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An umbrella review: Corticosteroid therapy for adults with acute asthma

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Abstract

The objective of this ‘umbrella’ review is to synthesize the evidence and provide clinicians a single report which summarizes the state of knowledge regarding the use of corticosteroids in adults with acute asthma. Systematic reviews in the Cochrane Library and additional clinical trials published in English from 1966 to 2007 in MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL and references from bibliographies of pertinent articles were reviewed. Results indicate that the evidence base is frequently limited to small, single-center studies. Findings suggest that therapy with systemic corticosteroids accelerates resolution of acute asthma and reduces the risk of relapse. There is no evidence that corticosteroid doses higher than standard doses (prednisone 50–100 mg equivalent) are beneficial. Oral and intravenous corticosteroids, as well as intramuscular and oral corticosteroid regimens appear to be similarly effective. A non-tapered 5–10 day course of corticosteroid therapy appears to be sufficient for most discharged patients. Combinations of oral and inhaled corticosteroids on emergency department/hospital discharge may minimize the risk of relapse.

Keywords

asthma; asthma exacerbation; adults; acute asthma; corticosteroids; treatment; hospital; emergency department; review

INTRODUCTION

Asthma is a common respiratory disorder characterized by chronic airway inflammation, airflow obstruction, and episodic symptoms such as wheeze, chest tightness, dyspnea and cough.¹ Despite major advances in our understanding of the pathogenesis of asthma, episodes

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of acute asthma requiring emergency department visits and hospitalizations are common. In the United States alone, for example, there are about 2 million emergency department visits and 500,000 hospitalizations for acute asthma each year.²

Acute asthma is most often precipitated by respiratory viral infections and/or environmental exposures to irritants (e.g., air pollution) and/or allergens.^{3–7} These triggers dramatically augment airway inflammation, airflow obstruction, and respiratory symptoms. Over the past 50 years, there have been numerous randomized clinical trials that have established corticosteroids as the cornerstone of anti-inflammatory therapy in adults presenting to the emergency department or hospitalized for acute asthma.^{1,8} Corticosteroids reduce the amplification of the inflammatory cascade by altering transcriptional and post-transcriptional regulation, and may also have non-genomic actions.⁹

Data from randomized clinical trials have been examined in a number of high quality systematic reviews conducted by members of the Cochrane Airways Group (CAG) and published in the Cochrane Library. Such reviews, however, have each focused on specific aspects of corticosteroid use (e.g., dose).^{10–14} Treatment decisions by clinicians, however, include not only the corticosteroid dose, but other aspects of corticosteroid use, including the route of therapy (inhaled vs. oral vs. intramuscular vs. intravenous), duration of therapy, and use of fixed-dose vs. tapering regimens. Thus, clinicians would need to read multiple reviews to have sufficient information to provide evidence-based care in this population.

The objectives of the current “umbrella” review are to synthesize the findings from multiple reviews and additional randomized clinical trials that have been published since^{15–28} into a single document for easy use by clinicians. More specifically, this report will address the following clinically relevant questions in patients presenting to the emergency department or hospitalized for acute asthma:

1. Does systemic corticosteroid therapy (compared to no corticosteroids) improve outcomes?
2. What dose of systemic corticosteroid therapy is needed?
3. Is intravenous corticosteroid therapy superior to oral corticosteroid therapy?
4. What duration of corticosteroid therapy is needed?
5. Is an oral corticosteroid taper superior to a fixed-dose corticosteroid regimen after discharge home?
6. Is a single dose of depot intramuscular corticosteroids superior to a multi-dose oral corticosteroid regimen?
7. Is combination therapy with inhaled and systemic corticosteroids superior to systemic corticosteroids alone?

METHODS

Evidence acquisition

For each question, we conducted a literature search for systematic reviews performed by CAG and searched for additional randomized clinical trials in the following electronic literature databases: MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL. Additional articles were identified by hand-searching 20 respiratory journals, references identified in the retrieved articles, and queries of content experts. A detailed description of the search methodology is provided elsewhere.²⁹ We limited the search to English-language articles in adults published from 1966 to 2007. The level of evidence was graded based on the following criteria:³⁰

Level of evidence	Explanation
A	Well-designed randomized clinical trials in relevant populations
B	Randomized clinical trials with minor limitations or overwhelmingly consistent evidence from observational studies
C	Observational studies using case-control and cohort designs
D	Expert opinion, case reports, or reasoning (e.g., based on data from similar populations)
X	Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm

Based on the level of evidence, we graded recommendations by consensus as follows:³⁰

Recommendation	Level of Evidence
Strong recommendation (S)	A, B, or X
Recommendation (R)	B, C, or X
Option (O)	A, B, C, or D
No recommendation (NR)	D

A recommendation grade “S” means, that on the basis of the review, we believe that the benefits of the recommended approach clearly exceed the harms and that the quality of the evidence supporting this approach is either excellent or impossible to obtain. Clinicians should follow such guidance unless a compelling rationale for choosing an alternative approach is present. A recommendation grade “R” means that we believe that the benefits exceed the harms, but the quality of the evidence supporting this recommendation is not as strong. Clinicians should generally follow this guidance, but could adopt an alternate approach based on additional clinical information and patient preferences. A recommendation grade “O” means either that the quality of the evidence is inadequate or that well-designed studies have failed to demonstrate that one approach is superior to the alternate approach. Clinicians should adopt a flexible approach and choose the option that incorporates appropriate clinical factors, including patient preference and convenience. A recommendation grade “NR” is made when there is inadequate information about the balance between benefits and harms of various approaches. Clinician decision-making is not constrained based on evidence alone; patient preference should have a substantial role in the decision-making.

