Corticosteroids for treatment of sore throat: a systematic review and meta-analysis of randomised trials

Journal:	*BMJ*
Manuscript ID	BMJ.2017.039974.R1
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	28-Jul-2017
Complete List of Authors:	Sadeghirad, Behnam; McMaster University, Department of Health Research Methods, Evidence, and Impact (HEI); Kerman University of Medical Sciences, HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health Siemieniuk, Reed; McMaster University, Department of Health Research Methods, Evidence, and Impact (HEI); University of Toronto, Medicine Brignardello-Petersen, Romina; McMaster University, Department of Health Research Methods, Evidence, and Impact (HEI); Universidad de Chile, Faculty of dentistry Papola, Davide; University of Verona, Department of Public Health and Community Medicine, Section of Psychiatry Lytvyn, Lyubov; Oslo University Hospital Vandvik, Per; Innlandet Hospital Trust-divisjon Gjøvik, Department of Medicine; University of Oslo, Institute of Health and Society, Faculty of Medicine Merglen, Arnaud; University of Geneva, Division of General Pediatrics, University Hospitals of Geneva & Faculty of Medicine Guyatt, Gordon; McMaster University, Department of Health Research Methods, Evidence, and Impact (HEI) Agoritsas, Thomas; McMaster University, Department of Health Research Methods, Evidence, and Impact (HEI); University Hospitals of Geneva, Division of General Internal Medicine & Division of Clinical Epidemiology
Keywords:	Corticosteroids, Sore throat, Meta-analysis, GRADE, Pain relief, Acute pharyngitis

Corticosteroids for treatment of sore throat: a systematic review and meta-analysis of randomised trials

Authors

Behnam Sadeghirad *pharmacist and methodologist* [1,2] *, Reed A. C. Siemieniuk *general internist and methodologist* [1] *, Romina Brignardello-Petersen *methodologist and biostatistician* [1,3], Davide Papola *psychiatrist and methodologist* [4], Lyubov Lytvyn *methodologist* [5], Per Olav Vandvik *associate professor* [6,7], Arnaud Merglen *pediatrician* [8], Gordon H. Guyatt *distinguished professor* [1], Thomas Agoritsas *assistant professor* [1,9]

Authors affiliation

1. Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada
2. HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
3. Faculty of dentistry, University of Chile, Santiago, Chile
4. Department of Public Health and Community Medicine, Section of Psychiatry, University of Verona, Italy
5. Oslo University Hospital, Oslo, Norway
6. Department of Medicine, Innlandet Hospital Trust -Division Gjøvik, Oslo, Norway
7. Institute of Health and Society, Faculty of Medicine, University of Oslo, Norway
8. Division of General Pediatrics, University Hospitals of Geneva & Faculty of Medicine, University of Geneva, Geneva, Switzerland
9. Division of General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Switzerland.

* Dr Sadeghirad and Dr Siemieniuk contributed equally to this work.

Corresponding author:

Behnam Sadeghirad, PharmD, MPH, PhD (c)

sadeghb@mcmaster.ca

Abstract

Objective: To estimate the benefits and harms of using corticosteroids as an adjunct treatment for sore throat.

Design: Systematic review and meta-analysis of randomized control trials.

Data sources: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and trial registries up to May 2017 as well as the reference lists of eligible trials, and related reviews.

Study selection: Randomised controlled trials addressing the addition of corticosteroids to standard clinical care, for patients five years or older in emergency department and primary care settings, with clinical signs of acute tonsillitis, pharyngitis, or the clinical syndrome of sore throat. We included trials irrespective of language or publication status.

Review methods: Reviewers identified studies, extracted data, and assessed the quality of the evidence, independently and in duplicate. A parallel guideline committee (*BMJ* Rapid Recommendation) provided input on the design and interpretation of the systematic review, including the selection of outcomes important to patients. We performed meta-analyses using random effects model, and assessed the quality of evidence using the GRADE approach.

Results: In the ten trials enrolling 1426 individuals that we found eligible, patients receiving single low dose corticosteroids were twice as likely to experience pain relief after 24 hours (relative risk [RR] 2.2, 95% CI: 1.2 to 4.3; risk difference 12.4%; moderate quality evidence) and 1.5 times more likely to have no pain at 48 hours (RR 1.5, 95% CI: 1.3 to 1.8; risk difference 18.3%; high quality). The mean time to onset of pain relief in patients treated with corticosteroids was 4.8 hours earlier (95% CI: -1.9 to -7.8; moderate quality), and the mean time to complete resolution of pain was 11.1 hours earlier (95% CI: -0.4 to -21.8; low quality) than in those treated with placebo. The absolute pain reduction at 24 hours (visual analogue scale 0-10) was greater in patients treated with corticosteroids (mean difference: 1.3; 95% CI: 0.7 to 1.9; moderate quality). None of the included studies reported adverse effects attributable to treatment.

Conclusion: Single low-dose corticosteroids provides pain relief in patients with sore throat, without evidence of adverse effects.

Introduction

Sore throat is among the most common presenting complaints in both emergency departments and outpatient care settings. It is the cause of about 5% of medical visits in children and about 2% of all adult outpatient visits.[1-3] The most common cause of sore throat is acute pharyngitis caused by self-limiting viral infections; thus, pain management with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) represents the mainstay of care.[4 5]

Treatment of sore throat with antibiotics also provides modest benefit in reducing symptoms and fever when the infection is bacterial, but their use may contribute to antibiotic resistance.[6 7] Although most sore throat cases have a viral aetiology, and the risk of secondary complications is low, clinicians frequently prescribe antibiotics.[4 8] This may be due to clinicians' perception that patients seeking care expect a course of antibiotics; however, pain relief may be more important to patients.[8]

Corticosteroids represent an additional therapeutic option to achieve symptom relief. Randomized control trials (RCTs) suggest that a short course of low-to-moderate dose corticosteroids probably provides symptomatic benefit to patients with sore throat.[9-12] Despite this evidence, clinicians do not commonly use steroids. Reasons may include uncertain applicability of the evidence to patients with less severe disease, as the initial RCTs enrolled only patients with severe sore throat presenting to emergency departments, almost all of whom received antibiotic therapy.

This systematic review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation program (www.magicproject.org) and *the BMJ*. The aim of the project is to respond to new potentially practice changing evidence and provide a trustworthy practice guideline in a timely manner.[13] In this case, the stimulus was the recent TOAST (Treatment Options without Antibiotics for Sore Throat) trial, which randomized over 500 patients with sore throat presenting to their primary care clinician and were not initially prescribed antibiotics; the TOAST authors reported beneficial effects of using corticosteroids.[14] In the light of this new potentially practice changing evidence, we updated the latest Cochrane review[10] addressing the effectiveness and safety of corticosteroids as an adjunct therapy for sore throat in addition to standard care, compared to standard care alone. This systematic review informed the parallel guideline published in a multi-layered electronic format on bmj.com[15] and MAGICapp (https://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn).

Methods

Protocol registration

The protocol for this systematic review is registered with PROSPERO: CRD42017067808.

Guideline panel and patient involvement

According to the BMJ Rapid Recommendations process,[13] a guideline panel provided critical oversight to the review and identified populations, subgroups, and outcomes of interest. The panel included clinicians, methodologists, and patients with experience of sore throat. Patients received personal training and support to optimise contributions throughout the guideline development process. The patient panel members led the interpretation of the results based on what they expected the typical patient values and preferences to be, as well as the variation between patients.

Search strategy

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant published RCTs based on the strategy reported in the most recent Cochrane systematic review,[10] modified under the guidance of a research librarian (**Appendix 1**). We limited the search from January 1, 2010, which included a two month overlap with the previous Cochrane review search,[10] to May 1, 2017. We did not apply language restrictions. We reviewed reference lists from eligible new trials and related reviews for additional eligible RCTs, and searched ClinicalTrials.gov for ongoing or unpublished trials, and for additional data from published trials.

Study selection

Two reviewers independently screened the titles and abstracts of all identified studies using *a priori* selection criteria. Subsequently, two reviewers independently assessed eligibility of the full-texts of potentially eligible studies. Reviewers resolved discrepancies through discussion, or, if needed, by adjudication from a third reviewer.

We included RCTs that compared corticosteroids with standard of care or placebo, and enrolled adults and/or children above the age of five years in emergency departments and primary care settings with a clinical syndrome of sore throat (painful throat, odynophagia, or pharyngitis).

We excluded studies of participants who were hospitalized or immunocompromised, and those with infectious mononucleosis, sore throat following any surgery or intubation (post-operative sore throat), gastroesophageal reflux disease, croup, or peritonsillar abscess.

Our outcomes of interest were as follows: (i) complete resolution of pain at 24 hours and at 48 hours; (ii) mean time to onset of pain relief; (iii) mean time to complete resolution of pain; (iv) absolute reduction of pain at 24 hours; (v) duration of bad/non-tolerable symptoms (e.g. problems for eating, drinking, swallowing); (vi) recurrence/relapse of symptoms; (vii) days

missed from school or work; (viii) need for antibiotics; and (ix) rate of treatment-related adverse events (as reported by authors).

Data abstraction and risk of bias assessment

Reviewers extracted the following data, independently and in duplicate: (i) general study information (author's name, publication year, and study location), (ii) study population details (sample size, age, diagnosis, and percentage of participants with confirmed group A beta-hemolytic streptococcus [GAS] pharyngitis or culture positive for bacterial pathogens), (iii) setting (primary care versus hospital emergency department), (iv) details on the intervention and comparison (e.g. type, dosage form, duration, and dose of corticosteroids; type of control group), (iv) co-interventions (proportion of participants who received antibiotics and/or analgesics), and (v) outcomes as listed above.

In RCTs with more than two arms, we extracted data from the arm closest to a single-dose regimen, or data from the arm that received corticosteroid as adjunct therapy to standard of care rather than instead of standard of care. In RCTs with data for both oral and parenteral corticosteroids, we used oral data for the main analysis and used intramuscular data for the appropriate subgroup analysis.

Two reviewers independently assessed risk of bias using the modified Cochrane risk of bias instrument[16 17] that addresses the following issues: random sequence generation, allocation concealment, blinding of study participants, healthcare providers, and outcome assessors, incomplete outcome data, and other potential sources of bias. Reviewers classified studies at high risk of bias when they had rated at least one item as high risk of bias.

To assess the quality of evidence, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach that classifies evidence as high, moderate, low, or very low quality based on considerations of risk of bias, consistency, directness, precision, and publication bias.[18] We resolved disagreements between reviewers in data extraction, and assessments of risk of bias or quality of evidence by discussion and, if needed, by third party adjudication. We used the MAGICapp platform to generate the GRADE Summary of Findings table.

Data synthesis and statistical methods

For continuous outcomes, we calculated the mean difference and its corresponding 95% confidence interval (CI). For dichotomous outcomes, we calculated the relative risk (RR) and its corresponding 95% CI, and calculated the absolute effect by multiplying the RR and its CI with the estimated baseline risk. The median of the placebo group of included RCTs provided the baseline risk.

Statistical heterogeneity was determined using the Q statistic and I^2. We used the DerSimonian–Laird random-effects model for the meta-analysis of all outcomes. Regardless of the observed statistical heterogeneity, we conducted the following pre-specified subgroup analyses when each subgroup was represented by at least two studies: age (children vs. adults), postulating a larger effect in adults; administration route of corticosteroids (oral vs. parenteral), postulating a larger effect for parenteral; presence or absence of culture-positive for a bacterial pathogen or direct antigen test for GAS, postulating a larger effect in patients with positive test results; initial setting (emergency departments vs. family practice), postulating a larger effect in patients consulting at the emergency department; and place of subsequent care (hospitalized vs. outpatient), postulating a larger effect among the hospitalized patients. For subgroup analysis, we tested for interaction using a chi-square significance test.[19] We planned to examine publication bias using funnel plots for outcomes in which 10 or more studies were available.[20] Data were analysed using STATA software (Version 14.2, Texas, USA).

Results

Description of included studies

We identified 2349 titles and abstracts through our literature search, of which 46 proved potentially eligible and 36 were excluded for the following reasons: (i) not randomized trials (n = 19), (ii) no sore throat/acute pharyngitis (n = 14), (iii) corticosteroids were not among the interventions or were not compared with a placebo/usual care (n = 3). **Figure 1** provides the details of study selection process.

Please, insert Figure 1 here.

We included 10 RCTs that proved eligible enrolled 1426 individuals. Eight studies recruited patients from hospital emergency departments[21-28] and two from primary care practice.[14 29] Three studies enrolled children,[25-27] and seven studies adults.[14 21-24 28 29] **Table 1** presents study details.

Please, insert Table 1 here.

Among the included studies, four RCTs proved to be at high risk of bias.[21 22 24 26] One study,[24] had issues in more than one category of risk of bias. The remaining three studies had issues in concealing the treatment allocation, incomplete outcome reporting, and blinding of outcome assessors. **Appendix 2** summarizes the risk of bias assessments.

Table 2 summarizes findings of all outcomes. Interactive tables summarizing findings are available online at https://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn

Pain

In the five RCTs that reported complete symptom resolution at 24 hours,[14 23 27-29] patients who received a single dose of corticosteroids were twice as likely to experience complete symptom resolution than placebo patients (RR 2.2, 95% CI: 1.2 to 4.3; I^2 = 68.8%, 22.4% vs 10.0%; moderate quality evidence; **Figure 2, Table 2**). All studies reporting this outcome were at low risk of bias. Tests of interaction showed no evidence of any subgroup effect (**Appendix 3**).

In the four RCTs that reported complete resolution of pain at 48 hours,[14 27-29] patients treated with corticosteroids were 50% more likely to experience complete resolution (RR 1.5, 95% CI: 1.3 to 1.8; I^2 = 3.2%, 60.8% vs 42.5%; high quality; **Figure 3, Table 2**). These four studies were all at low risk of bias, and tests of interaction showed no evidence of any subgroup effect (**Appendix 3**).

Please, insert Figure 2 and 3 here.

In the eight studies that reported mean time to onset of pain relief,[14 21-26 28] patients who received corticosteroids experienced onset of pain relief on average 4.8 hours earlier than

those who received placebo (95% CI: -1.9 to -7.8; I^2 = 78.3%; moderate quality, **Figure 4, Table 2**). We found no evidence of subgroup effect for this outcome (**Appendix 3**).

Please, insert Figure 4 here.

Time to complete resolution of pain was reported in six studies.[14 21 22 25 26 28] On average, patients receiving a single dose corticosteroid experienced complete resolution 11.1 hours earlier (95% CI: -0.4 to -21.8; I^2 = 84.5%; low quality, **Figure 5, Table 2**). In our subgroup analysis, we found a significantly larger effect among those treated with IM corticosteroids (MD = -22.4, 95% CI: -27.3 to -17.5 and MD = -1.5, 95% CI: -12.6 to 9.5, for IM and oral corticosteroids, respectively; p for test of interaction: 0.001); we found no other subgroup effect (**Appendix 4**).

Please, insert Figure 5 here.

Meta-analysis from eight studies that assessed pain using visual analogue scale (ranging from 0 meaning no pain to 10 meaning maximum pain) at baseline and after 24 hours,[14 21-26 29] showed a 1.3 points lower pain score among patients treated with corticosteroids compared to those treated with placebo at 24 hours (95%CI: 0.7 to 1.9; I^2 = 65.1%, moderate quality, **Figure 6, Table 2**). We found no evidence of subgroup effect for this outcome (**Appendix 4**).

Please, insert Figure 6 here.

To assess the possibility that there was selective reporting, we examined the magnitude of effect on the time to onset of pain relief, time to complete resolution of pain, and absolute pain reduction in studies that did and did not report resolution of pain at 24 and 48 hours. We found that the magnitude of effect on the other pain outcomes was similar is both sets of studies, making selective reporting less likely (**Appendix 5**).

Please, insert Table 2 here.

Other outcomes

In a single study,[14] authors reported a possible decrease in the likelihood of receiving antibiotics in patients treated with corticosteroids (RR 0.8; 95%CI: 0.6 to 1.1, moderate quality). Three studies[25 26 29] suggested a possible lower risk of recurrence/relapse of the symptoms (RR 0.5; 95%CI: 0.2 to 1.7; I^2 = 22.8%, moderate quality, **Appendix 6, Table 2**).

Kinderman et al [29] reported that 22/40 (55%) patients treated with corticosteroids and 27/39 (69%) taking placebo took time off work due to sore throat (RR = 0.8; 95%CI: 0.6 to 1.1). Marvez-Valls et al [22] reported that adult patients treated with corticosteroids missed an average of 0.4 ± 1.4 days; patients in the placebo arm missed an average of 0.7 ± 1.4 days (mean difference = - 0.3 days, 95%CI: -0.87 to 0.27). None of the trials reported duration of bad/non-tolerable symptoms.

Three studies reported adverse events, in both steroids and comparator arms. Hayward et al reported two serious adverse events (hospitalizations due to pharyngeal or peritonsillar abscess, tonsillitis, and pneumonia) in the corticosteroids group (0.68%) and 3 in the placebo group (1.06%). Olympia et al reported 1 out of the 57 (1.8%) children in the corticosteroids group and 2 out of the 68 (2.9%) children in the placebo group developed a peritonsillar abscess (moderate quality, **Table 2**).

Discussion

We found primarily moderate to high quality evidence that one or two low doses of corticosteroids reduces the intensity and duration of pain - pain scores at 24 hours, complete resolution of pain at 24 and at 48 hours, time to onset of pain relief, and time to complete pain relief - in patients with acute sore throat. Results were consistent across studies, and across all pain outcomes (**Table 2**). The pain reduction achieved is modest: for example, mean time to complete resolution of pain is approximately 11 hours shorter, and approximately 18% more patients will have complete pain relief at 48 hours. At 24 hours, the mean improvement in pain scores is approximately 13mm on a visual analogue scale from 0 to 100mm (with the minimal important difference being approximately 10mm).[30]

Whether corticosteroids reduce recurrence/relapse of symptoms, number of days missed from school or work, duration of bad/intolerable symptoms, or antibiotic use, remains uncertain. Regarding the safety of the short courses and low doses of corticosteroids, studies reported very few adverse effects, with no apparent increase in events in corticosteroid treated patients.

Strengths of this review include explicit eligibility criteria; a comprehensive search developed with a research librarian; duplicate assessment of eligibility, risk of bias, and data abstraction; consideration of all patient-important outcomes; consideration of selective reporting bias; consideration of possible subgroup effects; and rigorous use of the GRADE approach to rate quality of evidence. The limitations of our review have to do with the underlying evidence. Only three trials explicitly reported adverse events, and they did so inconsistently[14 23 26].

