COCHRANE COMMENTARIES

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Title
Antibiotics for prolonged wet cough in children

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What is this review about?
The clinical efficacy and risk of harm of antibiotics in treating children with prolonged wet cough who do not have a chronic respiratory condition.

What are the findings?
In the antibiotic group:

- Number needed to treat for beneficial outcome (NNTB) of 3 (95%CI 2-4)
- Uncertain risk of increase in adverse events (OR 1.88, 95% CI 0.62-5.69)

What are the findings based on?
An update of a review published in 2005[1]including one Australian [2]and two Swedish randomised controlled trials[3,4] (see Table 1).

Of 190 randomised children, 171 (90%) completed the 3 trials. All participants were children <18 years old, mean age for the studies ranging from 21 months to 6 years. In the two Swedish

studies[3, 4] prolonged cough was defined as cough lasting >10 days: in one 50% of children who had cough >3 weeks[3] and in the other mean cough duration was 3-4 weeks[4]. In the Australian study[2] the median length of cough was approximately 3 months (11-15 weeks).

The two Swedish studies did not mention the quality of the cough in their publications, but contact by the review authors confirmed that at least 75% of children had wet cough[3,4]. Two studies were classified as low risk of bias[2,4]. One was at risk of detection bias due to inadequate blinding of personnel, participants and outcome assessors[5].

The open randomised study compared one week of erythromycin with a "no treatment" group. The two other trials compared amoxicillin/clavulanic acid (Augmentin™) and placebo. There were important differences to usual practice and between studies. There were also differences in outcome assessment, with clinical assessment the primary outcome for two studies, and a validated cough diary for one (Table 1).

The primary outcome for the meta-analysis was children "not cured"or "not substantially improved" at follow-up and resulted in a pooled odds ratio of 0.15 (95%CI 0.07- 0.31) (Figure 1). Based on these results, one child would be cured for every three treated with antibiotics (NNTB= 3, 95% CI 2-4). Progression of disease resulting in additional medical therapy was available for two studies[3,4] with an overall need for antibiotics of 36% for controls compared to 5% requiring further antibiotics in the treatment group (OR 0.10; 95% CI 0.03-0.34; NNTB=4; 95% CI 3-5). Adverse events monitoring varied between studies, as shown in Table 1.

Table 1. Characteristics of included studies.

Study	Study design & inclusion criteria	Participants	Age group (years)	Intervention	Control group	Follow-up post-randomisation	Primary outcomes, OR (95%CI)	Secondary outcomes, OR (95%CI)
Darelid et al. (1993)[3]	Open randomised trial, cough >10 days	n=88, >75% with wet cough >50% with cough > 3weeks	0.5- 6	Erythromycin, 25mg/kg BD for 7days oxymetazoline nasal drops salbutamol (oral) allowed nasopharyngeal swab at baseline and F/U	No placebo, oxymetazoline nose drops, salbutamol (oral) allowed	Day 8	**paediatrician assessment** 0.1 (0.03 -0.28)	**adverse events (assume no adverse events in control group as not reported)**, 3.52 (0.14-88.76) **% needing additional antibiotics,** 0.06 (0.01-0.29) clinical symptom score (parents) nasal pathogen elimination
Gottfarb et al. (1994)[4]	Double-blind randomised controlled trial cough > 10 days cough score e 8	n=52, >75% with wet cough median duration cough 3-4 weeks	0.6-7, median: 2.6	amoxicillin/clavulanic acid, 20mg/kg/day for 7 days nasopharyngeal swabs & serology (pertussis &mycoplasma) at baseline and F/U	Placebo for 7 days	Days 12-14	**paediatrician assessment** 0.21 (0.05 – 0.78)	**adverse events,** 1.0 (0.18-5.48) **% needing additional antibiotics,** 0.31 (0.03-3.34) parental assessment of recovery number of coughing attacks/day until D8
Marchant et al. (2012)[2]	Parallel double-blind randomised controlled trial wet cough >3 weeks	n=50, median duration cough 11-15weeks	0.5-18, median: 1.7-2.8	amoxicillin/clavulanic acid, 22.5mg/kg BD for 14days bronchoscopy and lavage prior	Placebo for 14 days	end of trial = Days 15-16 end of study = Day 28	**cough resolution (>75% reduction in cough score) or cessation of coughing e3days** 0.25 (0.06-1.05)	**adverse events,** 2.88 (0.5-16.48) mean absolute change in cough score change in score at end of study

OR = odds ratio, CI = confidence interval, bold = outcome used in meta-analysis

Implications for practice

The available evidence suggests that a short course of oral antibiotics for children presenting with prolonged cough is efficacious in eliminating cough symptoms. However, for clinical care chronic cough is defined as cough lasting more than 4-8 weeks and treatment with antibiotics is not recommended in the setting of sub-acute cough (cough <4 weeks) as it is important that children are not treated with antibiotics unnecessarily. Children included in this meta-analysis may have experienced spontaneous cough resolutionand may not have had wet cough, as the quality of the cough was not specifically defined.

