Respiratory Medicine (2004) **98**, 275–284

respiratoryMEDICINE

Corticosteroid therapy for acute asthma

B.H. Rowe[a,b,*], M.L. Edmonds[a,b], C.H. Spooner[a], B. Diner[c], C.A. Camargo, Jr.[d,e]

[a]*Division Emergency Medicine, University of Alberta, 1G1.43 Walter Mackenzie Centre, 8440-112 Street, Edmonton, Alberta, Canada T6G 2B7*
[b]*Capital Health Authority, Edmonton, Alberta, Canada*
[c]*Department of Emergency Medicine, Emory University Hospital, Atlanta, GA, USA*
[d]*Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA*
[e]*Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

Received 24 October 2002; accepted 15 November 2003

KEYWORDS
Asthma;
Inhaled corticosteroids;
Relapse;
Admission

Summary Asthma is a chronic inflammatory disease, which is characterised by reversible airflow obstruction in response to a variety of stimuli. Exacerbations in response to airway irritants are part of the natural history of asthma, but often they also represent a failure in chronic treatment. Presentations to emergency departments and other acute care settings are common and frequently lead to hospitalisation and other complications. After treatment, however, most patients are discharged to the care of their primary care physician for further management. This review highlights the role of systemic and inhaled corticosteroids as mainstays of treatment in the acute and sub-acute phase of an exacerbation. These agents form the basis of most current clinical practice guidelines, yet their use is not universal. We will review the evidence for the use of these agents that arises from the Cochrane Collaboration of Systematic Reviews contained in the Cochrane Library.

Introduction to acute asthma

Asthma is an important healthcare problem worldwide. Over 27 million people in the USA have at some time received a diagnosis of asthma, and the attack prevalence (those experiencing an emergency department visit for an exacerbation in the past year) is about 1.8 million.[1] Although asthma affects more children than adults, the burden of illness is high in both groups, and the costs associated with asthma are staggering. In 1998, the indirect and direct expenditures for asthma exceeded 12 billion dollars in the USA.[2] In Canada, the cost reached $600 million; 25% of these costs were expended on acute care of asthma (emergency department visits and hospitalisation).[3] Emergency department visits are estimated to cost $324 (Canadian dollars) a visit and more than twice that amount a day for hospitalisation.[2]

Emergency department presentations are precipitated by many factors, but the most common reasons include a superimposed upper respiratory tract infection, environmental allergens or poor control of chronic asthma. Emergency visits are important events for asthmatics and families, as they represent a vulnerable point in the illness and

*Corresponding author. Division of Emergency Medicine, University of Alberta, 1G1.43 Walter Mackenzie Centre, 8440-112 Street, Edmonton, Alberta, Canada T6G 2B7. Tel.: +780-407-6707; fax: +-780-407-3314.
E-mail address: brian.rowe@ualberta.ca (B.H. Rowe).

0954-6111/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2003.11.016

are associated with significant morbidity, patient and parent apprehension and occasional mortality. For these reasons, the assessment and treatment of acute asthma has been the focus of considerable research and efforts to develop clinical practice guidelines.[4,5] Despite the many national attempts to standardise and improve asthma care, wide gaps still remain between what is known to be effective treatment and what is practised.[6] The discrepancy can be attributed mainly to physician variation in asthma diagnosis and lack of clarity in treatment options for this common disorder. This review outlines the role of airway inflammation in the presentation of acute asthma and the effect of corticosteroids (both inhaled and systemic) in successful treatment.[7]

Cochrane Airway Group reviews

Selecting the most effective treatment of acute asthma has been the subject of considerable study; nevertheless, unlike other areas of cardio-respiratory care, many of the studies are small and the evidence conflicting. This paper attempts to summarise research results on the main anti-inflammatory agents used in the treatment of asthma during an exacerbation. In doing so, we will rely heavily on systematic review evidence from a number of important studies published in the Cochrane Database of Systematic Reviews, an electronic publication of the Cochrane Collaboration. In particular, we will focus on the data available in the reviews compiled by the Airway Review Group. These have been routinely regarded as high quality and have been extensively quoted.[8] These systematic reviews use standardised and rigorous methods to summarise and combine the best evidence from individual randomised controlled trials pertaining to a specific topic area. The results represent Level I evidence for treatment decisions.[9]

Corticosteroids

Some of the first controlled clinical trials in acute asthma were conducted in the UK in the late 1950s using corticosteroids (CS), one of the first effective therapeutic agents for asthma. Today, there is a large body of research in this field that is at times conflicting and difficult to understand. Before embarking on an examination of the clinical literature to attempt to resolve the confusion, some definitions are necessary. Throughout this discussion, the term 'systemic corticosteroid' (SCS) refers to oral, intramuscular or intravenous routes of corticosteroid administration. SCS will be contrasted to 'inhaled corticosteroids' (ICS), which includes the following: corticosteroid medication taken by metered dose inhaler, with or without a spacer, dry powder inhaler or nebuliser. We should also point out that since the emergence of inhaled agents, a gradual change in preferred route has occurred. Although SCS were the mainstay of treatment for many years, they have now largely been replaced by ICS for the initial and preferred treatment of chronic asthma. It is important to note that the literature on SCS in the treatment of acute asthma is older and often methodologically weaker than that involving ICS agents. This will be discussed in the context of the Cochrane Collaboration.

