV₁)

Four trials reported data for absolute FEV₁ (Danish Trial 1997; Dutch Trial 1995; UK Trial 1996; UK Trial 1997). Analyses of absolute FEV₁ based on all participants randomised were reported for the 1997 Danish trial, but as no SDs were reported or have been provided subsequently, these data cannot be included in the [Data and analyses](#) section (Danish Trial 1997). After the first three-month treatment period in this trial, FEV₁ fell by a mean of 32 ml in the budesonide group (n = 30) compared with 187 ml in the placebo group (n = 25). The between group difference in change from baseline was reported by the authors as not significant (P = 0.08). When both three-month treatment periods were examined together, representing six months of treatment, absolute change in FEV₁ after six months of treatment was 2 ml for the budesonide and -98 ml for the placebo group, reported by the authors as not statistically significant (P > 0.1) (Danish Trial 1997).

In the Dutch cross-over trial, mean FEV₁ was reported as similar at the end of both six-week treatment periods, being 2.3 L after budesonide and 2.2 L after placebo. These data were based on 12 of the original 16 participants randomised (Dutch Trial 1995). Further data (including SDs) are not available from the authors, so these data cannot be included in the [Data and analyses](#) tables. In the 1996 UK trial, after six months of fluticasone or placebo, mean absolute FEV₁ tended to be higher in the treatment (n = 18) than in the placebo group (n = 15), but this was not statistically significant, mean difference (MD) 0.16 L (95% CI -0.27 to 0.59) (UK Trial 1996). Three participants in the placebo group were not included in this analysis (less than 15% exclusions). After 24 months of treatment, no significant differences between groups

were observed but this analysis was based on less than half (n = 17) of the 36 participants originally randomised, MD 0.24 L (95% CI -0.34 to 0.82). The authors were contacted but were unable to provide further data for this trial (UK Trial 1996).

In the 1997 UK cross-over trial, mean % predicted FEV₁ (SD) was similar at the end of both six-week treatment periods, being 66% (16.7) after fluticasone and 67% (23.0) after placebo, with 95% CI for the difference reported as -8% to 4% (UK Trial 1997). These data were based on 22 of 23 participants originally randomised. The data are not entered into the [Data and analyses](#) tables as first period data could not be extracted.

Changes in % predicted FEV₁ at different time points were recorded in three trials (Belgian Trial 2007; CF WISE 2006; Swiss Trial 1996). In the Belgian trial data were reported after six and 12 months pre- and post-salbutamol bronchodilator (Belgian Trial 2007). No significant difference was found in the percent predicted FEV₁ between those in the treatment (n = 12) and placebo (n = 15) groups: pre salbutamol at six months, MD 4.00% (95% CI -7.08% to 15.08%); post salbutamol at six months, MD -2.00% (95% CI -11.79% to 7.79%); pre salbutamol at 12 months, MD 2.00% (95% CI -12.12% to 16.12%); post salbutamol at 12 months, MD -1.00% (95% CI -12.42% to 10.42%) (Belgian Trial 2007). In the CF WISE trial no significant difference was found after six months between those participants who continued treatment (n = 84) and those who were withdrawn (n = 87), MD 3.00% (95% CI -2.55% to 8.55%) (CF WISE 2006). Additionally, in this trial, no change in lung function was found in the fluticasone group in those switching from a different ICS (budesonide or beclomethasone) to fluticasone (CF WISE 2006). In the Swiss trial, where treatment was given for 30 days as an inpatient and assessed at 30 days, there was an improvement in % predicted FEV₁ in those given (n = 25) and not given (n = 24) beclomethasone and the between group difference in this improvement was reported by the authors as not statistically significant (Swiss Trial 1996). From the data reported, the MD at discharge was 3.60% (95% CI -5.13% to 12.33%) (Swiss Trial 1996).

Following communication with the authors of the Canadian trial, data have been provided which showed no significant difference at baseline in FEV₁ (Canadian Trial 1997). Illustrations were also provided which the authors interpreted as showing that lung function did not alter through the trial in either group over a nine-month period. However, no actual data were available beyond baseline (Canadian Trial 1997).

b. Forced vital capacity (FVC)

Five trials measured absolute FVC (Danish Trial 1983; Danish Trial 1997; Dutch Trial 1995; UK Trial 1996; UK Trial 1997). In the 1983 Danish trial, median (range) % predicted FVC was 91% (51% to 112%) and 78% (46% to 116%) after 16 weeks of treatment in the beclomethasone and placebo groups respectively, using data from 13 of the originally randomised 24 matched

pairs (Danish Trial 1983). This trial was based on randomisation within matched pairs, but this was not reflected in the analyses which compared group means rather than within-pair differences (Danish Trial 1983). In the 1997 Danish trial, FVC data were not reported but the authors noted that these followed the same pattern as FEV₁ after three months and six months of treatment (Danish Trial 1997). In the Dutch cross-over trial, absolute mean FVC was similar after both six-week treatment periods (3.6 L on budesonide and 3.3 L on placebo) (Dutch Trial 1995). In the 1996 UK trial, FVC was recorded but not reported (UK Trial 1996). In the 1997 UK cross-over trial, mean (SD) FVC was 78.4% predicted (12.6) for the active treatment period and 77.4% (21.9) for the placebo treatment period (UK Trial 1997). The data are not entered into the Data and analyses tables as first-period data could not be extracted.

Three trials recorded change data for FVC (Belgian Trial 2007; CF WISE 2006; Swiss Trial 1996). In the Swiss trial, between-group differences in change in % predicted FVC after 30 days of treatment were reported by the authors as not statistically significant, being 9.9% for the beclomethasone group and 7.9% for the control group (Swiss Trial 1996). From the data reported, we have calculated the MD at discharge as -0.80% (95% CI -10.02% to 8.42%) (Swiss Trial 1996). In the Belgian trial there was no significant difference found in the change in % predicted FVC at six months, MD -1.00% (95% CI -8.06% to 6.06%) or 12 months, MD 1.00% (95% CI -10.42% to 12.42%) (Belgian Trial 2007). No significant difference was found in the % predicted FVC after six months in the withdrawal trial, where the MD was calculated to be 0.00% (95% CI -4.95% to 4.95%) (CF WISE 2006).

Secondary outcomes

1. Changes in bronchial hyperreactivity as measured by challenge with a bronchoconstricting agent such as histamine, methacholine or cold air

In the Dutch trial, analyses based on 12 participants were reported as showing significant increases in mean log PC20 histamine and geometric mean PC20 histamine in the budesonide treatment period, but no equivalent data or report were given for the placebo period (Dutch Trial 1995). In the 1997 Danish trial, histamine PC20 was performed in 41 of 55 recruited participants, reported to increase by significantly more dose steps in those on budesonide compared with those on placebo, MD in change in histamine dose steps was reported in the full published paper as 1.13% (95% CI 0.01% to 2.26%) ($P < 0.05$) (Danish Trial 1997). Response to exercise was reported as unchanged. Bronchial hyperreactivity was measured with metacholine challenge in the Turkish trial and found to be unchanged between groups (Turkish Trial 2008).

2. Number of days in hospital for respiratory exacerbations

In the Canadian trial, there was no significant difference in the number of patient days in hospital at the nine-month follow up, MD -0.10 days (95% CI -12.51 days to 12.31 days) (Canadian Trial 1997). The CF WISE withdrawal trial reported no significant difference in the time until the first exacerbation between the participants who continued treatment and those who were withdrawn from fluticasone (CF WISE 2006). No significant difference was found in the number of respiratory exacerbations between groups in the Belgian trial (Belgian Trial 2007).

3. Number of days on intravenous antibiotic for respiratory exacerbations

In the Canadian trial, there was no significant difference in the number of patient days on antibiotics at the nine-month follow up, MD -4.40 days (95% CI -50.44 to 41.64) (Canadian Trial 1997).

There was no difference in intravenous (or oral) antibiotic use between the two groups in the CF WISE trial (CF WISE 2006). In the 1997 UK trial, no significant change in respiratory symptom scores was reported between the two six-week treatment periods (UK Trial 1997).

Although participants in the 1996 UK trial kept a symptom diary card, data were not reported (UK Trial 1996). In the Dutch trial, a small but significant ($P < 0.05$) improvement in cough or dyspnoea after six weeks of treatment was reported by adults randomised to budesonide (Dutch Trial 1995).

