Emergency Department Corticosteroid Use for Allergy or Anaphylaxis Is Not Associated With Decreased Relapses

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Study objective: Corticosteroids (steroids) are often used to mitigate symptoms and prevent subsequent reactions in emergency department (ED) patients with allergic reactions, despite a lack of evidence to support their use. We sought to determine the association of steroid administration with improved clinical outcomes.

Methods: Adult allergy-related encounters to 2 urban EDs during a 5-year period were identified and classified as "anaphylaxis" or "allergic reaction." Regional and provincial databases identified subsequent ED visits or deaths within a 7-day period. The primary outcome was allergy-related ED revisits in the steroid- and nonsteroid-exposed groups, adjusting for potential confounders with a propensity score analysis; secondary outcomes included the number of clinically important biphasic reactions and deaths.

Results: Two thousand seven hundred one encounters (473 anaphylactic) were included; 48% were treated with steroids. Allergy-related ED revisits occurred in 5.8% and 6.7% of patients treated with and without steroids, respectively (adjusted odds ratio [OR] 0.91; 95% confidence interval [CI] 0.64 to 1.28), with a number needed to treat (NNT) to benefit of 176 (95% CI NNT to benefit 39 to ∞ to NNT to harm 65). The adjusted OR in the anaphylaxis subgroup was 1.12 (95% CI 0.41 to 3.27). In the allergic reaction group, the adjusted OR was 0.91 (95% CI 0.63 to 1.31), with an NNT to benefit of 173 (95% CI NNT to benefit 38 to ∞ to NNT to harm 58). In the steroid and nonsteroid groups, there were 4 and 1 clinically important biphasic reactions, respectively. There were no deaths.

Conclusion: Among ED patients with allergic reactions or anaphylaxis, corticosteroid use was not associated with decreased relapses to additional care within 7 days. [Ann Emerg Med. 2015;66:381-389.]

Please see page 382 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Allergy-related emergency department (ED) visits are common, affecting an estimated 3.8 per 1,000 persons annually, representing approximately 1.0% of all ED visits.[1] A range of causes can trigger allergic reactions, including food, insect stings, medications, and idiopathic causes,[2] with severity ranging from mild symptoms to serious illness or death.[3]

Importance

In addition to epinephrine and antihistamines, corticosteroids (subsequently referred to as "steroids") are a class of medications administered commonly in the ED treatment of allergic reactions.[4,5] A national study of EDs in the United States reported steroids to be the second most common medication prescribed for allergic reactions after H1 antihistamines, with use increasing from 22% to 50% during a 12-year period.[1] Rationale for steroid therapy is based on its anti-inflammatory effect and proven benefit in other similar atopic conditions such as asthma.[6] Studies examining the effectiveness of systemic steroid therapy in asthma for patients discharged from the ED have demonstrated a significant reduction in the number of relapses to additional care.[6] The desired result of steroid administration in the treatment of allergic reactions is a reduced risk of biphasic reactions, decreased severity of reactions, and decreased ED return visits for worsening or ongoing allergy-related symptoms. However, there is no evidence to support this practice.[7,8]

Given that even short courses of steroids have been implicated in adverse events such as hyperglycemia, bony necrosis, and psychiatric symptoms,[9] their routine use in

Editor's Capsule Summary

What is already known on this topic

Corticosteroids are widely administered for allergic reactions.

What question this study addressed

Do steroids decrease the likelihood of relapse after emergency department (ED) discharge?

What this study adds to our knowledge

In this observational study of 2,701 ED visits for allergy, there was a similar frequency of ED revisits within 7 days in the 48% of patients who had received steroids versus those who had not.

How this is relevant to clinical practice

Corticosteroids do not lessen relapse in ED patients with allergic reactions.

patients with allergic reactions must be carefully balanced against the perceived benefits.

Goals of This Investigation

The primary aim of this study was to determine the association of steroid administration in ED allergy patients with decreased relapses to additional care within a 7-day follow-up period. Secondary aims included identifying potential benefits of steroids in decreasing death, clinically important biphasic reactions, or all-cause repeated ED visits.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study took place at 2 urban academic teaching hospitals in Vancouver, British Columbia, affiliated with the University of British Columbia. St. Paul's Hospital is a tertiary care referral center with approximately 70,000 annual ED visits, and Mount St. Joseph's Hospital is an affiliated community center with approximately 25,000 annual ED visits. The 2 study hospitals use a common comprehensive electronic medical record. All investigations, medications, consultations, and outpatient prescriptions are facilitated by the electronic physician order entry system, with time-stamped digital records. For every patient encounter, emergency physicians are required to complete an electronic summary with the primary diagnosis (previously validated[10]), as well as all procedures, follow-up arrangements, and outpatient prescriptions. There was no defined protocol for allergic reactions, and physicians managed patients in an individualized manner, including steroid administration and other ED management. Steroids are not a treatment option in local ambulance protocols. The 2 sites are among 6 EDs in the Vancouver Coastal Health region, which maintains a regional database, recording visits through the patient's unique provincial health number. The institutional review boards and affiliated ethics committees of Providence Health Care, the University of British Columbia, and Vancouver Coastal Health approved this study.