Inflammation and Corticosteroids

There have been many mechanisms proposed to explain the effect of corticosteroids on airway inflammation; however, this venue does not provide the opportunity to explain them all in detail. Overall, research suggests that systemic corticosteroids suppress multiple components of allergic and non-allergic airway inflammation, including cell recruitment, adhesion molecule expression or release, airway permeability and production of cytokines potentially involved in airway immunity or remodelling.[10]

Traditional pharmacology teaching suggested that CS agents enter the cell and attach to steroid receptors affecting protein synthesis. This mechanism was thought to require many hours to produce a measurable effect. However, there is mounting evidence that there is more than one specific mechanism to explain the CS effects observed in asthma.

Clearly, the full effects of corticosteroids are not seen immediately, and this is important.[10] SCSs prevent the amplification of the inflammatory cascade. Specifically, they interfere with the synthesis of inflammatory mediators and prevent migration or activation of inflammatory cells. They are thought to up-regulate the beta-receptor, resulting in improved bronchodilation. At the cellular level, they change the expression of genes, and this mechanism explains the observation that their effect occurs over a longer period of time.

In addition, there seems to be another mechanism that may account for effects obtained over a

shorter period. CS agents are graded on strength based on their blanching effect, and this early effect seems to be related to vascular activity. Non-specific vascular effects at the level of the airway may result in vasoconstriction, a decrease in capillary membrane permeability, and may also decrease mucous production. In both mechanisms, once the inflammatory reaction has been initiated, corticosteroids do not affect the mediators that have already been released.

The short-term effect, especially observed with inhaled agents, has been found in other airway diseases. Many investigators have now confirmed the rapid onset of action of inhaled corticosteroids in croup, another 'airway' disease common in the emergency department setting.[11] It is likely that a similar role may be in played by CS agents in the treatment of acute asthma.[12] The mechanisms for this CS effect would be similar to those outlined previously for SCSs in general; however, the role of direct vasoconstriction may be more important using the inhaled route. Some basic science evidence suggests that another mechanism to explain the action of ICSs involves decreased recruitment of inflammatory precursors from bone marrow to the lung.[13,14] This is very promising research, and provides further evidence to suggest that the action of ICS and SCS may be different.

Emergency department care

The overall goal of emergency department care is to provide safe and effective treatment for the bronchospasm associated with the acute presentation and then to initiate effective anti-inflammatory treatment. Early treatment of acute asthma has generally focused on the use of inhaled (usually through a nebuliser) short-acting β_2-agonists because of their undisputed and rapid effect on relieving bronchospasm and associated breathing dysfunction. There is increasing support, particularly in children, for adding anticholinergic agents (ipratropium bromide [IB]) to β_2-agonist therapy in moderate to severe exacerbations.[15,16] In another Cochrane review, in which beta-agonist and systemic corticosteroids were given to all patients, the addition of intravenous magnesium sulfate ($MgSO_4$) reduced hospitalisation (odds ratio [OR] = 0.1; 95% CI: 0.04–0.27) and improved pulmonary functions (mean increase in peak expiratory flow: 52 l/min; 95% CI: 27–77) in severe asthma exacerbations.[17] Considerable differences in patient factors, emergency department treatment and discharge care for patients with asthma have been found between Canada and USA.[17] It is likely that similar differences could be demonstrated between North America and other non-North American locations.

In addition to the treatments that address immediate bronchoconstriction, early use of anti-inflammatories is a cornerstone of appropriate treatment. The approaches described below should reduce the need for hospitalisation and ensure that patients receive the appropriate treatment required to prevent relapse and reduce the potential for a serious negative outcome (e.g. intubation or death).

Systemic corticosteroids

The airway oedema and increased secretions associated with the inflammation in acute asthma can be effectively treated with SCS. The early use (i.e. within 90 min of arrival) of SCS delivered by either oral or intravenous (IV) routes is a principal treatment choice in published evidence-based asthma guidelines.[4,5] A meta-analysis investigating this issue determined that the early use of SCS for acute asthma in the emergency department significantly reduced admission rates compared with placebo (Fig. 1; OR = 0.50; 95% CI: 0.31–0.81); with the NNT being 8 (95% CI: 5–20).[18] This benefit was more pronounced for those not already receiving corticosteroids (OR = 0.37; 95% CI: 0.19–0.70) and those experiencing a severe exacerbation (OR = 0.35; 95% CI: 0.21–0.59). The effects of SCS on pulmonary functions were variable in the short term, mainly due to insufficient reporting of results. Side-effect profiles were similar between all SCS treatment routes and placebo, suggesting that emergency department treatment with SCS is safe.

