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Inhaled Corticosteroids for Cystic Fibrosis: A Review of Clinical Effectiveness

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Abbreviations

BHR	bronchial hyperactivity
CF	cystic fibrosis
CI	confidence interval
ESR	erythrocyte sedimentation rate
FCV	forced vital capacity
FEV_1	forced expiratory volume in one second
hs-CRP	high sensitive C-reactive protein
ICS	inhaled corticosteroids
RCT	randomized controlled trial
SD	standard deviation
WBC	white blood cells

Context and Policy Issues

Cystic fibrosis (CF) is a rare chronic genetic disease that affects multiple systems in the body including the respiratory tract, pancreas, gastro-intestinal tract and liver.[1,2] The disorder is caused by mutations of the CF transmembrane conductance regulator (CFTR) gene. Approximately, one in 25 Canadians carries an abnormal CFTR gene, and CF occurs in children who inherit two abnormal genes, one from each parent.[3] It is estimated that one in every 3,600 children born in Canada has CF, with more than 4,300 Canadian children, adolescents, and adults with CF attending specialized CF clinics.[3] The disease has no cure at present, and it is the most common fatal genetic disease affecting Canadian children and young adults[3] Lung disease is the most prominent manifestation of CF, and it is reported to account for nearly 85% of deaths.[4] Respiratory tract abnormalities in CF patients cause mucus plugging of the airways, bronchial wall thickening due to inflammation, increased susceptibility to respiratory tract infection, and airway destruction.[1,2] Much of the pulmonary damage begins with lung inflammation.[5] Although a normal inflammatory response is beneficial to host defence mechanisms, and helps to prevent the spread of infection, the excessive inflammation seen in CF patients is harmful as it contributes to the disease and associated death.[1] One of the goals in the treatment of cystic fibrosis is to reduce lung inflammation.[4] Corticosteroids are potent anti-inflammatory drugs which have been widely used in the treatment of a variety of diseases with underlying inflammation including asthma and chronic obstructive pulmonary disease (COPD).[1,4] They exert direct inhibitory effects on many inflammatory cells, and regular use of inhaled corticosteroids (ICS) has been reported to reduce the number of mast cells within the airways, decrease airway microvascular leakage, and lessen mucus production.[4] Although benefit of its use in CF has not been proven, ICS has been widely prescribed as anti-inflammatory agents to treat children and adults with CF empirically.[1,4,5]

The objective of this report is to summarize the evidence regarding the clinical effectiveness of ICS for the treatment of CF.

Research Question

What is the clinical effectiveness of inhaled corticosteroids for the management of patients with cystic fibrosis?

Key Findings

Evidence of limited quality from one systematic review reporting study-level findings and one randomized controlled trial suggested that routine use of inhaled corticosteroids in children and adult cystic fibrosis patients is not significantly more effective than placebo or non-steroid medication in improving lung function as indicated by forced expiratory volume in one second (FEV1) and forced vital capacity (FVC).

Evidence of limited quality from one systematic review and one retrospective study analyzing registry data reporting study-level finding suggested that inhaled corticosteroids use in cystic fibrosis patients may significantly reduce growth rate in terms of height compared with placebo.

Evidence of limited quality from one retrospective study analyzing registry data suggest that the use of inhaled corticosteroids in children (six to 12 years old) with cystic fibrosis may decrease the yearly rate of decline in lung function.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline and Embase on the OVID platform, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009, and February 8, 2019.

Selection Criteria and Methods

One reviewer screened the citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with cystic fibrosis (all ages, all care settings) - Subgroup of interest: patients without comorbid asthma
Intervention	All formulations of inhaled corticosteroids (e.g., budesonide, fluticasone, beclomethasone, ciclesonide)
Comparator	Systemic corticosteroids, standard of care, no treatment, or placebo
Outcomes	Clinical effectiveness (e.g., benefits such as improvement of pulmonary function test, peak expiratory flow, residual lung volume, other measures of lung function); Safety (e.g., harms such as effects on growth in children)
Study Designs	Health technology assessment, systematic reviews and meta-analyses, randomized controlled trials, and non-randomized studies.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1; they were duplicate publications or were published before 2009.

Critical Appraisal of Individual Studies

The included systematic review[1] was critically appraised using the AMSTAR-2 checklist,[6] while the randomized controlled trial (RCT)[7] and the retrospective cohort study[8] were critically appraised using the Downs and Black checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 303 citations were identified in the literature search. Following screening of titles and abstracts, 297 citations were excluded, and six potentially relevant reports from the electronic search were retrieved for full-text review. The grey literature search did not identify any additional relevant publications. Of the six potentially relevant articles, three papers were excluded for various reasons, and three publications met the inclusion criteria and were included in this report. These comprised one systematic review,[1] one RCT,[7] and one retrospective cohort study based on registry data.[8] Appendix 1 presents the PRISMA[10] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One systematic review,[1] one single center, single-blind RCT,[7] and one retrospective cohort study based on registry data,[8]were included in this report. The systematic review[1]assessed the effectiveness of regular ICS use in children and adults with CF compared with not using them. It included 13 RCTs and quasi RCTs published from 1995 to 2008 and identified by a comprehensive literature search spanning 1995 to 2016. The systematic review[1] was first published in 2000 and has undergone updates in 2004, 2005, 2008, and 2016. The latest edition was included in this report. Eleven of the trials were placebo-controlled, while two were not. One of the two was a withdrawal study in which participants who were already taking ICS (inhaled fluticasone) were randomized to continue the fluticasone treatment or to start placebo. In the other trial, patients in the control arm were not given any treatment.

The RCT[7] and retrospective cohort study based on registry data[8] were published in 2017, and 2011, respectively.

