Effectiveness of Steroid Therapy in Acute Exacerbations of Asthma:

A Meta-analysis

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The objective of this study was to determine the effect of steroid therapy on pulmonary function, admission rates, and relapse rates in patients presenting with acute exacerbations of asthma. Computerized MEDLINE and SCIENCE CITATION searches were combined with review of reference lists from book chapters and articles to identify published randomized trials on steroid interventions. Over 700 articles were reviewed by two independent reviewers who identified 30 relevant randomized controlled trials for analysis. Study validity was independently assessed by two reviewers and information regarding populations, interventions, and outcomes was abstracted. Binary outcomes were combined and reported as odds ratios (OR), using the Mantel-Haenszel method. Individual and pooled effect sizes (ES) were determined for pulmonary function data. The authors found that the use of steroids early in the treatment of asthmatic exacerbations reduces admissions in adults (common OR 0.47; 95% confidence interval (CI) 0.27, 0.79) and children (OR 0.06-0.42). They found steroids effective in preventing relapse in the outpatient treatment of asthmatic exacerbations (OR 0.15; CI 0.05, 0.44). Oral and intravenous steroids appear to have equivalent effects on pulmonary function in acute exacerbations (ES −0.07; CI −0.39, 0.25). The authors conclude that overall, steroid therapy provides important benefits to patients presenting to emergency departments with acute exacerbations of asthma. Further research into dosage, alternative routes of administration, and alternative outcome measures is needed. (Am J Emerg Med 1992;10:301-310. Copyright © 1992 by W.B. Saunders Company)

Glucocorticoid agents have been used in the treatment of asthma since 1950.[1] Their use in the treatment of asthmatic exacerbations has been a subject of debate since the publication of the first major article revealing the beneficial effects of intravenous steroids in acute asthma.[2] Despite early encouraging reports regarding drug efficacy, acceptance of steroids in clinical practice has been less than complete, especially in the area of acute asthmatic exacerbations. This may be due to the fear of producing adverse effects associated with long-term steroid use[3] and to the inconsistent results of clinical trials. In fact, one recent article has questioned their role in the early emergency department management of exacerbations.[4] The result is a state of relative confusion regarding the dose, route of administration, and usefulness of these agents in the treatment of acute asthmatic exacerbations presenting to an emergency department setting. The situation has changed surprisingly little since the statement by Collins et al in 1975[5]:

> Although synthetic steroids are considered to play an essential part in the treatment of severe asthma unresponsive to bronchodilators, wide variation exists in the dosage of corticosteroids recommended for the treatment of this condition. Neither the best route of administration nor the speed of response to the drug is agreed.

The purpose of this paper is to review the literature on the effectiveness of steroid administration in the treatment of patients presenting, usually to an emergency department, with an acute exacerbation. The questions specifically addressed are:

1. Do steroids reduce the complications (ie, hospital admission rates, need for repeat assessment following discharge, long-term outcome) when prescribed for patients with acute exacerbations of asthma?
2. What is the relative effectiveness of varying steroid doses ("high dose" versus "low dose")?
3. Does the parenteral (intravenous [IV], intramuscular [IM]) route improve outcomes when compared with administration of similar strength dosage via the oral route?
4. Do steroids improve pulmonary function tests (PFTs) over the first 24 hours of treatment in acute exacerbations?
5. Does a tapering regimen of steroids improve outcomes, such as relapse rates, in the first month following acute use?

PRESENT STATE OF KNOWLEDGE

Literature search strategies discussed below were used to identify review papers concerning steroid use in the treatment of asthmatic exacerbations seen in the emergency department setting. Eighty-seven review articles have been published over the past 6 years. No paper was identified that met published criteria for overviews.[6]

While several consensus conference reports contained sections on the emergency management of asthma,[7,8] their review of the literature could not be considered complete or unbiased. Variable steroid dosage regimens (30-50 mg prednisone) are recommended, inhaled steroids are rarely men-

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tioned, and intravenous steroids are regularly proposed (again at varying doses) in the treatment of acute asthmatic exacerbations. The disparity in recommendations confirmed the need for a more formal overview of this topic.

METHODS

Identification of Studies

A computerized search was conducted to identify appropriate literature on the topic of steroid use in the acute exacerbation of asthma. We searched for studies published in the English language using MEDLINE (Compact Cambridge, Cambridge Scientific Inc, Bethesda, MD) for the years 1966 to February 1991. The following terms were used in the search: (1) ASTHMA {MeSH or tw} AND (2) ADRENAL CORTEX HORMONES {MeSH or tw} AND NOT (3) REVIEW OR LETTER. Other sources of relevant articles were content experts, review articles, textbooks,[9-11] and a 1980-1990 SCIENCE CITATION search. Two references[12,13] were used for the years 1984-1990 and two[14,15] for the years 1980-1984. Finally, a reference list comprised of the included papers was sent to the primary author of each relevant paper and several local experts. These experts were asked to identify missing papers or unpublished literature on the topic.