There has been some debate over the use of IV versus oral corticosteroids in the emergency department; however, this now seems to be focused on identifying which patients require the IV route compared with the oral route. There is no evidence from controlled trials or meta-analyses to suggest the advantage offered by corticosteroids in moderate to severe asthma is related to the route of administration. Further systematic review evidence on dosing suggests that high-dose corticosteroids, at least in hospitalised patients, are no more effective than moderate and low doses.[19]

Applying this information to practice requires a clear understanding that not all levels of severity have been assessed with sufficient rigor to confirm

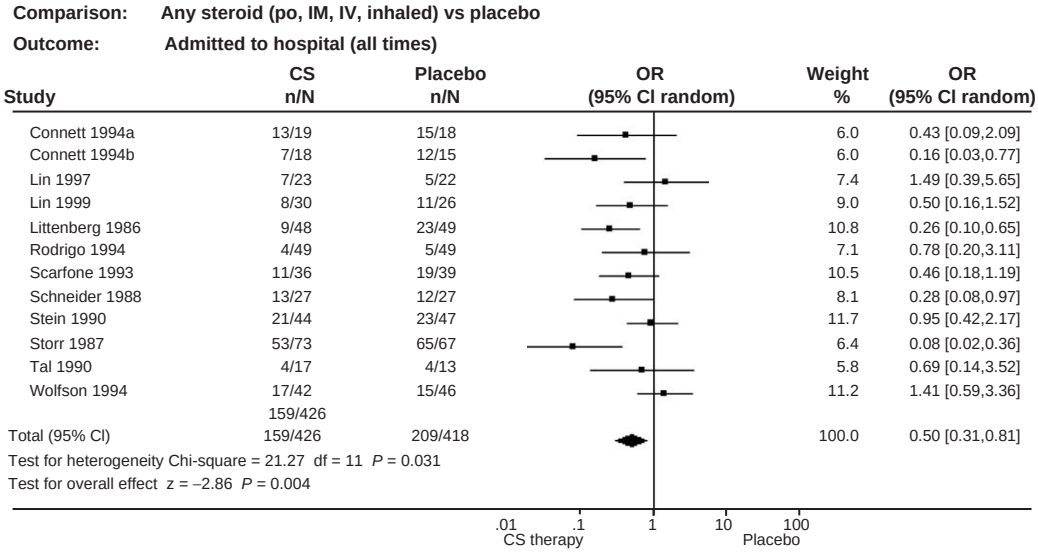

Figure 1 Systematic review evidence for reducing admissions in acute asthma using early systemic corticosteroids.

Table 1 Anti-inflammatory drugs and doses commonly used in the treatment of acute asthma.

Drug	Adult dose	Paediatric dose
Systemic corticosteroids		
Hydrocortisone (Solucortef; in ED)	250–500 mg IV	5–10 mg/kg IV (max: 250 mg)
Methyl-prednisolone (Solumedrol; in ED)	80–125 mg IV	1–2 mg/kg IV (max:125 mg) 4 mg/kg IM
Prednisone (in ED)	40–50 mg po	1 mg/kg po (max: 50 mg)
Prednisolone (in ED)	Limited evidence	2 mg/kg po
Dexamethasone (in ED)	Limited evidence	10 mg IM or
Prednisone (at discharge)	40–50 mg po qd for 5–10 days; tapering not required)	1–2 mg/day divided bid or qd for 5–7 days; tapering not required)
Inhaled corticosteroids		
Budesonide (in ED)	1–2 mg nebulised	Limited evidence; 1–2 mg nebulised
Fluticasone (in ED)	500–1000 lg/dose	Limited evidence
Flunisolide (in ED)	Up to 2 g/h X 6 h	Limited evidence
Budesonide (at discharge)	800–1600 lg/day for up to 21 days	Limited evidence
Fluticasone (at discharge)	500–1000 lg/day for up to 21 days	Limited evidence
Flunisolide (at discharge)	Up to 2000 lg/day for up to 21 days	Limited evidence

Bid, twice a day; ED, emergency department; IM, intramuscular; IV, Intravenous; limited evidence, untested in this setting; po, by mouth; qd, every day.

equivalency of systemic routes. Until further evidence is available, it seems reasonable to select oral agents as the first-line choice while reserving IV corticosteroids for individuals who are too dyspneic to swallow, are obtunded or intubated or are unable to tolerate oral medications (e.g. vomiting). It is not important what corticosteroid agent or dose (e.g. high, moderate or low) is provided,[19] as long as SCS is administered early. The decision on SCS delivery should be based on cost, availability and patient factors (Table 1). The main issue to remember is the need to start systemic corticosteroids early and consistently for patients with moderate to severe acute asthma.