Country of Origin

Reviewers from The United Kingdom authored the systematic review.[1] Twelve of the trials included in the systematic review[1] were conducted in Europe (Austria, Belgium, Denmark, Germany, Ireland, The Netherlands, Turkey, and The United Kingdom) while one trial was

conducted in Canada. The RCT[7] included in this report was conducted in Turkey whereas the retrospective cohort study[8] was conducted in Belgium based on Belgian CF registry data.

Patient Population

The systematic review[1] included trials in patients with CF who had been diagnosed by clinical criteria and sweat or genetic testing, or both, regardless of age or clinical severity. Overall, a total 506 patients were randomized across the 13 included trials, with sample sizes ranging between 7 and 171. Ten trials reported sex distribution, with 49.6% (206 out of 415) randomized male patients across them. Patients' ages were not uniformly reported. Three trials were conducted in children, four included both children and adults, four enrolled only adults, and two did not state whether the enrolled patients were children or adults, or both were recruited. Information on setting was not adequately described, although it was reported that in 12 trials, all treatment was given on an outpatient basis.

For the RCT,[7]all CF patients over six years of age attending a pediatric pulmonology clinic of a university hospital were eligible. Patients were excluded if they had used systemic steroids within the previous six months, ICS within the last two months, had pulmonary exacerbation within the previous four weeks, had a history of asthma and atopy in the family and the child, and if they were unable to perform spirometry. A total of 32 patients were randomized to treatment or control arms of the RCT.[7] However, three patients in the placebo group were withdrawn, and analysis was based on the remaining 29 patients. Two of the patients were withdrawn due to allergic bronchopulmonary aspergillosis and the other patient was excluded upon her parents' request.[7] The mean age (standard deviation [SD]) of patients was 11.3 (3.0) years and 9.5 (2.74) years in the intervention control arms, respectively. Overall, there was no statistically significant difference between the two groups in terms of demographic features, clinical status, symptom scores, inflammatory markers, and pulmonary function tests at baseline.

For the retrospective cohort study,[8] registry data of 852 CF patient were analyzed. Data of patients six years of age or older were eligible if ICS use data were available in at least two consecutive years, along with entries on lung function and height. The majority (53.3%) of patients were male. Data were excluded if patients used oral steroids or had a transplant.

Interventions and Comparators

In the systematic review,[1] the ICS assessed in the primary studies were beclomethasone, budesonide, and fluticasone. Treatment duration ranged between 30 days and two years. The drugs were given in two to four divided doses, with the total daily doses ranging from 1600 mcg to 2000 mcg (2 mg) for budesonide, 1500 mcg to 1600 mcg for beclomethasone, and 800 mcg to 1000 mcg for fluticasone. Eleven primary studies of the systematic review[1] were placebo-controlled trials. One trial in the systematic review[1] had a non-steroid medication as comparator, and for another primary study (conducted in hospitalized patients) the control group was not given any intervention, not even placebo.

In the RCT[7] included in this report, patients were randomized to receive nebulized budesonide 2 mg per day or nebulized 0.9% normal saline as placebo for eight weeks. The retrospective cohort study,[8] was about general ICS use. No specific ICS was identified by name, dose, or frequency of application. According to the authors, inhaled therapies in the source registry were recorded annually as absent or present (e.g., ICS yes/no and bronchodilators yes/no).

Outcomes

In the systematic review,[1] objective lung function outcomes were reported as forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC). Four primary studies assessed FEV_1 and five evaluated FVC outcomes. Three trials reported bronchial hyperactivity outcomes following challenge with histamine or methacholine. Three trials each provided information about the number of days in hospital for respiratory exacerbations or the number of days on intravenous antibiotic for respiratory exacerbations. One trial assessed improvement in exercise tolerance outcomes, but the instrument used for the assessment was not identified, and it is unknown whether or not it was validated. Two trials provided information about impact on growth after ICS therapy. Although there was a brief mention of change in nutritional indices and quality of life observation from one trial included in the systematic review[1] there was not enough information for further discussion in this report.

In the RCT,[7] the outcomes of interest were clinical symptoms, pulmonary function as determined by FEV_1 and FVC scores, bronchial hyperactivity (BHR) after methacholine challenge, and changes in inflammatory markers such as high sensitive C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR). In the retrospective cohort study,[8] the outcomes of interest were yearly decline in percent predicted FEV_1 or FVC, effect on growth, and insulin use.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the systematic review included in this report are provided in Appendix 3.

Systematic review

The systematic review[1] had a clearly stated research objective and inclusion and exclusion criteria. The population, intervention, and control of interest, as well as the outcome measures, were defined. Although the protocol was published before the first publication of the systematic review,[1] there was no explicit statement that it was established or registered before the conduct of the study began. The systematic review[1] included RCTs and quasi-RCTs identified by a comprehensive literature search strategy, which included searching multiple data bases, the references of selected trials for potentially relevant studies. Also, literature searches have been conducted periodically since the first publication in 2000, and the systematic review[1] has been updated four times, with the current update performed in 2016. Study selection and data extraction were performed independently by two reviewers, with no disagreement between them. However, the authors did not explain the rationale for limiting study selection to RCTs and quasi-RCT designs. The reviewers assessed the risk of bias of the individual primary studies of the systematic review[1] based on the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions.[11] Due to incomplete reporting, unavailable data, and differences in methods used to summarize data, the authors of the systemic review[1] reported study-level findings from its primary studies without conducting meta-analyses. Ten of the trials included less than 50 patients (eight had less than 30), and there was no report of any of the trials performing sample size calculation to determine if they were sufficiently powered to detect statistically significant differences between treatment arms. The authors of the systematic review[1] rated the general methodological quality of the included trials as unclear. The quality of the RCT[7] and retrospective cohort study[8] included in this report was limited by issues such as uncertainty regarding power to detect intergroup differences and lack of randomization, respectively.

