**Effect of oral dexamethasone without immediate antibiotics compared with placebo on acute sore throat in adults: a Randomized Clinical Trial**

**Gail Nicola Hayward** D.Phil**\*1, Alastair D Hay**MD**2, Michael V Moore**M.Sc3**, Sena Jawad** M.Sc1**, Nicola Williams** M.Sc1**, Merryn Voysey** M.Biostat**1, Johanna Cook** B.A.**1, Julie Allen** B.A.**1, Matthew Thompson** D.Phil**4, Paul Little** MD**3, Rafael Perera** D.Phil**1, Jane Wolstenholme** PhD**5, Kim Harman** DHealth**3, Carl Heneghan** D.Phil**1**

Corresponding author: Dr Gail Hayward, Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter Woodstock Road, Oxford, OX2 6GG gail.hayward@phc.ox.ac.uk 01865 289357

1. Nuffield Department of Primary Care Health Sciences, University of Oxford
2. Centre for Academic Primary Care, NIHR School for Primary Care Research, School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK
3. Primary Care and Population Sciences, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST
4. Department of Family Medicine, University of Washington, Seattle, WA 98195, USA
5. Nuffield Department of Population Health, University of Oxford

**Date of revision: 15/3/17**

**Word count: 3640**

#### Key Points

**Question:** Does a single dose of dexamethasone in the absence of antibiotics provide symptom relief for acute sore throat in adults presenting to primary care?

**Findings:** In this randomized clinical trial including 565 adults, the proportion achieving complete symptom resolution at 24 hours was 22.6% with dexamethasone and 17.7% with placebo. This was not a significant difference. At 48 hours significantly more adults experienced complete resolution in the dexamethasone group (35.4%) than the placebo group (27.1%).

**Meaning:** Among adults presenting to primary care practices with acute sore throat, a single dose of oral dexamethasone did not increase the likelihood of symptom resolution at 24 hours, but provided a small likelihood of benefit at 48 hours

**Abstract**

**Importance:** Acute sore throat poses a significant burden on primary care, and is a source of inappropriate antibiotic prescribing. Corticosteroids could be an alternative symptomatic treatment.

**Objective:** To assess the clinical effectiveness of oral corticosteroids for acute sore throat in the absence of antibiotics.

**Design, Setting and Participants:** Double-blind placebo controlled randomised trial (April 2013 to February 2015, 28 day follow-up completed April 2015) conducted in 42 family practices in South and West England, enrolling 576 adults (691 assessed, 82 not eligible, 33 declined) recruited on the day of presentation to primary care with acute sore throat not requiring immediate antibiotic therapy. Exclusion criteria included recent corticosteroids or antibiotics.

**Intervention:** Single oral dose of 10mg dexamethasone (n=293) or identical placebo (n=283).

**Main outcome measures:** Primary: proportion of participants experiencing complete resolution of symptoms at 24 hours. Secondary: complete resolution at 48 hours, duration of moderately bad symptoms (based on a Likert scale, 0=normal, 6= as bad as it could be), visual analogue symptom scales (0-100mm; no symptom to worst imaginable), healthcare attendance, days missed from work or education, consumption of delayed antibiotics or other medications, adverse events.

**Results:** Among 565 eligible patients who were randomized (median age 34 years; 75.2% women, 100% completed the intervention), 288 received dexamethasone and 277 placebo. The proportion of participants with complete resolution of symptoms at 24 hours was not significantly different between dexamethasone (65/288) and placebo (49/277) groups; (Risk difference (RD) 4.7%; 95%CI -1.8% to 11.2%; Relative Risk (RR) 1.28; 95%CI 0.92 to 1.78, p=.14) Results were similar in those receiving no antibiotics or delayed antibiotics. At 48 hours, more participants experienced complete resolution in the dexamethasone group; (RD 8.7%; 95%CI 1.2% to 16.2%; RR 1.31; 95%CI 1.02 to 1.68, p=.03); a difference also observed in patients not offered delayed antibiotics (RD 10.3%; 95%CI 0.6% to 20.1%; RR 1.37; 95%CI 1.01 to 1.87, p=.046). There were no significant differences in any other secondary outcomes.

**Conclusions and Relevance:** Among adults presenting to primary care with acute sore throat, a single dose of oral dexamethasone compared with placebo did not increase the proportion of patients with resolution of symptoms at 24 hours. However, there was a significant difference at 48 hours.

**Trial Registration:** ISRCTN17435450 http://www.isrctn.com/ISRCTN17435450

**Introduction**

Acute sore throat is one of the commonest infections presenting to primary care [1](#_ENREF_1), with almost 1 in 10 people consulting annually (from 1997 to 2006) [2](#_ENREF_2). Sore throats resulted in 92 million estimated visits by adults to primary care practices and emergency departments in the United States between 1997 and 2010 (averaging 6.6 million annually); with unnecessary antibiotic prescribing costs of at least $500 million [3](#_ENREF_3). Antibiotics are prescribed in 60% of UK primary care sore throat consultations[4](#_ENREF_4) and the trend is not decreasing [3](#_ENREF_3),[5](#_ENREF_5) despite the low risks of suppurative complications, limited symptomatic benefit[6](#_ENREF_6) and national guidelines advising against prescriptions [7](#_ENREF_7),[8](#_ENREF_8). There is a need to find alternative strategies that reduce symptoms, reduce the burden of acute illness and reduce antibiotic consumption.