In comparison to previous systematic reviews,[9 10] we included two additional RCTs [14 24] that approximately doubled the number of participants. Results from our meta-analysis are consistent with previous findings that corticosteroids reduce pain at 48 hours and probably reduce other pain outcomes. In addition to enhanced precision with the additional studies, our meta-analysis adds to the existing evidence in that we considered absolute in addition to relative effect measures, providing a clear picture of the magnitude of effect.[31] In part due to input from guideline panel, we considered additional outcomes that participating patients considered important, including risk of symptom recurrence, duration of bad/non-tolerable symptoms, need for antibiotic prescription, and days missed from school or work. An important additional contribution of the new evidence is that it extends the applicability beyond patients with severe sore throat treated with antibiotics for GAS pharyngitis in the emergency department, to a broader range of patients not treated with antibiotics.

We explored, and were able to dismiss, subgroup effects, with one exception: the reduction in mean to complete resolution of pain was greater with intramuscular than oral corticosteroids. The subgroup effect and its direction was specified a priori, the difference between subgroups is relatively large (approximately 21 hours), and chance appears an unlikely explanation ($p <$

0.001). Credibility of the effect is , however, undermined [32] as the effect modification is suggested by comparison between rather than within studies and we found no similar difference in any other outcome. In addition, the only RCT that compared oral and IM dexamethasone treatment reported no significant difference in any outcome.[23]

Recent observational studies have raised the possibility of extremely rare but serious adverse effects following short courses of corticosteroids.[33] The quality of this evidence is, for a number of reasons, very low with respect to the question at hand. The studies use observational designs from large data bases with suboptimal verification of diagnoses; serious confounding by indication raising the possibility that the association is a result of the underlying disease process (e.g. acute inflammation or exacerbation) rather than the corticosteroids themselves; and indirectness in that the doses used in the sore throat RCTs are lower, and the duration considerably shorter, than those used in the observational studies. Among the paediatric population, a recent overview of reviews looked at evidence from 44 RCTs on conditions requiring very short course of steroids (i.e. asthma, bronchiolitis, croup, wheeze, and pharyngitis/tonsillitis) and reported no major adverse events.[34]

Despite prior evidence that corticosteroids may be beneficial, several groups and guidelines currently recommend against their routine use on the basis that evidence was only applicable to patients with severe pharyngitis who were also prescribed antibiotics in an emergency department.[1 35 36] The body of evidence now includes a broader representation of patients. The largest and most recent RCT included 565 patients presenting to their general practitioner rather than an emergency department, and none of the patients initially received antibiotics.[14] We found no subgroup differences with respect to patient group: the evidence appears to apply equally to patients who did and did not receive antibiotics. The evidence also appears to apply equally to patients with sore throat from GAS pharyngitis and some GAS-negative sore throat.

In the five trials that reported co-interventions, approximately 80% of the participants received additional analgesics such as acetaminophen and NSAIDs. Therefore, a single dose of corticosteroids appears to further reduce pain when used in combination with other analgesic therapies. Although the benefits are relatively small, many patients are likely to consider them important. With available evidence suggesting that adverse effects are rare or absent, and serious adverse effects very rare or absent, the addition of one or two doses of steroids to the symptomatic management of sore throat is likely to appeal to many patients.

Acknowledgement

We would like to thank Rachel Couban, librarian at McMaster National Pain Centre Research, for her advice on the search strategies. We also would like to thank members of the Rapid

Recommendations panel for critical feedback on outcome and subgroup selection, and manuscript feedbacks.

Competing interest

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work. RAS, AM, and GHG are members of the GRADE working group. There are no other relationships or activities that could appear to have influenced the submitted work.

Funding and support

None.

Authors contribution

TA, RAS, POV, GHG conceived the study idea. BS, RAS, RBP, TA coordinated the systematic review. BS, RAS, TA wrote the first draft of the manuscript. BS, LL designed the search strategy. BS, RAS, LL, DP, RBP screened abstracts and full texts. BS, RAS, RBP, DP acquired the data and judged risk of bias in the studies. BS performed the data analysis. All authors interpreted the data analysis and critically revised the manuscript.

Ethical approval

Not required.

Data sharing

All data is freely available within the appendices.

Data access

BS had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Patient involvement

Five patient representatives were full members of the guideline panel, and contributed to the selection and prioritisation of outcomes, values and preferences assessments, and critical feedback to the protocol for the systematic review and the BMJ Rapid Recommendations manuscript.

Transparency declaration

BS is the guarantor and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been

omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Table 1: Characteristics of studies included in the systematic review

Study	Setting	Population	Mean Age	No. randomized (intervention / control)	Pathogen positive* (%)	Type of steroid	Dose and duration	Antibiotic use intervention group (%)	Antibiotic use control group (%)	Analgesic use intervention group (%)	Analgesic use control group (%)
Hayward, 2017 [4]	Primary care	Adults	34.0	293/283	14.9	Dexamethasone (oral)	10 mg – single dose	39.9	39.0	77.1	78.9
Tasar, 2008 [28]	ED	Adults	31.3	31/42	NR	Dexamethasone (IM)	8 mg – single dose	100	100	100	100
Niland, 2006 [27]	ED	Children	7.7**	30/30	100.0	Dexamethasone (oral)	0.6 mg/kg, max. dose 10mg – single dose	NR	NR	NR	NR
Olympia, 2005 [26]	ED	Children	11.9	75/75	55.2	Dexamethasone (oral)	0.6 mg/kg, max. dose 10mg – single dose	47.1	63.0	35.1	41.2
Kinderman, 2005 [29]	Primary care	Adults	33.9	40/39	57.5	Prednisone (oral)	60 mg – single dose (100%) or for 2 days (50%)	51.4	63.2	NR	NR
Bulloch, 2003 [25]	ED	Children	9.7	92/92	46.2	Dexamethasone (oral)	0.6 mg/kg, max. dose 10mg – single dose	48.9	43.5	NR	NR
Ahn, 2003 [24]	ED	Adults	NR	36/36	45.0	Dexamethasone (oral)	5 mg for 2 days	100	100	100	100
Wei, 2002 [23]	ED	Adults	28.1	42/38	39.0	Dexamethasone (oral and IM)	10mg – single dose	100	100	100	100
Marvez-Valls, 1998 [22]	ED	Adults	29.2	46/46	53.26	Betamethasone (IM)	2 mL injection – single dose	100	100	NR	NR
O'Brien, 1994 [21]	ED	Both	26.4	31/27	NR	Dexamethasone (IM)	10 mg – single dose	100	100	NR	NR

ED: Emergency Department; NR: Not Reported.

*Culture-positive or positive test for group A beta-hemolytic streptococcus (GABHS) rapid test.

** Median (IQR: 6 – 12 years

Table 2: Summary of findings

Population: Patients with sore throat
Intervention: Corticosteroids (local or systemic)
Comparator: No corticosteroids

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Summary
		No corticosteroids	Corticosteroids		
Complete Resolution of Pain at 24 hours	**Relative risk: 2.24** (CI 95% 1.17 - 4.29) Based on data from 1049 patients in 5 studies	**100 per 1000**	**224 per 1000**	**Moderate** [1,2,3] Due to inconsistency and imprecision	Corticosteroids probably increase the chance of complete resolution of pain at 24 hours
		Difference: 124 more per 1000 (CI 95% 17 more - 329 more)			
Complete Resolution of Pain at 48 hours	**Relative risk: 1.43** (CI 95% 1.21 - 1.7) Based on data from 1076 patients in 4 studies	**425 per 1000**	**608 per 1000**	**High** [3]	Corticosteroids increase the chance of complete resolution of pain at 48 hours
		Difference: 183 more per 1000 (CI 95% 89 more - 298 more)			
Recurrence/relapse of symptoms	**Relative risk: 0.52** (CI 95% 0.16 - 1.73) Based on data from 372 patients in 3 studies	**65 per 1000**	**34 per 1000**	**Moderate** [3,4,5] Due to serious imprecision	Corticosteroids probably have no important effect on the chance that symptoms recur.
		Difference: 31 fewer per 1000 (CI 95% 55 fewer - 47 more)			
Antibiotics prescription	**Relative risk: 0.83** (CI 95% 0.61 - 1.13) Based on data from 342 patients in 1 studies Follow up: 28 days	**564 per 1000**	**468 per 1000**	**Low** [6] Due to very serious imprecision	Corticosteroids may decrease the chance of taking antibiotics in patients given a prescription with instructions to take the antibiotic if unimproved or worse.
		Difference: 96 fewer per 1000 (CI 95% 220 fewer - 73 more)			
Mean times to onset of pain relief (hours)	Based on data from 907 patients in 8 studies	**12.3 hours (Median)**	**7.4 hours (Mean)**	**Moderate** [3,7,8,9] Due to inconsistency and imprecision	Corticosteroids probably shorten the time until pain starts to improve.
		Difference: MD 4.8 fewer (CI 95% 7.8 fewer - 1.9 fewer)			
Mean time to complete resolution of pain (hours)	Based on data from 720 patients in 6 studies	**44.0 hours (Mean)**	**33.0 hours (Mean)**	**Low** [3,7,8,10] Due to serious imprecision and inconsistency	Corticosteroids may shorten the duration of pain.
		Difference: MD 11.1 fewer (CI 95% 21.8 fewer - 0.4 fewer)			
Pain reduction 24 hours	Scale: High better Based on data from 1247 patients in 8 studies	**3.3 (Mean)**	**4.6 (Mean)**	**Moderate** [3,7,8,11] Due to inconsistency and imprecision	Corticosteroids probably reduce the severity of pain at 24 hours
		Difference: MD 1.3 higher (CI 95% 0.7 higher - 1.9 higher)			
Duration of bad/non-tolerable symptoms	-	-	-	-	There were no studies providing information about this outcome
		Difference: null lower (CI 95% null lower - null lower)			
Days missed from work or school	Based on data from 181 patients in 2 studies Follow-up: up to 14 days.	Two RCTs reported days missed from work/school. In Kinderman et al, 22 out of 40 (55%) patients in the steroids group took time off work and 27 out of 39 (69%) patients in the placebo group took time off work (Relative risk 0.79; 95%		**Moderate** [12,13] Due to serious imprecision and some concerns of risk of bias	Corticosteroids probably have no important effect on the days missed from work or school.

		confidence interval 0.56 to 1.13). Marvez-Valls et al reported the average time patients in each arm missed from work/school. In the intervention group adult patients missed an average of 0.4 (SD: 1.4) days and in the placebo arm patients missed an average of 0.7 (SD: 1.4) days (mean difference 0.30 days, 95% CI -0.28 to 0.88).		
Adverse events	Based on data from 808 patients in 3 studies Follow-up: up to 10 days	One study (Hayward et al.) reported 2 serious adverse events (hospitalizations due to pharyngeal or peritonsillar abscess, tonsillitis, and pneumonia) in the corticosteroids group (0.68%) and 3 in the placebo group (1.06%). In another study (Olympia et al), 1 out of the 57 (1.8%) children in the corticosteroids group and 2 out of the 68 (2.9%) children in the control group developed a peritonsillar abscess. In the same study, 3 out of 57 (5.3%) children in the corticosteroid group and 2 out of 68 (2.9%) of children in the placebo group had to be hospitalized due to dehydration. Finally, another study (Wei et al.) reported that 1 patient who received corticosteroids (3%) had hiccups.	**Moderate**[14]	Corticosteroids probably do not increase the risk of adverse events.

1 Considerable statistical heterogeneity (I^2: 68.8 %). Decided not to rate down, because the clinical inconsistency was deemed as not important, since all the results of included studies have similar clinical implication.

2 The limits of the confidence interval suggest a very small benefit in one extreme, and a patient important benefit in the other. Because the imprecision is linked to the inconsistency, we decided to rate down the certainty of the evidence only by one level.

3 Publication bias was not statistically tested due to small number of studies.

4 Decided not to rate down for risk of bias as one of the three RCTs was judged to be at high risk of bias due to missing participant data.

5 The confidence interval suggests that corticosteroids increase the chance of recurrence of symptoms in now extreme, while it suggests corticosteroids decrease this chance in the other extreme.

6 The confidence interval suggest that corticosteroids could largely reduce the chance of taking antibiotics in one extreme, while it suggest that corticosteroids could slightly increase this chance in the other extreme.

7 Decided not to rate down for risk of bias as equal number of RCTs was judged to be at high and low risk of bias, but the P value for test of interaction showed no difference between the two estimates.

8 There was large unexplained clinical and statistical inconsistency.

9 The confidence interval suggests a very small benefit in one extreme, and a benefit that some patients may consider important in the other extreme. Since this imprecision was a result of the inconsistency, we decided to rate down the certainty of the evidence only by one level.

10 The confidence interval suggests a trivial benefit in one extreme and a benefit that would be considered patient important by most patients in the other extreme.

11 The confidence interval suggests a very small benefit in one extreme and a patient-important benefit in the other. Since this imprecision was related to the inconsistency, we decided to rate down only by one level.

12 One of the studies was at high risk of bias due to concerns with regards to allocate concealment.

13 The studies showed that corticosteroids could increase the days missed from school or work in one extreme, while they could decrease them in the other extreme.

14 The high risk of bias studies showed similar results as the low risk of bias studies; however, there may be a high risk of selective outcome reporting.

Figure legends

Figure 1: Flow diagram for study selection

Figure 2: Forest plot showing relative risk (RR) for complete resolution of pain at 24 hours for corticosteroid vs. placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

Figure 3: Forest plot showing relative risk (RR) for complete resolution of pain at 48 hours for corticosteroid vs. placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

Figure 4: Forest plot showing the weighted mean difference (WMD) in mean time to onset of pain relief (hours) between corticosteroids and placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled mean difference was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

Figure 5: Forest plot showing the weighted mean difference (WMD) in mean time to complete resolution of pain (hours) between corticosteroids and placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled mean difference was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

Figure 6: Forest plot showing the weighted mean difference (WMD) in absolute reduction of pain (0-10, 0 being no pain and 10 maximum pain) between corticosteroids and placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled mean difference was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

References

1. 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. doi: 10.1111/j.1469-0691.2012.03766.x [published Online First: 2012/04/27]
2. Principi N, Bianchini S, Baggi E, et al. No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2013;32(2):151-60. doi: 10.1007/s10096-012-1747-y [published Online First: 2012/09/21]
3. Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics* 2010;126(3):e557-64. doi: 10.1542/peds.2009-2648 [published Online First: 2010/08/11]
4. Herath VC, Carapetis J. Sore throat: Is it such a big deal anymore? *The Journal of infection* 2015;71 Suppl 1:S101-5. doi: 10.1016/j.jinf.2015.04.010 [published Online First: 2015/04/29]
5. Kenealy T. Sore throat. *BMJ clinical evidence* 2011;2011 [published Online First: 2011/04/12]
6. Costelloe C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2010;340:c2096. doi: 10.1136/bmj.c2096 [published Online First: 2010/05/21]
7. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *The Cochrane database of systematic reviews* 2013(11):Cd000023. doi: 10.1002/14651858.CD000023.pub4 [published Online First: 2013/11/06]
8. van Driel ML, De Sutter A, Deveugele M, et al. Are sore throat patients who hope for antibiotics actually asking for pain relief? *Annals of family medicine* 2006;4(6):494-9. doi: 10.1370/afm.609 [published Online First: 2006/12/07]
9. Hayward G, Thompson M, Heneghan C, et al. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2009;339:b2976. doi: 10.1136/bmj.b2976 [published Online First: 2009/08/08]
10. Hayward G, Thompson MJ, Perera R, et al. Corticosteroids as standalone or add-on treatment for sore throat. *The Cochrane database of systematic reviews* 2012;10:Cd008268. doi: 10.1002/14651858.CD008268.pub2 [published Online First: 2012/10/19]
11. Korb K, Scherer M, Chenot JF. Steroids as adjuvant therapy for acute pharyngitis in ambulatory patients: a systematic review. *Annals of family medicine* 2010;8(1):58-63. doi: 10.1370/afm.1038 [published Online First: 2010/01/13]
12. Wing A, Villa-Roel C, Yeh B, et al. Effectiveness of corticosteroid treatment in acute pharyngitis: a systematic review of the literature. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2010;17(5):476-83. doi: 10.1111/j.1553-2712.2010.00723.x [published Online First: 2010/06/12]
13. Siemieniuk RA, Agoritsas T, Macdonald H, et al. Introduction to BMJ Rapid Recommendations. *BMJ (Clinical research ed)* 2016;354:i5191. doi: 10.1136/bmj.i5191 [published Online First: 2016/09/30]
14. Hayward GN, Hay AD, Moore MV, et al. Effect of Oral Dexamethasone Without Immediate Antibiotics vs Placebo on Acute Sore Throat in Adults: A Randomized Clinical Trial. *Jama* 2017;317(15):1535-43. doi: 10.1001/jama.2017.3417 [published Online First: 2017/04/19]
15. Aertgeerts B, Agoritsas T, Siemieniuk RAC, et al. Corticosteroids for sore throat: a clinical practice guideline. *BMJ (Clinical research ed)* 2017; (*submitted for publication*)
16. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi: http://dx.doi.org/10.1136/bmj.d5928

17. Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *Journal of clinical epidemiology* 2012;65(3):262-7. doi: 10.1016/j.jclinepi.2011.04.015 [published Online First: 2011/12/28]
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-26. doi: 10.1136/bmj.39489.470347.AD
19. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326(7382):219.
20. Sterne JA, Sutton AJ, Ioannidis J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
21. O'Brien JF, Meade JL, Falk JL. Dexamethasone as adjuvant therapy for severe acute pharyngitis. *Annals of emergency medicine* 1993;22(2):212-5. [published Online First: 1993/02/01]
22. Marvez-Valls EG, Ernst AA, Gray J, et al. The role of betamethasone in the treatment of acute exudative pharyngitis. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 1998;5(6):567-72. [published Online First: 1998/07/11]
23. Wei JL, Kasperbauer JL, Weaver AL, et al. Efficacy of single-dose dexamethasone as adjuvant therapy for acute pharyngitis. *The Laryngoscope* 2002;112(1):87-93. doi: 10.1097/00005537-200201000-00016 [published Online First: 2002/01/22]
24. Ahn JH, Woo WK, Kim YS, et al. Efficacy of adjuvant short term oral steroid therapy for acute pharyngitis. *Korean Journal of Otolaryngology-Head and Neck Surgery* 2003;46(11):971-74.
25. 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):601-8. doi: 10.1067/mem.2003.136 [published Online First: 2003/04/25]
26. 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):278-82. doi: 10.1001/archpedi.159.3.278 [published Online First: 2005/03/09]
27. Niland ML, Bonsu BK, Nuss KE, et al. 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):477-81. doi: 10.1097/01.inf.0000219469.95772.3f [published Online First: 2006/05/30]
28. Tasar A, Yanturali S, Topacoglu H, et al. Clinical efficacy of dexamethasone for acute exudative pharyngitis. *The Journal of emergency medicine* 2008;35(4):363-7. doi: 10.1016/j.jemermed.2007.11.029 [published Online First: 2008/05/13]
29. Kiderman A, Yaphe J, Bregman J, et 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):218-21. [published Online First: 2005/04/06]
30. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analog pain score for children. *Annals of emergency medicine* 2001;37(1):28-31. doi: 10.1067/mem.2001.111517 [published Online First: 2001/01/06]
31. Alonso-Coello P, Carrasco-Labra A, Brignardello-Petersen R, et al. Systematic reviews experience major limitations in reporting absolute effects. *Journal of clinical epidemiology* 2016;72:16-26. doi: 10.1016/j.jclinepi.2015.11.002 [published Online First: 2015/11/13]
32. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ (Clinical research ed)* 2010;340:c117. doi: 10.1136/bmj.c117 [published Online First: 2010/04/01]
33. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ (Clinical research ed)* 2017;357:j1415. doi: 10.1136/bmj.j1415 [published Online First: 2017/04/14]
34. Fernandes RM, Oleszczuk M, Woods CR, et al. The Cochrane Library and safety of systemic corticosteroids for acute respiratory conditions in children: an overview of reviews. *Evidence-based child health : a Cochrane review journal* 2014;9(3):733-47. doi: 10.1002/ebch.1980 [published Online First: 2014/09/23]

35. Management of sore throat and indications for tonsillectomy, A National Clinical Guideline. Edinburgh, Scotland: Scottish Intercollegiate Guideline Network (SIGN), April, 2010.
36. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012;55(10):1279-82. doi: 10.1093/cid/cis847 [published Online First: 2012/10/24]

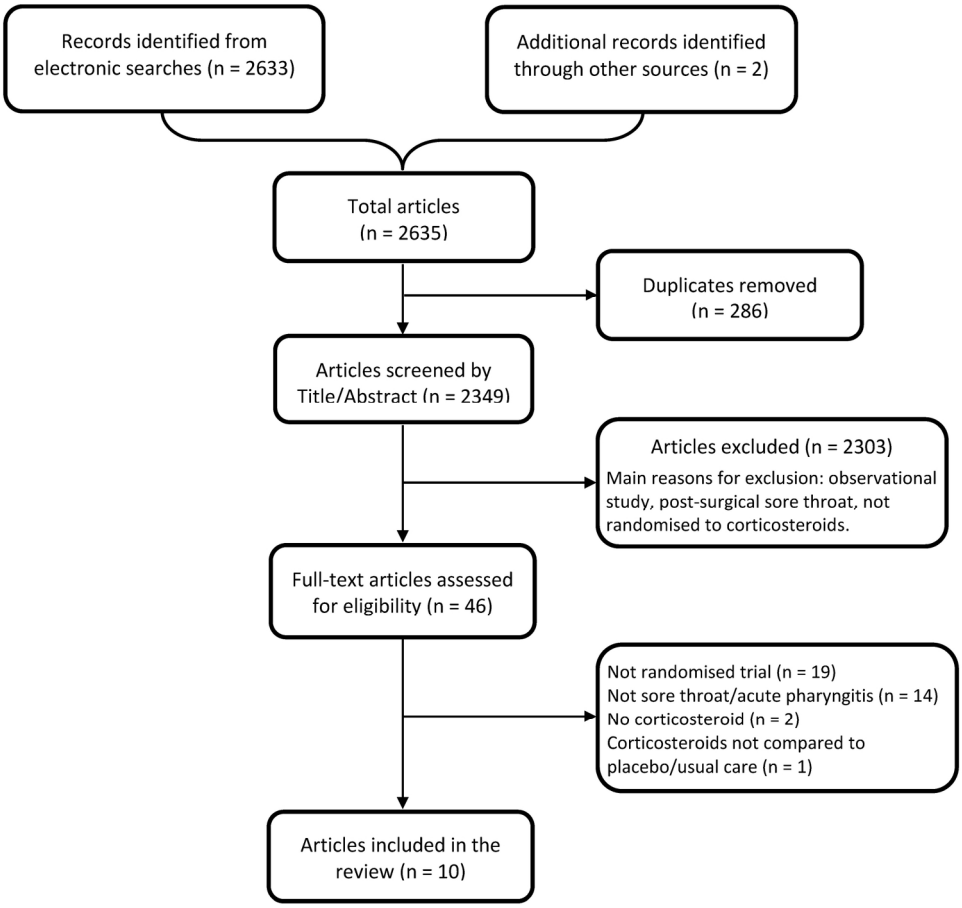


Figure 1: Flow diagram for study selection

171x162mm (300 x 300 DPI)

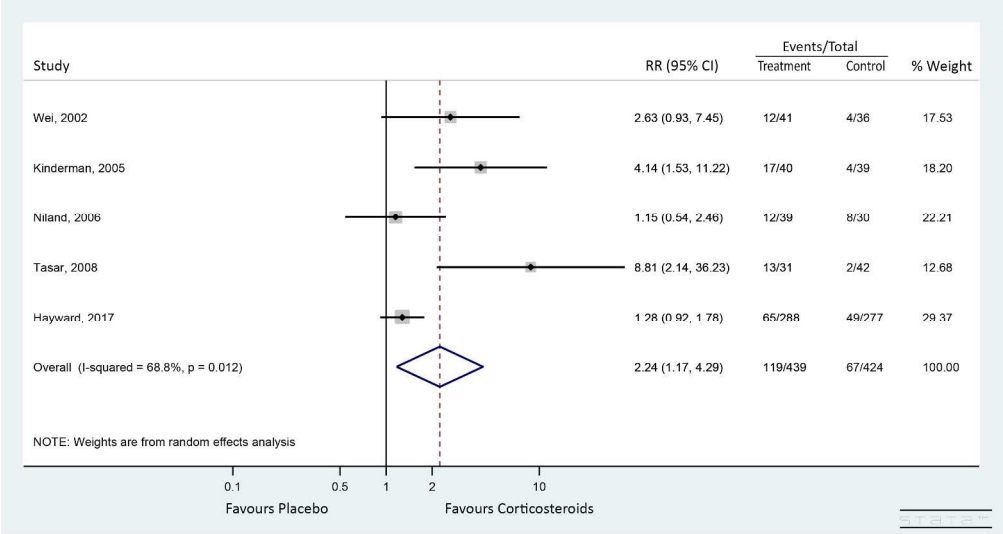


Figure 2: Forest plot showing relative risk (RR) for complete resolution of pain at 24 hours for corticosteroid vs. placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

268x143mm (300 x 300 DPI)

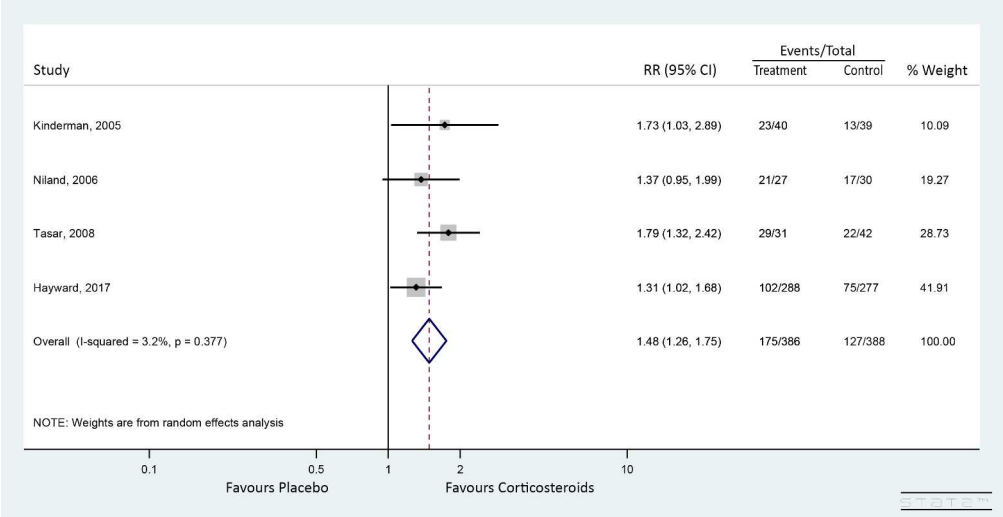


Figure 3: Forest plot showing relative risk (RR) for complete resolution of pain at 48 hours for corticosteroid vs. placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

268x138mm (300 x 300 DPI)

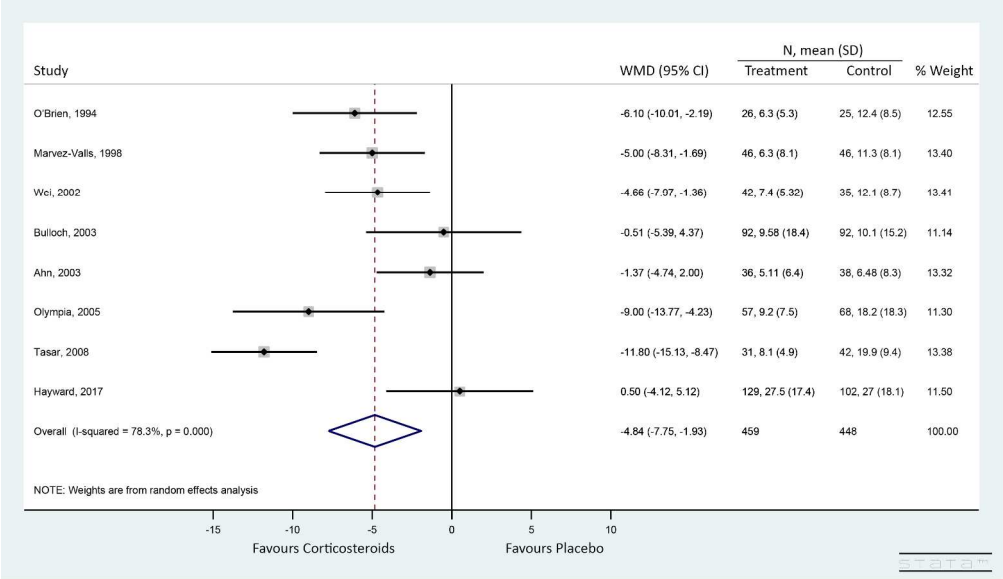


Figure 4: Forest plot showing the weighted mean difference (WMD) in mean time to onset of pain relief (hours) between corticosteroids and placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled mean difference was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

269x155mm (300 x 300 DPI)

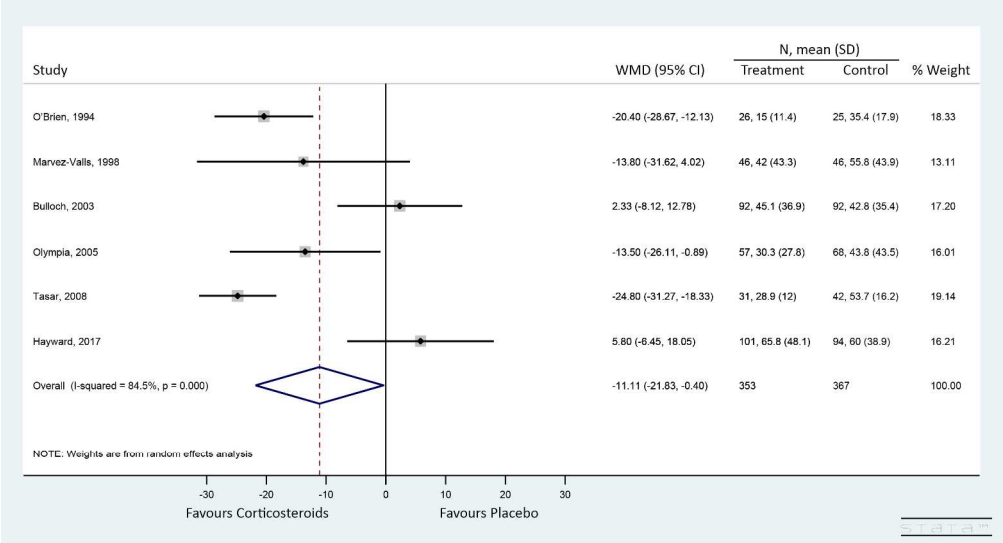


Figure 5: Forest plot showing the weighted mean difference (WMD) in mean time to complete resolution of pain (hours) between corticosteroids and placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled mean difference was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

268x145mm (300 x 300 DPI)

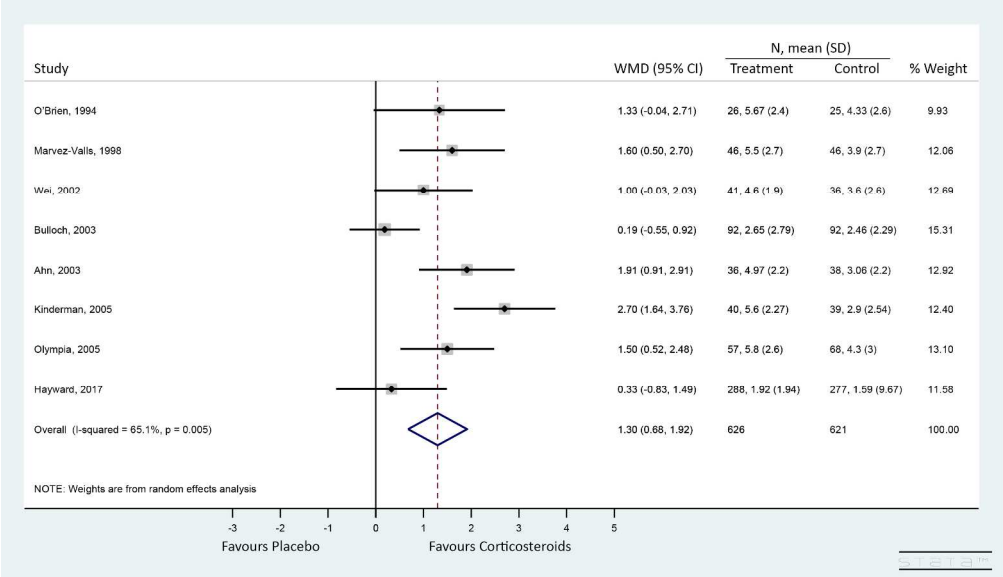


Figure 6: Forest plot showing the weighted mean difference (WMD) in absolute reduction of pain at 24 hours (0-10, 0 being no pain and 10 maximum pain) between corticosteroids and placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled mean difference was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

269x155mm (300 x 300 DPI)

Appendices

Appendix 1: search terms and strategies

MEDLINE and CENTRAL search strategy, EMBASE search strategy

MEDLINE (OVID)

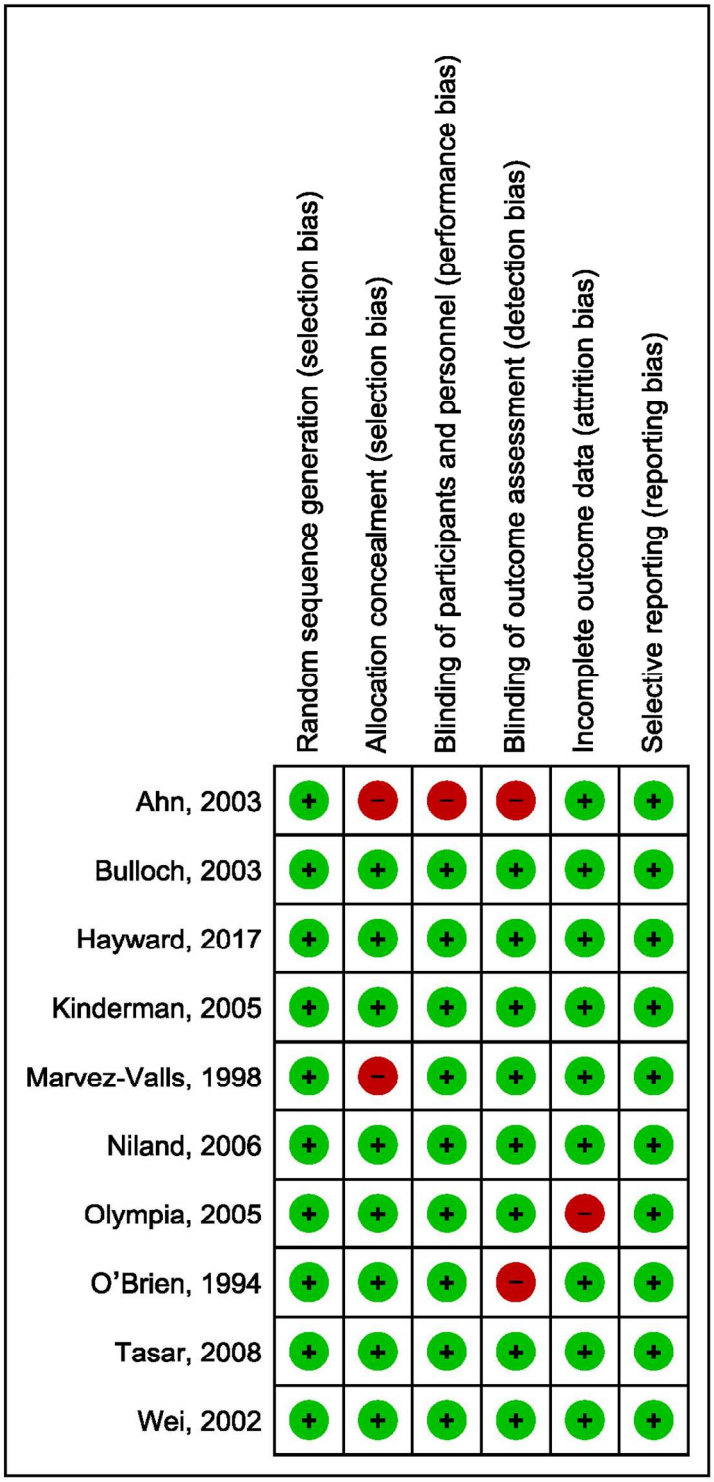
1. exp Tonsillitis/
2. tonsillit*.tw.
3. exp Pharyngitis/
4. pharyngit*.tw.
5. exp Laryngitis/
6. laryngit*.tw.
7. pharyngotonsillit*.tw.
8. nasopharyngit*.tw.
9. rhinopharyngit*.tw.
10. (throat* adj3 (sore or inflam* or infect*)).tw.
11. exp Streptococcus/
12. Streptococcal Infections/
13. (streptococc* or gabhs).tw.
14. ("s. pyogenes" or "s pyogenes").tw.
15. ("s. pneumoniae" or "s pneumoniae").tw.
16. or/1-15
17. steroid*.tw,nm.
18. corticosteroid*.tw,nm.
19. exp Glucocorticoids/
20. glucocorticoid*.tw,nm.
21. exp Hydroxycorticosteroids/
22. hydroxycorticosteroid*.tw,nm.
23. exp Pregnenediones/
24. hydrocortisone.tw,nm.
25. hydroxypregnenolone.tw,nm.
26. pregnenolone.tw,nm.
27. tetrahydrocortisol.tw,nm.
28. cortodoxone.tw,nm.
29. cortisone.tw,nm.
30. corticosterone.tw,nm.
31. triamcinolone.tw,nm.
32. prednisone.tw,nm.
33. prednisolone.tw.
34. paramethasone.tw,nm.
35. methylprednisolone.tw,nm.

