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# Oral Corticosteroids for Acute Lower Respiratory Infection: Are We Ready to Drop This Practice?

*Hay AD, Little P, Harnden A, et al. Effect of oral prednisolone on symptom duration and severity in nonasthmatic adults with acute lower respiratory tract infection: a randomized clinical trial. JAMA 2017;318:721–30.*

## Study Overview

Objective. To assess the effects of oral corticosteroids for acute lower respiratory tract infection in adults without asthma or COPD.

Design. Multi-center, placebo-controlled, randomized clinical trial.

Setting and participants. This study was conducted at 4 UK centers (the Universities of Bristol, Southampton, Nottingham, and Oxford) between July 2013 and October 2014. Patients with acute cough (≤ 28 days) and at least 1 of the following lower respiratory tract symptoms (phlegm, chest pain, wheezing, or shortness of breath) were recruited by family physicians and nurses. Patients with chronic pulmonary disease, who had received asthma medication in the past 5 years, required hospital admission, or required same-day antibiotics were excluded. Patients were randomized by variable block size into prednisolone or placebo groups in a 1:1 ratio, stratified by center.

Intervention. Participants were asked to take 2 tablets of either 20-mg oral prednisolone or placebo tablets once daily for 5 days. The medications, which looked and tasted identical, were packaged into numbered packs by an independent pharmacist and were delivered to the family practices to be distributed to the enrolled patients. Participants were invited to report daily, using web or paper version, the severity of symptoms using a scale 0 to 6, along with twice-daily peak flow, for 28 days or until symptom resolution. Participants received shopping vouchers. Medical notes were reviewed at 3 months for new diagnosis of asthma, chronic obstructive pulmonary disease, whooping cough, and lung cancer.

Main outcome measures. The primary outcomes were the duration of moderately bad or worse cough (defined as the number of days from randomization to the last day with a score of at least 3 points prior to at least 2 consecutive days with a score of less than 3, up to a maximum of 28 days); and the mean severity score (range 0–6) of the 6 main symptoms (cough, phlegm, shortness of breath, sleep disturbance, feeling generally unwell, and activity disturbance) on days 2 to 4.

Main results. 401 patients were randomized; 25 patients were lost to follow-up, leaving 173 in prednisolone group and 161 in placebo group for analysis. The prednisolone group was slightly more likely to be male, older, and to have received an influenza vaccine. 96% were white. Symptom diaries were returned by 94% of patients. For primary outcome 1, duration of moderately bad or worse cough, the median time to recovery from moderately bad or worse cough was 5 days (interquartile range, 3–8 days) in both groups. There was no difference after sensitivity analysis (multiple imputation of missing data, per-protocol analysis, and adjusting for day of recruitment). Primary outcome 2, the mean symptom severity score, after adjustment for center and baseline measure, was lower (hazard ratio, –0.20) in the prednisolone group compared with the placebo group; however, after secondary additional adjustment for age, sex, influenza vaccine, and smoking, the difference was not statistically significant. Secondary

outcomes included total duration and severity of each symptom up to 28 days, duration of abnormal peak flow up to 28 days, cough duration of any severity up to 56 days, antibiotic use, patient satisfaction, adverse events were not different between the two groups. There were no new urinary or visual symptoms and none of the patients reporting fatigue, thirst, or dry throat had diabetes.

Conclusion. Oral corticosteroids should not be used for acute lower respiratory tract infection symptoms in adults without asthma because they do not reduce symptom duration or severity.

## Commentary

This study by Hay et al prospectively recruited patients with acute respiratory illness presenting to an outpatient setting within multiple centers for a placebo-controlled randomized study to evaluate the effectiveness of oral corticosteroids for acute lower respiratory tract infection. Patients with pre-existing lung disease such as asthma or COPD were excluded. This study showed moderate-dose oral prednisolone (20 mg twice a day for 5 days) did not reduce the duration of cough, and there was no statistically significant differences in primary and secondary outcomes between the 2 groups.

The beneficial effect of corticosteroids is thought to be due to its anti-inflammatory effect and decreasing harmful cytokines, which can be elevated during acute respiratory illness. In patients with severe pneumonia, patients potentially benefitted from corticosteroids by achieving clinical stability faster, reducing risk for treatment failure or ARDS and reducing hospital length of stay. However, corticosteroids are associated with hyperglycemia, myopathy, superinfection, osteopenia, and increased risk for gastrointestinal bleeding [1]. Corticosteroids have shown benefit repeatedly in patients with pneumonia severe enough to require hospitalization or intensive care unit stay [2–7].

The use of oral corticosteroids in non-critical acute respiratory tract illness without underlying obstructive lung disease has been a somewhat common practice (15%) [8]. However, no study to date firmly supports the use of oral corticosteroids in this patient group. A recently published randomized study attempted to determine if there is a benefit of oral dexamethasone in patients with acute sore throat, and found none [9]. No randomized controlled data has been published on the outpatient use of oral corticosteroids for acute lower respiratory illness.

The current study offers further evidence against the use of oral corticosteroids for acute, non-critical inflammation of the respiratory tract in nonasthmatic patients. Strengths of the study include its blinded and randomized study design and large number of patients. However, there are some limitations. Acute lower respiratory infection is associated with a wide spectrum of causative organisms and severity. It is possible that the beneficial effects of corticosteroids are only measurable when disease severity is high and there will be a systemic inflammatory response. In addition, outcome measurement was limited to a few items, namely patient-reported symptom score and duration. Furthermore, they measured the peak flow adjunctively. Without underlying airway hyperreactivity, substantial differences in peak flow are unlikely to be evident, limiting the usefulness of this as an indicator of disease in patients without chronic pulmonary disease.

Other study limitations include low patient recruitment rate, a large number of patients who did not have moderately bad cough at presentation or during the first 2 days, absence of baseline biomarkers (such as inflammatory, microbiological, spirometric or radiographic) and patient-reported outcome measures, and a sample largely homogenous in ethnicity with a small number of smokers. It is unclear whether similar results could be achieved in a more diverse population and with a greater percentage of smokers. In addition, although overall both groups were well balanced, including the number of patients taking over-the-counter cough suppressants and delayed antibiotics, the tracking of other concurrent therapies such as NSAIDs or acetaminophen was not included in the study design and the type of antibiotic was not tabulated. Such concurrent drugs could have masked a true benefit of oral corticosteroids.

## Applications for Clinical Practice

This study will help prevent excessive prescription of oral corticosteroids for acute minor lower respiratory infection that requires only outpatient treatment. However, the evidence is limited to patients in stable condition. Patients with more severe acute lower respiratory infection, such as patients requiring hospitalization, may still benefit from a short course of oral corticosteroids.

Furthermore, patients with underlying obstructive airways disease such as asthma or COPD should still be considered for oral corticosteroid therapy depending on their clinical circumstances.

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