Therefore, uncertainty exists about reported study-level outcomes. The discussion and interpretation of the results were done taking into account the risk of bias in the individual primary studies of the systematic review. The authors declared sources of funding and potential conflict of interest, which did not seem likely to affect the independence and objectivity in the conduct of the study or the interpretation of its findings.

For both the RCT[7] and the retrospective cohort study[8], the objectives of the study, the characteristics of the patients included, and the interventions of interest were described clearly. The main outcomes to be measured, and the main findings of the study were well reported, and both studies[7,8] evaluated the outcomes with standard, widely used measures (e.g., FEV1 and FVC), and applied appropriate statistical tests to assess the outcomes.

Patients in the RCT[7] were randomized to the treatment arms by an investigator who was blinded to their clinical status. There was no statistically significant difference between the two treatments groups in the patients' demographic features and clinical condition at baseline, excerpt *Pseudomonas colonization* and total white blood cell count in the sputum were significantly different at baseline. The impact of difference in these two parameters on the reported outcomes is unclear. Although 32 patients were randomized, three patients in the placebo group were withdrawn for various reasons, and it is unknown how the exclusion impacted the baseline randomization effect. The RCT[7] was designed as a single-blinded study with the placebo not matching the intervention. Thus, a risk existed that knowledge of the treatment arm to which a patient was assigned could introduce bias. Sample size calculations were not performed to determine the power of the study to detect significant differences in outcomes between the treatment arms. Thus, it cannot be ruled out that the reported findings may be due to chance. Also, the statistical analysis was not based on the intention-to-treat population, although the impact on the outcomes of including 29 instead of 32 patients in analysis is unknown. The authors of the RCT[7] did not declare potential sources of conflict of interest or sources of funding for the study.

Data for the retrospective cohort study[8] were obtained from a national registry reported to cover more than 95% of all CF patients in the country (Belgium). Therefore, it was likely that the data in the study were representative of the CF population, and the patients had been attended by healthcare staff at facilities that were representative of the treatment of the majority of patients in the country. However, retrospective studies lack the risk-diminishing property of randomization and are inherently likely to have more systemic biases. Further, confounders such the specific ICS and the doses at which they were used, concomitant therapies, and distribution of these across the treatment groups were not described; and there was no evidence that adequate adjustment were made for confounding in the analyses. The authors of the retrospective cohort study declared that they had no potential sources of conflict of interest.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Inhaled corticosteroids for Cystic Fibrosis

Lung function and bronchial hyperactivity

One systematic review[1] reporting study-level findings found that the use of ICS did not significantly improve lung function (as determined by FEV_1 and FVC scores) in CF patients

compared with placebo (five trials), non-steroid medication (one trial), or withdrawal from the use of ICS (one trial). Bronchial hyperactivity after histamine or methacholine challenge was also not significantly different with ICS compared with placebo (two trials). One trial in the systematic review[1] reported a statistically significant ($p < 0.05$) improvement in cough or dyspnea in adult CF patients after six weeks of treatment with budesonide compared with placebo. However, it was unclear whether or not this resulted from a significant reduction in bronchial hypereactivity or other underlying factors.

One RCT[7] found that percent predicted FEV_1 and predicted FVC scores in children with CF who were treated with nebulized budesonide for eight weeks were not statistically significantly different from those who were on placebo for the same treatment duration. There was also no statistically significant difference in the bronchial reactivity score between the two groups.

One retrospective study analyzing registry data found that the difference in the decline in percent predicted FEV_1 between users of ICS and non-users after one year was statistically significant in favor of the users in the overall population (1.07%, $p = 0.001$) and in children six to 12 years old (2.56%, $p = 0.0003$), but not children aged from 13 to 17 years (0.69%, $p = 0.3624$) or adults patients 18 years of age or older (0.46%, $p < 0.2487$).[8]

Number of days in hospital

One systematic review[1] found no significant difference in the time until the first exacerbation between the CF patients who continued treatment and those who were withdrawn from using inhaled fluticasone (one trial). Also, the systematic review[1] found no statistically significant difference in the number of respiratory exacerbations or number of patient days in hospital between CF patients who used ICS and those who did not (two trials).

Number of days on intravenous antibiotic for respiratory exacerbations

One systematic review[1] found that the use of ICS did not result in a statistically significant difference in the respiratory symptom scores or the number of patient days on antibiotics compared to placebo (two trials) or withdrawal from using inhaled fluticasone (one trial)

Improvement in exercise tolerance

One systematic review[1] found that CF patients who used of ICS had similar dyspnea scores as patients who were on placebo, both at rest and during exercise (one trial). Also, sputum production scores were similar between the groups. However, the scale used in these measurements was not specified, and it is unknown if it was validated.

Change in growth velocity

One systematic review[1] found that CF patients treated with ICS showed statistically significantly lower growth in height after 12 months compared to those on placebo (one trial). The difference in height remained and widened in the 12 months following discontinuation of the ICS.

Quality of life

One systematic review[1] found no statistically significant change in well-being scores between CF patients involved in a cross-over trial using ICS or placebo in either of two six-week treatment periods (one trial). However, a formal measurement of quality of life was not done..

Clinical Symptoms

One RCT[7] found that clinical symptoms scores in children with CF who were treated with nebulized budesonide for eight weeks were not statistically significantly different from those who were on placebo for the same treatment duration.

Inflammation Markers

One RCT[7] found that after eight weeks of treatment, changes in inflammation markers such as hs-CRP and ESR with nebulized budesonide were not statistically significantly different than with placebo in children with CF.