4. Objective or subjective improvement in exercise tolerance

In the Dutch trial, comparing the budesonide with placebo groups, the mean score was, respectively, 0.38 and 0.54 for dyspnoea at rest, 0.98 and 0.97 for dyspnoea on exercise, 1.14 and 1.20 for cough and 2.3 and 2.3 for sputum production (scores were from zero to three with three being most severe) (Dutch Trial 1995).

5. Change in nutritional indices

In the 1997 UK trial, no significant change in appetite scores was reported between the two six-week treatment periods (UK Trial 1997).

a. change in growth velocity

The main outcome of the Belgian trial was the effect on long-term growth and height was measured at three-monthly intervals during the trial period of one year and then for a further follow-up year (Belgian Trial 2007). During the first 12 months there was a significant difference in growth rate of 1.53 cm between groups, MD -1.53 cm (95% CI -2.37 cm to -0.69 cm). The authors reported that participants did not “catch up” height in the

12 months following fluticasone discontinuation and a difference in growth rate of 2.4 cm was reported between the two groups after 24 months. In a subgroup of these participants growth data taken two years after treatment discontinuation showed “persistent growth impairment”. Height data was provided to the review authors for paediatric participants in the CF WISE trial (CF WISE 2006). It was found that there was no significant difference in height in the participants, 42 fluticasone, 38 placebo, for whom data was available over the eight months trial duration, MD 0.60 cm (95% CI -0.46 cm to 1.66 cm).

6. Quality of life

In the 1997 UK trial, no significant change in well-being scores was reported between the two six-week treatment periods (UK Trial 1997).

7. Adverse effects

Specific adverse effects were reported in two trials (Danish Trial 1997; UK Trial 1997).

In the 1997 Danish trial, overall there were 17 adverse events in the budesonide compared with 13 in the placebo group (Danish Trial 1997). It is unclear whether the numbers reported relate to individuals or individual episodes, although from the data presented it would appear that these are episodes. The budesonide group attended more frequently for outpatient visits than the placebo group (174 and 146 respectively). Hoarseness of voice and monilia (oral thrush) were reported more often in the budesonide group (six and three occasions and four and two occasions respectively), as were haemoptysis, pharyngitis and chest pain (two, three, one respectively in budesonide group compared with no reports in placebo group). Before and at the end of the trial, 15 participants were subjected to an adrenal function test (adrenocorticotrophic hormone (ACTH) stimulation test). One participant in each group had an abnormal response, which was found before the trial but in both cases the response had normalized by the end of the trial. It was reported that the response to ACTH did not differ between groups before or after treatment.

In the 1997 UK trial, two potentially drug-related adverse episodes were reported. One child in the fluticasone group developed peeling of the fingers for three days (in reality it is unlikely this relates to ICS), and another coughed for five minutes on one occasion after inhaling fluticasone (given as dry powder) (UK Trial 1997). The Canadian trial was halted prematurely because it was noted that six out of the 17 participants enrolled had become colonised with *Pseudomonas aeruginosa* for the first time (Canadian Trial 1997). When the code was broken, five of the six participants enrolled were from the active treatment group (n = 9) and one from the placebo group (n = 8). In addition one participant from the active group, previously negative for both *Pseudomonas aeruginosa* and *Burkholderia cepacia*, grew *Burkholderia cepacia* for the

first time. Subsequently, the authors identified 56 out of 133 participants attending this clinic who were being treated with inhaled steroids, of whom nine had become culture-positive for *Pseudomonas aeruginosa* between three months and three years after starting this treatment.

In the CF WISE trial (CF WISE 2006) adverse effects were classified as:

1. CF pulmonary symptoms - 118 fluticasone, 132 placebo;
2. CF non-pulmonary symptoms - 4 fluticasone, 12 placebo;
3. Symptoms not relating to CF - 13 fluticasone 17 placebo.

In the paper it was reported that fewer participants in the fluticasone group withdrew from the trial due to lung-related adverse events (9% compared to 15%) with a relative risk (RR) of 0.59 (95% CI 0.12 to 1.48). There was one drug-related case of oral candidiasis in a participant taking fluticasone. In addition, there was no significant increase in rescue bronchodilator use between the groups (CF WISE 2006).

In the Belgian trial (Belgian Trial 2007) there was no increase in isolation of *Pseudomonas aeruginosa* between the two groups of participants.

8. Survival

There were no deaths in the CF WISE trial (CF WISE 2006); the remaining trials did not report this outcome.

DISCUSSION

Methodological issues

The effectiveness of long-term treatment with inhaled corticosteroids is of clinical relevance in view of its widespread use in clinical practice in Europe and North America. However, the findings of this review suggest that evidence to support this practice is still lacking. The review identified 13 trials reporting the use of inhaled steroids in 506 people with CF aged between six years and 55 years. The methodological quality of the earlier trials was difficult to assess from published information, specifically with respect to concealment of allocation and the method used to generate random sequence. Although further information on this has been provided from some investigators, concealment of allocation (a key feature of trial validity) remains inadequate or unclear for most of the earlier trials.

Trials were heterogeneous with respect to inclusion criteria, specifically age, severity of pulmonary involvement, clinical diagnosis of asthma and chronic lung infection with *Pseudomonas aeruginosa*. Trials also differed in duration of treatment. Treatment effects were assessed for short periods only in the cross-over trials (six weeks) but for longer periods in the parallel trials. Only one parallel trial reported treatment given over a two-year period, but follow up

and reporting at this interval are incomplete. Spirometric indices of lung function were measured in most trials, but could not be combined in this review due to incompletely reported or unavailable data, as well as to differences in methods used to summarise data. Although five of the nine investigators contacted following the first issue of this review have supplied further information, a pooled estimate of treatment effects for lung function outcomes has not proved possible. This is either because data are no longer available or because data related to widely different stages of follow up.

Inflammatory markers have been reported as outcomes in a significant proportion of the trials identified, although these were not specified as prior outcomes for this review. The relevance of changes in inflammatory markers to long-term clinical status is uncertain, but it is likely that the reduction of inflammation would be of long-term benefit. In a small uncontrolled study (hence not eligible for inclusion in this systematic review) in children under 13 years, there was a decrease in neutrophil concentration in bronchoalveolar lavage after two months of therapy with beclomethasone dipropionate, although there was no change in IL-8 concentration (Wojtczak 2001). In contrast, other important outcomes, such as nutritional status and quality of life, were almost never reported. Long-term survival was not reported in any trial; but, given the increasing survival from this condition (especially in childhood), it is unlikely to be an appropriate outcome measure. Symptoms were measured in three trials and in one trial a small, but statistically significant, improvement of uncertain clinical relevance was noted in scores for dyspnoea at rest and cough. The Epidemiologic Study of Cystic Fibrosis (ESCF) is a multicentre longitudinal observational study of people with CF in the USA and Canada which has enrolled over 18,000 participants (Morgan 1999). A follow-up study looked at therapies used in the centres that reported better lung function results for their clinics (Padman 2007). No differences were found for use of ICS between the 12 centres whose median clinic lung function was in the upper ($n = 755$ children) versus the 12 centres in the lower quartile ($n = 743$ children).

Adverse effects

Adverse effects were not consistently assessed, although in most trials total daily dose of ICS was at the threshold identified in a systematic review as being associated with adrenal suppression (Lipworth 1999). Hoarseness of voice and oral candida were reported to be increased in those taking ICS in one trial, but this observation requires confirmation. An important concern relates to the risk of acquisition of *Pseudomonas aeruginosa* infection in those treated with corticosteroids. Although one trial was halted prematurely out of this concern, the data available are not conclusive (Canadian Trial 1997). However, a retrospective study of 83 participants under 10 years of age, found no significant effect of the use of ICS on the risk of early *Pseudomonas aeruginosa* acquisition,

including those on higher doses (Minicucci 2003). Growth in childhood is always a concern with long-term corticosteroid use, and this includes inhaled corticosteroids. The Belgian trial has shown that one year of high-dose fluticasone adversely affected growth which did not catch up in the subsequent year (and in a subgroup followed for two years) (Belgian Trial 2007). However, the large difference in growth could have been due in part to the age difference between groups, 9.0 years for the placebo group and 8.2 years for the fluticasone group which might lead to a greater effect of pubertal growth over 24 months in the older (placebo) group. This was the first trial to look at growth over a reasonably long period and has provided important evidence that ICS can do harm in children with CF. Finally, there have been reports of children and adults with CF who developed adrenal insufficiency and sometimes Cushing's syndrome whilst taking ICS (400 to 1200 mcg/day) together with itraconazole for allergic bronchopulmonary aspergillosis, due to cytochrome P450 inhibition (Main 2002; Parmar 2002; Skov 2002).