36. dexamethasone.tw,nm.
37. clobetasol.tw,nm.
38. beclomethasone.tw,nm.
39. betamethasone.tw,nm.
40. budesonide.tw,nm.
41. (efcortesol or hydrocortone or solu-cortef).tw,nm.
42. (betnelan or betnesol).tw,nm.
43. (medrone or solu-medrone or depo-medrone).tw,nm.
44. kenalog.tw,nm.
45. (novolizer or pulmicort or symbicort).tw,nm.
46. (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm.
47. (deflazacort or calcort).tw,nm.
48. or/17-47
49. clinical trial.mp. or clinical trial.pt. or random*.mp. or tu.xs.
50. 16 and 48 and 49
51. limit 50 to ed=20100101-20171231

EMBASE (OVID)

1. exp tonsillitis/
2. tonsillit*.tw.
3. exp pharyngitis/
4. pharyngit*.tw.
5. exp laryngitis/
6. laryngit*.tw.
7. pharyngotonsillit*.tw.
8. nasopharyngit*.tw.
9. rhinopharyngit*.tw.
10. (throat* adj3 (sore or inflam* or infect*)).tw.
11. exp streptococcus/
12. exp streptococcus infection/
13. (streptococc* or gabhs).tw.
14. ("s. pyogenes" or "s pyogenes").tw.
15. ("s. pneumoniae" or "s pneumoniae").tw.
16. or/1-15
17. steroid*.tw,nm.
18. corticosteroid*.tw,nm.
19. exp glucocorticoid/

20. glucocorticoid*.tw,nm.
21. exp hydroxycorticosteroid/
22. hydroxycorticosteroid*.tw,nm.
23. exp pregnane derivative/
24. hydrocortisone.tw,nm.
25. hydroxypregnenolone.tw,nm.
26. pregnenolone.tw,nm.
27. tetrahydrocortisol.tw,nm.
28. cortodoxone.tw,nm.
29. cortisone.tw,nm.
30. corticosterone.tw,nm.
31. triamcinolone.tw,nm.
32. prednisone.tw,nm.
33. prednisolone.tw.
34. paramethasone.tw,nm.
35. methylprednisolone.tw,nm.
36. dexamethasone.tw,nm.
37. clobetasol.tw,nm.
38. beclomethasone.tw,nm.
39. betamethasone.tw,nm.
40. budesonide.tw,nm.
41. (efcortesol or hydrocortone or solu-cortef).tw,nm.
42. (betnelan or betnesol).tw,nm.
43. (medrone or solu-medrone or depo-medrone).tw,nm.
44. kenalog.tw,nm.
45. (novolizer or pulmicort or symbicort).tw,nm.
46. (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm.
47. (deflazacort or calcort).tw,nm.
48. or/17-47
49. random*.tw. OR placebo*.mp. OR double-blind*.tw.
50. 16 and 48 and 49
51. limit 50 to dd=20100101-20171231



Appendix 2: summary of risk of bias assessments among the included RCTs.

Appendix 3: Results of the meta-analysis and subgroup analysis of RCTs assessing the effects of single-dose corticosteroids on complete resolution of pain at 24 and 48 hours, and relapse of the symptoms

Outcome/subgroups		No. of trials	RR	95% CI		No. of participants		I^2	P value for interaction
				Lower	Upper	Intervention	Control		
Complete resolution of pain at 24 hours**	Adults	4	2.9	1.2	6.9	507	453	75.2	0.261
	Children	1	1.2	0.5	2.5	51	38	-	
	Intramuscular	2	4.6	1.6	13.0	96	84	33.0	0.335
	Oral	4	1.7	1.0	3.0	514	473	54.1	
	Primary care	2	2.1	0.7	6.6	410	369	79.6	0.815
	ED	3	2.7	0.9	8.1	148	122	71.2	
	Total	**5**	**2.2**	**1.2**	**4.3**	**558**	**491**	**69.0**	**-**
Complete resolution of pain at 48 hours**	Adults	3	1.5	1.2	1.9	513	468	33.0	0.853
	Children	1	1.4	0.95	1.99	48	47	-	
	Intramuscular	1	1.8	1.3	2.4	60	64	-	0.188
	Oral	3	1.4	1.1	1.7	501	451	0.0	
	Primary care	2	1.4	1.1	1.7	453	404	0.0	0.405
	ED	2	1.6	1.2	2.1	108	111	13.9	
	Total	**4**	**1.5**	**1.3**	**1.8**	**561**	**515**	**3.2**	**-**
Relapse of the symptoms	Adults	1	0.2	0.0	2.0	41	44	-	***
	Children	2	0.5	0.2	1.7	199	173	22.8	
	Low risk of bias	2	0.5	0.2	1.7	199	173	22.8	***
	High risk of bias	1	0.2	0.0	4.0	60	31	-	
	Total	**3**	**0.5**	**0.2**	**1.7**	**199**	**173**	**22.8**	**-**

ED: emergency department; RR: relative risk;

*Culture-positive or positive test for group A beta-hemolytic streptococcus (GABHS) rapid test.

** All RCTs for this outcome were at low risk of bias.

*** Due to small number of trials, we did not perform a statistical test of interaction between the two group.

Appendix 4: Results of the meta-analysis and subgroup analysis of RCTs assessing the effects of single-dose corticosteroids on mean time to onset of pain relief and to complete resolution of pain, and absolute pain reduction score (at 24 hours)

		No. of trials	Mean difference	95% CI		No. of participants		I^2	P value for interaction
				Lower	Upper	Intervention	Control		
Mean time to onset of pain relief	Adults	6	-4.9	-8.2	-1.5	310	288	81.0	0.986
	Children	2	-4.8	-13.1	3.6	149	160	83.2	
	Intramuscular	4	-7.0	-10.3	-3.6	456	448	73.0	0.090
	Oral	5	-3.0	-6.1	-0.1	459	448	64.2	
	Primary care	1	0.5	-4/1	5.1	129	102	-	**
	ED	7	-5.5	-8.5	-2.6	330	346	77.0	
	Pathogen positive*	4	-5.6	-8.0	-3.2	122	128	0.0	0.651
	Pathogen negative	4	-4.1	-10.0	1.8	147	105	66.6	
	Low risk of bias	4	-4.8	-7.8	-1.9	459	448	78.3	0.810
	High risk of bias	4	-5.1	-8.1	-2.1	165	177	59.5	
	Total	**8**	**-4.8**	**-7.8**	**-1.9**	**459**	**448**	**78.3**	**-**
Mean time to complete resolution of pain	Adults	4	-14.1	-26.8	-1.3	204	207	84.4	0.613
	Children	2	-5.2	-20.7	10.3	149	160	72.1	
	Intramuscular	3	-22.4	-27.3	-17.5	103	113	0.0	0.001
	Oral	3	-1.5	-12.6	9.5	250	254	62.6	
	Primary care	1	5.8	-6.5	18.1	101	94	-	0.281
	ED	5	-14.5	-24.6	-4.5	252	273	79.7	
	Pathogen positive*	3	-7.5	-22.3	7.2	92	112	59.7	0.886
	Pathogen negative	3	-9.6	-34.1	14.8	96	86	69.8	
	Low risk of bias	3	-6.0	-27.4	15.4	224	228	93.3	0.302
	High risk of bias	3	-17.7	-24.2	-11.3	129	139	0.0	
	Total	**6**	**-11.1**	**-21.8**	**-0.4**	**353**	**367**	**84.5**	**-**
Absolute pain reduction (at 24 hours)	Adults	6	1.5	0.9	2.2	477	461	52.1	0.322
	Children	2	0.8	-0.5	2.1	149	160	77.3	
	Intramuscular	3	1.5	0.8	2.2	624	621	0.0	0.695
	Oral	6	1.3	0.5	2.0	626	621	74.3	
	Primary care	2	1.5	-0.8	3.9	328	316	88.5	0.781
	ED	6	1.2	0.6	1.8	298	305	49.9	
	Pathogen positive*	3	1.2	-0.2	2.6	92	112	75.9	0.926
	Pathogen negative	3	1.3	-1.3	3.9	96	86	84.0	
	Low risk of bias	4	1.0	-0.1	2.2	461	444	-	0.353
	High risk of bias	4	1.6	1.1	2.2	165	177	80.8	
	Total	**8**	**1.3**	**0.7**	**1.9**	**626**	**621**	**65.1**	**-**

ED: emergency department; RR: relative risk;

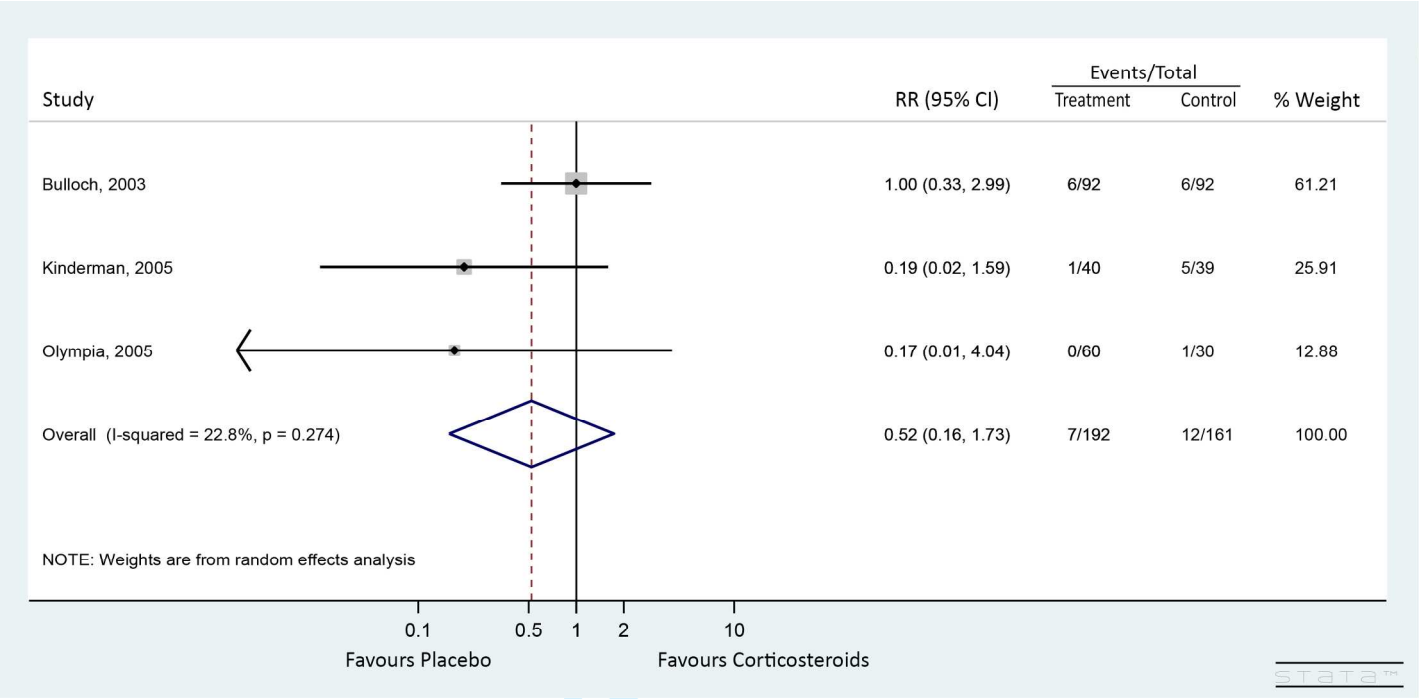
*Culture-positive or positive test for group A beta-hemolytic streptococcus (GABHS) rapid test.

** Due to small number of trials in one subgroup, we did not perform a statistical test of interaction between the two group.

Appendix 5: point estimates for outcomes across included articles to investigate selective outcome reporting

study	Pain at 24 hours	Pain at 48 hours	Time to onset of pain relief	Time to complete resolution of pain	Absolute Pain Reduction	Relapse of symptoms
	RR	RR	MD	MD	MD	RR
O'Brien, 1994	-	-	-6.1	-20.4	1.3	-
Marvez-Valls, 1998	-	-	-5.0	-13.8	1.6	-
Wei, 2002	2.6	-	-4.7	-	1.0	-
Bulloch, 2003	-	-	-0.5	2.3	0.2	1.0
Ahn, 2003	-	-	-1.4	-	1.9	-
Kinderman, 2005	4.1	1.7	-	-	2.7	0.2
Olympia, 2005	-	-	-9.0	-13.5	1.5	0.2
Niland, 2006	1.2	1.4	-	-	-	-
Tasar, 2008	8.8	1.8	-11.8	-24.8	-	-
Hayward, 2017	1.3	1.3	0.5	5.8	0.3	-

RR: relative risk; MD: mean difference



Appendix 6: Forest plot showing relative risk (RR) for relapse/recurrence of symptoms for corticosteroid vs. placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centred on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian–Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (centre line of diamond, dashed line). The solid vertical line is the line of no effect.

Corticosteroids for sore throat: a clinical practice guideline

Journal:	*BMJ*
Manuscript ID	Draft
Article Type:	Practice
BMJ Journal:	BMJ
Date Submitted by the Author:	n/a
Complete List of Authors:	Aertgeerts, Bert; Katholieke Universiteit Leuven, Public Health and Primary Care Agoritsas, Thomas; McMaster University, Department of Clinical Epidemiology and Biostatistics; University Hospitals of Geneva, Division of General Internal Medicine & Division of Epidemiology Siemieniuk, Reed; McMaster University, Clinical Epidemiology & Biostatistics; University of Toronto, Medicine Burgers, Jako; Dutch College of General Practitioners, guideline development and research Bekkering, Geertruida; Academic Centre for General Practice, Department of Public Health and Primary Care, KU Leuven Merglen, Arnaud; University Hospitals of Geneva, Departments of Child and Adolescent Medicine van Driel, Mieke; The University of Queensland, School of Medicine, Discipline of General Practice Vermandere, Mieke; Academic Centre for General Practice, Department of Public Health and Primary Care, KU Bullens, Dominique; Pediatric Immunology, Department of microbiology and immunology, KU Okwen, Patrick; Bali District Hospital Niño, Ricardo; Head and Neck Surgery. Clinica del Country Van den Bruel, Ann; University of Oxford, Department of Primary Care Health Sciences Lytvyn, Lyubov; Universitetet i Oslo Det medisinske fakultet, Institute of Health and Society Berg-Nelson, Carla; The Society for Participatory Medicine; Arizona Senior Academy Chua, Shunjie; Ministry of Health Holdings Pte Ltd Leahy, Jack; UK Cochrane Centre Raven, Jennifer; Cochrane Consumers Group Weinberg, Michael; - Sadeghirad, Behnam ; Kerman University of Medical Sciences, Research Center for Modeling in Health, Institute for Futures Studies in Health Vandvik, Per; Innlandet Hospital Trust-divisjon Gjøvik, Department of Medicine Brignardello-Petersen, Romina; McMaster University,

Keywords:	

Corticosteroids for sore throat: a clinical practice guideline

Bert Aertgeerts, *general practitioner, professor*[1,2]; Thomas Agoritsas, *general internist, assistant professor*[3,4]; Reed A.C. Siemieniuk, *general internist, methodologist*[3,5]; Jako Burgers, *general practitioner, professor*;[6,7] Geertruida E. Bekkering, *methodologist*[1,2]; Arnaud Merglen, *pediatrician*[8]; Mieke van Driel, *general practitioner, professor*[9]; Mieke Vermandere, *general practitioner*[1]; Dominique Bullens, *paediatrician, professor*[10,11]; Patrick Mbah Okwen, *general practitioner*[12]; Ricardo Niño, *otorhinolaryngologist*[13]; Ann van den Bruel, *general practitioner, associate professor*[14,15]; Lyubov Lytvyn, *patient liaison expert*[16]; Carla Berg-Nelson, *patient representative*[17,18]; Shunjie Chua, *patient representative*[19]; Jack Leahy, *patient representative*[20]; Jennifer Raven, *patient representative*[21]; Michael Weinberg, *patient representative*[22]; Behnam Sadeghirad, *methodologist*[3,23]; Per O. Vandvik, *general internist, associate professor*[15,24]; Romina Brignardello-Petersen, *methodologist and biostatistician*[2,25]

[1]Academic Centre for General Practice, Department of Public Health and Primary Care, KU Leuven
[2] CEBAM, Belgian Centre for Evidence-Based Medicine, Cochrane Belgium.
[3] Department of Health Research Methods, Evidence, and Impact, McMaster University, 1280 Main St West, Hamilton, Ontario, Canada L8S 4L8
[4] Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, CH-1211, Geneva, Switzerland
[5] Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[6] Dutch College of General Practitioners, Utrecht, The Netherlands
[7] School CAPHRI, Department Family Medicine, Maastricht, The Netherlands
[8] Division of General Pediatrics, University Hospitals of Geneva & Faculty of Medicine, University of Geneva, Geneva, Switzerland
[9] Primary Care Clinical Unit, Faculty of Medicine, University of Queensland, Brisbane, Australia
[10] Pediatric Immunology, Department of microbiology and immunology, KU Leuven
[11] Pediatric allergy, Clinical division of pediatrics UZ Leuven, Leuven Belgium
[12] Bali District Hospital, Bali and Centre for Development of Best practices in Health Yaounde, Cameroon
[13] Otorhinolaryngology - Head and Neck Surgery. Clinica del Country. Bogota-Colombia
[14] NIHR Oxford Diagnostic Evidence Cooperative, Oxford, UK
[15] Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[16] Oslo University Hospital, Forskningsveien 2b, Postboks 1089, Blindern 0317 Oslo, Norway
[17] The Society for Participatory Medicine
[18] Arizona Senior Academy, United States of America
[19] MOH Holdings, 1 Maritime Square, Singapore, Singapore 099253
[20] Cochrane UK, London UK
[21] Cochrane Consumers Group, Halifax, Canada
[22] Washington DC, USA
[23] HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

[24] Department of Medicine, Innlandet Hospital Trust - division Gjøvik, Norway
[25] Faculty of Dentistry, Universidad de Chile

Correspondence:
Bert Aertgeerts, MD, PhD
Kapucijnenvoer 33, Blok J, P7001, 3000 Leuven, Belgium.
Email: bert.aertgeerts@kuleuven.be

(MAIN INFOGRAPHIC - including the recommendation and summary of findings**)**

What is the role of a single dose of oral corticosteroids for those with acute sore throat? An expert panel make a weak recommendation in favour of corticosteroid use. The panel produced these recommendations based on a linked systematic review triggered by a large randomised trial published in April 2017.[1] This trial reported that corticosteroids increased the proportion of patients with complete resolution of pain at 48 hours. Box 1 shows all of the articles and evidence linked in this Rapid Recommendation package. The infographic provides the recommendation together with an overview of the absolute benefits and harms of corticosteroids in the standard GRADE format. Table 2 below shows any evidence that has emerged since the publication of this article. Clinicians and their patients can find consultation decision aids to facilitate shared decision-making in MAGICapp. (https://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn)

What you need to know:

- Sore throat is one of the most common reasons for visiting a primary care physician.
- We make a weak recommendation to use a single dose of oral corticosteroids, in addition to standard care, for patients suffering from acute sore throat.
- This rapid recommendation package was triggered by a trial published in JAMA in April 2017, and a linked systematic review.
- Further research is not likely to alter this recommendation.
- The recommendation is weak because the importance that patients place in reducing pain severity and duration varies widely. Shared decision-making is appropriate to help patients make choices in line with their values.