Selection of Participants

We identified all patient encounters between April 1, 2007, and March 31, 2012, with an ED discharge diagnosis code of "allergic reaction." This code was the sole option available to physicians to select in the ED electronic medical record for any allergy- or anaphylaxis-related ED visit.

The following encounters were excluded: the patient was younger than 17 years, the primary diagnosis (as coded by the treating physician) was asthma with allergic reaction coded as a secondary diagnosis, the patient was not assessed by a nurse or a physician, the patient had a preexisting condition known to cause nonallergic angioedema, the allergen was deemed to be an angiotensin-converting enzyme inhibitor, or the patient was receiving an oral steroid medication before ED presentation. Study participants for whom the total length of stay in the hospital (whether admitted or not) was greater than 24 hours were excluded from the primary analyses of subsequent allergy-related ED visits but were included in the secondary outcomes of biphasic reactions and mortality.

Data Collection and Processing

Three investigators—2 medical students and 1 ED faculty physician (J.L., T.W.Y., and B.E.G., respectively)—systematically reviewed all index and follow-up encounters after training on a set of 50 records. Standard criteria for chart reviews as recommended by Gilbert et al[11] and Worster et al[12] were adhered to, with weekly meetings held to review data collection and resolve disputes. This was a secondary analysis of a previous study,[13] and abstractors were unaware of the study hypothesis. Charts with conflicting data prompted adjudication with 2 independent reviewers reaching consensus. If a variable of interest was not mentioned in any location on the ED chart, it was considered to be not applicable to the patient encounter. Missing data were noted in data collection. Data were abstracted onto a standardized spreadsheet (Microsoft Excel 2011; Microsoft, Redmond, WA). All index visits were evaluated with the definitions of anaphylaxis (adapted from the National

Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria[3]) and "clinically important biphasic reaction," both of which have been described previously (see Figure 1 for definitions).[13]

Five percent of the index visits were randomly selected for a second independent review, and interrater reliability was reported. Cohen's κ statistic was calculated for several key variables: whether the patient encounter satisfied the definitions for anaphylaxis, skin involvement, mucosal tissue involvement, wheeze or stridor, syncope, and gastrointestinal symptoms (see Figure 1 for definitions).

Using the patient's unique provincial health number, the study cohort was linked to both the Vancouver Coastal Health regional database and the British Columbia Vital Statistics registry to identify all patients who returned to any regional ED or died within the province, respectively, during the 7-day follow-up period. Subsequent visits were considered allergy related if the patient presented with the same complaint as on the index visit or if the attending physician deemed that the presentation was due to allergic cause. Disagreements were adjudicated through consensus after further chart review.

Outcome Measures

The primary outcome was the number of subsequent allergy-related ED visits within 7 days (a "relapse") in the steroid- and nonsteroid-exposed groups. Steroid exposure was defined as steroid treatment in the ED or with outpatient therapy postdischarge. Secondary outcomes within 7 days included all-cause mortality, the number of clinically important biphasic reactions, and the number of participants with repeated ED visits for any reason. In addition, we analyzed the primary outcome in the following a priori subgroups: patients who satisfied the definition of anaphylaxis; those classified as having "allergic reaction," and those in whom the offending allergen was "known" or "likely" (Figure 1). To determine whether an extended course of steroids was required to influence the

Anaphylaxis: Any of the following 3 numbered criteria must be satisfied:

1. Both of the following must be satisfied:
   a. Skin or mucosal tissue involvement
   b. One of the following:
      i. Respiratory compromise
      ii. Systolic blood pressure <90 mm Hg or syncope
2. Two of the following must be satisfied after exposure to a "likely" allergen:
   a. Skin or mucosal tissue involvement
   b. Respiratory compromise
   c. Systolic blood pressure <90 mm Hg or syncope (concurrent to other symptoms)
   d. Gastrointestinal symptoms
3. Systolic blood pressure <90 mm Hg after exposure to a known allergen

Skin Involvement: Urticaria, rash, pruritus, or swelling of the face or ears. Localized pruritus or rash that was deemed the result of trauma or an obvious insect bite was not considered as fulfilling the definition of "skin involvement."