Corticosteroids inhibit transcription of pro-inflammatory mediators in airway endothelial cells, responsible for pharyngeal inflammation and symptoms of pain, [9](#_ENREF_9) and are beneficial in other upper respiratory tract infections such as acute sinusitis [10](#_ENREF_10) and croup [11](#_ENREF_11). Short courses of oral steroids have been shown to be safe, in the absence of contraindications [12](#_ENREF_12). A systematic review reported that participants with a sore throat, taking a single dose of steroid, were three times more likely to experience complete resolution within 24 hours [13](#_ENREF_13). However, antibiotics were prescribed to participants in both steroid and placebo groups in all trials and only one trial recruited participants from primary care. Therefore evidence for corticosteroids for this sore throat in primary care, in the absence of antibiotics, is still lacking.

The primary objective of the TOAST (Treatment Options without Antibiotics for Sore Throat) trial was to investigate, in adults aged 18 years and over with acute sore throat not requiring immediate antibiotic therapy, whether a single dose of oral dexamethasone compared with placebo increased resolution of symptoms at 24 hours after consultation.

**Methods**

**Study design and participants**

A multicentre, individually randomised double-blind placebo-controlled parallel group trial in 42 General Practice (GP) clinics in South and West England. Recruitment started on 12th April 2013 and completed recruitment on 27th February 2015. Participants were followed for 28 days after randomization (follow up completed on 16th April 2015). The research protocol was approved by the National Research Ethics Committee South Central (12/SC/0684). (Study registration**:** ISRCTN17435450). Written informed consent was obtained for all participants.

Full details of the trial design, inclusion and exclusion criteria are available (Supplement 1). Briefly, included participants were: aged ≥18 years, presenting to a primary care clinician (GP or practice nurse) with acute symptoms (onset within the last 7 days) of sore throat and odynophagia (pain on swallowing) judged by the clinician to be due to an infection, but not to need immediate antibiotics and had capacity and willingness to give consent and complete the trial paperwork. Exclusion criteria included: recent (<1 month) use of inhaled or oral corticosteroids or adenotonsillectomy, recent use (<14 days) of antibiotics, clear alternative diagnosis (e.g. pneumonia).

**Randomisation, concealment and masking**

Randomisation (1:1) was stratified by study centre and by receipt of a delayed antibiotic prescription. A randomisation list using block randomisation with variable blocks of size 2, 4, or 6 was computer generated by an independent statistician for manufacturing. Each site was allocated to hold 2 sets (for those receiving antibiotic prescription and those not) of packs of 2- 3 blocks of blinded pre-randomised medication. Participants in the intervention group received a single dose of 10mg oral dexamethasone as 5 x 2mg dexamethasone tablets over-encapsulated by a single size 1 gelatine capsule. The control group received lactose over-encapsulated with an identical capsule. Overencapsulation for both intervention and placebo was performed by Nottingham University Hospital NHS Trust Pharmacy. Participants, health care providers, and researchers were unaware of the allocation of the patient and remained unaware until trial completion.

**Procedures**

Participants were recruited on the day of presentation to their GP practice with symptoms of sore throat and pain on swallowing. Eligibility was assessed and informed consent obtained. Baseline clinical features and a throat swab were obtained. Rapid streptococcal antigen tests were not available to clinicians. The clinician was free to decide to offer no antibiotic prescription or a delayed antibiotic prescription with their usual instructions; typically to ‘cash it in’ if symptoms had not improved in 48 hours. Participants were randomised and observed to take the trial medication. Primary outcome data was collected at 24 and 48 hours via text message or telephone, from days 0-7 using a patient symptom diary and review of the patient’s electronic medical records at one month.

**Outcome measures**

The primary outcome was the complete resolution of sore throat at 24 hours as reported by the patient by either text message or telephone contact. Secondary outcomes were 1) complete resolution of sore throat at 48 hours; 2) duration of moderately bad symptoms recorded by validated[14](#_ENREF_14) 7 day symptom diary (based on a Likert scale (0 = normal, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad, 6 = as bad as it could be.); 3) patient reported time to onset of pain relief and time to complete symptom resolution; 4) change in ratings of sore throat pain, pain on swallowing and difficulty swallowing on a visual analogue scale (0 – 100mm, no pain to worst pain imaginable, no difficulty to worst imaginable); 5) consumption of delayed antibiotic prescription for sore throat; 6) time missed from work or education; 7) attendance or telephone contact at any healthcare facility (including GP clinic, urgent care clinic, emergency department, or hospital admission) within 28 days with symptoms or complications associated with sore throat (defined as direct suppurative complications or presentation with sore throat symptoms) and, 8) use of over-the counter medications and prescription medications in the first 7 days. eMethods detail deviations from or amendments to our protocol since the inception of the trial and the reasons for this. Data were collected concurrently during the trial to inform a cost-effectiveness analysis which will be reported in a separate publication.

**Statistical Analysis**

**Sample size**

Based on our systematic review [13](#_ENREF_13), the minimum absolute increase in resolution of pain at 24 hours with corticosteroids was 18% (11% *vs.* 29%) and the average was 27%. To achieve 18% increase in resolution with 90% power and 5% alpha, required 226 participants.