Box 1. Linked articles in this BMJ Rapid Recommendations cluster

- Sadeghirad B, Siemieniuk RA, Brignardello-Petersen R, et al. Corticosteroids for treatment of sore throat: a systematic review and meta-analysis of randomized trials. BMJ 2017;xxx:xxx[2]
  - Review of all available randomised trials that assessed corticosteroids as adjunct treatment versus standard care for sore throat.
- MAGICapp (https://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Box 2. Education in practice

- How do you currently approach giving advice for those with acute sore throat? Do you consider offering corticosteroid use?
- The recommendation for corticosteroid use is weak, and patient's preferences are likely to vary as to whether they want to take up the offer. What information could you share with your patient to help them reach a decision together?
- Acute sore throat is common in many clinical settings. How might you share this information with colleagues to learn together?
- Having read the article, can you think of one thing you have learned which might alter how you consult with patients with sore throat?
- How often do you practice shared decision-making for such preference-sensitive decisions?

Current practice

Acute sore throat is defined as pain in the throat for less than 14 days. Acute sore throat could be caused by pharyngitis, nasopharyngitis, tonsillitis, peritonsillar abscess, or retropharyngeal abscess. Some patients with sore throat also suffer from headache, fever, muscle stiffness, cough, and general malaise.

Acute sore throat is very common, but only a minority of patients will visit their general practitioner (GP).[3] A survey reported that the main reasons are to establish the cause of the symptoms, obtain pain relief, and to gain information on the course of the disease.[4] Data from Dutch and Flemish primary care databases show that for every 1000 consecutive patients consulting a GP, 50 present with an acute sore throat[5 6]. In the US, more than 92 million visits by adults to primary care practices and emergency departments between 1997 and 2010 were recorded.[7] Sore throat presenting as acute tonsillitis is also the commonest cause for emergency admission to ENT services in US.[8]

Acute sore throat is a self-limiting disease, and typically resolves after 7 to 10 days in adults and 2 to 7 days in children.[9] Most infections are of viral origin; only a few are caused by a bacterial infection, of which group A beta-hemolytic streptococcus, sometimes Haemophilus Influenzae or Moraxella catarrhalis, are the most common pathogens. Evidence suggests that the time to resolution is not associated with the type of pathogen.[9] About 2% of patients initially presenting with sore throat will have a mononucleosis infection caused by an Epstein-Barr virus, which could prolong the duration of symptoms.[10]

Some patients experience unacceptable morbidity, inconvenience, and miss school or work due to recurrent sore throat.[11] Pain is a frequent reason for work or school absence. Complications of sore throat are rare: about 0.2% of patients with tonsillitis will develop a peritonsillar abscess.[12]

The diagnosis of an acute sore throat is based on signs and symptoms. The Centor clinical prediction rules can be used to help predict whether the sore throat is caused by a bacterial pathogen, and thus can influence the decision to prescribe an antibiotic or not.[13 14]

Most guidelines recommend paracetamol or ibuprofen as the first-choice treatment.[15] The use of steroids is mentioned in few, and generally discouraged (Table 1). Antibiotics are probably not helpful for pain relief in an episode of acute sore throat caused by viruses, but may help those with a bacterial infection.[16 17] Recommended management of sore throat vary widely. Table 1 summarizes current guidelines for the treatment of acute sore throat.

Table 1. Current guidance for treatment in patients with sore throat

	Ibuprofen	Paracetamol	Antibiotics	Steroids for adults	Steroids for children
EBM guidelines[13]	Supportive	Supportive	Conditionally	Supportive	No
SIGN[8]	Supportive	supportive	Conditionally	Not supportive	No comment
NHG[14]	Supportive	Supportive	Conditionally	Not recommended	No comment
BC guidelines[15]	No comment	No comment	Against	No comment	No comment
UpToDate[16]	Against	No comment	No comment	Supportive	No comment

How the recommendation was created

A large randomised controlled trial published in April 2017[1] found that corticosteroids increased the proportion of patients with complete resolution of symptoms at 48 hours. However, corticosteroids did not appear to decrease the duration of moderately bad symptoms, pain severity, health care attendance, days missed from school or work, or the consumption of delayed antibiotics. This study adds to the body of evidence that suggests that, although corticosteroids probably have benefits in patients with sore throat, these benefits may be modest.[18-21] The Rapid Recommendations team felt that the study, when considered in context of the full body of evidence, might change practice.[22]

Our international panel, including general practitioners, general internists, paediatricians, an otorhinolaryngologist, epidemiologists, methodologists, statisticians, and people with lived experience of sore throat, decided what was the scope of the recommendation and the outcomes that are most important to patients. After a parallel team conducted a systematic review on the benefits and harms of corticosteroids,[2] and a systematic search for evidence about patient's values and preferences (Web Appendix 1), the panel met to discuss the evidence and formulate a recommendation. No person had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (Web Appendix 2).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation[22 23], including using the GRADE approach to critically appraise the evidence and create recommendations (Web Appendix 3).[24] The panel considered the balance of benefits, harms, and burdens of the drug, the quality of the evidence for each outcome, typical and expected variations in patient values and preferences, and acceptability.[25] Recommendations can be strong or weak, for or against a course of action.

The Evidence

The linked systematic review reports the effects of corticosteroids when added to standard care in patients with acute sore throat.[2]

Infographic 2 gives an overview of the number and types of patients included, the study funding, and patient involvement, as well as a summary of the benefits and harms of corticosteroids for treating acute sore throat.

The panel identified 8 patient-important outcomes needed to inform the recommendation: complete resolution of pain, time to onset of pain relief, pain severity, need for antibiotics, days missed from school or work, recurrence of symptoms, duration of bad or non-tolerable symptoms, and adverse effects. The included studies reported on all patient-important outcomes, except for duration of bad or non-tolerable symptoms. Regarding pain, the panel appraised the likelihood of complete resolution of pain at 24 hours and 48 hours, as well as the mean time to complete resolution of pain, and the mean time to onset of pain relief.

Since the randomised controlled trials focused on patients who did not have recurrent episodes of sore throat, the panel was less confident of the applicability of the evidence to such patients, and the recommendation therefore does not apply to them. Similarly, the panel did not consider patients with sore throat following surgery or intubation, nor patients with immunocompromising conditions.

Infographic 2: Randomised trial characteristics.

Included evidence from 10 randomised clinical trials that enrolled approximately 1500 patients		
	Mean of means	Range of means across trials
Number of patients enrolled	153	58 - 576
Age (mean years at baseline)	25.6	9.7 - 34.0
Sex (% women)	57.0	37.6 – 75.2
Streptococcus positive (% of patients)	51.3	14.9 – 100
Antibiotic prescription (% of patients)	77.5	39.5 – 100
Analgesic use (% of patients)	83.2	38.1- 100
Type of steroid	80% of trials studied dexamethasone (75% oral, 25% intramuscular), 10% studied prednisone, and 10% betamethasone	
Setting	80% of trials were conducted in emergency departments and 20% in primary care practices	
Exclusion criteria	Hospitalised or immunocompromised patients, and those who have infectious mononucleosis, sore throat following surgery or intubation (post-operative sore throat), gastroesophageal reflux disease, croup, or peritonsillar abscess	
Funding	80% of trials did not report the source of funding and 20% of trials reported non-industry funding	

Patient involvement	No trials involved patients in design or conduct

Understanding the recommendation

The panel is confident that the recommendation applies to almost all patients with acute sore throat; children and adults, severe and not severe sore throat, patients who receive immediate antibiotics and those who receive deferred antibiotics, and patients who seek care in the emergency department as well as those who attend a primary care practice. The systematic review contained adequate representation from such groups and settings, and results were consistent (i.e. absence of credible subgroup effects) for example between trials of children and adults, and those seen in emergency departments and in primary care offices.[2]

Absolute benefits and harms

The first infographic explains the recommendation and provides an overview (GRADE Summary of Findings) of the absolute benefits and harms of corticosteroids. Estimates of baseline risk for effects come from the control arms of the trials.[2]

The panel was confident that:

- Corticosteroids increase the chance of complete resolution of pain at 24 and 48 hours, reduce the severity of pain, and shorten the time to onset of pain relief (GRADE high to moderate quality evidence).
- Corticosteroids are unlikely to reduce recurrence or relapse of symptoms, or days missed from school or work (GRADE moderate quality evidence).
- A single dose of corticosteroids is unlikely to cause serious adverse events.
    - The randomised trials did not report any major event attributable to steroids (GRADE moderate quality evidence).
    - The panel also considered evidence from observational studies that used higher doses of steroids. A large retrospective US cohort study of private insurance claims assessed adverse events in 327,452 adults who received an outpatient prescription of steroids.[26] There was a small absolute increase in the rate of sepsis, venous thromboembolism, and fracture in the first 30 days (GRADE low quality of the evidence, due to suboptimal verification of diagnosis in large databases, and confounding by indication[26]). The panel agreed that such events seemed unlikely with only one-dose steroids.
    - Similarly, among pediatric populations, indirect evidence from a meta-analysis of 44 randomised trials did not report any major adverse events in patients with conditions requiring very short course of steroids (e.g. asthma, bronchiolitis, croup, wheeze and pharyngitis/tonsillitis).[27]
- It is unlikely that new information will change interpretation for outcomes that are high to moderate quality of evidence.

The panel was less confident about whether:

- Corticosteroids reduced antibiotic use, due to a lack of improvement or worsening of symptoms in patients not prescribed antibiotics immediately when consulting the physician (GRADE low quality evidence)
- Corticosteroids reduced the average time to complete resolution of pain (GRADE low quality evidence).

Values and Preferences

The weak recommendation for corticosteroids reflects a high value on a modest reduction of symptom severity and the time that it takes to achieve such improvement, and a substantial and important increase in the chance of complete resolution of pain at 48 hours. The panel, including the patient representatives, felt that the values and preferences are likely to vary greatly across patients, which justifies a weak recommendation. For example, achieving complete pain resolution 12 hours earlier may be of little importance for patients who feel less busy in their daily life, have higher tolerance to pain, or whose symptoms are not so severe; whereas it may be very important to patients whose ability to go to school or to perform at work are compromised, caregivers wishing to reduce their children's pain, or patients experiencing their pain as severe.

The panel believes that there is great variability in how much reduction in pain severity or time to complete pain resolution each patient would consider important. However, the greater the reduction in hours to achieve complete resolution of pain, the more likely it is that typical patients would place high value on those outcomes. Patients who place a high value in reducing the symptoms by any amount (eg. patients with lower tolerance to pain or those with severe symptoms) are more likely to accept receiving corticosteroids.

The weak recommendation for corticosteroids also reflects the concerns that the panel had with acceptability. Specifically, treating a condition that is usually not severe and is self-limiting with a drug that many patients, practitioners, and other stakeholders know is almost always used for more severe diseases.

The systematic search for empirical data on patients' values and preferences related to sore throat did not identify unique information that was relevant for the recommendation (Web Appendix 1).

Practical issues and other considerations

Infographic 3 outlines the key practical issues for patients and clinicians discussing adjunct steroids for sore throat, which are also accessible along with the evidence as decision aids to support shared decision-making in MAGICapp. Steroids are typically given as 10 mg dexamethasone (or adapted to weight for children: 0.6 mg/kg, up to a maximum dose of 10mg), typically taken as pill or intramuscular injection.

The risks may outweigh the benefits when larger cumulative doses of corticosteroids are given to patients who experience multiple episodes of sore throat, either through multiple visits or for patients who self-medicate if prescribed more than one pill for their previous episode. To mitigate this issue, clinicians should administer the medication in office if possible, or prescribe only one dose per visit.

INFOGRAPHIC 3: Practical issues

PRACTICAL ISSUE	Steroids	Both steroids and no steroids
MEDICATION ROUTINE	One (or two) doses of steroids, taken as pill(s) or intramuscular injection(s).	May require concomitant antibiotics, and or over the counter pain relievers.
TESTS & VISITS		May need additional visits if symptoms do not resolve or worsen.
ADVERSE EFFECTS	Serious adverse events are unlikely with one-dose steroids. There may be risks with repeated doses across multiple episodes of sore throat, or through self-medication.	
EMOTIONAL WELL-BEING	May cause transient sleep disturbance and excitability, although infrequently with one-dose steroids.	
PREGNANCY & NURSING	Dexamethasone crosses the placenta, and is generally avoided during pregnancy. There is, however, probably no risk of malformation.	
COSTS & ACCESS	Inexpensive, available by prescription.	
FOOD & DRINKS	May increase appetite, particularly in children.	

Costs and resources

The panel focused on the patient-perspective rather than that of society when formulating the recommendation. Given the low cost of corticosteroids for treating sore throat, implementation of this recommendation is unlikely to have an important impact on the costs for health funders, although it remains uncertain whether it may increase the proportion of patients visiting a doctor to get a prescription of corticosteroids.

Uncertainties for future research

Key research questions to inform decision makers and future guidelines include:

- Are there any severe adverse effects of using one-dose of steroids for treating sore throat?
- What are the effects of corticosteroids, in addition to standard care, in patients with recurrent episodes of acute sore throat?

Box. How patients were involved in the creation of this article:

Five people with lived experience of sore throat were full panel members. These panel members identified important outcomes, and led the discussion on values and preferences. These patient representatives agreed that while small reductions in pain severity and time to complete pain resolution (for example 12 compared to 24 hours) were important to them, these values may not be shared by all patients; they expected moderate to great variability in how much importance other patients would place in small reductions in pain. These panel members participated in the teleconferences and email discussions and met all authorship criteria.

Table 2 New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article				

Footnote

This *BMJ Rapid Recommendation* article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicproject.org) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats.

Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualization of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

Acknowledgements

Data supplements on bmj.com

Appendix 1: Results of the search for evidence about patients values and preferences
Appendix 2: Full list of authors' declarations of interests
Appendix 3: Methodology for development of *BMJ* Rapid Recommendations
Appendix 4: All electronic multilayered information available on the MAGICapp

Competing interests

All authors have completed the *BMJ Rapid Recommendations* interests disclosure form and a detailed, contextualised description of all disclosures is reported in Web Appendix 1. As with all *BMJ Rapid Recommendations,* the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

Funding

This guideline was not funded.

Transparency declaration

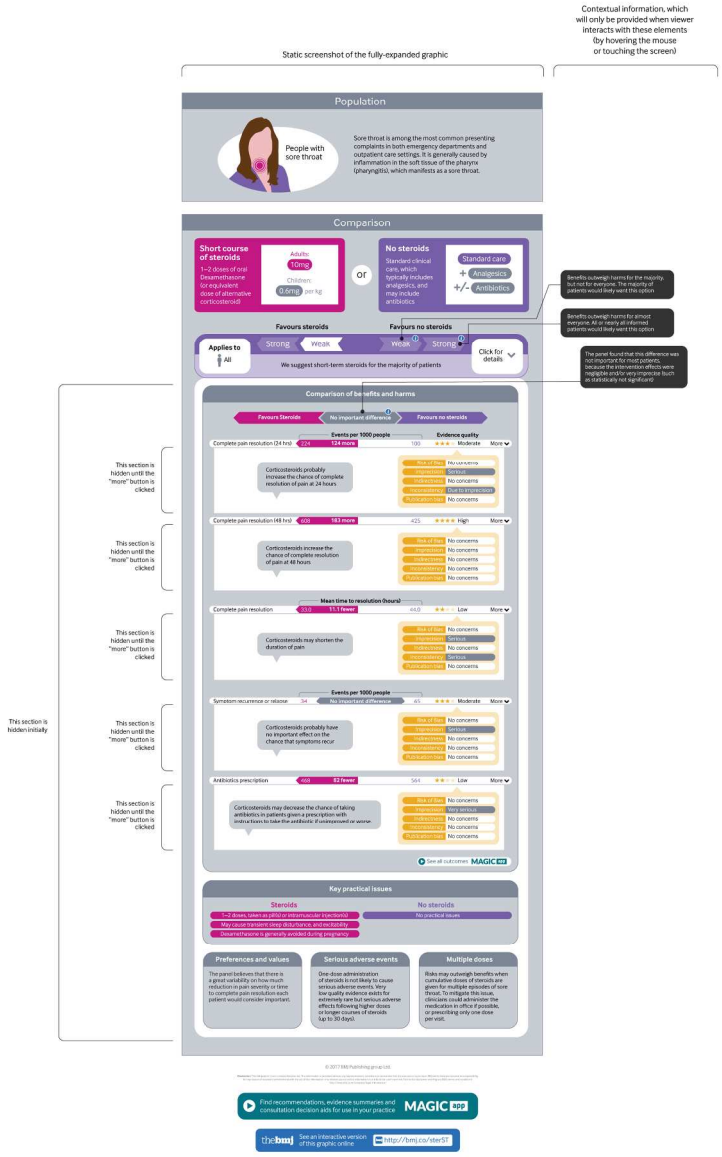
B. Aertgeerts affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

REFERENCES

1. Hayward GN, Hay AD, Moore MV, et al. Effect of Oral Dexamethasone Without Immediate Antibiotics vs Placebo on Acute Sore Throat in Adults: A Randomized Clinical Trial. *Jama* 2017;317(15):1535-43. doi: 10.1001/jama.2017.3417 [published Online First: 2017/04/19]
2. Sadhegirad B, Siemieniuk R, Brignardello-Petersen R, et al. Corticosteroids for treatment of sore thoat: a systematic review and meta-analysis of randomized trials. *BMJ (Clinical research ed)* 2017:Submitted for publication.