Two authors independently provided evidence-grading assessments on the seven clinical questions posed in this review. Disagreements were resolved by adjudication by a third author.

EVIDENCE SYNTHESIS

1. Does systemic corticosteroid therapy (compared to no corticosteroids) improve outcomes? (Table 1)

Nine placebo-controlled randomized trials enrolled a total of about 500 patients with acute asthma;^{15–17,31–36} 481 were recruited in the emergency department, and 52 were recruited from the inpatient (hospitalized) setting. These studies largely focused on short-term outcomes (within 6 to 12 hours) after a single dose of systemic corticosteroids vs. placebo; a notable exception is one study that examined 14-day outcomes after a 10-day course of systemic corticosteroids vs. placebo.¹⁶ A systematic review of six of these trials^{31–33,34–36} reported a trend toward reduced hospital admission rates in adults presenting to the emergency department who were treated with systemic corticosteroids, usually within 90 minutes of emergency department arrival (OR: 0.58; 95% CI, 0.32 to 1.07).¹⁰ The effect of corticosteroids on pulmonary function was variable in the short-term, mainly due to insufficient reporting of results in the individual trials. Side effect profiles were similar between all corticosteroid treatment routes and placebo, suggesting that early treatment with corticosteroids is safe.

In addition, there have been 2 placebo-controlled randomized clinical trials that evaluated the benefit of systemic (oral¹⁶ and intravenous¹⁷) corticosteroids in a total of 52 adults hospitalized

for acute asthma. Despite the small number of participants, results indicate that systemic corticosteroids significantly accelerated the resolution of acute asthma (symptoms, examination, and lung function) in this population. For example, there is a significantly greater improvement in airflow obstruction (forced expired volume in 1 second (FEV₁)) with corticosteroid therapy compared to placebo (0.43L vs. 0.0L, $p < 0.02$).¹⁷

Taken together, these studies in emergency department and hospitalized patients provide Level B evidence that systemic corticosteroids provide clinically meaningful benefits in patients presenting with acute asthma. The vast majority of studies, however, were of small size ($n = 38$ – 98 patients per study), and only two were multi-center studies.^{15,16}

2. What dose of systemic corticosteroid therapy is needed? (Table 2)

Direct comparisons of different doses of systemic corticosteroids were not identified in emergency department patients. In a systematic review of hospitalized patients, corticosteroid dose regimens were classified as very high dose (> 450 mg/day prednisone equivalent), high dose (101 to 450 mg/day prednisone equivalent) or standard dose (≤ 100 mg/day prednisone equivalent) using standard conversions.¹¹ Of nine randomized clinical trials in adults presenting to the emergency department and subsequently admitted to the hospital, six randomized clinical trials (total $N = 272$)^{18,37–41} provided sufficient data to contribute to the pooled analysis. Overall, there were no clinically or statistically significant differences in FEV₁ % predicted between the 3 groups after 24, 48 or 72 hours, despite the approximate 55-fold range of corticosteroid doses used. At 48 hours, the weighted mean difference (WMD) in FEV₁ was -3.3% predicted (95% CI, -12.4 to 5.8%) for the standard vs. high dose comparison, -1.9% predicted (95% CI, -8.1 to 4.3%) for the high vs. very high dose comparison and $+0.5\%$ predicted (95% CI, -7.8 to 8.8%) for the standard vs. very high dose comparison. Also there were no clinically or statistically significant differences in FEV₁ at 24 hours in patients treated with 50 mg/d prednisone equivalent vs. very high dose; the pooled WMD in FEV₁ was $+7.2\%$ predicted (95% CI, -2.3 to $+16.7\%$), favoring patients treated with the *standard* dose.^{37,38}

While patients with respiratory failure requiring mechanical ventilation were excluded from these randomized clinical trials, analyses restricted to patients with severe episodes (an initial post-bronchodilator FEV₁ $< 50\%$ predicted) also failed to identify significant benefits of very high doses compared to standard doses in this subset (WMD in FEV₁ at 48 hours low vs. high $+2.3\%$ predicted (95% CI, -6.6 to 11.2%)).¹¹ In addition, there were no significant differences in side effects or rates of respiratory failure among the varying doses of corticosteroids. While these studies were not designed to ‘prove’ equivalence (i.e., not equivalency trials), this body of evidence (Hospital, Level B; Emergency department, Level D, extrapolating from studies in hospitalized patients) in patients without respiratory failure does not favor using higher than standard doses of corticosteroids.

