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Inhaled corticosteroids in the emergency department treatment of acute asthma

by

Marcia Edmonds

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A thesis submitted to the Faulty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *Inhaled corticosteroids in the emergency department treatment of acute asthma* submitted by Marcia Edmonds in partial fulfillment of the requirements for the degree of Master of Science in Medical Sciences - Public Health Sciences.

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January 22, 2001

Abstract

This thesis examined the use of inhaled corticosteroids (ICS) in the emergency department (ED) treatment of acute asthma. Two meta-analyses were performed: one to assess if ICS should be administered to patients in the ED, the second to assess their use after ED discharge.

Search strategy: Cochrane Airways Review Group RCT register, bibliographies, pharmaceutical companies, and authors.

Main outcomes: admission, relapse, pulmonary function, symptoms

Main Results: There was a decreased odds of admission in patients treated with ICS in the ED (OR 0.30, 95% CI 0.16 to 0.57); whether there is an additional benefit when systemic corticosteroids (CS) are used is unclear. There was a non-significant trend to less asthma relapses with the addition of ICS to CS therapy after discharge (OR 0.68, 95% CI 0.46 to 1.02), and no significant difference between the treatments when ICS was compared to CS (OR 1.0, 95% CI 0.66, 1.52) in mild asthma.

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Abbreviations

ß-agonist	Beta-2 agonist
95% CI	95% confidence limits
AQLQ	Asthma quality of life questionnaire
ARG	Airways Review Group
BDP	Beclomethasone dipropionate
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systematic Reviews
CS	Systemic corticosteroids
ED	Emergency department
FEV-1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ICS	Inhaled corticosteroids
κ	Kappa
MARC	Multicentre Asthma Research Collaboration
MDI	Metered dose inhaler
NNT	Number needed to treat
OR	Odds ratio
p	p-value
PEFR	Peak expiratory flow rate
PFTs	Pulmonary function tests
PI	Pulmonary index
PIS	Pulmonary index score
RCT	Randomized controlled trial
RevMan	Review Manager, 4.0.1 software program
SD	Standard deviation
SMD	Standardized mean difference
WMD	Weighted mean difference

Chapter one

1.1 Acute asthma: Definition, description of the problem, and treatment approach

Asthma is a common, chronic, inflammatory disorder of the airways, characterized clinically by recurrent episodes of wheezing, breathlessness, chest tightness, and cough. Airflow obstruction is evident during these episodes, and may reverse either spontaneously or with treatment. The diagnosis of asthma is based on the presence of episodic symptoms of airflow obstruction that is at least partially reversible, and the exclusion of alternate diagnoses(1). Mild exacerbations of asthma may resolve spontaneously or be treated by the patient at home with a variety of available medications; more severe exacerbations will often require a visit to a health care provider (e.g. a doctor's office, a clinic, or the emergency department).

Acute asthma is a common presenting complaint to the emergency department (ED) with almost 2 million ED visits per year for acute asthma in the United States(2). Of the 1.5 million annual ED visits in Alberta, 28,000 are for acute asthma; 40% are for multiple visits by the same patient(3). Moreover, patients with acute asthma seen in the ED are often those with the greatest needs (i.e. socio-economically disadvantaged, more severe asthma, etc.) and are receiving the least services (i.e. often not affiliated with a family physician, not taking inhaled corticosteroids, infrequently able to see specialists, etc). The management of asthma accounts for nearly $500 million in medical expenditures every year in Canada(4); the treatment of acute asthma accounts for nearly a quarter of these costs. Overall, patients with acute asthma are an important group to study.

Approximately 15-25% of patients presenting to the ED with acute asthma require admission to the hospital, and, of those discharged from the ED after apparently successful treatment, 10-20% will relapse within two weeks(5;6). Along with the

potential need for admission, and the significant relapse rate and associated costs, there is the potential for uncommon but serious sequelae from asthma exacerbations, including intubation, barotrauma, and death. As well, there are marked effects on work or school performance, and quality of life due to acute asthma in those patients discharged from the ED.

As a result of the importance of this disease, several national(7-9) and international(10) guidelines have been produced for the management of acute asthma in the emergency department. The first line of standard therapy for acute asthma in the emergency department includes bronchodilators, usually short acting ß-agonists such as salbutamol. These may either be nebulized or administered via a metered-dose inhaler using a spacer device(11). The addition of inhaled anticholinergics has been proposed for moderate to severe exacerbations to treat airway hyper-reactivity(12;13). In addition, most patients are given systemic corticosteroids (CS) to deal with the underlying inflammation(14). Despite familiarity with the treatment of asthma, and the presence of these guidelines, practice variation within and among emergency departments is substantial. Moreover, there are still many controversies regarding the optimal treatment of asthmatics in the emergency department, and many unanswered questions for the emergency physician.

1.2 Systemic corticosteroids in asthma

The use of corticosteroids to treat acute asthma dates back to at least the early 1900s, when adrenal extract was first used to treat asthma. Despite many developments in the treatment of asthma in the ensuing 100 years, corticosteroids remain an essential

component of asthma therapy. The familiar synthetic corticosteroids, for oral or intravenous use, were first introduced in the 1950s, and it was in the early 1970s when the lipid-soluble, topically active corticosteroids (beclomethasone) for inhalation were added to the therapeutic options for asthma(15).

Inflammation is well-recognized as a major factor in asthma, and the role of CS as powerful anti-inflammatory medications in the treatment of asthma, as well as countless other conditions, is well accepted. Despite this, the exact mechanisms responsible for the beneficial effects of corticosteroids in asthma is not entirely clear. Diverse effects on varied steps in the inflammatory response have been elucidated, including effects on the transcription of genes responsible for cytokine production and the synthesis of cytokine receptors, decreased survival and inhibition of eosinophils and other inflammatory cells, and decreased plasma exudation and mucus secretion in the airways(16). As well, glucocorticoids decrease airway hyperresponsiveness, and increase the number of beta-2 receptors in lung tissue(17).

CS have been used in acute asthma therapy since the 1950s; despite numerous trials both in vitro and in vivo, there remain many controversies about how and when they should be administered. Traditionally it was believed that the benefit of CS only became apparent after several hours, time enough for effects on gene transcription and the production of inflammatory mediators to occur(18). Recently it has become apparent that there are more rapid effects in laboratory studies, with changes apparent in beta-receptor number and sensitivity within the first 1-2 hours of administration of CS(19;20). Others have proposed that more rapid effects of steroids may be due to decreased membrane permeability or vasoconstriction(21;22). One clinical trial

supported a rapid improvement in pulmonary function tests (within 2 hours) in patients given CS(23); most other trials suggest the clinical effects are significantly slower. The clinical relevance of this rapid action of CS is not yet clear, and most clinical trials and systematic reviews have supported the view that the effect of CS only becomes apparent several hours after administration(14;24). While these studies and reviews support a clinical benefit of CS use in acute asthma, with decreased admission rates and improved symptoms, the effect appears to be relatively slow, requiring several hours to occur, and demonstrated effects on lung function are small or not clearly apparent in most studies(25;26).

1.3 Inhaled corticosteroids in asthma

Administering corticosteroids by inhalation, both within the ED and after discharge from this setting, is an attractive option for many reasons; not only are the drugs delivered directly to the lungs, where their effects appear to be most needed, but this route also has the potential to avoid the side effects of systemic corticosteroid use. The introduction of the first lipid-soluble steroids amenable to inhalational use was a significant improvement in asthma therapy; newer inhaled corticosteroids (ICS) are designed to maximize the local anti-inflammatory effects of the drugs, while minimizing systemic effects due to their poor systemic absorption and high first-pass metabolism(16;27).

ICS were a major advance in the therapy of chronic asthma for many patients who were previously dependent on daily or frequent intermittent use of oral corticosteroids for control of their asthma. The beneficial effect of these drugs in

allowing many asthmatics to decrease or eliminate the need for chronic oral steroids and the concomitant side effects of prolonged steroid use was recognized early and has been shown to be present for many different ICS preparations and delivery systems(28-31). As well, ICS have been shown to decrease the frequency of asthma exacerbations and improve quality of life in asthmatics not dependent on oral steroid use, and improve pulmonary function over the long term(32). Traditional thinking cautioned against the use of ICS in acute asthma because of the possible risk of increased cough and bronchospasm attributed to inhaled steroids(33;34). The beneficial effects of ICS were thought to be observed when ICS agents were used over a prolonged period of time, when the airways were relatively stable. These requirements were thought to be necessary to permit adequate delivery of inhaled drugs to the distal airways. Most recent guidelines still recommend them as predominately a therapy for chronic asthma(35;36). None of the current guidelines for the management of asthma mention ICS as a significant component in the management of acute asthma while in the ED. They are recognized as a component of therapy after discharge from the ED and are mentioned in the management of patients admitted to hospital with acute asthma in recent Canadian guidelines, although the level of evidence for this was rated as weak(9).

In 1989, Salmeron et al demonstrated that ICS were useful in maintaining the improvement in pulmonary function tests induced by a short course of oral corticosteroids in unstable chronic asthma, and found that there were minimal associated side effects(37). Another study investigated time to improvement of

pulmonary function testing and bronchial reactivity after the introduction of ICS; improvements were seen as early as 6 hours after the first dose of ICS(38).

Basic science evidence also supports the presence of an acute effect of inhaled ICS. Similarly to CS, ICS have been found to rapidly restore beta-receptor number and function in patients who have been administered regular beta-agonists(39), with the potential for greater effects due to direct local delivery of high concentrations of the drugs. Others have suggested that there may be local effects from vasoconstriction from direct delivery of steroids to the airways(22;24) (similar to the "blanching" effects seen with topical application of steroids, used to evaluate the potency of various topical steroids). Preliminary evidence suggests that there may be a unique effect to certain ICS involving decreased recruitment of inflammatory precursors from bone marrow to the lung(21;40). Other studies have shown rapid effects on the number of eosinophils in the airway after a single dose of inhaled budesonide, and decreased airway responsiveness 6 hours after treatment(41). These effects do not appear to be due to an significant bronchodilating effect of the ICS agents themselves(42).

1.4 The clinical questions

The evidence would suggest that ICS have the potential to be of benefit in the treatment of acute asthma. Whether this is due to enhanced local delivery of the drugs, unique local effects such as vasoconstriction, or systemic effects of the inhaled drugs that are different than those of the systemically administered corticosteroids is unclear. From reviewing the literature and the available guidelines, there are many unanswered questions about how and when these drugs should be used in the emergency

department. Should patients be given this therapy on initial presentation to the emergency department, with the anticipation of a benefit in the ensuing minutes to hours? Or is this a therapy that should be prescribed upon discharge from the emergency department, in the aim of decreasing repeat visits and asthma symptoms, or improving quality of life, over the following days to weeks?

1.5 The role of a systematic review

In answering these questions, there are several approaches the clinician may use. Searching the literature and critically appraising the resulting articles is one approach to some clinical questions; however, due to the countless clinical questions encountered on a regular basis, the time and expertise required to search and appraise the literature, and the existence of conflicting answers in the literature, for most clinicians this goal quickly becomes unattainable. One may also search for and use the results of narrative reviews and recommendations of experts in the field, or other summaries of evidence such as clinical practice guidelines. A third option is to look for a systematic review and/or meta-analysis that addresses the clinical question.

A systematic review is a type of observational study that comprehensively locates, critically appraises, summarizes, and attempts to reconcile the published evidence on a clearly defined problem. Such a review can be either qualitative or quantitative. A quantitative systematic review, or meta-analysis, uses statistical methods to combine the results of two or more studies to produce an overall estimate of the effect of an exposure or treatment. In contrast, a qualitative review summarizes the primary studies but does not statistically combine the results. The terms systematic

review and meta-analysis will be used interchangeably in discussing quantitative systematic reviews in the rest of this paper.

Explicit, systematic methods are important in both qualitative and quantitative reviews to limit the influences of bias on the results of the reviews, and to produce the most valid results. Psychologists and social scientists drew attention to the systematic steps needed to minimize bias and random errors in reviews of research in the 1970s and early 1980s. It was not until the late 1980s attention was drawn to the poor scientific quality of healthcare review articles(43).

Since that time, there has been rapid growth in both the number of published systematic reviews in medical journals, and the number of publications that address the rigorous methods necessary to conduct and report a valid systematic review(44-46). First, the research question that the review is to address must be clearly defined before starting the review. The patient populations, interventions under study, and outcomes to be measured must be specified.

Systematically searching the literature for relevant trials pertaining to the question is essential, to attempt to identify all relevant trials. Search strategies that include foreign language literature, and attempt to uncover unpublished trials are preferable, to decrease the effects of publication bias on the results of the review. Another form of bias that may affect a systematic review is how trials are selected for inclusion (selection bias). To minimize the influence of selection bias, the methods used to search for trials, and to select trials for inclusion and exclusion, should be defined prior to starting the search, and described when reporting the review.

Trial design affects the outcomes of trials markedly; this makes it important to assess the quality of the individual trials included in a systematic review. There are several scoring systems available to allow uniform assessment of the quality of randomized trials(47); the quality scores can then be used in conducting sensitivity analyses to assess the effects of study quality on the outcomes of the review.

Once trials have been selected for inclusion in the review, decisions about whether it is appropriate to combine the results of the individual trials to obtain an overall pooled result must be made. In some cases, combining data across trials may result in firm conclusions about the benefit or harm of a treatment that were not apparent from the individual trials, as the resultant larger sample sizes will increase the statistical power. This may be of particular benefit when several relatively small, under-powered trials have been conducted which arrive at inconclusive results. This has been noted to be a particular problem in trials in acute asthma(48;49). In other cases, combining data may be problematic due to differences in the design of the trials, or a lack of appropriate trials. These findings are not without value; they may be used to derive appropriate recommendations for future research. A third situation may occur when relevant, apparently similar trials are found with discordant results. This may be apparent as visually (when the results for the individual trials are displayed graphically) or statistically significant heterogeneity (tested using a chi squared statistic for heterogeneity). In this case, researchers need to investigate the possible causes, and determine if it is appropriate to present an overall "average" effect. A summary of discordant results is another strength of a systematic review(50).

In summary, a rigorously conducted systematic review has the potential to be of benefit in several ways. In some cases it may provide firm conclusions about the effect of a treatment that were not apparent from the individual trials. Furthermore, it can provide information as to whether the findings can be generalized across populations, settings, and treatment variations, or define where the findings vary significantly in particular subgroups(51). In other cases, a systematic review may more clearly define areas where further research is needed. It has been suggested that a meta-analysis should be attempted prior to embarking on any clinical trial to establish what is already known in the area(52). Others have recommended that an up-to-date systematic review and meta-analysis should be included in the discussion section in reports of new clinical trials, to allow readers to view the results in conjunction with the relevant evidence(53).

1.6 The Cochrane Collaboration

The Cochrane Collaboration is an international, multi-disciplinary organization that aims to produce, maintain, and promote accessibility of high-quality systematic reviews in many areas of health care, to aid users in making well-informed decisions. It was founded in 1993, and is named after the late British epidemiologist, Dr. Archie Cochrane. Dr. Cochrane believed that the best evidence about the effectiveness of various medical therapies was not readily available for making decisions since it was contained in thousands of randomized controlled trials scattered throughout the medical literature. He advocated the use of a systematic process to locate relevant trials, summarize them, and update the results regularly, in the form of systematic reviews.

The Collaboration promotes the production of high-quality reviews in a number of ways. First, a protocol must be submitted prior to commencing a review; efforts are made to prevent duplication of reviews. There must be a well-defined research question, and the criteria used to select trials for inclusion must be specified. Rigorous and comprehensive search techniques are required to reduce publication bias. The Collaboration also encourages trialists to provide information about unpublished or ongoing trials in the Cochrane Controlled Trials Register (CCTR). The quality of included trials must be appraised using criteria for concealment of allocation; use of other methods in addition to this is strongly encouarged. Data must be abstracted from articles in a way that is reproducible and checked for errors; which data will be used for comparisons should be specified *a priori*. Measures of effect can be summarized, where it is deemed appropriate, using an odds ratio or relative risk for dichotomous data; continuous data are summarized using a mean difference. The authors of the review then provide an interpretation of the results, and make recommendations for clinical practice, as well as for further research in the area(44).

Support is provided to individual 'reviewers' by the Cochrane Collaboration in a number of ways. There are a number of Collaborative Reviews Groups (CRG) within the Collaboration. Support staff may assist the groups in a number of ways, such as providing assistance with searching the literature and retrieving articles, translation of foreign language articles and guidance with statistical methods. Quality control is at least as high as that for peer-reviewed medical journals(54); internal reviews are completed by two editors within the CRG, followed by external review by at least one expert in the field. Training in methods of systematic reviews is provided when

necessary, and technical support is also provided in the form of RevMan, a software package developed by the Cochrane Collaboration for analyzing and reporting reviews. Once accepted, reviews are published electronically by Update Software in electronic form, in the Cochrane Library under the Cochrane Database of Systematic Reviews (CDSR), which is updated quarterly. Authors are encouraged to regularly update reviews to include new research results and responses to criticisms. It has been shown that Cochrane reviews have greater methodological rigor, and are more frequently updated than those published in traditional paper-based journals(55).

