# Anti-inflammatory treatment after discharge home from the emergency department in adults with acute asthma

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Airway inflammation from respiratory infections or exposure to allergens, irritants, or both leads to increased airflow obstruction and respiratory symptoms in patients with acute asthma. Anti-inflammatory therapy with systemic corticosteroids (CSs) is therefore a cornerstone of the management of patients with acute asthma, particularly those presenting to the emergency department (ED).[1,2] After initial management in the ED, most patients improve sufficiently to be discharged home with instructions to complete a short course of daily oral corticosteroids (OCSs) and short-acting inhaled bronchodilators as needed for symptom relief. Unfortunately, up to one third of patients who initially respond to therapy relapse within the first 3 to 4 weeks after ED discharge (eg, require treatment escalation, urgent care or ED visits, or hospitalizations for asthma).[3,4] The propensity of many patients to relapse after ED discharge has led to a number of randomized clinical trials evaluating alternative outpatient anti-inflammatory treatment strategies in this population, including the use of inhaled corticosteroids (ICSs), intramuscular corticosteroids (IMCSs), and non-corticosteroid anti-inflammatory regimens.

The objective of this systematic review is to synthesize the results of randomized clinical trials in adults with acute asthma, comparing alternative outpatient anti-inflammatory treatment strategies to reduce the risk of relapse after discharge home from the ED. More specifically, this systematic review examined the following anti-inflammatory treatment options in adults after ED discharge: (1) IMCSs versus OCSs, (2) ICSs versus OCSs, (3) combination of ICSs plus OCSs versus OCSs alone, and (4) noncorticosteroid anti-inflammatory agents (macrolide antibiotics and leukotriene modifiers) in addition to systemic corticosteroids. This report updates previously published systematic reviews in acute asthma[5-7] with subsequently published studies and provides a single document summarizing this body of literature for easy use by clinicians.

*Abbreviations used*
ED: Emergency department
ICS: Inhaled corticosteroid
IMCS: Intramuscular corticosteroid
OCS: Oral corticosteroid
RCT: Randomized clinical trial

## METHODS

The following key words and combinations were used for the search: asthma exacerbation + discharge + medication; acute asthma + discharge medication; asthma + emergency department + discharge medication; asthma + emergency + department + adherence; and severe + asthma + adherence + emergency + department.

Additional details of the methodology for all literature reviews in this supplement are provided in the introduction to this supplement.[8] The task force specified the level of evidence used to justify the recommendations being made, and the system used to describe the level of evidence is also defined in the introduction to this supplement.

## RESULTS

The literature search identified 37 clinical randomized controlled trials (RCTs) and 5 meta-analyses potentially relevant to the study questions. After excluding noneligible studies, 5 RCTs were identified comparing IMCSs with OCSs; 1 meta-analysis of 7 trials comparing ICSs with OCSs, 2 of which were specifically in adults; 1 meta-analysis of 3 trials comparing ICSs plus OCSs versus OCSs alone; and 2 RCTs of noncorticosteroid anti-inflammatory agents.

### IMCSs versus OCS

There are 5 randomized, placebo-controlled clinical trials comparing IMCSs with OCSs in a total of 599 adults with acute asthma (Table I).[4,9-12] All 5 trials used a double-dummy design (IMCS plus oral placebo vs intramuscular placebo plus OCS) to keep patients and investigators masked to treatment assignment. These studies compared a single dose of various formulations of IMCSs with a 5- to 8-day course of OCSs and assessed outcomes

