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Effect of Oral Prednisolone on Symptom Duration and Severity in Nonasthmatic Adults With Acute Lower Respiratory Tract Infection
A Randomized Clinical Trial

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IMPORTANCE Acute lower respiratory tract infection is common and often treated inappropriately in primary care with antibiotics. Corticosteroids are increasingly used but without sufficient evidence.

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

DESIGN, SETTING, AND PARTICIPANTS Multicenter, placebo-controlled, randomized trial (July 2013 to final follow-up October 2014) conducted in 54 family practices in England among 401 adults with acute cough and at least 1 lower respiratory tract symptom not requiring immediate antibiotic treatment and with no history of chronic pulmonary disease or use of asthma medication in the past 5 years.

INTERVENTIONS Two 20-mg prednisolone tablets (n = 199) or matched placebo (n = 202) once daily for 5 days.

MAIN OUTCOMES AND MEASURES The primary outcomes were duration of moderately bad or worse cough (0 to 28 days; minimal clinically important difference, 3.79 days) and mean severity of symptoms on days 2 to 4 (scored from 0 [not affected] to 6 [as bad as it could be]; minimal clinically important difference, 1.66 units). Secondary outcomes were duration and severity of acute lower respiratory tract infection symptoms, duration of abnormal peak flow, antibiotic use, and adverse events.

RESULTS Among 401 randomized patients, 2 withdrew immediately after randomization, and 1 duplicate patient was identified. Among the 398 patients with baseline data (mean age, 47 [SD, 16.0] years; 63% women; 17% smokers; 77% phlegm; 70% shortness of breath; 47% wheezing; 46% chest pain; 42% abnormal peak flow), 334 (84%) provided cough duration and 369 (93%) symptom severity data. Median cough duration was 5 days (interquartile range [IQR], 3-8 days) in the prednisolone group and 5 days (IQR, 3-10 days) in the placebo group (adjusted hazard ratio, 1.11; 95% CI, 0.89-1.39; $P = .36$ at an $\alpha = .05$). Mean symptom severity was 1.99 points in the prednisolone group and 2.16 points in the placebo group (adjusted difference, −0.20; 95% CI, −0.40 to 0.00; $P = .05$ at an $\alpha = .001$). No significant treatment effects were observed for duration or severity of other acute lower respiratory tract infection symptoms, duration of abnormal peak flow, antibiotic use, or nonserious adverse events. There were no serious adverse events.

CONCLUSIONS AND RELEVANCE 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.

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Supplemental content

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Acute lower respiratory tract infection, defined as an acute cough with at least 1 of the symptoms of sputum, chest pain, shortness of breath, and wheeze,[1] is one of the most common conditions managed in primary care internationally. In 2009-2011, an estimated 65% to 75%[2,3] of patients were prescribed antibiotics despite good evidence that they do not reduce symptom duration or severity[4] and guidelines to the contrary.[1] Annual antibiotic prescribing costs are estimated at US $726 million in the United States[5] and US $300 million for consultations and antibiotics in the United Kingdom.[6]

Antimicrobial resistance is one of the greatest challenges to modern public health.[7] Primary care is responsible for 80% of health service antibiotic prescribing,[2,8] with a high proportion regarded as unnecessary[2] and contributing to antimicrobial resistance.[9] Both US[10] and UK[11] national antimicrobial resistance action plans recommend finding alternatives to antibiotics, but none is currently proven for acute lower respiratory tract infection in adults.

Symptoms of acute lower respiratory tract infection are similar to those of exacerbated asthma.[12] Bronchial epithelial changes are similar in people with and without asthma during a respiratory tract infection, with both groups showing reductions in forced expiratory volume and airways inflammation,[12] and prolonged acute lower respiratory tract infection symptoms are thought to be due to bronchial hyperresponsiveness.[13] Oral and inhaled corticosteroids are highly effective for acute asthma, but US, British, and European guidelines do not provide guidance on whether corticosteroids should be used for acute lower respiratory tract infection. Despite this, US and European clinicians are increasingly using oral and inhaled steroids, with 1 US study[14] reporting oral prednisolone use in 15% of adults without asthma with acute lower respiratory tract infection.

A previous systematic review[15] found insufficient evidence regarding the role of inhaled corticosteroids and found no oral corticosteroid studies for acute lower respiratory tract infection. The aim of the current study was to investigate the effects of a moderate dose of oral corticosteroids in adults without asthma presenting to primary care with acute lower respiratory tract infection.

Key Points

Question Does a moderate dose of oral corticosteroid reduce the duration or severity of acute lower respiratory tract infection in adults without asthma presenting to primary care?

Findings In this randomized trial of 401 adults with symptoms of acute lower respiratory tract infection, treatment with oral prednisolone, 40 mg/d for 5 days, compared with placebo did not significantly reduce the median duration of moderately bad or worse cough (5 days in each group) or the mean severity of symptoms between days 2 and 4 (1.99 vs 2.16 points out of 6).

Meaning These findings do not support the use of oral steroids for the treatment of acute lower respiratory tract infection in the absence of asthma.