Selection of Studies

The MEDLINE reference list was independently reviewed by two researchers (B.H.R., J.L.K.) and clearly irrelevant articles were discarded. If the title or the abstract suggested any possibility of relevance, the article was retrieved. The following inclusion criteria were used to select studies: (1) design: randomized controlled trial or quasi-experimental (eg, alternate day or sequential allocation); (2) patients: asthmatic patients whose acute exacerbation was the primary reason for assessment and exclusion of patients with chronic airflow limitation. Patients less than 24 months old were excluded due to the difficulty of making a diagnosis of asthma in this population; (3) interventions: primary research question involved treatment with either parenteral (IV, IM) or oral glucocorticoids; (4) outcomes—any of: hospitalization rate, relapse rate, pulmonary functions, quality of life, or clinical score.

Each relevant paper was assessed by two independent reviewers; disagreements were settled by consensus. Following selection, each paper was independently rated on the basis of the following features using a three point scale: (1) blinding of the participants to the treatment, (2) description of allocation process, (3) description of randomization, (4) presence of cointervention, (5) outcome measures, and (6) completeness of follow-up. These criteria were used to provide methodological weights for the included papers and were to be used in the sensitivity analysis.

Data Collection

A data collection form was completed for all papers meeting the inclusion criteria. Abstracted data included: title, author(s), year of publication, population studied, patient demographics, intervention (steroid used, dosage, route of administration, duration, timing), outcomes, percent follow-up, follow-up timing, pulmonary function and other outcomes, incidence of side effects, and statistical analysis.

Data Analysis

For the relevance and validity ratings, agreement was calculated and reported as simple agreement and chance corrected agreement using the κ coefficient.[16] Information from forms was entered onto a Macintosh SE computer (Apple Computer, Inc; Cupertino, CA); descriptive analysis was completed using StatView SE (Abacus Concepts, Inc; Berkeley, CA). Data were pooled for the following groups: (1) any steroid by any route versus placebo; (2) parenteral versus oral steroid; and (3) high or moderate dose versus low dose.

When different steroid preparations were used, the dose was converted to the prednisone or prednisolone pharmacologic equivalent using the tables provided by Siegel.[17] Those studies that reported steroids doses as mg/kg/d were divided by four (to adjust to every 6-hour dosing schedules) and multiplied by 70 kg (median weight of adult subjects). Equivalent prednisone doses between 10-30 mg were classified as "low", 31-60 mg as "moderate", and above 60 mg as "high".[7,8,17]

For this overview, outcomes were classified as physiologic (PFTs) or clinical (rates of hospitalization and relapse). Functional outcomes (eg, quality of life) were not used in any of the studies. For pulmonary function testing, % predicted FEV-1 was most often reported. If not available, absolute FEV-1 or occasionally peak expiratory flow rate was used. The effect of treatment in each study was computed using the effect size described by Glass.[18] The effect size (ES) is the ratio of the mean difference and the pooled SD. The mean difference is the mean in the treatment group minus the mean in the control group for the selected PFT. The pooled SD is computed by pooling the SDs of the two groups, treatment and control, at the time of outcome assessment.

An adjustment was necessary to account for differences between PFTs in the treatment and control groups at baseline. To account for these differences, the baseline difference between the PFTs (eg, baseline $FEV\text{-}1_{treatment}$ − baseline $FEV\text{-}1_{control}$) was added to the control population at outcome assessment. When pooled statistics were calculated, studies were weighted by the inverse of the variance. Pooled ESs were considered large if they were greater than 0.8, moderate if ≥ 0.4 but less than 0.8, and small if <0.4.[18]

If the SD was not available, the standard error was used to calculate the SD by multiplying it by the square root of the treatment sample size (n). In some cases where tables were unavailable, graphs were enlarged and values were approximated. This technique was required for seven studies.[13,15,19-23] The confidence intervals (CI) were used to estimate the SD from some graphs. Finally, if unable to obtain SD data from these sources, the initial pulmonary function SD was used.

Effect sizes and associated 95% CI were calculated for each study.[24] Total and subgroup pooled effect sizes were calculated for the studies meeting the inclusion criteria, and homogeneity was tested using methods described by Hedges.[24] Binary outcomes (ie, admission and relapse rates) were pooled using the Mantel-Haenszel technique,[25] and

95% CI for the common odds ratio were calculated using Cornfield's method.[25] The Breslow-Day method was used to test for homogeneity.[26]

The number of patients needed to treat[27] to prevent one 'complication' (relapse or admission) was calculated using the formula number needed to treat (NNT) = 1 ÷ (BI − SI),[28] where BI (baseline incidence) is the incidence of complication in the control group and SI (steroid incidence) is the incidence of complication in the intervention group.