1.7 The proposal

Searching the literature regarding the use of ICS in the emergency department treatment of acute asthma revealed that several relatively small, potentially relevant trials had been published in this topic area. Some of these trials investigated the use of ICS for patients with acute asthma while in the ED. Other trials administered ICS after emergency department discharge in the first days to weeks after an asthma exacerbation. Many had non-significant results, possibly related to the small sample sizes, and the conclusions drawn in the studies varied widely.

To address the questions of if and how emergency physicians should employ ICS in the treatment of acute asthma, two systematic reviews have been prepared. The first review deals with the question of whether there is a benefit of ICS therapy when administered early in the ED treatment of acute asthma, examining immediate outcomes including admission, pulmonary function tests while in the ED, and side effects. The second systematic review addresses the question of whether ICS therapy should be

prescribed upon discharge from the ED, using outcomes including asthma relapse, quality of life, and symptoms. This review addresses two possible roles for ICS after ED discharge; either in addition to CS therapy, to provide additional benefit, or the possibility of using ICS alone, in place of CS therapy.

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Chapter two

Inhaled corticosteroids in the emergency department

2.1 Introduction

Acute asthma is a common presenting complaint to the emergency department (ED). In the United States, acute asthma accounts for almost 2 million ED visits per year(1). Approximately 15-25% of these patients will require admission to the hospital, and, of those discharged from the ED after apparently successful treatment, approximately 10-20% will relapse within the subsequent two weeks(2;3). Given the magnitude of the asthma problem, it is not surprising that several national(4-6) and international(7) guidelines have been produced for the management of acute asthma.

There is general agreement that bronchodilators (ß-agonists - e.g. salbutamol, albuterol) and anti-inflammatory medications (systemic corticosteroids (CS) - e.g. prednisone) are first-line agents for acute asthma. ß-agonists are used to provide rapid symptom relief, whereas corticosteroids are used to counter airway inflammation and hasten resolution of the asthma exacerbation. However, there remain numerous controversies regarding the optimal agent, dose, frequency of delivery, and route of delivery for both bronchodilators and corticosteroids in the acute setting. Current practice patterns usually include the use of nebulised ß-agonists and oral or intravenous corticosteroids given early in the ED treatment of acute asthma(2;3). While inhaled corticosteroids (ICS) are used more commonly after ED discharge(8), their use is uncommon in the ED setting(9;10). Given the practice variation with respect to ICS treatment in acute asthma care(2;3;10), it is realistic to assume that a systematic review in this area should provide direction for treatment or further research.

ICS have the potential to be of benefit in the acute treatment of asthma. They have been shown to be effective alternatives to oral steroids in long-term asthma therapy, where they can be used to reduce or even eliminate oral corticosteroid requirements(9). Potential advantages of ICS in acute asthma therapy might include their reduced systemic side effects, direct delivery to the airways, and a greater efficacy in reducing airway reactivity and edema either alone or in addition to CS(11;12). Furthermore, ancillary evidence from studies of patients with croup suggests that ICS agents may act on the airway over the short term to improve outcomes(13).

To date, only a limited number of trials have examined the use of ICS in acute asthma and they have yielded inconsistent results. We are not aware of a published systematic review on the role of ICS in the treatment of acute asthma in the ED. The objective of this meta-analysis was to determine the effect of ICS therapy for patients treated for acute asthma in the ED, when used in addition to standard therapy.

2.2 Materials and Methods

Protocol: Before the start of the research, a protocol was developed to reduce the influence of bias on the results of the review. In the protocol, criteria for study inclusion were clearly outlined:

1. Design: Only randomized controlled trials (RCTs) or quasi-RCTs (e.g. allocation on alternate days of the week) were to be included.
2. Population: Studies including either children or adults were to be included, and age was one of the pre-specified subgroups. Studies involving young children (<2 years) with bronchiolitis were excluded.
3. Intervention: Patients were to receive single or multiple dose ICS compared with placebo early in their ED therapy. They may also have received additional asthma medications (such as CS by other routes, beta-agonists, ipratropium bromide, theophylline compounds, magnesium sulfate, or anti-histamines); data for co-interventions were recorded or requested from the authors when it was not reported in the studies. A secondary analysis was performed for studies comparing ICS alone with CS alone.
4. Outcomes: All patient outcomes were considered; the primary dichotomous outcome was admission to hospital.

Search: A number of strategies were employed in a comprehensive search for potential studies. The Cochrane Airways Review Group (ARG) has developed an "Asthma and Wheez* RCT" register through a standardized, comprehensive search of EMBASE, MEDLINE, and CINAHL. In addition, hand searching of 20 respiratory care journals

with the highest yield for respiratory publications has been completed, and trials have been added to the register. Finally, the register is updated with searches of CENTRAL, the Cochrane Collaboration's clinical trials register. The ARG register contains studies published in a variety of foreign languages, and we did not exclude trials on the basis of language. The current systematic review includes ARG register updates to July 2000.

Search of this register was completed using the following terms: (Emerg* OR acute OR status) AND (dexa* OR deca* OR fluticasone OR Flovent OR beclomethasone OR Becloforte OR budesonide OR Pulmicort OR flunisolide OR Aerobid OR Bronalide OR triamcinalone OR Beclovent OR Azmacort OR Vanceril OR Becotide OR Flixotide OR Aerobec).

Additional efforts to locate potential trials included searching reference lists of all available primary studies and review articles to identify potentially relevant citations, contacting authors of the primary studies and other asthma researchers regarding the existence of other published or unpublished research in the area, and contacting the scientific advisors of the pharmaceutical companies known to manufacture ICS agents. As well, hand searching of abstracts from the last three years of the Society for Academic Emergency Medicine (published in Academic Emergency Medicine), the last five years of the American College of Chest Physicians (published in Chest) and the British Thoracic Society (published in Thorax) was completed. Abstracts from the 1997-1999 abstracts-on-disk from the American Thoracic Society (published in Am J Respir Crit Care Med) meetings also were searched.

Selection: The selection of articles for the review involved a 2-step process. From the title, abstract and key words/MESH headings, two reviewers (MLE, BHR) independently examined the output generated from the computer search to identify

potentially relevant trials for full review. Then, from the full text of the relevant studies, or from contact with authors/pharmaceutical companies in the case of unpublished studies, the same 2 reviewers independently selected trials for inclusion in the review. Agreement was measured using the kappa (κ) statistic.

Quality Assessment: Trials were then assessed for methodological quality using 2 methods, independently by 2 reviewers (MLE, BHR). First, using the assessment of allocation concealment, trials were scored using the following principles:

Grade A: Adequate concealment

Grade B: Uncertain

Grade C: Clearly inadequate concealment

Second, the methodological quality of studies was also assessed using the Jadad criteria(14). One point is allocated for randomisation, blinding, and description of withdrawals and dropouts; an extra point can be added for methods of randomisation and blinding that are well-described and adequate. Studies that use a clearly inadequate method of randomisation or blinding (such as alternating patients) lose the point allocated. The maximum score is 5 points and studies scoring below 3 points are usually regarded as being of low methodological quality. Inter-observer reliability was measured for both quality scales by using the κ statistic.

Where possible, the authors of the trials were contacted and provided confirmation of data extracted from the trials and some were able to provide additional information for the review. When this was not possible, data extraction was performed independently by 2 reviewers (BHR, MLE). For one trial, expansion of graphic representations of data from the manuscript was used to estimate missing data. The data were checked and entered onto the computer by one reviewer.

Trials were combined using Review Manager (Update Software, Oxford, version 4.0.4). For continuous variables, a weighted mean difference (WMD) or standardised mean difference (SMD) and 95% confidence interval (CI) was calculated for each study. The use of WMD is common in many systematic reviews and is the difference between the experimental and control group outcomes, when similar units of measure are used. One of the outcomes, the clinical score, or pulmonary index, was reported on different scales between studies, so the SMD, which uses the standard deviation of the individual studies to calculate a standardized effect size for each study, was used to combine the results. For similar studies, a pooled WMD or SMD and 95% CI was calculated, with weights based on the inverse of the variance. For dichotomous variables, an odds ratio (OR) with 95% confidence intervals (95% CI) was calculated for individual studies. OR for similar studies were pooled using the DerSimonian and Laird method, when using a random effects model, and this method was also used to estimate the absolute risk reduction and the number needed to treat. For pooled effects, heterogeneity was tested using the DerSimonian and Laird method; $p < 0.05$ was considered statistically significant. Results are reported using a fixed effects model, using a Mantel-Haenzel method, except where there was significant heterogeneity, in which case the random effects model is used. When there was no significant heterogeneity, the results for fixed and random effects models were very similar.

Three specific subgroups were planned *a priori*. One was to compare outcomes in adults and children. The second was to compare outcomes in patients with severe asthma to those with less severe asthma (categorised by % predicted PEFR, and by the placebo group admission rate). The final subgroup was to compare outcomes with high versus low dose. High dose was defined as 2 mg or more of beclomethasone dipropionate (BDP)

equivalent. Sensitivity analyses were conducted on fixed versus random effects, and methodologic quality.

2.3 Results

Search: 352 articles were identified in the initial computer search, of which 187 were original citations (53%). From these, 15 articles were deemed potentially relevant by one or both of the two reviewers, with very good agreement ($\kappa = 0.78$). Six further articles were identified by other methods (author contact [1], searching abstracts [2], update searches [3]). A total of 21 articles were reviewed for final inclusion, with 11 articles being selected for final inclusion (7 in the primary analysis, and 4 in the secondary analysis [comparing ICS alone Vs CS alone]), with excellent agreement ($\kappa = 1.0$).

Trials: The majority (6/7) of the studies in the primary analysis were published after 1996. Three were from centres in Canada, and one was from each of the following countries: India, Uruguay, the Philippines, and South Africa. One of these studies(15) was available in abstract form only, and attempts to contact the authors were unsuccessful so it was not possible to include data from this study in the meta-analysis. All four studies included in the secondary analysis were published after 1994; one was from each of Canada, India, Israel, and the United States. (See tables 2.1 and 2.2)

Three of the studies in the primary analysis involved children(15-17), and four involved adults(11;18-20). In the adult studies, the populations varied from only those with severe asthma (FEV1 < 40-50% predicted or investigator assigned severity; 3 studies), to only those with mild to moderate asthma (FEV1 = 40-70% predicted; 1 study). All of the pediatric studies excluded patients with very severe asthma (pulmonary index >13 or equivalent) or with mild asthma (pulmonary index <8 or equivalent). All

four of the studies in the secondary analysis included only children; three included only children with mild to moderate asthma exacerbations(21-23) while one included children with moderate to severe asthma(24).

ICS were administered early in the course of ED treatment, usually at the time of the first beta-agonist treatment. Two of these studies gave a single dose of ICS(16;20) while the other studies gave multiple doses (from three(17) to 18(11)) over 3 to 8 hours. Total doses ranged from low (beclomethasone 200 ug (20)) to very high (flunisolide 18 mg(11)). The route of administration was via nebulizer or MDI with spacer in the pediatric studies, and via MDI with spacer in all adult studies. In the secondary analysis of ICS versus CS, three studies gave a single dose of ICS(22-24), and one gave 3 doses(21), and ICS doses ranged from relatively low (budesonide 1600 ug(23)) to high (dexamethasone 1.5 mg/kg(22)). All four studies used 2 mg/kg of oral prednisolone or prednisone in the CS group.

Co-interventions included various beta-agonists in all studies. Systemic corticosteroids were given to both the experimental and control groups in two studies(16;18) while they were withheld from both experimental and control groups in four studies during the study period(11;15;19;20). In one study, systemic corticosteroids and aminophylline were given to patients who failed to improve after two hours of treatment, while maintaining the study blinding(17). In the other five studies where information on co-interventions was available, none of the patients received theophylline, magnesium, or ipratropium bromide during the study period.

Outcomes were determined at variable times but usually included pulmonary function tests or a clinical score (in pediatric studies), and hospital admission rates. The criteria for admission, and the timing of admission decisions, varied among the trials, with

only one trial reporting pre-specified admission criteria. Reporting of symptom scores and adverse effects also were variable, and further information about adverse effects had to be provided by authors. Data for vital signs were frequently reported, or were requested from the authors. Length of hospital stay was reported in four studies(16-19) and rate of relapse was determined in one study(16) but follow up time and method of reporting was variable and so they were not used for a comparison. In the secondary analysis of ICS Vs CS, little information was available on PFTs, clinical scores, or adverse effects, so only admission rates were compared.

Quality scoring: Overall, the methodological quality of the included trials was high. Most of the trials were double blind, placebo controlled, and were reported as using concealment of allocation. Most trials reported a sufficient number of outcomes. Using the Jadad method, all six studies were rated as "strong". Using the Cochrane methodology, four studies were rated as having blinded allocation(11;16;18;19). It was unclear whether allocation was blinded in two studies(17;20). All four studies in the secondary analysis were rated as "strong" by the Jadad criteria, although it was not clear if allocation was blinded in one of the studies(21).

Outcomes: Results from this meta-analysis are reported by outcome. The main results are reported as overall effects of ICS versus placebo. The main subgroups are based on the nature of the standard therapy (ß-agonists alone, or ß-agonists plus systemic corticosteroids). Subgroups based on age group (children versus adults) and dose are reported. All results are based on the fixed effects model unless otherwise reported. Admission rates for the secondary analysis (comparing ICS versus CS therapy) are reported separately at the end of the results.

Admission to Hospital: In the five studies where admission rates were reported, there was a significant reduction in hospital admissions in the ICS-treated group compared to the non-ICS treated groups (OR: 0.30; 95% CI: 0.16 to 0.57). There was no significant heterogeneity (p=0.62) in the study results. (See figure 2.1)

Pulmonary function tests: In the four adult studies and one pediatric study, a variety of pulmonary function tests were recorded over the ED stay. Three studies recorded both percent predicted and absolute FEV-1 and PEFR, at 30 minute to one hour time intervals over a 3 to 12 hour ED stay. One study reported only FEV-1 at 0 and 1 hour only. The one pediatric study that recorded PFTs(17) reported only percent predicted peak flow at 2 hours. Results were pooled at 1, 2, 3-4 and 5-6 hours after the start of treatment.

Pooled results showed a benefit of ICS therapy on percent predicted FEV-1 at 2 hours post treatment (WMD: 5.0%; 95% CI: 0.4 to 9.7), without significant visual or statistical heterogeneity (p=0.51). There was a trend towards benefit at 1 and 3-4 hours that was not statistically significant, with increasing visual heterogeneity (p=0.15) at 3-4 hours. At 6 hours post treatment, there was no significant difference between the treatments; the largest study with the most marked benefit of ICS therapy followed patients for three hours so did not contribute to the six-hour analyses. Absolute FEV-1 analyses did not show statistically significant differences between the treatments and there was marked heterogeneity. This was most marked at one hour (p<0.01); despite adjusting for the baseline difference in the trial with the largest difference, significant heterogeneity remained. This heterogeneity was present in the two (p=0.08) and 3-4 hour analyses as well (p=0.02).

There was also heterogeneity in the analysis for absolute PEFR in both the two and 3-4 hour analyses. There was no statistically significant heterogeneity in the analyses for percent predicted PEFR ($p>0.1$ at all time intervals); there was a small, statistically significant benefit of ICS therapy at both one and two hours (1 hour WMD: 5 percent predicted, 95% CI: 0.4 to 11; 2 hours WMD: 8 percent predicted, 95% CI: 3 to 13).

Clinical scores: One pediatric study(16) used a clinical score (pulmonary index score) as the primary outcome, with a possible total score of 0 to 12. One of the adult studies(11) also used a clinical index, calculated as the average score for 3 items (dyspnea, wheeze, and accessory muscle use) graded from 0 to 3. The SMD was used to combine the clinical scores. At four hours there was a small, statistically significant difference in clinical score between the groups favouring those treated with ICS (0.41 SD; 95% CI: 0.07 to 0.75), with no significant heterogeneity ($p=0.29$).

Vital signs: Vital signs obtained at the conclusion of the study period (prior to emergency department discharge or admission) were reported in some of the included studies, or requested from the authors where available. Data for heart rate, respiratory rate, oxygen saturation and systolic blood pressure could be pooled. There was statistically significant heterogeneity in the comparison for respiratory rates, but despite the statistical disparity in the study results, the magnitude of the difference in mean respiratory rate between the treatment groups was quite small in all of the studies (0-3 breaths/minute). Furthermore, there were no significant differences in any of the vital signs between the treatment groups. In ICS treated group, respiratory rate increased 0.6 breaths/min (95% CI: –1.7 to 2.8)(random effects), heart rate increased 3.5 beats/min (95% CI: -0.8 to 7.8), oxygen saturation increased 0.5% (95% CI: -0.5 to 1.4), systolic blood pressure increased 0 mm Hg, (95% CI –6 to +6).