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**TABLE I.** Randomized clinical trials comparing IMCSs with OCSs after ED discharge (total n = 599 participants)

| Reference | Study design* | Treatment groups† | Country | Age (y) | No. (%)‡ | Follow-up (d)§ | Relapse (%)‖ |
|---|---|---|---|---|---|---|---|
| Hoffman and Fiel, 1988[9] | RCT, double-dummy | Methylprednisolone sodium acetate, 80 mg IM, vs methylprednisolone, 32 mg BID PO with an 8-day taper | United States | 15–55 | 16/18 (89) | 5-7 | 20.0% vs 0%, $P$ = NS |
| Lee et al, 1992[10] | RCT, double-dummy | Dexamethasone, 10 mg IM, vs dexamethasone, 1.5 mg BID PO with an 8-day taper, vs double placebo (IM and PO) | Taiwan | 16–60 | 52/52 (100) | 7 | 5.9% vs 6.2%, $P$ = NS |
| Shuckman et al, 1998[11] | RCT, double-dummy | Triamcinolone diacetate, 40 mg IM, vs prednisone, 40 mg/d PO × 5 days | United States | 18–50 | 154/168 (92) | 7 | 9.0% vs 14.5%, $P$ = NS |
| Chan et al, 2001[4] | RCT, double-dummy | Betamethasone sodium phosphate, 6 mg, + betamethasone acetate, 6 mg IM, vs prednisone, 50 mg/d PO × 7 days | Canada | >18 | 159/171 (93) | 21 | 36.8% vs 31.0%, $P$ = NS |
| Lahn et al, 2004[12] | RCT, double-dummy | Methylprednisolone acetate, 160 mg IM, vs methylprednisolone, 32 mg PO with an 8-day taper | United States | 18–45 | 180/190 (95) | 21 | 18.5% vs 22.7%, $P$ = NS |

*IM*, Intramuscularly; *BID*, twice daily; *PO*, by mouth; *NS*, not significant.
*Double-dummy refers to use of a placebo in both treatment groups.
†Corticosteroid treatment groups.
‡Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.
§Follow-up period during which outcomes were compared between treatment groups.
‖Relapse during the follow-up period in the IMCS versus OCS groups, as defined in individual studies (eg, need for treatment intensification, ED visit, or hospitalization).

over a 5- to 21-day period. Rates of study completion were high, ranging from 89% to 100%. Overall, there were no significant differences in symptoms, lung function parameters, or rates of relapse between the 2 treatment groups. Some studies, however, reported a higher rate of complications at the injection sites (eg, pain or bruising) in patients who received IMCSs. For example, in the study by Lahn et al,[12] mean pain scores (3.3/10 vs 1.9/10, $P < .05$) and rates of bruising (8% vs 0%, $P < .05$) were significantly higher in the IMCS group compared with those in the OCS group at the follow-up visit. Taken together, these studies suggest that IMCSs represent a similarly effective regimen in preventing relapse after ED discharge compared with several days' therapy with OCSs.

## ICSs versus OCSs

For more information, see Table II.[13,14] A meta-analysis by Edmonds et al[7] evaluated the results of 7 trials comparing ICSs with OCSs in patients with acute asthma. In this meta-analysis 4 trials focused on pediatric populations and 1 study focused on patients presenting to their primary care physicians' offices. The remaining 2 trials, in a total of 269 adults, compared high-dose ICSs with OCSs for 7 to 10 days, using a double-dummy design, in adults with acute asthma discharged from the ED after initial therapy.[13,14] Rates of study completion were high (96%[13] and 89%[14]), and there were no significant differences in relapse or other outcomes, including need for rescue medications, improvements in lung function, asthma symptoms, and quality of life. The low relapse rates in the control groups (7% at 7 days[13] and 12% at 10 days[14]), together with lung function measurements on ED discharge ($FEV_1$ of 64% of predicted value[13] and peak expiratory flow of 407 L/min[14]), suggest that participants in this study had mild or moderate forms of acute asthma. There were also no significant differences in outcomes when analysis included all patients (adults and children) across the 7 trials.[7]

