Critical Review Form
Therapy

PGY-4

Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. Chest. 2004 Aug;126(2):362-8.

Objectives: **"to test the hypothesis that a single IM dose of depot methylprednisolone would reduce relapse rates at 10 days (*ie*, the primary end point) and 21 days (*ie*, the secondary end point) compared to an oral tapering course of methylprednisolone given to asthmatic patients who have been discharged from the ED following treatment for an acute exacerbation." (p. 363)**

Methods: **This randomized, controlled trial was conducted in the emergency departments (EDs) of two hospitals between November, 1997 and November, 2002. Patients aged 18 to 45 years being treated for an acute asthma exacerbation with a peak expiratory flow rate (PEFR) between 40% and 70% of predicted were eligible for enrollment. Exclusion criteria were history of other chronic lung disease; use of systemic corticosteroid within the previous month; known or suspected bacterial pneumonia; current use of theophylline, mast cell stabilizers, or an inhaled anticholinergic agent; contraindication to corticosteroid administration; or allergy to methylprednisolone.**

All patients received an IV injection of methylprednisolone (1 mg/kg) as well as nebulized β-agonists. Patients were randomized to receive either IM methylprednisolone (160 mg depot) plus an 8-day supply of an oral placebo, or an IM injection of saline plus an 8-day tapering dose of oral methylprednisolone. Follow-up occurred by telephone after day 10 and day 21. The primary outcome was relapse rate by day 10, defined as any unscheduled visit to a doctor's office, clinic, or ED for persistent or worsening asthma symptoms. The secondary outcome was relapse rate between days 11 and 21.

A total of 190 patients were enrolled, of whom 3 were later excluded due to protocol violations. An additional seven patients were lost to follow-up and excluded from the primary analysis. Of the remaining 180 patients, 92 received IM methylprednisolone and 88 received oral methylprednisolone. The mean age was 33 years and 22% and 34% were male in the IM and oral methylprednisolone groups, 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. "The medication was prepared and block-randomized by a research pharmacist

		who used a computer-generated set of random numbers to package the medications in balanced blocks of 20...." (p. 363)
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. "The randomization code was held by the pharmacist and was not broken during the course of the study." (p. 363) This should be sufficient to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	No. Three of the enrolled patients (1.6%), all in the oral methylprednisolone group, were excluded from the analysis for protocol violations. While this was not a true intention to treat analysis, the small number of patients excluded makes it unlikely that the results were significantly adversely affected.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. The proportion of male patients was significantly higher in the oral methylprednisolone group (34% vs. 22%). More importantly, significantly more patients in this group had a history of prior intubation (9.8% vs. 3.2%). Patients were similar with respect to history of tobacco use, duration of symptoms, initial vital signs, and initial PEFR.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Likely no. Unfortunately, the IM injection (methylprednisolone or saline) was injected by a nurse who was not blinded to the treatment, but who "was instructed not to provide the patient, physician, or study personnel with any information about the contents of the syringe." (p. 363) Despite this, it seems likely that patients and physicians remained blinded to group allocation and were not subject to performance bias. The oral methylprednisolone and oral placebo were identical in appearance and in identical containers.
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	Uncertain. The authors provide no information regarding who performed telephone follow-up and whether or not they were aware of group

		allocation.
4.	Was follow-up complete?	Mostly yes. A total of 7 patients (3.8%) were lost to follow-up, with an equal distribution between the two groups. This small loss to follow-up is unlikely to have contributed significant attrition bias.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• 10-day relapse rates were similar in the IM and PO methylprednisolone groups: 14.1% vs. 13.6%, risk difference 0.5% (95% CI -9.6% to 10.6%). • 21-day relapse rates were also similar between the groups: 18.5% vs. 22.7%, risk difference -4.2% (95% CI -16.1% to 7.6%).
2.	How precise was the estimate of the treatment effect?	See above. This was a rather small study with very wide confidence intervals that include the possibility of a clinically significant difference in efficacy.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Somewhat. This study was conducted at two urban emergency departments and included patients with significant exacerbations of chronic asthma (PEFR 40% to 70% predicted) who were discharged home. This patient population would likely be quite similar to ours. Differences in standard of care between this study and our current practice, such as the use of a tapered dose of methylprednisolone versus a burst of prednisone, the exclusion of patients using inhaled anticholinergics, may have some small effect on outcomes and affect external validity.
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 found no difference in relapse rates with the use of a single dose of IM methylprednisolone compared to a tapering oral dose, the study was quite small and the confidence intervals surrounding the results do not rule out a clinically meaningful difference in outcomes.

		Additionally, we rarely use a taper of oral methylprednisolone in the outpatient management of asthma exacerbations, which may somewhat limit the external validity of the results.

Limitations:

1. **It is unclear if this was a consecutive or convenience sample. There is no description of eligible patients that were not screened for enrollment and no comparison to those patients that were enrolled.**

2. **The authors provide no information regarding who performed telephone follow-up and whether or not they were aware of group allocation (observer 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. **This was a rather small study with very wide confidence intervals that include the possibility of a clinically significant difference in efficacy.**

Bottom Line:

This small, randomized controlled trial demonstrated no difference in relapse rates when comparing a single dose of IM methylprednisolone with a tapering oral dose in patients discharged from the ED for an acute asthma exacerbation. The study suffered some flaws in terms of reporting, but is primarily limited by sample size.