3. Is IV corticosteroid therapy superior to oral corticosteroid therapy? (Table 3)

Direct comparisons of IV and oral corticosteroid agents were not identified in emergency department patients. In a randomized clinical trial of 70 adults hospitalized for acute asthma, ¹⁸ investigators failed to identify clinically meaningful or statistically significant differences in FEV₁ or length of hospital stay between patients treated with oral corticosteroids (200 mg/day or 400 mg/day prednisone equivalent) or IV corticosteroids (625 mg/day or 1,250 mg/day prednisone equivalent) regimens, despite substantially higher (1.5 to 6-fold higher) daily corticosteroid doses in the IV corticosteroid groups. There were also no significant differences in the rate of side effects. Thus, the available evidence (Level B in hospitalized patients; Level D in emergency department patients) does not support the superiority of IV over oral corticosteroid therapy.

4. What duration of corticosteroid therapy is needed? (Table 4)

No emergency department-based studies exist comparing different durations of corticosteroid therapy following discharge in adults were identified. Two small randomized clinical trials examined the benefit of different total durations of systemic corticosteroid therapy in 64 adults hospitalized for acute asthma (including therapy received during hospitalization: 5 vs. 10 days,¹⁹ and 10 vs. 17 days).²⁰ These studies used 40 mg/day¹⁹ or 0.5 mg/kg/day²⁰ prednisone equivalent doses after hospital discharge and all patients were discharged on daily inhaled corticosteroid therapy. Patients on chronic oral corticosteroids or requiring mechanical ventilation for near-fatal asthma were excluded from both studies. Lung function (PEFR) and relapse rates were similar in the treatment groups; the studies failed to identify any benefit of extending systemic corticosteroid therapy beyond a total of 5 to 10 days. Once again, while these findings cannot be interpreted as proving equivalence, the weight of evidence (Level B in hospitalized patients; Level D in emergency department patients) does not favor any particular duration beyond 5 days in adults.

5. Is an oral corticosteroid taper superior to a fixed-dose corticosteroid regimen after discharge home? (Table 5)

Tapering regimens of corticosteroids, in which the dose of corticosteroids is gradually reduced, offer the theoretical advantage of minimizing the risks of worsening airway inflammation, suppressed hypothalamic-pituitary-adrenal axis, and relapse when corticosteroids are discontinued compared to shorter fixed-dose regimens. However, slowly tapering regimens tend to be longer and more complicated for patients than fixed-dose regimens, which may increase the risk of corticosteroid-related adverse effects and non-adherence to therapy, respectively.⁴²

Two randomized clinical trials compared an eight-day fixed-dose course of oral corticosteroids (40 mg/d prednisone equivalent) to an eight-day taper of oral corticosteroids in patients discharged home from the emergency department.^{21,22} The two trials were small (total N = 41 participants) and excluded patients using inhaled or systemic corticosteroids within the previous two weeks. There were no significant differences between groups in FEV₁% predicted, rates of relapse at day 12 or 21 after discharge, or suppression of the hypothalamic-pituitary-adrenal axis.

Three randomized clinical trials in 113 hospitalized adults evaluated the benefit of adding an oral corticosteroid taper after completing a six to fourteen day course of systemic corticosteroids.^{23–25} All patients were discharged home on inhaled corticosteroids and patients requiring mechanical ventilation were excluded from two^{23,24} of the three studies. Follow-up four weeks^{24,24} and 12 weeks²⁵ after discharge failed to detect differences in lung function, relapse rates, symptoms, or rates of adrenal suppression. Thus, the evidence from emergency department and hospitalized populations does not demonstrate a benefit from using oral corticosteroid tapers compared to a fixed-dose regimen.

6. Is a single dose of depot intramuscular corticosteroids superior to a multi-dose oral corticosteroid regimen? (Table 6)

Non-adherence to corticosteroid therapy (inhaled or systemic) is surprisingly common (about 50%) in patients discharged from the emergency department or hospital following initial therapy for acute asthma, and is one of the main factors associated with relapse.^{43–45} Intramuscular formulations can ensure that patients continue to receive corticosteroids following discharge from the emergency department or hospital. Five randomized clinical trials in adults have examined the relative benefits of intramuscular corticosteroids compared to oral corticosteroids for the outpatient treatment of acute asthma following discharge from the emergency department.^{13,26} These randomized clinical trials (575 adults) compared oral vs.

intramuscular corticosteroids after emergency department discharge in patients with acute asthma.^{26–28,46,47} No similar studies have been conducted in patients discharged after a hospital stay.

A single intramuscular corticosteroid dose was compared to fixed-dose corticosteroid regimens in two studies^{27,28} and to an oral corticosteroid regimen with gradually decreasing doses (taper) in three studies.^{26,46,47} Overall, there were no significant differences in relapse rates between intramuscular and oral corticosteroids at 10 days (RR = 0.73; 95% CI, 0.49 to 1.09) or at 21 days (RR = 1.03; 95% CI, 0.73 to 1.44).²⁶ Some studies, however, reported a higher rate of complications at the injection site (e.g., pain, bruising) in patients who received intramuscular corticosteroids. For example, in the study by Lahn et al.,²⁶ the mean pain at injection site (on a scale of 10 (higher scores indicate more pain): 3.3 vs. 1.9, $p < 0.05$) and rates of bruising at the injection site (8% vs. 0%, $p < 0.05$) were significantly higher in the intramuscular compared to the oral corticosteroid group. Thus, Level B evidence in emergency department patients (and Level D evidence from hospitalized patients) does not support the superiority of depot intramuscular corticosteroids over a multi-dose oral corticosteroid regimen; however, there is evidence of more injection-site adverse effects in patients receiving intramuscular corticosteroids.

