

Antibiotics for persistent cough or wheeze following acute bronchiolitis in children (Protocol)

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[Intervention Protocol]

Antibiotics for persistent cough or wheeze following acute bronchiolitis in children

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ABSTRACT

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

To determine the effectiveness of antibiotics compared to a control (no treatment or placebo) for persistent respiratory symptoms following acute bronchiolitis (within six months).

BACKGROUND

Description of the condition

Bronchiolitis is a common acute respiratory infectious condition, with a high prevalence worldwide (Chang 2009). It is a clinically diagnosed syndrome manifested by tachypnoea (rapid breathing) with crackles or wheeze in very young children. Multiple viruses and some bacteria can cause bronchiolitis, including respiratory syncytial virus, influenza, human metapneumovirus, rhinovirus, influenza, parainfluenza, adenovirus, and mycoplasma.

In the acute phase (< 14 days), antibiotics have only been recommended in the treatment of bronchiolitis when a secondary bacterial infection is suspected. In acute bronchiolitis, a Cochrane review (Spurling 2011) found “minimal evidence to support the use of antibiotics for acute bronchiolitis”.

Although bronchiolitis is usually a self-limiting condition, typically lasting from three to seven days, a number of children continue to display respiratory symptoms following acute bronchiolitis. Swingler 2000 reported that 39% of infants were still symptomatic after 14 days, 18% after 21 days and 9% after 28 days. (Swingler 2000). Other studies have shown that 40% to 50% of those hospitalised have a “grumbling, sometimes protracted, respiratory syndrome of persistent cough and recurrent viral-induced wheeze” (SIGN 2006). While symptoms such as cough and wheezing in post-acute bronchiolitis may be mild, they have the potential to increase burden of disease and some children present or represent to secondary care. Furthermore, in some settings, recurrent hospitalisations for bronchiolitis are common (Bailey 2009), thus increasing the burden (morbidity, social, economic, etc.) of disease. Also, cohort studies have suggested that bronchiolitis may trigger the development of asthma (Sigurs 2000; Carroll 2009). The possible biological mechanism giving rise to the persistent respiratory symptoms are likely multifactorial. In bronchiolitis, airway oedema occurs, the airway epithelium is affected and the ciliary damage can persist for 13 to 17 weeks (Wong 2005). Cilia are an important component of the airway’s clearance mechanism. Damage of airway cilia and the possible impairment of the innate immunity in severe bronchiolitis (Halfhide 2008) predisposes these infants to secondary bacterial infection. Persistent or delayed resolution of airway oedema, or secondary bacterial infection in the airways (endobronchial infection) related to persistent ciliary damage can cause wheeze, cough or both.

Description of the intervention

In the presence of endobronchial infection, antibiotics are a potentially beneficial intervention for post-acute bronchiolitis. Antibiotics may be given orally, intravenously, or via nebuliser. The efficacy of antibiotics in the acute or non-acute phase may be possibly influenced by study setting. For example, in non-affluent settings where bacterial colonisation of the nasopharynx is higher than in

affluent urban settings (Leach 1994), antibiotics are possibly more effective when dense bacterial load is present in the upper airways.

How the intervention might work

Antibiotics may be useful in treating the symptoms of post-acute bronchiolitis, by eliminating the secondary bacterial infection in the airways. Lower airway bacterial infection following viral respiratory infection has been well described in airway cells in vitro (Didierlaurent 2008), as well as in clinical studies (McCullers 2006).

In addition to an antibacterial effect, the anti-inflammatory properties of antibiotics, such as macrolides, may have an additional effect through its immunomodulatory effect and influence on neutrophilic inflammation (Giamarellos-Bourboulis 2008; Zarogoulisidis 2011), thus reducing airway oedema.

Elimination of the endobronchial infection and/or inflammation, may reduce airway secretions and/or oedema, and thus consequently improve the persistent respiratory symptoms.