3. Evans CE, McFarlane AH, Norman GR, et al. Sore throats in adults: who sees a doctor? *Canadian family physician Medecin de famille canadien* 1982;28:453-8. [published Online First: 1982/03/01]
4. van Driel ML, De Sutter A, Deveugele M, et al. Are sore throat patients who hope for antibiotics actually asking for pain relief? *Annals of family medicine* 2006;4(6):494-9. doi: 10.1370/afm.609 [published Online First: 2006/12/07]
5. NIVEL Primary care database: Netherlands Institute for Health Services Research; 2012 [Available from: https://www.nivel.nl/en/dossier/nivel-primary-care-database.
6. Truyers C, Goderis G, Dewitte H, et al. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC medical informatics and decision making* 2014;14:48. doi: 10.1186/1472-6947-14-48 [published Online First: 2014/06/08]
7. Barnett ML, Linder JA. Antibiotic prescribing to adults with sore throat in the United States, 1997-2010. *JAMA internal medicine* 2014;174(1):138-40. doi: 10.1001/jamainternmed.2013.11673 [published Online First: 2013/10/05]
8. 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):368-74. doi: 10.1111/coa.12299 [published Online First: 2014/11/25]
9. Thompson M, Vodicka TA, Blair PS, et al. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ (Clinical research ed)* 2013;347:f7027. doi: 10.1136/bmj.f7027 [published Online First: 2013/12/18]
10. Rea TD, Russo JE, Katon W, et al. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr virus. *The Journal of the American Board of Family Practice* 2001;14(4):234-42. [published Online First: 2001/07/19]
11. Management of sore throat and indications for tonsillectomy. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network 2010.
12. Little P, Stuart B, Hobbs FD, et al. Predictors of suppurative complications for acute sore throat in primary care: prospective clinical cohort study. *BMJ (Clinical research ed)* 2013;347:f6867. doi: https://dx.doi.org/10.1136/bmj.f6867
13. Aalbers J, O'Brien KK, Chan WS, et al. Predicting streptococcal pharyngitis in adults in primary care: a systematic review of the diagnostic accuracy of symptoms and signs and validation of the Centor score. *BMC medicine* 2011;9:67. doi: 10.1186/1741-7015-9-67 [published Online First: 2011/06/03]
14. Ebell MH, Smith MA, Barry HC, et al. The rational clinical examination. Does this patient have strep throat? *Jama* 2000;284(22):2912-8. [published Online First: 2001/01/09]
15. Chiappini E, Regoli M, Bonsignori F, et al. Analysis of different recommendations from international guidelines for the management of acute pharyngitis in adults and children. *Clinical therapeutics* 2011;33(1):48-58. doi: 10.1016/j.clinthera.2011.02.001 [published Online First: 2011/03/15]
16. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *The Cochrane database of systematic reviews* 2006(4):Cd000023. doi: 10.1002/14651858.CD000023.pub3 [published Online First: 2006/10/21]
17. van Driel ML, De Sutter AI, Habraken H, et al. Different antibiotic treatments for group A streptococcal pharyngitis. *The Cochrane database of systematic reviews* 2016;9:Cd004406. doi: 10.1002/14651858.CD004406.pub4 [published Online First: 2016/09/12]
18. Hayward G, Thompson M, Heneghan C, et al. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2009;339:b2976. doi: 10.1136/bmj.b2976 [published Online First: 2009/08/08]

19. Hayward G, Thompson MJ, Perera R, et al. Corticosteroids as standalone or add-on treatment for sore throat. *The Cochrane database of systematic reviews* 2012;10:Cd008268. doi: 10.1002/14651858.CD008268.pub2 [published Online First: 2012/10/19]
20. Korb K, Scherer M, Chenot JF. Steroids as adjuvant therapy for acute pharyngitis in ambulatory patients: a systematic review. *Annals of family medicine* 2010;8(1):58-63. doi: 10.1370/afm.1038 [published Online First: 2010/01/13]
21. Wing A, Villa-Roel C, Yeh B, et al. Effectiveness of corticosteroid treatment in acute pharyngitis: a systematic review of the literature. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2010;17(5):476-83. doi: 10.1111/j.1553-2712.2010.00723.x [published Online First: 2010/06/12]
22. Siemieniuk RA, Agoritsas T, Macdonald H, et al. Introduction to BMJ Rapid Recommendations. *BMJ (Clinical research ed)* 2016;354:i5191. doi: 10.1136/bmj.i5191 [published Online First: 2016/09/30]
23. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ (Clinical research ed)* 2016;354:i5085. doi: 10.1136/bmj.i5085 [published Online First: 2016/09/30]
24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]
25. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *Journal of clinical epidemiology* 2013;66(7):726-35. doi: 10.1016/j.jclinepi.2013.02.003 [published Online First: 2013/04/11]
26. Agoritsas T, Merglen A, Shah ND, et al. Adjusted Analyses in Studies Addressing Therapy and Harm: Users' Guides to the Medical Literature. *Jama* 2017;317(7):748-59. doi: 10.1001/jama.2016.20029 [published Online First: 2017/02/28]
27. Fernandes RM, Oleszczuk M, Woods CR, et al. The Cochrane Library and safety of systemic corticosteroids for acute respiratory conditions in children: an overview of reviews. *Evidence-based child health : a Cochrane review journal* 2014;9(3):733-47. doi: 10.1002/ebch.1980 [published Online First: 2014/09/23]



Infographic 1

752x1058mm (72 x 72 DPI)

Appendix 1. Search for values and preferences literature

Search strategy and data sources

We performed a systematic literature search for studies on values and preferences from three databases (Medline, Embase, PsycINFO), with a values and preferences filter developed by Alonso-Coello et al (manuscript submitted), from inception until 09 May 2017.

Selection criteria

We included studies on children or adults with sore, painful or uncomfortable throat. The outcomes we considered eligible were 1) health state value studies (e.g. measures between 0, i.e. death, and 1, i.e. perfect health, elicited through techniques such as standard gamble, time trade-off and visual-analog scale); 2) direct choice studies (e.g., choice when presented with decision aid, probabilistic trade-off techniques, discrete choice, conjoint analysis willingness to pay, randomized controlled trials on preferences); 3) studies on non-utility measurement of health states (e.g. surveys); and 4) qualitative studies (e.g. focus groups, semi-structured interviews). We excluded 1) patients with complications (e.g. esophageal cancer) who would not be treated for their symptoms in primary care, 2) non-primary studies (e.g. clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints); 3) case report, and case series; and 4) studies reporting overall health related quality of life.

Results

The literature search yielded 5,385 citations, of which 4,196 remained after removing duplicates (Figure 1). A total of 99 studies were screened in full text, of which 97 were excluded, with reasons. Title and abstract, as well as full text screening, was conducted independently and in duplicate. Two studies were eligible for review[1,2].

Shaik and colleagues[1] conducted a study to develop patient-reported outcome measure from patient diaries from US, reported by 113 children aged 5-15 yrs and/or their carers. They had considered 23 symptom measures reported in literature, and chose 8 based on importance, which they calculated as patient/carer reported prevalence of symptom multiplied by mean severity. The 8 most important outcomes were as follows: sore throat, abdominal pain, headache, pain with swallowing, fever, eating less, playing less, decreased activity.

Addey and colleagues[2] surveyed 3,514 adults with sore throat experience in past 12 months about 1) physical symptoms, 2) emotional descriptors, and 3) health seeking behaviors. They reported emotional descriptors as barely affected (16%), and other mild symptoms (e.g. cannot concentrate, low energy; 84%). They also reported health behaviours, where patients chose the following options: if symptoms don't disappear quickly take medication (44%), as soon as symptoms appear take medication (29%), only take medication when severe (20%), prefer to avoid medication and put up with discomfort (7%).

Neither of the studies provided unique data that were not discussed by the panel. Based on the empirical data, the panel had chosen appropriate patient important outcomes, and considered variability in patient values and preferences regarding sore throat management.

References

1. Shaikh N, Martin JM, Casey JR, Pichichero ME, Wald ER, Colborn DK, Gerber MA, Kearney DH, Balentine TL, Haralam MA, Hoberman A. Development of a patient-reported outcome measure for children with streptococcal pharyngitis. Pediatrics. 2009 Oct 1;124(4):e557-63.
2. Addey D, Shephard A. Incidence, causes, severity and treatment of throat discomfort: a four-region online questionnaire survey. BMC Ear, Nose and Throat Disorders. 2012 Aug 10;12(1):9.

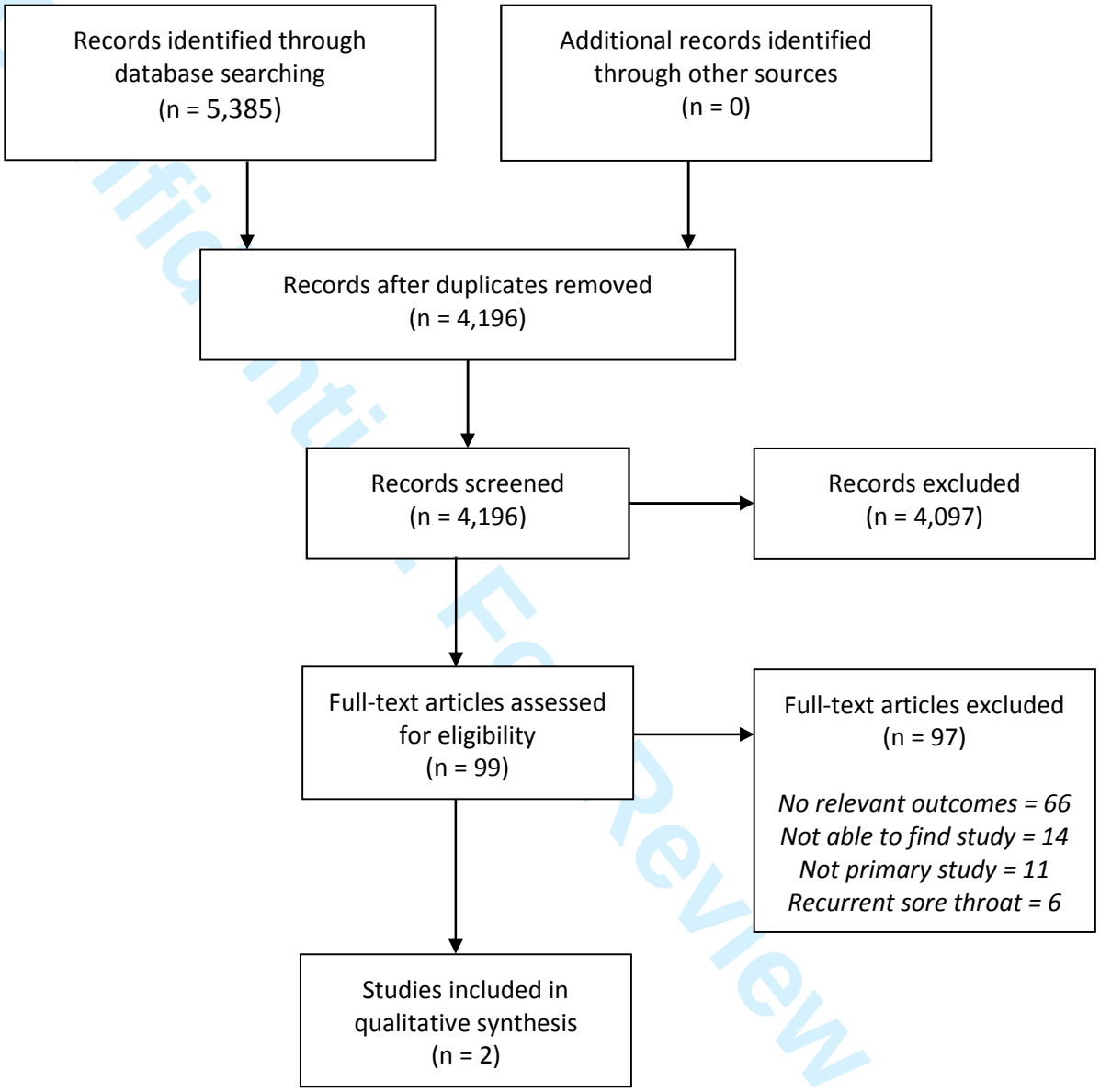


Figure 1. PRISMA flow diagram.

Appendix 2: Full list of authors' declarations of interests

Pre-screening

All panel members were pre-screened for conflicts of interest prior to the guideline process that resulted in the *BMJ* Rapid Recommendations. The pre-screening was performed by the RapidRecs Executive team from the non-profit organisation MAGIC (www.magicproject.org) with support and approval from at least two unconflicted *BMJ* editors. No financial conflicts of interest were allowed (specifically, no financial ties to pharmaceutical companies with any stake in steroids or antibiotics) and intellectual and professional conflicts of interest were managed appropriately (see appendix 4: Methods for *BMJ* Rapid Recommendations). Panel members could not have a conflict for the past three years and do not anticipate a conflict arising in the foreseeable future, which we defined as at least one year.

We excluded one potential panel member who had expressed interest because they did not meet the BMJ Rapid Recommendation standards for conflicts of interest.

Disclosures

Financial disclosures: No panel members had any financial conflicts of interest to disclose related to this clinical question.

Professional disclosures: The majority of the panel members routinely see patients with sore throat. The department which Jako Burgers if affiliated, Dutch College of General Practitioners, published a guideline on acute sore throat in 2015. Ann van Bruel recently published an opinion article in the British Journal of General Practice on pharmacy-based testing for strep A in patients with sore throat. No other professional conflicts of interest to disclose.

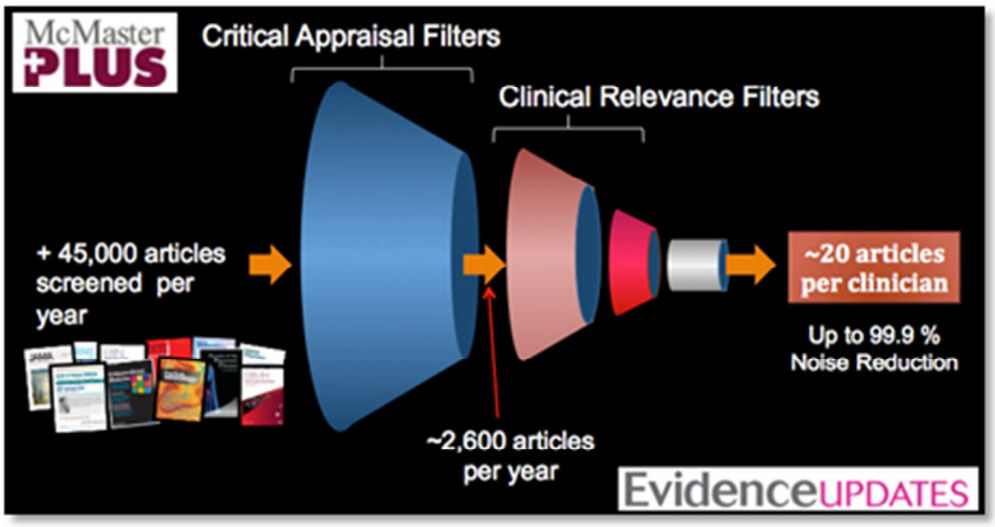
Intellectual disclosures: Behnam Sadeghirad, Reed Siemieniuk, Per Vandvik, Lyubov Lytvyn, Thomas Agoritsas, and Romina Brignardello-Petersen, participated in the writing the complementary systematic review that formed the evidence base for this guideline. Bert Artgeerts, Reed Siemieniuk, Lyubov Lytvyn, Behnam Sadeghirad, and Romina Brignardello-Petersen contributed to the systematic review of values and preferences in the appendix. Reed Siemieniuk, Arnaud Merglen, Thomas Agoritsas, Per Vandvik, Lyubov Lytvyn, and Gordon Guyatt are members of the GRADE Working Group: BMJ Rapid Recommendations adheres to GRADE methods. No panel member had any other intellectual conflict to disclose.

About *BMJ* Rapid Recommendations

Translating research to clinical practice is challenging. Trustworthy clinical practice recommendations are one useful knowledge translation strategy. Organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence. *BMJ* Rapid Recommendations aims to create trustworthy clinical practice recommendations based on the highest quality evidence in record time. The project is supported by an international network of systematic review and guideline methodologists, people with lived experience of the diseases or conditions, clinical specialists, and front-line clinicians. This overview is one of a package that includes recommendations and one or more systematic reviews published by the *BMJ* group and in MAGICapp (http://www.magicapp.org). The goal is to translate evidence into recommendations for clinical practice in a timely and transparent way, minimizing bias and centred around the experience of patients. *BMJ* Rapid Recommendations will consider both new and old evidence that might alter established clinical practice.

Process overview

1. On a daily basis, we monitor the literature for practice-changing evidence:
    a. Formal monitoring through McMaster Premium LiteratUre Service (PLUS)



b. Informal monitoring the literature by *BMJ* Rapid Recommendations expert groups, including clinician specialists and patients

2. The *RapidRecs* executive team and editors at *The BMJ* choose which clinical questions to pursue among the identified potentially-practice changing evidence, based on relevance to a wide audience, widespread interest, and likelihood to change practice.