Adverse effects: No serious or important adverse events related to ICS therapy were reported in any of the studies. Three studies did not report any significant adverse effects of the treatments which was confirmed by the authors(16;18;19) and a fourth study did not report any adverse effect data, although author confirmation was not successful(20). One study reported on a number of adverse events, with no significant differences between the groups(11).

Subgroup/Sensitivity Analyses: Three subgroup analyses were specified *a priori*: age (children vs. adults), severity, and dose of ICS.

Age group: Pulmonary function tests results could not be compared because of a lack of data in the pediatric studies. There was no evidence of a difference in the OR for admission between children (OR: 0.17; 95% CI: 0.04 to 0.79) and adults (OR: 0.38; 95% CI: 0.18 to 0.80).

Severity: Three of the adult trials included moderate to severe asthmatics; one included mild to moderate asthmatics. Both pediatric studies included moderate-severe asthma exacerbations. The small number of trials and difference in protocols between the trials did not permit meaningful comparisons of asthma severity between the trials.

Dosage: The third subgroup analysis was designed to compare high dose versus low dose therapy (high dose therapy defined as greater than or equal to the equivalent of 2 mg of beclomethasone dipropionate). Three studies used high dose therapy; three studies used low dose therapy. The most beneficial effect on pulmonary function test results occurred in the two studies using the most extreme doses of ICS: the highest (18 mg flunisolide(11)) and lowest (200 ug beclomethasone(20)). Again, the small number of

trials and different protocols did not permit meaningful comparison of the dose of ICS used.

Protocols: One clear difference in the studies included in this meta-analysis was the type of treatment used in the control group. Four studies compared ICS vs. placebo, and two studies compared ICS plus CS vs. CS alone. Subgroup analysis by study protocol showed a similar trend toward benefit in both subgroups. In the 3 studies comparing ICS vs. placebo (with no systemic corticosteroid) where the number of hospital admissions were reported, there was a statistically significant benefit of ICS therapy (OR: 0.21; 95% CI: 0.08 to 0.53), while in the other subgroup (ICS+CS vs. CS alone) there was a non-significant trend toward benefit of ICS therapy (OR: 0.45; 95% CI: 0.18 to 1.12).

Secondary analysis:

Four trials compared ICS vs. CS, all involving only pediatric patients. A total of 313 patients were included in these studies; 159 ICS treated, and 154 CS treated. Only admission to hospital was analyzed. There was marked heterogeneity between the study results ($p<0.01$) which precluded meaningful pooling. There were insufficient data in this subgroup to perform subgroup analyses to further investigate the source of the heterogeneity; pooling using the random effects model did not demonstrate a significant difference between the groups (OR=0.89; 95% CI: 0.2 to 4.5). However, in view of the heterogeneity and wide confidence intervals, this result should be interpreted with caution. (See figure 2.2)

2.4 Discussion

This systematic review examined the evidence for the use of ICS in the ED management of acute asthma. The primary meta-analysis is based on six studies that included 352 patients (179 ICS Vs 173 non-ICS treatment). The pooled results showed a beneficial effect of ICS therapy in preventing hospital admission, with a 61% reduction in admission following the administration of ICS in the ED. Given an admission rate of 26% in the non-ICS group, approximately six patients would require ICS treatment to prevent one admission (95% CI: 4 to 12). There was also a trend towards improved PFTs in ICS treated patients, with a statistically significant improvement of 5% predicted FEV-1 and 8% predicted PEFR at 2 hours. The drug was well tolerated, with no apparent change in vital signs or adverse effects related to ICS therapy.

Although these results showed a homogenous, beneficial effect of ICS therapy in preventing hospital admission among the six trials, the role of ICS therapy in acute asthma is far from clear. The main issue identified related to differences in the standard therapy. Despite evidence of a beneficial effect of systemic corticosteroids in acute asthma therapy(25), four studies compared ICS versus placebo without concomitant systemic CS in either the intervention or control groups. Only two of the studies administered systemic CS to both groups, comparing ICS to placebo in addition to standard CS treatment(16;18). Both of these studies were relatively small and this subgroup did not demonstrate a statistically significant benefit of ICS therapy. However, there was a trend towards benefit of ICS in this subgroup, and the lack of demonstrated difference may be due to a Type 2 error.

This meta-analysis demonstrated a beneficial effect of ICS on percent predicted FEV-1 and PEFR at 2 hours; however, the difference between the groups was small. The

minimum difference in pulmonary function tests that is considered clinically significant has been debated, but infrequently studied. A minimum improvement of 10-12% in FEV-1(4), or approximately 30-50 L/min in PEFR(26;27), is likely necessary to demonstrate an important clinical difference; however, most of this research is based on chronic asthma. Based on these guidelines, the improvement of 5% in the FEV-1 at 2 hours, or 7% in the PEFR would be of questionable clinical significance. There may a number of factors contributing to the heterogeneity in the results of the absolute FEV-1 and PEFR. The most apparent is due to baseline differences in pulmonary function tests between the groups, which were statistically and clinically significant. Other explanations would include differences between the studies in the populations, interventions, designs, and methods of measuring the pulmonary function tests; however, the small number of studies did not permit meaningful analysis of these differences.

The pulmonary index (PI) has been shown to correlate with pulmonary function test results including FEV-1, FEV-1/FVC, and FEV_{25-75}%, and with hospital admission (28). Two of the trials used clinical scores which were quite similar to the pulmonary index. A small, statistically significant improvement in clinical score between the groups of 0.41 SD (95% CI: 0.07 to 0.75) was demonstrated at 3-4 hours. This difference would represent an insignificant clinical change for most patients. For example, from the cited studies, this would represent an improvement from 0.1 points in clinical index(11) to 0.8 in the pulmonary index score(16). Moreover, in view of the use of a SMD to combine different scores, and the small magnitude of the difference, this result and any conclusions based on it should be viewed with caution.

Very few adverse effects of ICS therapy were reported in any of the studies, and this was confirmed with corresponding authors. It is of note that increased cough or

bronchospasm occasionally attributed to ICS therapy(29) was not noted in any of the studies. The lack of effect on vital signs also supports the safety of ICS therapy.

Although subgroup analyses based on age (adults versus children), dose (high versus low dose), and asthma severity were proposed, the small number and size of the trials, and the differences in protocols and outcomes did not permit many comparisons to be made. Admission to hospital was the most frequently reported outcome, and point estimates for admission ORs were similar between age and dose subgroups with no apparent heterogeneity. However, subgroup comparisons should be interpreted with caution in this meta-analysis, as all comparisons are made between rather than within studies, and the differences in effect sizes are small(30).

A secondary analysis was performed including four studies (all involving only children) where ICS alone were compared to CS alone; because of the small number of studies and diverse outcomes reported in the studies, only admission rates were compared. There was significant heterogeneity between the studies for the odds of admission, which did not permit meaningful pooling. Pooling of admission data using the random effects model resulted in an odds ratio close to one, with wide confidence intervals; this result does not exclude the possibility of either treatment being significantly better (or worse) than the other. The small number of studies, and the small number of outcomes amenable to pooling, precluded further investigation of the source of the heterogeneity.

There is a possibility of publication bias in this meta-analysis, in that by missing unpublished negative trials, the effect of ICS therapy may be overestimated. However, a comprehensive search strategy was conducted, with a systematic strategy to avoid bias. Attempts to find unpublished trials also were made, including extensive correspondence with the authors of six of the ten trials as well as other experts in the field, searching of

abstracts from recent conferences, and contact with the pharmaceutical companies which manufacture ICS. One unpublished trial was identified(15), but we were unable to contact the author; the abstract stated that group treated with ICS had a trend towards improvement in percent predicted FEV-1 that was not statistically significant. We recognise that more negative, unpublished trials may exist. However, of note, three of the six published trials in the primary analysis did not show a beneficial effect of ICS on the primary outcome of the trial. The search of the published literature was comprehensive and has been updated, so it is unlikely that any published trials were missed.

There is also a possibility of selection bias. However, we attempted to minimise this bias by employing two independent reviewers, so that studies were excluded for consistent and appropriate reasons.

Notwithstanding the above concerns, the weight of evidence suggests that ICS may reduce admissions and improve pulmonary functions when used early in the treatment of acute asthma. The use of ICS is associated with few side effects, and therefore, it should be considered for patients with moderate to severe acute asthma. Guidelines should be changed to reflect these findings.

Despite these results, many questions regarding the role of ICS in the emergency department treatment of acute asthma remain unanswered. Most importantly, additional research is required to determine if ICS provides additional benefit when used in addition to CS therapy. As well, further study is required to define the optimal dose, agent, and duration of CS therapy, and to determine if the beneficial effect is confined to a subgroup of ED patients, particularly those with severe asthma.

Table 2.1: Study Populations

	Study ID	Location Year	Total Sample	Age Group	Initial Pulmonary Function: PEFR (mean) Absolute (L/min)	Initial Pulmonary Function: PEFR (mean) % predicted	Initial Pulmonary Function: Initial PIS/PI
ICS vs placebo	Afilalo (19)	Canada, 1999	54	Adults	241	56.5	NR
	Olaivar (15)	Phillipines, 1999	65	Children	NR	NR	NR
	Pansegrouw (20)	South Africa, 1992	40	Adults	Initial FEV1 1.05 L/min	NR	NR
	Rodrigo (11)	Uruguay, 1998	94	Adults	158	31.6	NR
	Singhi (17)	India, 1999	60	Children	NR	54	NR
ICS+CS vs CS	Guttman (18)	Canada, 1997	60	Adults	175	39.4	NR
	Sung (16)	Canada, 1998	82	Children	NR	NR	7 (median PI)
ICS alone vs CS alone	Devidayal (21)	India, 1999	80	Children	NR	63	NR
	Scarfone (22)	US, 1995	111	Children	NR	NR	10 (median PIS)
	Schuh (24)	Canada, 2000	100	Children	NR	43	NR
	Volovitz (23)	Israel, 1998	22	Children	179	58	8.7 (mean PIS)

Note: NR = not reported; PI = pulmonary index; PIS = pulmonary index score, PEFR = peak expiratory flow rate.

Table 2.2: Study Design

	Study	Type of ICS	ICS Regimen	Control Regimen	CS Regimen	Reported Outcomes	Overall Conclusion	Jadad Quality Score
ICS vs placebo	Afilalo (19)	Beclometha-sone MDI and spacer	1 mg at 0, 0.5, 1, 2, 4 hours	Placebo MDI at same time intervals	None	FEV1, hospitalization, vitals, admission rate	Not effective	5
	Olaivar (15)	Budesonide, nebulized	0.5 mg at 0, 20, 40 min	Placebo, nebulized at same time intervals	None	FEV-1%, hospitalization, CS use	Not effective	Not rated
	Pansegrouw (20)	Beclometha-sone, MDI	200ug at 5 min	Placebo MDI at 5 min	None	FVC, FEV1, symptoms	Effective	3
	Rodrigo (11)	Flunisolide, MDI and spacer	1 mg q10 min x 3 hours	Placebo MDI at same time intervals	None	PFTs, clinical index, admission rate, side effects	Effective	5
	Singhi (17)	Budesonide, MDI and spacer	400 ug q30 min x 3	Placebo MDI at same time intervals	None	Clinical indices, admission rate	Effective	3
ICS plus CS vs CS	Guttman (18)	Beclometha-sone, MDI and spacer	1 mg at 0, 0.5, 1, 2, 4, 6, 8 hours	Placebo MDI at same time intervals	Methylpred nisolone 80 mg at 0h, 60 mg at 6h in both groups	PFTs, vitals, admission rate	Not effective	5
	Sung (16)	Budesonide, nebulized	2 mg at start of trial	Placebo, nebulized	Prednisone 1 mg/kg in both groups	PIS, vitals, admission rate, relapse	Trend to benefit; need larger study.	5
ICS alone vs CS alone	Devidayal (21)	Budesonide, nebulized	800 ug q30 min x 3 doses	Predniso-lone 2 mg/kg po	(control group only)	PEFR, PI, clinical indices	ICS better than CS	4
	Scarfone (22)	Dexametha-sone, nebulized	1.5 mg/kg at 5 min	Prednisone 2 mg/kg po	(control group only)	PIS, admission, relapse	No difference	4
	Schuh (24)	Fluticasone, MDI with spacer	2 mg at start of trial	Prednisone 2 mg/kg po	(control group only)	PFTs, vital signs, admission rate	CS better than ICS	5
	Volovitz (23)	Budesonide, turbuhaler	1600 ug at start of trial	Predniso-lone 2 mg/kg po	(control group only)	PIS, admission, PEFR	ICS at least as effective as CS	5

Note: PFTs = pulmonary function tests, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second

Figure 2.1 **ICS vs placebo: analysis of admissions.**

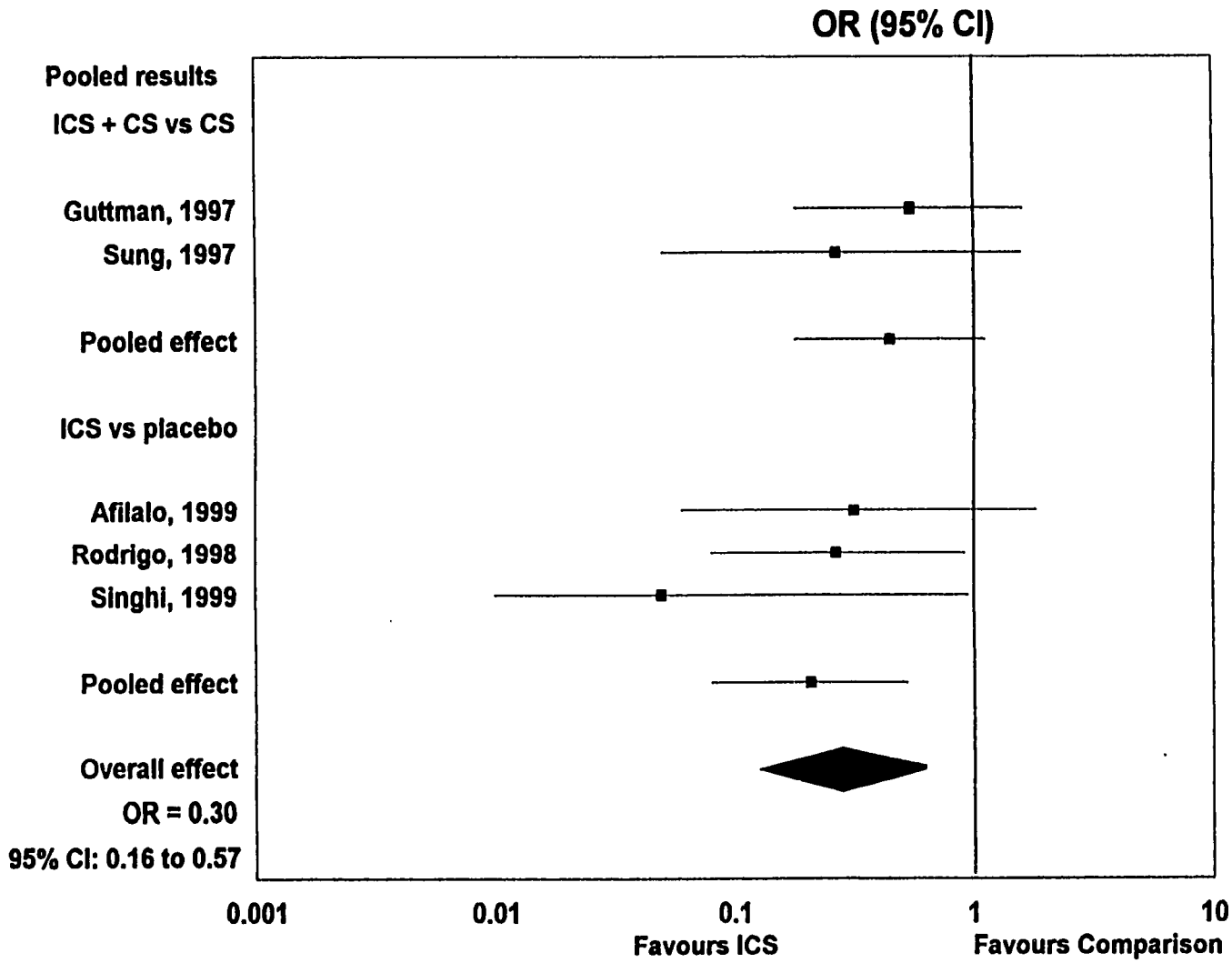
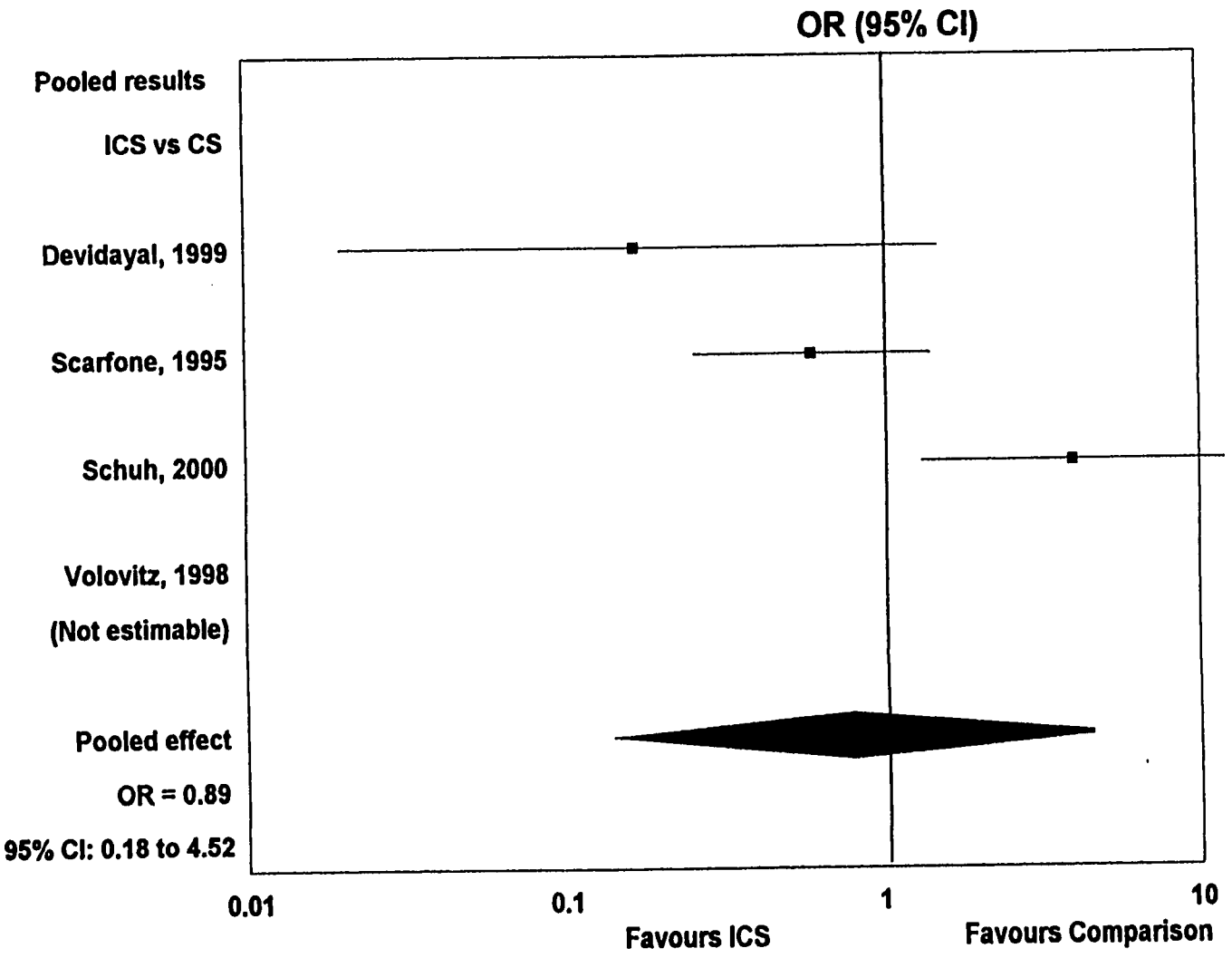


