

Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years

ABSTRACT

N/A

Setting: Birth cohort of general population of Zealand region, Denmark.

Patients: At the age of 1 week, 700 infants were recruited and observed via daily parental diaries until the age of 3 years. Included in the trial were children who developed recurrent troublesome lung symptoms, defined as: 5 episodes in 6 months of cough, dyspnoea or wheeze severely affecting the well-being of the child; 4 weeks of continuous symptoms; severe episode requiring admission or treatment with oral steroids. Three months of inhaled fluticasone was given at the diagnosis of recurrent troublesome lung symptoms and continued for another 6 months if symptoms recurred.

Intervention: Children older than 1 year of age were assessed by a study physician at each acute episode (≥ 3 consecutive days of cough, dyspnoea or wheeze severely affecting the well-being of the child) and randomly allocated to azithromycin (10 mg/kg/day for 3 days) or placebo. Hypopharyngeal aspirates were analysed by viral PCR and bacterial culture. Additional treatment, including montelukast, β_2 agonist therapy or prednisolone, was given at the clinician's discretion. Parents and investigators were blinded.

Exclusion criteria: Macrolide allergy, heart, liver, neurological or kidney disease; evidend of pneumonia (C reactive protein level of >50 mg/L; respiratory rate ≥ 50 breaths/min or fever $\geq 39^\circ$ C).

Primary outcome: Duration of respiratory symptoms after treatment, measured by parental diary cards.

Secondary outcomes: The time from treatment to the next episode, the number of episodes that turned into severe exacerbations and the duration of β_2 agonist use after treatment.

MAIN RESULTS

Of 273 children diagnosed with recurrent troublesome lung symptoms, 72 with a total 158 episodes were randomised to treatment with azithromycin or placebo. At assessment, 18% children had wheeze. Ten episodes (five in each group) were excluded from analysis due to missing data or non-ingestion of treatment. Mean symptom duration was 3.4 days in the azithromycin group and 7.7 days in the placebo group (63.3% reduction, $p<0.0001$). The effect was increased when azithromycin was given earlier in the illness (83% reduction if given prior to day 6). The effects were largely independent of the positive isolation of

bacteria or viruses, bar the isolation of *Haemophilus influenzae*, which increased the treatment effect.

Azithromycin reduced the duration of the use of β_2 agonists but did not reduce the time to next episode of troublesome lung symptoms (HR 0.95, CI 0.65 to 1.4, $p=0.84$). Too few episodes requiring hospitalisation or oral steroids occurred for analyses.

CONCLUSION

Azithromycin significantly reduces the duration of acute spells of asthma-like symptoms in children aged 1–3 years.

Abstracted from: Stokholm J, Chawes LB, Vissing HN, *et al.* Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016;4:19–26.

COMMENTARY

One-third of preschool children wheeze, and some go on to develop asthma.¹ Asthma-like symptoms, such as cough, wheeze, and breathlessness, often result in emergency attendances.² Current acute treatments in preschool children include oral steroids, β_2 agonists and leukotriene receptor antagonists. Evidence is limited for antibiotics as primary treatment.³

This trial suggests azithromycin may be beneficial for acute asthma-like symptoms. Achieving the power calculation target, small (1%) dropout rate and using an intention-to-treat analysis add to the methodological strength. Early azithromycin use shortened symptom duration (83% risk reduction). The authors did not specify which symptoms were shortened. It may, therefore, have only reduced coughing, which itself may have been caused by bacterial infection.

Blind treatment of all wheezy preschoolers with azithromycin could cause microbial resistance. A study is needed to determine whether azithromycin is beneficial to the subgroup whose wheeze fails to respond to β_2 agonists and likely need admission. Additionally, a comparison of azithromycin versus penicillins to clarify whether the effect is antibacterial or antineutrophil.

This trial suggests azithromycin has a large treatment effect in reducing the duration of asthma-like symptoms. However, widespread use for preschool wheeze/asthma could result in harm, for example, an increased incidence of macrolide resistance, allergy and gastrointestinal side effects. Given that this is often a mild self-resolving disorder, we would limit azithromycin for acute wheezy episodes potentially needing admission.

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