ICS withdrawal

The CF WISE trial is the largest trial of ICS in children and adults with CF (CF WISE 2006). This trial showed that during the first six months after stopping ICS therapy, there was no apparent impact (adverse or beneficial), on the onset of acute chest exacerbations, decline in lung function, antibiotic prescribing and rescue bronchodilator use. Replacing the ICS with placebo was found to be safe as there was no significant increase in lung-related adverse effects leading to withdrawal from the trial, nor an increased need for oral corticosteroids. Many individuals with CF who are on ICS may no longer need them, but caution is advised due to the non-significant increase in lung-related adverse effects seen in the placebo group.

Why no benefit?

The lack of proven benefit of ICS may be due to the failure of clinical trials to provide the evidence for a benefit that does exist. The published trials of ICS have a number of flaws, which include small participant numbers, short treatment periods, inadequate drug dosages, and in one case lack of a placebo group. The alternative view is that benefit has not been proven because there is no benefit. Delivering inhaled drugs in sufficient quantities to the airways which are blocked by viscous mucus may be a factor. Poor inhaler technique, especially in children, can also be a problem. More relevant may be the nature of the airway inflammation in CF. It is predominantly neutrophilic and in other airway conditions where neutrophils predominate, for example severe asthma and acute bronchiolitis, corticosteroids are also not particularly effective (Green 2002; Patel 2004). Although there is proven benefit in certain aspects of COPD management (NICE 2004), a biopsy

study showed that three months of fluticasone did not reduce the neutrophilic inflammation, despite improvement in symptoms and exacerbation rate (Hattotuwa 2002). Budesonide and fluticasone, and to a lesser extent beclomethasone, have been shown to prolong neutrophil survival by inhibiting apoptosis, so it might be that ICS are even promoting inflammation in CF airways (Zhang 2001).

Conclusions

Previous versions of this review have concluded that “evidence from these trials is insufficient to establish if inhaled corticosteroids have a beneficial or harmful effect in people with CF”. The pendulum of risk/benefit has slowly swung towards risk with the publication of the Belgian Trial and away from benefit with the CF WISE 2006 (Belgian Trial 2007; CF WISE 2006). What is still not proven though is whether ICS can significantly reduce lung inflammation when given long term. This is important since if ICS slowed progression of CF lung disease, treatment should lead to improved morbidity and mortality. However, the downstream effects, i.e. lung function and symptoms, have not been shown to improve with ICS. Given constraints over large RCTs in CF (relatively small population of potential participants, difficulties with meaningful outcome measures, financial limitations) and the fact that use of ICS is not high in research priorities, it is doubtful that such a trial will ever take place. For now, ICS should be used for symptomatic relief of recurrent wheezing that is not responsive to bronchodilators alone. Furthermore, the prescribing practice for an individual with CF should become more like that for an asthmatic. Justification is needed to start ICS, reassessment is necessary to see whether they are having an effect (particularly on any tight cough or wheeze), and consideration is always given to reducing the dose or stopping the drugs altogether. It is likely though that the majority of people with CF taking ICS no longer need to do so. This view has been reflected in the North American consensus document that states “...for patients with CF, 6 years and older, and without asthma or ABPA, the Cystic Fibrosis Foundation recommends against the routine use of inhaled corticosteroids to improve lung function and to reduce exacerbations” (Flume 2007). A similar view has been expressed at a European CF Society consensus meeting held in April 2008, the resulting

document of which is in preparation.

AUTHORS' CONCLUSIONS

Implications for practice

This review has found little evidence from existing trials to support the practice of routinely prescribing inhaled steroids in CF. Specifically, we cannot conclude that inhaled steroids are beneficial but there is some evidence that at a high dose, they adversely effect growth. There is also some evidence that withdrawal of ICS in the majority of those already being treated with them is safe. We recommend that the use of ICS should be restricted to those with symptomatic wheezing and in whom benefit has been proven. Individuals should be regularly reassessed to see whether ICS are having an effect and consideration should always be given to reducing the dose or stopping the drugs altogether.

Implications for research

The principle unanswered question is whether long-term ICS can reduce the exuberant lung inflammation so common in people with CF, and whether they can slow the rate of decline in lung function and improve survival. Unfortunately it is unlikely that a randomised controlled trial with sufficient power and length of follow-up will be conducted, given research priorities in CF and the difficulties of measuring lung inflammation.

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REFERENCES

References to studies included in this review

Austrian Trial 1995 *{published data only}*

Eichler I, Wojnarowski C, Frischer T, Renner S, Koller DY, Gotz M. Inhaled corticosteroids suppress increased eosinophil cationic protein concentration in patients with cystic fibrosis [abstract]. *Pediatric Pulmonology* 1995;Suppl 12:326. [CFGD Register: IB14a;]

Wojnarowski C, Gotz M, Eichler HG, Frischer T, Koller DY, Eichler I. Topical steroid act anti-inflammatorily by patients with cystic fibrosis [abstract]. *Monatsschrift Fur Kinderheilkunde*. 1995; Vol. 143:218. [CFGD Register: IB14c;]

* Wojnarowski C, Götz M, Eichler HG, Frischer T, Renner S, Koller DY, et al. Inhaled corticosteroids suppress inflammation in patients with cystic fibrosis [abstract]. 20th European Cystic Fibrosis Conference; 1995 June 18-21; Brussels, Belgium. 1995:Poster P98. [CENTRAL: 291657; CFGD Register: IB14b; CRS: 5500100000001649;]

Belgian Trial 2007 *{published data only}*

* De Boeck K, De Baets F, Malfroot A, Desager K, Mouchet F, Proesmans M. Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients?. *European Journal of Pediatrics* 2007;166(1):23-8. [CFGD Register: IB49;]

Canadian Trial 1997 *{published data only}*

* Schmidt J, Davidson AGF, Seear M, Wong LTK, Peacock D, Gravelle A, et al. Is the acquisition of pseudomonads in cystic fibrosis patients increased by use of inhaled corticosteroids? Unexpected results from a double blind placebo controlled study [abstract]. *Pediatric Pulmonology* 1997;Suppl 14:293. [CFGD Register: IB18;]

CF WISE 2006 *{published data only}*

Balfour-Lynn IM, Lees B, Hall P, Phillips G, Khan M, Flather M, et al. CF WISE - Multicentre randomised controlled trial of withdrawal of inhaled corticosteroids [abstract]. *Pediatric Pulmonology* 2005;40(Suppl 28):123-4. [CFGD Register: IB48a;]

* Balfour-Lynn IM, Lees B, Hall P, Phillips G, Khan M, Flather M, et al. Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2006;173(12):1356-62. [CFGD Register: IB48b;]

Danish Trial 1983 *{published data only}*

Schiøtz P, Jørgensen M, Winge Flensborg E, Fero O, Husby S, Hoiby N, et al. A longitudinal study of immune complex activity and inflammatory response in sputum sol-phase of CF patients: influence of local steroid treatment [abstract]. Proceedings of the 11th European Cystic Fibrosis Conference; 1982; Brussels. 1982:51. [CFGD Register: IB1b;]

* Schiøtz PO, Jørgensen M, Flensborg EW, Faero O, Husby S, Hoiby N, et al. Chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis. A longitudinal study of

immune complex activity and inflammatory response in sputum sol-phase of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infections: influence of local steroid treatment. *Acta Paediatrica Scandinavica* 1983;72(2):283-7. [CENTRAL: 30682; CFGD Register: IB1a; CRS: 550010000000167; PUBMED: 6340415]

Danish Trial 1997 *{published data only}*

Bisgaard H, Nielson K H, Sov M, Mosfeldt E, Bjerre B, Pedersen S, et al. Inhaled steroid treatment of CF patients with chronic pseudomonas aeruginosa (P.a.) lung infection [abstract]. *Pediatric Pulmonology* 1994;18(Suppl 10):395. [CFGD Register: IB12a;]

* Bisgaard H, Pedersen SS, Nielsen KG, Skov M, Laursen EM, Kronborg G, et al. Controlled trial of inhaled budesonide in patients with cystic fibrosis and chronic bronchopulmonary pseudomonas aeruginosa infection. *American Journal of Respiratory and Critical Care Medicine* 1997;156(4 Pt 1):1190-6. [CFGD Register: IB12c;]