Figure 2.2 **ICS vs CS: analysis of admissions.**



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Chapter three

Inhaled corticosteroids after emergency department discharge

3.1 Introduction

Acute asthma is a common presenting complaint to the emergency department (ED). In the United States, acute asthma accounts for nearly 2 million ED visits per year(1). Approximately 15-25% of these patients will require admission to the hospital, and for those discharged from the ED after apparently successful treatment, approximately 10-20% will relapse within the subsequent two weeks(2). The enormity of the asthma problem overall has led to the creation of several national(3-5) and international(6) asthma guidelines.

There is general agreement that ß-agonists (e.g. salbutamol, albuterol) and systemic corticosteroids (CS) (e.g. prednisone) are first-line agents for acute asthma. ß-agonists are used to provide rapid symptom relief, whereas corticosteroids are used to counter airway inflammation and hasten resolution of the asthma exacerbation. There remain numerous controversies, however, regarding the optimal dose, frequency, and route of delivery of these medications.

Current practice for patients discharged after assessment and treatment in the ED usually involves the use of short-acting ß-agonists and oral corticosteroids prescribed for 5-10 days after discharge in a majority of cases(7;8). While the evidence for oral corticosteroids is strong, the evidence and recommendations for the role of inhaled corticosteroids (ICS) in the management of acute asthma after discharge are inconsistent. Recent Canadian guidelines include inhaled corticosteroids as an integral component of

asthma therapy after emergency department discharge(5); whereas recent American guidelines mention ICS as an option in this setting(9).

This conflicting evidence is also reflected in practice. For example, in Canadian EDs, use of ICS is as high as 69% at discharge, whereas in US centres use is lower (<15%)(10). When ICSs are prescribed, they may either be used with(10-12) or as a replacement for oral corticosteroids(13). Given the practice variation with respect to ICS treatment in acute asthma care(8;10), a systematic review in this area has the potential to provide direction for treatment and further research.

ICSs may be of benefit in the acute setting. The possible advantages of ICSs in acute asthma therapy might include their reduced systemic side effects, direct delivery to the airways, and a greater efficacy in reducing airway reactivity and edema either alone or in addition to systemic corticosteroids(14;15). Furthermore, ancillary evidence from studies of other airway diseases suggests that ICS agents may act over the short term to improve outcomes(16). They have been shown to be effective alternatives to CS in long-term asthma therapy, where they can reduce or even eliminate CS requirements(17).

Several recent trials have examined the use of ICSs in acute asthma upon emergency department discharge and they have yielded conflicting results(11-13). The current research was designed to produce summary evidence using literature searching and meta-analytic techniques in an attempt to generate stronger conclusions and recommendations.

3.2 Materials and Methods

Protocol: Before the start of the research, a protocol was developed to reduce the influence of bias on the results of the review. In the protocol, criteria for study inclusion were clearly outlined:

1. Design: Only randomized controlled trials (RCTs) or quasi-RCTs (e.g. allocation on alternate days of the week) were to be considered for inclusion.
2. Population: Studies including either children or adults were considered for inclusion, and age was one of the pre-specified subgroups. Studies involving young children (<2 years of age) with bronchiolitis were excluded.
3. Intervention: Patients were to have been treated in an ED or equivalent for acute asthma, and at discharge, must have been randomised to receive ICS treatment, either in addition to, or as a substitute for, standard CS therapy. ICS administration was defined as any corticosteroid agent administered by MDI, other inhaler, or nebulizer after ED discharge. Participants were permitted to receive additional asthma medications (such as intramuscular corticosteroids, ß-agonists, ipratropium bromide, theophylline compounds, antibiotics, or anti-histamines). Data for these co-interventions were recorded or requested from the authors directly when this information was incompletely reported.

There were two distinct types of studies in this systematic review, which form two separate parts of the review. In the first type of study, the treatment groups compared ICS in addition to CS versus CS alone. In the second type of study, the treatment groups compared ICS alone versus CS alone.

4. Outcomes: All patient outcomes were considered; however, the primary dichotomous outcome was acute asthma relapse (defined as an unscheduled visit for worsening asthma). Other outcomes were asthma specific quality-of-life (AQLQ), pulmonary function tests (PFTs), ß-agonist use, relapse to hospitalization, any report of adverse side effects, and symptoms.

Search: A number of strategies were employed in a comprehensive search for potential studies. The Cochrane Airways Review Group (ARG) has developed an "Asthma and Wheez* RCT" register through a standardized, comprehensive search of EMBASE, MEDLINE, and CINAHL. In addition, hand searching of 20 respiratory care journals with the highest yield for respiratory publications has been completed, and trials have been added to the register. Finally, the register is updated with searches of CENTRAL, the Cochrane Collaboration's clinical trials register. The ARG register contains studies published in a variety of foreign languages, and we did not exclude trials on the basis of language. The current systematic review includes ARG register updates to July 2000.

Searching of this register was completed using the following terms: (Emerg* OR acute OR status) AND (dexa* OR deca* OR fluticasone OR Flovent OR beclomethasone OR Becloforte OR budesonide OR Pulmicort OR flunisolide OR Aerobid OR Bronalide OR triamcinalone OR Beclovent OR Azmacort OR Vanceril OR Becotide OR Flixotide OR Aerobec).

Additional efforts to locate potential trials included searching reference lists of all available primary studies and review articles to identify potentially relevant citations,

contacting authors of the primary studies and other asthma researchers regarding the existence of other published or unpublished research in the area, and by contacting the scientific advisors of the various pharmaceutical industries that manufacture known ICS agents. As well, hand searching of abstracts from the last three years of the Society for Academic Emergency Medicine (published in *Academic Emergency Medicine*), the last five years of the American College of Chest Physicians (published in *Chest*) and the British Thoracic Society (published in *Thorax)* was completed. Abstracts from the 1997-1999 abstracts-on-disk from the American Thoracic Society (published in *Am J Respir Crit Care Med*) meetings were also searched.

Selection: The selection of articles for the review involved a two-step process. From the title, abstract and key words/MESH headings, two reviewers (MLE, BHR) independently examined the output generated from the computer search to identify potentially relevant trials for full review. Then, from the full text of the relevant studies, or from contact with authors/pharmaceutical companies in the case of unpublished studies, the same 2 reviewers independently selected trials for inclusion in the review. Agreement was measured using the kappa (κ) statistic.

Quality assessment: Trials were then assessed for methodological quality using two methods, independently by two reviewers (MLE, BHR). First, using the assessment of allocation concealment, all trials were scored using the following principles(18):

Grade A: Adequate concealment

Grade B: Uncertain

Grade C: Clearly inadequate concealment

Second, the methodological quality of studies was also documented using the Jadad criteria(19). One point is allocated for randomisation, blinding, and description of withdrawals and dropouts; an extra point can be added for methods of randomisation and blinding that are well-described and adequate. Studies that use a clearly inadequate method of randomisation or blinding (such as alternating patients) lose the point allocated. The maximum score is 5 points and studies scoring below 3 points are usually regarded as being of low methodological quality. Inter-observer reliability was measured for both quality scales using the κ statistic.

Data abstraction: When possible, the authors of trials were contacted and provided confirmation of data extracted from the published trials and some were able to provide additional information for the review. When this was not possible, data extraction was performed independently by 2 reviewers (MLE, BHR). As many of these trials were unpublished, a large amount of data were obtained directly from the primary investigators or the pharmaceutical companies in a specified format. The data were entered into the computer program by one reviewer.

Statistical Considerations: Trials were combined using Review Manager (Update Software, Oxford, version 4.0.4). For continuous variables, a weighted mean difference (WMD) and 95% confidence interval (95% CI) were calculated for each study, and a pooled WMD and 95% CI were calculated for similar studies, with weights based on the inverse of the variance. The use of the WMD is common in many systematic reviews and is the difference between the experimental and control group outcomes, when similar units of measure are used. For dichotomous variables, an odds ratio (OR) with 95% CI was calculated for individual studies. OR for similar studies were pooled

using the DerSimonian and Laird method, when using a random effects model, and this method was also used to estimate the absolute risk reduction and the number needed to treat (NNT). For pooled effects, heterogeneity was tested using the DerSimonian and Laird method; $p < 0.05$ was considered statistically significant. Results are reported using the fixed effects model, using a Mantel-Haenzel method, except where there was significant heterogeneity, in which case the random effects model is used. When there was no significant heterogeneity, the results for fixed and random effects model were very similar.

As previously discussed, two separate comparisons were performed: one comparing ICS plus CS versus CS alone, and the second comparing ICS alone versus CS alone. Within these comparisons, three specific subgroup analyses were planned *a priori*. The first was to compare studies of adults to those of children. The second was to compare patients with severe asthma to those with less severe asthma (categorised by % predicted peak expiratory flow rate [PEFR], and by the placebo group admission rate). The final subgroup was to compare the effect of ICS on the odds of asthma relapse in males versus females. However, due to the small number of studies, only the gender subgroup analysis was performed in the comparison of ICS plus CS versus CS alone.

3.3 Results

Search: 352 articles were identified in the computer search, of which 187 were original citations. From these, a total of 12 articles were identified as being potentially relevant, with moderate agreement ($\kappa = 0.57$) between the two reviewers. An additional 20 studies were identified from hand searching, review of the reference lists, contact with authors, update searches, and contact with the pharmaceutical industry. Thirty-two full articles were reviewed for inclusion. Full texts were obtained for published articles; further information was sought about unpublished studies from the authors. From these 32 studies, ten were identified by both reviewers for inclusion, with complete agreement ($\kappa = 1.0$). Three trials compared ICS plus CS versus CS alone; seven trials compared ICS alone versus CS alone. The results for the two comparisons will be discussed separately.

ICS plus CS versus CS alone

Three studies compared ICS plus CS versus CS alone(11;12;20), of which two were unpublished at the time of this writing. (See tables 3.1 and 3.2)

Co-interventions included various inhaled ß-agonists in all studies. The studies permitted concurrent medications to be continued, including theophylline, ipratropium bromide, and long-acting ß-agonists, although they did not permit them to be started during the study; overall, these agents were infrequently used. Relapse outcomes were reported in all three studies, while other outcomes were variably reported.

Quality scoring: Overall, the methodological quality of the trials was high, with all three demonstrating good concealment of allocation, and all three receiving a Jadad score of 5, indicating high-quality. In all three of the studies, compliance was reported.

In two of the studies, compliance was high, with over 90% compliance with oral CS in both studies, and over 70% compliance with ICS in one of the studies(20), and over 90% compliance with ICS in the second study(11). In the third study, self-reported compliance was much less (approximately 55%)(12).

Outcomes:

Asthma Relapse: There were no statistically significant differences in asthma relapse between patients treated with ICS and those treated without ICS. However, there was a trend towards benefit of ICS at both 7-10 (OR: 0.72; 95% CI: 0.48 to 1.10) and 20-24 days (OR: 0.68; 95% CI: 0.46 to 1.02) follow-up. The pooled results did not demonstrate significant heterogeneity at 7-10 (p=0.94) or 20-24 (p=0.64) days (See Figure 3.1).

Subgroup analyses by gender did not show significant differences in the ORs for relapse between males and females. The OR for relapse for males at 7-10 days was 0.96 (95% CI: 0.21 to 4.43), while the OR for relapse for females was 0.79 (95% CI: 0.34 to 1.52). There was visual heterogeneity, which was not statistically significant (p=0.15). At 20-24 days, the OR for relapse for males was 0.60 (95% CI: 0.22 to 1.62), while for females it was 0.78 (95% CI: 0.30 to 1.99). Again there was visual heterogeneity in the subgroups; however, this did not reach statistical significance (p=0.13). The random effects model was used for this subgroup due to the extent of heterogeneity.

Hospital Admission: Hospital admission rates were reported in two studies and were rare events overall (2% of patients). There was no difference demonstrated in

hospital admissions between the groups (OR: 0.99; 95% CI: 0.39 to 2.52), and no significant heterogeneity between the two studies (p=0.53).

PFTs: Two trials recorded PEFR (absolute and percent predicted). There were no demonstrated differences between the groups in either absolute or percent predicted PEFR, and the point estimates for the difference between the groups included WMD = 0 at all times.

ß-agonist use: There was no significant difference in ß-agonist use between the groups at 7-10 days (WMD: 0.5 inhalations/day; 95% CI: –0.5 to 1.5) with no significant heterogeneity (p=0.29). At 20-24 days, visual and statistical heterogeneity (p=0.04) were identified; however, the overall difference was small (WMD: 0.1 inhalations/day; 95% CI: -2.3 to 2.1) using the random effects model.

Quality of life: Two trials reported quality of life outcomes. Pooled results did not show a significant effect of ICS at either 7-10 or 20-24 days, but there was marked heterogeneity at 20-24 days (p<0.01), with one trial showing a significant benefit of ICS and the other showing no effect. (Improvement in AQLQ in ICS treated group at 7-10 days: WMD=0.2; 95% CI: -0.1 to 0.5; at 20-24 days, WMD=0.3; 95% CI: –0.4 to 1.0 using a random effects model).

Asthma Symptoms: Two studies recorded data on cough, dyspnea, and wheeze on a seven-point Likert scale. At 7-10 days, there was no statistical difference between the groups for any of the symptoms, although there was statistical and visual heterogeneity between the trials for dyspnea. At 20-24 days, there was visually and statistically significant heterogeneity in all three outcomes, with one trial showing a strong, statistically significant benefit of ICS therapy for all three outcomes, and the other not

demonstrating any effect of ICS therapy. Pooling of the results using the random effects model did not produce statistically significant differences between the groups. Furthermore, the point estimates for the difference were all < 0.5, which would not be considered clinically important(21).