Inhaled corticosteroids

Although inhaled corticosteroids are usually considered a treatment for chronic asthma, emerging evidence supports their use in the emergency department setting for acute asthma. A Cochrane systematic review on this topic[12] suggests that using ICS early in the emergency for acute asthma

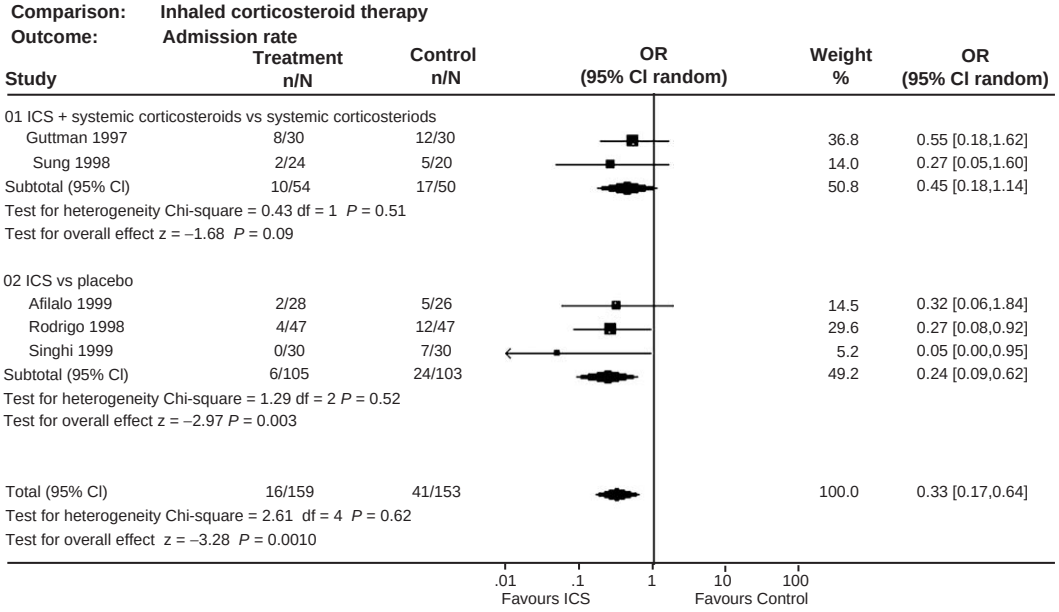

Figure 2 Systematic review evidence for reducing admissions in acute asthma using inhaled corticosteroids. ICS, inhaled corticosteroids.

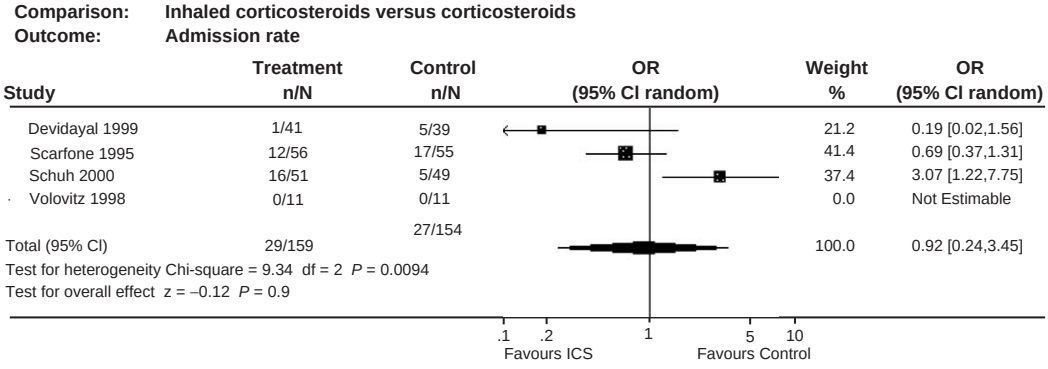

Figure 3 Systematic review evidence for admission when replacing systemic with inhaled corticosteroids in acute asthma. ICS, inhaled corticosteroids.

reduces admissions (Fig. 2; OR = 0.33; 95% CI: 0.17, 0.64) and improves pulmonary function (mean increase in peak expiratory flow: 8.0%; 95% CI: 3–13) compared with placebo. However, in several of the studies included in this review, systemic corticosteroids were not given to either the treatment or control group, thus limiting the power of the review to determine the additive benefit of ICS in this setting.

A recent study found that there may be drawbacks to replacing systemic corticosteroids with ICS in the treatment of acute asthma.[20] In this randomised double-blind study, patients received ICS versus oral corticosteroids in addition to standard $ß_2$-agonist therapy. Participants treated with oral corticosteroids experienced better outcomes and were admitted less frequently than participants treated with ICS. Combined with the previous meta-analysis data (Fig. 3), these results suggest that ICS may be useful as an adjunct to systemic corticosteroids, but not as a replacement choice.[12,21] Additional research is needed in this area to determine the optimal dose, frequency and drug to be used, and to clarify the magnitude of the additional benefit when ICS are being given concurrently with SCS.