Methods

Study Design, Recruitment, and Baseline Assessment

Ethical approval for this study was granted by the Central Bristol Research Ethics Committee (12/SW/0180) and all patients gave written informed consent. The Oral Steroids for Acute Cough (OSAC) trial was a multicenter, placebo-controlled, individually randomized study conducted between July 2013 and October 2014. Family physicians and nurses (recruiting clinicians) were trained in study procedures by 4 centers at the Universities of Bristol, Southampton, Nottingham, and Oxford. They were asked to assess eligibility in consecutive patients: age 18 years or older and presenting for an acute (≤28 days) cough as the main symptom with at least 1 lower respiratory tract symptom (phlegm, chest pain, wheezing, or shortness of breath) in the previous 24 hours. Patients were excluded if they were clinically suspected to have or their medical records showed evidence of chronic pulmonary disease; had received any asthma medication in the past 5 years; met National Institute for Health and Clinical Excellence criteria for severe infection/complications[1]; required same-day hospital admission; or required same day antibiotics (see Supplement 1 for full list). Participants were recruited on the day of or the day following presentation. Following consent, demographic and clinical data were collected, including self-reported ethnicity using UK-approved[16] categories, to assess sample representativeness.

Randomization and Concealment

The treatment allocation schedule was computer generated by a statistician independent of the trial team. Randomization to prednisolone or placebo in a 1:1 ratio used a variable block size (4, 6, 8, and 10) and was stratified by center. Allocated medication was added to numbered participant packs by pharmacists independent of the team. All packs were identical and centers distributed 4 packs at a time to family practices. Following eligibility confirmation, participants were given the next pack.

Intervention and Masking

Participant packs contained either ten 20-mg oral prednisolone tablets (Galen Pharma GmbH) or placebo tablets matched on dimension, appearance, and taste (Piramal Healthcare Ltd). Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription). The dose and duration of prednisolone was selected to reflect the dose and duration known to be effective for acute asthma.[17] Participants, recruiting clinicians, and the trial team were masked to treatment allocation until data analyses were complete.

Follow-up

Participants were invited to report (using web or paper versions) the presence and severity of symptoms using a validated[18] diary shown to be sensitive to change.[4,19] Symptoms were measured using a scale from 0 (no problem) to 3 (moderately bad) and up to 6 (as bad as it could be). All symptoms were measured daily, with twice-daily peak expiratory flow, for 28 days or until symptom resolution. Cough was measured for a further 28 days in case of late treatment effects. A research nurse telephoned participants weekly to support symptom diary

completion. Participants were given £5 (US $6.60) shopping vouchers at 14 and 28 days. Medical notes were reviewed at 3 months for new diagnoses of asthma, chronic obstructive pulmonary disease, whooping cough, and lung cancer.

Primary Outcomes

Two primary outcomes were assessed. The first was 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. This was regarded as the more important of the 2 primary outcomes because cough was the main presenting symptom of the illness, and it included measures of both duration and severity. The second primary outcome was 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; the mean score was calculated across the symptoms for each day and then an overall mean was calculated, with a maximum value of 6.

Secondary Outcomes

Secondary outcomes specified a priori were total duration and severity of each symptom up to 28 days (cough, phlegm, shortness of breath, wheeze, blocked/runny nose, chest pain, fever, muscle aching, headache, sleep disturbance, feeling generally unwell, activity disturbance), duration of moderately bad or worse and any cough up to 56 days, duration of abnormal peak flow, antibiotic use, adverse events, reconsultation with evidence of illness deterioration, patient satisfaction with treatment, and intention to use the same treatment if it were to be available in the future (more detail about the derivation of these outcomes is provided in Supplement 1). Quality of life, National Health Service treatment, and investigation costs are not reported in this article.

Subgroup Analyses

Prespecified potential treatment effect modifiers were age; prior cough duration; presence of wheeze; antibiotic use; β-agonist use; smoking status; history of hay fever, asthma, or eczema; and new diagnoses (at 3 months) of asthma, chronic obstructive pulmonary disease, whooping cough, or lung cancer. Baseline impression of severity of illness was added as a post hoc subgroup analysis because the investigators determined it was important to differentiate between participants with severe vs mild symptoms.

Sample Size Calculation

The distributions of both primary outcomes were expected to be positively skewed; hence, sample size calculations were based on the log-normal distribution. The mean durations of moderately bad or worse cough and symptoms severity score (days 2-4) were estimated to be 5.8 (SD, 4.1) days and 2.3 (SD, 1.1) points, respectively.[19] This corresponds to 1.56 (SD, 0.64) log days (or a geometric mean of 4.74 days) for cough duration and 0.73 (SD, 0.45) points on the log scale (or a geometric mean of 2.08) for severity of symptoms. Because there were no previous studies of oral steroids to inform the minimum clinically important difference in both outcomes, the investigative team considered the balance of potential benefits and adverse effects and reached a minimum clinically important difference consensus of 20%, corresponding to a geometric mean in the active treatment group of 3.79 days (mean, 1.33 log days) for duration of cough and 1.66 points (mean, 0.51 log points) for severity of symptoms. Allowing for 20% attrition, 218 participants needed to be randomized per group to retain 174 at follow-up and achieve 90% power with a 2-sided $\alpha = .05$ for primary outcome one. A final achieved sample size of 174 participants per group would provide 89% power to detect a 20% reduction in severity of symptoms, with an adjusted 2-sided $\alpha = .001$ to reflect the second primary outcome status (Supplement 1).

