Antibiotics for preventing recurrent sore throat (Protocol)

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Antibiotics for preventing recurrent sore throat

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Editorial group: Cochrane Ear, Nose and Throat Disorders Group.

Citation: Ng GJY, Vu AN, Tan S, Del Mar CB, van Driel ML. Antibiotics for preventing recurrent sore throat. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD008911. DOI: 10.1002/14651858.CD008911.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review will look at recurrence after the administration of antibiotics in patients who have experienced three or more sore throats in a year. We will include participants with recurrent sore throats, defined as three or more episodes of sore throat in a year.

BACKGROUND

Description of the condition

Throat infections (known as 'sore throat', 'pharyngitis' or 'tonsillitis' if principally affecting the tonsils) affect the respiratory mucosa of the throat. The vast majority are self-limiting, that is they remit spontaneously. Throat infections cause inflammation of the mucosa and very rarely invasive infection of the potential spaces within and surrounding the oropharynx. They cause the clinical syndrome of throat pain, redness, swelling and enlarged lymph nodes, together with any number of other symptoms of acute respiratory infection. Causes include bacteria, viruses or, uncommonly, fungi. Other causes of sore throat (sometimes accompanying systemic disease) include trauma, tumours and gastro-oesophageal reflux disease. Determining the aetiological agent clinically is sometimes difficult. Acute sore throats are more common in children aged three to 13 years (30% to 40%) than in children aged less than three years (5% to 10%) or adults (5% to 15%) (eTG 2010).

Recurrent pharyngitis and tonsillitis has been defined in many different ways in different studies (Blakley 2009). A definition was developed by Paradise who studied the effect of tonsillectomy in children with severe recurrent tonsillitis: seven episodes in one year, five episodes per year for two years, or three or more episodes per year for three years (the 'Paradise criteria'). These arbitrary cut-off points were once used to guide tonsillectomy decision-making. In 2000, less stringent criteria were adopted and implemented by the American Academy of Otolaryngology & Head and Neck Surgery (AAO-HNS) in their 2000 guideline. That suggested that tonsillectomy was indicated if a patient contracts "three or more attacks of sore throat per year despite adequate medical therapy" (AAO-HNS 2000). This position has now changed significantly with the publication of the Academy’s new, evidence-based guideline in 2011 (AAO-HNS 2011). This new guidance endorses the original, and more stringent, "Paradise criteria".

Repeated episodes of acute pharyngitis/tonsillitis can cause a significant burden on families (absence from school or work) or society (healthcare costs) (Roos 1995). In a US-based survey, a relatively small proportion of children between four and 15 years old (1%) experienced repeated Group-A beta-haemolytic streptococci infections.
(GABHS) episodes in a three-year period, with the highest incidence between four and six years old (St Sauver 2006). However, at the population level this represents a significant number. The long-term sequelae of sore throat include suppurative complications (quinsy, acute otitis media, acute sinusitis) and non-suppurative complications (e.g. acute rheumatic fever, acute glomerulonephritis) (Del Mar 2006; eTG 2010; Ilyas 2008). Currently there are no good data on the natural history of recurrent sore throat (eTG 2010). However, an observational study on the symptoms and complications of sore throat is currently being performed in the UK (DESCARTE). In our review we define recurrent sore throat as three or more self-reported episodes of sore throat per year.

**Description of the intervention**

Conventional methods to treat acute sore throat include antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics (e.g. paracetamol) and corticosteroids. Antibiotics are commonly used against any bacteria that may be causing the infection in the throat, however this is controversial. In some countries (e.g. the USA) it is routine to culture the throat to establish whether Streptococcus is the infecting agent and treatment is based on the result of the culture (Bisno 2002). In other countries it is routine to use (imperfect) decision algorithms to best-guess the cause of the symptoms (Mathys 2007). There are large differences in clinical practice between countries (Froom 1990) and between primary care clinicians (Howie 1971). Adverse effects of antibiotic therapy include nausea, diarrhoea, major and minor allergic reactions and antibiotic resistance. Compared to the other methods of treatment, bar tonsillectomies, antibiotics provide more than pain relief as they potentially remove the source of infection.