Mucosal Tissue Involvement: Swelling of lips, tongue, or pharynx.

Respiratory Compromise: Wheeze or stridor on auscultation, hypoxemia (oxygen saturation <95%), or respiratory rate >22 breaths/min.

Gastrointestinal Symptoms: Abdominal pain or vomiting that is present in the ED.

Known Allergen: A substance that had previously caused an allergic reaction to the patient.

Likely Allergen: A substance that (1) the patient was exposed to before the development of symptoms; (2) was deemed the cause of the allergic reaction by the attending physician; and (3) had not previously caused a known reaction.

Allergic Reaction: A clinical patient presentation in which the criteria for anaphylaxis were not met but the attending physician deemed the cause of the signs or symptoms to be a result of allergic processes (as demonstrated by the discharge diagnosis code).

Clinically Important Biphasic Reaction: Recurrent or new signs or symptoms occurring after an initial allergy-related presentation that satisfy the definition for anaphylaxis, without any obvious further exposure to an offending allergen. If certain signs or symptoms were present on the index visit and did not resolve or improve before the subsequent visit, they were not considered "recurrent" or "new" and thus were not used in the classification of biphasic reaction in subsequent visits.

Figure 1. Definitions of anaphylaxis, allergic reaction, and clinically important biphasic reaction.

primary outcome, we examined patients who received ED steroid treatment and compared those who were and were not prescribed steroids after ED discharge (referred to as "extended course versus only ED steroids").

To achieve high power in our study, we used the largest possible sample size, collecting data from the earliest possible date in which regional linkages were available, up until the date of project commencement. With approximately 3,000 ED encounters with the diagnosis of allergic reaction during this period, we estimated that 10% of encounters would be excluded, with an overall primary outcome rate of 6.5%.[13] We hypothesized that clinicians would deem the effect of steroids on the primary outcome clinically unimportant if the number needed to treat were in excess of 30, corresponding to an absolute risk difference of 3.3%. Thus, assuming an equal sample size in both groups and an α of .05, we projected a power of 0.94 to detect a difference between primary outcome rates of 65 of 1,350 (4.8%) and 110 of 1,350 (8.1%) in the steroid and nonsteroid groups, respectively.

Primary Data Analysis

Microsoft Excel 2008 (Microsoft) was used for data entry and R statistical software (Foundation for Statistical Computing, Vienna, Austria) was used for analysis. Dichotomous variables are reported as percentages and 95% confidence intervals (CIs) with continuity correction. Normally distributed variables are reported as means with SDs and non-normally distributed variables as medians with interquartile ranges. Vital statistics measures were occasionally recorded in the charts as "within normal range" (involving <1% of patients). For these cases, we randomly imputed a value from the following ranges: 100 to 140 mm Hg, 12 to 18 breaths per minute, and 96 to 100% for systolic blood pressure, respiratory rate, and oxygen saturation, respectively. For vital statistics measures that were missing (2% to 4% of observations), we randomly imputed a value from the range of observed nonmissing values. Univariate associations were calculated with a χ^2 analysis or a Fisher's exact test (the latter test was used for rare expected or observed outcomes), a 2-sample *t* test, and a Mann-Whitney test for binomial, continuous parametric, and continuous nonparametric variables, respectively. We used logistic regression to model the effect of steroid exposure on the primary outcome, with covariate adjustment for the propensity score. Odds ratios (ORs) with associated 95% CIs are reported as the primary measure of association.

The propensity score was determined by regressing the exposure (any steroid use) on the following potential confounders, chosen a priori: age, sex, allergy precipitant (drug, food, other, or unknown), whether the allergen was known (versus likely or unknown), history of allergies, history of asthma, use of epinephrine (likely indicates that the treating clinician considered the patient as having anaphylaxis), ambulance arrival, skin involvement, mucosal tissue involvement, gastrointestinal symptoms, wheeze or stridor, and syncope; and the following continuous clinical parameters (as recorded at ED arrival): systolic blood pressure, respiratory rate, and oxygen saturation. These variables were chosen to ensure adjustment for both disease severity at presentation and other nondisease-related factors that may also be associated with the exposure and the outcome (age, sex, and precipitant). Propensity-score-adjusted logistic regression models were then run for each outcome and subgroup individually, including only the exposure of the steroid use and the propensity score measure as independent variables.