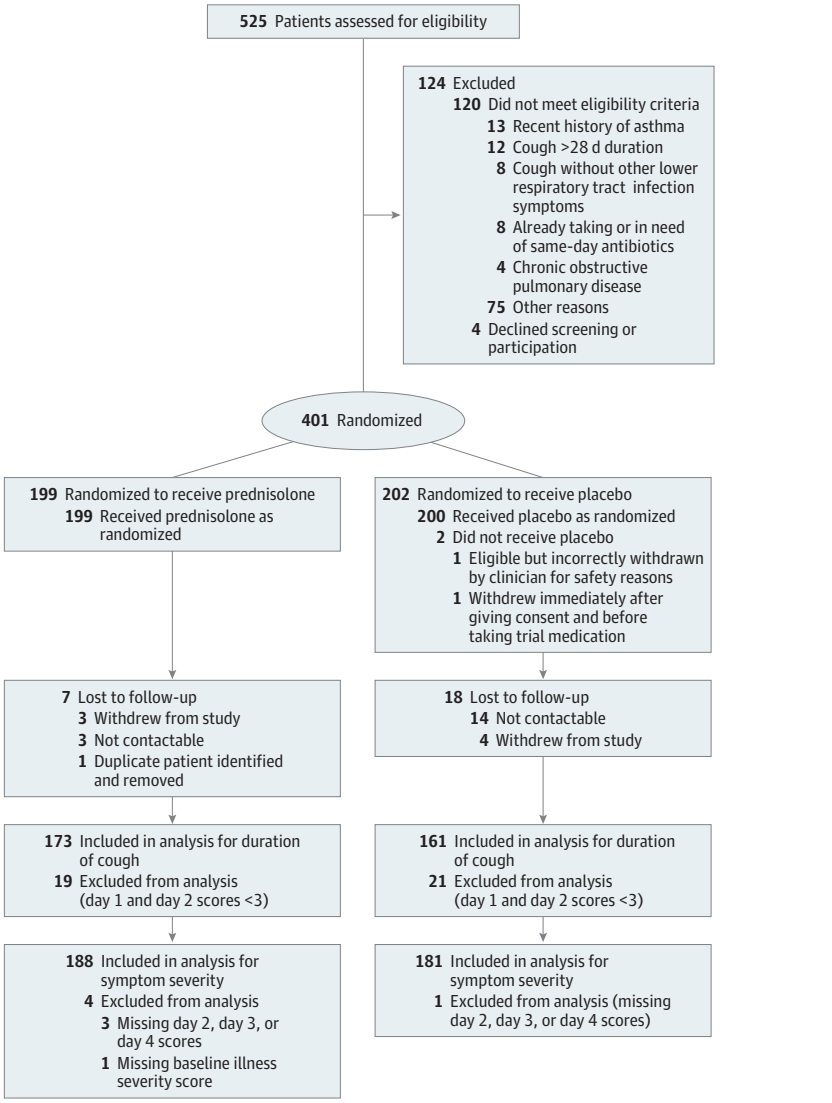
Statistical Analyses

A prespecified analysis plan was approved by the trial steering and data monitoring committees and the study protocol was published before data collection had finished (Supplement 2). Changes that were made to the statistical analysis plan after the analysis was begun are also described in Supplement 2. All analyses were performed in Stata software, version 13.1.[20]

The primary comparative analyses considered patients in the groups to which they were randomized, without imputation for missing outcome data. These analyses were adjusted for center (Bristol, Nottingham, Oxford, and Southampton) and the relevant baseline measure (prior cough duration [1-28 days] for duration of moderately bad or worse cough and patient-reported illness severity in last 24 hours for severity of symptoms [0 = completely well; 10 = extremely unwell]). Time-to-event methods were used to analyze the duration of moderately bad or worse cough. Semiparametric Cox proportional hazard models were used (to enable comparison with previous studies) and the assumption of proportional hazards checked by visual inspection of log-log survival curves and calculation of Schoenfeld residuals.[21] Hazard ratios were reported comparing the instantaneous rate of resolution of cough between the prednisolone and placebo groups, with 95% confidence intervals and *P* values. To assist interpretation against the minimum clinically important difference of a 20% reduction in time to resolution, for which hazard ratios are unhelpful, parametric Weibull accelerated failure time models were used to present cough duration treatment effects as time ratios. Such models can be formulated as proportional hazards or accelerated failure time models; hence, hazard ratios were also produced from the Weibull models to ensure comparability with the Cox models.

To further aid interpretation, we calculated absolute measures of effect for the primary outcome of duration of moderately bad or worse cough. There is no single absolute measure of treatment effect for time-to-event data because it varies over the duration of follow-up; it can, however, be calculated at a specific time point. Of particular clinical interest is day 7, because this is a time in the illness trajectory when clinicians and patients want to know about expected benefits, and when steroids should have affected symptoms if effective. Survival curves were produced from the Cox regressions at given values of center (Bristol) and duration of prior cough (median value). Predicted survival probabilities at day 7 in the prednisolone and placebo groups were obtained and an absolute risk difference estimated as the survival probability in the prednisolone group minus that in the placebo group. Ninety-five

Figure 1. Participant Flow Through the Oral Steroids for Acute Cough Trial



percent confidence intervals were obtained using the method proposed by Altman and Andersen.[22]

Mean severity score from days 2 to 4 was considered in linear regression models. Models considered mean severity score and log mean severity score, and distributional checks of residuals were undertaken to determine the most appropriate model. Differences between the prednisolone and placebo groups are reported with 95% confidence intervals and *P* values.