Post-emergency department care

The goal of post-emergency department care is to return each patient to a level of functioning commensurate with the current definition of asthma 'control'. According to some national guidelines, control means that the patient is using

rescue beta-agonists less than four times a week, is sleeping through the night and is performing their regular daily activities (e.g. work and exercise) without limitations resulting from asthma.[4] Achieving these goals would require that patients receive the appropriate treatment (e.g. medications, education, and compliance discussion) required to prevent or attenuate the next exacerbation of asthma.

Post-emergency department systemic corticosteroids

About 12–17% of patients treated for acute asthma in the emergency department will relapse within 2 weeks of discharge, many because of unresolved inflammation that leaves the airways sensitive to inhaled irritants.[22,23] Guidelines strongly encourage treatment with systemic corticosteroids after discharge from the emergency department for an asthma exacerbation to reduce this high risk of relapse.[4,5] Compelling evidence for this approach is found in a Cochrane systematic review comparing post-emergency department CS treatment to placebo.[22] Significantly fewer patients in the corticosteroid group relapsed in the first week compared with placebo (Fig. 4; OR = 0.35; 95% CI: 0.17–0.73). This reduced risk continued over the first 21 days (OR = 0.33; 95% CI: 0.13, 0.82). The corticosteroid group also had less need for β_2-agonists (mean difference: three less activations per 24 h; 95% CI: −5.5 to −1.0). Changes in pulmonary function tests and side-effects, while rarely reported, failed to demonstrate differences between the treatment groups.

A subgroup analysis indicated that intra-muscular (IM) corticosteroids and a 7–10-day tapering course of corticosteroids were similarly effective. IM therapy may be best reserved for patients with questionable compliance, inability to afford the price of an oral prescription or those who are otherwise unreliable (i.e. cognitive impairment intoxication). The review established that the associated NNT was 13 (95% CI: 7–91) treated patients to prevent one relapse after an exacerbation of asthma.[22–24]

Small sample sizes in the RCTs conducted to date did not permit an examination of the relative effectiveness of various regimens, and definitive recommendations concerning dose or dosing protocol(s) cannot be provided. However, a 40–50 mg dose (prednisone equivalent) of oral corticosteroid once a day for a short period (5–10 days) seems appropriate for most patients discharged with an acute asthma episode; this dose will also improve compliance. The need to 'taper' a short course of oral corticosteroids seems unwarranted,[25,26] especially when ICSs are being used concurrently.[27]

Post-emergency department inhaled corticosteroids

In US emergency departments, most patients with acute asthma are discharged and prescribed a short course (5–7 days) of oral corticosteroids. Less information is available on the use of inhaled

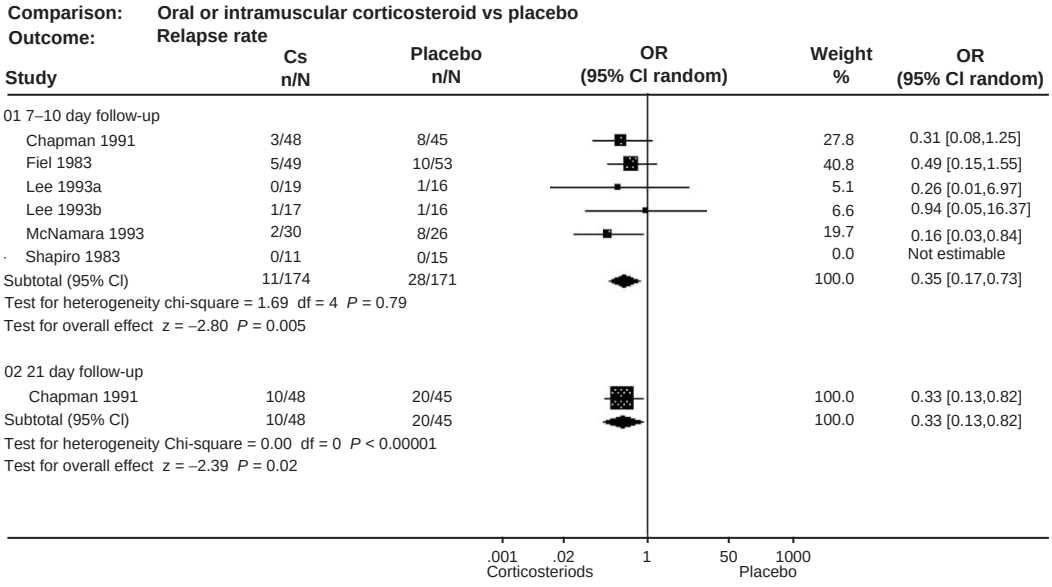

Figure 4 Systematic review evidence for reducing relapses after discharge in acute asthma using systemic corticosteroids. CS, corticosteroids.