Adverse effects

One systematic review[1] reported adverse events findings from three trials. Although 17 adverse events occurred in the ICS group compared to 13 in the placebo group, it was unclear whether the numbers were for the individual patients or episodes of adverse events. Adverse events reported more commonly in the ICS group than comparator were hoarseness of voice (six versus three) and oral thrush (four versus two) hemoptysis (two versus zero), pharyngitis (three versus zero), and chest pain (1 versus zero). One trial reported peeling of the fingers for three days in one child and cough for five minutes in another. Although both children were on the fluticasone, it is unclear if these adverse events were related to the medication. In another trial, five of nine patients in the ICS group (55.6%) and one in eight patients in the placebo group (12.5%) became colonized with *Pseudomonas aeruginosa* for the first time leading to a premature termination of the study.

Limitations

Findings from the primary studies included in the systematic review[1] could not be combined due to incompletely reported or unavailable data, as well as to differences in methods used to summarize data. Thus the systematic review[1] does not provide the benefit of an effect estimates synthesized from multiple studies. The primary studies of the systematic review[1] are old, published from 1983 to 1999 for ten of them, and from 2006 to 2008 for the remaining three. It was not indicated whether any of them performed sample size calculations to evaluate the power to detect significant differences between groups, and no information was provided about the potential conflict of interest of the authors and sources of funding for the studies. There was also a lack of evidence that the RCT[7] included in this report was sufficiently powered to detect any difference between study groups. The limitations of the retrospective cohort study[8] include its inherent risk of bias due to lack of randomization, and absence of information about the kind of ICS, the doses and frequencies of application, and concomitant medications the patients used. Also, information about adverse events was scanty, reported by three of the 13 primary studies in the systematic review[1] (with one trial providing data that were difficult to interpret), and not reported in the RCT[7] or the retrospective cohort study[8] included in this report. These constitute sources of uncertainty about the reliability of the results reported. The included RCT[7] found no statistically significant difference in changes in inflammatory markers with ICS and placebo. However, it is unclear what the level of change in inflammatory makers in CF patients is considered minimally clinically important. Overall, the studies[1,7,8] included in this report had inactive comparators (e.g., placebo) although one trial in the systematic review[1] compared ICS to an unidentified non-steroid medication. Thus, there was insufficient evidence of how ICS compares with systemic corticosteroids and standard of care, which are comparators of interest for this report (Table 1). Also, none of the included studies provided data on the subgroup of interest: patients without comorbid asthma. The

Canadian trial included in the systematic review[1] was terminated prematurely, making it difficult to draw any conclusions.[1] Therefore, the findings and conclusions of the studies[1,7,8] included in this report were based mainly on studies conducted in Europe, and it is unclear whether they are generalizable in the Canadian context.

Conclusions and Implications for Decision or Policy Making

Information and data about the clinical effectiveness of inhaled corticosteroids (ICS) for the management of patients with cystic fibrosis (CF) were sourced from one systematic review[1] reporting study-level findings from 13 trials, one randomized controlled trial (RCT),[7] and one retrospective cohort study based on analysis of registry data.[8] The systematic review[1] and the RCT[7] found no statistically significant difference between CF patients who were treated with ICS compared with those who were not, in terms of lung function and bronchial hyperactivity, clinical symptoms, number of days in hospital or on antibiotics for respiratory exacerbations, exercise tolerance, and quality of life. However, the retrospective cohort study[8] found that annualized percent predicted decline in forced expiratory volume in one second (FEV_1) was statistically significantly lower with ICS use in children with CF aged six to 12 years. The findings of the retrospective study[8] is in alignment with a 2008 American registry analysis in children CF, which showed less lung-function decline after starting inhaled corticosteroid use.[12] Thus, findings from these two retrospective registry data analyses suggest that the use of ICS in young children with CF may decrease the rate of decline in lung function before significant loss occurred.

Short-term outcomes were reported in the primary studies of the systematic review[1] and the RCT[7] whereas the retrospective registry data analysis[8] reported findings after a year of ICS use. However, it is unclear whether the conflicting results about lung function from the systematic review[1] and the retrospective registry data analysis[8] is due to the differences in duration of ICS treatment limitations associated with the studies. Therefore, further research, adequately powered, designed to be of sufficiently long period, and addressing issues such as standardized dosing, uniform measures of efficacy, and well delineated short-term and long-term effectiveness of ICS in different age categories CF patients, may help to reduce uncertainty. Studies defining a minimally clinically important difference (MCID) in inflammatory markers may also be necessary to track changes and adopt appropriate interventions before significant loss in lung function occurred.