For both primary outcomes, secondary analyses additionally adjusted for factors demonstrating imbalance at baseline (difference >5% for binary and >0.5 SD for continuous outcomes) and for smoking because it is known to be prognostically important.[15]

Analyses of secondary outcomes used regression models as appropriate. Consideration of potential effect modifiers used formal tests of interaction. We calculated absolute measures of effect for time-to-event secondary outcomes as described above for the primary outcome. Absolute risk differences were also obtained (with 95% confidence intervals) for the binary secondary outcomes of antibiotic use (up to 7 and 28 days), patient satisfaction, and intention to use the same treatment if it were to be available. Sensitivity analyses considered multiple imputation of missing data (using a 2-fold fully conditional specification algorithm),[23,24] treatment adherence, day of recruitment, and inclusion of those with no moderately bad or worse cough at baseline (post hoc) (see Supplement 1 for details).

Results

Enrollment and Study Population

Fifty-eight family physicians and 50 practice nurses based in 54 family practices assessed 525 patients for suitability, of whom 401 were eligible, consented, and were randomized, 199 to prednisolone and 202 to placebo (**Figure 1**), equating a mean patient recruitment rate of 0.5 patients per month per practice.

Table 1. Baseline Characteristics of Randomized Patients by Treatment Group

Characteristics	Prednisolone Group (n = 198)	Placebo Group (n = 200)
Center, No. (%)		
Bristol	118 (60)	113 (57)
Oxford	39 (20)	45 (23)
Southampton	24 (12)	21 (11)
Nottingham	17 (9)	21 (11)
Demographics and medical history		
Male, No. (%)	82 (41)	66 (33)
Age, mean (SD), y	50.0 (16.1)	44.8 (15.5)
Weight, median (IQR), kg[a]	77.0 (64.5-91.0)	76.0 (66.5-90.5)
Height, median (IQR), cm[b]	168.0 (161.0-175.0)	168.0 (163.0-176.0)
White race/ethnicity, No. (%)[c]	188 (95)	193 (97)
Occupation, No. (%)		
Employed	137 (69)	143 (72)
Unemployed	17 (9)	21 (11)
Retired	41 (21)	30 (15)
Full-time education	3 (2)	6 (3)
Deprivation score, median (IQR)[d]	11.0 (5.0-23.0)	12.0 (5.0-23.0)
Smoking status, No. (%)[e]		
Current	31 (16)	38 (19)
Past	63 (32)	55 (28)
Never	104 (53)	106 (53)
Living with smoker, No. (%)[f]	25 (14)	32 (16)
Received asthma medication >5 y prior, No. (%)[g]	10 (5)	8 (4)
Personal history of hay fever, No. (%)[h]	41 (22)	46 (24)
Personal history of eczema, No. (%)[i]	30 (16)	26 (14)
Family history of asthma, hay fever, or eczema, No. (%)[j]	73 (40)	76 (40)
Influenza vaccination in last 12 mo, No. (%)	63 (32)	44 (22)
Recruited in winter (October-March), No. (%)	112 (57)	114 (57)
Clinical characteristics and management		
Prior duration of cough, median (IQR), d	13.0 (7.0-20.0)	10.0 (6.0-17.5)
Sputum present within last 24 h, No. (%)[k]	149 (76)	156 (78)
Shortness of breath present within last 24 h, No. (%)	146 (74)	133 (67)
Wheeze present within last 24 h, No. (%)[k]	88 (45)	98 (49)
Chest pain present within last 24 h, No. (%)	88 (44)	97 (49)
Patient-reported illness severity score at assessment, median (IQR)[l]	6.0 (5.0-7.0)	5.0 (4.0-7.0)
Pulse, mean (SD), /min	77.8 (12.3)	77.7 (11.8)
Temperature, mean (SD), °C	36.6 (0.5)	36.6 (0.4)
Oxygen saturation, mean (SD), %[m]	97.5 (1.3)	97.8 (1.1)
Abnormal peak flow <80% of expected, No. (%)[n]	87 (44)	79 (40)
Respiratory rate, mean (SD), /min[o]	15.4 (2.5)	15.0 (2.4)
Abnormal respiratory rate (>20/min), No. (%)	2 (1)	1 (1)
Chest retraction or prolonged expiration, No. (%)	0	1 (1)
Wheeze or rhonchi on auscultation, No. (%)	11 (6)	11 (6)
Crackles or crepitations on auscultation, No. (%)[p]	4 (2)	6 (3)
Bronchial breathing, No. (%)	0	2 (1)
Taken prescribed β-agonist in past 24 h, No. (%)	9 (5)	3 (2)
Over-the-counter drugs taken for current cough, No. (%)	128 (65)	139 (70)
Given delayed antibiotic prescription, No. (%)	22 (11)	25 (13)

Abbreviation: IQR, interquartile range.

[a] Weight data missing for 2 in the prednisolone group.

[b] Height data missing for 1 in the prednisolone group.

[c] Race/ethnicity data missing for 1 in the placebo group.

[d] English Index of Multiple Deprivation scores (range, 0-100; higher scores indicate higher levels of deprivation). Data missing for 2 in the prednisolone group and 7 in the placebo group.

[e] Smoking status data missing for 1 in the placebo group.

[f] Living with smoker data missing for 15 in the prednisolone group and 5 in the placebo group.

[g] Personal history of asthma data missing for 10 in the prednisolone group and 7 in the placebo group.

[h] Personal history of hay fever data missing for 10 in the prednisolone group and 11 in the placebo group.