Bisgaard H, Petersen SS, Nielsen KG. Topical steroid treatment ameliorate lung pathophysiology of patients with cystic fibrosis and chronic pseudomonas AER [abstract]. *European Respiratory Journal* 1996;9(Suppl):174S. [CFGD Register: IB12b;]

Dutch Trial 1995 *{published data only}*

* van Haren EH, Lammers JW, Festen J, Heijerman HG, Groot CA, van Herwaarden CL. The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respiratory Medicine* 1995;89(3):209-14. [CFGD Register: IB9;]

German Trial 1999 *{published data only}*

* Daulatbaev N, Viel K, Behr J, Loitsch S, Buhl R, Wagner TOF, Bargon J. Effects of short-term inhaled fluticasone on oxidative burst of sputum cells in cystic fibrosis patients. *European Respiratory Journal* 1999;14(5):1150-5. [CFGD Register: IB26;]

Irish Trial 1995 *{published data only}*

* Hayes J, Cosgrave C, O'Connor C, FitzGerald M. The effect of high dose inhaled corticosteroids on levels of sputum of plasma elastase and IL8 in patients with mild cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1995;151(4 Suppl):A248. [CFGD Register: IB8a;]

Hayes J, Cosgrave C, O'Connor C, FitzGerald MX. The effect of high dose inhaled corticosteroids on levels of sputum or plasma elastase IL-8 in patients with mild cystic fibrosis. *Irish Journal of Medical Science* 1995;164(2):165. [CFGD Register: IB8b;]

Swiss Trial 1996 *{published data only}*

Nikolaizik WH, Schoni MH. Effect of inhaled corticosteroids on lung function of cystic fibrosis patients -

a prospective study [abstract]. *European Respiratory Journal* 1994;7:430S. [CFGD Register: IB15b;]

* Nikolaizik WH, Schöni MH. Pilot study to assess the effect of inhaled corticosteroids on lung function in patients with cystic fibrosis. *Journal of Pediatrics* 1996;128(2):271–4. [CFGD Register: IB15c;]

Schöni MH, Nikolaizik. Parallel group study to assess the effect of inhaled corticosteroids on lung function in patients with cystic fibrosis [abstract]. *Israel Journal of Medical Sciences* 1996;32(Suppl):S190. [CENTRAL: 291577; CFGD Register: IB15a; CRS: 550010000001585;]

Turkish Trial 2008 {published data only}

Uyan ZS, Unluguzel G, Haklar G, Cakir E, Oktem S, Ersu R, et al. The effect of inhaled steroids on bronchial hyperactivity, oxidative status, clinical and inflammatory parameters in patients with cystic fibrosis [abstract]. *Journal of Cystic Fibrosis* 2008;7(Suppl 2):S68. [CFGD Register: IB50a;]

Uyan ZS, Unluguzel G, Haklar G, Cakir E, Oktem S, Ersu R, et al. The effect of inhaled steroids on bronchial hyperactivity, oxidative status, clinical and inflammatory parameters in patients with cystic fibrosis [abstract]. Proceedings of European Respiratory Society Annual Congress; 2007 Sep 15-19; Stockholm, Sweden. 2007: 646s. [CFGD Register: IB50b;]

UK Trial 1996 {published data only}

* Nieman R, Williams S, Maden C, Knight R, Hodson M. A double-blind placebo-controlled study comparing the effects of the inhaled corticosteroid fluticasone propionate 500 mcg BID with placebo in adults with cystic fibrosis [abstract]. *American Journal of Respiratory and Critical Care Medicine* 1996;153:A72. [CFGD Register: IB16;]

UK Trial 1997 {published data only}

* Balfour-Lynn I, Klein N J, Dinwiddie R. Randomised controlled trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis. *Archives of Disease in Childhood* 1997;77(2):124–30. [CFGD Register: IB17d;]

Balfour-Lynn I, Klein N J, Dinwiddie R. Sputum Interleukin-10 in Cystic Fibrosis [abstract]. *Pediatric Pulmonology* 1996;22(Suppl 13):324. [CFGD Register: IB17b;]

Balfour-Lynn IM, Klein NJ, Dinwiddie R. Trial of inhaled corticosteroids (Fluticasone Propionate) in children with cystic fibrosis (CF) [abstract]. *Israel Journal of Medical Sciences* 1996;32(Suppl):S190. [CENTRAL: 291194; CFGD Register: IB17a; CRS: 5500100000001273;]

Balfour-Lynn IM, Klein NJ, Lavery A, Dinwiddie R. Effect of inhaled corticosteroids on airway nitric oxide levels in children with CF [abstract]. *Pediatric Pulmonology* 1996;Suppl 13:324. [CFGD Register: IB17c; CRS: 5500100000010644;]

References to studies excluded from this review

Australia Trial 2000 {published data only}

* McElrea MS, O'Donnell SR, Francis PW. The effects of high-dose inhaled beclomethasone dipropionate (BDP)

on lung function and sputum albumin in children with cystic fibrosis (CF) [abstract]. *Pediatric Pulmonology* 2000;30(Suppl 20):301. [CFGD Register: IB31;]

Bessaci 2008 {published data only}

Bessaci K, Milliot M, Zahm J, Vilprey M, Coraux C, Mauran P, et al. Effects of inhaled association of salmeterol-fluticasone propionate on lung and epithelial cell functions in cystic fibrosis children [abstract]. *Pediatric Pulmonology* 2008;43(Suppl 31):384. [CFGD Register: IB51b;]

Bessaci K, Milliot M, Zahm JM, Coraux C, Mauran P, Vitry F, et al. Effects of inhaled salmeterol-fluticasone propionate on lung and epithelial cell functions in cystic fibrosis children: a double blind crossover study [abstract]. *Journal of Cystic Fibrosis* 2008;7(Suppl 2):S66. [CFGD Register: IB51a;]

USA Trial 1996 {published data only}

* Wojtczak HA, Kerby GS, Wagener JS, Copenhaver SC, Gotlin RW, Riches DW, et al. Beclomethasone dipropionate reduced airway inflammation without adrenal suppression in young children with cystic fibrosis: a pilot study. *Pediatric Pulmonology* 2001;32(4):293–302.

Wojtczak HA, Wagener JS, Kerby G, Gotlin R, Accurso F. Effect of inhaled beclomethasone dipropionate on airway inflammation in children with cystic fibrosis [abstract]. *Pediatric Pulmonology* 1996;22(Suppl 13):323–4.

USA Trial 1998 {published data only}

Wojtczak HA, Wagener JS, Sontag MK, Accurso FJ. Bronchoalveolar lavage assessment of airway delivery of fluticasone propionate via pressurised metered dose inhaler in infants and young children with cystic fibrosis. *Pediatric Pulmonology* 1998;S19:341. [CFGD Register: IB22a;]

* Wojtczak HA, Sontag MK, Wagener JS, Accurso FJ. Inhaled corticosteroid treatment in infants and young children with cystic fibrosis [abstract]. *Pediatric Pulmonology* 1999;28(Suppl 19):105–6. [CFGD Register: IB22b;]

References to studies awaiting assessment

Kapustina 2008 {published data only}

Kapustina T, Fedorova V, Voronkova A, Kapranov N. Long-term treatment with corticosteroids and bone mineral density in patients with cystic fibrosis [abstract]. European Respiratory Society Annual Congress; 2008 Oct 4-8; Berlin, Germany. 2008:214s. [CFGD Register: IB94;]

Additional references

ABPI 1999

Association of the British Pharmaceutical Industry. *Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000*. London: Datapharm Publications Ltd, 1999.

Armstrong 1995

Armstrong DS, Greenwood K, Carzino JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly-diagnosed cystic fibrosis. *BMJ* 1995;310(6994):1570–72.

Balfour-Lynn 1999

Balfour-Lynn IM, Dezateux C. Corticosteroids and ibuprofen in cystic fibrosis (letter). *Thorax* 1999;**54**(7):657.

Balfour-Lynn 2002

Balfour-Lynn IM, Elborn JS. "CF asthma": what is it and what do we do about it?. *Thorax* 2002;**57**:742–8.

Balfour-Lynn 2007

Balfour-Lynn IM. Anti-inflammatory approaches to cystic fibrosis airways disease. *Current Opinion in Pulmonary Medicine* 2007;**13**:522–8.

Balfour-Lynn 2008

Balfour-Lynn IM. Personal communication with UK CF Trust and CFF October 2008.