The causal risk difference of steroid compared with nonsteroid use on the primary outcome was estimated by taking the difference in predicted probability of an allergy-related subsequent ED visit under the conditions of both exposure and nonexposure to steroids for each individual and averaging the differences across all patients. Bootstrapping was used to construct a 95% CI around this estimate.

RESULTS

Between April 1, 2007, and March 31, 2012, there were 428,634 ED visits to the 2 study sites. Overall, 2,995 patient encounters were identified with discharge diagnoses of allergic reaction within the records of the 2 EDs, yielding 2,701 eligible ED encounters (Figure 2).

There was excellent interrater agreement for the variables skin involvement (κ=0.93; 95% CI 0.84 to 1.0), mucosal tissue involvement (κ=0.83; 95% CI 0.74 to 0.92), wheeze or stridor (κ=0.98; 95% CI 0.95 to 1.0), syncope (κ=1.0; 95% CI 0.99 to 1.0), gastrointestinal symptoms (κ=1.0; 95% CI 0.99 to 1.0), and anaphylaxis (κ=1.0; 95% CI 0.97 to 1.0) on the randomly selected sample of 135 charts.

Characteristics of Study Subjects

Characteristics of the 2,701 patient encounters can be seen in Table 1, along with missing variables. Although the steroid and nonsteroid groups were similar in most aspects, the steroid group demonstrated a higher proportion of patients who were transported by ambulance, who had mucosal tissue involvement, who had wheeze or stridor, and who were treated with epinephrine, and the group included a higher proportion of patients classified as having anaphylaxis.

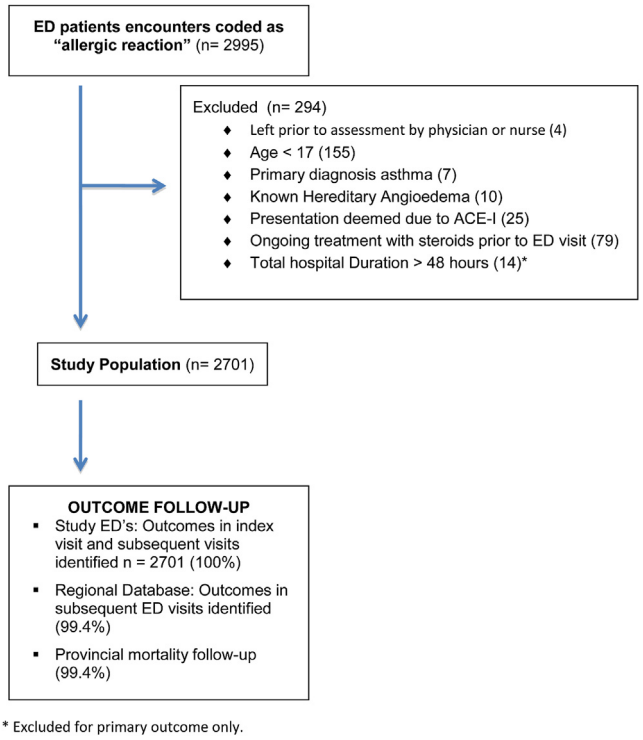

Figure 2. Flow diagram.

Main Results

Corticosteroids were administered to 1,181 patients (44%) in the ED, with 469 (17%) receiving parenteral formulation and 786 (29%) receiving oral prednisone (74 patients received oral and intravenous). A prescription for oral steroid (prednisone in all cases) at ED discharge was recorded in 813 (30%) cases, with a median dose of 50 mg (interquartile range 50, 50) and duration of 5 days (interquartile range 3.0, 5.0). Overall, 1,288 patients (48%) received steroids either in the ED or postdischarge.

During the 7-day follow-up period, there were 170 primary outcomes (6.3%; 95% CI 5.4% to 7.2%) of an allergy-related revisit (Table 2). In the steroid group, 75 patients (5.8%) revisited, and in the nonsteroid group, 95 revisited (6.7%; unadjusted OR=0.86; 95% CI 0.63 to 1.17). After adjustment for differences in baseline variables (Table 3), the propensity score showed an OR of 0.91 (95% CI 0.64 to 1.28). The causal risk difference was estimated as 0.57% (95% CI –1.53% to 2.63%), demonstrating that number needed to treat with steroids to prevent 1 additional ED revisit was 176 (95% CI number needed to treat to benefit=39 to ∞ to number needed to treat to harm=65).