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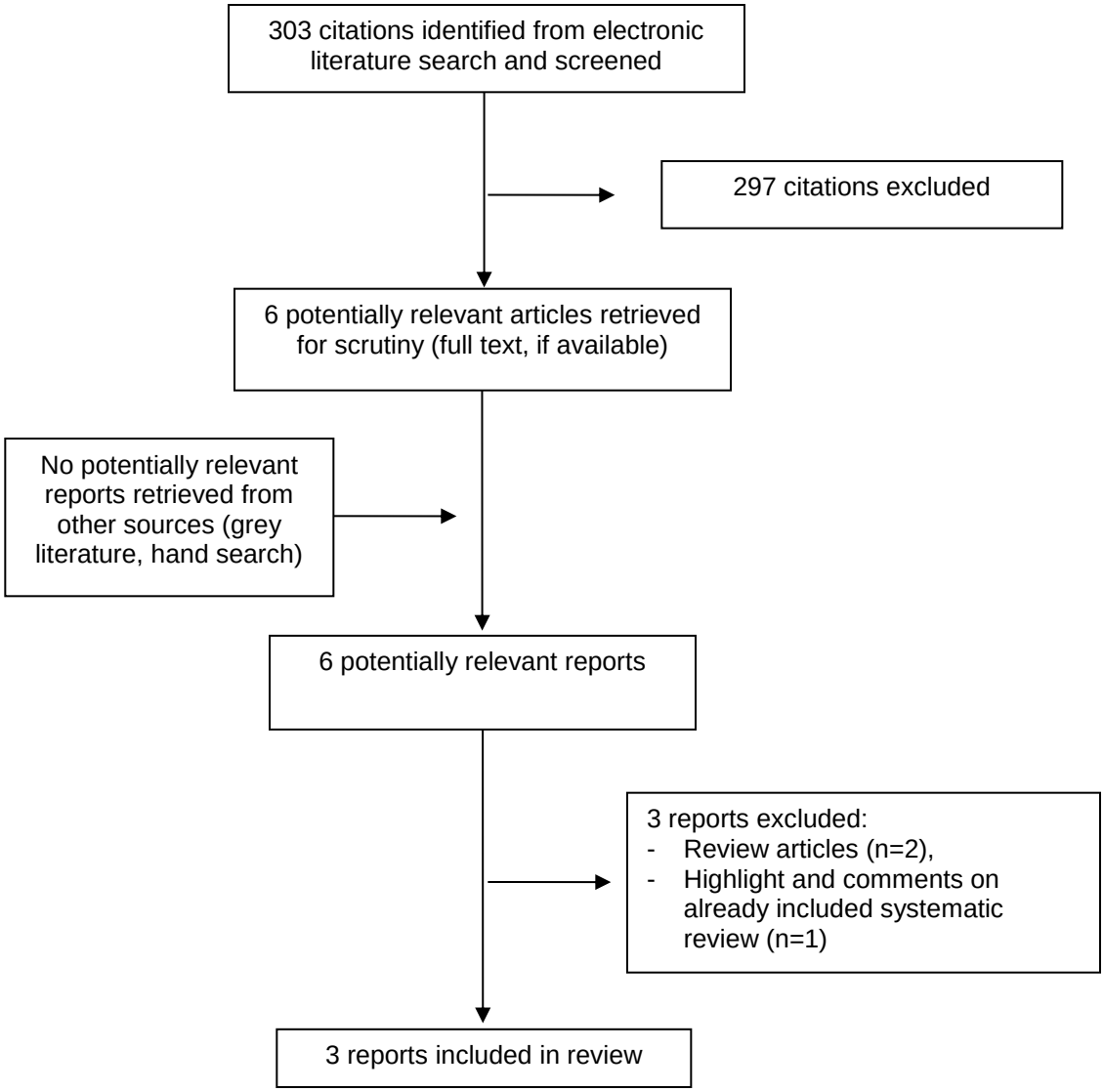
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review[1]

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Balfour-Lynn,[1] 2016	Systematic review of 13 RCTs (reported in 26 citations)	506 CF patients diagnosed with CF aged between six and 55 years *	ICS (beclomethasone, budesonide, fluticasone, and placebo	• Lung function measurements (FEV_1 and FVC), • BHR, • Das in hospital • Days on antibiotic usage, • Growth (changes in height) • Adverse events. Durations of follow-up were not reported for the individual studies. Ten of the included studies reported treatment durations varying from four weeks to two years, and three did not report duration of treatment.

* Ten trials provided patients' age data. Three trials were in children only, four in adults only and four were mixed ages. Two trials did not provide patients' ages.

BHR = bronchial hypereactivity; CF = cystic fibrosis; FEV_1 = forced eviction fraction in one second; FVC = forced vital capacity; ICS = inhaled corticosteroids; RCT = randomized controlled trial

Table 3: Characteristics of Included Randomized Controlled Trial[7]

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Uyan,[7] 2017	Single-blinded RCT	29 CF patients older than six years old (mean age: 10.5 ± 2.9 years) who had two abnormal sweat tests (chloride concentration > 60 mEq/L)	Nebulized budesonide at 2 mg daily dose versus 0.9% normal saline as placebo	• Clinical symptoms, • Pulmonary function (FEV_1 and FVC), • BHR, and • Inflammatory markers (oxidative burst, hs-CRP, or ESR).

BHR = bronchial hyperactivity; CF = cystic fibrosis; ESR = erythrocyte sedimentation rate; FEV_1 = forced eviction fraction in one second; FVC = forced vital capacity; hs-CRP = high sensitive C-reactive protein; mEq/L = milliequivalent per liter; RCT = randomized controlled trial;

Table 4: Characteristics of Included Retrospective Cohort Study[8]

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
De Boeck,[8] 2011	NRCS (retrospective cohort study) based on registry data analysis	Data from 852 CF patients six years of age or older were eligible, provided entries on lung function, height and ICS use were available in at least two consecutive years. Majority (53.3%) were male. Data were excluded if patients used oral steroid or had transplant	ICS use versus no ICS	• Lung function as determined by changes in yearly percent predicted FVC and FEV_1 scores), • Growth as assessed by changes in height and • Insuline use

BHR = bronchial hyperactivity; CF = cystic fibrosis; FEV1 = forced eviction fraction in one second; FVC = forced vital capacity; ICS = inhaled corticosteroids, NRCS = non-randomized controlled study

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of the Included Systematic Review[1] using AMSTAR 2[6]

