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Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial

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Summary

Background Bacteria and viruses are equally associated with the risk of acute episodes of asthma-like symptoms in young children, suggesting antibiotics as a potential treatment for such episodes. We aimed to assess the effect of azithromycin on the duration of respiratory episodes in young children with recurrent asthma-like symptoms, hypothesising that it reduces the duration of the symptomatic period.

Methods In this randomised, double-blind, placebo-controlled trial, we recruited children aged 1–3 years, who were diagnosed with recurrent asthma-like symptoms from the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort; a birth cohort consisting of the general Danish population of Zealand, including Copenhagen. Exclusion criteria were macrolide allergy, heart, liver, neurological, and kidney disease, and, before each treatment, one or more clinical signs of pneumonia (respiratory frequency of ≥50 breaths per min; fever of ≥39°C; C-reactive protein concentration of ≥476·20 nmol/L [≥50 mg/L]). Each episode of asthma-like symptoms lasting at least 3 days was randomly allocated to a 3-day course of azithromycin oral solution of 10 mg/kg per day or placebo after thorough examination by a study physician at the Copenhagen Prospective Studies on Asthma research unit. Each episode was randomly allocated independently of previous treatment from a computer-generated list of random numbers in blocks of ten (generated at the Pharmacy of Glostrup). Investigators and children were masked until the youngest child turned 3 years of age and throughout the data validation and analysis phases. The primary outcome was duration of the respiratory episode after treatment, verified by prospective daily diaries and analysed with Poisson regression. Analyses were per protocol (excluding those without a primary outcome measure or who did not receive treatment). This trial is registered with ClinicalTrials.gov, number NCT01233297.

Findings Between Nov 17, 2010, and Jan 28, 2014, we randomly allocated 158 asthma-like episodes in 72 children (79 [50%] to azithromycin and 79 [50%] to placebo). The mean duration of the episode after treatment was 3·4 days for children receiving azithromycin compared with 7·7 days for children receiving placebo. Azithromycin caused a significant shortening of the episode of 63·3% (95% CI 56·0–69·3; p<0·0001). The effect size increased with early initiation of treatment, showing a reduction in episode duration of 83% if treatment was initiated before day 6 of the episode compared with 36% if initiated on or after day 6 (p<0·0001). We noted no differences in clinical adverse events between the azithromycin (18 [23%] of 78 episodes included in final analysis) and placebo (24 [30%] of 79) groups (p=0·30), but we did not investigate bacterial resistance patterns after treatment.

Interpretation Azithromycin reduced the duration of episodes of asthma-like symptoms in young children, suggesting that this drug could have a role in acute management of exacerbations. Further research is needed to disentangle the inflammatory versus antimicrobial aspects of this relation.

Funding Lundbeck Foundation, Danish Ministry of Health, Danish Council for Strategic Research, Capital Region Research Foundation.

Introduction

Childhood asthma is often preceded by recurrent episodes of troublesome lung symptoms in relation to airway infections in the first years of life.[1,2] Treatment of such episodes represents a major unmet clinical need; they are the most common cause of admission to hospital in young children, are a reason for stress and anxiety for families, and cause a major draw on health-care resources.[3–5]

We discovered in our birth cohort, the Copenhagen Prospective Studies on Asthma in Childhood 2000 ($COPSAC_{2000}$; a previous birth cohort of children born to mothers with asthma), that airway bacteria (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*) and respiratory viruses (at least one of picornavirus, respiratory syncytial virus, coronavirus, parainfluenzavirus, influenza virus, human metapneumovirus, adenovirus, or bocavirus) are equally closely associated with episodes of asthma-like symptoms in the first 3 years of life.[6] Bacteria and viruses occurred together in most cases, challenging the previous

Lancet Respir Med 2016; 4: 19–26

Published Online December 15, 2015 http://dx.doi.org/10.1016/S2213-2600(15)00500-7

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Research in context

Evidence before this study

Findings from a publication from the Copenhagen Prospective Studies on Asthma in Childhood showed that both bacteria and viruses are equally associated with the risk of acute episodes of asthma-like symptoms in young children, suggesting that antibiotics such as azithromycin could help in management of such episodes. We searched PubMed up to Oct 15, 2010, with no language limits, for various combinations of the search terms "RCT", "childhood", "asthma", "wheeze", and "antibiotics". We identified all previous randomised controlled trials of treatment with antibiotics for asthma and wheezy exacerbations, but focused mainly on childhood asthma. The search led us to new articles, but also identified other relevant old publications for background material. Investigators of two randomised trials concluded no beneficial effect of β-lactam treatment for acute exacerbations, which has led to present guidelines not recommending antibiotic treatment for episodes of acute asthma-like symptoms.