There were no deaths identified during any of the index visits or within the follow-up period for any patient at either of the study hospitals (0/2,715). Of the 2,698 of 2,715 patients (99.4%) for whom a provincial data linkage could be established, there were no deaths identified in British Columbia within the 7-day follow-up period. There were a total of 5 clinically important biphasic reactions (5/2,715) identified in the study cohort, with 4 of 1,297 (0.31%) in the steroid group and 1 of 1,418 (0.071%) in the nonsteroid group (crude OR 4.38; 95% CI 0.43 to 215.80). Because of the rarity of these outcomes, no reliable adjusted statistical analysis could be performed.

One hundred thirty-four patients (5.0%) had a subsequent visit that was deemed to be unrelated to allergy. In examination of any subsequent ED visit within 7 days, this occurred for 298 patients (11%), for 10% of those treated with steroids, and 12% not treated with steroids (adjusted OR 0.87; 95% CI 0.67 to 1.14).

In examination of data for only patients who satisfied the criteria for anaphylaxis (n=473), the primary outcome was observed for 15 of 348 (4.3%) versus 7 of 125 (5.6%) for those treated with and without steroids, respectively (adjusted OR 1.12; 95% CI 0.41 to 3.27). Among patients classified as having allergic reaction (n=2,228), the primary outcome was observed for 60 of 940 (6.4%) versus 88 of 1,288 (6.8%) for those treated with and without steroids, respectively (adjusted OR 0.91; 95% CI 0.63 to 1.31), with a causal risk difference of 0.58% (95% CI –1.73%, 2.70%) and corresponding number needed to treat to benefit of 173 (95% CI number needed to treat to benefit=38 to ∞ to number needed to treat to harm=58). Among the subgroup of patients with a known or "likely" precipitant, 4.9% of those treated with steroids had a subsequent allergy-related visit compared with 6.9% of those not treated with steroids (adjusted OR 0.80; 95% CI 0.52 to 1.20).

In a secondary analysis of patients treated with ED steroids, comparing those who were prescribed steroids after ED discharge (6.1%) and those who were not (5.3%), no relapse differences were apparent (adjusted OR 1.1; 95% CI 0.66 to 1.86).

LIMITATIONS

The study took place at 2 urban Canadian EDs and results may vary in other settings. Clinical impression is the basis for the diagnosis of allergic reaction and this is a potential source of error. Errors may have been made in the classification of anaphylaxis or allergic reaction because of missing data. Unmeasured or conflicting variables may have been associated with both exposures and outcomes. We cannot confirm that patients filled their prescription for or tolerated their full course of outpatient steroids.

In the evaluation of subsequent ED visits, it is possible that a seemingly unrelated visit was in fact the result of

Table 1. Baseline characteristics and ED treatments.*

Variable	Steroid Group (n=1,288)		No-Steroid Group (n=1,413)	
	n or Median	Missing (%)	n or Median	Missing (%)
Age (IQR), y	34 (27–47)	0	35 (26–49)	0
Female sex (%)	751 (58)	0	896 (63)	0
LOS (IQR), h	2.5 (1.6–3.7)	0	1.5 (1.0–2.1)	0
History of allergies (%)	850 (66)	0	791 (56)	0
History asthma (%)	225 (17)	0	150 (11)	0
Ambulance arrival (%)	275 (21)	0	189 (13)	0
SBP (IQR), mm Hg	130 (116–143)	20 (1.6)	127 (115–140)	38 (2.7)
SBP <90 mm Hg (%)	43 (3.3)	20 (1.6)	51 (3.6)	38 (2.7)
Respiratory rate (IQR), bpm	18 (16–20)	23 (1.8)	18 (16–20)	41 (2.9)
Respiratory rate >22 bpm (%)	121 (9.4)	23 (1.8)	64 (4.5)	41 (2.9)
Oxygen saturation (IQR), %	98 (97–100)	35 (2.7)	98 (97–99)	66 (4.7)
Oxygen saturation <95% (%)	104 (8.1)	35 (2.7)	100 (7.1)	66 (4.7)
Allergen known/suspected (%)	932 (72)	0	1,066 (75)	0
Drug (1/0) (%)	266 (21)	0	436 (31)	0
Food (1/0) (%)	542 (42)	0	400 (28)	0
Other (1/0) (%)	126 (10)	0	232 (16)	0
Allergen unknown (%)	354 (27)	0	346 (24)	0
Skin involvement (%)	991 (77)	71 (5.5)	954 (68)	91 (6.4)
Mucosal tissue involvement (%)	345 (27)	364 (28)	142 (10)	444 (31)
Wheeze or stridor (%)	149 (12)	118 (9.2)	33 (2.3)	156 (11)
Syncope (%)	16 (1.2)	548 (43)	12 (0.8)	566 (40)
Gastrointestinal symptoms (%)	44 (3.4)	437 (34)	38 (2.7)	524 (37)
Steroids used in ED (%)	1,181 (92)	0	0	
Hydrocortisone, IV (%)	269 (21)	0		
Methylprednisolone, IV (%)	192 (15)	0		
Dexamethasone, IV (%)	10 (0.8)	0		
Prednisone, PO (%)	786 (61)	0		
Postdischarge prednisone, PO (%)	813 (63)	0		
Epinephrine used (%)†	538 (42)	0	178 (13)	0
Anaphylaxis (%)	348 (27)	0	125 (8.8)	0
Admission to hospital (%)	7 (0.5)	0	4 (0.3)	0