Strengths	Limitations
Balfour-Lynn,[1] 2016	
• The research questions and inclusion criteria for the review covered the components of PICO • The report was based on a comprehensive literature search strategy and included RCTs and quasi-RCTs • The study selection was performed independently by two reviewers with no disagreement between the authors as to which trials should be included. • Data extraction was performed independently by each author using a standard data extraction form • The included studies were described in adequate detail, and a list of excluded studies with justification for the exclusions was provided • The risk of bias in individual studies that were included in the review was assessed using the criteria for evaluating risk of bias described in the Cochrane Handbook for Systematic Reviews of Interventions.[11] • All the included studies were checked reporting bias • and the results reported along with other quality evaluation outcomes • The discussion and interpretation of the results was done taking into account the risk of bias in the individual studies included in the systematic review. • The authors declared potential sources of conflict of interest, including sources of funding for conducting the systematic review.	• Although the protocol was published before the first publication of the review, there was no explicit statement that the review methods were established or registered before the conduct of the study commenced. • The rationale for selecting RCTs and quasi-RCTs and no other study designs for inclusion in the systematic review was not explained • Study-level outcomes were reported without pooling or meta-analysis due to heterogeneity, incomplete reporting or unavailable data, as well as to differences in methods used to summarize data. • Ten of the studies included less than 50 patients, and there was no report of sample size calculation to evaluate the power of any of the trials to detect significant differences between groups. Therefore, the reliability of the reported study-level outcomes is unclear. • There was no information about the potential sources of conflict interest of the authors of the primary studies, or how the studies were funded • The findings and conclusions of the systemic review were based mainly on studies conducted in Europe, and it is unclear whether they are generalizable in the Canadian context.

ICS = inhaled corticosteroids; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial;

Table 6: Strengths and Limitations of the included Randomized Controlled Trial [7] using Downs and Black Checklist[9]

Strengths	Limitations
Uyan,[7] 2017	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly, • Patients were randomized to their study groups by an investigator who was blinded to their clinical status • There was no statistically significant difference between the two groups in terms of demographic features, clinical status, symptom scores, inflammatory markers, pulmonary function tests, bronchodilator response, or MCT results at baseline • The statistical analyses used to assess the main outcomes were appropriate • The main findings were evaluated with standard widely used measures (e.g., FEV_1 and FVC)	• The study was designed as a single-blinded study with the placebo not matching the intervention. Thus, a risk existed that knowledge of the treatment arm to which a patient was assigned could introduce bias. • Some measure of clinical symptoms such as cough, wheezing, dyspnea, and sputum amount and color were scored by the patients using a subjective scoring system and may be sources of uncertainty. • Although 32 patients were randomized, three patients in the placebo group were excluded, and analysis was based on the remaining 29 patients. It is unknown how the exclusion impacted the randomization effect and the reported outcomes. • Sample size calculations were not performed to determine the power of the study to detect significant differences in outcomes between the treatment arms. Thus the risk of a type 1 error cannot be ruled out. • Pseudomonas colonization and total WBC count in the sputum were significantly higher in the treatment group than the placebo group at baseline. The effect of the difference on the reported outcomes in unclear. • A description of adverse events that may resulted from the intervention was reported • The study was conducted in children, and it is unknown whether its findings will be generalizable in adults CF patients. • The patients who participate in the study were recruited from the pediatric pulmonology clinic in a university hospital in Turkey, and it is unknown id they will be representative of the general CF population in Canada. Thus, the generalizability of the study findings in the Canadian context is unknown. • The authors did not declare potential conflict of interest or sources of funding for the study

WBC = white blood cells; RCT = randomized controlled trial

Table 7: Strengths and Limitations of the Included Retrospective Cohort Study[8] using Downs and BlackChecklist[9]

Strengths	Limitations
De Boeck, 2011[8]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly, • Data for the study were obtained from a national registry reported to cover >95% of all CF patients in the country. Therefore, it was likely that the data in the study were representative of the CF population, and it was likely that the patients had been attended to by the staffs at places and facilities that were representative of the treatment of the majority of patients in the country. • The statistical tests used to assess the main outcomes were appropriate • The main outcomes were evaluated with standard widely used measures (e.g., FEV_1 and FVC) • The authors declared no potential sources of conflict of interest.	• Retrospective studies lack the risk-diminishing property of randomization and are inherently likely to have more systemic biases. • Registry data are not as reliable as data collected from well conducted clinical trials. • There was no information on the specific ICS, the dose of the drug used, and concomitant therapies which could have confounded the reported outcomes • A clear description of the distributions of potential confounders in each group was not provided. • There was no evidence that adequate adjustment were made for confounding in the analyses • The study was based on Belgian CF registry data, and the generalizability of the findings in the Canadian context is uncertain. • A description of adverse events that may resulted from the intervention was reported

WBC = white blood cells; NRCS = non-randomized controlled study

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings of the Included Systematic Review[1]

Main Study Findings *	Authors' Conclusion
Balfour-Lynn,[1] 2016	
Lung function **1. Forced expiratory volume in one second** None of the included studies found a statistically significant difference in FEV1 between CF patients who were treated with ICS and those who were not. • In one trial, the FEV1 fell by a mean of 32 ml in the budesonide group (n = 30) compared with 187 ml in the placebo group (n = 25) after three months treatment. After six months of treatment, the absolute change in FEV1 was 2 ml for the budesonide versus -98 ml for the placebo. • The mean FEV1 in the Dutch cross-over trial (n=12) was 2.3 L budesonide versus 2.2 L for placebo at the end of both six-week treatment periods. • The mean difference (MD) in mean absolute FEV1 after six months therapy in the 1996 UK trial of fluticasone (n = 18) versus placebo (n = 15) was 0.16 L (95% CI: -0.27 to 0.59) in favor of fluticasone, but this was not statistically significant. The MD between group after 24 months of treatment was also no statistically significant (0.24 L; 95% CI: -0.34 to 0.82), although analysis was based on 17 of the 36 patients randomized initially. • Data from 22 of 23 patients initially randomized in the 1997 UK cross-over trial showed that the mean percent predicted FEV1 (SD) was 66% and 67% (95%CI: -8% to 4%) for fluticasone and placebo, respectively at the end of 12 weeks (two six-week periods). • In the Belgian trial, the six months MD in percent predicted FEV1 between patients on ICS (n = 12) and those on placebo (n = 15) was 4.00% (95% CI: -7.08% to 15.08%) pre-salbutamol, and -2.00 % (95%CI: -11.79%to 7.79%) post salbutamol. The 12 months MD was 2.00% (95% CI: -12.12% to 16.12%) pre-salbutamol, and while -1.00% (95% CI: -12.42% to 10.42%), post- salbutamol. Statistical significance was not observed at either time point. • In the CF WISE trial, the six months MD in percent predicted FEV1 between patients who continued ICS treatment (n = 84) and those who were withdrawn (n = 87) was 3.00% (95% CI -2.55% to 8.55%). • In the Swiss trial, the MD in percent predicted FEV1 between inpatients given beclomethasone for 30 days (n = 25) and those who were not (n = 24) was 3.60% (95% CI -5.13% to 12.33%) at discharge. **2. Forced vital capacity (FVC)** None of the included studies found a statistically significant difference in FVC between CF patients who were treated with	"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 affect 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."[1] p. 17