Based on previous data, antibiotic prescriptions are offered to an estimated 50% of participants presenting with sore throat[2](#_ENREF_2) therefore in order to recruit at least 226 participants who were not offered antibiotics 566 participants were recruited, allowing for 20% loss to follow-up.

**Statistical Methods**

The primary outcome was analysed using a log-binomial regression model adjusted for centre and receipt of a delayed prescription for antibiotics. Complete resolution of sore throat by 48 hours was analysed in the same way.

Time to onset of pain relief and to complete pain resolution was analysed using a Cox regression model adjusting for receipt of a delayed antibiotic prescription and centre. Participants who did not provide a valid time in their symptom diary (a time without am or pm specified and outside the feasible range of times for the study) were excluded from this analysis. The duration of moderately bad or worse symptoms was analysed using a negative binomial model adjusting for centre, delayed prescription at baseline and including completed diary days as an offset. Time missed from work or education was analysed using linear regression adjusted for centre and delayed antibiotic prescription. Re-consultation (attendance or telephone contact) at healthcare facility (Emergency Department, Out-of Hours Primary care or in hours Primary care) with symptoms or complications of sore throat, use of over the counter and prescription medications and uptake of delayed antibiotic prescriptions were analysed using the same methods as the primary outcome. Sore throat complications were defined priori as direct suppurative complications such as quinsy and paratonsillar abscess; a post-hoc definition which included otitis media, sinusitis or cellulitis was also analysed.

For visual analogue scale data, the area under the curve (AUC) was calculated using the trapezoidal rule using estimates from a mixed effects repeated measures model adjusting for symptom at baseline, centre and delayed antibiotic prescription with a treatment and time interaction. The AUCs between the 2 groups were then compared using a t-test. A linear regression model was fitted to the change from baseline to day 1 and to day 2 of the symptom diary.

All available data from participants who withdrew from the study were included. For the analysis of resolution of symptoms at 24 and 48 hours, participants were classified as having no resolution of symptoms if data were missing. P values < 0.05 were considered significant and were two-sided. There was no adjustment to p values to account for multiple comparisons. All secondary outcomes are considered exploratory. Analyses were conducted using Stata version 13.

**Methods for subgroup analyses**

The analyses of the primary and secondary outcomes were repeated in the delayed antibiotic prescription and no antibiotic prescription subgroups as the study was powered for analysis within these subgroups separately. Additional subgroup analyses were pre-specified in the statistical analysis plan prior to unblinding of the study data and employed interaction tests. The effect of sore throat severity at baseline (defined using Centor score [15](#_ENREF_15) with a cut off of <3 and ≥3) was assessed by including an interaction term in the log binominal regression model between treatment group and patient severity. The effect of rescue medication use (any patient reported analgesic medication) in the first 48 hours, and presence of streptococcus on throat swabs were analysed in the same way.

**Methods for sensitivity analyses**

For the analysis of resolution of symptoms at 24 and 48 hours, it was assumed that participants who did not provide a response did not have resolution of their sore throat symptoms. Sensitivity analyses, where missing data was assumed resolved, replaced by multiple imputation and excluded (a complete case analysis) were performed.

Many participants experienced onset of pain relief or complete resolution of pain but failed to report the time to onset of pain relief or time to complete resolution of pain. A sensitivity analysis which substituted the missing time with the time in the day that the diary was completed on the day of recruitment was performed. Thus time was computed in whole days for these participants.

**Results**

576 participants were recruited from 42 GP clinics; 11 (1.9%) were ineligible and excluded from the analysis (see figure 1). Reasons for ineligibility included: under 18 (3); recent use of antibiotics (2); recent use of inhaled steroids (4); duration of sore throat (1) previous participation in TOAST trial (1), resulting in 565 participants included in the primary analysis (288 dexamethasone and 277 placebo). 36 (6%) participants had no information for the primary outcome and were included in the analysis as no resolution of symptoms. The median age of trial participants was 33.7 years (IQR 26.3 to 45.8) in the dexamethasone group and 34.3 years (IQR 26.0 to 45.0) in the placebo group. 75.2% of participants were female and 76.8% were employed or in education. 39.5% of eligible participants were offered a delayed antibiotic prescription (see figure 1 for study flow diagram). Baseline characteristics of recruited participants were similar between groups (Table 1). eTable 1 details clinician scores of patient symptoms at baseline, which were also similar between groups.

**Complete resolution of sore throat**

For the primary outcome, a single dose of oral dexamethasone did not significantly increase the proportion of participants reporting complete resolution of their sore throat at 24 hours. 22% (65/288) of participants receiving dexamethasone and 17.7% (49/277) of participants receiving placebo reported complete resolution within 24 hours, RR 1.28 (95%CI, 0.92 to 1.78, p=.14), RD 4.7% (-1.8% to 11.2%) (figure 2). There was also no significant difference at 24 hours in the subgroup of participants not offered antibiotics (dexamethasone 43/173; 24.9%, placebo 32/169; 18.9%), RR 1.31 (0.87 to 1.96; p=.19) RD 5.9% (-2.7% to 14.6%) or in those participants offered a delayed antibiotic prescription (dexamethasone 22/115; 19.1%, placebo 17/108; 15.7%), RR 1.19 (0.67 to 2.11, p = .55); RD 3.2% (-6.5% to 12.9%). Findings were stable in all sensitivity analyses, (eTables 2 - 4).