LOS, Length of stay; *IQR*, interquartile range; *SBP*, systolic blood pressure; *bpm*, breaths/min; *IV*, intravenous; *PO*, oral route.
*Categorical variables reported as number (with percentages), and non-normally distributed variables as medians (with IQR).
†Intramuscular, subcutaneous, or IV.

allergic processes. It is possible that a proportion of patients with subsequent allergy-related ED visits had repeated allergen exposures; however, a repeated ED visit, whether provoked by a new stimulus or a recurrent reaction (both of which, in theory, could be modified by steroid administration), is a clinically relevant outcome. Physicians on the index visit may have instructed patients to return to the ED for reassessment, although this was not typical practice in the study EDs. Clinically important biphasic reactions and subsequent visits may have been missed for

Table 2. Outcomes and propensity score analysis.

Primary Outcome, Secondary Outcomes, Secondary Analysis	Steroids (%)	No Steroids (%)	Unadjusted OR	95% CI	Adjusted OR	95% CI
Primary outcome: allergy-related visits						
Full cohort (n=2,701)	75 (5.82)	95 (6.72)	0.86	0.63–1.17	0.91	0.64–1.28
Anaphylaxis (n=473)	15 (4.31)	7 (5.60)	0.76	0.31–2.03	1.12	0.41–3.27
Allergic reaction (n=2,228)	60 (6.39)	88 (6.83)	0.93	0.66–1.30	0.91	0.63–1.31
Known or likely precipitant (n=1,998)	46 (4.94)	73 (6.85)	0.71	0.48–1.03	0.80	0.52–1.20
Secondary outcomes (all examining full cohort)						
Any subsequent ED visit within 7 days	128 (9.94)	170 (12.03)	0.81	0.63–1.03	0.87	0.67–1.14
Clinically important biphasic reactions	4 (0.31)	1 (0.07)	4.38	0.43–215.80		
Mortality	0	0				
Secondary analysis						
Extended course vs only ED steroids	43 (6.09)	25 (5.26)	1.17	0.71–1.96	1.1	0.66–1.86

Table 3. Crude ORs of covariates entered into propensity score analysis, on primary outcome.

Covariate	OR	95% CI of OR
Precipitant other	1.77	1.18–2.59
Skin involvement	1.60	1.10–2.38
Precipitant drug	1.35	0.96–1.88
Likely allergen	1.28	0.93–1.76
Precipitant unknown	1.28	0.91–1.79
Syncope	1.15	0.18–3.88
Mucosal tissue involvement	1.10	0.73–1.61
Age, per year increase	1.02	1.01–1.02
Oxygen saturation, per % decrease	1.01	0.92–1.09
SBP, per 1 mm Hg decrease	1.00	0.99–1.01
Sex, male vs female	0.99	0.72–1.36
Gastrointestinal symptoms	0.97	0.34–2.19
RR, per 1 bpm increase	0.94	0.88–1.00
Epinephrine used	0.87	0.60–1.24
History of allergies	0.83	0.61–1.14
Ambulance arrival	0.73	0.45–1.13
History of asthma	0.72	0.42–1.16
Wheeze or stridor	0.58	0.24–1.16
Known allergen	0.45	0.26–0.72
Precipitant food	0.36	0.24–0.54

RR, Respiratory rate.

patients who presented to an ED out of the region; similarly, deaths of patients who died outside of the province would not have been recorded.

It is possible that steroid administration had an influence on primary and secondary outcomes and that prudent physician care predicted these complications and administered steroids in appropriate cases. However, with no reliable data to predict poor outcomes this scenario is unlikely. Furthermore, we calculated a propensity score to adjust for measured factors that would influence this decision. Our data indicate that physicians were more likely to administer steroids to sicker patients; however, our propensity score analysis, adjusting for markers of disease severity and other possible confounders, failed to show any association between steroid administration and the primary outcome. Because of the small number of outcomes in our subgroup analysis of those classified as having anaphylaxis, the estimate of the adjusted OR may be unreliable (for this reason, we did not calculate a causal risk difference in this group). In addition, we were unable to assess whether patient symptoms were ameliorated with steroid treatment.