Side effects: Two studies recorded data on hoarseness and sore throat. There were no statistically significant differences between the treatment groups at any time for either side effect. At 7-10 days, the odds ratio for hoarseness in the group receiving ICS treatment was 0.88 (95% CI: 0.53 to 1.46) and at 20-24 days it was 0.60 (95% CI: 0.36 to 1.01). There was no significant heterogeneity at either time interval (7-10 days: p=0.6; 20-24 days: p=0.33). For sore throat, the odds ratio was 0.73 (95% CI: 0.43 to 1.24) at 7-10 days, and 0.64 (95% CI: 0.35 to 1.16) at 20-24 days, with no significant heterogeneity (7-10 days: p=0.91 and 20-24 days: p=0.25).

Sensitivity Analyses: Asthma relapse rates in the primary analyses were calculated as intention-to-treat. Because of marked differences in the rate of follow-up between the trials, the analyses were repeated excluding all patients who were lost to follow-up. The odds ratios for asthma relapse were very similar to those in the primary analysis, with no statistically significant differences between the groups (7-10 days, OR=0.72; 95% CI: 0.47 to 1.10; 20-24 days, OR=0.70; 95% CI: 0.47 to 1.05).

ICS alone versus CS alone

Seven studies compared ICS alone to CS alone(13;22-27); three were unpublished at the time of this writing. (See tables 3.1 and 3.2)

Co-interventions included various inhaled ß-agonists in all studies. The studies allowed concurrent medications, including theophylline, ipratropium bromide, and long-acting ß-agonists to be continued, although, they were infrequently used in all but one study where approximately 57% of the patients were on oral ß-agonists and 55% were on xanthines(25).

Only one of the four pediatric studies reported asthma relapse rates as an outcome, while it was reported in all three adult studies. One of the three adult studies used change in forced expiratory volume in one second (FEV-1) as the primary outcome(25), and one of the adult studies used asthma relapse rates as the primary outcome(23). The third adult study used "treatment failure" as the primary outcome. Patients were categorised as a treatment failure if (a) PEFR fell below 60% of the best/predicted value on two consecutive occasions, or (b) a symptom score of 3 (indicating the symptoms were the same or worse than on entry to the study) was recorded on three or more consecutive days, or (c) the patient withdrew because of uncontrolled symptoms or an adverse event related to asthma(13). This outcome was pooled with the data for asthma relapse from other studies in the analyses.

Length of treatment and follow-up in the studies of ICS versus CS was seven days in five of the studies, although two of these studies also recorded absolute PEFR at 21 days (but no other outcomes at these times)(22;26). The other two studies followed patients for 16(13) and 24 days(27).

Quality scoring: Overall, the methodological quality of the seven trials was high. Using the Jadad method, all seven studies were rated as "strong", with four studies receiving a score of five, and three studies receiving a score of four. Using the Cochrane methodology score, all seven studies were rated as having blinded allocation (after confirmation with the authors in several cases).

Compliance was measured in five of the seven studies, but information on compliance was only available in two, where the compliance with both regimens was reported to be greater than 90%(23;27).

Outcomes: *Asthma Relapse:* Only four of seven studies reported asthma relapse rates, and one of these studies had no patients who relapsed. At 7-10 days, there was no demonstrated difference in asthma relapse between the groups (OR: 1.0; 95% CI: 0.66 to 1.52). (See Figure 3.2) There was no significant heterogeneity between the studies (p=0.88). Only two studies followed patients beyond 10 days, one of which had no relapses, and at a 16-day follow-up, there was no significant difference in relapse between the groups (OR: 1.26; 95% CI: 0.80 to 1.98).

Hospital Admission: Only two studies reported hospital admission rates, and there were no admissions in either of these studies.

PFTs: Six studies reported absolute PEFR at 7-10 days, and four studies at 16-21 days, while only two studies reported % predicted PEFR, at both times. At 7-10 days, the difference in absolute PEFR between the two groups was not statistically significant, with the PEFR in the ICS treated group 11.0 L/min (95% CI: -1 to 23) higher than in the CS treated group. At 20-24 days, there was a statistically significant improvement in PEFR

in the ICS treated group of 15.2 L/min (95% CI: 2 to 29). There was no statistically significant heterogeneity (7-10 days: p=0.19; 20-24 days: p=0.41). There was no significant difference between the groups for % predicted PEFR at either time interval, with the point estimates for the difference being very small (<1% predicted).

ß-agonist use: This information was only available in two studies, at 7-10 days only. There was no significant difference between the treatment groups in ß-agonist use (WMD: 0.1 more puffs/day in the ICS treated group; 95% CI: -0.4 to 0.7)

Quality of life: Only two studies reported quality of life information. There was no significant difference between the groups in quality of life (SMD: -0.1; 95% CI: -0.4 to 0.1) at 7-10 days.

Asthma Symptoms and Side Effects: Due to insufficient and varied reporting, there was inadequate information to determine the effect of treatment on asthma symptoms, or any adverse effects of treatment. However, the rate of side effects was low and balanced in each study, where this information was reported.

3.4 Discussion

This systematic review examined the best available evidence for the use of ICS in the management of asthmatics upon discharge from the emergency department or other acute care settings. There are several important findings that arise from this meta-analysis. First, despite an exhaustive search and the existence of recommendations supporting the use of ICS in the out-patient treatment of acute asthma(5;9) only 10 trials were identified, many of which were small, and there were marked variations in the study protocols. Clearly this is an area where further research is urgently needed.

Second, there were two distinct potential roles for ICS therapy in this setting: either in addition to standard therapy with CS, or as a substitute for CS. For both types of studies in this review, (ICS + CS versus CS; ICS versus CS), most pooled results did not demonstrate significant differences between the treatment approaches. This lack of statistical significance has very different implications for the two comparisons, and the two approaches will therefore be discussed separately.

ICS plus CS versus CS

There were a total of 909 patients included in the studies: 455 treated with ICS plus CS, and 454 treated with CS alone. The pooled results of studies on the effect of the addition of ICS to standard CS therapy failed to demonstrate a statistically significant benefit on the primary outcome, asthma relapse, despite a trend in favour of ICS. In addition, there appeared to be no benefit on the secondary outcomes of hospital admission or pulmonary function tests. Interpretation of the other pooled outcomes (e.g. quality of life, ß-agonist use, and asthma symptoms) were limited by statistically significant heterogeneity and variable reporting.

For the primary outcome, asthma relapse, there was no significant difference demonstrated between the treatment groups, although there was a trend towards a benefit of ICS at both 7-10 and 20-24 days. At 20-24 days, the odds ratio for admission was 0.68 (95% CI: 0.46 to 1.02). If this point estimate is valid (and the lack of significance is due to an overall small sample size), this would suggest that the addition of ICS therapy to standard CS therapy in 27 patients would prevent one asthma relapse (NNT). The 95% confidence intervals indicate this NNT may be as large as preventing one relapse for

every 11 patients treated, or that ICS therapy may *cause* one relapse for every 50 patients treated.

There was no significant effect of ICS therapy demonstrated on PFTs. The point estimates for the differences between the groups for absolute PEFR were less than 5 L/min or less than 3% predicted at all time intervals. This is consistent with the systematic reviews of ICS therapy in the ED treatment of asthma, and of CS therapy in the ED treatment of asthma, where there was minimal effect of CS therapy on PFTs, despite beneficial effects on other outcomes(7;28;29).

There was heterogeneity among the studies for several of the secondary outcomes, including ß-agonist use, symptoms, and quality-of-life. This heterogeneity may affect the pooled result for the primary outcome as well, potentially obscuring a subgroup of patients in whom ICS therapy may provide a more marked benefit. To further investigate the heterogeneity, normally differences between the studies in the design, populations, outcomes, and the interventions used need to be considered. One potential explanation for the heterogeneity between the studies might be the dose of ICS used. The study that showed clear benefit of ICS on several outcomes(11) used high dose ICS, while the two studies that did not show a beneficial effect of ICS used moderate dose ICS(12;20). However, this is a between-study comparison made after the completion of the review, and should only be considered as a hypothesis for future research. The small number of studies did not permit other meaningful comparisons to be made in this systematic review.

A subgroup analysis to compare gender differences in response to ICS therapy was planned *a priori*. Despite the presence of a statistically and clinically important

gender difference in one study(20), the gender-treatment interaction did not reach statistical significance in this meta-analysis and heterogeneity was demonstrated. While it is unclear at this time if this sub-group finding is valid, the hypothesis warrants exploration in future research.

The role of ICS in chronic stable asthma is clear; however, the role of adding ICS for emergency physicians and other health care providers treating acute asthma remains unclear. Since many patients with severe acute asthma already meet criteria for treatment with ICS by current guidelines, adding the agent may be a wise "preventive" measure. In mild or moderate acute asthma where there is a low risk of relapse, treatment may not be immediately beneficial. Since the treatment appears safe and side effects are uncommon, the main issue in these cases may be the cost of the drug.

ICS alone versus CS alone

The results from this section of the review are based on seven studies; four published and three unpublished (all in abstract form only). A total of 1204 patients were studied; 612 were treated with ICS, and 592 were treated with CS. Unfortunately, despite the relatively large number of patients included in these studies, the studies reported different outcomes. Consequently, smaller numbers of patients contribute to each of the individual outcomes.

There was no statistically significant difference between the treatments for asthma relapse, at either 7-10 or 16-21 days. The important question to be answered is whether or not there is sufficient information to conclude these two treatments are equivalent. At 7-10 days, the OR for relapse was 1.0, with the 95% confidence interval from 0.66 to

1.52. This range in the 95% confidence interval includes the possibility that the use of ICS in place of CS may prevent one asthma relapse for every 20 patient treated, or that it may *cause* one additional relapse for every 19 patients treated. Only one study contributed data to the 16-day outcome, with an OR for relapse of 1.26 (95% CI: 0.80 to 1.99). This corresponds to one extra relapse for every 24 patients treated with ICS instead of CS (95% confidence intervals: one extra relapse per eight people treated, to one less relapse for every 26 patients treated). Based on these wide confidence intervals for the primary analysis, equivalence cannot be claimed.

These studies also included only patients with relatively mild asthma, as evidenced by the inclusion criteria and relapse rates. One of the studies defined relapse as the failure of symptoms or peak flow to improve, a definition at variance with other studies included in this review. This definition would likely include less "severe" relapses, and it is not clear if this is an appropriate surrogate outcome for relapses resulting in an additional acute care visit(13). This was the largest study contributing to this outcome (403 of 684 total patients), and were its data not included, the range of uncertainty for the treatment effect would be much greater.

Several studies used absolute PEFR as the primary outcome. There was a small, statistically significant improvement in PEFR in the group treated with ICS at 20-24 days, with an improvement of 15 L/min compared with the CS treated group. The minimum difference in PFTs that is considered clinically significant has been infrequently studied in this setting. In the adult population, a minimum improvement of approximately 30 L/min in PEFR(30), or a 10-12% predicted rise in PEFR(31) is likely necessary to demonstrate a clinically important difference. The small improvement in

peak flow demonstrated here would be unlikely to be clinically important to patients, particularly in the absence of any other demonstrated benefits of ICS therapy. As well, there was no difference between the groups in percent predicted PEFR at the same time interval.

Other outcomes, including quality of life, asthma symptoms scores, and side effects were recorded and reported in diverse ways, with little information that was amenable to pooling. Many of the trials used new scales with questionable validity for measuring these outcomes(13;22;24;26). In addition, the information for several of the outcomes was reported incompletely, precluding the incorporation of these results in the meta-analyses.

In the conclusions for six of the seven trials, it was stated that ICS therapy may be substituted for CS therapy after an acute asthma attack, as there were no significant differences demonstrated between the treatments. Five of these trials (four of which were published in abstract form only) did not present a power calculation or mention the possibility of type II error in drawing these conclusions. Four of the trials based their conclusions on a lack of statistically significant differences in PFTs between the treatment groups. However, this may not be an appropriate outcome to use in assessing clinical equivalence. PFTs have not been shown to be responsive to treatment with corticosteroid agents in other systematic reviews in acute asthma (7;28;29;32), despite improvements in other clinical markers. The sixth trial presented a post-hoc sample size calculation that demonstrated that very large differences (200% relative difference in admission rates) would have been necessary to demonstrate a statistically significant difference between the treatments(23). The seventh trial concluded they were unable to

show important differences between the treatments, and did present an *a priori* sample size calculation. However, the investigators were unable to accrue the required number of patients in the trial and had a calculated power of only 57% to demonstrate a clinically significant difference in relapse rates(13).

It is not surprising that these studies, and a meta-analysis of them, failed to generate conclusive results, as the trials were relatively small. For asthma relapse, if baseline asthma relapse rates were 10%, to show a 50% reduction in the risk of relapse (5% absolute risk reduction), 621 patients would be required in each arm of a trial to demonstrate this difference with a power of 80% and alpha level of 5%. If the goal was to demonstrate a 25% relative risk reduction (2.5% absolute risk reduction), 2764 patients would be needed in each group (for a total sample size of 5528 patients).

While these studies provide some evidence that ICS therapy alone may be effective in patients with mild asthma exacerbations after ED discharge, there is insufficient evidence at this point to support the use of ICS, rather than CS, as the standard of care. Moreover, the cost differences between the two are also an important consideration (with an approximate cost of $0.10 per day for prednisone, versus $1-2 per day for inhaled steroids). If further trials in this area support a conclusion of equivalence between these therapies, there would need to be evidence of other compelling reasons to use ICS in place of CS therapy, such as side effect profile, symptom control, or compliance, which were not evident in this systematic review. As well, severe asthmatics were not included in these studies, so these results cannot be extrapolated to this population.

There is a possibility of publication bias in this meta-analysis. By missing unpublished negative trials, we may be over-estimating the effect of ICS therapy when used in addition to CS therapy, or we may be missing trials that would add more support to the conclusion that ICS are as efficacious as CS in mild asthmatics. However, a comprehensive search of the published literature was conducted, and attempts to uncover unpublished trials were made by corresponding with authors and the pharmaceutical companies that manufacture ICS. Five of the ten trials included in this review were unpublished; however, we recognise that more unpublished trials may exist.

There is also a possibility of selection bias. However, two independent reviewers selected studies for inclusion, and criteria for study inclusion and exclusion were explicitly specified. Finally, this is a rapidly evolving area, and it will be important to re-evaluate this topic area in near future.

Many questions remain unanswered regarding the use of ICS in the treatment of acute asthma after ED discharge. There is insufficient evidence that ICS therapy is beneficial when used in addition to standard CS therapy in this setting; further research involving severe asthmatics, high dose therapy, and gender subgroups appears warranted. There is some evidence that high dose ICS therapy may substitute for CS in mild asthma exacerbations upon ED discharge; there is no evidence for this practice in moderate or severe asthma exacerbations. As well, further research in this area should focus on clearly defined, clinically important outcomes, with clear, *a priori* definitions of equivalence, and adequate sample sizes to address these questions.