7. Is combination therapy with inhaled and systemic corticosteroids superior to systemic corticosteroids alone? (Table 7)

Adding daily inhaled corticosteroids to a short course of systemic corticosteroids offers patients the potential benefit of further suppressing airway inflammation after completing a course of systemic corticosteroids, during the resolution phase of acute asthma. It also provides a 'teachable moment' in which appropriate inhaler technique and adherence to treatment for chronic asthma (e.g., inhaled corticosteroids) to *prevent* future episodes of acute asthma can be reviewed and reinforced. Three randomized clinical trials have evaluated the utility of combining inhaled and oral corticosteroids compared to oral corticosteroids alone following emergency department discharge;^{48–50} two have been published as full-length manuscripts.^{48,49} No randomized clinical trials in hospitalized adults were identified.

Pooled results from these emergency department-based studies, representing a total N = 909 adults in the three trials, indicate a non-significant trend towards fewer relapses after discharge in the group treated with combination corticosteroid therapy (OR: 0.68; 95% CI, 0.46 to 1.02)¹⁴ with side effects of hoarseness and sore throat being significantly higher in the inhaled corticosteroid group. Of note, observational studies using administrative data of ED⁵¹ and hospitalized⁵² patients suggest that inhaled corticosteroid therapy significantly reduces the risk of relapse after discharge. Moreover, patients with *acute* asthma are more symptomatic than patients with moderate or severe forms of *chronic* asthma, two groups for which national guidelines already recommend inhaled corticosteroid therapy.¹ Thus, Level B evidence (emergency department patients) and Level C evidence (hospitalized patients), favors the use of combination of inhaled and oral corticosteroids.

CONCLUSIONS

Given the current state of the science, how should clinicians treat these patients (Tables 8 & 9)?

The current evidence is based largely on a small number of relatively under-powered, single-center randomized clinical trials which excluded patients with respiratory failure requiring mechanical ventilation (Level B–D Evidence). Until more definitive evidence from larger-scale, multi-center randomized clinical trials is available, we make the following recommendations:

1. Initiate anti-inflammatory therapy with systemic corticosteroids in patients presenting to the emergency department or hospital with acute asthma (recommendation grade “R” for emergency department and hospitalized patients);
2. Use a prednisone-equivalent dose of 50–100 mg daily (recommendation grade “O” for emergency department and hospitalized patients), since higher doses do not appear to provide additional benefit;
3. Unless patients are unable to take medications by mouth (e.g., in severe distress, obtunded, intubated, or vomiting) or failed an oral regimen, use oral corticosteroids as first-line therapy for acute asthma since it is simpler and less costly to administer than IV corticosteroids (recommendation grade “O” for emergency department and hospitalized patients);
4. Continue oral corticosteroid therapy on discharge home from the emergency department or during and after hospitalization for a total of 5 to 10 days (recommendation grade “R” for emergency department and hospitalized patients);
5. A fixed-dose oral corticosteroid regimen should be prescribed to minimize the complexity of the treatment regimen and optimize adherence to therapy after discharge home (recommendation grade “R” for emergency department and hospitalized patients);
6. Intramuscular corticosteroids appear similarly effective to oral regimens, though have increased injection-site adverse effects. Therefore, intramuscular corticosteroids should be considered an option only for patients unwilling or unable to take oral corticosteroids after discharge home (recommendation grade “O” for emergency department and hospitalized patients).
7. Use a combination oral and inhaled corticosteroids on emergency department or hospital discharge to minimize the risk of relapse (recommendation grade “R” for emergency department and hospitalized patients).

What major directions for research should be pursued?

Large-scale, multi-center trials of corticosteroid use are needed to provide a more definitive evidence base for the management of acute asthma; studies in patients with respiratory failure (e.g., those who undergo mechanical ventilation) are urgently needed. In addition, there is emerging evidence that leukotriene modifiers (e.g., montelukast, zafirlukast), when initiated in the emergency department during acute asthma, may rapidly improve lung function and reduce the risk of relapse after emergency department discharge.^{53,54} A recent randomized clinical trial failed to show a benefit for improving relapse rates when LABAs were added to inhaled and systemic corticosteroids (vs. inhaled and systemic corticosteroids alone) at the time of discharge from the emergency department (10.1% vs. 14.7%, $p=0.42$).⁵⁵ Thus, further large, multi-center clinical trials are needed to clarify the incremental benefit (and risk) of combining corticosteroids with other agents (e.g., inhaled/oral corticosteroids with long-acting bronchodilators, inhaled/oral corticosteroids with leukotriene modifiers) during acute asthma.

Limited evidence exists in chronic asthma that treatment strategies that incorporate decisions to suppress eosinophilic airway inflammation (measured directly by induced sputum eosinophils, or indirectly by exhaled nitric oxide) provide better control of asthma and fewer episodes of acute asthma compared to treatment decisions based on assessment of symptoms and lung function alone.^{56, 57} While potentially appealing, given the cost and availability of these tests, further research is needed to evaluate the clinical benefit of incorporating biomarkers of eosinophilic airway inflammation in the acute care setting.^{58,59}

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Does systemic corticosteroid therapy (compared to no corticosteroids) improve outcomes?