3. We incorporate the evidence into the existing body of evidence and broader context of clinical practice via:

a. a rapid and high-quality systematic review and meta-analysis on the benefits and harms with a focus on the outcomes that matter to patients

b. parallel rapid recommendations that meet the standards for trustworthy guidelines[1] by an international panel of people with relevant lived experience, front-line clinicians, clinical content experts, and methodologists.

c. The systematic review and the recommendation panel will apply standards for trustworthy guidelines.[1,2] They use the GRADE approach, which has developed a transparent process to rate the quality (or certainty) of evidence and grade the strength of recommendations.[3,4]

d. Further research may be conducted including:

i. A systematic review of observational studies to identify baseline risk estimates that most closely represent the population at the heart of the

clinical question, a key component when calculating the estimates of absolute effects of the intervention

ii. A systematic review on the preferences and values of patients on the topic.

4. Disseminate the rapid recommendations through

a. publication of the research in *BMJ* journals

b. short summary of recommendations for clinicians published in *The BMJ*

c. press release and/or marketing to media outlets and relevant parties such as patient groups

d. Links to BMJ Group's *Best Practice* point of care resource

e. MAGICapp which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others who wish to re-examine or consider national or local adaptation of the recommendations.

Who is involved?

Researchers, systematic review and guideline authors, clinicians, and patients often work in silos. Academic journals may publish work from any one or combinations of these groups of people and findings may also be published in the media. But it is rare that these groups work together to produce a comprehensive package. *BMJ-RapidRecs* circumvents organisational barriers in order to provide clinicians with guidance for potentially practice-changing evidence.

Our collaboration involves

a. The *RapidRecs* group with a designated Executive team responsible for recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels.. The *RapidRecs* group is part of MAGIC (www.magicproject.org), a non for profit organization that provides MAGICapp (www.magicapp.org) an authoring and publication

platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices.[5]

b. *The BMJ* helps identifiying practice-changing evidence on key clinical questions, coordinates the editorial process and publishes the package of content linking to the MAGICapp that is presented in a user friendly way.

METHODS FOR THE RAPID RECOMMENDATIONS

The formation of these recommendations adheres to standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interests, as well as transparent and systematic processes for assessing the quality of evidence and for moving from evidence to recommendations.[1,2,6]

Guidance on how the panel is picked and how they contribute

Panel members are sought and screened through an informal process.

The following panel members are important

- At least one author of the individual systematic reviews
- At least one patient representative with lived experience of the disease or condition. This person receives patient-oriented documents to explain the process and is allocated a linked panel member to empower their contribution.
- A full spectrum of practicing clinicians involved in the management of the clinical problem and patients it affects, including front-line clinicians with generalist experience and those with deep content clinical and research expertise in the particular topic.
- Methodological experts in health research methodology and guideline development

Any potential conflicts of interest are managed with extreme prudence:

- No panel member can have a financial interest – as assessed by the panel chair, the *Rapidrecs* executive team or *The BMJ* editors as relevant to the topic
- No more than two panel members with an intellectual interest on the topic (typically having published statements favouring one of the interventions).

Illustrative example: For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, the panel recruitment of content experts and community panel members was challenging. Content experts in this area are infectious diseases experts, many of whom have financial conflicts of interests through interactions with the pharmaceutical industry through advisory boards and participation in industry-funded trials. The group reached out to more than 17 potential panel members who were eventually excluded from participating because of conflicts – notably, all of these persons had not disclosed any relevant conflicts on related and recent publications in the topic area. Many more potential panel members were not recruited because of publicly declared conflicts. The chair and MAGIC team were able, with considerable effort and ingenuity, to recruit several excellent and unconflicted content experts.

How the panel meets and works

The international panel communicates via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiorecorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three timepoints, with circulated documents by e-mail in advance:

1. At the initiation of the process to provide feedback on the systematic review protocol (for example, on selection of patient-important outcomes and appropriate prespecified analysis of results) before it is performed.
2. At the evidence summary stage with discussion, feedback and agreement on draft evidence (GRADE evidence profile) prepared by the Chair and the methods editor based on the systematic review.
3. At the recommendation formulation phase with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Following the last teleconference the final version of the recommendations is circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission to *The BMJ*. Additional teleconferences are arranged as needed.

Illustrative example: For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, two large-group teleconferences were arranged. First, content experts provided crucial input to evidence assessment (e.g. subgroups to identify). For the recommendation formulation phase the panel needed two teleconferences to discuss all elements in detail, followed by more than 100 e-mails with specific issues to be sorted out. Multiple teleconferences were held to allow the scheduling flexibility required so that all could participate.

How we move from research findings to recommendations

What information is considered?

The panel considers best current evidence from available research. Beyond systematic reviews - performed in the context of the *BMJ* Rapid Recommendations - the panel may also include a number of other research papers to further inform the recommendations.

How is a trustworthy guideline made?

The Institute of Medicine (IOM)'s guidance on out how trustworthy guidelines should be developed and articulated key standards as outlined in the table below.[1] The standards are similar to those developed by the Guideline International Network (G-I-N).[2] These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). The table below lays out how we hope to meet the standards for our rapid recommendations:

1. Establishing transparency

"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"*
● This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content is available. ● We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.
2. Managing conflicts of interest **"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",**
● Interests of each panel member are declared prior to involvement and published with the rapid recommendations ● No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ* ● No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic. ● The Chair must have methods expertise, a clinical background and no financial or intellectual interests. ● Funders and pharmaceutical companies have no role in these recommendations.

3. Guideline Development Group Composition **"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"**
● *The RapidRecs* group will aim to include representation from most or every major geographic region in the world, with specific efforts made to achieve gender-balance. ● We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available ● Patient-representatives will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.
4. Clinical Practice Guideline–Systematic Review Intersection **"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes".**
● Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendaiton. ● The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication and continuity in the process

5. Establishing Evidence Foundations for and Rating Strength of Recommendations

"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"

- The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.[6] For each recommendation systematic and transparent assessments are made across the following key factors:
  - Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)[4]
  - Quality of the evidence[7]
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)
- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. patophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE.[8]

- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus process customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations

"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats in MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.[9]
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and or with an individual patient.

7. External review

"External reviewers should comprise a full spectrum of relevant stakeholders…., authorship should be kept confidential….., all reviewer comments should be considered….a rationale for modifying or not should be recorded in writing…. a draft of the recommendation should be made available to general public for comment.."

- At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy
- A *BMJ* series adviser with methodological and/or statistical expertise will review the *BMJ* Rapid Recommendations publication and the systematic reviews.
- The *Rapidrecs* panel will be asked to read and respond to the peer review comments and make amendments where they judge reasonable
- *The BMJ* and *RapidRecs* executive team may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period of six months after publication.

8. Updating

"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"

- The *Rapidrecs* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates of the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and

submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

References:

1. Laine C, Taichman DB, Mulrow C. Trustworthy clinical guidelines. *Annals of internal medicine.* 2011;154(11):774-775.
2. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Annals of internal medicine.* 2012;156(7):525-531.
3. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *Bmj.* 2008;336(7652):1049-1051.
4. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology.* 2011;64(4):383-394.
5. Vandvik PO, Brandt L, Alonso-Coello P, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. *Chest.* 2013;144(2):381-389.
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj.* 2008;336(7650):924-926.
7. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology.* 2011;64(4):401-406.
8. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *Journal of clinical epidemiology.* 2013;66(7):726-735.
9. Kristiansen A, Brandt L, Alonso-Coello P, et al. Development of a novel, multilayered presentation format for clinical practice guidelines. *Chest.* 2015;147(3):754-763.

Corticosteroids for sore throat

Main editor

Bert Aertgeerts, Romina Brignardello-Petersen, Thomas Agoritsas, Behnam Sadeghirad

WikiRecs group

A BMJ-Rapid Recommendation on corticosteroids for sore throat. This is the 5th BMJ-RapidRec, initiated in response to an RCT by Hayward and Colleages, published in JAMA April 18, 2017 (http://jamanetwork.com/journals/jama/article-abstract/2618622). Roles: Panel Chair: Bert Aertgeerts Methods Editors: Romina Brignardello-Petersen Oversight from RapidRecs executive: Thomas Agoritsas Systematic Review Lead: Behnam Sadeghirad

Contact

Language

en

Start Date

15.06.2017

Last Edit

16.06.2017

Disclaimer

Sections

Summary of recommendations

1 - Corticosteroids for acute sore throat

Weak Recommendation

We suggest using corticosteroids in addition to standard care in patients with sore throat

Steroids are typically given as 10 mg dexamethasone (or 0.6 mg/kg for children, up to a maximum dose of 10mg), taken as a single pill (or as an intramuscular injection). Clinicians could administer the medication in office if possible, or prescribe only one dose per visit, to mitigate the risk of a larger cumulative dose of corticosteroids in case of multiple episodes of sore throat.

2 - BMJ Rapid Recommendations Methods and Process

1 - Corticosteroids for acute sore throat

Weak Recommendation

We suggest using corticosteroids in addition to standard care in patients with sore throat

Steroids are typically given as 10 mg dexamethasone (or 0.6 mg/kg for children, up to a maximum dose of 10mg), taken as a single pill (or as an intramuscular injection). Clinicians could administer the medication in office if possible, or prescribe only one dose per visit, to mitigate the risk of a larger cumulative dose of corticosteroids in case of multiple episodes of sore throat.

Practical Info

- Steroids are typically given as 10 mg dexamethasone (or adapted to weight for children: 0.6 mg/kg, up to a maximum dose of 10mg), typically taken as pill (or intramuscular injection).
- We suggest administering the medication in office if possible, or prescribing only one dose per visit, to mitigate the risk of a larger cumulative dose of corticosteroids in case of multiple episodes of sore throat either through multiple visits, or for patients who would self-medicate after having been prescribed more than one pill in their previous episode.

Who does this recommendation apply to?

The panel is confident the recommendation applies to almost all patients with acute sore throat; children and adults, severe and not severe sore throat, patients who receive immediate antibiotics and those who receive deferred antibiotics, and patients who seek care in the emergency department as well as those who attend to a primary care practice. The systematic review contained adequate representation from such groups and settings and showed consistency (i.e. absence of credible subgroup effects) in the results shown between trials of children and adults, those seen in emergency departments and those in primary care offices.

Since the randomised controlled trials focused on patients who did not have recurrent episodes of sore throat, the panel was less confident of the applicability of the evidence to such patients and the recommendation does not apply to them. Similarly the panel did not consider patients with sore throat following any surgery or intubation, nor immunocompromised patients.

Key Info

Benefits and harms Small net benefit, or little difference between alternatives

Patients who receive corticosteroids in addition to standard care have, on average, an 18% more chance of achieving complete resolution of pain at 48 hours after treatment. These patients also probably have, on average, a 12% more chance to achieve complete pain resolution at 24 hours after treatment. Corticosteroids probably reduce, on average, the time to onset of pain relief by 5 hours, the time to complete resolution of pain by 11 hours, and the severity of pain by 1.3 points on a 10 point scale.

Corticosteroids may decrease the chance of taking antibiotics in patients given a prescription with instructions to take the antibiotic if unimproved or worse by 10%. They probably have no important effect on the chance that symptoms recur and the days missed fom school or work.

When prescribed at the doses used for treating acute sore throat, corticosteroids probably do not increase the risk of major adverse events .

Quality of evidence Moderate

We have high certainty in the benefits of corticosteroids in increasing the chance of complete resolution of pain at 48 hours. We have moderate certainy in the benefits of corticosteroids in increasing the chance of complete resolution of pain at 24 hours, reducing the time of onset of pain relief, and reducing the severity of pain. This is due to the confidence intervals of the estimates of these benefits showing that such benefits could be very small and not patient-important in some cases.

We have low certainty in the benefits of corticosteroids in reducing the time to complete resolution of pain due to studies showing

inconsistent results. We also have low certainty in the benefits of corticosteroids in decreasing the chance of taking antibiotics in patients given a prescription with instructions to take the antibiotic if unimproved or worse, due to imprecise results that suggest that in some cases, antibiotic presription might increase.

We have moderate certainty in the lack of a patient important benefit of corticosteroids in the chance of symptom recurrence and days missed from school or work due to imprecise results that suggest that corticosteroids could improve or worsen these outcomes, but that the effect would not be patient-important.

We have modedrate certainty that corticosteroids do not increase the risk of major adverse events when prescribed at the doses used for treating acute sore throat. Certainty is moderate due to concerns about selective reporting of this outcome in the randomized trials.

Preference and values

Substantial variability is expected or uncertain

Patients are likely to place a high value on a small but somewhat important reduction of symptoms severity and the time that it takes to achieve such improvement, and an important increase in the chance of complete resolution of pain at 48 hours. The values and preferences, however, are likely to vary greatly across patients, which justifies the strength of the recommendation. For example, achieving complete pain resolution 12 hours earlier may be of little importance for patients who feel less busy in their daily life, have higher tolerance to pain, or whose symptoms are not so severe; whereas it may be important to patients whose abilities to perform at work are compromised, caregivers willing to reduce their childrens' in pain, or patients experiencing their pain as severe.

The panel believes that there is a great variability on how much reduction in pain severity or time to complete pain resolution each patient would consider important. The greater the reduction in hours to achieve complete resolution of pain, the more likely it is that typical patients would place high value on those outcomes. Patients who place a high value in reducing the symptoms by any amount (eg. patients with lower tolerance to pain or those with severe symptoms) are more likely to accept the offer of corticosteroids.

Resources and other considerations

Important issues, or potential issues not investigated

Due to the low costs of corticosteroids for treating sore throat, implementation of this recommendation is unlikely to have an important impact on the costs for health funders.

Acceptability of corticosteroids may be a challenge. Some stakeholders may have concerns about treating an usually non-severe and self-limiting disease with a drug that is not considered as standard of care.

In addition, there may be an increase in the risk of a larger cumulative dose of corticosteroids in case of multiple episodes of sore throat, either through multiple visits, or for patients who would self-medicate after having been prescribed more than one pill in their previous episode.

Rationale

We issue a weak recommendation for corticosteroids in addition to standard care because the desirable consequences probably outweight the undesirable consequences. Yet we believe that there is great variability in the value patients would place on the small benefits, despite the very low likelihood of harms. There may be an increase in the risk of a larger cumulative dose of corticosteroids in case of multiple episodes of sore throat, either through multiple visits, or for patients who would self-medicate after having been prescribed more than one pill in their previous episode. To mitigate this issue, we suggest administering the medication in office if possible, or prescribing only one dose per visit.

Acceptability of this intervention may also differ, as it may be perceived as treating a condition that is usually not severe and is self-limiting with a drug that many patients, practitioners, and other stakeholders perceive is most often used for more severe diseases only.

Due to their low cost, resources did not play an important role when formulating this recommendation.

Clinical Question/ PICO

Population: Patients with sore throat
Intervention: Corticosteroids
Comparator: No corticosteroids

Outcome Timeframe	Study results and measurements	Absolute effect estimates No corticosteroids	Corticosteroids	Certainty in effect estimates (Quality of evidence)	Summary
Complete Resolution of Pain at 24 hours	Relative risk 2.24 (CI 95% 1.17 - 4.29) Based on data from 1,049 patients in 5 studies. (Randomized controlled)	**100** per 1000	**224** per 1000 Difference: **124 more** per 1000 (CI 95% 17 more - 329 more)	**Moderate** Due to inconsistency and imprecision	Corticosteroids probably increase the chance of complete resolution of pain at 24 hours
Complete Resolution of Pain at 48 hours	Relative risk 1.43 (CI 95% 1.21 - 1.7) Based on data from 1,076 patients in 4 studies. (Randomized controlled)	**425** per 1000	**608** per 1000 Difference: **183 more** per 1000 (CI 95% 89 more - 298 more)	**High**	Corticosteroids increase the chance of complete resolution of pain at 48 hours
Recurrence/ relapse of symptoms	Relative risk 0.52 (CI 95% 0.16 - 1.73) Based on data from 372 patients in 3 studies. (Randomized controlled)	**65** per 1000	**34** per 1000 Difference: **31 fewer** per 1000 (CI 95% 55 fewer - 47 more)	**Moderate** Due to serious imprecision	Corticosteroids probably have no important effect on the chance that symptoms recur.
Antibiotics prescription during the episode	Relative risk 0.83 (CI 95% 0.61 - 1.13) Based on data from 342 patients in 1 studies. (Randomized controlled) Follow up 28 days	**564** per 1000	**468** per 1000 Difference: **96 fewer** per 1000 220 fewer - 73 more	**Low** Due to very serious imprecision	Corticosteroids may decrease the chance of taking antibiotics in patients given a prescription with instructions to take the antibiotic if unimproved or worse.
Mean times to onset of pain relief Hours	Based on data from: 907 patients in 8 studies. (Randomized controlled)	**12.3** hours (Median)	**7.4** hours (Mean) Difference: **MD 4.8 fewer** (CI 95% 7.8 fewer - 1.9 fewer)	**Moderate** Due to inconsistency and imprecision	Corticosteroids probably shorten the time until pain starts to improve.

Mean time to complete resolution of pain hours	Based on data from: 720 patients in 6 studies. (Randomized controlled)	**44** hours (Mean) **33** hours (Mean) Difference: **MD 11.1 fewer** (CI 95% 21.8 fewer - 0.4 fewer)	**Low** Due to serious imprecision and inconsistency	Corticosteroids may shorten the duration of pain.
Pain reduction at 24 hours	Measured by: Reduction in VAS Scale: 0-10 High better Based on data from: 1,247 patients in 8 studies. (Randomized controlled)	**3.3** points (Mean) **4.6** points (Mean) Difference: **MD 1.3 more** (CI 95% 0.7 more - 1.9 more)	**Moderate** Due to inconsistency and imprecision	Corticosteroids probably reduce the severity of pain at 24 hours
Duration of bad/ non-tolerable symptoms				There were no studies providing information about this outcome
Days missed from work or school	Based on data from 181 patients in 2 studies	Two RCTs reported days missed from work/ school. In Kinderman et al, 22 out of 40 (55%) patients in the steroids group took time off work and 27 out of 39 (69%) patients in the placebo group took time off work (Relative risk 0.79; 95% confidence interval 0.56 to 1.13). Marvez-Valls et al reported the average time patients in each arm missed from work/ school. In the intervention group adult patients missed an average of 0.4 (SD: 1.4) days and in the placebo arm patients missed an average of 0.7 (SD: 1.4) days (mean difference 0.30 days, 95% CI -0.28 to 0.88).	**Moderate** Due to serious imprecision and some concerns of risk of bias	Corticosteroids probably have no important effect on the days missed from work or school.
Adverse events	Based on data from 808 patients in 3 studies	One study (Hayward et al.) reported 2 serious adverse events (hospitalizations due to pharyngeal or peritonsillar abscess, tonsillitis, and pneumonia) in the corticosteroids group (0.68%) and 3 in the placebo group (1.06%). In another study (Olympia et al), 1 out of the 57 (1.8%) children in the corticosteroids group and 2 out of the 68 (2.9%) children in the control group developed a peritonsillar abscess. In the same study, 3 out of 57 (5.3%) children in the corticosteroid group and 2 out of 68 (2.9%) of children in the placebo group had to be hospitalised due to dehydration. Finally, another study (Wei et al.) reported that 1 patient who received corticosteroids (3%) had hiccups.	**Moderate** Due to serious risk of bias	Corticosteroids probably do not increase the risk of adverse events.