Sensitivity Analyses

Differences between study results (heterogeneity) may be qualitative or quantitative, and can arise from a number of sources.[29] First, they can be the result of chance. Other sources of heterogeneity include differences between studies with respect to study design, population, intervention, or outcome measurement. Whenever heterogeneity occurs, attempts to explain it are warranted.

A priori, it was felt that differences between steroid studies may arise as a result of differences in populations (adults versus children) or study design. When heterogeneity was encountered, these subgroup analyses were performed in an attempt to explain the findings. Interventions and outcome measures were thought to be similar in the various study categories.

RESULTS

Selection

Six hundred sixty-seven articles were identified between the years 1966-1990 in the initial MEDLINE literature search. Two independent reviewers selected 84 papers that appeared relevant from this search. The simple agreement was 0.94 for this assessment. SCIENCE CITATION searching (B.H.R.) identified 169 citations. Many papers were identified in both of the computerized searches; only four of 26 SCIENCE CITATION articles on the topic of steroid treatment met the criteria for retrieval. Review of the citations in books, conferences, and included papers yielded only five additional articles for relevance assessment. Finally, experts provided two articles not discovered by other methods of searching.[30,31] Both were recent articles that were not yet listed by MEDLINE. Unpublished literature was requested but was not identified, and non-English language literature was not examined.

Ninety-five papers were retrieved and assessed for relevance. Of these, 30 met the inclusion criteria.[2,4,12-15,19-23,30-48] Simple agreement on relevance was 0.96 and κ was 0.90. Disagreements were resolved by consensus and were generally the result of minor errors or misunderstanding. Studies were excluded at this stage if they were: nonrandomized—89% (58/65); included treatment of nonacute asthmatics or nonasthmatic patients—8% (5/65); did not include specific steroid interventions—2% (1/65); or involved only infants (age <2 years)—2% (one/65). The discussion is confined to included papers; a full reference list is available from the authors upon request.

Validity assessment revealed high simple agreement for all criteria (0.96-0.79). Inter-rater agreement was excellent (0.9) for assessment of study blinding, however only moderate agreement for validity assessments of allocation, cointervention, outcomes, and follow-up (κ 0.48-0.37). This may be explained by the scoring scales developed for these assessments and low numbers of studies where disagreement occurred. These results are summarized in Table 1. Following validity assessment, two papers were excluded because they did not fit any of the categories for analysis. One examined equivalent but different types of steroid treatment in acute asthma,[42] while the other examined length of IV treatment in patients hospitalized with asthma.[45]

Description of Eligible Studies

The included papers were generally North American (73%), published during the 1980s (73%), and concerned patients admitted to hospital (67%). Anthropometric data were well described in 60% of papers; 57% described excluded patients clearly, while descriptions of included patients were variable. Prior treatment was poorly documented. Nine of the papers (30%) dealt with pediatric asthma. Beyond stating that their study was randomized, authors described allocation clearly in only 26% of cases. Double-blind strategies were common (80%); however informed consent was documented in only 67% of studies.

The mean sample size was 40 patients, varying from six to 140. Multiple statistical tests were performed, with a mean of 12.1 (varying from 0 to 27). Adjustments for multiple testing were not performed, and 89% made no mention of possible type I errors. Finally, despite concern regarding the side effects of these medications, fewer than 23% of the studies reported this information. The study quality was variable, and there was no significant correlation between higher quality scores and year of publication (Pearson $r = .31$; $P = .14$).

Outpatient Treatment of Acute Exacerbations

Three studies met the inclusion criteria and addressed the topic of oral steroid versus placebo treatment of outpatient exacerbations of asthma.[12,30,32] The data for these studies are reported in Table 2. Outcomes were reported as relapse rates at 7-10 days following treatment, and the common odds ratio was 0.15 (CI 0.04, 0.44). The test for heterogeneity was not significant ($P = .72$). These data indicate that oral steroid treatment in patients discharged from an emergency department following an asthmatic exacerbation significantly reduces the number of future relapses compared with placebo. Only one study reported long-term follow-up (21 days) of patients following treatment.[30] This paper revealed that patients from both placebo and steroid treatment groups relapsed at a similar rate. This suggests that following steroid

TABLE 1. Validity Assessment of 30 Included Papers by Independent Reviewers

Validity Criteria	Simple Agreement	Estimated κ
1. Blinding	0.96	0.90*
2. Allocation	0.87	0.48*
3. Co-intervention	0.82	0.37*
4. Outcomes	0.92	0.48*
5. Follow-up	0.79	0.41†

* Weighted κ using quadratic weights.
† Unweighted κ.