Table 1

Participants				Intervention		Results				
Inclusion criteria			Site							
Number	Age, range (yrs)	Pulmonary function (L/sec or % predicted)	# Recruitment sites	Recruitment location	Dose (prednisone equivalent), corticosteroid, route & frequency	Duration of follow-up	Pulmonary Function	Hospitalization during index visit	Relapse after discharge	
									Symptoms	Rescue medication use
Medical Research Council ¹⁶ , 1956	32	>14	13	I	88 mg HC PO on day 1 tapered to 0mg on day 10 vs. placebo PO	14d			↓*	
McFadden ¹⁵ , 1976	38	16-44	2	E	62 mg HC IV vs 125mg HC IV vs. 250mg HC IV vs. placebo IV × 1	6h	↑			↓
Fanta ¹⁷ , 1983	20	18-45	1	E	0.5mg/kg HC IV bolus, then 0.1mg/kg/hr HC IV vs. placebo IV × 24 hrs	12h	↑*			
Littenberg ³³ , 1986	97	≥ 18	1	E	156 mg MP IV vs. placebo IV × 1	1wk	↓	↓*	↑	↓*
Schneider ³⁵ , 1988	56	“adult”	1	E	38 mg/kg MP IV vs. placebo IV × 1	6h		↓	↓*	
Stein ³⁶ , 1990	91	18-45	1	E	156 mg MP IV vs. placebo IV × 1	12h	↓	↑	↓	↑
Rodrigo ³⁴ , 1994	98	18-50	1	E	125 mg HC IV vs. placebo IV × 1	6h	↓	↑	↑	
Lin ³¹ , 1997	45	≥ 18	1	E	156 mg MP IV vs. placebo IV × 1	1h	↓	↑		
Lin ³² , 1999	56	≥18	1	E	156 mg MP IV vs. placebo IV × 1	2h	↑*	↓		

Number of participants with baseline data reported is shown above; may be less than the number enrolled. All studies randomized, double-masked, placebo-controlled. No inhaled corticosteroids in intervention.

[^] Stein³⁶: all pts received 40mg MP IV Q6hr if still getting therapy after 6 hrs.

E=Emergency Department, I=Inpatient ward, MP= methylprednisolone, HC=hydrocortisone, IV=intravenous, PO=by mouth.

↑* Statistically significant (p-value <0.05) increase for systemic corticosteroid group compared to placebo

↑ Increase in systemic corticosteroid group compared to placebo group, but not statistically significant difference (p-value >0.05)

↓* Statistically significant (p-value <0.05) decrease for systemic corticosteroid group compared to placebo

↓ Decrease in systemic corticosteroid group compared to placebo group, but not statistically significant difference (p-value >0.05)

What dose of systemic corticosteroids is needed?

Participants				Intervention		Results					
Inclusion criteria				Placebo controlled	Dose (prednisone equivalent), corticosteroid, route & frequency	Duration of follow-up	Pulmonary function	Length of Stay	Relapse after discharge	Symptoms	Rescue medication use
Number	Age, range (yrs)	Pulmonary function (% predicted)	FEV1 <50%								
Haskell ³⁹ , 1983	38.6 [†]			N	19 mg MP IV q6h vs. 50mg MP IV q6h vs. 156 mg MP IV q6h × 72h	3d	↑*				
Harrison ⁴¹ , 1986	16–50	PEFR ≤30%		Y	Placebo IV plus 45mg PS PO ×1 then 15mg PS PO q8h × 1d vs. 0.8mg/kg HC IV bolus then 0.8mg/kg q6h HC continuous IV plus 45mg PS PO × 1, then 15mg PS PO q8h × 1d	24h	↑				
Ratto ¹⁸ , 1988	18–64	PEFR <50%		N	100mg MP PO BID vs. 100mg MP PO QID vs. 156 mg MP IV q6h vs. 312 mg MP IV q6h × 3d	3d	↑	↓			
Engel ³⁸ , 1990	46.8 [†]	FEV1 <60%		Y	50mg/d PS PO taper × 18d vs. 1250mg MP IV × 1	12wk	↑	↓			↓
^ Bowler ³⁷ , 1992	18–65	None stated		N	62 mg HC IV q6h × 48h then 20mg/d PR PO vs. 250mg HC IV q6h × 48h then 40mg/d PR PO vs. 625mg HC IV q6h × 48h then 60mg/d PR PO. PR PO was tapered over 12d in all groups..	12d	↓			↑	
Marquette ⁴⁰ , 1995	18–65	FEV1 <50%		N	1.3mg/kg/d MP IV vs. 7.5mg/kg/d MP IV × 48h	44h	↑	↓			

Number of participants with baseline data reported is shown above; may be less than the number enrolled. All studies except Ratto¹⁸ double-masked. All studies began in emergency department and followed subjects as inpatients. No studies included inhaled corticosteroids in intervention.

[^] Bowler³⁷ study conducted at 2 sites; all other studies are single-site.

[†] Age range not given; presented as mean years.

BID= twice per day, IV= intravenous, MP=methylprednisolone, HC=hydrocortisone, PO= by mouth, PS= prednisolone, PR=prednisone, QID = four times/day.