Table 3.1: Study populations

	Study ID	Location Year	Total Sample	Age Group	Initial Pulmonary Function: PEFR (mean) Absolute (L/min)	Initial Pulmonary Function: PEFR (mean) % predicted	Prior ICS use
ICS +CS vs CS	Brenner (12)	USA 1998	104	Adults	380	76.4 (after ED Rx)	Not within 1 week
	Camargo (20)	USA 2000	517	Adults	220	47 (initial)	Not within 4 weeks
	Rowe (11)	Canada 1999	188	Adults	390	50 (initial)	Not within 1 week
ICS alone vs CS alone	Bingham (22)	UK/South Africa/ Singapore 1999	321	Children (4-16yr)	175	NR	2% previously on ICS
	Fitzgerald (23)	Canada 2000	175	Adults	407	NR	Low dose only (35%)
	Francis (24)	UK 1999	56	Children (6mo-4yr)	NR	NR	No
	Levy (13)	UK 1996	513	Adults	NR	75	78% already on ICS
	Nana (25)	Thailand 1999	84	Adults	NR	FEV1 64%	35%
	Verona (26)	UK 1999	143	Children (3-15yr)	194	NR	<1% previously on ICS
	Volovitz (27)	Israel 1998	22	Children (6-16yr)	248	79	No

Note: NR=not reported, FEV1=forced expiratory volume in 1 second, PEFR=peak expiratory flow rate

Table 3.2: Study design

Protocol	Study	Type of ICS	ICS Regimen	Control Regimen	Reported Outcomes	Overall Conclusion	Jadad Quality Score
ICS +CS vs CS	Brenner (12)	Flunisolide by MDI with spacer	1 mg bid for 24 days and oral prednisone 40 mg/day for 5 days	Prednisone 40 mg/day for 5 days	Relapse, peak flow, symptoms, side effects, ß-agonist use	Not effective	5
	Camargo (20)	Fluticasone by diskhaler	250 ug bid for 20 days and oral prednisone 50 mg/day for 5 days	Prednisone 50 mg/day for 5 days	Relapse, ß-agonist use, mini AQLQ, symptoms, side effects	Not effective	5
	Rowe (11)	Budesonide by turbuhaler	800 ug bid for 21 days and oral prednisone 50 mg/day for 7 days	Prednisone 50mg/day for 7 days	Relapse, relapse to admission, AQLQ, ß-agonist use, symptoms, side effects	Effective	5
ICS alone vs CS alone	Bingham (22)	Fluticasone by nebuliser	1 mg bid for 7 days	Prednisolone 2 mg/kg/day for 4 days, then 1 mg/kg/day for 3 days	Absolute PEFR, symptom scores, ß-agonist use, clinical index	Equivalent to CS for pulmonary function tests	4
	Fitzgerald (23)	Budesonide by turbuhaler	600 ug qid for 7-10 days	Prednisone 40mg/day for 7 days	Relapse, PFTs, AQLQ, symptoms, side effects	Equivalent	5
	Francis (24)	Fluticasone by nebuliser	1 mg bid for 7 days	Prednisolone 2 mg/kg for 4 days then 1 mg/kg for 3 days	Symptoms, clinical index, ß-agonist use	Equivalent	4
	Levy (13)	Fluticasone by MDI with spacer	1 mg bid for 16 days	Prednisolone 40 mg/day tapering over 16 days	Relapse, treatment failure, side effects, symptoms	Not different	5
	Nana (25)	Budesonide by turbuhaler	1600 ug bid for 7 days	Prednisolone 40 mg/day tapered over 7 days	PFTs, relapse, symptoms, ß-agonist use, side effects	No difference	5
	Verona (26)	Fluticasone by MDI with spacer	500 ug big for 7 days	Prednisolone 2 mg/kg for 4 days, then 1 mg/kg for 3 days	PEFR, symptoms, ß-agonist use, clinical index	ICS better for PEFR, otherwise no difference	4
	Volovitz (27)	Budesonide by turbuhaler	1600 ug qid tapering over 24 days	Prednisolone 2mg/kg/day tapering over 8 days	PEFR, symptoms, side effects, relapse, ß-agonist use	ICS at least as effective as CS	5

Note: PEFR=peak expiratory flow rate, MDI=metered dose inhaler, AQLQ=asthma quality of life questionnaire, PFTs=pulmonary function tests

Figure 3.1 ICS + CS vs CS alone - analysis of relapses.

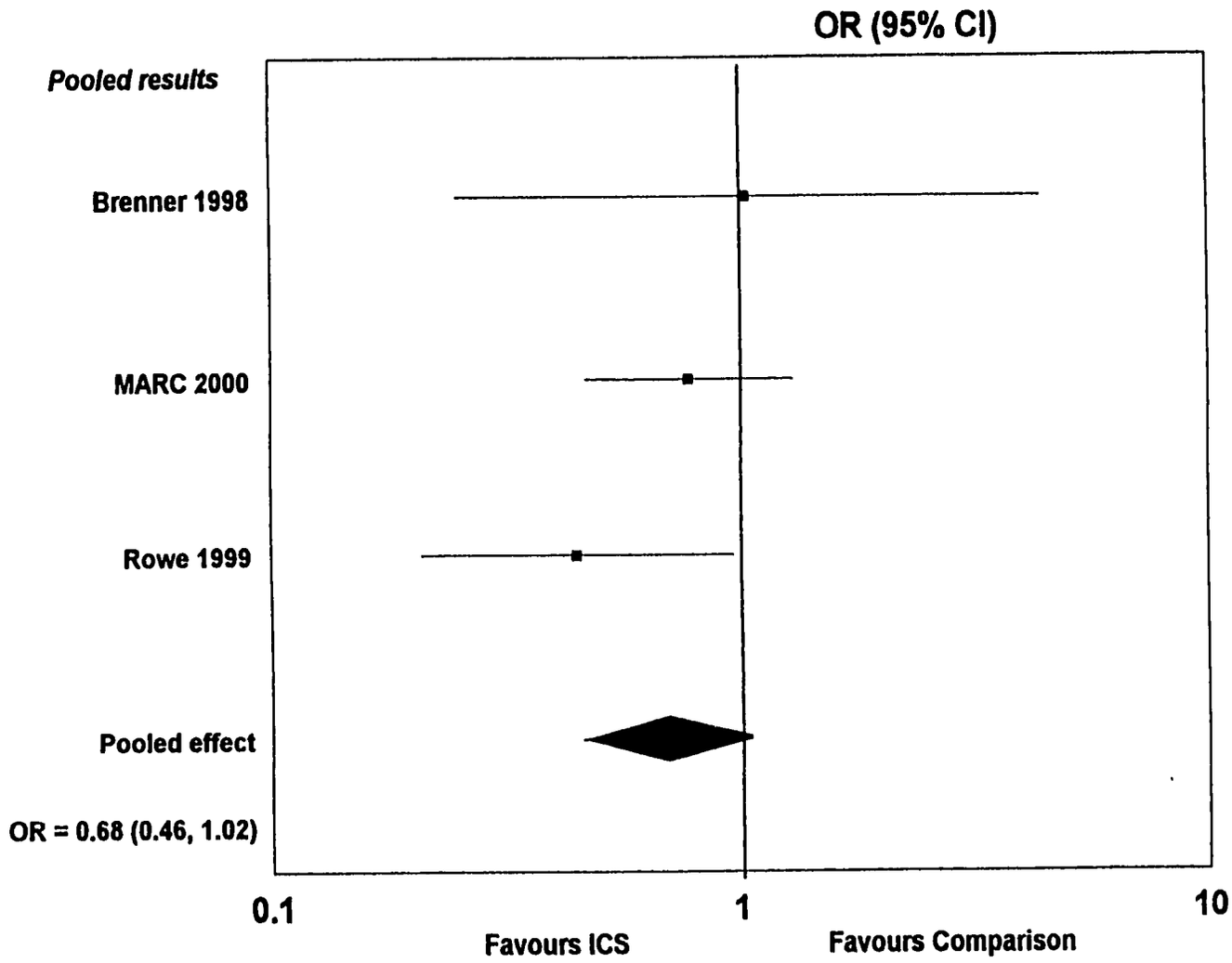
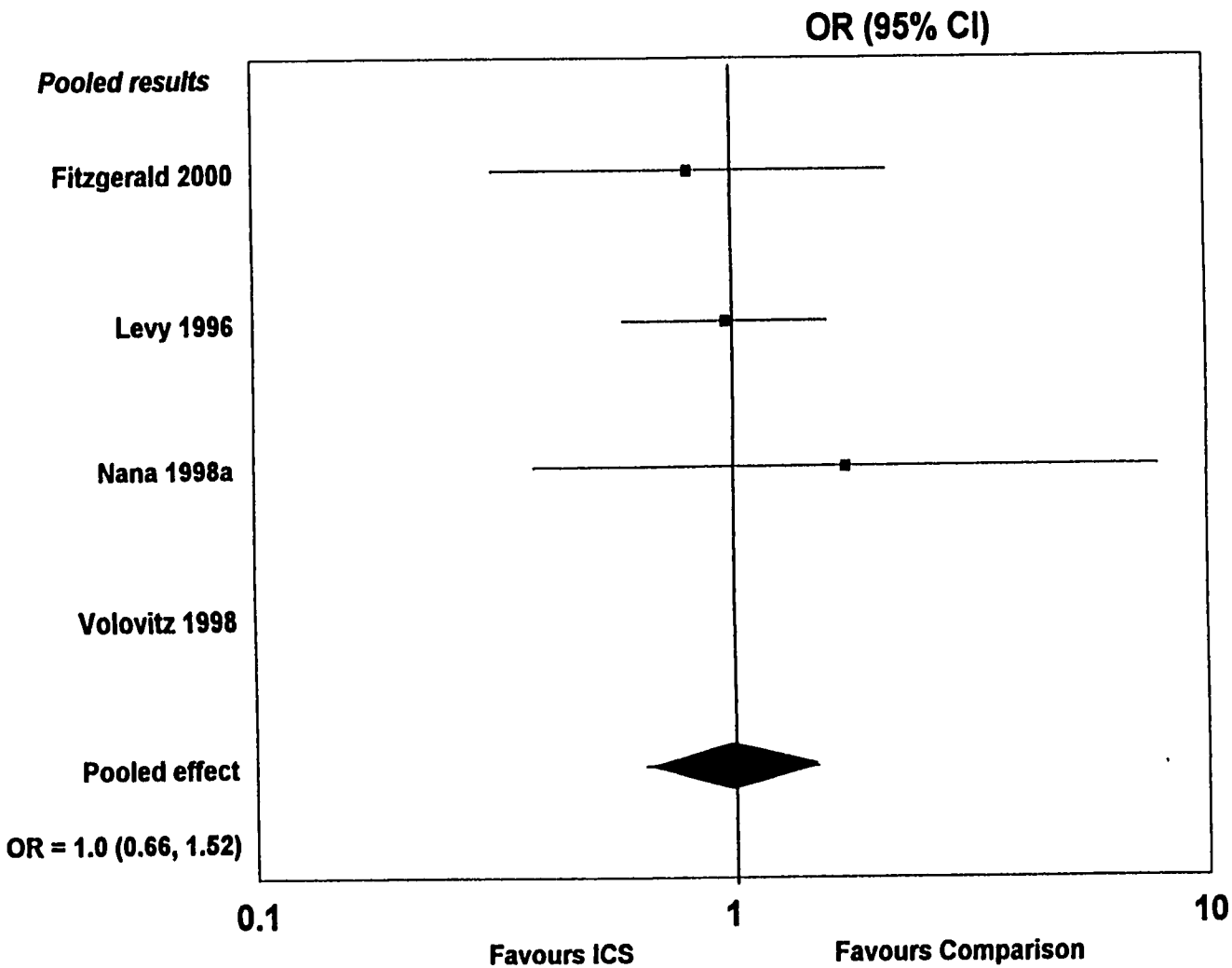


Figure 3.2 **ICS vs CS: analysis of relapses.**



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Chapter four

4.1 Introduction

Emergency physicians diagnose and treat patients with acute asthma on a frequent basis; despite extensive research and the presence of several consensus statements on the treatment of acute asthma, there remain many areas of controversy regarding the optimal management of these patients. One reason for this may be the type of research upon which decisions are made. For example, evidence commonly arises from small clinical trials, often underpowered to detect meaningful differences. Until recently, the paucity of published systematic reviews of the evidence limited the ability for consensus to develop.

Through systematic reviews, many treatments have now been shown to be effective (e.g. inhaled ß-agonists, corticosteroids, anticholinergics, magnesium), some have been found to be detrimental (e.g. aminophylline, intravenous ß-agonists), while still others have failed to show any important differences (e.g. heliox). Using accepted methods, this thesis examined the use of inhaled corticosteroids (ICS) in the emergency department (ED) management of acute asthma in the form of two meta-analyses: one on the use of ICS in the early ED treatment of acute asthma, and the second on the use of ICS after ED discharge.

Following these endeavours, there still remain unanswered questions about the use of ICS in the emergency department. However, the two reviews establish what is known about the use of ICS in this setting, and define areas where future research is needed. The overall conclusions and research implications of the two reviews will be discussed in turn.

4.2 The early emergency department use of ICS

The ten studies included in this review were all of high quality, and the main differences included the severity of asthma, the dose and type of ICS used, and the nature of the comparison therapy. The differences between the trials in the nature of the comparison therapy were not anticipated. Systemic corticosteroids (CS) are considered the standard of care for the management of acute asthma while in the ED; despite this, four of the ten trials did not administer CS to either the treatment or control groups. Perhaps more surprising, four trials compared ICS alone versus CS alone, despite lack of prior conclusive evidence from basic science research or phase I or II studies suggesting that it may be appropriate to substitute ICS for CS in this setting. It was decided that it was not appropriate to combine the studies comparing ICS versus placebo (either with CS in both groups, or in neither group) with those studies where ICS was compared versus CS, so two separate comparisons were performed in this review.

ICS versus placebo

In the comparison of ICS versus placebo, a strong, statistically significant benefit of CS therapy was demonstrated. Of the two subgroups included, only the subgroup comparing ICS versus placebo in the absence of systemic corticosteroids reached statistical significance. The subgroup comparing ICS plus CS versus CS alone showed a similar trend to benefit that did not reach statistical significance. Although it seems reasonable to combine these subgroups to generate an overall result, and there was no significant heterogeneity (either statistical or visual) between the results, whether most clinicians will consider this sufficient evidence to support the use of ICS in this setting is

unclear. If another small to moderate sized trial with similar results were performed in the subgroup comparing ICS versus placebo when CS are used in both treatment groups, the results would likely reach statistical significance, providing the clinician with more conclusive evidence for this practice. In any case, in the absence of demonstrated risks of ICS therapy in this review, it appears ICS therapy is safe and likely to be of some benefit.

Further research is necessary to determine if the effects of ICS differ in certain populations, particularly in those with mild versus moderate-severe exacerbations. One study included only patients poorly responsive to ß-agonist therapy and showed a marked benefit of ICS therapy(1); basic science evidence would further support this hypothesis(2;3). Subgroup analyses suggested that the effects were most pronounced in those with severe exacerbations; however, the subgroup comparisons were weak. As well, the optimal drug, dose, and frequency of administration remain unclear at this point in time.

ICS alone versus CS alone

The second comparison examined the use of ICS alone, in place of CS therapy. Only admission rates were examined, due to the disparity of other outcomes recorded and reported in these trials. There was marked heterogeneity in the results of the four trials; of concern, the largest trial found that ICS therapy was inferior to standard CS therapy. From the current evidence, it would appear that further clinical trials in this area are not warranted, unless further evidence suggests ICS therapy may in fact be superior to CS therapy in certain clinical settings. Several other small trials have been performed comparing ICS versus CS therapy in patients hospitalized for severe acute asthma(4-9); a

systematic review of these trials may provide further information, but in the absence of compelling reason to continue these comparisons, the ethics of conducting these trials in severely ill patients is questionable.

4.3 The use of ICS upon ED discharge

The ten studies included in this review were all high quality studies, and differences were again evident in the severity of asthma, the dose and type of ICS used, and the nature of the comparison therapy. Similar to the in-ED review, two separate comparisons were made; one of studies comparing ICS plus CS versus CS alone, and the second comparing ICS alone versus CS alone. There were trials comparing ICS alone versus placebo, with no CS therapy in either group; these studies were not included in the meta-analysis since CS therapy is already considered the standard of care in acute asthma after ED discharge.

ICS plus CS versus CS alone

Three studies compared ICS plus CS versus CS alone. Overall, there was no significant difference between the groups for the primary outcome (asthma relapse), although there was a trend toward benefit of ICS. All the studies included only adult patients with moderate to severe asthma exacerbations. All three used a fixed-dose course of oral prednisone; two used moderate-dose ICS while one used high-dose ICS. All three studies were high quality randomised controlled trials.

Although the overall result suggests there may not be a benefit to adding ICS therapy to the treatment for all asthmatics after emergency department discharge, there remain unanswered questions. There was heterogeneity among the study results for several of the secondary outcomes. The reasons for this heterogeneity were not clear; whether it was dues to differences in the populations, interventions, outcomes, or design of the trials, or to random chance, remains purely speculation following this review. The most evident reason may be the drug dose employed, as the trial using high-dose therapy found the most marked benefit of ICS. Further study on high-dose therapy, and severe asthmatics, may be warranted. As well, an individual patient data meta-analysis may help clarify where future research should be directed.

A pre-specified subgroup comparison by gender was performed; there was again heterogeneity between the study results. The largest trial found the presence of a significant gender difference in the response to ICS therapy, with a beneficial effect found only in males. This is consistent with a recently reported trial in chronic asthma, where males had a significantly greater benefit from ICS than females(10). Further research is needed to clarify this issue.

ICS alone versus CS alone

Seven trials were included in this comparison. Overall there were no significant differences found between the therapies, but caution is required in the interpretation of the results of the individual trials, and of the pooled result. All of these trials included only patients with mild asthma exacerbations, as seen in the low overall relapse rates, and the baseline pulmonary function test results or clinical scores. Very high-dose ICS was

employed in all of the trials, and the type of ICS used varied between the trials. None of the trials provide any support for the use of low or moderate dose ICS in this setting, or for the use of ICS alone in patients with more than mild asthma exacerbations.

The outcomes reported in the trials varied. The scales used to measure symptom scores, side effects, and quality-of-life varied between the trials, and some used categorical scales for these outcomes. Not only were the majority of the methods for measuring these outcomes not validated, but it also makes comparisons between trials difficult and precludes pooling in meta-analyses. Four trials reported asthma relapse rates; all had relatively low rates overall, decreasing the chances of finding a significant difference between the treatment groups. Although the overall results for asthma relapse were non-significant and the point estimates close to one, the confidence intervals were wide.