Balough 1995

Balough K, McCubbin M, Weinberger M, Smits W, Ahrens R, Fick R. The relationship between infection and inflammation in the early stages of lung disease from cystic fibrosis. *Pediatric Pulmonology* 1995;**20**(2):63–70.

Barnes 1992

Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Report of a workshop held in Eze, France, October 1992. *American Review of Respiratory Disease* 1993;**148**(4 Pt 2):S1–26.

Booth 1995

Booth H, Richmond I, Ward C, Gardiner PV, Harkawat R, Walters EH. Effect of high dose inhaled fluticasone propionate on airway inflammation in asthma. *American Journal of Respiratory and Critical Care Medicine* 1995;**152**(1):45–52.

Burdon 1980

Burdon JG, Cade JF, Sutherland PW, Pain MC. Cystic fibrosis and bronchial hyperreactivity: concomitant defects or cause and effect?. *Medical Journal of Australia* 1980;**2**(2):77–8.

Calpin 1997

Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. *Journal of Allergy and Clinical Immunology* 1997;**100**(4):452–7.

Cheng 1999

Cheng K, Ashby, Smyth R. Oral steroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: 10.1002/14651858.CD000407.pub2]

Djukanovic 1992

Djukanovic R, Wilson JW, Britten KM, Wilson SI, Walls AF, Roche WR, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *American Review of Respiratory Disease* 1992;**145**(3):669–74.

Drake 2002

Drake AJ, Howells RJ, Shield JPH, Prendiville A, Ward PS, Crowne PC. Symptomatic adrenal insufficiency presenting with hypoglycaemia in children with asthma receiving high dose inhaled fluticasone propionate. *BMJ* 2002;**324**(7345):1081–2.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analysis involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**:140–9.

Flume 2007

Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *American Journal of Respiratory and Critical Care Medicine* 2007;**176**(10):957–69.

Green 2002

Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;**57**(10):875–79.

Hattotuwa 2002

Hattotuwa KL, Gizycki MJ, Ansari TW, Jeffery PK, Barnes NC. The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. *American Journal of Respiratory and Critical Care Medicine* 2002;**165**(12):1592–6.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2008

Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]*. The Cochrane Collaboration, 2008.

Hilliard 2005

Hilliard TN, Balfour-Lynn IM. Anti-inflammatory agents a clinical perspective. In: Bush A editor(s). *Progress in Respiratory Research Cystic Fibrosis*. Basel: S Karger AG, 2005:187–94.

Khan 1995

Khan TZ, Wagner JS, Bost T, Martinez J, Accurso FJ, Riches DW. Early pulmonary inflammation in infants with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1995;**151**(4):1975–82.

Koch 1997

Koch C, McKenzie SG, Kaplowitz H, Hodson ME, Harms HK, Navarro J, et al. International practice patterns by age and severity of lung disease in cystic fibrosis: data from the Epidemiologic Registry of Cystic Fibrosis (ERCF). *Pediatric Pulmonology* 1997;**24**(2):147–154.

Koehler 2004

Koehler DR, Downey GP, Swezey NB, Tanswell AK, Hu J. Lung inflammation as a therapeutic target in cystic fibrosis. *American Journal of Respiratory Cell and Molecular Biology* 2004;**31**(4):377–81.

Konstan 1994

Konstan MW, Hilliard KA, Norvell EM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients

- with stable, clinically mild lung disease suggest ongoing infection and inflammation. *American Journal of Respiratory and Critical Care Medicine* 1994;**150**(2):448–54.
- Konstan 1999**
Konstan MW, Butler SM, Schidlow DV, Morgan WJ, Julius JR, Johnson CA, for the Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Patterns of medical practice in cystic fibrosis: Part II. Use of therapies. *Pediatric Pulmonology* 1999;**28**(4):248–54.
- Lipworth 1999**
Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Archives of Internal Medicine* 1999;**159**(9):941–55.
- Macdessi 2003**
Macdessi JS, Randell TL, Donaghue KC, Ambler GR, Van Asperen PP, Mellis CM. Adrenal crises in children treated with high-dose inhaled corticosteroids for asthma. *Medical Journal of Australia* 2003;**178**(5):214–6.
- Main 2002**
Main KM, Skov M, Sillesen IB, Dige-Petersen H, Muller J, Koch C, et al. Cushing's syndrome due to pharmacological interaction in a cystic fibrosis patient. *Acta Paediatrica* 2002;**91**(9):1008–11.
- Minicucci 2003**
Minicucci L, Severi G, Cresta L, Giannattasio A, Lorini R, Haupt R. Impact of inhaled corticosteroids on the risk of early *Pseudomonas aeruginosa* acquisition in cystic fibrosis. *Acta Paediatrica* 2003;**92**(6):684–7.
- Mitchell 1978**
Mitchell I, Corey M, Woenne R, Krastins IR, Levison H. Bronchial hyperactivity in cystic fibrosis and asthma. *Journal of Pediatrics* 1978;**93**(5):744–8.
- Morgan 1999**
Morgan WJ, Butler SM, Johnson CA, Colin AA, FitzSimmons SC, Geller DE, et al. Epidemiologic study of cystic fibrosis: design and implementation of a prospective, multicenter, observational study of patients with cystic fibrosis in the U.S. and Canada. *Pediatric Pulmonology* 1999;**28**(4):231–41.
- NICE 2004**
National Institute for Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national clinical guideline for management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; Vol. 59, issue Suppl 1.
- Padman 2007**
Padman R, McColley SA, Miller DP, Konstan MW, Morgan WJ, Schechter MS, et al. Infant care patterns at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. *Pediatrics* 2007;**119**(3):e531–7.
- Parmar 2002**
Parmar JS, Howell T, Kelly J, Bilton D. Profound adrenal suppression secondary to treatment with low dose inhaled steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 2002;**57**(8):749–50.
- Patel 2001**
Patel L, Wales JK, Kibirige MS, Massarano AA, Couriel JM, Clayton PE. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. *Archives of disease in childhood* 2001;**85**(4):330–4.
- Patel 2004**
Patel H, Platt R, Lozano JM, Wang EEL. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD004878.pub2]
- Renkema 1996**
Renkema TE, Schouten UP, Koeter GH Postma DS. Effects of long-term treatment with corticosteroids in COPD. *Chest* 1996;**109**(5):1156–62.
- Russell 2004**
Russell G. The use of inhaled corticosteroids during childhood: plus ca change. *Archives of Disease in Childhood* 2004;**89**(10):893–5.
- Schulz 1995**
Schulz K, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association* 1995;**273**(5):408–12.
- Skov 2002**
Skov M, Main KM, Sillesen IB, Muller J, Koch C, Lanng S. Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. *European Respiratory Journal* 2002;**20**(1):127–33.
- Smeeth 2003**
Smeeth L, Boullis M, Hubbard R, Fletcher AE. A population based case-control study of cataract and inhaled corticosteroids. *British Journal of Ophthalmology* 2003;**87**(10):1247–51.
- Taylor 1999**
Taylor AV, Laoprasert N, Zimmerman D, Sachs MI. Adrenal suppression secondary to inhaled fluticasone propionate. *Annals of Allergy, Asthma & Immunology* 1999;**83**(1):68–70.
- Tobin 1980**
Tobin MJ, Maguire D, Keen D, Tempany E, Fitzgerald MX. Atopy and bronchial reactivity in older patients with cystic fibrosis. *Thorax* 1980;**35**(11):807–13.
- Todd 1996**
Todd G, Dunlop K, McNaboe J, Ryan MF, Carson D, Shields MD. Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996;**348**(9019):27–9.
- Todd 2002**
Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Archives of Disease in Childhood* 2002;**87**(6):457–61.
- van Grunsven 1999**
van Grunsven PM, van Schayck CP, Molema J, Akkermans RP, van Weel C. Effect of inhaled corticosteroids on

bronchial responsiveness in patients with “corticosteroid naive” mild asthma: a meta-analysis. *Thorax* 1999;**54**(4): 316–22.

Walters 1995

Walters S. Association of cystic fibrosis adults (UK) Survey 1994 - Analysis and Report. Cystic Fibrosis Trust 1995.

Walters 2001

Walters S. Personal communication June 14 2001.

Weir 1993

Weir DC, Burge PS. Effects of high dose inhaled beclomethasone dipropionate 750 micrograms and 1500 micrograms twice daily and 40 mg per day oral prednisolone on lung function, symptoms and bronchial hyperresponsiveness in patients with non-asthmatic chronic airflow obstruction. *Thorax* 1993;**48**(4):309–16.