↑* Statistically significant (p-value <0.05) increase for lower doses compared to higher doses

↑ Increase in lower doses compared to higher doses, but not statistically significant difference (p-value >0.05)
↓* Statistically significant (p-value <0.05) decrease for lower doses vs. higher doses
↓ Decrease in lower doses compared to higher doses, but not statistically significant difference (p-value >0.05)

Is intravenous (IV) corticosteroid therapy superior to oral corticosteroid therapy?

Participants			Intervention	Results						
Inclusion criteria										
Ratto ¹⁸ , 1988	Number	70	Pulmonary function (% predicted) PEFr <50%	Dose (prednisone equivalent), corticosteroid, route & frequency 100mg MP PO BID vs. 100mg MP PO QID vs. 156 mg MP IV q6h vs. 312 mg MP IV q6h × 3d	Duration of follow-up 3d	Pulmonary function	Length of Stay	Relapse after discharge	Symptoms	Rescue medication use
	Age, range (yrs)	18–64								

Number of participants with baseline data reported is shown above; may be less than the number enrolled. Randomized but not double-masked. Study began in emergency department and followed subjects as inpatients. Did not include inhaled corticosteroids in intervention. BID= twice per day, QID= four times per day, MP= methylprednisolone, IV=intravenous, PO=by mouth.

- ↑* Statistically significant (p-value <0.05) increase for oral group compared to IV group
- ↑ Increase in oral group compared to IV group, but not statistically significant difference (p-value >0.05)
- ↓* Statistically significant (p-value <0.05) decrease for oral group compared to IV group
- ↓ Decrease in oral group compared to IV group, but not statistically significant difference (p-value >0.05)

What duration of CS therapy is needed?

Table 4

Participants			Intervention		Results					
Inclusion criteria			Dose (prednisone equivalent), corticosteroid, route & frequency		Duration of follow-up	Pulmonary function	Length of stay	Relapse	Symptoms	Rescue medication use
Number	Age range (yrs)	Pulmonary function (% predicted)								
Hasegawa ²⁰ , 2000	51 [^]	None stated	100mg MP IV q8h × 3d then 0.5mg/kg/d PS PO × 14d vs. 100mg MP IV q8h × 3d then 0.5mg/kg/d PS PO × 7d		6mo	↑		↔		
Jones ¹⁹ , 2002	16-60	PEFR <65%	40mg/d PS PO × 5d then 40mg/d PS PO days 6-10 vs. 40mg/d PS PO × 5d then placebo PO days 6-10		21d	↑		↑	↓ *	↑

Number of participants with baseline data reported is shown above; may be less than the number enrolled.

[^] Age range not given; data reported as mean (yrs).

Both studies recruited from inpatient ward. Inhaled CS used in all intervention groups. PS= prednisolone, PO=oral, IV=intravenous

↑* Statistically significant (p-value <0.05) increase for longer duration compared to shorter duration

↑ Increase in longer duration compared to shorter duration but not statistically significant difference (p-value >0.05)

↓* Statistically significant (p-value <0.05) decrease for longer duration compared to shorter duration

↓ Decrease in longer duration vs. shorter duration, but not statistically significant difference (p-value >0.05)

↔ Same number of events with same number of participants in each group

Is an oral corticosteroid taper superior to a fixed-dose corticosteroid regimen after discharge home?

Table 5

Participants				Intervention		Results		
Inclusion criteria				Site				
	Number	Age range (yrs)	Pulmonary function (% predicted)	# Recruitment sites	Recruitment site	Dose (prednisone equivalent), corticosteroid, route & frequency	ICS in all intervention groups?	Duration of follow-up 12wk
Lederle ²⁵ , 1987	43	62.8*	None stated	1	I	60mg/d PR PO × 8d, then 45mg PR × 7wk taper vs. 60mg/d PR PO × 8d, then 45mg/d PR × 7d taper, then placebo × 6wks 40mg/d PS PO × 10d then 40mg/d PS PO × 8d taper vs. 40mg/d PS PO × 10d then placebo PO × 8d 40mg/d PS PO until discharge, then 40mg PS PO × 14d taper vs. 40mg/d PS PO until discharge, then placebo PO × 14d	Y	↑
O'Driscoll ²⁴ , 1993	35	16–55	PEFR ≤ 65%	2	I		Y	↑
Hatton ²³ , 1995	35	16–80	None stated	1	I		Y	↑
Cydulka ²¹ , 1998	15	19–50	FEV1 ≥ 70%	1	E	75mg MP IV × 1 then 40mg/d PR PO × 8d taper vs. 75mg MP IV × 1 then 40mg/d PR PO × 8d 40mg/d PS PO × 8d taper vs. 40mg/d PS PO × 8d	N	↓
Karan ²² , 2002	26	16–70	FEV1 ≥ 70%	1	E		Y	↓

Number of participants with baseline data reported is shown above; may be less than the number enrolled.

* Age range not given; data presented as mean (yrs). All studies randomized. All except Karan³⁶ double-masked and placebo-controlled.

MP=methylprednisolone, PO=by mouth, PS=prednisolone, PR=prednisone

↑* Statistically significant (p-value <0.05) increase for tapered dose group vs. fixed-dose group

↑ Increased in tapered dose group vs. fixed-dose group, but not statistically significant difference (p-value >0.05)

↓* Statistically significant (p-value <0.05) decrease for tapered dose group vs. fixed-dose group

↓ Decreased in tapered dose group vs. fixed-dose group, but not statistically significant difference (p-value >0.05)

Is a single dose of depot intramuscular corticosteroids superior to a multi-dose oral corticosteroid regimen?