TABLE 2. The Effectiveness of Oral Steroids in the Treatment of Patients With Acute Exacerbations of Asthma Discharged From the Emergency Department as Measured by Relapse Rates for Rescue Treatment

Reference	Treatment	n	Follow-up Method	Outcome	RR	OR (95% CI)
Fiel et al[12]						
Treatment group	32 mg prednisolone*	34 patients (adults)	7-10 day by telephone or	Further ED care	0%	0.23 (.03-1.2)
Control group	Placebo	42 patients	in person	Symptoms	37%	
Chapman et al[30]						
Treatment group	Prednisone 40 mg (tapered)	48 patients (adults)	7-14 day in person; 21 day	Relapse rate Symptoms	10%	0.02 (.004-0.88)
Control group	Placebo	45 patients	by telephone	PFTs β-agonist use	29%	
Harris et al[32]						
Treatment group	Prednisone 30-40 mg/d	22 patients (ages: 2-28 y)	7-14 day in person	Relapse rate Symptoms	6%	0.04 (0-0.99)
Control group	Placebo	19 patients		PEFR	21%	

NOTE: Pooled OR = 0.15 (0.05-0.44); Breslow-Day NS (χ^2 = 1.9; df = 2; P = .72).
ABBREVIATIONS: RR, relapse rate; ED, emergency department; PFTs, pulmonary function tests: a variety; PEFR, peak expiratory flow rate.
* Tapering dose over 8 days.

withdrawal patients are no more at risk for relapse than the comparison nonsteroid-treated group.

Emergency Department Steroid Use and Admission Rates

Five studies addressed the effect of early steroid administration in preventing hospital admissions for patients presenting with exacerbations of asthma.[4,31,34,35,48] The results are presented in Table 3. All were randomized trials in which outcome assessment was blind to treatment. Three publications examined the effectiveness of intravenous steroid[4,35,48]; one used IM administration,[31] and the other oral steroids.[34] Medication was administered within 30 minutes of arrival in the emergency department. Admissions were assessed at approximately 3 to 6 hours depending on the

TABLE 3. Summary of Five Published Studies of the Early Administration of Steroids to Prevent Hospitalization in Patients Presenting With an Exacerbation of Asthma to an Emergency Department

Reference	Treatment	n	Clinical Assessment Timing	Admission Rates	OR (95% CI)
Stein and Cole[4]					
Treatment group	IV solumedrol	44 patients (adults)	≈6.5 hours + PFTs	18%; {6 hrs = 48%}	0.95
Control group	IV placebo	47 patients	Criteria set	13%; {6 hrs = 49%}	(0.38-2.3) {at 6 hours}
Tal et al[31]					
Treatment group	IM methylprednisolone	17 patients (children)	≈3 hours + symptoms	23%	0.42
Control group	IM placebo	13 patients	No criteria	31%	(0-1.0)
Storr et al[34]					
Treatment group	Oral prednisone	67 patients (children)	≈5 hours + PFTs	70%	0.06
Control group	Oral placebo	73 patients	No criteria	91%	(0.01-0.31)
Littenberg and Gluck[35]					
Treatment group	IV solumedrol (125 mg)	48 patients (adults)	≈4 hours + PFTs	18%	0.26
Control group	IV placebo	59 patients	No Criteria	49%	(0.09-0.71)
Schneider et al[48]					
Treatment group	IV methylprednisolone	27 patients (adults)	≈6 hours	19%	0.28
Control group	IV placebo	27 patients	Criteria set	44%	(0.06-1.12)

NOTE: Overall test for homogeneity: P = .013. Subgroup analysis: adults → common OR = 0.47 (0.27-0.79); test for homogeneity P = .27; children → test for homogeneity P = .03.
SYMBOL: +, in addition to clinical assessment.

study. One publication included children who were less than 24 months old.[31] Only data presented for ages >24 months were used from this study.

There were statistically significant differences among the results of these studies (P = .013). Using the a priori sensitivity analysis based on population differences (adults versus children), combining studies did not result in clinically important heterogeneity. This analysis revealed that steroids significantly reduced admission rates in adults (odds ratio [OR] 0.47; CI 0.27, 0.79).[4,35,48] Children also benefited from steroid administration in the emergency department, although the two studies provide slightly different effect estimates. While statistically significant, this heterogeneity is not clinically important since both studies illustrate a dramatic benefit of steroid use in children.[31,34] Thus, steroid use is strongly supported in the younger age groups as well as in adults as a treatment strategy to prevent hospital admissions.

Parenteral (Intravenous/Intramuscular) Versus Oral Steroids in Treatment of Acute Exacerbation

Six studies were included that compared parenteral and oral steroid in the treatment of an acute exacerbation of asthma.[19,23,36-38,40] Outcome assessment of patients given IV compared with oral steroids was made after 24 hours using PFTs. All studies were placebo controlled and allocation was randomized. Two studies were excluded from this analysis because no 24-hour pulmonary function data were available[91,95]; the remaining studies all report PFT data and are displayed in Table 4. From these publications the pooled ES was −0.073 SD (CI −.39, .25). The test for heterogeneity was not significant (P = .63). One SD equals approximately 18% predicted FEV-1, suggesting a mean difference of 1.3% and an upper 95% CI of 5% favoring oral administration.