[i] Personal history of eczema data missing for 14 in the prednisolone group and 10 in the placebo group.

[j] Family history of hay fever, eczema, or asthma data missing for 16 in the prednisolone group and 11 in the placebo group.

[k] Sputum and wheeze data missing for 1 in the prednisolone group.

[l] Patient-reported illness severity scores: 0 (completely well) to 10 (extremely unwell); data missing for 1 prednisolone participant.

[m] Oxygen saturation data missing for 1 in the prednisolone group.

[n] Baseline abnormal peak flow data missing for 1 in the prednisolone group.

[o] Respiratory rate data missing for 2 in the prednisolone group and 1 in the placebo group; data collected only for those with a normal rate.

[p] Includes unilateral and bilateral.

Two placebo group patients requested complete withdrawal immediately after randomization, and a duplicate patient was subsequently identified in the prednisolone group (the participant remained in the group to which he/she was first allocated), leaving a sample of 398. Enrollment was stopped when the required number of participants was achieved. At baseline, participants had a mean age of 47.4 (SD, 16.0) years; 37% were men; 3.5% had diabetes; 17% were currently smoking; 5% had received asthma medication more than 5 years previously; 77% reported phlegm, 46% chest pain, 47% wheezing, and 70% shortness of breath; and 42% had abnormal (defined as <80% expected) peak flow. Baseline characteristics were similar between the groups with respect to deprivation, smoking status, weight, height, and clinical characteristics of the acute lower respiratory tract infection, although compared with placebo,

Table 2. Primary Analyses

	Prednisolone Group		Placebo Group		Prednisolone vs Placebo			
	No. of Participants	Outcome Value	No. of Participants	Outcome Value	Hazard Ratio (95% CI)	*P* Value[a]	Time Ratio (95% CI)[b]	*P* Value
Duration of moderately bad or worse cough, median (95% CI), d (censored at 28 d)	173	5 (4-5)	161	5 (4-6)				
Adjusted for center and baseline[c]					1.11 (0.89-1.39)	.36	0.91 (0.76-1.10)	.34[a]
Secondary additional adjustment[d,e]					1.09 (0.87-1.37)	.44	0.92 (0.76-1.12)	.40[a]
Symptoms severity score, mean (95% CI) (days 2-4)[f]	188	1.99 (1.85-2.13)	181	2.16 (2.00-2.32)				
Adjusted for center and baseline measure[c,g]					−0.20 (−0.40 to 0.00)[h]			.05[i]
Secondary additional adjustment[d,e,g]					−0.17 (−0.37 to 0.04)[h]			.11[i]

[a] α = .05.

[b] Time ratio can be interpreted as the relative increase or decrease in time to resolution of moderately bad or worse cough in the prednisolone group vs the placebo group.

[c] Baseline measure of duration of cough is prior duration of cough (1-28 days) and of mean symptoms severity score is patient-reported illness severity (range, 0-10).

[d] Adjusted for center, baseline, factors showing baseline imbalance (age, sex, and influenza vaccine), and smoking.

[e] Smoking status data missing for 1 placebo participant.

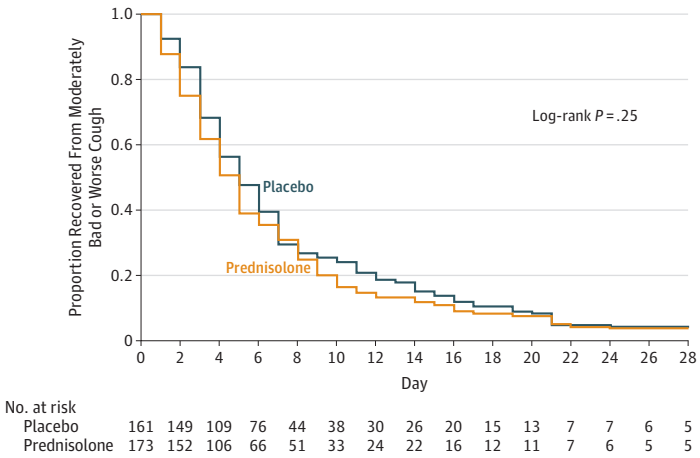
[f] See Methods section for derivation of mean symptoms severity score (0 [least severe] to 6 [most severe]).

[g] Patient-reported illness severity data missing for 1 prednisolone participant.

[h] Data for symptoms severity scores are differences in means (95% CI).

[i] α = .001.

Figure 2. Kaplan-Meier Analysis of Time to Recovery From Moderately Bad or Worse Cough



The median duration of follow-up for recovery from moderately bad or worse cough was 5 days (interquartile range, 3-8 days) in the prednisolone group and 5 days (interquartile range, 3-10 days) in the placebo group.

the prednisolone group was slightly more likely to be male, be older (and hence retired), and have received an influenza vaccine in the last 12 months (**Table 1**).

Primary Outcome Data Completeness

Symptom diaries were returned by 374 participants (94%; 192 in the prednisolone group and 182 in the placebo group). For duration of moderately bad or worse cough, data were available for 334 participants (84%), with 40 reporting an initial cough severity of less than 3 points (that is, not moderately bad or worse) and 24 lost to follow-up. For severity of symptoms, follow-up data were available in 370 (93%). However, 1 participant in the prednisolone group had no baseline measure of illness severity and this participant's data could not be used in the adjusted analysis. Patients who withdrew or were lost to follow-up were younger (median, 30 years vs 49 years), were less likely to be white (85% vs 97%), were more likely to be employed (86% vs 69%), and had a higher English Index of Multiple Deprivation score (median score, 18 vs 11).