**How the intervention might work**

A Cochrane Review assessing the effect of antibiotics in acute sore throat found that antibiotics showed only slight benefit in achieving symptom reduction (Del Mar 2006). Most patients (90%) are symptom-free by seven days, regardless of whether antibiotic therapy is used or not. Antibiotics provide benefit in reducing the incidence of suppurative (e.g. quinsy) and non-suppurative complications (e.g. acute rheumatic fever and acute glomerulonephritis, attributed to infection with GABHS), but the numbers needed to treat to prevent one case are high (Del Mar 2006).

It is not clear if more benefit can be expected from treatment with antibiotics in patients with frequent recurring episodes of acute sore throat.

**Why it is important to do this review**

Long-term antibiotics are sometimes used to prevent recurrent sore throat, however there is conflicting evidence regarding their effectiveness (eTG 2010). Furthermore, the effectiveness of antibiotics in reducing the number of recurrent episodes in pre-existing recurrent sore throat has not been reviewed in a Cochrane Review and meta-analysis. However, frequent use of antibiotics adds to the burden of antibiotic resistance in the community. Adequate management of frequent sore throat episodes therefore benefits both patients and society. The results of this review will inform clinical practice guidelines on the management of recurrent acute sore throat.

The effect of antibiotics on pre-existing recurrent sore throats was also not directly addressed in the Cochrane Review of tonsillectomy or adeno-tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis (Burton 2009). The question posed by that review differs from ours in that it focused on tonsillitis and defined recurrent as two or more episodes in a 12-month period.

**OBJECTIVES**

This review will look at recurrence after the administration of antibiotics in patients who have experienced three or more sore throats in a year. We will include participants with recurrent sore throats, defined as three or more episodes of sore throat in a year.

**METHODS**

Criteria for considering studies for this review

**Types of studies**

Randomised controlled trials (RCTs) or cluster-RCTs. We will include studies that follow up patients for a minimum of 12 months post-antibiotic therapy.

**Types of participants**

Adults and children who present in any clinical setting suffering from pre-existing recurrent sore throat according to a clinical definition (where recurrent is three or more episodes per year).

**Types of interventions**

Intervention
All antibiotics by any route of administration, at any dose and for any duration. We will exclude combinations of antibiotics.

**Comparison**
Placebo.

**Types of outcome measures**

**Primary outcomes**
1. Incidence of sore throat recurrence measured by the number of self-reported episodes per year (patients will be followed for a minimum of 12 months post-antibiotic therapy; we will then calculate results as occurrence per year); and cumulative severity measured in days of disability for incident cases.
2. Adverse effects (including diarrhoea, thrush, rashes, nausea etc.).

**Secondary outcomes**
1. Days off work, absence from school.
2. Incidence of complications (quinsy, acute rheumatic fever, acute glomerulonephritis, acute otitis media etc.).

**Search methods for identification of studies**
We will conduct systematic searches for randomised controlled trials. There will be no language, publication year or publication status restrictions.

**Electronic searches**
We will search the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, current issue); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; ISRCTN; ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform) and Google. We will model subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we will combine subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials in MEDLINE (as described in *The Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1, Box 6.4.b. (Handbook 2008)) and with adapted versions of this filter in EMBASE.

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) using the terms shown in Appendix 1.

**Searching other resources**
We will scan the reference lists of identified publications for additional trials and contact trial authors where necessary. In addition, we will search PubMed, TRIPdatabase, NHS Evidence - ENT & Audiology and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials.