Despite the fact that the treatments appeared similar in the management of patients after discharge with very mild asthma, there is no evidence to support this practice in more severe asthma exacerbations. In the absence of basic science evidence to suggest that the use of ICS alone is likely to be significantly better than CS therapy, or evidence of significant harm of CS therapy, further investigations of this type are not warranted.

4.4 Implications for Research

Several areas have already been identified and discussed where the evidence for or against the use of ICS is inadequate. Some methodologic issues in the trials are common to both reviews (and to acute asthma research in general).

All of the trials included in the two reviews were double-blind, randomised controlled trials of high quality. However, there were several important differences between the trials that limit the ability of meta-analyses to draw strong conclusions. The most evident difference was the nature of the comparison therapy used in the various trials. There are several published trials comparing ICS therapy versus placebo, with no systemic corticosteroid use in either group, both in the ED treatment of acute asthma, and after discharge from the ED. These trials have all been recently performed and published, despite the fact that CS therapy has been accepted as an integral component of acute asthma therapy for several years already. The conduct of these trials exposes patients to increased risk of uncontrolled acute asthma, and the results do not add important information to our existing knowledge.

Several trials also compared ICS therapy alone versus CS therapy alone. Although the treatments appeared similar in very mild asthmatics after ED discharge, the possibility of one therapy being significantly worse was not excluded. Again, in the absence of evidence of significant harm of CS therapy, or basic science evidence to support this practice, further investigations of this type are not warranted.

A number of different ICS agents are currently available. Although it has been proposed that the various ICS are similar if used at equivalent doses, it is not clear if the different drugs are indeed interchangeable. Several methods of determining the potency

of inhaled steroids have been developed for chronic asthma, although this is an area of continuing controversy(11). The comparability of the various inhaled steroids in acute asthma is even less clear. A variety of delivery systems are available for drug administration in acute asthma; whether one is superior to the others is uncertain. Further research is necessary to clarify these issues.

The use of clearly defined outcomes, and standardization of which pulmonary function tests are used and reported, would be beneficial in reporting primary trials in acute asthma, and for the creation of meta-analyses. In addition, research is needed to examine which outcomes are most reliable and responsive in acute asthma research, and to define what constitutes a clinically significant difference in these outcomes. This is of particular importance for pulmonary function tests, where there is a paucity of evidence documenting either reliability or responsiveness in acute asthma research, despite routine use. Only recently has a trial been published investigating what amount of change in pulmonary function tests is clinically important in acute asthma, and this trial was small(12). For several other outcomes, such as symptoms and side effects, commonly used, validated scoring systems need to be developed and used. As well, the optimal length of follow-up, and timing of assessment of outcomes is not clear, although in many trials the length of follow-up was relatively short (3-4 hours for in-ED studies, or 7 days for outpatient studies), potentially decreasing the chance of finding significant differences between the treatment groups.

Although the overall quality of the trials included in this review was high, most were small trials, with the inherent susceptibility to baseline differences between the groups, and greater likelihood of type 2 errors, a common problem in trials of acute

asthma. Five of the seven trials comparing ICS therapy alone with CS therapy alone after ED discharge claimed equivalence of the two treatments, with no mention of sample size calculations or power. This is remarkable, considering the volume of literature published on equivalence trials(13;14) and the problems of small clinical trials in acute asthma(15;16). Although meta-analyses can assist in drawing further conclusions from small trials, the marked differences in the assessment of outcomes and length of follow-up limited the amount of data amenable to pooling. Future clinical trials in acute asthma need to be designed using clearly defined, clinically important outcomes, with a priori definitions of what will be considered a clinically important difference in these outcomes, and adequate sample sizes to detect these differences. Larger sample sizes would also make the trials less susceptible to baseline differences between the groups, which were evident in some of these trials.

4.5 Summary for Clinicians

Inhaled steroids may be beneficial in the emergency department treatment of acute asthma. Adding ICS to the standard therapies including CS, inhaled ß-agonists, and inhaled anti-cholinergics for patients with moderate to severe exacerbations may reduce hospital admission rates, without any evidence of harmful effects.

After discharge from the ED, compliance should be encouraged in patients already on ICS therapy, and an increase in dose of ICS should be considered for patients on low or moderate-dose therapy. In patients not already on ICS, many will meet criteria for adding ICS to their chronic asthma therapy(17;18), and ICS therapy can be initiated along with CS on discharge from the ED. In patients not on ICS who do not meet any criteria for ICS therapy, the risks, benefits, and costs of therapy should be discussed with the patient, and follow-up with the patient's own physician should be encouraged.

Some patients presenting with acute asthma to the ED will refuse or question the need for CS therapy. Substitution of ICS for CS while in the ED cannot be supported by these reviews; for patients who do not consent to CS therapy, the use of ICS alone will provide some benefit while in the ED. After discharge, patients with mild asthma exacerbations may be treated with ICS alone; however, the evidence that this is as efficacious as CS is incomplete. This finding cannot be generalized to patients with more severe asthma; this group should be treated with CS (with the addition of ICS in many cases) unless compelling reasons to avoid CS therapy are present, and close follow-up can be ensured.

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Appendix A

Protocols

Early use of inhaled corticosteroids in the emergency department treatment of acute asthma

and

Inhaled corticosteroids in acute asthma following emergency department discharge

Title: A systematic review of the efficacy of inhaled corticosteroids in the treatment of acute asthma: early emergency department treatment [protocol].

Authorship: Marcia L Edmonds, Carlos A Camargo, Jr., Charles V Pollack, Brian H Rowe.

Contact Person: Dr. Brian Rowe, University of Alberta Faculty of Medicine, 1G1.63 Walter Mackenzie Centre, 8440-112th Street, Edmonton, Alberta, CANADA T6G 2B7

BACKGROUND

Acute asthma is a common presenting complaint to the emergency department (ED). In the United States, acute asthma accounts for 1.5 to 2 million ED visits per year [1, 2]. Approximately 20% of these patients will require admission to the hospital, and, of those discharged from the ED after apparently successful treatment, approximately 10-20% will relapse within the subsequent two weeks [3]. The enormity of the asthma problem overall has led to the creation of several national [4-6] and international [7] asthma guidelines.

There is general agreement that bronchodilators (ß-agonists - e.g., salbutamol, albuterol) and anti-inflammatories (systemic corticosteroids - e.g., prednisone) are first-line agents for acute asthma. ß-agonists are used to provide rapid symptom relief, whereas corticosteroids are used to counter airway inflammation and hasten resolution of the asthma exacerbation. However, there remain numerous controversies on the optimal medication amount, dosing frequency, and route of delivery. Current practice patterns usually include the use of ß-agonists and oral or intravenous (IV) corticosteroids given early in the ED treatment of acute asthma [3]. However, the use of ICS are uncommon in the acute setting, and generally these agents are reserved for the patients who are discharged [8]. Given the practice variation with respect to inhaled corticosteroids (ICS) treatment in acute asthma care [3,8], it is realistic to assume that a systematic review in this area should provide direction for treatment or further research.

ICSs have the potential to be of benefit in the acute setting. They have been shown to be effective alternatives to oral steroids in long-term asthma therapy, where they can reduce or even eliminate oral corticosteroid requirements[9]. Potential advantages of inhaled corticosteroids in acute asthma therapy might include their reduced systemic side effects, direct delivery to the airways, and a greater efficacy in reducing airway reactivity and edema either alone or in addition to systemic corticosteroids [10]. Furthermore, ancillary evidence from non-asthma studies suggests that ICS agents may act over the short term to improve outcomes [11].

To date, several small trials have examined the use of ICSs in acute asthma and they have yielded inconsistent results; however, systematic literature searching and meta-analytic techniques are required prior to the generation of firm conclusions or recommendations. We are not aware of a published systematic review on the role of inhaled steroids in the treatment of acute asthma in the ED.

OBJECTIVE

The objective of this review is to determine the effect of early ICS therapy on outcomes in the ED treatment for acute asthma.

Specific Aims
To quantify the effect of single or multiple dose ICS therapy in the ED treatment of acute asthma, when used in addition to standard therapies. The specific outcomes will include the effect of ICS therapy on:

(1) pulmonary function tests (PFTs) such as peak expiratory flow rates, absolute (PEFR) and % predicted (% pred PEFR); forced expiratory volume in 1 second (FEV-1 and % predicted FEV-1);
(2) hospital data (e.g., discharge/admission rate, subsequent relapse, intubation rate, etc);
(3) adverse effects;
(4) vital signs.

CRITERIA FOR STUDY SELECTION

Study Design
To be considered, clinical studies must be randomised controlled trials.

Types of Participants
Studies including only patients presenting to an ED or its equivalent will be considered for inclusion in the systematic review. If patients from other settings can be removed easily from the study (for example if stratified randomisation was employed) the data may also be used. Studies recruiting paediatric or adult participants will be reviewed, although this designation will form one of the subgroup analyses.

Types of Interventions
Patients must be randomised to receive either single or multiple dose inhaled corticosteroids early in the ED treatment. "Inhaled corticosteroids " administration will be defined as any corticosteroid agent administered by MDI or nebulizer in the ED. Asthmatic patients also may receive additional asthma medications (such as IV/PO/IM corticosteroids, oral/intravenous/subcutaneous beta-agonists, ipratropium bromide, theophylline compounds, magnesium sulfate, or anti-histamines) but selected studies must report these co-interventions.

Types of Outcomes
All patient outcomes will be considered, however the primary outcome will be admission to hospital. Pulmonary function tests, any report of adverse side effects, and other physiologic outcomes (e.g., pulse rate, respiratory rate, arterial oxygen saturation, blood pressure, arterial pH, etc.) will also be examined. Attempts will be made to contact study primary investigators to determine their willingness to provide additional data. Intention-to-treat analyses will be calculated.

SEARCH STRATEGY FOR IDENTIFICATION OF TRIALS

The Cochrane Airways Group has developed an "Asthma and Wheez* RCT" register through a comprehensive search of EMBASE, MEDLINE, and CINAHL. In addition, hand searching of the top 20 respiratory care journals has been completed, and trials have been added to the register. Randomised controlled trials are identified in the register using the following search strategy: (placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study).

Search of this register will be completed using the following terms:

a) Emerg* OR acute OR status AND
b) dexa* OR deca* OR fluticasone OR Flovent OR beclomethasone OR Becloforte OR budesonide OR Pulmicort OR flunisolide OR Aerobid OR Bronalide OR triamcinalone OR Beclovent OR Azmacort OR Vanceril OR Becotide OR Flixotide OR Aerobec

Additional efforts to locate potential trials will be as follows:

Reference lists of all available primary studies and review articles will be reviewed to identify potentially relevant citations.

Inquiries will be made regarding other published or unpublished trials known or supported by the authors of the primary studies so that these results may be included in this review.

The scientific advisors of the various pharmaceutical industries that manufacture known ICS agents (ASTRA: budesonide; GLAXO Wellcome: fluticasone, beclomethasone; Forest: flunisolide; etc.) will be contacted for any unpublished, or interim results on relevant research.

An advanced search of the Cochrane Controlled Trials Register (CCTR) will be completed using the above search strategy. On the 1998, V3 CL, the CCTR contained over 191,000 CCTs.

Personal contact with colleagues, collaborators and other trialists working in the field of asthma will be made to identify potentially relevant studies.

METHODS OF THE REVIEW

In Step I, on the basis of a search of Title, Abstract and Key Words/MESH Headings, two reviewers (CAC, BHR) will independently examine the output generated from the computer search. Any potentially relevant articles will be obtained.

In Step II, from the full text of potentially relevant articles, the same reviewers will assess each study in terms of: population, intervention, outcome, and study design. Agreement on relevance and inclusion will be measured separately using simple agreement and kappa statistics. Disagreement will be resolved by consensus or third party adjudication.

Methodological quality assessment will be performed using two methods and independently by two reviewers (CVP, CAC). First, using the Cochrane approach to assessment of allocation concealment, all trials will be scored and entered using the following principles:

Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment

In addition, each study will be assessed using the 0 to 5 scale described by Jadad [11] and summarised as follows:

1) Was the study described as randomised? (1=yes; 0=no)
2) Was the study described as double-blind? (1=yes; 0=no)
3) Was there a description of withdrawals and dropouts? (1=yes; 0=no)
4) Was the method of randomisation well described and appropriate? (1=yes; 0=no)
5) Was the method of double blinding well described and appropriate? (1=yes; 0=no)
6) Deduct 1 point if methods for randomisation or blinding were inappropriate.

Inter-observer reliability will be measured for both quality scales by using simple agreement, kappa, and weighted kappa statistics.

In Step III, data from included trials will be extracted independently by two reviewers (MLE, BHR) and entered into the Cochrane Collaboration software program (Review Manager, V 3.0).

STATISTICAL CONSIDERATIONS

Trials will be combined using the Review Manager (Version 3.0). For continuous variables, a random effects weighted mean difference (WMD) or standardised mean difference (SMD) and 95% confidence interval (CI) will be calculated for each study. All similar studies will be pooled using random effects WMD and 95% CIs. For dichotomous variables, a random effects odds ratio (OR) with 95% confidence intervals (95% CI) will be calculated for individual studies. All similar studies will be pooled using random effects OR and 95% CIs. For pooled effects, heterogeneity will be tested using the Breslow-Day test; $p < 0.05$ will be considered statistically significant.

If significant heterogeneity exists, the groups will be divided on the following manner:

a) Population: pediatric vs adult

b) Population: severity of asthma (as measured by peak expiratory flow rate < 40% predicted vs. ≥ 40% predicted, by peak expiratory flow rate < 50% predicted vs. ≥ 50% predicted and by the admission rate);

In addition, sensitivity analyses will be performed using the following domains:

a) Methodological quality: papers with Jadad criteria 3-5 vs. <3; Cochrane Collaboration criteria: A vs. B or C
b) Random effects vs. fixed effects modelling
c) Intervention: dose comparisons (high vs. low); high dose will include 2 mg or more of BDP equivalent.

Comparisons will include:

Comparison 1.0: any ICS vs. placebo therapy

Outcome: **Admission Rate**
Subgroups:
1) Pediatric vs. Adult
2) Severity

Outcome: **PFTs**
Subgroups:
1) Pediatric vs. Adult
2) Severity

Outcome: **Symptoms**
Subgroups:
1) Pediatric vs. Adult
2) Severity

Outcome: **Adverse Effects**
Subgroups:
1) Pediatric vs. Adult
2) Severity

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Title: A systematic review of the efficacy of inhaled corticosteroids in the treatment of acute asthma: treatment following emergency department discharge.

Authors:
Marcia L Edmonds, Carlos A Camargo, Jr., Barry E Brenner, Brian H Rowe.

Contact Person:
Dr. Brian Rowe, Division of Emergency Medicine, University of Alberta Faculty of Medicine and Oral Health Sciences, 1G1.63 Walter Mackenzie Centre, 8440-112th Street, Edmonton, Alberta, CANADA T6G 2B7

BACKGROUND

Acute asthma is a common presenting complaint to the emergency department (ED). In the United States, acute asthma accounts for nearly 2 million ED visits per year [1, 2]. Approximately 15-25% of these patients will require admission to the hospital, and, of those discharged from the ED after apparently successful treatment, approximately 10-20% will relapse within the subsequent two weeks [3]. The enormity of the asthma problem overall has led to the creation of several national [4-6] and international [7] asthma guidelines.

There is general agreement that bronchodilators (ß-agonists - e.g., salbutamol, albuterol) and anti-inflammatories (systemic corticosteroids - e.g., prednisone) are first-line agents for acute asthma. ß-agonists are used to provide rapid symptom relief, whereas corticosteroids are used to counter airway inflammation and hasten resolution of the asthma exacerbation. However, there remain numerous controversies on the optimal dose, frequency, and route of delivery of these medications.

Current practice for patients discharged after assessment and treatment in the ED usually include the use of ß-agonists and oral corticosteroids prescribed for 5-14 days after discharge in a majority of cases [3]. While oral corticosteroids may be prescribed as fixed-dose treatments [8], complicated tapering regimens also have been described. The use of inhaled corticosteroids (ICS) is uncommon and inconsistent in the management of acute asthma after discharge. For example, in Canadian EDs, use is as high as 69% at discharge, whereas in US centers use is lower (<15%) [9]. When ICSs are prescribed, they may either be used with [9,10,11] or as a replacement for oral corticosteroids [12]. Given the practice variation with respect to ICS treatment in acute asthma care [3,9], it is realistic to assume that a systematic review in this area should provide direction for treatment or further research.

ICSs have the potential to be of benefit in the acute setting. They have been shown to be effective alternatives to oral steroids in long-term asthma therapy, where they can reduce or even eliminate oral corticosteroid requirements [13]. Potential advantages of ICSs in acute asthma therapy might include their reduced systemic side effects, direct delivery to the airways, and a greater efficacy in reducing airway reactivity and edema either alone or in addition to systemic corticosteroids [14]. Furthermore, ancillary evidence from non-

asthma studies suggests that ICS agents may act over the short term to improve outcomes [15].