Practical issues	No corticosteroids	Corticosteroids	Both
 Medication routine	One (or two) doses of steroids, taken as pill(s) or intramuscular injection(s)		May require concomitant antibiotics, and or over the counter pain relievers
 Tests and visits			May need additional visits if symptoms do not resolve or worsen
 Adverse effects, interactions and antidote	Serious adverse events are unlikely with one-dose steroids. But there may be risks with repeated doses across multiple episodes of sore throat (or through self-medication).		
 Emotional well-being	May cause transient sleep disturbance, and excitability (although infrequently with one-dose steroids)		
 Pregnancy and nursing	Dexamethasone crosses the placenta, and is generally avoided during pregnancy. There is, however, almost no risk of malformation.		
 Costs and access	Inexpensive, available by prescription		
 Food and drinks	May increase appetite (particularly in children)		

Details about studies used and certainty down- and upgrading

Complete **Intervention:** Systematic **Risk of bias: No serious** All studies are low RoB. ;

Resolution of Pain	review **Baseline/comparator:** Control arm of reference used for intervention	**Inconsistency: No serious** The magnitude of statistical heterogeneity was high, with I^2: 68.8 %. However, the clinical inconsistency is not important, as all the studies provide results that have a similar clinical implication. ; **Indirectness: No serious** **Imprecision: Serious** The limits of the confidence interval suggest a very small benefit in one extreme, and a patient important benefit in the other. Because the imprecision is linked to the inconsistency, we decided to rate down the certainty of the evidence only by one level. ; **Publication bias: No serious** Not statistically tested due to small number of studies. ;
Complete Resolution of Pain	**Intervention:** Systematic review **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** All studies are categorised as low RoB. ; **Inconsistency: No serious** The magnitude of statistical heterogeneity: I^2 = 3.2%. ; **Indirectness: No serious** **Imprecision: No serious** Low number of patients ; **Publication bias: No serious** Not statistically tested due to small number of studies. ;
Recurrence/relapse of symptoms	**Intervention:** Systematic review **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** 1 of the 3 RCTs was judged as high risk of bias due to missing participant data. ; **Inconsistency: No serious** The magnitude of statistical heterogeneity was low, with I^2: 22.8 %. ; **Indirectness: No serious** **Imprecision: Serious** The confidence interval suggests that corticosteroids increase the chance of recurrence of symptoms in now extreme, while it suggests corticosteroids decrease this chance in the other extreme. ; **Publication bias: No serious** Not statistically tested due to small number of studies. ;
Antibiotics prescription	**Intervention:** Primary study **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Very Serious** The confidence interval suggest that corticosteroids could largely reduce the chance of taking antibiotics in one extreme, while it suggest that corticosteroids could slightly increase this chance in the other extreme. ; **Publication bias: No serious**
Mean times to onset of pain relief	**Intervention:** Systematic review **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** 4 high risk of bias and 4 low risk of bias RCTs. P value for test of interaction: 0.775 ; **Inconsistency: Serious** There is large unexplained clinical and statistical inconsistency. ; **Indirectness: No serious** **Imprecision: No serious** The confidence interval suggest a very small benefit in one extreme, and a benefit that some patients may consider important in the other extreme. Since this imprecision was a result of the inconsistency, we decided to rate down the certainty of the evidence only by one level. ; **Publication bias: No serious** Not statistically tested due to small number of studies. ;
Mean time to complete resolution of pain	**Intervention:** Systematic review **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** 3 high risk of bias and 3 low risk of bias RCTs. However, the high risk of bias trials showed similar results than the low risk of bias trials. ; **Inconsistency: Serious** Large unexplained clinical and statistical heterogeneity. ; **Indirectness: No serious** **Imprecision: Serious** The confidence interval suggests a trivial benefit in one extreme and a benefit that would be considered patient important by most patients in the other extreme. ; **Publication bias: No serious** Not statistically tested due to small number of studies. ;
Pain reduction	**Intervention:** Systematic review	**Risk of bias: No serious** 4 high risk of bias and 4 low risk of bias RCTs. P value for test of interaction: 0.774 ;

	Baseline/comparator: Control arm of reference used for intervention	**Inconsistency: Serious** High statistical inconsistency. In addition, the trials suggest different magnitudes of effect. ; **Indirectness: No serious** **Imprecision: No serious** The confidence interval suggest a very small benefit in one extreme and a patient-important benefit in the other. Since this imprecision was related to the inconsistency, we decided to rate down only by one level. ; **Publication bias: No serious** Not statistically tested due to small number of studies. ;
Days missed from work or school	**Intervention:** Primary study	**Risk of bias: No serious** One of the studies was high risk of bias due to concerns with regards to allocate concealment. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** The studies showed that corticosteroids could increase the days missed from school or work in one extreme, while they could decrease them in the other extreme. ; **Publication bias: No serious**
Adverse events	**Intervention:** Primary study	**Risk of bias: Serious** The high risk of bias studies show similar results than the low risk of bias studies. However, there may be a high risk of selective outcome reporting ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

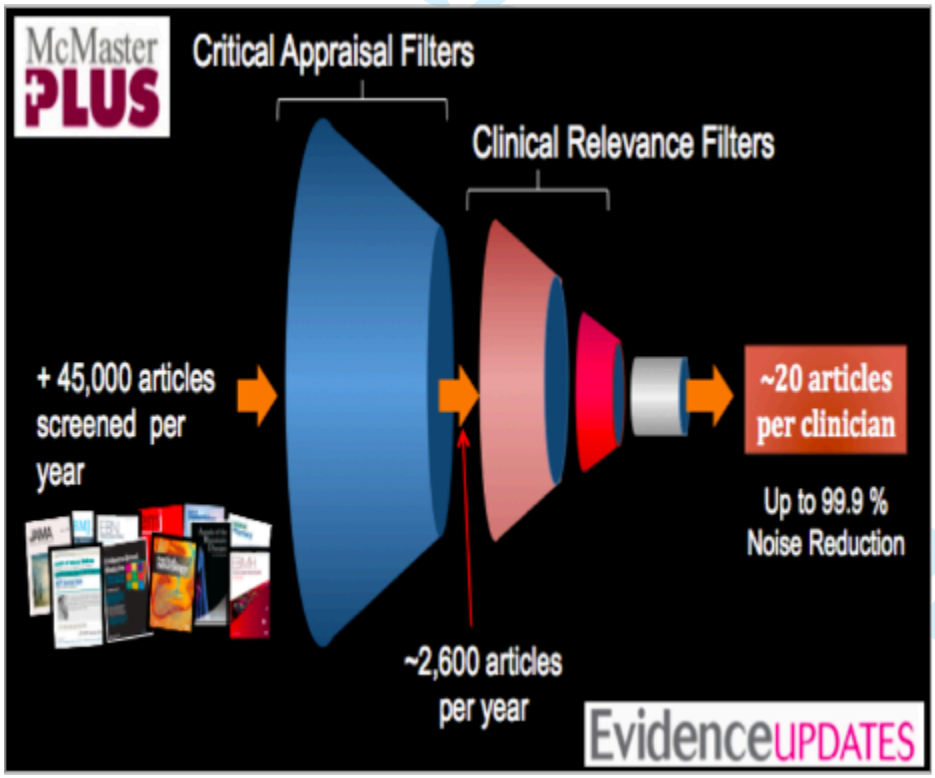
2 - BMJ Rapid Recommendations Methods and Process

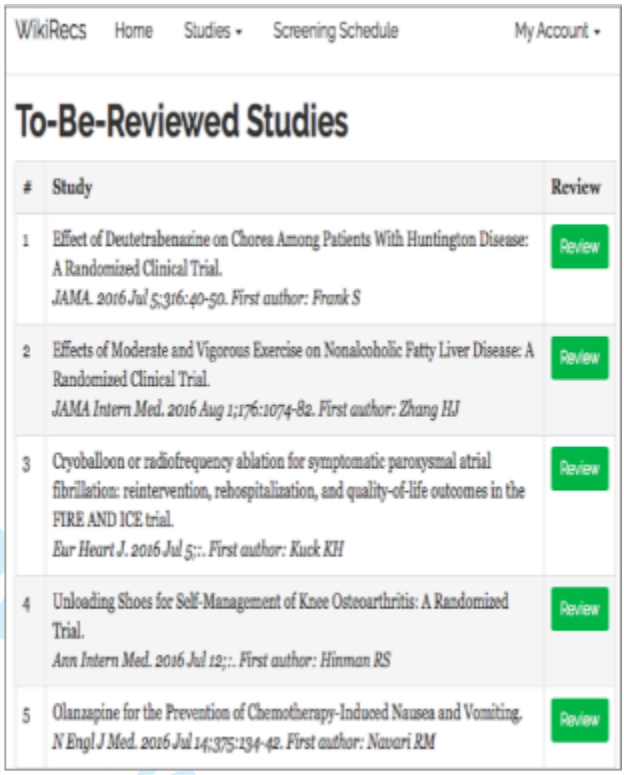
About BMJ Rapid Recommendations

Translating research to clinical practice is challenging. Trustworthy clinical practice recommendations are one useful knowledge translation strategy. Organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence. *BMJ* Rapid Recommendations aims to create trustworthy clinical practice recommendations based on the highest quality evidence in record time. The project is supported by an international network of systematic review and guideline methodologists, people with lived experience of the diseases or conditions, clinical specialists, and front-line clinicians. This overview is one of a package that includes recommendations and one or more systematic reviews published by the *BMJ* group and in MAGICapp (http://www.magicapp.org). The goal is to translate evidence into recommendations for clinical practice in a timely and transparent way, minimizing bias and centred around the experience of patients. *BMJ* Rapid Recommendations will consider both new and old evidence that might alter established clinical practice.

Process overview

1. On a daily basis, we monitor the literature for practice-changing evidence:
   - Formal monitoring through McMaster Premium LiteratUre Service (PLUS)
   - Informal monitoring the literature by *BMJ* Rapid Recommendations expert groups, including clinician specialists and patients





2. The *RapidRecs* executive team and editors at *The BMJ* choose which clinical questions to pursue among the identified potentially-practice changing evidence, based on relevance to a wide audience, widespread interest, and likelihood to change practice.
3. We incorporate the evidence into the existing body of evidence and broader context of clinical practice via:
   - A rapid and high-quality systematic review and meta-analysis on the benefits and harms with a focus on the outcomes that matter to patients
   - Parallel rapid recommendations that meet the standards for trustworthy guidelines1 by an international panel of people with relevant lived experience, front-line clinicians, clinical content experts, and methodologists.
   - The systematic review and the recommendation panel will apply standards for trustworthy guidelines.[1,2] They use the GRADE approach, which has developed a transparent process to rate the quality (or certainty) of evidence and grade the strength of recommendations.[3,4]
   - Further research may be conducted including:
     - A systematic review of observational studies to identify baseline risk estimates that most closely represent the population at the heart of the clinical question, a key component when calculating the estimates of absolute effects of the intervention.
     - A systematic review on the preferences and values of patients on the topic.

4. Disseminate the rapid recommendations through:
   - Publication of the research in *BMJ* journals
   - Short summary of recommendations for clinicians published in *The BMJ*
   - Press release and/or marketing to media outlets and relevant parties such as patient groups
   - Links to *BMJ* group's *Best Practice* point of care resource
   - MAGICapp which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others who wish to re-examine or consider national or local adaptation of the recommendations.

Who is involved?

Researchers, systematic review and guideline authors, clinicians, and patients often work in silos. Academic journals may publish work from any one or combinations of these groups of people and findings may also be published in the media. But it is rare that these groups work together to produce a comprehensive package. *BMJ-RapidRecs* circumvents organisational barriers in order to provide clinicians with guidance for potentially practice-changing evidence.

Our collaboration involves:
1. The *RapidRecs* group with a designated Executive team responsible for recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels.. The *RapidRecs* group is part of MAGIC (www.magicproject.org), a non for profit organization that provides MAGICapp (www.magicapp.org) an authoring and publication platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices.[5]
2. *The BMJ* helps identifiying practice-changing evidence on key clinical questions, coordinates the editorial process and publishes the package of content linking to the MAGICapp that is presented in a user-friendly way.

METHODS FOR THE RAPID RECOMMENDATIONS

The formation of these recommendations adheres to standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interests, as well as transparent and systematic processes for assessing the quality of evidence and for moving from evidence to recommendations.[1,2,6]

Guidance on how the panel is picked and how they contribute

Panel members are sought and screened through an informal process. The following panel members are important:
- At least one author of the individual systematic reviews.
- At least one patient representative with lived experience of the disease or condition. This person receives patient-oriented documents to explain the process and is allocated a linked panel member to empower their contribution.
- A full spectrum of practicing clinicians involved in the management of the clinical problem and patients it affects, including front-line clinicians with generalist experience and those with deep content clinical and research expertise in the particular topic.
- Methodological experts in health research methodology and guideline development.

Any potential conflicts of interest are managed with extreme prudence:
- No panel member can have a financial interest – as assessed by the panel chair, the *RapidRecs* executive team or *The BMJ* editors as relevant to the topic.
- No more than two panel members with an intellectual interest on the topic (typically having published statements favouring one of the interventions).

Illustrative example: For the BMJ *Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, the panel recruitment of content experts and community panel members was challenging. Content experts in this area are infectious diseases experts, many of whom have financial conflicts of interests through interactions with the pharmaceutical industry through advisory boards and participation in industry-funded trials. The group reached out to more than 17 potential panel members who were eventually excluded from participating because of conflicts – notably, all of these persons had not disclosed any relevant conflicts on related and recent publications in the topic area. Many more potential panel members were not recruited because of publicly declared conflicts. The chair and MAGIC team were able, with considerable effort and ingenuity, to recruit several excellent and unconflicted content experts.*

How the panel meets and works

The international panel communicates via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiorecorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three timepoints, with circulated documents by e-mail in advance:

1. At the initiation of the process to provide feedback on the systematic review protocol (for example, on selection of patient-important outcomes and appropriate prespecified analysis of results) before it is performed.
2. At the evidence summary stage with discussion, feedback and agreement on draft evidence (GRADE evidence profile) prepared by the Chair and the methods editor based on the systematic review.
3. At the recommendation formulation phase with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Following the last teleconference the final version of the recommendations is circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission to The BMJ. Additional teleconferences are arranged as needed.

Illustrative example: For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, two large-group teleconferences were arranged. First, content experts provided crucial input to evidence assessment (e.g. subgroups to identify). For the recommendation formulation phase the panel needed two teleconferences to discuss all elements in detail, followed by more than 100 e-mails with specific issues to be sorted out. Multiple teleconferences were held to allow the scheduling flexibility required so that all could participate.

How we move from research findings to recommendations

What information is considered?

The panel considers best current evidence from available research. Beyond systematic reviews - performed in the context of the BMJ Rapid Recommendations - the panel may also include a number of other research papers to further inform the recommendations.

How is a trustworthy guideline made?

The Institute of Medicine (IOM)'s guidance on out how trustworthy guidelines should be developed and articulated key standards as outlined in the table below.[1] The standards are similar to those developed by the Guideline International Network (G-I-N).[2] These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). The table below lays out how we hope to meet the standards for our rapid recommendations:

1. Establishing transparency **"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible."***
• This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content i available. • We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.
2. Managing conflicts of interest **"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",**
• Interests of each panel member are declared prior to involvement and published with the rapid recommendations. • No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ*. • No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issu for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic. • The Chair must have methods expertise, a clinical background and no financial or intellectual interests. • Funders and pharmaceutical companies have no role in these recommendations.
3. Guideline Development Group Composition **"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG."**
• The RapidRecs group will aim to include representation from most or every major geographic region in the world, with specific efforts made achieve gender-balance. • We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews

addressing values and preferences to guide outcome choices and relative weights of each outcome, where available.
- Patient-representatives will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.

4. Clinical Practice Guideline–Systematic Review Intersection
"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes."

- Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendaiton.
- The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication an continuity in the process.

5. Establishing Evidence Foundations for and Rating Strength of Recommendations
"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations."

- The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.[6] For each recommendation systematic and transparent assessments are made across the following key factors:
  - Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)[4]
  - Quality of the evidence[7]
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)

- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. pathophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE.[8]
- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus proce customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations
"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated."

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.[9]
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and with an individual patient.

7. External review
"External reviewers should comprise a full spectrum of relevant stakeholders...., authorship should be kept confidential....., all reviewer comment should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available t general public for comment..."

- At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy.
- A *BMJ* series adviser with methodological and/or statistical expertise will review the *BMJ* Rapid Recommendations publication and the systematic reviews.
- The *RapidRecs* panel will be asked to read and respond to the peer review comments and make amendments where they judge reasonable.
- *The BMJ* and *RapidRecs* executive team may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period o six months after publication.

8. Updating
"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence."

- The *RapidRecs* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

References

1. Laine C, Taichman DB, Mulrow C. Trustworthy clinical guidelines. Annals of internal medicine. 2011;154(11):774-775.
2. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. Annals of internal medicine. 2012;156(7):525-531.
3. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. Bmj. 2008;336(7652):1049-1051.
4. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-394.
5. Vandvik PO, Brandt L, Alonso-Coello P, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. Chest. 2013;144(2):381-389.
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-926.
7. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-406.
8. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. Journal of clinical epidemiology. 2013;66(7):726-735.
9. Kristiansen A, Brandt L, Alonso-Coello P, et al. Development of a novel, multilayered presentation format for clinical practice guidelines. Chest. 2015;147(3):754-763.

References