Why it is important to do this review

A small but not insignificant number of children with acute bronchiolitis have persistent problems after the acute viral infection (for a variety of reasons) and these children are usually seen in secondary and tertiary practice. This group of children are clinically treated with a variety of medications such as antibiotics, bronchodilators, inhaled (Fox 1999) and oral corticosteroids (Blom-Danielle 2007), and leukotriene receptor antagonists (Kim 2010). This clinical issue has been identified as an area that needs more research (SIGN 2006). Further, use of any medications may result in adverse events, and persistence of symptoms also influence burden of disease and health economics. Thus, a systematic review of the benefits, or otherwise, of using antibiotics in the post-acute bronchiolitis phase will be useful to guide clinical practice.

OBJECTIVES

To determine the effectiveness of antibiotics compared to a control (no treatment or placebo) for persistent respiratory symptoms following acute bronchiolitis (within six months).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) comparing antibiotics with controls (placebo or no treatment) given in the post-acute phase of bronchiolitis.

Types of participants

Inclusion criteria: previously well children (aged < 2 years) with bronchiolitis (as defined by study authors) who have been treated with antibiotics beyond the acute bronchiolitis period (>14 days). Exclusion criteria: children with any underlying chronic disease such as lung disease (cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, aspiration, etc.), cardiac disease, and immunodeficiency (primary or secondary).

Types of interventions

All types of antibiotics, given beyond the acute period (>14 days). This includes antibiotics prescribed for acute bronchiolitis that goes beyond the acute phase of 14 days.

Types of outcome measures

Primary outcomes

1. Proportion of participants who were not cured at follow-up (up to six months).
2. Proportion readmitted for a respiratory illness within six months.

We will determine the proportion of participants who failed to improve on treatment (antibiotics or placebo), and the mean clinical improvement, using the following hierarchy of assessment measures (where two or more assessment measures are reported in the same study, we will use the outcome measure that is listed first in the hierarchy).

1. Objective measurements of cough/wheeze indices (cough or wheeze recordings, cough receptor sensitivity, and airway hyper-responsiveness).
2. Symptomatic measures, as assessed by parents or carers (quality of life, Likert scale, Visual Analogue scale, level of interference of respiratory symptoms, and diary cards).
3. Symptomatic measures, as assessed by clinicians (Likert scale, Visual Analogue scale, level of interference of respiratory symptoms, and diary cards).

Secondary outcomes

1. Proportion of participants who were not substantially improved at follow-up (up to six months).
2. Mean difference in cough or wheeze indices (diary, frequency, scores, and quality of life).
3. Proportion of participants with recurrent wheeze (within six months of intervention).

4. Proportion of participants experiencing adverse effects of the intervention.

5. Proportion of participants experiencing complications (e.g. requirement for medication, or pneumonia).

We will select complete resolution of symptoms as the primary outcome, as previously well children should completely recover after an episode of acute bronchiolitis. As different studies may use different outcome measurements to signify a cure, we will define a hierarchy of outcomes, where we consider objective markers superior to subjective measurements. Pneumonia and recurrent wheeze (some with requiring repeat hospitalisation) have been reported in cohort studies of bronchiolitis (Bailey 2009). Thus we will consider readmission for a respiratory infection and recurrent wheeze as important outcomes.

Search methods for identification of studies

Electronic searches

The Cochrane Airways Group's Trials Search Co-ordinator will perform the search; we will identify trials using the following databases.

- The Cochrane Airways Group Register of Trials
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE (Ovid)
- EMBASE (Ovid)
- ClinicalTrials.gov

The proposed MEDLINE strategy is listed in [Appendix 1](#). We will adapt this for use in the other databases. We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of the included studies and relevant review articles for additional references. We will also contact authors of identified trials, where appropriate, to seek further identification of other published and unpublished studies.

Data collection and analysis

Selection of studies

Two authors (GM, AC) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, adjudication sought from another author (PM).

Data extraction and management

Two authors (GM, AC) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (PM). We will manage data in Review Manager 5.1 (RevMan 2011), and according to recommendations in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear.