Wojtczak 2001

Wojtczak HA, Kerby GS, Wagener JS, Copenhaver SC, Gotlin RW, Riches DW, et al. Beclomethasone dipropionate reduced airway inflammation without adrenal suppression in young children with cystic fibrosis: a pilot study. *Pediatric Pulmonology* 2001;**32**(4):293–302.

Zhang 2001

Zhang X, Moilanen E, Kankaanranta H. Beclomethasone, budesonide and fluticasone propionate inhibit human

neutrophil apoptosis. *European Journal of Pharmacology* 2001;**431**(3):365–71.

References to other published versions of this review

Balfour-Lynn 2000

Balfour-Lynn I, Walters S, Dezateux C. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2000, Issue 1. [DOI: 10.1002/14651858.CD001915]

Balfour-Lynn 2009

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD001915.pub2]

Balfour-Lynn 2012

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD001915.pub3]

Balfour-Lynn 2014

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: 10.1002/14651858.CD001915.pub4]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Austrian Trial 1995

Methods	Randomised, double-blind, placebo-controlled, parallel trial
Participants	15 CF participants with acute pulmonary exacerbation. Age not given (but was in a paediatric department)
Interventions	All given a 2-week course of intravenous antibiotics. Beclomethasone or placebo started concurrently and continued for 22 weeks. Beclomethasone 500 mcg 3 times a day administered by large volume spacer
Outcomes	Serum eosinophil cationic protein and myeloperoxidase.
Notes	Authors contacted: no reply. Trial not published in full (3 abstracts) - all available information on methodological quality, as presented in primary paper, is reported here

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No figures.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported.
Other bias	Unclear risk	Trial had never been published in a peer-reviewed journal.

Belgian Trial 2007

Methods	Randomised, double-blind, case controlled, multicentred trial
Participants	29 pre-pubertal children (20 from 1 centre and 9 from another centre) who were clinically stable (defined as at least 2 months after any hospital admission and 2 weeks after a respiratory exacerbation) with FEV ₁ at least 60% predicted. Excluded if had intake of oral or inhaled steroids for more than 2 weeks within past 6 months or any intake of these drugs including intranasal steroids within last 4 weeks or a clinical diagnosis of aspergillosis or participating in another clinical trial
Interventions	Fluticasone 500 mcg dry powder inhaler twice daily or lactose placebo dispensed in identical canister
Outcomes	Change in % predicted FEV ₁ and change in FEV ₁ 20 minutes after inhalation of 400 mcg salbutamol by large plastic spacer device, serum IgG levels, Brasfield chest X-ray scores, number of respiratory exacerbations, positive <i>P.aeruginosa</i> culture, height.
Notes	Of the 20 initially included participants 2 were excluded. 1 participant discontinued treatment after 3 months and 1 did not keep follow-up appointments

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated that used random number sequence.
Allocation concealment (selection bias)	Unclear risk	Not mentioned in text.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded. Placebo dispensed in identical canister, so probably participant and clinician blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 15% of participants were excluded. Of the 20 initially included participants, 2 were excluded (1 discontinued treatment after 3 months and 1 did not keep follow-up appointments)
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Canadian Trial 1997

Methods	Randomised, double-blind, placebo-controlled, parallel trial
Participants	17 (9 male) clinically diagnosed people with CF aged 6 - 17 years attending the CF clinic at British Columbia Children's Hospital, Vancouver. Mean age 7.5 years in fluticasone group and 9.2 years in placebo group
Interventions	Fluticasone 500 mcg given twice daily via a metered dose inhaler and aerosol spacer or matched placebo. Proposed duration of treatment: 1 year
Outcomes	Lung function: FEV ₁ , FVC, FEF ₂₅₋₇₅ ; oxygen saturation; sputum or throat bacteriology; weight, height and clinical status. All variables measured at baseline and at 3-monthly intervals throughout the trial. Duration of follow up was 9 months
Notes	Trial was halted prematurely because of concerns about possible increased frequency of pulmonary colonisation with <i>P. aeruginosa</i> among trial participants. Authors contacted: randomised in blocks of 4 using sealed envelopes; written informed consent was obtained; age and sex distribution and lung function data by random group provided. Trial not published in full (1 abstract)

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised in blocks of 4, but method of randomisation not stated
Allocation concealment (selection bias)	Low risk	Sealed envelopes used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded. Fluticasone or matched placebo delivered in same way
Incomplete outcome data (attrition bias) All outcomes	Low risk	Trialists provided data to authors as requested.
Selective reporting (reporting bias)	High risk	Clinical status and nutritional indices were specified as outcomes in the Canadian trial but have not been reported to date
Other bias	Unclear risk	Trial was halted prematurely and trial results have never been published in a peer-reviewed journal

CF WISE 2006

Methods	Randomised, double-blind, placebo-controlled withdrawal trial of 8 months duration
Participants	171 (86 male) participants aged over 6 years, diagnosed with CF and attending 18 paediatric and adult UK CF centers. Age range 6 - 53 years. Mean age 14 years in fluticasone group and 15.8 years in placebo group. Participants excluded if had used oral corticosteroids within the previous 3 months or very high dose of ICS. Eligibility - age over 6 years, FEV ₁ ≥40% predicted.
Interventions	Fluticasone propionate given at equivalent dose to ICS participant taking before trial entry or placebo via a volumatic spacer
Outcomes	Primary outcome - time to first respiratory exacerbation. Secondary outcomes - lung function FEV ₁ , FVC; unplanned courses of intravenous or oral antibiotics; rescue bronchodilator usage. Subgroup analysis - age, atopy, steroid dose, baseline FEV ₁ , Pseudomonas status.
Notes	2 month run-in period during which all participants received fluticasone propionate. Dose unchanged if previously receiving fluticasone, but if previously on budesonide or beclomethasone, this was changed to fluticasone at a 2:1 ratio

Risk of bias
Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by permuted blocks of 4. Local investigators recruited participants in each centre and then telephoned a dedicated randomisation service at the Royal Brompton Hospital Clinical Trials and Evaluation Unit to give participant details. Randomisation was performed in permuted blocks of 4 to balance the stratifying variables and centres. Participants were stratified for age (<17 or ≥17 years), FEV ₁ (40 - 60%, 61 - 80% and >80% predicted), and atopic status (yes/no). Participants were randomised in equal proportions to withdrawal of fluticasone and non-withdrawal of fluticasone
Allocation concealment (selection bias)	Low risk	Randomisation was carried out independently at the Clinical Trials & Evaluation Unit of Royal Brompton Hospital and allocation of individuals was carried out over the telephone to the trial centres. The study drug randomisation number was given to the investigator and faxed to the Pharmacy department at the Royal Brompton Hospital who then sent out the corresponding

		drug pack to the pharmacy at the local hospital, which provided it to the participant
Blinding (performance bias and detection bias) All outcomes	Low risk	All trial personnel and participants were blinded to treatment (placebo)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was based on all participants.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Danish Trial 1983

Methods	Randomised, double-blind, placebo-controlled, parallel trial
Participants	48 CF participants (29 male) including children and adults age 4 - 29 years with a 'typical history of CF and markedly elevated sweat electrolytes in repeated tests'. Matched in pairs according to clinical score and, if possible, age and sex. Chronic <i>P. aeruginosa</i> lung infections for more than 6 months with 2 or more serum pseudomonal precipitins
Interventions	Beclomethasone 400 mcg or placebo 4 times a day for 16 weeks via metered dose inhaler. Treatment started on last day of 2-week course of intravenous carbenicillin and tobramycin given as hospital inpatient
Outcomes	PEFR, FVC, chest X-ray score, erythrocyte sedimentation rate, white blood count, serum immunoglobulins, serum albumin, serum haptoglobin, serum pseudomonal precipitins before and after treatment in both groups
Notes	Authors contacted: participants matched in pairs by clinical score and randomised within pairs, but allocation concealment remains unclear; informed verbal consent given; data provided on age and sex distribution but not lung function. Original data no longer available

Risk of bias**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants matched in pairs by clinical score and randomised within pairs. Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No details available.