Time Course and Benefit of Steroids in Treatment of Acute Asthma

The effectiveness of steroid therapy measured by pulmonary function in the first 36 hours of treatment has been reported in eight randomized controlled clinical trials.[2,13-15,30,22,43,46] Of these, two papers were excluded from this meta-analysis; one due to inadequate data reporting,[14] and the other reported results using a symptom measure which precluded combining results.[2] The six remaining papers are detailed in Table 5; all but one[43] were inpatient studies. Common ES for pulmonary function were calculated for each assessment time: 12, 24 and 36 hours. There was insufficient information to pool other outcomes such as blood gases or symptoms.

There was statistically significant heterogeneity in the combined data at the 12-hour assessment (P = .01). Sensitivity analyses were inadequate to explain the heterogeneity on the basis of either the population or methodologic quality. Pooled results for the 24-hour assessment revealed similar

TABLE 4. Summary of Studies Which Use Pulmonary Function Tests to Compare Parenteral *vs* Oral Routes for the Administration of Steroids in the Treatment of Acute Exacerbations of Asthma

Reference	Treatment	n	Pulmonary Function Testing and Outcomes	Assessment: Time and Mean (SD)	Effect Size (and 95% CI)
Engel et al[36]					
Treatment group	IV methylprednisolone	8 Patients* (Adults)	—% Predicted PEFR	24 hours‡ 79 (18)%	+0.053
Control group	Oral prednisolone*	10 Patients (Adults)	—other PFTs —laboratory	24 hours 78 (18)%	(−.92, .98)
Jonsson et al[19]					
Treatment group	IV methylprednisolone	11 Patients (Adults)	—% Predicted FEV-1	24 hours‡ 72 (15.4)%§	+0.44
Control group	Oral methylprednisolone*	11 Patients (Adults)	—ABGs —Other PFTs	24 hours 65 (15.2)%§	(−.4, 1.3)
Ratto et al[38]					
Treatment group	IV methylprednisolone*	36 Patients (Adults)	—% Predicted FEV-1	24 hours 55 (18)%	−0.14
Control group	Oral methylprednisolone	34 Patients (Adults)	—H. .ital Days —T· .icity	24 hours 58 (24)%	(−.61, .33)
Harrison et al[23]					
Treatment group	IV hydrocortisone†	23 Patients (Adults)	—% Predicted PEFR	24 hours‡ 52 (21)%	−0.255
Control group	Oral prednisolone	24 Patients (Adults)	—nil	24 hours 58 (25)%	(−.82, .31)

NOTE: Pooled effect size = −0.073 (95% CI: −0.39, 0.25); test for homogeneity: P = .63.

ABBREVIATIONS: PEFR, peak expiratory flow rate; ABG, arterial blood gases; FEV-1, forced expiratory volume at 1 second.

* High dose.

† Intravenous group received oral steroids as well.

‡ Values extrapolated from enlarged figure.

§ Baseline SD used.

TABLE 5. Summary of Time Course of Pulmonary Function Changes for Studies Comparing Steroids to Placebo in the Treatment of Acute Exacerbations of Asthma

Reference	Treatment	n	Therapy	6-Hour ES	12-Hour ES	24-Hour ES	36-Hour ES
Fanta et al[13]							
Treatment group	IV hydrocortisone	11	8 hours post-ED IV aminophylline; IM β & inhaled β agonist	2.3 (1.2,3.4)	4.9 (3.2,6.6)	3.3 (2.3,4.2)	NA
Control group	IV placebo	9					
Pierson et al[15]							
Treatment group	Various IV steroids	30	Failure to respond in ED; IV aminophylline oxygen; fluids; β wet nebulized	NA	0.36 (−.36,1.1)	0.49 (−.14,1.1)	NA
Control group	IV placebo	15					
Younger et al[20]							
Treatment group	IV methylprednisolone	22	IV aminophylline; β agonist; IV fluids; oxygen	NA	0.30 (−.29,.89)	0.35 (−.23,1.1)	0.30 (−.29,.89)
Control group	IV placebo	23					
Shapiro et al[43]							
Treatment group	Oral methylprednisolone	13	outpatient; theophylline	NA	NA	−0.25 (−1.2,.71)	NA
Control group	Oral placebo	15					
Kattan et al[22]							
Treatment group	IV steroid	10	following ED tr IV aminophylline; oxygen; inhaled β agonist	NA	0.00 (−.41,.41)	−0.29 (−1.2,.61)	−0.36 (−1.3,.55)
Control group	No placebo	9					
Loren et al[46]							
Treatment group	Oral prednisone	9	"worsening" symptoms; inhaled β agonist; oral fluids; rest	NA	1.12 (.06,2.2)	0.99 (−.06,.2)	0.62 (−.5,1.7)
Control group	Oral placebo	7					

NOTE: Pooled ESs: 12 Hours → test for homogeneity: $P = .01$; 24 Hours → test for homogeneity (all studies): $P = .01$; 24 Hours → children only ES SD = 0.25 (−.07,.57)[15,20,22,43,46]; (test for homogeneity: $P = .50$); 36 Hours → children only studies: ES SD = 0.2 (−.24,.64); (test for homogeneity: $P = .30$).
ABBREVIATIONS: ES, effect size; tr, treatment; NA, not available.

heterogeneity ($P = .01$). When only pediatric studies were combined there was not significant heterogeneity ($P = .5$) and the ES was moderate (0.34). When 36-hour pulmonary function was examined, the ES was small (0.2) and there was not significant heterogeneity ($P = .30$).