Participants in the dexamethasone group were significantly more likely to experience complete resolution of symptoms by 48 hours, RR 1.31 (1.02 to 1.68, p=.03) RD 8.7% (1.2% to 16.2%), NNT 12; 7 to 146). 35.4% (102/288) of participants in the dexamethasone group compared to 27.1% (75/277) of participants in the placebo group reported resolution (figure 2). In those not offered antibiotics, dexamethasone significantly increased resolution, (dexamethasone 65/173; 37.6%, placebo 46/169; 27.2%), RR 1.37 (1.01 to 1.87; p=.46); RD 10.3% (0.6% to 20.1%) NNT 10; 6 to 234), but no significant difference was observed for participants offered a delayed prescription, (dexamethasone 37/115; 32.2%, placebo 29/108; 26.8%), RR 1.19 (0.79 to 1.79; p=.41) RD 6.3% (-5.5% to 18.0%). Findings were stable to all sensitivity analyses (eTables 2-4).

Reported use of over the counter medications which contained analgesics (topical and oral) for symptom relief in the first 48 hours was similar in both groups (dexamethasone 148/192; 77.1%, placebo 153/194; 78.9%) and was not significantly different in participants reporting complete resolution of their symptoms at 48 hours, (interaction effect 1.05; 0.61 to 1.79; p=.86).

Neither severity of sore throat at baseline (interaction effect at 24 hours: 0.59 (95%CI 0.16 to 2.14) p=.42); 48 hours: 0.52 (0.25 to 1.11) p=.09) nor the presence of streptococcus on throat swabs were moderators of group differences (interaction effect at 24 hours: 1.93 (0.37 to 5.51) p=.22; 48 hours: 1.13 (0.52 to 2.45) p=.75).

**Patient symptom outcome measures**

Overall, the number of days of moderately bad symptoms was not significantly different between the two groups, nor for the subgroups receiving no antibiotic or delayed antibiotics (eTable 5). Visual analogue scale ratings of sore throat pain, pain on swallowing and difficulty swallowing showed no significant differences in change from baseline to day 1, change from baseline to day 2, or in the AUC summary statistic, either overall or for either subgroup (eTable 6).

There were no significant differences between groups in time to onset of pain relief, or time to complete resolution of pain, either overall or in antibiotic subgroups (Table 2). A sensitivity analysis including all participants who reported onset or complete resolution of symptoms but failed to report a valid time had similar findings (eTable 7).

**Effect on healthcare use, medication use and productivity**

Of the 157 participants given a delayed prescription who reported this outcome, 37/79 (46.8%) in the dexamethasone group reported consuming the delayed prescription within 7 days, compared to 44/78 (56.4%) in the placebo group, (RR 0.83, 95%CI, 0.61 to 1.13; p=.23; RD -9.4%, 95%CI -25.0% to 6.1%). In participants not offered a delayed prescription, fewer than 5% reported taking antibiotics in the first 48 hours (3/119 (2.5%) dexamethasone, 5/124 (4.0%) placebo, post-hoc analysis). There were no significant differences in the use of pain relief medications (topical and oral), antibiotics for sore throat or antibiotics for other conditions, or the proportion of participants missing any time away from work or education between dexamethasone and placebo groups (Table 3). Dexamethasone also did not result in a significant difference in the mean number of hours missed from work or education (mean difference 0.24 hours longer in dexamethasone group; 95% CI, -2.14 to 2.61, p=.85). There were no significant differences in the number of participants re-consulting at emergency departments, urgent care, or their usual GP clinic for symptoms or suppurative complications of sore throat (Table 3). Adopting a wider definition of sore throat complications to include otitis media, sinusitis or cellulitis[6](#_ENREF_6) in a post hoc analysis did not change our findings: all patients, RR 1.39 (95%CI 0.86 to 2.24 p=.18, RD: 3.0% 95%CI -1.5% to 7.5%); No antibiotics RR 1.32 (0.77 to 2.26 p=.31, RD: 3.2% 95%CI -3.9% to 10.4%); Delayed antibiotics RR 1.60 (0.56 to 4.60 p=.38, RD: 2.9% 95%CI -2.9% to 8.6%).

**Serious adverse events**

There were five serious adverse events. Of the 2 recorded in participants receiving dexamethasone, only 1 was considered related to the trial (hospital admission with parapharyngeal abscess). The three serious adverse events in the placebo group were due to hospital admission with peritonsillar abscess, hospital admission with severe tonsillitis, and hospital admission with pneumonia with subsequent death in the community.

**Discussion**

For patients attending primary care with sore throat not judged to require immediate antibiotics, no significant benefit of dexamethasone on complete resolution of symptoms at 24 hours was found. However, at 48 hours dexamethasone resulted in a significant increase in the proportion of participants reporting complete resolution, requiring on average 12 patients to be treated for one additional patient to experience symptom resolution. A similar effect was evident in the subgroup of participants not offered a delayed antibiotic prescription. No significant differences were observed in participant-reported duration of moderately bad symptoms, visual analogue scale ratings, time to onset and time to complete resolution of symptoms, or time away from school or work when comparing dexamethasone to placebo groups. Three study participants, two receiving placebo and one dexamethasone, required hospitalisation related to sore throat, a similar complication rate to previous observational studies of sore throat in primary care[16](#_ENREF_16). Re-attendance with symptoms or complications of sore throat was similar in both groups.