**Data collection and analysis**

**Selection of studies**
Initially we will analyse the titles and abstracts from the searches. We will acquire the full text of studies that potentially meet the eligibility criteria. We will also obtain full-text articles if eligibility of the study cannot be determined due to insufficient information supplied in the abstract or absence of an abstract. Two authors (GN and ST) will independently assess study eligibility to ensure they meet the inclusion criteria of the review. Any disagreements over which studies to include will be resolved by discussion and consensus or if disagreement cannot be resolved by these methods, a third author will be consulted (CDM). Where clarification is required, we will contact the study authors to request the relevant information. We will document reasons for exclusion of studies.

**Data extraction and management**
Two authors (GN and ST) will independently extract data using standardised, pre-piloted data collection forms. Collection forms will include:
1. authors;
2. publication year;
3. name of journal;
4. participants (including total number, demographics, duration and characteristics of illness etc.);
5. intervention (type of antibiotic, route and duration); and
6. results (outcome measures, time points, effect, statistical significance, adverse effects).

Any disagreements will be resolved by discussion and consensus or if disagreement cannot be resolved by these methods, a third author (CDM) will be consulted. Where clarification is required, we will contact the study authors to request the relevant information. If disagreement remains unresolved, we will report disagreement in the review.

We will tabulate extracted information in a spreadsheet using Microsoft Excel before entering data into RevMan 5 (RevMan 2008). We will make all statistical conversions using a computer to ensure...
complete recording, as advised in Chapter 7.8 'Managing data' in the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2008).

Assessment of risk of bias in included studies
Two authors (AV and GN) will independently assess the risk of bias of each trial using the standard Cochrane criteria (Handbook 2008), with the following to be taken into consideration:

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5, which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry. This involves answering a pre-specified question whereby a judgement of ‘Yes’ indicates low risk of bias, ‘No’ indicates high risk of bias, and ‘Unclear’ indicates unclear or unknown risk of bias.

Any disagreements will be resolved by discussion and consensus or if disagreement cannot be resolved by these methods, a third author (MVD) will be consulted. Where clarification is required, we will contact the study authors to request the relevant information. If disagreement remains unresolved, this will be reported in review.

Measures of treatment effect
For numerical data, if outcomes are measured in the same way we will use the mean difference (MD) (+/- standard deviation (SD)) to compare the differences between groups. We will combine trials that measure the same outcome but use different methods by using the standardised mean difference (SMD).

For dichotomous data, we will present the results as odds ratios (OR) with 95% confidence intervals (CI).

Unit of analysis issues
The unit of analysis will be the unit of randomisation. For repeated observations on participants, we will avoid unit of analysis errors by defining different outcomes based on different periods of follow up and performing separate analyses. For events that may re-occur, we will take care to avoid unit of analysis issues. In the case of cluster-randomised trials we will make appropriate adjustment for clustering according to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2008).

Dealing with missing data
We will perform intention-to-treat analysis when possible (assuming missing data as treatment failure).

Assessment of heterogeneity
We will assess heterogeneity between trials with a two-stepped approach. First, we will assess heterogeneity at face value (e.g. when populations differ substantially or where setting and/or treatment are different). Second, we will assess statistical heterogeneity by performing a Chi² test and calculating the I² statistic. Cut-off values for the I² statistic will follow the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2008).

We will describe identified sources of heterogeneity.

Assessment of reporting biases
We will investigate reporting biases (such as publication bias) using funnel plots when there are 10 or more studies eligible for meta-analysis. If the outcomes are dichotomous, we will assess the funnel plot using the approach proposed by Egger (Egger 1997). For continuous outcomes, we will assess the funnel plot using the tests proposed by Harbord (Harbord 2006).

Data synthesis
We will synthesise data using Review Manager software (RevMan 5.0) (RevMan 2008).

In the absence of important heterogeneity we will use a fixed-effect model. We will not pool trials found to be heterogeneous, or in the case of statistical heterogeneity, we will pool using a random-effects model (Handbook 2008).

Subgroup analysis and investigation of heterogeneity
Subgroup analyses will include:
1. children versus adults;
2. children under two years versus older children; and
3. risk of bias (low versus high risk of bias).