Measures of treatment effect

For dichotomous variables, we will calculate individual and pooled statistics as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes measured on the same metrics, we plan to calculate the individual and pooled statistics as mean differences (MDs) with 95% (CIs). For continuous outcomes measured on different metrics, we will combine data with a standardised mean difference (SMD).

Unit of analysis issues

Cross-over and cluster-randomised trials are not appropriate for the target population and therefore we will not include them.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data when necessary.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity we will explore it by prespecified subgroup analysis. We will consider levels of heterogeneity greater than 50% as substantial.

Assessment of reporting biases

Where we suspect reporting bias, we will attempt to contact study authors and ask them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by conducting a sensitivity analysis. We plan to investigate publication bias by visually inspecting a funnel plot if we are able to meta-analyse 10 or more trials in a single outcome.

Data synthesis

We plan to create a Summary of findings table using the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and by using GRADEpro software. We plan to include only the following outcomes: proportion of participants who were not cured at follow-up; proportion readmitted for a respiratory illness within six months; and serious adverse events.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Type of control arm (placebo/no treatment).
2. Severity (hospitalised versus non-hospitalised).
3. Macrolides versus other types of antibiotics.
4. Short (≤ 7 days) versus longer (> 7 days) courses of antibiotics.
5. Antibiotics commencement (≤ 14 days or > 14 days of onset of bronchiolitis).
6. Setting of study (affluent versus non-affluent setting).

Sensitivity analysis

We plan to remove studies considered to be at a high or unclear risk of bias for methodological quality from the meta-analysis, and examine any change in the summary statistic.

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practice in respiratory diseases. *European Journal of Clinical Pharmacology* 2011;**67**:1–25.

* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE (Ovid) search strategy

1. exp Bronchiolitis/
2. Respiratory Syncytial Virus Infections/
3. bronchioliti\$.tw.
4. RSV\$.tw.
5. or/1-4
6. Cough/
7. Respiratory Sounds/
8. cough\$.tw.
9. wheez\$.tw.
10. post-viral\$.tw.
11. post-acute\$.tw.
12. co.fs.
13. Recurrence/
14. or/6-13
15. 5 and 14
16. post-RSV\$.tw.
17. post-bronchiolit\$.tw.
18. 15 or 16 or 17
19. exp Anti-Bacterial Agents/
20. antibiotic\$.tw.
21. exp Macrolides/
22. (macrolide\$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).tw.
23. (penicillin\$ or amoxicillin or amoxicillin or ampicillin or benzylpenicillin or cloxacillin or dicloxacillin or flucloxacillin or piperacillin or ticarcillin or sulbactam).tw.
24. (cephalosporin\$ or cephalixin or cephacolor or cefaclor or cefepime or cefotaxime or cephamycin\$ or cefotetan or cefoxitin or cefmetazole or cefpirome or cefpodoxime or ceftazidime or ceftriaxone or cephamandole or cephalosporin).tw.
25. (fluoroquinolone\$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).tw.
26. (tetracycline\$ or doxycycline or methacycline or minocycline).tw.
27. (amikacin or gentamicin or neomycin or netilmicin).tw.
28. (clindamycin or lincomycin).tw.
29. (chloramphenicol or amantadine or cotrimoxazole or trimethoprim).tw.
30. or/19-29
31. 18 and 30
32. exp Child/
33. exp Pediatrics/
34. exp infant/
35. exp adolescent/
36. (paediatric\$ or pediatric\$ or child\$ or adolescen\$ or infant\$ or young\$ or preschool\$ or pre-school\$ or newborn\$ or new-born\$ or neonat\$ or neo-nat\$).tw.

37. or/32-36

38. 31 and 37

We will combine this search with the Cochrane recommended filter to identify RCTs ([Lefebvre 2011](#)).

HISTORY

Protocol first published: Issue 6, 2012

CONTRIBUTIONS OF AUTHORS

The protocol was written by GM and AC. PM reviewed the protocol.

DECLARATIONS OF INTEREST

All authors are involved in a RCT on the efficacy of azithromycin to reduce the respiratory burden of bronchiolitis in indigenous children hospitalised with bronchiolitis ([Chang 2011](#)).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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