This trial found a RR of 1.28 (95%CI, 0.92 to 1.78) for complete resolution at 24 hours, which was lower than effect sizes seen in previous studies of use of oral corticosteroids in sore throat (RR ranging from 1.67 to 4.41)[13](#_ENREF_13). However, all previous trials gave antibiotics to patients in both corticosteroid and placebo groups. It is possible that there is a synergistic effect of corticosteroids and antibiotics in sore throat, such as that suggested for acute sinusitis, where oral corticosteroid monotherapy was ineffective for symptom relief in a primary care based trial, but corticosteroids in addition to antibiotics offer evidence of benefit [17](#_ENREF_17),[18](#_ENREF_18).

A second explanation for the smaller effect size in this study is that corticosteroids are most beneficial for severe sore throat. Two previous randomised trials [19](#_ENREF_19),[20](#_ENREF_20) have reported outcomes following a single dose of oral dexamethasone on a subgroup of rapid Group A streptococcus antigen negative children (total 154) where antibiotics were offered only after throat swab results or subsequent healthcare contact. The trial including children with a minimum subjective pain score demonstrated reduced symptom duration and greater pain reduction, whereas the trial where 24% of children initially reported mild pain found no effect on symptom duration.

Since this study aimed to evaluated dexamethasone in the absence of antibiotics, participants requiring immediate antibiotics, likely to have the most severe sore throat, were excluded, resulting in a different population to trials based in emergency departments. 42% of adults had purulent tonsils in a previous ED trial [21](#_ENREF_21), compared to 10% of our trial population. More severe symptoms might correlate with more severe inflammation and therefore the anti-inflammatory benefits of corticosteroids would be greater in this patient group. In this trial the test of interaction between severity or streptococcal presence and outcome revealed no significant effect, but this analysis was limited by the small number of participants in these groups (14.5% and 15.2% respectively).

To our knowledge, this is the first trial to evaluate the benefits of oral corticosteroids for acute sore throat in primary care, where the majority of patients with sore throat are managed, and to evaluate the benefits of oral corticosteroids in the absence of antibiotics. Compliance with our medication was 100% and our primary outcome measure was collected on 93.6% of participants. Participants allocated to placebo and dexamethasone groups were well balanced at baseline. The features of the population recruited were similar to that in a previous large observational cohort of participants presenting to primary care with sore throat [16](#_ENREF_16).

This study has several limitations. This trial may have recruited a less severe patient group by excluding those requiring immediate antibiotics. Children were also excluded, where three trials [19](#_ENREF_19),[20](#_ENREF_20),[22](#_ENREF_22) have demonstrated a significant benefit of corticosteroids in addition to antibiotics. The return rate of symptom diaries or follow-up questionnaires was 75%, similar to return rates for other sore throat trials in primary care [23](#_ENREF_23), however, poor completion of diaries resulted in lower rates for two outcome measures. The primary outcome was not validated, but it is widely used in trials and systematic reviews of acute sore throat interventions [13](#_ENREF_13),[21](#_ENREF_21),[22](#_ENREF_22),[24](#_ENREF_24),[25](#_ENREF_25) and was chosen in order to ensure a timely and high response rate, key in evaluating response in acute infection. Other symptom measures used in the study have been validated in primary infectious disease research [14](#_ENREF_14). In addition, this study was underpowered to detect a modest effect on the primary outcome or to detect difference in side effect profiles. A larger study may have identified a statistically significant difference between the treatment arms.

There is still uncertainty about the role of oral corticosteroids for patients presenting in primary care with sore throat. Corticosteroids may have clinical benefit in addition to antibiotics for severe sore throat, for example to reduce hospital admissions in those unable to swallow fluids or medications. There have been no trials of corticosteroids in these patient groups [26](#_ENREF_26). A recent systematic review of 3 small trials suggests early but unsustained symptomatic benefit in peritonsillar abscess[27](#_ENREF_27) with one trial demonstrating a reduction in duration of hospitalisation.

Side effects of corticosteroids may be more significant in patients with co-morbidities, such as diabetes and heart failure, who were excluded from this trial. Given that patients could receive a larger cumulative dose of corticosteroids through multiple primary care attendances with sore throat, the potential longer term impacts of increased steroid consumption (e,g. osteoporosis, hypertension) should also be considered.

**Conclusion**

Among adults presenting to primary care practices with acute sore throat, a single dose of oral dexamethasone compared with placebo did not increase the proportion of patients with resolution of symptoms at 24 hours. However, there was a significant difference at 48 hours.