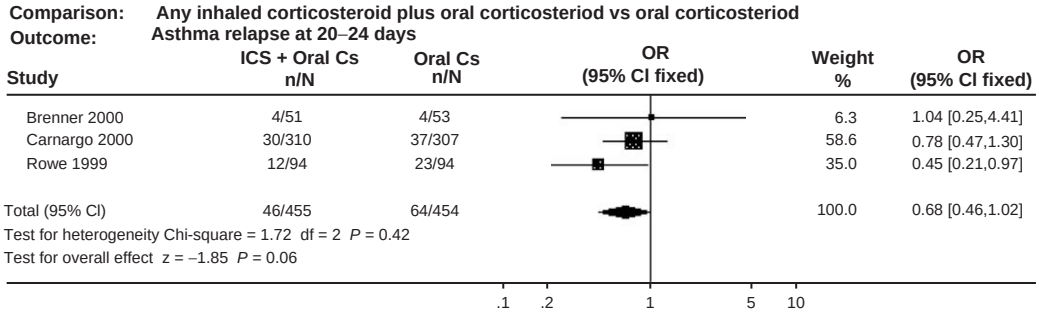

Figure 5 Systematic review evidence for reducing relapses after discharge in acute asthma using inhaled corticosteroids. CS, corticosteroids; ICS, inhaled corticosteroids.

corticosteroids; however, available data indicate impressive practice variation in ICS use after emergency department discharge. For example, in US sites associated with a large North American emergency department airway research network (http://healthcare.partners.org/marc), only 25% of discharged patients were prescribed an inhaled corticosteroid if they were not already regularly taking one[28] whereas, in Canadian sites, more than 50% of similar patients were treated with an ICS at discharge.[29]

Emerging evidence supports the use of combined inhaled and oral corticosteroids upon discharge from the emergency department.[27] Two published randomised controlled trials[27,30] and one abstract,[31] when pooled, result in a favourable effect.[32] The pooled effect shows a trend in favour of the ICS plus oral corticosteroid group having fewer relapses after discharge than the oral corticosteroid alone group (Fig. 5; OR = 0.68; 95% CI: 0.46–1.02).[32] The lack of clear benefit may be surprising to some readers; however, remember there were only three known trials in this review, and the heterogeneity may be explained by either trial quality or dosing of agents. In the only study demonstrating clear benefit, the dose was considerably higher than in the other two.[33] Further research on the appropriate dose of ICS agent is clearly needed. Clinically, the results of this review indicate that clinicians should counsel patients already taking ICS about compliance.[34–36]

Considering that many of the patients with acute asthma who present to the emergency department show features associated with poorly controlled chronic asthma,[36] they represent vulnerable patients who are ideal candidates for inhaled corticosteroids. In fact, treatment of asthma with ICS in such patients is the key to 'regaining control' over the longer term. Consequently, one could argue that those patients not already taking ICS agents should be considered for long-term inhaled therapy in conjunction with oral prednisone after discharge. In most studies, 'long-term' implies treatment for at least 3 weeks; however, chronic therapy may be indicated in many patients on the basis of the underlying severity of the disease and the control of symptoms after treatment. For patients with more severe illness, adding ICS to oral corticosteroids would clearly be the optimal treatment strategy.

The dose and duration of inhaled and oral corticosteroids should be based on recent history of symptom control, healthcare utilisation and quality-of-life indicators. Evidence is particularly conflicting in the area of ICS. For example, a recent administrative database study examining patients who were discharged from the emergency department suggested that a prescription for ICS significantly reduced relapses; however, the prescribed dose did not seem to influence outcome.[37] In addition, Australian investigators completed a systematic review confirming the flat dose–response ICS curve in chronic asthma.[38] In the systematic review,[32] subgroup evidence shows that higher doses of inhaled corticosteroids may be more effective. Given this information, it would seem that treatment must be individualised and the lowest does at which control is maintained targeted.[37,38]

Several recent publications have examined the effect of replacing oral corticosteroids with high-dose ICS. These generally compare oral prednisone to very high doses of ICS in acute mild asthma after discharge. Although the systematic review failed to demonstrate a significant difference in asthma relapse between the two treatments (OR = 1.0; 95% CI: 0.48–1.42), these results need to be interpreted cautiously.[32] Although the evidence implies equivalence, these results are not conclusive owing to the width of the confidence intervals and the inclusion of only patients with mild asthma exacerbations. Given the limited data on this issue to date, use of ICS alone should be reserved for

patients with very mild asthma exacerbations and patients who refuse or cannot take oral corticosteroids. Compared with the traditional short course of prednisone, ICS are expensive and more difficult for patients and families to use. Given that there is potential for added benefit with combined therapy, future research should focus on this important comparison.