Table 8: Summary of Findings of the Included Systematic Review[1]

Main Study Findings *	Authors' Conclusion
ICS and those who were not • In one trial (Danish 1983), data from 13 matched pairs of patients showed that the median (range) percent predicted FVC after 16 weeks of treatment was 91% (51% to 112%) for beclomethasone and 78% (46% to 116%) for placebo. • One cross-over trial (1995 Dutch) reported that the absolute mean FVC after both six-week treatment periods was 3.6 L for budesonide and 3.3 L for placebo. • In the 1997 UK cross-over trial, patients treated with ICS had a mean (SD) FVC was 78.4% predicted compared with 77.4% for those on placebo. • In the Swiss trial involving hospitalized patients, the between group MD at discharge in change in percent predicted FVC after 30 days treatment with beclomethasone versus placebo was calculated to be -0.80% (95% CI: -10.02% to 8.42%). • In the Belgian trial, the MD in the change in percent predicted FVC was -1.00% (95% CI -8.06% to 6.06%)at six months and 1.00% (95% CI -10.42% to 12.42%) at 12 months. • In the CF WISE withdrawal trial, the calculated MD in the percent predicted FVC after six months was to be 0.00% (95% CI: -4.95% to 4.95%) **Changes in bronchial hyperactivity** • One trial (Danish trial) reported that bronchial hyperactivity was induced by significantly more histamine dose steps of in CF patients on budesonide compared with those on placebo (MD=1,13%; 95% CI: 0.01% to 2.26%; p<0.05). However, another trial (Turkish trial) found no between-group change in bronchial hyperactivity between CF patients challenged with methacholine and those who were not • One trial (the Dutch trial) reported a significant (p < 0.05) improvement in cough or dyspnea in adult CF patients after six weeks of treatment with budesonide compared with placebo. It was unclear whether or not this resulted from a significant reduction in bronchial hypereactivity or other underlying factors **Number of days in hospital for respiratory exacerbations** • A Canadian trial found 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) • The CF WISE withdrawal trial reported no significant difference in the time until the first exacerbation between the patients who continued treatment and those who were withdrawn from fluticasone. • One trial (the Belgian trial) found no significant	

Table 8: Summary of Findings of the Included Systematic Review[1]

Main Study Findings *	Authors' Conclusion
difference in the number of respiratory exacerbations between groups. **Number of days on intravenous antibiotic for respiratory exacerbations** • A Canadian trial found 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) • The CF WISE withdrawal trial reported no significant difference in intravenous (or oral) antibiotic use between the patients who continued treatment and those who were withdrawn from fluticasone. • The 1997 UK cross-over trial found no significant change in respiratory symptom scores between the two six-week treatment periods. **Exercise tolerance** • On trial (the Dutch trial), found no significant difference in objective or subjective improvement in exercise tolerance between CF patients on budesonide and those on placebo. • The mean dyspnea score was 0.38 budesonide and 0.54 for placebo at rest and 0.98 and 0.97, respectively on exercise. • On a zero to three scale with three being most severe, cough scores were 1.14 and 1.20 while sputum production scores were 2.3 and 2.3 for budesonide and placebo, respectively. **Change in growth velocity** • One trial (Belgian trial) reported a significant difference in growth rate of 1.53 cm between groups in the first 12 months in favor of patients on placebo compared with those on fluticasone (MD = -1.53 cm, 95% CI: -2.37 cm to -0.69 cm). The difference in growth rate between the two groups had increased to 2.4 cm after 24 months • In the CF WISE withdrawal trial, analysis of data from the fluticasone (n=42) and placebo (n=38) groups found no significant difference in patients' heights over the eight months trial duration (MD = 0.60 cm; 95% CI: -0.46 cm to 1.66 cm). **Quality of life** • One trial (1997 UK trial) found no statistically significant change in well-being and appetite scores using a visual analogue scale between CF patients involved in a cross-over trial using ICS or placebo in either of two six-week treatment periods (one trial). However, a formal measurement of quality of life was not done	

Table 8: Summary of Findings of the Included Systematic Review[1]

Main Study Findings *	Authors' Conclusion
Adverse effects • In the 1997 Danish trial, overall there were 17 adverse events in the budesonide compared with 13 in the placebo group. Adverse events reported more commonly in the ICS group were hoarseness of voice (six versus) three occasions and oral thrush (four versus two) hemoptysis (two versus zero), pharyngitis (three versus zero), and chest pain (1 versus zero). • The 1997 UK trial reported peeling of the fingers for three days in one child and cough for five minutes in another. Although both children were on the fluticasone, it is unclear if these were adverse events of the medication. • The Canadian trial was prematurely halted because five of nine patients in the ICS group (55.6%) and with one in eight patients in the placebo group (12.5%) become colonized with *Pseudomonas aeruginosa* for the first time.	

