Critical Review Form
Therapy

Rehrer MW, Liu B, Rodriguez M, Lam J, Alter HJ. A Randomized Controlled Noninferiority Trial of Single Dose of Oral Dexamethasone Versus 5 Days of Oral Prednisone in Acute Adult Asthma. Ann Emerg Med. 2016 Nov;68(5):608-613.

Objectives: **"to evaluate whether a single dose of oral dexamethasone plus 4 days of placebo is not inferior to 5 days of oral prednisone in the treatment of adults with mild to moderate asthma exacerbations to prevent relapse..." (p. 608)**

Methods: **This prospective, randomized controlled trial was conducted in the ED of Highland Hospital in Oakland, CA between 2011 and 2015. Adult patients aged 18 to 55 years presenting with an acute asthma exacerbation requiring more than one nebulized albuterol treatment were screened for eligibility by the respiratory therapist. Exclusion criteria were lack of a working telephone number, pregnancy, previous allergic reaction to corticosteroids, use of oral corticosteroids within 2 weeks of presentation, history of COPD or pulmonary fibrosis, history of HIV, history of CHF, active varicella, active tuberculosis, or history of diabetes mellitus. Patients were also excluded if they required BiPAP or intubation, or if they were admitted to the hospital.**

Patients were randomized in a 1:1 fashion to receive either 60 mg of PO prednisone in the ED, along with four more daily doses, or 12 mg of oral dexamethasone, followed by four days of placebo. Patients were contacted by telephone two weeks after the ED visit and a survey was completed at that time. The primary outcome was relapse, defined as an unscheduled visit to a healthcare provider for additional asthma treatment or return to an ED for worsening asthma within fourteen days. Secondary outcomes included adverse effects and asthma symptoms at the time of the survey.

Out of 1677 patients assessed for eligibility, 465 were randomized (227 to dexamethasone and 238 to prednisone). Ten patients in the dexamethasone group and 6 from the prednisone group were admitted (and hence excluded), and a further 44 patients in the dexamethasone group and 29 in the prednisone group were lost to follow-up. This left 173 patients analyzed in the dexamethasone group and 203 in the prednisone group. The median age was 32 years in both groups, and 47% and 51% in each group were female, respectively.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized in a 1:1

		fashion to receive either oral prednisone or oral dexamethasone.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Once the electronic study medication order was placed, a randomization table maintained by the pharmacy assigned subjects to one of the 2 treatment arms." (p. 609) This should be sufficient to prevent subversion of the randomization process (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "We performed descriptive statistics with standard analytics based on intention-to-treat principles." (p. 610) The authors make no mention of crossover between the groups and did not assess for medication compliance.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, use of inhaled steroids at home, recent ED visits, hospital admission in the previous year, prior need for intubation, smoking history, and initial vital signs and peak flow. Patients were also similar with respect to use of continuous nebs in the ED, number of nebs received, and discharge peak flow.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "The capsules were identical and prepared by Advantage Pharmaceuticals, which was otherwise not involved in the trial. Because the capsules were identical, the treating provider, nurse, pharmacist, and study participant were unable to discern the medication administered." (p. 609)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	No. Two-week telephone interview was conducted by staff who were blinded to allocation group. Additionally, the data analysis team was blinded to allocation arm.
4.	Was follow-up complete?	No. There was an overall 16% loss to follow-up; loss to follow-up was 20% in the dexamethasone group and 12.5% in the prednisone group. This disparity in loss to

		follow-up between groups significantly increases the risk of attrition bias.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• The primary outcome occurred in 12.1% of patients in the dexamethasone group and 9.8% of the prednisone group for a risk difference of 2.3% (95% CI -4.1% to 8.6%). ○ The upper limit of the 95% CI crosses the prespecified noninferiority threshold of 8%. • The two groups demonstrated similar rates of hospitalization and similar rates of subjective improvement in symptoms. • Adverse event rates were also mostly similar between the groups.
2.	How precise was the estimate of the treatment effect?	See above. The 95% CI was rather wide, and did cross the noninferiority threshold of 8%.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. This study was conducted at a large, urban ED in the US and included patients with asthma exacerbations requiring at least 2 nebulized albuterol treatments who were then discharged home from the ED. These patients should be similar to many patients we encounter, with similar prognosis.
2.	Were all clinically important outcomes considered?	No. The authors looked at asthma relapse rates, which is quite important, but did not evaluate quality of life, return to work, or medication compliance. They also did not look at the frequency of albuterol use following ED discharge.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study did not demonstrate the noninferiority of a single dose of a dexamethasone when compared to five days of prednisone, there was still no statistically significant difference in the primary outcome between the groups. The study's primary limitation appears to be its sample size; a large sample size could more easily demonstrate noninferiority. Had loss to follow-up not been so large, a larger sample size would have been available for analysis and potentially a narrow enough confidence interval would have been achieved.

Limitations:

1. **The study understandably excluded patients without a working telephone number, but this would likely represent a group of patients with lower socioeconomic status who could potentially have worse overall prognoses (external validity).**

2. **There was an overall 16% loss to follow-up, with a fairly broad disparity between the groups that significantly increases the risk of attrition bias.**

3. **The authors failed to assess several other patient-centered outcomes, including time to return to work/normal activities, frequency of albuterol use, and medication compliance.**

4. **Despite there being no statistically significant difference between the groups for the primary outcome, the study was not able to demonstrate noninferiority.**

Bottom Line:

This well-blinded, randomized controlled trial comparing a single dose of oral dexamethasone with a 5-day course of oral prednisone in patients with asthma being discharged from the ED found no statistically significant difference in relapse rates at 14 days (risk difference of 2.3%; 95% CI -4.1% to 8.6%). Because the upper limit of the confidence interval exceeded the predefined noninferiority threshold of 8%, the authors could not conclude that a single dose of oral dexamethasone was not inferior to a 5-day course of oral prednisone. This study was limited by significant loss-to-follow up with a disparity between the groups, raising the possibility of attrition bias.