We did not quantify the number of subsequent ED encounters caused by steroid adverse drug reactions (these were not included in allergy-related visits but were included in all-cause visits). Accurately determining the causality or contribution of a medication adverse effect in ED encounters (for example, a psychiatric patient who presents with hallucinations or a diabetic patient with an elevated blood sugar level) is inherently problematic and beyond the scope of this article's objectives.

DISCUSSION

In this study of patients with 2,701 allergy-related ED visits, 48% of whom received steroids, steroid use was not found to be superior to no steroid use with respect to allergy-related ED revisits at 7 days. Our causal risk difference was very small (0.57%), suggesting that steroid administration does not prevent ED recidivism. The upper bound of the CI indicates that physicians would need to treat a minimum of 39 patients with steroids to prevent 1 relapse. Applying our hypothesis that a clinician would consider a number needed to treat to benefit of more than 30 a clinically unimportant benefit, these data suggest that a decision not to administer steroids is clinically noninferior to steroid use in the prevention of allergy-related ED revisits. However, we cannot rule out the possibility that treatment is actually associated with an increased risk of subsequent allergy-related ED visits.

Similarly, we were unable to detect a benefit of steroid administration for all-cause ED visits. Additional secondary outcomes of clinically important biphasic reactions and mortality were rare or nonexistent, making reliable statistical analyses unfeasible, and thus we are unable to draw conclusions about these outcomes.

To identify a subgroup of similar patients affected by severe allergic reactions and evaluate this group for clinical outcomes, we based our definition of anaphylaxis on the 2006 National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network[3] definition for anaphylaxis and applied this to all patient encounters. With the goal of identifying a more homogeneous group of patients with "true" allergic reactions, we performed a subgroup analysis for those who had a known or likely offending allergen identified. There were no statistically significant associations observed in these groups. Furthermore, we tested the hypothesis of whether a multiple-day course of steroids would be required for benefit but found no differences when comparing patients treated only in the ED and those with steroid use continuing postdischarge.

There is a lack of research examining the efficacy of steroids in patients with allergic reactions or anaphylaxis.[2,7,14] A recent Cochrane review failed to identify any appropriate studies examining this question.[7] Although not designed to evaluate the effectiveness of steroids, several studies examining the incidence of biphasic reactions have reported the proportion treated with steroids. This is relevant because the chief concern of the

emergency physician when discharging a patient with allergy-related symptoms is the subsequent development of a life-threatening anaphylactic reaction. Lee et al[15] identified 21 patients with biphasic reactions from a cohort of 541 patients with anaphylaxis; steroids were administered for 85% and 100% of those with uniphasic and biphasic reactions, respectively. Ellis and Day[16] identified 20 biphasic reactions in a cohort of 103 ED patients with anaphylaxis. They reported that 35% of the patients with biphasic reactions had been treated with steroids in comparison with 55% in the uniphasic group. Brady et al[17] identified 67 ED patients with anaphylaxis and reported 2 with biphasic reactions, both of whom were treated with intravenous steroids. Smit et al[18] collected data on 282 ED patients with anaphylaxis and identified 15 biphasic reactions; 87% of the patients were treated with steroids (in comparison with 92% of the remainder of the cohort).

Despite a lack of evidence to support the use of steroid therapy for allergic reactions, this practice appears to be common. Cohort studies examining ED patients with allergic reaction and anaphylaxis have reported steroid use in 51% to 92% of patients,[5,16-20] which is in keeping with our population. A large epidemiological study described 12.4 million allergy-related ED visits in the United States during a 12-year period. Steroid use was reported overall in 38% of visits, with an increase observed from 22% to 50% during the study period. This represents a large subset of the population (approximately half a million per year in the United States) that is exposed to an unproven intervention and who may be at risk of subsequent steroid-related adverse effects.