Dosage of Steroids in the Treatment of Exacerbations of Asthma

The five studies that met the inclusion criteria[21,33,41,44,47] are summarized in Table 6. One study was excluded due to insufficient reporting of data.[44] Of the remaining papers, three dealt with treatment of hospitalized patients[21,41,47] and one dealt with the treatment of outpatients.[33] Three comparisons of high dose to low dose and two comparisons of moderate dose to low dose were available for analysis. When all studies were combined a trend towards improved outcome with high or moderate doses was observed, however this was not statistically significant (ES = 0.16; 95% CI = −17, .49). When analysis was restricted to the methodologically strongest studies,[21,33,47] a common effect size of 0.54 SD (95% CI = .1, .98) was produced when high or moderate doses were compared with low doses.

Tapering

One controlled trial was identified that addressed the issue of steroid tapering.[39] No significant difference was found in the relapse rate and symptoms between posthospitalized patients using short tapering (over 1 week) compared with long tapering (over 7 weeks) of oral steroids. We were unable to identify other papers comparing tapering with abrupt discontinuation of steroids that fit the eligibility criteria.

DISCUSSION

Physicians who assess and treat patients presenting with an asthmatic exacerbation are faced with many difficult decisions, including when to discharge, how aggressively to treat, and what medications to use. The literature is conflicting, particularly regarding the use of oral, IV, or IM steroids. Recent advances have increased our awareness about the role of inflammation in the pathophysiology of asthma,[9,10] making the use of steroids theoretically more appealing. However, no previous systematic overview existed covering the issues of steroid treatment in the acute exacerbation. Thus most clinicians were left with an unclear picture of the field.

TABLE 6. Summary of Five Studies Comparing Various Dosing Regimens in the Treatment of Acute Exacerbations of Asthma

Reference	n	Dosage Expressed as Prednisone Equivalence	Steroid: Site Route Duration	Additional Treatments	Assessment: PFT (type) Mean (SD)	Effect Size (95% CI)
Webb[33]	10	LD: 14 mg/d	Outpatient	β-agonists nil else	Combined as LD 331.3 (81.7)	LD vs MD: 0.41 (−0.4, 1.1)
	10	LD: 28 mg/d	Oral doses		364.8 (77.5)	
	10	MD: 42 mg/d	×2 wk			
Haskell et al[21]	8	LD: 12 mg/d	In hospital	IV aminophylline β-agonists fluids oxygen	55 (22.6)%*	LD vs MD: 0.47 (−0.5, 1.5)
	8	MD: 32 mg/d	IV		64 (11.3)%*	LD vs HD: 0.58 (−0.4, 1.6)
	8	HD: 100 mg/d	×3 d		66 (11.3)%*	
Harfi et al[47]			In hospital	IV aminophylline antibiotics oxygen		
	10	LD: 24 mg/d			155 (52) PEFR	LD vs HD: 0.44 (−0.4, 1.3)
	11	HD: 240 mg/d	IV "Maximum of 4 d"		179 (52) PEFR	
Raimondi et al[41]			In hospital	IV aminophylline β-agonists "hydration" oxygen	55.6 (13.0)%	
	20	LD: 25 mg/d				LD vs HD: −0.4 (−0.9, 0.3)
	20	HD: 350 mg/d	IV		48.3 (18.3)%	
(quasi RCT)			×5 d			

NOTE: All studies: pooled ES SD = 0.16 (−.17,.49); test for homogeneity: P = .20. MD or HD vs LD: pooled ES SD = 0.54 (.1,.98); test for homogeneity: P = .97[21,33,47]; MD vs LD; pooled ES SD = 0.43 (−.17, 1.04); test for homogeneity: P = .90.[21,33,47] HD vs LD: pooled ES SD = 0.5 (−.11, 1.11); test for homogeneity: P = .84.[21,33,47]

ABBREVIATIONS: LD, prednisone equivalent dose of <30 mg every 6 hours; MD, prednisone equivalent dose 30 < × ≥ 60 mg every 6 hours; HD, prednisone equivalent dose >60 mg every 6 hours.

* % predicted FEV-1.