## Combination of ICSs plus OCSs versus OCSs alone

For more information, see Table III.[15-17] Edmonds et al[5] performed a meta-analysis of 3 trials (total n = 912 adults) that investigated the efficacy of combining ICSs and OCSs versus use of OCSs alone in patients discharged from the ED after initial treatment for acute asthma.[15-17] Only 2 of these studies have been published.[15,16] Moderate-to-high doses of ICSs combined with 5- to 7-day courses of oral prednisone at 40 to 50 mg/d were compared with oral prednisone alone, and outcomes were assessed up to 20 to 24 days after ED discharge. The study by Rowe et al,[15] which had the highest follow-up rate (97%) and the highest overall relapse rate (19%) of all 3 studies, reported a significant reduction in the risk of relapse in patients assigned combination therapy versus an OCS alone (12.8% vs 24.5%, $P = .049$). In contrast, no significant differences in relapse rates by treatment group were reported in the other 2 studies. When data were pooled across all 3 studies, there was a nonsignificant trend toward a reduction in relapse rates with combination therapy (odds ratio for relapse with combination

**TABLE II.** Randomized clinical trials comparing ICSs versus OCSs after ED discharge (total n = 269 participants)

| Reference | Study design* | Treatment groups† | Country | Age (y) | No. (%)‡ | Follow-up (d)§ | Relapse (%)‖ |
|---|---|---|---|---|---|---|---|
| Nana et al, 1998[13] | RCT, double-dummy | Budesonide DPI, 1600 μg BID × 7 days, vs prednisolone, 40 mg/d with a 7-day taper | Thailand | 16–50 | 81/84 (96) | 7 | 11.9% vs 7.1%, $P$ = NS |
| Fitzgerald et al, 2000[14] | RCT, double-dummy | Budesonide DPI, 600 μg QID × 7-10 days, vs prednisone, 40 mg/d × 7-10 days | Canada | 15–50 | 151/185 (82) | 10 | 10% vs 11.8%, $P$ = NS |

*DPI*, Dry powder inhaler; *BID*, twice daily; *QID*, 4 times daily; *NS*, not significant.
*Double-dummy refers to use of a placebo in both treatment groups.
†Corticosteroid treatment groups.
‡Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.
§Follow-up period during which outcomes were compared between treatment groups.
‖Relapse during the follow-up period in the ICS versus OCS groups, as defined in individual studies (eg, need for treatment intensification, ED visit, or hospitalization).

therapy vs OCS alone, 0.68; 95% CI, 0.46-1.02). There were no significant differences in other pooled outcomes between treatment groups, including lung function, use of β-agonists, asthma symptoms, or adverse effects of ICSs (eg, hoarseness or sore throat).

### Noncorticosteroid anti-inflammatory agents

For more information, see Table IV.[3,18] Johnston and other Telithromycin in Acute Exacerbations of Asthma investigators[18] conducted a multicenter, double-blind, placebo-controlled clinical trial to compare the efficacy and safety of telithromycin (800 mg/d), a macrolide, in 278 adults with acute asthma presenting to the urgent care clinic, ED, or hospital. Findings indicate a significantly greater improvement in asthma symptoms in the telithromycin group compared with the placebo group during the 10-day treatment period (−0.3 points [0- to 6-point scale], $P$ = .004). Benefits were also noted in other outcomes during the treatment period, including a greater improvement in $FEV_1$ (0.63 vs 0.34 L, $P$ = .001). Interestingly, results were similar in patients with and without laboratory evidence of infection with atypical bacteria at enrollment. However, differences in lung function disappeared by the end of the 42-day follow-up period, and relapse rates were very low and similar in both treatment groups (1.5% each). Nausea was significantly more common in the telithromycin-treated versus placebo-treated patients (5.3% vs 0%, $P$ = .01), but other adverse events were uncommon and similar across treatment groups.

In a multicenter study Silverman et al[3] evaluated the effects of adding zafirlukast, an oral leukotriene receptor antagonist, or placebo to a standardized regimen of systemic corticosteroids and an inhaled $\beta_2$-agonist in 546 participants. Study participants were given a single oral dose of zafirlukast (160 mg or 20 mg) or placebo in the ED. Patients who were discharged from the ED (86% of all study participants) were enrolled in an outpatient phase and randomly assigned to continue treatment with 20 mg of zafirlukast twice daily or placebo by mouth for 28 days (in addition to other asthma medications). The zafirlukast group had a significantly lower 28-day relapse rate (primary outcome) compared with the placebo group (23.6% vs 28.9%, $P$ = .047), better lung function ($FEV_1$ of 2.49 vs 2.27 L), lower mean daytime symptom scores (0.82 vs 1.01), less frequent β-agonist use (3.3 vs 4.1 puffs/d, $P$ < .01), and fewer disruptions of daily activities (20% vs 26%, $P$ = .02). Adverse events were uncommon and similar between the treatment groups, including increases in alanine aminotransferase levels (1% vs 2%, $P$ = not significant).