Primary Analyses

Moderately Bad or Worse Cough Duration

The median duration of moderately bad or worse cough was 5 days (interquartile range, 3-8 days) in the prednisolone group and 5 days (interquartile range, 3-10 days) in the placebo group (**Table 2**). Kaplan-Meier survival curves were similar for both groups (**Figure 2**). Visual inspection of the log-log survival curves and calculation of the Schoenfeld residuals (*P* = .52) provided no evidence against proportional hazards. Comparing prednisolone with placebo, the Cox model adjusting for center and baseline cough duration resulted in a hazard ratio of 1.11 (95% CI, 0.89-1.39; *P* = .36 with α = .05). The hazard ratio represents the instantaneous risk of resolution from moderately bad or worse cough in the prednisolone group compared with placebo; a hazard ratio greater than 1 demonstrates a beneficial effect of prednisolone. The Weibull accelerated failure time model ratio was 0.91 (95% CI, 0.76-1.10), indicating that the time to resolution was reduced by 9% (0.45 days) with prednisolone compared with placebo (*P* = .34); the lower limit of the 95% CI did not exclude the

Table 3. Estimates of Absolute Between-Group Differences for Time-to-Event and Binary Outcomes

	Prednisolone Group			Placebo Group			
		Unresolved Symptoms at End of Day 7			Unresolved Symptoms at End of Day 7		Absolute Difference in % Unresolved (95% CI), Adjusted for Center and Baseline
	No. of Participants[a]	No. of Participants	% (95% CI)	No. of Participants[a]	No. of Participants	% (95% CI)	
Time-to-event outcomes, d							
Duration of moderately bad or worse cough	173	51	30.64 (23.89-37.63)	161	44	29.19 (22.33-36.38)	−3.61(−10.64 to 4.23)[b]
Duration of any cough	191	164	88.36 (82.86-92.18)	182	154	88.91 (83.34-92.70)	−1.28 (−4.07 to 1.00)[b]
Duration of abnormal peak flow	117	62	59.26 (49.56-67.71)	115	63	60.32 (50.67-68.67)	−2.89 (−14.10 to 6.83)[b]
Binary outcomes[c]							
Use of antibiotics	191			182			
Up to 7 d		15	7.85 (4.00-11.70)		15	8.24 (4.21-12.28)	−0.09 (−5.13 to 4.94)
Up to 28 d		28	14.66 (9.60-19.72)		34	18.68 (12.96-24.40)	−3.26 (−10.53 to 4.02)
Participants agreeing study tablets helped them feel better	178	60	33.71 (26.70-40.72)	171	43	25.15 (18.88-31.71)	7.74 (−1.85 to 17.34)
Participants who would take trial tablets in future	178	99	55.62 (48.25-62.99)	171	81	47.37 (39.81-54.93)	7.48 (−3.02 to 17.97)

[a] Number of participants with data available for the outcome of interest and included in the analysis.

[b] Absolute difference calculated as the percentage unresolved at end of day 7 in the prednisolone group minus the percentage in the placebo group. A negative value for the absolute risk difference indicates that a smaller percentage of participants in the prednisolone group have unresolved cough or abnormal peak flow at end of day 7 than participants in the placebo group. For time-to-event outcomes, adjusted analyses consider an "average" value of covariates: center = Bristol (where 60% of participants were recruited) and prior duration of cough = 12 days (median value in sample).

[c] Baseline measure for use of antibiotics is whether participant was given delayed antibiotic prescription at baseline (yes or no). No baseline measures were available for patient satisfaction or taking tablets in the future.

20% a priori minimum clinically important difference. Further (secondary analysis) adjustment for factors demonstrating possible imbalance at baseline (age, sex, and influenza vaccine in last 12 months) and smoking had no effect on the models (Table 2). The difference between the prednisolone group and the placebo group, expressed as the absolute difference in percentage with unresolved moderately bad or worse cough at day 7, was −3.61 (95% CI, −10.64 to 4.23) (**Table 3**); this can be interpreted as 3.61% fewer participants in the prednisolone group who still had an unresolved moderately bad or worse cough at the end of day 7.

Severity of Symptoms on Days 2 to 4

Mean symptoms severity scores (and residuals) were normally distributed. The mean symptoms severity scores were 1.99 (SD, 0.99) and 2.16 (SD, 1.09) points for the prednisolone and placebo groups, respectively. Adjusting for center and baseline illness severity, the mean symptoms severity difference was 0.20 point (95% CI, −0.40 to 0.00 point; $P = .05$ with a priori $\alpha = .001$) between prednisolone and placebo (Table 2). With a mean symptoms severity score of 2.16 in the placebo group, a difference of 0.20 equates to a relative reduction of 9.3%. The lower limit of the 95% CI of this reduction was 18.5% and excluded the 20% a priori minimum clinically important difference. Additional adjustment for factors demonstrating imbalance at baseline and smoking marginally attenuated the difference in means and reduced the strength of evidence against the null hypothesis (Table 2).

Sensitivity Analyses

None of the sensitivity analyses had any effect on the primary comparisons, including those with no moderately bad or worse cough at baseline, multiple imputation of missing data, per-protocol analysis, and adjusting for day of recruitment (eTable 1 in Supplement 1).