This meta-analysis has attempted to assimilate the best available evidence on steroid use in patients with acute asthma. Several important conclusions arise from the analyses. First, there is little doubt that steroid treatment is more effective than placebo in the outpatient treatment of asthmatic exacerbations (Table 2). The pooled analysis reveals that there is a statistically significant and clinically important reduction in relapses in the first 7 to 10 days for those patients treated with a course of oral steroids (OR 0.15; CI 0.05, 0.44). This result is supported by the recent findings in studies where early treatment of chronic unstable asthmatics with oral steroids at the first sign of an upper respiratory tract infection reduced the complications and severity of subsequent asthma exacerbations.[49,50]

Clear conclusions can be made from the literature regarding the treatment of exacerbations with steroids upon arrival in the emergency department (as early as 30 minutes after presentation). Early administration of steroids in adults (OR 0.47) and children (OR 0.07-0.42) leads to reduced admission rates. The decision to admit patients is based on multiple factors, and may include such factors as past asthma history, current exacerbation history, arrival and postbronchodilator PFTs, along with clinical and patient judgment. Most papers did not clearly describe their criteria for discharge/admission and this may explain the differences in opinion regarding this issue. Despite a recent report indicating that early use of steroids in the emergency department does not affect admission rates when the overall admission rate was low (18%),[4] overall, steroids appear to have benefit in this setting.

For both complications (admission and relapse rates), results may be interpreted using the NNT analysis (Table 7).[27,28] For instance, given a baseline relapse risk of 20%, six patients would need to be treated with steroid following discharge to prevent one relapse to an emergency department. Alternatively, given a baseline admission risk of 20%, 11 adults or six to 11 children would need to be treated with steroids early in their emergency department stay to prevent one admission. Moreover, it is only when the baseline risks of each complication are extremely low (5% or less) that not using steroids might be defended. It should be emphasized that all included studies defined exacerbations of asthma as patients who had experienced increased symptoms, reduced pulmonary function as measured by FEV-1, or an increased use of bronchodilators prior to arrival in the emergency department. These would represent moderate to severe exacerbations of asthma.

Data regarding the route of steroid administration and steroid dose in patients with exacerbations suggest changes in treatment approaches. For instance, the use of IV steroids has become routine for severely asthmatic patients.[35] The results of pooled analysis of oral versus IV steroids reveals that there is no evidence to suggest that one route improves

TABLE 7. Number of Patients Needed to Treat With Steroids to Prevent Asthmatic Complications Such as Relapses to the Emergency Department and Admission to the Hospital

Baseline Incidence	Number Needed to Treat		
	Prevention of Relapse*	Prevention of Admissions (Adults)†	Prevention of Admissions (Children)‡
0.05	24	36	21-36
0.10	12	20	11-20
0.15	8	14	7-14
0.20	6§	11§	6-11
0.30	4	8	4-8
0.40	3	6	3-6
0.50	2	5	2-5

* Odds ratio of 0.15 corresponding to steroid efficacy of 85%.
† Odds ratio of 0.47 corresponding to steroid efficacy of 43%.
‡ Odds ratio of 0.06-0.42 corresponding to steroid efficacy of 94-58%.
§ Number needed to treat with steroids when baseline incidence of both complications approximates that commonly found in literature.

pulmonary function more than the other (Table 4). Additionally, no significant difference was observed when such outcomes as relapse of disease following discharge,[37] changes in oxygen tension over the treatment period,[19] or symptoms[38] were compared between groups. With the added costs and potential minor complications of IV therapy, these results support the use of oral forms of steroids except in those patients too dyspneic to swallow or those with anticipated absorption problems.[38] Such a result should encourage emergency physicians to be more liberal with steroid administration in the emergency department.

The final analyses were performed to examine the time course of improvement in the treatment of asthmatic exacerbations with steroids. When studies comparing IV steroid and placebo in admitted patients were examined, the ESs for the first 12 hours demonstrated heterogeneity that could not be explained by a priori hypotheses. However, at least in pediatric patients, steroids do not significantly improve pulmonary function results compared with placebo treatment at 24 and 36 hours. While arterial hypoxemia improved in one study[15] and symptoms improved in another,[2] ESs for the commonly used PFTs included 0 (ie, were not significantly improved). One paper examining adult patients reports significant improvement at 6 (ES 2.3 SD), 12 (ES 4.9 SD), and 24 (ES 3.3 SD) hours. This is equivalent to differences of 10, 16, and 9 in percent predicted FEV-1. Insufficient data were available from other adult studies to corroborate this finding.

Steroid use has been shown to be effective in the treatment of asthmatics in other clinical settings. Why then would they be found to be ineffective in these patients admitted from the emergency department? Several potential explanations for these results exist. One reason may be that children and adults differ in their response to steroids in the acute phase of the disease. Since all of the studies pooled to calculate the ES were pediatric, this remains a possible explanation.