Discussion

This paper examined the evidence for the use of corticosteroids in acute asthma, mainly systematic reviews contained in the Cochrane Library. Although there are exciting advances being made in chronic asthma care with the introduction of long-acting beta-agonists[39] and leukotriene modifiers,[40] further evidence of effectiveness are required before recommending them as substitutes or adjuncts to inhaled and systemic corticosteroids in the emergency department or after discharge. Until there is sound evidence for their use, these newer interventions will remain secondary considerations. Furthermore, there is evidence that non-pharmacologic interventions, such as limited education,[41] asthma self-management programmes,[42] regular medical review[42] and appropriate referrals to specialists, may be effective in curbing the burden of acute asthma in the emergency department.

Acute exacerbations represent an opportunity for clinicians to review the longer-term pharmacological and non-pharmacological management of asthma. Adhering to an asthma plan to maintain long-term control is often problematic, especially in the areas of regular medication use and avoiding environmental triggers. The opportunity to introduce or reinforce helpful behaviours should not be lost. Given that asthma is a chronic disease, acute care physicians should encourage patients, whenever practical, to seek regular, longitudinal care for their asthma.

Conclusion

Asthma is a common, chronic and often debilitating disease. The treatment approaches to control bronchial inflammation summarised in this review provide hope for an early return to activities, reduced symptoms and improved quality of life in the sub-acute period after an exacerbation. Combining self-management skills and educational interventions with appropriate preventive medication provides patients with the best opportunity to maintain their optimal health status, and prevent an exacerbation or relapse in the future.

Acknowledgements

The authors would like to thank Mrs. Diane Milette for her secretarial support. In addition, the authors would like to acknowledge the work of the Airway Review Group staff (Mr. Stephen Milan and Toby Lasserson; and Mrs. Karen Blackhall) and the Review Group Editor (Professor Paul Jones) at the St. George's Hospital Medical School for their support with the development of reviews.

Dr. Rowe is supported by a salary award from the Canadian Institute of Health Research (CIHR) as a Research Chair in Emergency Airway Diseases (Ottawa, ON). Dr. Camargo is supported by grant HL-63841 from the National Institutes of Health, (Bethesda, MD).

Conflicts of interest

None declared by Dr. Edmonds, Ms. Spooner, or Dr. Diner. Drs. Camargo and Rowe have received study funding and speaking honoraria from GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, and Monahan-Trudell. Dr. Camargo has been a paid consultant for Aventis, GSK, MERCK, and Boehringer-Ingelheim. Dr. Rowe has served as a paid consultant for Boehringer-Ingelheim.

PRACTICE POINTS

- Provision of systemic corticosteroids in the emergency department reduces admissions to hospital from acute asthma.
- Dose and delivery method for systemic corticosteroids in the emergency department seem less important than early initiation.
- Discharge plans, including systemic corticosteroids, reduce relapses from acute asthma after discharge.
- Most acute asthma patients require the addition of inhaled corticosteroids to systemic corticosteroids after discharge; plans should be individualised.
- Review of preventive medication compliance and strategies to improve compliance should be discussed in the emergency department.

RESEARCH DIRECTIONS

- The role of different doses of inhaled corticosteroids after discharge with acute asthma requires further study.
- The role of newer agents (leukotriene modifiers and long-acting beta agonists), in combination with systemic and inhaled corticosteroids, requires further study.
- The role of clinical practice guidelines in improving the uptake of the use of systemic and inhaled corticosteroids requires further study.