**Table 1: Baseline characteristics of eligible patients**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All patients** | **No antibiotics** | **Delayed antibiotics** |
|   | **Dexamethasone** | **Placebo** | **Dexamethasone** | **Placebo** | **Dexamethasone** | **Placebo** |
| **(N= 288)** | **(N= 277)** | **(N= 173)** | **(N= 169)** | **(N= 115)** | **(N= 108)** |
| **Age (median ( IQR))** | 33.7 (26.3 to 45.8) | 34.3 (26.0 to 45.0) | 36.7 (27.0 to 48.3) | 37.0 (27.5 to 48.1) | 31.8 (24.0 to 43.2) | 31.9 (24.5 to 40.3) |
| **Male**  | 67 (23.3%) | 73 (26.4%) | 42 (24.3%) | 46 (27.2%) | 25 (21.7%) | 27 (25.0%) |
| **In Work or Education**  | 217 (75.3%) | 217 (78.3%) | 122 (70.5%) | 134 (79.3%) | 95 (82.6%) | 83 (76.9%) |
| **Smoker**  | 52 (18.1%) | 51 (18.4%) | 28 (16.2%) | 26 (15.4%) | 24 (20.9%) | 25 (23.2%) |
| **Study Centre**  |  |  |  |  |  |  |
| Bristol | 79 (27.4%) | 72 (26.0%) | 47 (27.2%) | 46 (27.2%) | 32 (27.8%) | 26 (24.1%) |
|  Oxford | 143 (49.7%) | 139 (50.2%) | 90 (52.0%) | 89 (52.7%) | 53 (46.1%) | 50 (46.3%) |
|  Southampton | 66 (22.9%) | 66 (23.8%) | 36 (20.8%) | 34 (20.1%) | 30 (26.1%) | 32 (29.6%) |
| **Duration of Sore Throat in days (mean (SD))** | 3.86 (1.67) | 3.91 (1.79) | 3.99 (1.68) | 4.14 (1.85) | 3.7 (1.60) | 3.5 (1.60) |
| **Duration of pain on swallowing in days (median, IQR)** | 3 (2 to 4) | 3 (2 to 4) | 3 (2 to 4) | 3 (2 to 5) | 3 (2 to 4) | 3 (2 to 4) |
| **Pharyngeal Inflammation** | 254 (88.2%) | 248 (89.5%) | 144 (83.2%) | 148 (87.6%) | 110 (95.8%) | 100 (92.6%) |
| **Self report of moderate or severe sore throat** | 277 (96.2%) | 268 (96.8%) | 165 (95.4%) | 164 (97.0%) | 112 (97.4%) | 104 (96.3%) |
| **Self report of moderate or severe difficulty swallowing** | 198 (68.9%) | 196 (70.8%) | 114 (65.9%) | 113 (66.9%) | 84 (73.0%) | 83 (76.9%) |
| **Tonsils visible on examination** | 201 (69.8%) | 190 (68.6%) | 113 (65.3%) | 110 (65.1%) | 88 (76.5%) | 80 (74.1%) |
| **Purulent tonsils**  | 30 (10.4%) | 31 (11.2%) | 11 (6.4%) | 5 (3.0%) | 19 (16.5%) | 26 (24.1%) |
| **Mean temperature (SD) in degrees Celsius** | 36.8 (0.5) | 36.8 (0.6) | 36.7 (0.5) | 36.8 (0.5) | 36.9 (0.5) | 36.8 (0.7) |
| **Centora Score ≥ 3**  | 41 (14.2%) | 40 (14.4%) | 14 (8.1%) | 12 (7.1%) | 27 (23.5%) | 28 (25.9%) |
| **Centor Score ≥ 4**  | 7 (2.4%) | 7 (2.5%) | 3 (1.7%) | 0 | 4 (3.5%) | 7 (6.5%) |
| **Throat swab Culture:** |   |   |   |   |   |   |
| **Group A streptococcus** | 30 (11.5%) | 33 (13.6%) | 17 (11.0%) | 16 (11.0%) | 13 (12.3%) | 17 (17.5%) |
| **Group C streptococcus** | 7 (2.7%) | 10 (4.1%) | 4 (2.6%) | 3 (2.1%) | 3 (2.8%) | 7 (7.2%) |
| **Group G streptococcus** | 1 (0.4%) | 3 (1.2%) | 1 (0.7%) | 1 (0.7%) | 0 (0%) | 2 (2.1%) |
| **Totalb** | 38 (14.6%) | 46 (19.0%) | 22 (14.3%) | 20 (13.8%) | 16 (15.1%) | 26 (26.8%) |

aThe [Centor(15) score](https://cks.nice.org.uk/sore-throat-acute#%21scenarioclarification/-498879) (range 0 – 4) uses the following criteria: presence of tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis, history of fever, and absence of cough) A score of 3 or 4 indicates a higher likelihood of a bacterial sore throat.

b63 swabs were lost in transit (28 dexamethasone 35 placebo), % of received swabs reported

**Table 2 Median time to onset of pain relief and median time to complete resolution of symptomsab**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | **Dexamethasone****Median****(25th – 75th centile)** | **N** | **Placebo****Median****(25th – 75th centile)** | **N** | **Hazard ratio (95%CI)** | **p value** |
| **Time to onset of pain relief in hours** |
| **Full cohort**  | 27.5 (21.0, 44.5)  | 129 | 27.0 (21.4, 45.8)  | 102 | 1.106 (0.850, 1.440)† | 0.452 |
| **No antibiotics** | 27.0 (19.7 to 37.0)  | 78 | 25.8 (20.9 to 44.7)  | 64 | 1.251 (0.887, 1.763)  | 0.202 |
| **Delayed antibiotics** | 30.7(22.8 to 62.9)  | 51 | 34.2 (23.3 to 54.1)  | 38 | 0.843 (0.543, 1.307)  | 0.445 |
| **Time to complete symptom resolution in hours** |
| **Full cohort** | 65.8 (41.0 to 105.9)  | 101 | 60.0 (39.8 to 92.3)  | 94 | 1.043 (0.781, 1.393)  | 0.776 |
| **No antibiotics** | 67.0 (40.2 to 96.9 | 61 |  54.0 (35.8 to 91.8)  | 60 | 0.996 (0.687, 1.442)  | 0.982 |
| **Delayed antibiotics** | 64.4 (43.4 to 116.8)  | 40 |  67.6 (41.5 to 96.4)  | 34 | 1.251 (0.771, 2.031)  | 0.365 |