Several recent trials have examined the use of ICSs in acute asthma upon emergency department discharge and they have yielded conflicting results [10,11,12]; however, systematic literature searching and meta-analytic techniques are required prior to the generation of firm conclusions or recommendations. We are not aware of a published systematic review on the role of ICS in the treatment of acute asthma following discharge from the ED.

OBJECTIVE

The objective of this review is to determine the effect of ICS therapy on outcomes in the treatment of acute asthma following discharge from the ED.

Specific Aims

To quantify the effect of ICS therapy on acute asthma following ED discharge, when used in addition to, or in place of, oral corticosteroids. The specific outcomes will include the effect of ICS therapy on:

relapse rates (repeat "urgent" asthma care)
hospital admission rates
beta-agonist use

CRITERIA FOR STUDY SELECTION

Study Design

To be considered, clinical studies must be randomised controlled trials.

Types of Participants

Studies including only patients discharged from an ED or its equivalent following assessment and treatment for acute asthma will be considered for inclusion in this systematic review. If patients from other settings can be removed easily from the study (for example if stratified randomisation was employed) the data may also be used. Studies recruiting paediatric or adult participants will be reviewed, although this designation will form one of the subgroup analyses.

Types of Interventions

Patients must be randomised to receive inhaled corticosteroid treatment upon discharge from ED. "Inhaled corticosteroids " administration will be defined as any corticosteroid agent administered by MDI or nebulizer after ED discharge. Asthmatic patients also may receive additional asthma medications (such as PO/IM corticosteroids, beta-agonists, ipratropium bromide, theophylline compounds, antibiotics, or anti-histamines) but selected studies must report these co-interventions.

In this systematic review, the treatment groups will either employ ICS combined with oral corticosteroids (ICS + oral CS vs. oral CS) or ICS alone (ICS vs. oral CS). In

both study types, the above co-interventions are expected to be provided to study patients similarly in both groups.

Types of Outcomes

All patient outcomes will be considered, however the primary outcome will be asthma relapse (an unscheduled visit for worsening asthma). The most important secondary outcome will be asthma specific quality-of-life. Finally, relapse to hospitalization, beta-agonist use, any report of adverse side effects, pulmonary function tests, and symptoms will also be considered. Attempts will be made to contact study primary investigators to determine their willingness to provide additional data. Intention-to-treat analyses will be calculated.

SEARCH STRATEGY FOR IDENTIFICATION OF TRIALS

The Cochrane Airways Group has developed an "Asthma and Wheez* RCT" register through a comprehensive search of EMBASE, MEDLINE, and CINAHL. In addition, hand searching of the top 20 respiratory care journals has been completed, and trials have been added to the register. Randomised controlled trials are identified in the register using the following search strategy: (placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study).

Search of this register will be completed using the following terms:

a) Emerg* OR acute OR status AND
b) dexa* OR deca* OR fluticasone OR Flovent OR beclomethasone OR Becloforte OR budesonide OR Pulmicort OR flunisolide OR Aerobid OR Bronalide OR triamcinalone OR Beclovent OR Azmacort OR Vanceril OR Becotide OR flixotide OR Aerobec

Additional efforts to locate potential trials will be as follows:

Reference lists of all available primary studies and review articles will be reviewed to identify potentially relevant citations.

Inquiries will be made regarding other published or unpublished trials known or supported by the authors of the primary studies so that these results may be included in this review.

The scientific advisors of the various pharmaceutical industries that manufacture known ICS agents (ASTRA: budesonide; GLAXO Wellcome: fluticasone, beclomethasone; FOREST: flunisolide; etc.) will be contacted for any unpublished, or interim results on relevant research.

An advanced search of the Cochrane Controlled Trials Register (CCTR) will be completed using the above search strategy. On the 1998, V3 CL, the CCTR contains over 191,000 CCTs.

Personal contact with colleagues, collaborators and other trialists working in the field of asthma will be made to identify potentially relevant studies.

Finally, since many of these trials may be unpublished, abstracts from the last five years of the Society for Academic Emergency Medicine (published in *Acad Emerg Med*), the American College of Chest Physicians (published in *Chest*) and the American Thoracic Society (published in *Am J Respir Crit Care Med*) meetings will be hand searched.

METHODS OF THE REVIEW

In Step I, on the basis of a search of Title, Abstract and Key Words/MESH Headings, two reviewers (MLE, BHR) will independently examine the output generated from the computer search. Any potentially relevant articles will be obtained.

In Step II, from the full text of potentially relevant articles, the same reviewers will assess each study in terms of: population, intervention, outcome, and study design. Agreement on relevance and inclusion will be measured separately using simple agreement and kappa statistics. Disagreement will be resolved by consensus or third party adjudication.

Methodological quality assessment will be performed using two methods and independently by two reviewers (MLE, CAC). First, using the Cochrane approach to assessment of allocation concealment, all trials will be scored and entered using the following principles:

Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment

In addition, each study will be assessed using the 0 to 5 scale described by Jadad et al. [16] and summarised as follows:

1) Was the study described as randomised? (1=yes; 0=no)
2) Was the study described as double-blind? (1=yes; 0=no)
3) Was there a description of withdrawals and dropouts? (1=yes; 0=no)
4) Was the method of randomisation well described and appropriate? (1=yes; =no)
5) Was the method of double blinding well described and appropriate? (1=yes; 0=no)
6) Deduct 1 point if methods for randomisation or blinding were inappropriate.

Inter-observer reliability will be measured for both quality scales by using simple agreement, kappa, and weighted kappa statistics.

In Step III, data from included trials will be extracted independently by two reviewers (MLE, BHR) and entered into the Cochrane Collaboration software program (Review Manager, V 3.0).

STATISTICAL CONSIDERATIONS

Trials will be combined using the Review Manager (Version 3.0). For continuous variables, a random effects weighted mean difference (WMD) or standardised mean difference (SMD) and 95% confidence interval (CI) will be calculated for each study. All similar studies will be pooled using random effects WMD and 95% CIs. For dichotomous variables, a random effects odds ratio (OR) with 95% confidence intervals (95% CI) will be calculated for individual studies. All similar studies will be pooled using random effects OR and 95% CIs. For pooled effects, heterogeneity will be tested using the Breslow-Day test; $p < 0.05$ will be considered statistically significant.

If significant heterogeneity exists, the groups will be divided on the following manner:

a) Population: paediatric vs. adult
b) Gender: male vs female response
c) Population: severity of asthma (as measured by initial peak expiratory flow rate < 40% predicted vs. ≥ 40% predicted, PEFR < 50% predicted vs. ≥ 50% predicted, and by the admission rate).

In addition, sensitivity analyses will be performed using the following domains:

a) Methodological quality: papers with Jadad criteria 3-5 vs. <3; Cochrane Collaboration criteria: A vs. B or C
b) Random effects vs. fixed effects modeling
c) Intervention: dose comparisons (high vs. low); high dose will include 2 mg or more of beclomethasone dipropionate (BDP) equivalent.

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3. Camargo CA Jr. Management of acute asthma in US Emergency departments: The Multicentre Asthma Research Collaboration [abstract]. Am J Respir Crit Care Med 1998; 157 (3 part 2):A623.
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14. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. Am J Respir Crit Care Med 1998;157:698-703.
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Appendix B

Data extraction forms

DATA FORM FOR INHALED STEROIDS IN THE ED LITERATURE

A1. STUDY ID..... REVIEWER.....

A2. COUNTRY..... YEAR.....

METHODS AND DESIGN

B1. POPULATION

	Number	Age (range)	Age (mean)	Age (SD)	Sex	Severity
Treatment						
Control						
Total						

B2. INCLUSION CRITERIA **EXCLUSION CRITERIA**

B3. BLINDING

[ ] Both [ ] Patients [ ] Neither / Not Stated

B4. PATIENT MAKE-UP

[ ] Consecutive patients
[ ] Random sample
[ ] Convenience Sample (by day of week, time, etc.)
[ ] Other (volunteers)
[ ] Unknown

B5. CONCEALMENT OF ALLOCATION

[ ] Adequate [ ] Unclear [ ] Inadequate [ ] Not used

B6. PRIOR ICS USED: [ ] YES [ ] NO _____%

B6. METHODOLOGICAL ASSESSMENT

1.	Was the study described as randomised?	[ ] Yes	[ ] No
2.	Was the study described as double-blind?	[ ] Yes	[ ] No
3.	Was there a description of withdrawals and dropouts?	[ ] Yes	[ ] No
4.	Was the method of randomisation well described and appropriate?	[ ] Yes	[ ] No
5.	Was the method of double blinding well described and appropriate?	[ ] Yes	[ ] No
6.	Deduct 1 point each if methods for randomisation or blinding were inappropriate		
		Deduct [ ] 1 point	[ ] 2 points

Total score: 1 point for each "Yes" answer **TOTAL:** _____

B6. DEFINITION OF SEVERITY: (describe)

INTERVENTIONS

C1. INTERVENTIONS

MEDICATION	ROUTE	DOSE	DURATION	NOTES
(a) Study Med:_____				
(b) Control:_____				

C2. COINTERVENTIONS

	ROUTE	DOSE	DURATION	NOTES
(a) Beta-agonists				
(b) Systemic steroids				
(c) Other	i)			
	ii)			
	iii)			

OUTCOMES

D1. ASSESSMENT OF OUTCOME (describe)

Definition of Admission: (describe)

PFTs:

SaO2:

Response:

Other:

D2. Outcomes.

Outcomes	Presentation		T1=		T2=	
	Rx	Plac	Rx	Plac	Rx	Plac
PFTs: 1. 2.						
Vitals HR RR BP O2 sat						
Symptom or clinical score						
Side effects 1. 2. 3.						
Admission # / n						
Other						

D2 Outcomes (continued)

Outcomes	T3=		T4=		T5=	
	Rx	Plac	Rx	Plac	Rx	Plac
PFTs: 1. 2.						
Vitals HR RR BP O2 sat						
Symptom or Clinical score						
Side effects 1. 2. 3.						
Admission # / N						
Other						

DATA FORM FOR INHALED STEROIDS UPON ED DISCHARGE

A1. STUDY ID..... REVIEWER.....

A2. COUNTRY..... YEAR.....

B. POPULATION AND DESIGN

B1. POPULATION

	Number	Age (range)	Age (mean)	Age (SD)	Sex	Severity
Treatment						
Control						
Total						

B2. INCLUSION CRITERIA	EXCLUSION CRITERIA

B3. BLINDING

[ ] Both
[ ] Patients
[ ] Neither / Not Stated

B4. PATIENT MAKE-UP

[ ] Consecutive patients
[ ] Random sample
[ ] Convenience Sample (by day of week, time, etc.)
[ ] Other (volunteers)
[ ] Unknown

B5. PRIOR ICS USED: [ ] YES [ ] NO _____%

B6. CONCEALMENT OF ALLOCATION

[ ] Adequate
[ ] Unclear
[ ] Inadequate
[ ] Not used

B7. METHODOLOGICAL ASSESSMENT

1. Was the study described as randomised? [ ] Yes [ ] No
2. Was the study described as double-blind? [ ] Yes [ ] No
3. Was there a description of withdrawals and dropouts? [ ] Yes [ ] No
4. Was the method of randomisation well described and appropriate? [ ] Yes [ ] No
5. Was the method of double blinding well described and appropriate? [ ] Yes [ ] No
6. Deduct 1 point each if the methods for randomisation or blinding were inappropriate **Deduct** [ ]1 point [ ] 2 points

Total score: 1 point for each "Yes" answer **Total:** _____

B8. DEFINITION OF SEVERITY:

C. INTERVENTION
C1. INTERVENTIONS

MEDICATION	ROUTE	DOSE	DURATION	NOTES
(a) Study Med.				
(b) Control				

C2. COINTERVENTIONS

	ROUTE	DOSE	DURATION	NOTES
(a) Systemic steroids				
(b) Beta agonists				
(c) Other	i)			
	ii)			
	iii)			

D. OUTCOMES

D1. RELAPSE DEFINITION—DESCRIBE:

D2. ASSESSMENT OF OUTCOME

Outcome	**Presentation/ Randomization**		**T1=**		**T2=**		**T3=**		**T4=**	
	Rx	Control	Rx	Control	Rx	Control	Rx	Control	Rx	Control
Relapse to additional care # / N										
Relapse to Admission # / N										
PFTs 1. **2.** **3.**										

Outcome	Presentation/ Randomisation		T1=		T2=		T3=		T4=	
	Rx	Control	Rx	Control	Rx	Control	Rx	Control	Rx	Control
Puffer use										
Quality of life										
Symptoms										
Other										

D4. COMPLIANCE MEASURED [ ] YES [ ] NO

D5. COMPLIANCE MEASUREMENT

[ ] Clearly defined and can be replicated by the reader in his/her own setting
[ ] Vague definition
[ ] No definition

Appendix C

Letter to Author

January 21, 1999.

Dear Dr.

RE: Inhaled corticosteroid use in acute asthma: A systematic review of the literature.

The Cochrane Collaboration of Systematic Reviews is a multi-disciplinary, collaborative volunteer organization whose mandate is to produce and disseminate overviews on a variety of medical topics. Within the Collaboration, the Airways Review Group is responsible for the production of overviews in the fields of asthma, bronchiectasis, COPD, and sleep apnea. Members of our group are currently involved in nearly 90 reviews covering a wide range of "airway" topics. Our central offices are housed at the St. George's Hospital Medical School in London, England.

We are in the process of completing a meta-analysis on the effect of inhaled corticosteroid (ICS) use in the treatment of patients with an acute exacerbation of asthma seen in the emergency department. We are specifically interested in randomized controlled trials where inhaled corticosteroids are used early in the ED treatment of asthma, and ICS is compared to placebo or systemic corticosteroids. This meta-analysis will include studies on both adult and paediatric patients.

Your work, entitled;

has been selected for inclusion in our meta-analysis. The research collaborators have also independently selected the articles shown on the accompanying sheet for inclusion. We are writing to you for several reasons. First, we wonder if you could provide additional references for published or unpublished research which might deserve inclusion in this overview. Secondly, as part of the Cochrane Collaboration methodology, we are interested in having the authors of included studies provide us with feedback on the data extracted from their article. As you can imagine, valid and reliable data extraction is necessary for the final version of the overview, which will be available on the Cochrane Library CD-ROM and disks. The responses we receive from authors will be acknowledged in the final "comments" section for every included study.

We look forward to hearing from you. Would you be so kind as to complete the following form and FAX it back to us as soon as it is convenient with you? Thank you in advance for your attention to these matters.

Yours sincerely,

Marcia Edmonds, MD
Division of Emergency Medicine
MSc Candidate

Brian H. Rowe, MD, MSc, CCFP(EM)
Research Director, Emergency Medicine
Associate Professor, University of Alberta
Co-Editor, Airways Review Group

Inhaled Steroids in the ED—Meta-Analysis

Name: Dr.
Study:

A. Are you aware of any additional studies that relate to the above mentioned papers?

☐YES ☐NO

If yes, please list:

1.

2.

3.

4.

B. Would you be able to provide feedback with respect to data extracted from your article?

☐ Yes, please contact me at this fax number: _____.

☐ No, however, _____ would be able to provide this service to your research team. He/she can be contacted at the following address and/or fax number:

☐ No, I would not be able to provide feedback to you.

The following articles have been included in the meta-analysis:

Guttman A, et al. The Effects of Combined Intravenous and Inhaled Steroids (Beclomethasone Dipropionate) for the Emergency Treatment of Acute Asthma. Acad Emerg Med 1997;4:100-106.

Pansegrouw DF. Acute resistant asthma caused by excessive beta-2-adrenoceptor agonist inhalation and reversed by inhalation of beclomethasone. S Afr Med J 1992;82:179-182.

Rodrigo G, Rodrigo C. Inhaled Flunisolide for Acute Severe Asthma. Am J Respir Crit Care Med 1998;157:698-703.

Scarfone RJ et al. Nebulized Dexamethasone Versus Oral Prednisone in the Emergency Treatment of Asthmatic Children. Ann Emerg Med 1995;26;480-486.

Sung L, Osmond MH, Klassen TP. Randomized, Controlled Trial of Inhaled Budesonide as an Adjunct to Oral Prednisone in Acute Asthma. Acad Emerg Med 1998;5:209-213.

The following articles have been excluded from the meta-analysis:

Joubert JR, Burger G, Shephard E. Inhalation therapy during acute asthma. The role of a combined steroid and beta-stimulant preparation. S Afr Med J 1985;68:381-384.

Morice AH, Morris D, Lawon-Matthew P. A comparison of nebulized budesonide with oral prednisolone in the treatment of exacerbations of obstructive pulmonary disease. Clin Pharmacol Ther 1996;60:675-8.

Singhi S. Steroids in Acute Asthma: Oral or Nebulized? Indian Pediatrics 1996;33:262-3.