References

1. Mannino DM, Homa DM, Pertowski CA, et al. Surveillance for asthma—United States 1960–1995. CDC Surveillance Summaries, April 24, 1998. *MMWR* 1998;**47**(No. SS-1):1–28.
2. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001;**107**:3–8.
3. Krahn MD, Berka C, Langlois P, Detsky AS. Direct and indirect costs of asthma in Canada. *Can Med Assoc J* 1996;**154**: 821–31.
4. Boulet L-P, Becker A, Berube D, Beveridge RC. Ernst P on behalf of the Canadian Asthma Consensus Group. Canadian asthma consensus report. *Can Med Assoc J* 1999;**161**(supp l):1–61.
5. National Asthma Education Program. Expert Panel Report II: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health: 1997.
6. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;**282**:1458–65.
7. O'Byrne PM. Airway inflammation and the pathogenesis of asthma. *Can Respir J* 1994;**1**:189–95.
8. Jadad AR, Moher M, Browman GP, et al. Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. *BMJ* 2000;**320**:537–40.
9. Guyatt GH, Sackett DL, Sinclair JC, et al. User's guide to the medical literature IX: a method of grading health care recommendations. *JAMA* 1995;**274**:1800–4.
10. Liu MC, Proud D, Lichtenstein LM, et al. Effects of prednisone on the cellular responses and release of cytokines and mediators after segmental allergen challenge of asthmaic subjects. *J Allergy Clin Immunol* 2001;**108**: 29–38.
11. Ausejo M, Saenz A, Pham B, et al. Glucocorticoids for croup (Cochrane review). In: The Cochrane library, Version 4. Oxford: Update Software; 2003.
12. Edmonds ML, Camargo CA Jr, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma (Cochrane review). In: The Cochrane Library, Version 4. Oxford: Update Software; 2003.
13. O'Byrne P. Asthma pathogenesis and allergen-induced late responses. *J Allergy Clin Immunol* 1998;**102**:S85–9.
14. O'Byrne PM, Gauvreau GM, Wood LJ. Interaction between haemopoietic regulation and airway inflammation. *Clin Exp Allergy* 1999;(suppl 2):27–32.
15. Plotnick LH, Ducharme FM. Should inhaled anticholinergics be added to B-agonists for treating acute childhood and adolescent asthma? A systematic review. *BMJ* 1998;**317**: 971–7.
16. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a meta-analysis of randomized clinical trials. *Ann Emerg Med* 1999;**34**:8–18.
17. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo Jr CA. Intravenous magnesium sulfate treatment for acute asthma in the emergency department (Cochrane review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
18. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids (Cochrane review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
19. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients (Cochrane Review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
20. Schuh S, Reisman J, Alshehri M, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med* 2000;**343**:689–94.
21. CPS. Global initiative for asthma: global strategy for asthma management and prevention, NHLBI/WHO workshop report, 95-3659, Bethesda, MD: National Institutes of Health; 1995.
22. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma (Cochrane review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
23. Emerman C, Woodruff P, Cydulka R, Gibbs M, Pollack C, Camargo Jr C. Clinical investigations: prospective multicenter study of relapse following treatment for acute asthma among adults presenting to the emergency department. *Chest* 1999;**115**:919–27.
24. Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. *Am J Emerg Med* 1992;**10**:301–10.
25. Verbeek PR, Gerts WH. Nontapering versus tapering prednisone in acute exacerbations of asthma: a pilot study. *J Emerg Med* 1995;**13**:715–9.
26. O'Driscoll BR, Karla S, Wilson M, Pickering CAC, Carrol KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. *Lancet* 1993;**341**:324–7.
27. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent relapse following discharge from the emergency department: a randomized controlled trial. *JAMA* 1999;**281**: 2119–26.
28. Camargo Jr CA, Clark S. Emergency department management of acute asthma between 1996–2001: potential impact of the 1997 NAEPP guidelines [abstract]. *J Allergy Clin Immunol* 2002;**109**(suppl):S156.
29. Rowe BH, Bota GW, Pollack CV, Emond SD, Camargo Jr CA. Management of acute asthma among adults presenting to Canadian versus US Emergency Departments [abstract]. *Ann Emerg Med* 1998;**32**:S2–3.
30. Brenner BE, Chavda KK, Camargo Jr CA. Randomized trial of inhaled flunisolide versus placebo among asthmatics discharged from the emergency department. *Ann Emerg Med* 2000;**36**:417–26.

31. Camargo Jr CA. For the MARC Investigators. Randomized trial of medium-dose fluticasone vs placebo after an emergency department visit for acute asthma [abstract]. *J Allergy Clin Immunol* 2000;**105**(1 Pt 2):S262.
32. Edmonds ML, Camargo CA Jr, Brenner B, Rowe BH. Inhaled steroids in acute asthma following emergency department discharge (Cochrane review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
33. Rowe BH, Edmonds ML. Inhaled corticosteroids for acute asthma after emergency department discharge. *Ann Emerg Med* 2000;**36**:477–80.
34. Stevenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. Is this patient taking the treatment as prescribed. *JAMA* 1993;**269**:2779–81.
35. Emond SD, Reed CR, Graff LG, Clark S, Camargo Jr CA. On behalf of the MARC Investigators Asthma education in the emergency department. *Ann Emerg Med* 2000;**36**: 204–11.
36. Emond SD, Camargo Jr CA, Nowak RM. 1997 national asthma education and prevention program guidelines: a practical summary for emergency physicians. *Ann Emerg Med* 1998;**31**:579–89.
37. Sin DD, Man SFP. Low-dose inhaled corticosteroid therapy and risk of emergency department visits for asthma. *Arch Intern Med* 2002;**162**:1591–5.
38. Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. *Med J Australia* 2003;**178**: 223–5.
39. Wilson AJ, Gibson PG, Coughlan J. Long acting beta-agonists versus theophylline for maintenance treatment of asthma (Cochrane review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
40. Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma (Cochrane review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
41. Gibson PM, Coughlan J, Wilson AJ, et al. Limited (information only) patient education for adults with asthma (Cochrane review). In: *The Cochrane library*, Version 4. Oxford: Update Software; 2003.
42. Gibson PM, Coughlan J, Wilson AJ, et al. Self-management education and regular practitioner review for adults with asthma (Cochrane review). In: *The Cochrane Library*, Version 4. Oxford: Update Software; 2003.