## DISCUSSION

The main findings of this systematic review of clinical trials in adults with acute asthma after ED discharge are as follows: (1) IMCS regimens appear to be as effective as OCS regimens in preventing relapse (total n = 599 participants); (2) in patients with mild-to-moderate acute asthma, ICS and OCS regimens are similarly effective in preventing relapse (total n = 269 participants); (3) there was a nonsignificant trend suggesting that combination therapy with ICSs and OCSs might be more effective than an OCS alone in preventing relapse (total n = 912 participants); and (4) additional studies are needed to examine the safety and efficacy of initiating macrolide antibiotics (in the absence of infection) and leukotriene modifiers after an episode of acute asthma.

Several studies have documented a link between low rates of patient adherence to asthma therapy and poorly controlled asthma, including increased risk of ED visits or hospitalizations for acute asthma.[19,20] Nonadherence to systemic corticosteroid treatment is even common immediately after ED or hospital discharge.[21-23] A single intramuscular dose of a long-acting (depot or repository) corticosteroid achieves a prolonged anti-inflammatory effect and might therefore be superior to discharging patients with an OCS regimen (which depends on patients to fill prescriptions and then use them appropriately). However, findings from this systematic review failed to detect differences in relapse rates or other efficacy outcomes between patients treated with IMCSs and OCSs, and 1 study found higher rates of injection-site pain and bruising with IMCSs. The available data are based on studies comparing IMCSs versus OCSs provided at ED discharge (not a prescription for an OCS), suggesting that the study designs might have underestimated the benefits of depot IMCSs that would be observed in clinical practice. Also, the studies were not designed as equivalency trials and therefore enrolled too few patients in any single study (range, 18-190 patients) to exclude the possibility of a small but clinically important reduction in the rate of relapse with IMCSs. Nevertheless, findings from studies to date suggest that IMCSs offer an attractive alternative in selected patients who are likely to have difficulty in obtaining or using an OCS after ED discharge.

There are ample data from clinical trials to support the use of ICSs in chronic asthma.[2,24] Results of this review suggest that adults with mild or moderate acute asthma discharged from the ED with ICSs or OCSs have similar short-term (≤10 days)

**TABLE III.** Randomized clinical trials comparing ICSs plus OCSs versus OCSs alone after ED discharge (total n = 912 participants)

| Reference | Study design* | Treatment groups† | Country | Age (y) | No. (%)‡ | Follow-up (d)§ | Relapse (%)‖ |
|---|---|---|---|---|---|---|---|
| Rowe et al, 1999[15] | RCT, double-dummy | Budesonide DPI, 800 μg BID × 3 weeks, + prednisone, 50 mg/d PO × 7 days, vs prednisone, 50 mg/d PO × 7 days | Canada | 18-60 | 186/191 (97) | 21 | 12.8% vs 24.5%, $P = .049$ |
| Brenner et al, 2000[16] | RCT, double-dummy | Flunisolide MDI, 1000 μg BID × 24 days, + prednisone, 40 mg/d PO × 5 days, vs prednisone, 40 mg/d PO × 5 days | United States | 18-50 | 73/104 (70) | 24 | 7.8% vs 7.5%, $P$ = NS |
| Camargo, 2000[17] | RCT, double-dummy | Fluticasone Diskhaler, 250 μg BID × 20 days, + prednisone, 50 mg/d PO × 5 days, vs prednisone, 50 mg/d PO × 5 days | United States | 12-54 | 517/617 (84) | 20 | 9.7% vs 12.0%, $P$ = NS |