Inclusion criteria										
Number	Age range (yrs)	Pulmonary function (% predicted or L/min)/frequency	Dose (prednisone equivalent), corticosteroid, route & frequency	ICS in all intervention groups? N	Duration of follow-up 7d	Pulmonary function ↓	Length of stay	Relapse after discharge ↓	Symptoms ↓*	Rescue medication use ↓
Hoffman ⁴⁶ , 1988	15–55	None stated	100 mg MP IM × 1 vs. 80mg MP PO × 8d taper	N	7d	↓		↑	↓†	↓
Lee ⁴⁷ , 1993	40†	None stated	62 mg DEX IM × 1 vs. 19 mg DEX PO × 8d taper	N	7d	↓		↑	↓†	↓
Schuckman ²⁸ , 1998	18–50	PEFR < 350	50mg TRI IM × 1 vs. 40mg/d PR PO × 5d	N	5d	↓		↓	↓	
Chan ²⁷ , 2001	≥18	None stated	90mg BET IM × 1 vs. 50mg/d PR PO × 7d	Y††	21d	↓		↑	↓	
Lahn ²⁶ , 2004	18–45	PEFR 40–70%	200mg MP IM × 1 vs. 40mg/dMP PO × 8d taper	Y¶	21d			↓		

Number of participants with baseline data reported is shown above; may be less than the number enrolled. All studies recruited patients who were being discharged from the emergency department after initial management of acute asthma and followed them once discharged. Lahn,²⁶ Chan²⁷ and Schuckman²⁸ were conducted at 2 sites. All studies randomized, double-masked, placebo controlled, with a double-dummy design; Lee⁴⁷ added a third arm with double placebo.

[†] Age range not provided; data presented as mean (yrs).

^{††} Recommended but not required,

[¶] If taking prior to emergency department visit.

IM= intramuscular, MP=methylprednisolone, DEX=dexamethasone, BET=betamethasone, TRI=triamcinolone, PO= by mouth, PR=prednisone.

↑* Statistically significant (p-value <0.05) increase for intramuscular group vs. oral group

↑ Increased in intramuscular group vs. oral group, but not statistically significant difference (p-value >0.05)

↓* Statistically significant (p-value <0.05) decrease for intramuscular group vs. oral group

↓ Decreased in intramuscular group vs. oral group, but not statistically significant difference (p-value >0.05)

↓[†] Decreased in intramuscular group and oral group each compared to placebo, but no statistically significant difference between intramuscular and PO groups (p-value >0.05)

Table 7

Is combination therapy with inhaled and systemic corticosteroids superior to systemic corticosteroids alone?

Inclusion criteria												
Number	Age range (yrs)	Pulmonary function (% predicted)	Dose (prednisone equivalent), corticosteroid, route & frequency									
			Duration of follow-up	Pulmonary function	Length of stay	Relapse after discharge	Symptoms	Rescue medication use				
Rowe ⁴⁸ , 1999	16–60	PEFR <80%	50mg/d PR PO × 7d & 1600mcg/d BUD INH vs. 50mg/d PR PO × 7d & placebo INH	21d	↓	↓*	↓*	↓*	↓*	↓*	↓*	
Brenner ⁴⁹ , 2000	18–50	PEFR≥70%	40mg/d PR PO × 5d & 2mg/d FLU INH vs. 40mg/d PR PO × 5d & placebo INH	24d	↑	↑	↑	↑	↑	↑*	↑*	
Camargo ⁵⁰ , 2000	12–54	PEFR <80%	50mg/d PR PO × 5d & 250mcg BID FP INH vs. 50mg/d PO × 5d & placebo INH	20d		↓	↓					

Number of participants with baseline data reported is shown above; may be less than the number enrolled. All studies randomized, double-masked, placebo controlled, with enrollment in the emergency department and outpatient follow-up. Camargo⁵⁰ conducted study at 41 sites; presented as abstract only.

INH= inhaled, PO= by mouth, PR=prednisone, BUD=budesonide, BID= twice per day, FLU=flutisolidide, FP=fluticasone.

↑* Statistically significant (p-value <0.05) increase for inhaled and systemic corticosteroids group compared to systemic only group.

↑ Increased in inhaled and systemic corticosteroids group compared to systemic only group, but not statistically significant difference (p-value >0.05)

↓* Statistically significant (p-value <0.05) decrease for inhaled and systemic corticosteroids group compared to systemic only group.

↓ Decreased in inhaled and systemic corticosteroids group compared to systemic only group, but not statistically significant difference (p-value >0.05)

Table 8

Evidence table for the use of corticosteroids in adults with acute asthma.