Alternatively, these outcome measures may not be sensitive to changes in the first 3 days of a treated exacerbation. Pulmonary function tests have a high within-patient variability, and may be unable to detect small yet clinically important changes. In addition, the determination of PFTs in the acute exacerbation may be unreliable, especially in younger children where effort may be difficult to maximize. Reliance on these measures may be hampering promising research. As Ward has pointed out, to detect a difference using PFTs, studies must be large[51]; most studies reviewed here do not satisfy this requirement. It is unlikely that further changes in asthmatic care will lead to large changes in pulmonary function; therefore, alternative outcome measures may need to be developed and used. For instance, development of a quality of life instrument for asthmatic patients has been completed and this may be a more sensitive and responsive measurement instrument.[52]

Finally, another theory that may explain these results suggests that asthmatic exacerbations may be characterized by fast and slow responses.[53] Patients presenting with asthmatic exacerbations may respond rapidly or slowly to treatment in the emergency department, and slow responders may represent those patients who have more inflammation or are steroid-resistant. Fast responders may benefit from early administration of steroids, by mechanisms that are poorly understood but probably represent influences on the β receptors. This area requires further study, but is supported by data that show admitted patients (slow responders) respond slowly to treatment, even when steroids are added (Table 6).

The data on high dose steroid versus moderate or low dose treatment are complex. When analysis is restricted to methodologically strong studies, the results indicate a tendency towards improvement in pulmonary function when moderate to high doses are compared with placebo. Due to the wide dosage range in the high-dose group, further research is needed to define the role of high-dose regimens. It is likely that very high-dose regimens add little to the outcomes of these patients, as the plateau in the log dose-response curve may be reached at lower doses. However, from the available information, it is impossible to estimate where such a plateau begins. The current analysis suggests that doses of less than 30 mg are suboptimal.

There are several limitations that must be discussed pertaining to this paper and a recent meta-analysis on this topic.[54] When reading and reporting meta-analysis results, it is helpful to have an organized approach. Recently, there have been several publications that specifically address this issue.[6,55]

The search strategies used in this meta-analysis included computerized MEDLINE, SCIENCE CITATION, book chapters, cited bibliographies, experts, and personal contact with authors. While a balance between exhaustive and practical was obtained, unpublished and foreign language papers have not been included. There were no foreign papers on steroid treatment in asthmatic exacerbations that could be added to this overview. This conclusion results from the fact that alternative search strategies did not reveal foreign publications on these particular topics. Unpublished literature was solicited but not forthcoming from those authors with expertise in the field. While these methods are not foolproof,

it seems unlikely that rigorous clinical steroid trials exist that would substantially alter these results.

We attempted to clearly define the research question by including only those studies that were randomized or quasi-randomized trials dealing with steroid treatment of patients with acute exacerbations of asthma, assessed using standardized outcome criteria. Using two independent reviewers and explicit inclusion criteria addressed biases in study selection. The agreement for inclusion of studies was high, and the comprehensive nature of the search reduced the opportunity to introduce personal bias in study selection.

Were we justified in combining the results of these studies? This question lies at the heart of meta-analysis. Generally, the purpose of pooling individual studies is to provide a general effect of treatment. It would appear sensible and appropriate to combine those studies using steroid therapy since the sample sizes of the individual studies are insufficient to reach a firm conclusion. In addition, the decision to combine results is based on demonstration of similarities in populations, interventions, and outcome measurements between studies. By dividing the papers into their respective categories, the issue of similarity was addressed. Restricting the analysis to randomized controlled trials resulted in the inclusion of only the strongest available clinical evidence. As a result of these maneuvers, the pooling of data was reasonable, although statistically significant heterogeneity was still found in some of the analyses.

When examining the quality of papers involving steroid treatment in acute asthmatic exacerbations, it is obvious that greater planning must be incorporated into further work if clarity is to emerge. Statistical planning and sample size calculation must be more carefully considered. Few papers were large enough to protect against type II error, and sample size considerations were rarely reported. Multiple statistical tests were frequent; some papers described more than 20 tests without correcting for multiple testing. Moreover, the potential danger of this strategy, in the form of increased chances of type I error, was not recognized.

Few studies included outcome measures other than PFTs. Their inherent variability, particularly in the acute exacerbation, emphasizes the need for further research into alternative measures, particularly assessment of factors that are important to the patient (quality of life, functional outcomes, symptoms, etc).

Despite these methodological limitations, the results of this work indicate several avenues of treatment change and future research. Steroid use in the treatment of acute exacerbations of asthma has been clarified. Steroid use reduces relapses if given to the discharged patient, and improves pulmonary function, albeit slowly, if given in moderate to high doses. The weight of evidence also supports the recommendation that steroid use in the early phase of emergency department treatment is beneficial in reducing hospital admission rates.

While it appears that steroid use in the acute asthmatic is effective, there is little evidence for the reliance on the IV route of administration. Since oral doses are rapidly absorbed,[56] it is not surprising that there is similar efficacy. In addition, our knowledge of the intracellular, delayed mechanism of steroid action supports this idea.[57] Finally, the use of the oral route of administration could reduce costs and minor complications (pain, phlebitis, etc) from the treatment of this disease. Further research must be completed regarding the optimum dose of steroid.

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