Are Antibiotics Effective in the Treatment of Children With Prolonged Wet Cough?

TAKE-HOME MESSAGE

Antibiotics may improve clinical cure and reduce progression of illness in children with prolonged wet cough.

METHODS

DATA SOURCES

Authors identified trials from the Cochrane Airways Trials Register, CENTRAL, MEDLINE OvidSP, and EMBASE OvidSP through September 2017, with no language restrictions. They evaluated reference lists of primary and review articles for additional studies. Finally, they searched ClinicalTrials.gov and the World Health Organization trial portal.

STUDY SELECTION

Two authors independently reviewed relevant studies and selected trials for inclusion. A third author adjudicated disagreements through discussion. The meta-analysis included all randomized controlled trials comparing antibiotics with placebo or no treatment among children younger than 18 years who had no known pulmonary conditions and prolonged wet cough (defined as cough >10 days with presence of lower airway secretions). Investigators planned to evaluate short-term treatment (<14 days), long-term antibiotics (>14 days), and intravenous antibiotics provided for at least 5 days. The

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This review does not reflect the views or opinions of the US government, Department of Defense or its components, US Army, US Air Force, or the SAUSHEC EM Residency Program.

Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Marchant JM, Petsky HL, Morris PS, et al. Antibiotics for prolonged wet cough in children (review). *Cochrane Database Syst Rev.* 2018;7:CD004822.**

Results

Outcome	No. of Studies (No. of Patients)	Relative Effect, OR (95% CI)	Evidence Quality (GRADE)	Heterogeneity (I^2), %
Patients not cured or substantially improved	3 (190)	0.15 (0.07–0.31)	Moderate	0
Patients with disease progression resulting in additional therapy	2 (125)	0.10 (0.03–0.34)	Moderate	20
Patients experiencing adverse effects*	3 (190)	1.88 (0.62–5.69)	Low	0

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *OR*, odds ratio.
*Adverse effects include diarrhea, nausea, rash, and allergic reactions.

Authors included 3 randomized controlled trials comprising 190 patients (171 who completed all study procedures) for analysis from an initial 4,337 studies identified. These 3 trials were single center, with 2 conducted in a pediatric outpatient clinic recruiting children with greater than 10 days of cough[2,3] and 1 in a pediatric

authors excluded trials comparing 2 or more antibiotics without a placebo arm.

DATA EXTRACTION AND SYNTHESIS

Two authors independently extracted data from included studies. Authors contacted the investigators of included studies for missing data when possible. Primary outcomes included children not cured or substantially improved according to the following hierarchy: objective measurements of cough indices, symptoms as assessed by the child, symptoms as assessed by parents or caregivers, symptoms as assessed by clinicians, airway markers obtained by bronchoalveolar lavage, sputum volume alone, and lung function test results alone. Secondary outcomes included disease progression requiring further medical therapy and antibiotic adverse effects. Authors calculated odds ratios with 95% confidence intervals (CIs) with fixed-effects models and calculated the number needed to treat for an additional beneficial outcome. Authors planned a priori subgroup analyses for children younger than 7 years, control type, variation in duration of treatment, and antibiotic type and planned sensitivity analyses. Investigators assessed heterogeneity with the I^2 and χ^2 tests, and 2 authors independently assessed risk of bias based on the *Cochrane Handbook for Systematic Reviews of Interventions*, with disagreements resolved by either consensus or discussion with a third author.[1] Authors assessed evidence quality with Grading of Recommendations Assessment, Development and Evaluation considerations.

respiratory outpatient clinic including children with cough greater than 3 weeks.[4] One open randomized study compared erythromycin for 7 days with no treatment,[2] and 2 double-blind studies compared amoxicillin/clavulanic acid (7 or 14 days) with placebo.[3,4] Mean age ranged from 21 months to 6 years. Antibiotics reduced the proportion of patients not cured at follow-up, with a number needed to treat for an additional beneficial outcome of 3 (95% CI 2 to 4). Antibiotics also decreased illness progression necessitating further therapy, with a number needed to treat for an additional beneficial outcome of 4 (95% CI 3 to 5) (Table). Adverse events were similar between groups. Authors did not identify significant heterogeneity. They determined 2 studies to be at high or unclear risk of bias and 1 study to be at low risk of bias. Evidence quality was moderate for all outcomes except for antibiotic adverse events (low quality). Subgroup and sensitivity analyses favored patients receiving antibiotics.