Summary of results from randomized clinical trials			Evidence grade [^]	Recommendation	Strength ^{^^}
Question					
1. Does corticosteroid therapy improve outcomes?	<i>Emergency department:</i> Systemic corticosteroid therapy reduces the need for hospitalization. <i>Hospital:</i> Corticosteroid therapy accelerates improvement in lung function.		B (Emergency department) B (Hospital)	Initiate systemic corticosteroids in emergency department and hospitalized patients for acute asthma.	R (Emergency department) R (Hospital)
2. What dose of systemic corticosteroid therapy is needed in the Emergency department/hospital?	<i>Emergency department:</i> No direct comparisons. <i>Hospital:</i> Doses higher than 50 to 100 mg/d prednisone equivalent do not further accelerate the rate of improvement in airflow obstruction (FEV ₁). There are no data, however, in patients with near fatal asthma requiring mechanical ventilation.		D (Emergency department) B (Hospital)	Systemic corticosteroids at doses of 50/100 mg/day are sufficient for emergency department and most hospitalized patients. Higher doses should be avoided to minimize the potential for adverse effects.	O (Emergency department) O (Hospital)
3. Is IV corticosteroid therapy superior to oral corticosteroid therapy?	<i>Emergency department:</i> No direct comparisons. <i>Hospital:</i> Lung function and length of hospital stay similar with IV or oral corticosteroid therapy.		D (Emergency department) B (Hospital)	Oral corticosteroids is appropriate in emergency department and hospitalized patients, except if unable to tolerate oral medications or failed an oral regimen.	O (Emergency department) O (Hospital)
4. What duration of corticosteroid therapy is needed?	<i>Emergency department:</i> No direct comparisons. <i>Hospital:</i> No compelling benefits beyond a total of 5–10 days therapy (40–50 mg/d prednisone equivalent). Patients were discharged on concomitant inhaled corticosteroids. No data in patients on chronic corticosteroid therapy or with near fatal asthma requiring mechanical ventilation.		D (Emergency department) B (Hospital)	A total of 5–10 days of corticosteroid therapy is sufficient for emergency department and most hospitalized patients. In general, longer durations should be avoided to minimize the potential for adverse effects.	R (Emergency department) R (Hospital)
5. Is an oral corticosteroid taper superior to a fixed-dose corticosteroid regimen after discharge home?	<i>Emergency department:</i> Similar benefits in lung function and relapse rates. <i>Hospital:</i> Similar benefits in lung function, symptoms, or relapse rates. Patients were discharged on concomitant inhaled corticosteroids. Patients with near fatal asthma requiring mechanical ventilation were excluded.		B (Emergency department) B (Hospital)	Fixed-dose oral corticosteroids is appropriate in most emergency department and hospitalized patients to optimize adherence after discharge home and avoid local complications associated with corticosteroid injections	R (Emergency department) R (Hospital)
6. Is a single dose of depot intramuscular corticosteroids superior to a multi-dose oral corticosteroid regimen after discharge home?	<i>Emergency department:</i> No differences in relapse rates. Intramuscular therapy can cause bruising, swelling, or pain at the injection site. <i>Hospital:</i> No data.		B (Emergency department) D (Hospital)	Intramuscular corticosteroid therapy is an effective alternative in patients in which there are strong concerns about poor adherence to therapy.	O (Emergency department) O (Hospital)
7. Does adding inhaled corticosteroids to systemic corticosteroids improve clinical outcomes after discharge home?	<i>Emergency department:</i> One well-designed randomized clinical trial indicates large reduction in risk of relapse; pooled results from 3 studies suggest a trend favoring combination corticosteroid therapy. <i>Hospital:</i> No data.		B (Emergency department) C (Hospital)	Combination therapy with inhaled and systemic corticosteroids at emergency department and hospital discharge is recommended.	R (Emergency department) R (Hospital)

[^] **Evidence grades:** A (Well-designed randomized clinical trials in relevant populations), B (Randomized clinical trials with minor limitations; overwhelmingly consistent evidence from observational studies), C (Observational studies using case-control and cohort designs), D (Expert opinion, case reports, reasoning), X (Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm).

Strengths of recommendations: (S) Strong recommendation, (R) Recommendation, (O) Option, or (NR) No recommendation.

Recommendations for corticosteroid dosing in adults with acute asthma.

Drug Class	
Oral corticosteroids Intravenous corticosteroids	Dose and agent
	Treatment in the Emergency Department/Hospital Prednisone: 50–100 mg PO single dose (QD for hospitalized patients). Methylprednisolone (Solumedrol): 40–80 IV single dose; QD for hospitalized patients; Cortisone (Solu-cortef): [^] 250–500 mg IV single dose in emergency department; QD for hospitalized patients.
Oral corticosteroids Intramuscular corticosteroids	After Emergency Department/Hospital discharge
	Prednisone: 40–50 mg PO QD for total 5–10 days. Methylprednisolone (Solumedrol): 80–160 mg IM single dose; Triamcinolone: 40–50 mg IM single dose; Dexamethasone (Decadron): 10 mg IM single dose; Betamethasone: 12 mg IM single dose. Fluticasone MDI 220 mcg/puff, 2 puffs BID; Budesonide 400 mcg/puff, 2 puffs BID; Flunisolide MDI 250 mcg/puff 4 puffs BID.

Inhaled corticosteroids (combined with systemic corticosteroids)

Abbreviations: IV: intravenous; IM: intramuscular; PO: oral; mg: milligrams; meg: micrograms; QD: once per day, BID: twice per day.

[^] Systemic corticosteroid dosing equivalents based on Goodman & Gilman's Pharmacology, 10e. McGraw-Hill Companies, Inc. 2001.