CF = cystic fibrosis; CI = confidence interval; FEV1 = Forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroids; MD = mean difference

* Study-level findings are reported because the authors could not combine outcomes in this systematic review due to incompletely reported or unavailable data, as well as to differences in methods used to summarize data in the primary studies.

Table 9: Summary of Findings of Included Randomized Controlled Trial[7]

Main Study Findings	Authors' Conclusion
Uyan,[7] 2017	
Lung Function • For FEV1%, the change in mean ± SD score from baseline to eight weeks treatment was 84.8 ± 18.1 to 81.9 ± 23.3, p = 0.32, with budesonide and 92.9 ± 28.1 to 88.6 ± 19.8, p = 0.23 with placebo. Thus, the intra-group change in symptoms score was not statistically significant for either group. The inter group comparison after treatment did not show a statistically significant difference between the two groups (p = 0.43). • For FVC%, the change in mean ± SD score from baseline to eight weeks treatment was 81.6 ± 15.3 to 82.2 ± 21.6, p = 0.84, with budesonide and 87.8 ± 18.7 to 84.7 ± 19.4, p = 0.36 with placebo. Thus, the intra-group change in symptoms score was not statistically significant for either group. The inter group comparison after treatment did not show a statistically significant difference between the two groups (p = 0.75). • The number of patients with BHR decreased from 8 (47%) to 6 (35%) from baseline to eight weeks treatment p = 0.84 with budesonide (p = 0.73) and increased from 6 (50) to 8 (67), p = 0.68 with placebo. Thus, the intra-group change in symptoms score was not statistically significant for either group. The inter group comparison after treatment did not show a statistically significant difference between the two groups (p = 0.70). **Clinical Symptoms** • The symptoms score in the budesonide group changed from 2.5 (IQT: 0.3–5.0); (p = 0.88) at baseline to 3.0 (2.0–4.0) after eight weeks treatment. For the placebo group, the symptom score change from 3.0 (1.0–4.0) to2.5 (0.0–4.0); p = 0.43. Thus, the intra-group change in symptoms score was not statistically significant for either group. The inter group comparison after treatment did not show a statistically significant difference between the two groups (p = 0.59). **Inflammation Markers** • For hs-CRP, change (IQR) from baseline to eight weeks treatment was 1.6 (0.5–7.4) to 1.0 (0.1–4.6), p = 0.23, with budesonide and 0.6 (0.2–1.9) to 0.3 (0.2–4.3), p = 0.93 with placebo. Thus, the intra-group change in symptoms score was not statistically significant for either group. The inter group comparison after treatment did not show a statistically significant difference between the two groups (p = 0.84). • For ESR, change (IQR) from baseline to eight weeks treatment was 20.5 (12.2–34.5) to 15.5 (6.7–30.7), p = 0.08, with budesonide and 21 (7.0–22.7) to 20 (7.7–32.7), p = 0.06 with placebo. Thus, the intra-group	In children with CF, eight weeks of nebulized budesonide at a 2 mg daily dose was not significantly more effective than placebo (0.9% normal saline at improving clinical symptoms, inflammatory markers and lung function scores.

Table 9: Summary of Findings of Included Randomized Controlled Trial[7]

Main Study Findings	Authors' Conclusion
change in symptoms score was not statistically significant for either group. The inter group comparison after treatment did not show a statistically significant difference between the two groups (p = 0.84).	

BHR = bronchial hyperactivity; CF = cystic fibrosis; ESR = erythrocyte sedimentation rate; FEV_1 = forced eviction fraction in one second; FVC = forced vital capacity; hs-CRP = high sensitive C-reactive protein; IQR = interquartile range; SD = standard deviation

Table 10: Summary of Findings of Included Retrospective Cohort Study[8]

Main Study Findings	Authors' Conclusion
De Boeck, 2011[8]	
Lung Function • The difference in the percent predicted FEV_1 between users of ICS and non-users at baseline was statistically significant in favor of the users in the overall population (5.89%, p < 0.0001), patients 18 years of age or older (5.05%, p < 0.0001,), and children aged from 13 to 17 years (4.43%, p = 0.0152); but not in children 6 to 12 years old (0.01%, p = 0.9921). • The difference in the decline in percent predicted FEV_1 between users of ICS and non-users after one year was statistically significant in favor of the users in the overall population (1.07%, p = 0.001) and in children 6 to 12 years old (2.56%, p = 0.0003), but not children aged from 13 to 17 years (0.69%, p = 0.3624) or adults patients 18 years of age or older (0.46%, p < 0.2487) • The proportion of observations with a yearly decline in FEV_1 >5% of predicted was lower in ICS treatment years (26% versus 33%; p = 0.0003). • Patients with baseline FEV_1 ≥ 90% of the predicted, had significantly higher annual rates of decline compared with those with FEV_1 <90% of predicted (1.9% versus 0.4%; p = 0.0084). • The effect of ICS use on FEV_1 decline was seen in patients with chronic Pseudomonas aeruginosa colonization (p = 0.0339) and those without (p = 0.0025) **Growth** • Growth was 4 mm per year lower in children six to 12 years who used ICS than those who did not. The difference was statistically significant (p = 0.0190). • There was no overall effect of ICS use on height (p = 0.2010) after adjusting for patient age and gender or in children 13 to 17 years of age (p = 0.3167). **Insulin Use** • Insulin use was reported in 7.8% of the years analyzed and found to be statistically insignificantly higher in ICS use (OR 1.3, 95% CI: 0.99 to 1.69; p = 0.0598)	

Appendix 5: Additional Reference of Potential Interest

Reason for exclusion: Published before January 1, 2009.

Ren CL, Pasta DJ, Rasouliyan L, et al. Relationship between inhaled corticosteroid therapy and rate of lung function decline in children with cystic fibrosis. J Pediatr 2008; 153: 746–751.