Clinical perspective

"Wet" or "productive cough" is caused by an abnormal increase in airway secretions. A wet cough can be caused by infection including pneumonia or upper respiratory tract viral infection (URTI), protracted bacterial bronchitis, suppurative lung disease or bronchiectasis. The "wet" characteristic helps differentiate the cough from alternative diagnoses such as asthma which is classically dry, episodic and usually associated with wheeze[6]. Studies have shown that parents, as well as physicians, are able to accurately differentiate between wet and dry cough[7].The most frequent cause of wet cough in children is acute viral upper respiratory tract infection (URTI). It is now generally accepted that acute cough may last up to four weeks, but usually begins to abate by the second or third week[8,9]. When the cough does not fit this classic URTI pattern, the child should be assessed for chronic wet cough.

The definition of chronic cough varies between guidelines but includes persistent cough lasting greater than four weeks, the definition used in the Australian CICADA guidelines[10,11]. British Thoracic Society guidelines written in 2008, defined chronic cough as cough lasting greater than eight weeks[8] to clearly differentiate from acute cough.

Most children with chronic wet cough will have protracted bacterial bronchitis[12], which is a chronic wet cough without specific signs and symptoms of an alternative diagnosis. The condition is caused by a bronchial infection with common respiratory pathogens typically *Haemophilus influenzae, Streptococcus pneumoniae* or *Moraxella catarrhalis*[13]. Antibiotics effective against these pathogens treat the condition though bacterial eradication. An assessment needs to be undertaken to differentiate post-viral or sub-acute cough from protracted bacterial bronchitis and other more serious causes of cough including bronchiectasis, cystic fibrosis, recurrent aspiration, infection due to immunodeficiency or inhaled foreign body[5]. Signs which suggest an alternate diagnosis include persistent chest signs on auscultation, recurrent sinopulmonary infections, haemoptysis, failure to thrive, clubbing, nasal polyps or chest wall deformity. Protracted bacterial bronchitis classically responds to two

weeks of oral antibiotics. However, due to the limited evidence the recommended duration of the course and the class of antibiotic recommended varies between guidelines[8,10,11].

Protracted bacterial bronchitis may lie within the same disease spectrum as bronchiectasis, the latter occurring in the setting of delayed antibiotic therapy and resulting in significant morbidity and mortality. The authors of this Cochrane review[5] noted that the studies included in this meta-analysis included participants whose symptomatology did not meet the current definition of chronic cough. As the studies were performed when the definition of chronic cough was of shorter duration, a decision was made by the Cochrane authors to include these studies in the meta-analysis. Children enrolled in these early studies may have been treated with antibiotics unnecessarily.

Indigenous children of Australia, New Zealand and Canada have been shown to have much higher rates of bronchiectasis than the non-Indigenous population[14-16]. It is particularly important to recognise protracted bacterial bronchitis in this cohort and commence treatment to try to prevent chronic lung disease. Unfortunately, none of the three studies included in the meta-analysis described the frequency and outcomes of Indigenous participants.

Cough is one of the most common acute presentations to doctors and leads to significant parental stress and financial burden [17,18]. Appropriate cough treatment also improves quality of life[19]. Persistent bacterial bronchitis is a simple clinical diagnosis if wet cough has not resolved spontaneously, and has lasted more than four weeks with no sign of improvement. Once recognised, evidence-based antibiotic therapy should be commenced. Of equal importance is reduction of inappropriate treatment with antibiotics for subacute cough, to prevent patient harm and risk of increased incidence of antimicrobial resistance in the community.

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Figure 1 Comparison of Antibiotics versus no antibiotics for wet cough in children, outcome children not cured or not substantially improved at follow-up.[5] (Reproduced with permission)

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 1 Children not cured or not substantially improved at follow-up (using intention-to-treat analysis)