In addition to the well-described long-term complications of chronic steroid use, there is also risk of serious adverse effects after short-term, high-dose therapy, as would be used in the treatment of allergic reactions. The incidence of psychiatric adverse effects is dose dependent, with an incidence between 2% and 60%,[21] mostly occurring within the first 7 to 14 days and ranging from mild depression and anxiety to psychosis with hallucinations.[22] Hyperglycemia is a well-documented adverse effect of steroids that can occur within hours of administration.[9] Although to our knowledge there is no literature on the incidence of clinically relevant hyperglycemia among short-term users, it is a consideration among vulnerable groups such as patients with diabetes. Several reports describe avascular necrosis after short-term steroid use.[9,23,24]

Previous data suggest that the use of steroid medications for the management of allergic reactions has become a widely accepted treatment.[1] Our large study, the first analysis of the effectiveness of this treatment to our knowledge, begs a reconsideration of this strategy because the assumption of benefit has not been confirmed. Ideally, a large ED-based randomized trial would be required to determine the true effectiveness of steroids for patients with allergic reactions. However, until these data are available, we encourage clinicians to consider the risk:benefit ratio of steroid treatment, and length of treatment, in patients before routine use, acknowledging those who may be at a higher risk of steroid-related complications.

In this cohort of 2,701 ED presentations caused by allergic reactions or anaphylaxis, corticosteroids were administered in 48% of cases. Physicians appear to prescribe corticosteroids more often in anaphylaxis than less severe allergic reactions. Despite this, after propensity score adjustment, corticosteroid treatment was not associated with decreased subsequent visits to the ED. Pragmatic clinical trials are urgently required to identify effective and safe treatment options for ED patients with allergic reactions.

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REFERENCES

1. Gaeta TJ, Clark S, Pelletier AJ, et al. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol*. 2007;98:360-365.
2. Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol*. 2011;127:587-593.e1-22.
3. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med*. 2006;47:373-380.
4. Beyer K, Eckermann O, Hompes S, et al. Anaphylaxis in an emergency setting—elicitors, therapy and incidence of severe allergic reactions. *Allergy*. 2012;67:1451-1456.
5. Lauritano EC, Novi A, Santoro MC, et al. Incidence, clinical features and management of acute allergic reactions: the experience of a single, Italian emergency department. *Eur Rev Med Pharmacol Sci*. 2013;17(suppl 1):39-44.
6. Rowe BH, Spooner CH, Ducharme FM, et al. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev*. 2007;(3):CD000195.
7. Choo KJL, Simons FER, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Cochrane Database Syst Rev*. 2012;(4):CD007596.
8. Simons FER. Pharmacologic treatment of anaphylaxis: can the evidence base be strengthened? *Curr Opin Allergy Clin Immunol*. 2010;10:384-393.
9. Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. *Otolaryngol Clin North Am*. 2010;43:753-768.
10. Xavier Scheuermeyer F, Grafstein E, Stenstrom R, et al. Thirty-day outcomes of emergency department patients undergoing electrical cardioversion for atrial fibrillation or flutter. *Acad Emerg Med*. 2010;17:408-415.
11. Gilbert EH, Lowenstein SR, Koziol-McLain J, et al. Chart reviews in emergency medicine research: where are the methods? *Ann Emerg Med*. 1996;27:305-308.
12. Worster A, Bledsoe RD, Cleve P, et al. Reassessing the methods of medical record review studies in emergency medicine research. *Ann Emerg Med*. 2005;45:448-451.
13. Grunau BE, Li J, Yi TW, et al. Incidence of clinically important biphasic reactions in emergency department patients with allergic reactions or anaphylaxis. *Ann Emerg Med*. 2014;63:736-744.
14. Simons FER, Sheikh A. Anaphylaxis: the acute episode and beyond. *BMJ*. 2013;346:f602.
15. Lee S, Bellolio MF, Hess EP, et al. Predictors of biphasic reactions in the emergency department for patients with anaphylaxis. *J Allergy Clin Immunol Pract*. 2014;2:281-287.
16. Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol*. 2007;98:64-69.
17. Brady WJ, Luber S, Carter CT, et al. Multiphasic anaphylaxis: an uncommon event in the emergency department. *Acad Emerg Med*. 1997;4:193-197.
18. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med*. 2005;28:381-388.
19. Cianferoni A, Novembre E, Mugnaini L, et al. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985-1996). *Ann Allergy Asthma Immunol*. 2001;87:27-32.
20. Lertnawapan R, Maek-a-nantawat W. Anaphylaxis and biphasic phase in Thailand: 4-year observation. *Allergol Int*. 2011;60:283-289.
21. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc*. 2006;81:1361-1367.
22. Kenna HA, Poon AW, de los Angeles CP, et al. Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry Clin Neurosci*. 2011;65:549-560.
23. Powell C, Chang C, Naguwa SM, et al. Steroid induced osteonecrosis: an analysis of steroid dosing risk. *Autoimmun Rev*. 2010;9:721-743.
24. McKee MD, Waddell JP, Kudo PA, et al. Osteonecrosis of the femoral head in men following short-course corticosteroid therapy: a report of 15 cases. *CMAJ*. 2001;164:205-206.