*DPI*, Dry powder inhaler; *BID*, twice daily; *PO*, by mouth; *NS*, not significant.
*Double-dummy refers to use of a placebo in both treatment groups.
†Corticosteroid treatment groups.
‡Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.
§Follow-up period during which outcomes were compared between treatment groups.
‖Relapse during the follow-up period in the ICS plus OCS versus OCS groups, as defined in individual studies (eg, need for treatment intensification, ED visit, or hospitalization).

outcomes. However, because these studies were not designed as equivalency studies, it is not possible to exclude clinically important differences in relapse rates between ICS and OCS regimens after discharge. Also, ICSs are more costly and difficult for patients to use compared with OCSs. Therefore we recommend using ICSs instead of OCSs only in patients with milder forms of acute asthma who are able to obtain, afford, and use ICSs appropriately; have difficulty tolerating OCSs because of adverse effects (eg, hyperglycemia or sleep disturbance); or both.

Observational studies suggest that ICS treatment (compared with no ICS treatment) might reduce acute asthma relapse rates after ED discharge by about 50%.[20,25,26] Many RCTs show that ICSs reduce exacerbations in patients with persistent asthma.[24] Results of this review (with >900 total participants), however, only found a trend toward a lower relapse rate when high-dose ICSs (vs placebo) are added to a 5- to 7-day OCS regimen. Thus the available evidence is insufficient to recommend combination corticosteroid therapy in all adults with acute asthma after ED discharge but does not rule out a clinically important benefit either, including a long-term benefit in reducing exacerbations.[24] A number of studies have documented low rates of ICS prescription at ED discharge in this population (16% to 24%),[27-29] even in patients with evidence of poorly controlled asthma (eg, a history of ED visits). Because national asthma guidelines recommend daily ICSs in patients with persistent asthma,[2,30] based on their documented efficacy in such patients, we recommend discharging patients with daily ICSs (in addition to a short course of an OCS) when there is evidence of persistent asthma between episodes of acute asthma. Based on current guidelines,[30] discharging patients with a daily ICS regimen in addition to a short course of an OCS should also be considered in patients with an exacerbation requiring OCSs in the prior 12 months. Because poor inhaler technique is common in patients presenting with acute asthma, all patients prescribed ICSs should receive adequate training before ED discharge.[31-33]

The antibacterial effects of macrolide antibiotics are well known, particularly against atypical bacteria, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. There is increasing awareness, however, that macrolides also possess separate immunomodulatory effects that could suppress airway inflammation and might be the basis for clinical benefits observed in patients with cystic fibrosis and diffuse panbronchiolitis.[34] There are now promising data (from 1 trial[18]), suggesting that a 10-day course of telithromycin, a macrolide antibiotic, initiated during acute asthma might improve symptom control and lung function. However, these effects were temporary and disappeared after treatment discontinuation, and no benefit on the risk of relapse was observed. Moreover, the US Food and Drug Administration recently added a "black box" warning regarding an increased risk of serious and possibly fatal hepatotoxicity after use of telithromycin.[35] Thus although promising, additional studies are needed about the role of macrolide antibiotics in acute asthma, and until then, we recommend against the use of macrolide antibiotics in the absence of other clinical indications (eg, concomitant community-acquired pneumonia).

Cysteinyl leukotrienes, potent mediators of airway inflammation and bronchoconstriction in patients with chronic asthma, can be further increased during episodes of acute asthma.[36,37] Results of a single trial[3] suggest that a 28-day course of the leukotriene receptor antagonist zafirlukast might significantly reduce relapse rates and improve lung function and symptoms when initiated in the ED and continued after ED discharge. As with macrolide antibiotics, these results are promising, and additional studies are needed to confirm the safety and efficacy of initiating leukotriene modifiers during and after acute asthma.