Secondary Outcomes

There were no significant effects on any symptom duration or peak flow up to 28 days or cough duration up to 56 days (**Table 4**). No significant effects were observed for antibiotic use; patient satisfaction or intention to use the same treatment if it were to be available in the future; nonserious adverse events (Table 4); expected, unexpected, or cough-related adverse events; or reconsultations (eTable 2 in Supplement 1). The nature of the adverse events was similar between the groups (eTable 3 in Supplement 1), no new urinary or visual symptoms were reported, and none of the patients reporting fatigue, thirst, or dry throat (eTable 3 in Supplement 1) had diabetes. There were no serious adverse events. Four participants (3 in the prednisolone group and 1 in the placebo group presented to the emergency department but were not hospitalized.

Subgroup Analyses

All 95% confidence intervals for the interaction effects included values consistent with no significant subgroup effect (eTable 4 in Supplement 1).

Discussion

In this randomized trial of 401 adults, 5 days of moderate-dose oral prednisolone did not reduce the duration of moderately bad or worse cough, or the severity of symptoms between

Table 4. Secondary Outcomes

	Prednisolone Group (n = 192)	Placebo Group (n = 182)	Comparison of Prednisolone vs Placebo, Adjusted for Center and Baseline[a]	P Value
Area under the curve, mean (95% CI)[b]				
Cough	40.16 (36.67-43.65)	42.88 (38.88-46.87)	−2.43 (−7.66 to 2.80)[c]	.36
Phlegm	25.48 (22.19-28.78)	30.01 (26.40-33.61)	−4.10 (−8.89 to 0.70)[c]	.09
Shortness of breath	16.10 (13.25-18.95)	18.39 (15.16-21.61)	−2.30 (−6.34 to 1.75)[c]	.27
Wheeze	12.32 (9.69-14.96)	13.24 (10.37-16.11)	0.18 (−3.27 to 3.64)[c]	.92
Blocked or runny nose	19.83 (16.38-23.28)	20.06 (17.12-23.00)	0.67 (−3.70 to 5.05)[c]	.76
Chest pain	6.64 (4.95-8.33)	9.59 (6.98-12.19)	−2.92 (−5.83 to −0.01)[c]	.05
Fever	2.98 (2.05-3.91)	3.45 (2.07-4.82)	−0.33 (−1.90 to 1.24)[c]	.68
Muscle ache	8.83 (6.71-10.96)	10.29 (7.53-13.06)	−1.61 (−4.99 to 1.77)[c]	.35
Headache	10.77 (8.27-13.28)	11.83 (8.89-14.77)	−0.62 (−4.34 to 3.09)[c]	.74
Sleep disturbance	20.80 (17.66-23.94)	22.11 (18.13-26.10)	−0.75 (−5.60 to 4.10)[c]	.76
Feeling generally unwell	19.83 (17.22-22.45)	22.68 (19.17-26.19)	−3.25 (−7.38 to 0.89)[c]	.12
Activity disturbance	14.29 (12.01-16.57)	19.07 (15.40-22.74)	−4.78 (−8.86 to −0.69)[c]	.02
Duration, median (95% CI), d[d]				
Moderately bad or worse cough (censored at 56 d)[e]	5 (4-5)	5 (4-6)	1.11 (0.89 to 1.39)[f]	.36
Any cough (censored at 56 d)[g]	18 (17-23)	20 (17-25)	1.13 (0.90 to 1.42)[f]	.29
Abnormal peak flow (censored at 28 d)[h]	10 (7-17)	11 (8-17)	1.10 (0.79 to 1.52)[f]	.58
No. (%) [95% CI][i]				
Antibiotic use				
Up to 7 d	15 (8) [4-12]	15 (8) [4-12]	0.98 (0.42 to 2.28)[j]	.96
Up to 28 d	28 (15) [10-20]	34 (19) [13-24]	0.78 (0.44 to 1.39)[j]	.39
Participants agreeing study tablets helped them feel better[k]	60 (34) [27-41]	43 (25) [19-32]	1.46 (0.92 to 2.34)[j]	.11
Participants who would take trial tablets in future	99 (56) [48-63]	81 (47) [40-55]	1.36 (0.89 to 2.08)[j]	.16
Adverse events[l]				
0	151 (77) [71-83]	162 (82) [76-87]	1.26 (0.77 to 2.07)[j,m]	.36
1	36 (18) [13-25]	24 (12) [8-17]		
>1	9 (5) [2-9]	12 (6) [3-10]		

[a] Baseline measure for cough area under the curve, duration of moderately bad or worse cough (56 days), any cough (56 days), and abnormal peak flow is prior duration of cough (days); for all symptoms (area under the curve) (with the exception of cough), baseline measure is presence or absence of symptom at baseline (previous 24 hours); and for antibiotic use, baseline measure is whether participant was given delayed antibiotic prescription (yes or no). No baseline measures were available for patient satisfaction, taking tablets in the future, or adverse events.

[b] For derivation of symptom area under the curve, see the eAppendix in Supplement 1.[25] Area-under-the-curve analysis includes 185 in the prednisolone group and 179 in the placebo group for cough; 184 in the prednisolone group and 179 in the placebo group for phlegm and shortness of breath; 183 in the prednisolone group and 179 in the placebo group for wheeze and sleep disturbance; and 182 in the prednisolone group and 179 in the placebo group for blocked or runny nose, chest pain, fever, muscle ache, headache, feeling generally unwell, and activity disturbance.