a2 participants (1 from each treatment group) were excluded from the time-to-event analysis for having time-to-event values outside the feasible range i.e., <0 or >200 hours. Participants who did not complete any days of their symptom diary were excluded from the analysis (n=174/565) alongside all who did not provide their time of pain relief nor whether the time is AM or PM (n=152/565). All who recorded “NA” in answer to "Has your sore throat become less painful in the last 24 hours?" are assumed to have missing data and excluded from the analysis (n=6/565).

bHazard ratios are from proportional hazards models adjusted for centre and delayed antibiotic prescription (where applicable).

**Table 3 Time away from work or education, medication use and health contactsa**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | **N** | **Dexamethasone** | **Placebo** | **RR (95% CI)** | **P value** | **RD (95% CI)** |
| **Re-consultation at health care facility**  |   |   |   |   |   |  |
| Overall | 565 | 31/288 (10.8%) | 20/277 (7.2%) | 1.48 (0.87 to 2.53) | 0.146 | 3.3% (-0.6% to 7.3%) |
| No antibiotics  | 342 | 23/173 (13.3%) | 16/169 (9.5%) | 1.40 (0.77 to 2.56) | 0.268 | 3.5% (-3.1% to 10.0%) |
| Delayed antibiotics  | 223 | 8/115 (7.0%) | 4/108 (3.7%) | 1.73 (0.54 to 5.50) | 0.356 | 3.2% (-1.8% to 8.2%) |
| **Patients missing work or education** |   |   |   |   |   |  |
| Overall | 411 | 61/202 (30.2%) | 73/209 (34.9%) | 0.86 (0.65 to 1.13) | 0.264 | -4.2% (-13.0% to 4.7%) |
| No antibiotics  | 254 | 32/123 (26.0%) | 39/131 (29.8%) | 0.87 (0.59 to 1.30) | 0.503 | -3.1% (-14.0% to 7.8%) |
| Delayed antibiotics  | 157 | 29/79 (36.7%) | 34/78 (45.6%) | 0.84 (0.58 to 1.23) | 0.372 | -6.2% (-21.3% to 8.9%) |
| **Antibiotics consumed for sore throat** |   |   |   |   |   |  |
| Overall | 417 | 50/206 (24.3%) | 59/211 (28.0%) | 0.83 (0.62 to 1.11) | 0.220 | -2.4% (-9.6% to 4.7%) |
| No antibiotics  | 260 | 16/127 (12.6%) | 17/133 (12.8%) | 0.99 (0.52 to 1.87)  | 0.971 | -0.2% (-8.3% to 7.9%) |
| Delayed antibiotics  | 157 | 34/79 (43.0%) | 42/78 (53.8%) | 0.80 (0.58 to 1.11)  | 0.178 | -10.8% (-26.4% to 4.7%) |
| **Antibiotics for other reasons** |   |   |   |   |   |  |
| Overall | 417 | 5/206 (2.4%) | 9/211 (4.3%) | 0.58 (0.20 to 1.70)  | 0.322 | -1.7% (-5.8% to 2.3%) |
| No antibiotics  | 260 | 5/127 (3.9%) | 6/133 (4.5%) | 0.86 (0.27 to 2.73) | 0.794 | 0.1% (-4.5% to 4.8%) |
| Delayed antibiotics  | 157 | 0/79 | 3/78 (3.8%) |   |   |  |
| **Pain relief preparations b** |   |   |   |   |   |  |
| Overall | 417 | 147/206 (71.4%) | 154/211 (73.0%) | 0.98 (0.87 to 1.10)  | 0.770 | -1.3% (-9.8% to 7.1%) |
| No antibiotics  | 260 | 88/127 (69.3%) | 98/133 (73.7%) | 0.94 (0.81 to 1.09) | 0.423 | -4.4% (-15.3% to 6.6%) |
| Delayed antibiotics  | 157 | 59/79 (74.7%) | 56/78 (71.8%) | 1.05 (0.88 to 1.25)  | 0.622 | 3.2% (-10.1% to 16.6%) |

a Log-binomial model adjusted for centre and delayed antibiotic prescription.\*\*Including lozenges linctus and sprays which contain a local anaesthetic or anti-inflammatory n = total number of participants providing data. RR= adjusted relative risk. RD=adjusted risk difference

bAnalysis includes only participants who provided follow-up information on the name of antibiotics used.

**Acknowledgements**

This study was run by the PC-CTU, Department of Primary Care Health Sciences, University of Oxford in conjunction with the Centre for Academic Primary Care, University of Bristol, and the Department of Primary Medical Care, University of Southampton. The authors wish to acknowledge the efforts of the teams in Oxford, Bristol and Southampton in managing sites, enabling recruitment and facilitating follow up.