**TABLE IV.** Randomized clinical trials evaluating noncorticosteroid treatments after ED discharge

| Reference | Study design | Treatment groups | Country | Age (y) | No. (%)* | Follow-up (d)† | Relapse (%)‡ |
|---|---|---|---|---|---|---|---|
| Johnston et al, 2006[18] | RCT, double-blind | Telithromycin, 800 mg/d PO, vs placebo, PO × 10 days | Multiple | 18-55 | 231/278 (83) | 42 | 1.5% vs 1.5%, $P$ = NS |
| Silverman et al, 2004[3] | RCT, double-blind | Zafirlukast, 160 mg or 20 mg PO × 1 and then 20 mg PO BID, vs placebo PO × 28 days | United States | 12-65 | 457/546 (84)§ | 28 | 23.6% vs 28.9%, $P$ = .047 |

*PO*, By mouth; *BID*, twice daily; *NS*, not significant.
*Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.
†Follow-up period during which outcomes were compared between treatment groups.
‡Relapse rates in the treatment versus placebo groups, as defined in individual studies (eg, need for treatment intensification, ED visit, or hospitalization).
§Six hundred forty-one patients were initially enrolled in the ED; 549 were eligible and enrolled in the outpatient (post-ED discharge) phase.

## SUMMARY OF RECOMMENDATIONS

1. Conditional: consider IMCSs* in patients who are likely to have difficulty in obtaining or using OCSs after ED discharge. Patients selected for IMCS therapy should be informed of an increased risk of local injection site complications (mostly pain or bruising) (Evidence Category B).
2. Conditional: consider a short course of a very high-dose ICS† instead of an OCS after ED discharge in patients with mild forms of acute asthma who are able to obtain, afford, and use ICSs correctly; have difficulty tolerating OCSs; or both (Evidence Category B). Such patients should receive adequate training about how to use ICSs before ED discharge.
3. Strong: recommend initiating daily ICSs‡ (in patients not already receiving a daily ICS) or continuing daily ICSs‡ (in patients already receiving a daily ICS) on ED discharge (in addition to a short course of an OCS)‡ for patients with a history compatible with persistent asthma,§ even between episodes of acute asthma (Evidence Category A). Conditional: consider initiating daily ICSs in patients who have required OCSs for an asthma exacerbation in the prior 12 months (Evidence Category D). Patients starting ICSs should receive adequate training about how to use them before ED discharge.
4. Additional studies are needed to evaluate the efficacy and safety of macrolides and leukotriene modifiers in adults with acute asthma after ED discharge before recommendations regarding their use can be made (Evidence Category B, no recommendation).

*In alphabetical order: betamethasone sodium phosphate, 6 mg, with betamethasone acetate, 6 mg, administered intramuscularly ×1; dexamethasone, 10 mg, administered intramuscularly ×1; methylprednisolone sodium acetate, 80 to 160 mg, administered intramuscularly ×1; or triamcinolone diacetate, 40 mg, administered intramuscularly ×1.

†Budesonide dry powder inhaler, 2400 to 3200 μg/d, inhaled in divided doses (2-4 times a day) for 7 to 10 days. Alternative regimens, in alphabetical order, with estimated equivalent daily dose[29] include flunisolide, 4000 to 5000 μg/d; fluticasone dry powder inhaler, 1000 to 1500 μg/d; mometasone dry powder inhaler, 800 to 1200 μg/d; triamcinolone acetonide, 3000 to 4000 μg/d.

‡Alphabetical order: daily inhaled budesonide dry powder inhaler, 1200 μg/d; flunisolide metered-dose inhaler, 2000 μg/d; fluticasone dry powder inhaler, 500 μg/d; mometasone dry powder inhaler, 400 μg/d; triamcinolone acetonide, 1500 μg/d, in divided doses (twice per day) for 3 to 4 weeks AND prednisone, 40 to 50 mg/d, for 5 to 7 days.

§Any of the following: prescribed daily controller use; daytime symptoms or use of rescue inhalers (eg, albuterol) more than twice a week; interference with sleep more than twice a month; activity limitation caused by asthma; exacerbations requiring systemic corticosteroids more than once a year; or airflow obstruction with $FEV_1$ less than 80% of predicted value.

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