[c] Difference in mean area under the curve (95% CI).

[d] Analysis of duration of moderately bad or worse cough (56 days) includes 173 prednisolone and 161 in the placebo group (participants without moderately bad or worse cough on day 1 excluded); analysis of duration of any cough (56 days) includes 191 in the prednisolone group and 182 in the placebo group; and analysis of duration of abnormal peak flow includes 117 in the prednisolone group and 115 in the placebo group (participants with normal peak flow on day 1 excluded).

[e] Five patients in each group had unresolved moderately bad or worse cough at day 28. Data for total duration (up to 56 days) obtained for 3 in the prednisolone group and 5 in the placebo group.

[f] Hazard ratio (95% CI).

[g] Sixty-one in the prednisolone group and 63 in the placebo group had unresolved cough (score <1) at day 28. Data for total duration (up to 56 days) obtained for 38 in the prednisolone group and 50 in the placebo group.

[h] Eighteen in the prednisolone group and 25 in the placebo group had abnormal peak flow at 28 days. Post hoc sensitivity analysis removed 6 in the prednisolone group rated at baseline as poor at measuring peak flow; there was no effect on the model.

[i] Antibiotic use analysis includes 191 in the prednisolone group and 182 in the placebo group; patient satisfaction analysis includes 178 in the prednisolone group and 171 in the placebo group.

[j] Odds ratio (95% CI).

[k] For derivation see the eAppendix in Supplement 1.

[l] Excludes the duplicate participant who did experience an expected adverse event during duplicate entry.

[m] Ordinal logistic regression, adjusting for center and baseline patient-reported illness severity; data missing for 1 participant.

days 2 and 4 adults without asthma who presented to primary care with acute lower respiratory tract infection. No effects were observed for duration and severity of any acute lower respiratory tract infection symptom, duration of abnormal peak flow, antibiotic use, or adverse events, including worsening of glycemic control in patients with diabetes.

This study has several strengths. It was an adequately powered, multicenter, fully masked, randomized trial with low rates of missing baseline and follow-up data. The design was pragmatic, using eligibility criteria easily reproduced in routine clinical practice and clinically relevant, validated[18] outcomes. The final sample included participants with high rates of self-reported sputum production and wheeze and was generalizable to adults without asthma presenting to primary care with acute lower respiratory tract infection in whom an immediate antibiotic is not necessary. With 398 participants, this trial

more than doubles the number of patients recruited to primary care trials of corticosteroids for acute lower respiratory tract infection[15] and, to our knowledge, is the first to investigate the effects of oral rather than inhaled steroids. The trial also contributes to a growing body of evidence suggesting that systemic and topical corticosteroids have a limited role in the treatment of common infections and their postinfectious complications in primary care.[26,27] This contrasts with an increasing number of studies suggesting that corticosteroids are effective for secondary-care patients with community-acquired pneumonia,[28] croup,[29] acute sinusitis,[30] and severe sore throat.[31]

This study also has several limitations. First, the low patient recruitment rate suggests that patients may have been selectively invited to participate, affecting the generalizability of the final sample. However, the rate was higher than a similar previous trial,[19] not all practices were active throughout the recruitment period, and the characteristics of the final sample appears representative of primary care adult patients with acute lower respiratory tract infection. Second, there was a higher than expected number of participants with zero duration of moderately bad or worse cough, although a sensitivity analysis including these participants did not influence the results. Third, other baseline biomarkers (eg, inflammatory, microbiological, spirometric, or radiographic) were not measured, and it is possible that patients with more severe, inflammatory, eosinophilic,[32,33] or microbiological (eg, rhinovirus)[34] etiology entered the trial or could have differentially benefited. However, the study used readily recognized, pragmatic entry criteria facilitating replication in routine clinical practice. Fourth, study eligibility criteria might have included some patients with chronic or postinfectious cough rather than acute lower respiratory tract infection. However, 100% of participants had evidence of active lower respiratory tract involvement (sputum, shortness of breath, wheeze, or chest pain) and more than 75% had a preconsultation cough duration of less than 21 days. Fifth, the study used a patient-reported outcome rather than an objective primary outcome measure (such as digitally measured cough severity). This was chosen because it was considered the strongest option in the presence of a fully masked intervention, it closely reflected patient priorities, and it allowed comparison with other trials.[4,19] Sixth, the lack of effects and a similar between-group pattern of adverse events could reflect poor adherence. However, this is unlikely because standard methods[35] were used to establish similar and high levels of adherence to both prednisolone and placebo, and adverse events were similar to another trial in which a similar dosage of prednisolone was proven effective.[35]

This trial suggests that oral corticosteroids should not be used in adult primary care patients without asthma or chronic obstructive pulmonary disease who do not require treatment with an immediate antibiotic. Further research is needed to establish effectiveness in primary care patients with more severe infections, such as those with elevated C-reactive protein levels or requiring immediate antibiotic treatment, and larger studies or meta-analysis are needed to address effects in subgroups, such as those with longer preconsultation illness and nonsmokers.[15]

Conclusions

Among adults without asthma who developed acute lower respiratory tract infection, the use of oral prednisolone for 5 days did not reduce symptom duration or severity. These findings do not support oral steroids for treatment of acute lower respiratory tract infection in the absence of asthma.

ARTICLE INFORMATION

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