Danish Trial 1983 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 15% of participants were excluded, but reasons given and numbers equal across groups. 5 participants (3 in the beclomethasone group) withdrawn because of clinical deterioration and started on beclomethasone. A further 6 either did not attend the control examination at clinic or discontinued inhalation therapy. As none from same matched pair data analysis carried out on 13 pairs (26 participants) only
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Danish Trial 1997

Methods	Randomised, double-blind, placebo-controlled, parallel trial. Randomised in balanced blocks of 4 participants. Treatment codes were not broken before clean file was declared by the data manager according to GCP recommendations
Participants	55 clinically diagnosed CF participants; eligible if: age 8 years (mean age 29 years) and over; continuous isolation of <i>P. aeruginosa</i> for at least 6 months or significant increase (not defined) in serum anti-pseudomonas antibodies. Excluded if asthma, allergic bronchopulmonary aspergillosis; colonisation with <i>Burkholderia cepacia</i> , pregnant, severely impaired cardiac, hepatic or renal function (not defined); treated with inhaled or oral steroids in previous 2 months
Interventions	Budesonide 800 mcg twice daily as a dry powder or lactose powder inhaled through a spacer device given as 2 consecutive treatment periods each of 3 months duration with 2-week elective course of intravenous antibiotics given at start and between 2 treatment periods
Outcomes	FEV ₁ , FVC, bronchial reactivity assessed by histamine PC20 and exercise test; Sputum inflammatory markers: tumour necrosis factor, interleukin-1 receptor antagonist, polymorphonuclear granulocyte elastase, free elastolytic activity; plasma inflammatory markers: polymorphonuclear granulocyte elastase, precipitating antibodies against <i>P. aeruginosa</i> ; adrenal function (ACTH stimulation test) in those under 18 years; compliance assessed by counting number of doses left in Turbuhalers at each clinic visit; adverse effects: hoarse voice, oral thrush, haemoptysis, cough, pneumothorax, chest pain, abscess, pharyngitis, pneumonia, infection or fever
Notes	

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Randomised in balanced blocks of 4 participants. Method of randomisation not stated	
Allocation concealment (selection bias)	Low risk	Stated that treatment codes were not broken before clean file was declared by the data manager according to GCP recommendations	
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed on both an 'intention-to-treat' and 'completed treatment' basis. Participants considered not to have completed treatment if period between intravenous courses was < 8 weeks or > 20 weeks or if sum of 2 treatment periods < 18 weeks or > 40 weeks	
Selective reporting (reporting bias)	Low risk	All outcomes reported.	
Other bias	Low risk	No other potential source of bias identified.	

Dutch Trial 1995

Methods	Double-blind, placebo-controlled, cross-over trial.
Participants	16 volunteers (mean age 27 years; range 16 - 45 years) with CF diagnosed by sweat test. All with baseline FEV ₁ > 25% predicted, no acute pulmonary exacerbation in previous 6 weeks, PC20 FEV ₁ histamine < 16 mg/ml. Excluded pregnant, currently taking oral steroids, severe concomitant disease; participants stopped sodium cromoglycate, antihistamines and theophylline preparations before trial
Interventions	Budesonide or placebo given for 6 weeks by blinded metered dose inhalers supplied by pharmaceutical company. Budesonide dose 200 mcg per puff, given as 4 puffs (800 mcg) twice daily. Run in period of 2 weeks, no washout period
Outcomes	Lung function tests: FEV ₁ , FVC, bronchial reactivity as assessed by histamine provocation, twice daily peak expiratory flow rates. Hospital admissions for respiratory exacerbations; antibiotic use; symptom diary

Dutch Trial 1995 (Continued)

Notes	Written to first author but left department with no forwarding details. All available information on methodological quality, as presented in primary paper, is reported here

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Low risk	Budesonide or placebo given by blinded metered dose inhalers supplied by pharmaceutical company
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded. Budesonide or placebo given for 6 weeks by blinded metered dose inhalers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear.
Selective reporting (reporting bias)	High risk	Hospital admissions and antibiotic usage were specified as outcomes, but no data were reported
Other bias	Unclear risk	No wash-out period described.

German Trial 1999

Methods	Randomised, open-labelled, prospective, parallel trial.
Participants	26 adults (13 males) with 'stable' CF (median age 26 years; range 16 years to 38 years). None on oral steroids and no ICS within 6 weeks
Interventions	Fluticasone propionate 500 mg bid as dry powder inhaler or control group (non-steroid medication) given for 6 weeks
Outcomes	Lung function tests: FEV ₁ , FVC, MEF ₂₅₋₇₅ ; sputum: leukocyte count, myeloperoxidase activity, baseline and stimulated superoxide anion release; self-reported symptoms elicited by questionnaire
Notes	Author contacted with request for information regarding allocation concealment and numbers of participants included in analysis of FEV ₁ outcome.

<i>Risk of bias</i>		<i>Risk of bias</i>

German Trial 1999 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prior to the trial, a random number row was generated, and participants with even and odd numbers were consecutively divided into the treatment and control groups. Low risk of bias because first participant allocated from random number row
Allocation concealment (selection bias)	High risk	Alternation used - risk of bias as investigators could foresee which group next participant would be allocated to
Blinding (performance bias and detection bias) All outcomes	High risk	Open label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Irish Trial 1995

Methods	Randomised, double-blind, placebo-controlled, cross-over trial
Participants	7 adults (4 male) with mild CF: mean (SE) % predicted FEV ₁ : 85.4 (6.4) %; mean (SE) % predicted FVC: 95.7 (6.4)%. All grew <i>P. aeruginosa</i> in sputum; 2 participants atopic (not defined).
Interventions	Beclomethasone 1500 mcg daily or matched placebo for 4 weeks with 4-week washout period
Outcomes	Spirometry and bronchial reactivity measured by methacholine challenge. Markers of inflammation in blood and sputum: alpha one protease inhibitor, neutrophil elastase and interleukin 8
Notes	Authors contacted: randomisation by 'envelope'; no full publication; no additional data provided

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by 'envelope'.

Irish Trial 1995 (Continued)

Allocation concealment (selection bias)	Low risk	Sealed envelopes used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was based on all participants.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the abstract.
Other bias	Unclear risk	Trial has never been published in a peer-reviewed journal.

Swiss Trial 1996

Methods	Randomised, parallel trial.
Participants	50 adults and children (mean age 19.8 years) with CF; minimum age 6 years; hospitalised for at least 30 days in a rehabilitation centre in Switzerland; no systemic or inhaled steroids in last 3 months; moderate to severe bronchial obstruction as evidenced by FEV ₁ < 55% predicted at time of entry. Participants who used systemically administered corticosteroids during the trial period were excluded post-randomisation. 49 completed trial, 25 in intervention group
Interventions	Beclomethasone 1500 mcg per day by metered dose inhaler through a spacer device administered either twice or three times a day for 30 days. Control group not given placebo inhalation and hence no blinding
Outcomes	Lung function tests: FEV ₁ , FVC; plethysmographic assessment of airway resistance and thoracic gas volume; single breath carbon monoxide diffusion test
Notes	Authors contacted: no reply.

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details given.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of a placebo in the control arm.

Swiss Trial 1996 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants who used systemically administered corticosteroids during the trial period were excluded post-randomisation
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Turkish Trial 2008

Methods	Randomised, but inadequate information given.
Participants	29 individuals with CF with mean age 10.5 years (69% female). Excluded if taken any form of steroids in last 2 months
Interventions	Treatment group (n = 17) received 2 mg/day nebulised budesonide. Control group (n = 12) received nebulised 'serum physiologic' [Is this 0.9% normal saline?]. No information given re length of treatment.
Outcomes	BHR by methacholine challenge. Oxidative damage - plasma MDA levels. Inflammation - hsCRP and oxidative burst of monocytes, sputum neutrophils, WBC
Notes	No results with statistical analysis given. They state that plasma MDA, WBC and sputum neutrophil % decreased significantly with budesonide; but no differences in BHR, clinical or inflammatory parameters Although this trial is included in the review, insufficient information is given so that it is not included in any analyses. The trial is available as an abstract only and is unpublished in full

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only, described as randomised but methods not discussed
Allocation concealment (selection bias)	Unclear risk	Abstract only, not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data given in abstract.
Selective reporting (reporting bias)	Unclear risk	Abstract only, insufficient information to make judgement.

Turkish Trial 2008 (Continued)

Other bias	Unclear risk	Trial has never been published in a peer-reviewed journal.

