CRITICAL REVIEW FORM:
THERAPY ARTICLES

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Citation: Grunau BE. et al., Emergency Department Corticosteroid Use for Allergy or Anaphylaxis Is Not Associated with Decreased Relapses. Ann Emerg Med. 2015 Oct;66(4):381-9. Epub 2015 Mar 25. PMID: 25820033.

Study Objective: Corticosteroids 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. Authors sought to determine the association of steroid administration with improved clinical outcomes.

Primary Outcome: Allergy-related ED revisits in the steroid- and nonsteroid-exposed groups within 7 days of visit (adjusted for potential confounders with a propensity score analysis.)

Secondary Outcome: The number of clinically important biphasic reactions and deaths or all-cause repeated ED visits within 7 days.

Study Methodology: Retrospective cohort study including 2701 encounters for allergic reactions from 2007-2012 in two teaching hospitals in Vancouver BC and 473 diagnosed with anaphylaxis taking place in 2 Emergency Departments in Vancouver over a 5-year period. **Inclusion criteria**: Age ≥ 18 with ED discharge diagnosis of "allergic reaction". **Exclusion criteria**: Asthma as primary diagnosis, hereditary angioedema, ACE inhibiter etiology, on steroids, total hospital duration > 24hrs

Investigators performed a standardized chart review, three separate reviewers with adjudication by consensus. Five percent of chart reviews were randomly selected for interrater reliability and kappa scoring for variables such as met criteria for anaphylaxis, skin involvement, mucosal tissue involvement, wheeze or stridor, syncope, and gastrointestinal symptoms.

GUIDE	COMMENTS
I. Are the results valid?	
A. Did experimental and control groups begin the study with a similar prognosis	No; breakdown of patient characteristics consistently showed that sicker patients with worse prognosis were more likely to receive steroids.
1. Were patients randomized?	This was not an RCT, but sicker patients tended to be more likely to receive steroids, so there were significant confounding variables present.
2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	n/a, not an RCT; by definition, retrospective cohort study is not blinded

3. Were patients analyzed in the groups to which they were randomized?	N/A No intention-to-treat groups in retrospective studies
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	No; patients receiving steroids were more likely to have also been diagnosed with anaphylaxis and receive epinephrine, and across virtually all examined variables, the patients that received steroids were sicker
5. Were patients aware of group allocation?	N/A
6. Were clinicians aware of group allocation?	N/A
7. Were outcome assessors aware of group allocation?	**No.** Authors state "outcome assessors (data abstractors) were not aware of the study hypotheses." (This is an important aspect of blinding that should occur with retrospective chart reviews. See Worster's Article on how to do a proper chart review)
8. Was follow-up complete?	**Yes.** Using the patient's unique provincial health number, the study cohort was linked to a national registry to identify all patients who returned to any regional ED or died within the province, respectively, during the 7-day follow-up period. This accounted **for** 99.4% of enrolled patients had follow-up
What are the results?	Steroids were given in 44% of the cohort in the ED 30% were D/C'd on oral steroid with a total of 170 primary outcomes **(6.3%;** 95% CI 5.4% to 7.2%) **Primary Outcome** **Steroid group**, 75 patients (5.8%) revisited, **Nonsteroid group**, 95 revisited (6.7%) revisited **Unadjusted** OR.0.86; 95% CI 0.63 to 1.17). Crosses 0 non-significant. Absolute Risk Reduction 6.7%-5.8% = 0.9% NNT = 1/ARR = 1/.009 = 111 the NNT is generally not calculated in CI's that are not significant. **After propensity scoring** OR of 0.91 (95% CI 0.64 to 1.28) also non-significant Authors report the causal risk estimate of 0.57% which was not clearly defined however 1/.0057= NNT of 176 **Secondary Outcomes** There were no deaths identified during any of the index visits or within the follow-up period for any patient 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) (non significant). When adjusting for those who satisfied criteria for anaphylaxis N=473 there was no statistical difference between the steroid and non-steroid groups OR 1.12; 95% CI 0.41 to 3.27)

1. How large was the treatment effect?	See above
2. How precise was the estimate of the treatment effect? (CI's?)	See above
III **How can I apply the results to patient care?**	
1. Were the study patients similar to my patient?	Hard to say. No racial distribution given. Urban population would be similar to ours.Their LOS <3hrs. seems sig shorter than our typical LOS
2. Were all clinically important outcomes considered?	Generally yes. Authors did not screen for adverse outcomes from EPI or steroids. No subgroup analysis regarding diabetics or older patients and their response to drug interventions
3. Are the likely treatment benefits worth the potential harm and costs?	**I would argue that the lack of a statistically significant difference between steroid and non-steroid groups (especially when the outcome variable is not related to acute anaphylaxis mortality/morbidity) is not an indication to hold steroid therapy for a patient in extremis.**

Limitations:

- Small sample size, especially with regard to anaphylaxis. (N=473 or 35%)
- Retrospective chart review with single search term "allergic reaction" could have missed a host of sick patients with alternative diagnoses such a syncope, respiratory arrest, cardiac arrest, etc.. Same applies to revisit complaints.
- Poorly generalizable to the population of interest (anaphylaxis) due to majority of patients having unspecified non-anaphylactic allergic reactions. Very specific patient population as well.
- Lack of analysis of adverse events hurts ultimate claim that steroids do more harm than good
- Unable to exclude confounding by repeat exposures rather than true biphasic reactions
- In theory, propensity matching helps control for the relatively non-random distribution of steroid use, however it literally flips the odds ratio (while maintaining statistical non-significance) when analyzing the most relevant subset of the study (anaphylactic patients)
- If patients are in extremis, there does not appear to be a significant downside in giving steroids based on the results of this particular study. Sicker patients clearly got steroids in this cohort.

Clinical Bottom Line:
This is one of many initial studies that helps chip away at the role of steroids in treatment of anaphylaxis, but should not dictate practice on its own. Given the large body of cohort studies demonstrating the apparent non-inferiority of holding steroid therapy, a large-scale randomized control trial testing the effects of steroids on acute anaphylaxis is warranted. The ultimate factor that will likely determine whether or not holding steroids becomes common practice will likely be based on comparing acute mortality/morbidity from anaphylaxis in patients who receive epinephrine and other standards of care plus steroids vs placebo, and contrasting this with analysis of post-anaphylaxis adverse events in the same two groups. At the current time, a cohort study that suggests that not giving steroids is non-inferior to giving steroids in preventing repeat ED visits in all-cause "allergic reactions" provides zero actionable evidence to change current clinical practice for treating anaphylactic patients in extremis. One criticism of this behavior however, is that clinicians commonly forego using epinephrine in the elderly or those with a history of cardiac risk factors which may predispose these patients to poor outcomes in those with true anaphylaxis.