Commentary

Approximately 10% of acute presentations to physicians are due to a coughing illness,[5] and prolonged cough in children has an association with greater parental stress.[6] The definition of pediatric prolonged cough is a cough lasting greater than 4 weeks. Classification includes wet (productive) versus dry, and the presence of lower airway secretions defines wet cough.[7,8] Studies have found protracted bacterial bronchitis to be the most common cause of wet cough in these patients.[9] The definition of protracted bacterial bronchitis is prolonged wet cough without signs or symptoms of an alternative cause that responds to 2 weeks of antibiotic therapy.[9] In pediatric patients with wet cough, one previous systematic review suggested that the majority of patients had lower airway infection with common respiratory bacteria from sputum, thus suggesting a potential benefit of antibiotic therapy.[10] However, the risk of adverse effects may outweigh the benefit of antibiotics in this clinical circumstance.

This meta-analysis sought to evaluate the current evidence in regard to antibiotics in children with prolonged wet cough. It found that antibiotics improved clinical cure rate (number needed to treat for an additional beneficial outcome of 3) and decreased illness progression (number needed to treat for an additional beneficial outcome of 4). Of 3 studies included, 2 examined amoxicillin/clavulanic acid,[3,4] whereas the third examined erythromycin.[2] Given the bacteriology demonstrated in pediatric patients with wet cough, antibiotics active against these respiratory pathogens may improve clinical cure. These results for pediatric prolonged cough differ from those of previous Cochrane Reviews about antibiotics for the common cold and bronchitis that suggested no benefit to antibiotic therapy.[11,12] The results of this current meta-analysis should not justify liberal use of antibiotics because the review included only 190 patients from 3 studies (2 with high or unclear risk of bias). Rather, consideration of risks and benefits is necessary, and primary care follow-up for patients who are otherwise well appearing is likely acceptable for these patients.

The inclusion of patients with cough for greater than 10 days is a limitation because it implies that study results apply to a potentially heterogeneous patient population with wide variation in terms of duration of symptoms. This heterogeneity may be problematic insofar as patients with longer duration of symptoms may be more likely to benefit from antibiotics. Indeed, many included patients had cough duration exceeding 3 weeks.[2-4] The randomization used in each of the included studies makes it likely that spontaneous resolution occurred equally in treatment and placebo groups. Nevertheless, the study findings may be less generalizable to patients with relatively shorter duration of symptoms (eg, 11 days). Other limitations of this meta-analysis include different antibiotics and dosages used. Studies used different treatment durations, and authors were unable to compare short- and long-term duration therapy. None of the included studies used long-term follow-up, and recurrence rates are not known. One included study specifically excluded patients with allergy,[2] which is important because allergic rhinitis and ongoing seasonal allergies are often implicated in prolonged cough. Results are limited to patients who otherwise appeared well and did not have other signs of underlying lung conditions. Finally, although authors found similar rates of adverse events in patients receiving antibiotics, this evidence was of low quality.

According to this meta-analysis, antibiotics may improve clinical cure and reduce progression of illness in children with prolonged wet cough who are otherwise well appearing and with no other known pulmonary conditions.[13] Further data are necessary to evaluate the specific duration of therapy with validated objective measures of outcome, subgroups such as individuals with allergic rhinitis and ongoing seasonal allergies, and the use of amoxicillin/clavulanic acid. More data about adverse effects of antibiotics in this patient population are also necessary.

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