UK Trial 1996

Methods	Randomised, double-blind, placebo-controlled, parallel trial
Participants	36 participants, aged 16 years to 41 years, with established CF pulmonary disease
Interventions	Fluticasone propionate 500 mcg twice daily via a metered dose inhaler and spacer or matching placebo given for 2 years
Outcomes	Home diary card of symptoms; domiciliary lung function tests using spirometer to measure FEV ₁ , FVC, PEFR.
Notes	At 24 months data on FEV ₁ were only available on 8 participants in the fluticasone group and 9 in the placebo group. Authors contacted: no full publication and no further data available

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no further details given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind. Fluticasone or matching placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 15% of participants were excluded, but reasons given and numbers equal across groups At 24 months data on FEV ₁ were only available on 8 participants in the fluticasone group and 9 in the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Trial has never been published in peer-reviewed journals.

UK Trial 1997

Methods	Double-blind, placebo-controlled, randomised, sequence cross-over trial
Participants	23 children (11 boys), mean age 10.3 years (range 7 years to 17 years) with clinically diagnosed CF; 65% homozygous and 30% heterozygous for delta F508. Eligible if aged 6 - 17 years, able to perform spirometry reliably, use a Diskhaler and produce sputum. Ineligible if: oral or inhaled corticosteroid use in previous 6 months, clinical diagnosis of asthma, use of sodium cromoglycate or beta-2 agonists in previous 6 months, lower respiratory infection requiring antibiotics in previous 3 weeks, CF-related diabetes, portal hypertension, allergic bronchopulmonary aspergillosis, <i>Burkholderia cepacia</i> in sputum.
Interventions	Fluticasone propionate by dry powder inhaler in 2 doses equivalent to 400 mcg per day or matched placebo given for 6-week period with 4-week washout period
Outcomes	Primary outcome measure: change from baseline in sputum inflammatory markers interleukin-8, tumour necrosis factor-alpha, free neutrophil elastase and neutrophil elastase bound to alpha 1 antiprotease. Covariates: atopic status, disease severity as assessed by FEV ₁ . Secondary outcomes: FEV ₁ , FVC, oxygen saturation, weekly retrospective symptom score, weekly score for well-being and appetite, compliance as assessed by unused disks
Notes	1 participant failed to comply with treatment so the efficacy sample used for analysis consisted of 22 participants. Authors contacted: randomised by sealed envelopes prepared by pharmaceutical company; lung function data provided

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but details of process not discussed
Allocation concealment (selection bias)	Low risk	Randomised by sealed envelopes prepared by pharmaceutical company
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded. Fluticasone propionate or matched placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 15% of participants were excluded.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	No other potential source of bias identified.

ACTH: adrenocorticotrophic hormone

BHR: bronchial hyperreactivity
 CF: cystic fibrosis
 FEF₂₅₋₇₅: forced expiratory flow rate
 FEV₁: forced expiratory volume at 1 second
 FVC: forced vital capacity
 GCP: good clinical practice
 hsCRP: high sensitivity C-reactive protein
 mcg: microgram
 MDA: malondialdehyde
P. aeruginosa: *Pseudomonas aeruginosa*
 PEF: peak expiratory flow rate
 SD: standard deviation
 SE: standard error
 WBC: white cell count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Australia Trial 2000	Unable to determine whether treatments were allocated by random or quasi-random methods
Bessaci 2008	Trial of seretide (which contains an inhaled steroid) plus salmeterol which is not a steroid. Since this trial does not consider an ICS alone, it can not be included
USA Trial 1996	Not a clinical trial - prospective observational study.
USA Trial 1998	Randomised double-blind trial but in this abstract the outcomes reported were not relevant to those specified in this review

ICS: inhaled corticosteroid

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kapustina 2008

Methods	Not clear if study was randomised and if so how.
Participants	40 children with CF (23 females and 17 males) aged 5 to 17.4 years. All patients have "severe" phenotype
Interventions	Group 1 (14 children): inhaled corticosteroids for mean (SD) 34.29 (37.62) months (minimum 6 months; maximum 120 months). Group 2 (26 children): oral steroids (0.5 mg/kg every other day) for mean (SD) 33.04 (37.98) months (minimum 1 month; maximum 185 months) All patients received adequate basic therapy including calcium (500-1000 mg/day) and vitamin D (200-400 IU/day) supplementation

Kapustina 2008 (Continued)

Outcomes	BMD (g/cm2) in the lumbar spine
Notes	Contacted authors for clarification on methods.

BMD: bone mineral density

CF: cystic fibrosis

IU: international units

DATA AND ANALYSES

Comparison 1. Inhaled corticosteroid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean absolute FEV ₁	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 24 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Per cent predicted FEV ₁	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At 30 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 At 6 months pre salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 At 6 months post salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 At 12 months pre salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 At 12 months post salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Per cent predicted FEV ₁ (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in per cent predicted FVC	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 At 30 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in per cent predicted FVC (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Average patient days in hospital	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 At 9 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Average patient days on antibiotics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 At 9 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Growth velocity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Growth velocity (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 After 8 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

WHAT'S NEW

Last assessed as up-to-date: 15 August 2016.

Date	Event	Description
22 August 2016	New citation required but conclusions have not changed	Since no new data have been added to the review, our conclusions remain the same
22 August 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

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 2000

Date	Event	Description
6 October 2014	New citation required but conclusions have not changed	Since we have not been able to include any new information at this update, our conclusions remain the same
6 October 2014	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references which were potentially eligible for inclusion in the review. We have updated the plain language summary in light of new guidance
24 September 2012	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Trials Register did not identify any new references for this review
24 September 2012	New citation required but conclusions have not changed	No new data were added; hence the conclusions of this review have not changed
6 October 2010	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified four new references to three trials. One of these was an additional reference to an already included trial (Turkish Trial 2008). One trial (two references) was excluded (Bessaci 2008) and one trial is listed as 'Characteristics of studies awaiting classification' until the authors can clarify the methods used in their study (Kapustina 2008).

(Continued)

26 April 2010	Amended	Contact details updated.
5 November 2008	New citation required and conclusions have changed	The background and discussion sections have been re-drafted; the conclusions and recommendations have been changed Sarah Walters has stepped down as co-author at this update.
5 November 2008	New search has been performed	The latest searches identified three new references to three studies. One of these references was to a study previously listed as Studies awaiting classification and this study has now been included in the review (CF WISE 2006). The other two new studies have both been included (Belgian Trial 2007 ; Turkish Trial 2008) ; A further study, previously listed as Studies awaiting classification has now been excluded (Australia Trial 2000).
19 June 2008	Amended	Converted to new review format.
24 April 2006	New search has been performed	A search of the Group's Trials Register did not identify any new references for this review. There has been a publication of the CF WISE trial (previously Balfour-Lynn 2001, personal communication - now Balfour-Lynn 2005)
16 May 2005	New search has been performed	The search of the Group's Cystic Fibrosis Trials Register identified one reference, which was subsequently found not to be eligible for inclusion within the review
19 February 2004	Amended	The lead reviewer is now Dr Ian Balfour-Lynn; Prof Carol Dezateux remains as a co-reviewer
19 February 2004	New search has been performed	One further trial has been identified for this updated review (German Trial 1999). This has not altered the conclusions of the earlier review. This update also includes some further information provided from authors of five earlier trials (Canadian Trial 1997 ; Danish Trial 1983 ; Irish Trial 1995 ; UK Trial 1996 , UK Trial 1997). This has allowed methodological quality to be more clearly defined in four trials and has provided data on primary and secondary outcomes as well as study population in three. Data have been entered into the review and are summarised in Data and Analyses (comparison 01, outcomes 05, 06, 07 and 08). Meta-analysis has not been possible reflecting heterogeneity in study design and unavailability of relevant data

CONTRIBUTIONS OF AUTHORS

Ian Balfour-Lynn contributed to the protocol, identification of trials and co-authored the review and finalised the updates in 2004, 2005 and 2008. Ian Balfour-Lynn acts as guarantor of the review.

Karen Welch contacted authors, extracted and analysed data for the 2008 update.

DECLARATIONS OF INTEREST

Ian Balfour-Lynn has been supported in clinical research by GlaxoSmithKline, and in attending clinical meetings (although not for over 10 years) by GlaxoSmithKline and AstraZeneca.

Karen Welch has no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In a post hoc change we added 'adrenal insufficiency' to the list of adverse events we planned to investigate.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Anti-Inflammatory Agents [*administration & dosage; adverse effects]; Budesonide [administration & dosage; adverse effects]; Cystic Fibrosis [*drug therapy]; Fluticasone [administration & dosage; adverse effects]; Glucocorticoids [administration & dosage; adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Humans; Middle Aged; Young Adult