Sources of funding / support

This paper presents independent research funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR). The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Access to Data statement

GH and MV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Role of the Sponsor

The sponsor had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest disclosures

Professor Thompson has received funding from Alere Inc. to conduct research on C-reactive protein point of care tests, has received funding from Roche Molecular Diagnostics for consultancy work, and is a co-founder of Phoresa Inc. which is developing point of care tests for primary care. Professor Heneghan has received expenses from the WHO, and holds grant funding from the NIHR, the NIHR School of Primary Care Research, The Wellcome Trust and the WHO.

# REFERENCES

1. Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ.* 2007;335(7627):982.

2. Gulliford M, Latinovic R, Charlton J, Little P, van Staa T, Ashworth M. Selective decrease in consultations and antibiotic prescribing for acute respiratory tract infections in UK primary care up to 2006. *J Public Health (Oxf).* 2009;31(4):512-520.

3. Barnett ML, Linder JA. Antibiotic prescribing to adults with sore throat in the United States, 1997-2010. *JAMA internal medicine.* 2014;174(1):138-140.

4. Gulliford MC, Dregan A, Moore MV, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *BMJ open.* 2014;4(10):e006245.

5. Hawker JI, Smith S, Smith GE, et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. *The Journal of antimicrobial chemotherapy.* 2014;69(12):3423-3430.

6. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *The Cochrane database of systematic reviews.* 2013;11:CD000023.

7. Excellence NIfHaC. *Respiratory Tract Infections - Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care.* London: National Institute for Health and Clinical Excellence.; 2008.

8. Pelucchi C, Grigoryan L, Galeone C, et al. Guideline for the management of acute sore throat. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2012;18 Suppl 1:1-28.

9. Mygind N, Nielsen LP, Hoffmann HJ, et al. Mode of action of intranasal corticosteroids. *The Journal of allergy and clinical immunology.* 2001;108(1 Suppl):S16-25.

10. Zalmanovici Trestioreanu A, Yaphe J. Intranasal steroids for acute sinusitis. *The Cochrane database of systematic reviews.* 2013;12:CD005149.

11. Russell KF, Liang Y, O'Gorman K, Johnson DW, Klassen TP. Glucocorticoids for croup. *The Cochrane database of systematic reviews.* 2011(1):CD001955.

12. Weinberger M. Safety of oral corticosteroids. *European journal of respiratory diseases. Supplement.* 1982;122:243-251.

13. Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ. Corticosteroids as standalone or add-on treatment for sore throat. *The Cochrane database of systematic reviews.* 2012;10:CD008268.

14. Watson L, Little P, Moore M, Warner G, Williamson I. Validation study of a diary for use in acute lower respiratory tract infection. *Family practice.* 2001;18(5):553-554.

15. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. *Medical decision making : an international journal of the Society for Medical Decision Making.* 1981;1(3):239-246.

16. Little P, Stuart B, Hobbs FD, et al. Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study. *The Lancet. Infectious diseases.* 2014;14(3):213-219.

17. Venekamp RP, Bonten MJ, Rovers MM, Verheij TJ, Sachs AP. Systemic corticosteroid monotherapy for clinically diagnosed acute rhinosinusitis: a randomized controlled trial. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2012;184(14):E751-757.

18. Venekamp RP, Thompson MJ, Hayward G, et al. Systemic corticosteroids for acute sinusitis. *The Cochrane database of systematic reviews.* 2014;3:CD008115.

19. Olympia RP, Khine H, Avner JR. Effectiveness of oral dexamethasone in the treatment of moderate to severe pharyngitis in children. *Archives of pediatrics & adolescent medicine.* 2005;159(3):278-282.

20. Bulloch B, Kabani A, Tenenbein M. Oral dexamethasone for the treatment of pain in children with acute pharyngitis: a randomized, double-blind, placebo-controlled trial. *Annals of emergency medicine.* 2003;41(5):601-608.

21. Wei JL, Kasperbauer JL, Weaver AL, Boggust AJ. Efficacy of single-dose dexamethasone as adjuvant therapy for acute pharyngitis. *The Laryngoscope.* 2002;112(1):87-93.

22. Niland ML, Bonsu BK, Nuss KE, Goodman DG. A pilot study of 1 versus 3 days of dexamethasone as add-on therapy in children with streptococcal pharyngitis. *The Pediatric infectious disease journal.* 2006;25(6):477-481.

23. Little P, Hobbs FD, Moore M, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *BMJ.* 2013;347:f5806.

24. Kiderman A, Yaphe J, Bregman J, Zemel T, Furst AL. Adjuvant prednisone therapy in pharyngitis: a randomised controlled trial from general practice. *The British journal of general practice : the journal of the Royal College of General Practitioners.* 2005;55(512):218-221.

25. Tasar A, Yanturali S, Topacoglu H, Ersoy G, Unverir P, Sarikaya S. Clinical efficacy of dexamethasone for acute exudative pharyngitis. *The Journal of emergency medicine.* 2008;35(4):363-367.

26. Bird JH, Biggs TC, King EV. Controversies in the management of acute tonsillitis: an evidence-based review. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2014;39(6):368-374.

27. Lee YJ, Jeong YM, Lee HS, Hwang SH. The Efficacy of Corticosteroids in the Treatment of Peritonsillar Abscess: A Meta-Analysis. *Clin Exp Otorhinolaryngol.* 2016;9(2):89-97.