Sensitivity analysis
If heterogeneity is present, we will examine the methodological and clinical characteristics of the included trials to explore the causes. We will then determine the impact of any clinical or methodological differences found by performing sensitivity analyses.

We will produce a summary table to report all sensitivity analyses.
**REFERENCES**

**Additional references**

**AAO-HNS 2000**


**AAO-HNS 2011**


**Bisno 2002**


**Blakley 2009**


**Burton 2009**


**Del Mar 2006**


**DESCARTE**


**Egger 1997**


**eTG 2010**


**Froom 1990**


**Handbook 2008**


**Harbord 2006**


**Howie 1971**


**Ilyas 2008**


**Matthys 2007**


**RevMan 2008**


**Roos 1995**


**St Sauver 2006**


*Indicates the major publication for the study*
APPENDICES

Appendix 1. Search strategy

#1 MeSH descriptor Pharyngitis explode all trees
#2 pharyngit*
#3 MeSH descriptor Nasopharyngitis explode all trees
#4 (Retropharyngeal OR Peritonsillar) NEAR Abscess
#5 nasopharyngit*
#6 MeSH descriptor Tonsillitis explode all trees
#7 tonsillit*
#8 (SORE* or INFLAMM* or INFECT*) NEAR THROAT
#9 Pharyngotonsillitis
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Anti-Bacterial Agents explode all trees
#12 MeSH descriptor Antibiotic Prophylaxis explode all trees
#13 MeSH descriptor Lactams explode all trees
#14 MeSH descriptor Quinolones explode all trees
#15 MeSH descriptor Macrolides explode all trees
#16 antibiot* OR (anti ADJ biot*) OR antimicrobial* OR (anti ADJ microbial*) OR bacteriocid* OR antibacterial* OR (anti ADJ bacterial*)
#17 penicillin* OR amoxicillin OR ampicillin OR clavulanic acid OR amoxiclav OR augmentin OR ticarcillin OR timentin OR flucloxacillin OR flumucil OR magnapen OR piperacillin OR tazocin
#18 cephalosporin* OR cefaclor OR distaclor OR cefadroxil OR baxan OR cefalexin OR ceporex OR keflex OR cefamandole OR kefadol OR cefazolin OR kefzol OR cefixime OR suprax OR cefotaxime OR cloran OR cefoxitin OR mecoxin OR cefpirome OR cefrom OR cefpodoxime OR orelox OR cefprozil OR cefzil OR cefradine OR velosol OR cefazidime OR fortum OR kefelin OR ceftriaxone OR rocephin OR cephalixin OR zinacef OR zinnat OR cefonicid OR aztreonam OR azactam OR imipenem OR cilastatin OR primaxin OR meropenem OR meronem OR tetracycline* OR deteclo OR demeclocyclin OR ledernycin OR doxycycline OR vibramycin OR minocycline OR minocinc OR oxytetracycline OR terramycin
#19 macrolide* OR erythromycin OR erymax OR erythrocin OR erythoped OR azithromycin OR zithromax OR clarithromycin OR klaricid OR telithromycin OR ketek OR trimoxazole OR seprin OR trimethoprim OR monotrim OR trimopan OR metronidazole OR flagyl OR metrolyl
#20 quinolone* OR ciprofloxacin OR ciproxin
#21 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 (#10 AND #21)
#23 MeSH descriptor Recurrence explode all trees
#24 recur* or recrudesc* or relaps* or reappear*
#25 MeSH descriptor Secondary Prevention explode all trees
#26 prophyla* or prevent*
#27 (#23 OR #24 OR #25 OR #26)
#28 (#22 AND #27)
HISTORY
Protocol first published: Issue 12, 2010

CONTRIBUTIONS OF AUTHORS
Gareth Ng, Anh Vu and Stephanie Tan wrote the protocol under guidance and supervision of Chris Del Mar and Mieke van Driel.

DECLARATIONS OF INTEREST
None known.