Added value of this study

This study is, to our knowledge, the first randomised controlled trial of azithromycin treatment of acute episodes of asthma-like symptoms in children aged 1–3 years with a history of recurrent episodes and its findings show a clinically significant shortening of symptom duration by 63% after intervention.

Implications of all the available evidence

Present guidelines do not recommend antibiotics for treatment of episodes of asthma-like symptoms in young children, yet antibiotics remain among the most commonly prescribed drugs in these episodes. Our findings suggest that azithromycin might be beneficial after medical assessment of an acute asthma-like episode in young children with a known history of such symptoms and without clinical signs of pneumonia. How the effect of azithromycin is compared with narrow-spectrum antibiotics and whether long-term effects are associated with recurrent use of azithromycin need to be investigated.

hypothesis that episodes with asthma-like symptoms in this age group are largely virally induced.[7–9] This finding suggested that bacteria might play an equal part in the pathogenesis of such episodes and that treatment with antibiotics might ameliorate symptoms. At present, guidelines do not recommend antibiotics for treatment of early asthma-like episodes,[10] yet they are widely used.[4] We did a randomised controlled trial (RCT) of azithromycin for treatment of episodes of troublesome lung symptoms in young children who were followed up prospectively in our new unselected Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$) birth cohort.[11]

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled trial, we recruited children from the $COPSAC_{2010}$ cohort, which is a single-centre, population-based birth cohort of 700 children recruited from the general Danish population of Zealand, including Copenhagen, at 1 week of age and followed up prospectively at the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) research unit (Copenhagen and Naestved, Denmark) with deep clinical phenotyping.[11] Children aged 1–3 years diagnosed with recurrent asthma-like symptoms (troublesome lung symptoms) as defined in the Procedures section were eligible each time they had an episode of troublesome lung symptoms lasting at least 3 days. Exclusion criteria were macrolide allergy, heart, liver, neurological, and kidney disease, and, before each treatment, one or more clinical signs of pneumonia (respiratory frequency of 50 breaths per min or higher, fever of 39°C or higher, or C-reactive protein [CRP] concentration of 476·20 nmol/L [50 mg/L] or higher). Most mothers from the $COPSAC_{2010}$ cohort also participated in other medical trials while pregnant and may have received dietary supplements or an influenza vaccination (NCT00856947, NCT00798226, and NCT01012557).[11,12] Additional details of baseline characteristics of the cohort are outlined in the $COPSAC_{2010}$ cohort design report.[11]

This trial was approved by the ethics committee for Copenhagen (H-3-2010-065), Danish Data Protection Agency (2010-41-5023), and Danish Health and Medicines Authority (2612-4329). Parents of children gave written and oral informed consent before enrolment of participants. The complete biobank is publicly available at the Danish National Biobank. The entire COPSAC dataset, including the RCT-specific data, are currently being transferred to a publicly available database (the Danish Data Archive).

For the **Danish National Biobank** see https://www.biobankdenmark.dk

For the **Danish Data Archive** see https://www.sa.dk

Randomisation and masking

Each episode of troublesome lung symptoms that occurred up to the age of 3 years or up to a maximum of seven treatments per child was randomised individually to either azithromycin or placebo. Treatments were randomly allocated at the Pharmacy of Glostrup (Copenhagen, Denmark) with a computer-generated list of random numbers in blocks of ten. Copies of the randomisation code were kept in sealed envelopes at the research site and the pharmacy. Investigators and participating families were masked to treatment assignment until the youngest child turned 3 years of age and throughout the data validation and analysis phases. Those assessing the primary outcome were masked; those doing subanalyses were not.

Procedures

Troublesome lung symptoms, consisting of cough, wheeze, or dyspnoea, severely affecting the wellbeing of the child, were monitored using daily diary cards filled out by the parents from birth.[11] We defined an episode as at least 3 consecutive days of troublesome lung symptoms, at which point we requested that the parents brought the child to the COPSAC research unit for an acute visit. We used the composite score of troublesome lung symptoms to describe asthma-like symptoms in the children, a score previously validated[13,14] and used in our clinical observational cohort studies of young children[13,15–17] and a randomised controlled trial.[19]

At each acute visit, the diary cards were reviewed with the family by trained COPSAC paediatricians to validate symptom definitions and severity. Additionally, the research paediatrician did a thorough physical examination, consisting of assessment of fever, tachypnoea, chest recessions, wheezing, and lung and heart auscultation, and examination of the skin, ears, nose, and throat. Furthermore, we measured CRP concentration (detection limit of 76·19–1523·84 nmol/L [8–160 mg/L]) in the peripheral blood with the QuickRead 101 instrument (Orion Diagnostica, Espoo, Finland). We collected a hypopharyngeal aspirate using a soft suction catheter passed through the nose into the hypopharynx, as previously described.[18] We cultured the samples and isolated the airway bacterial pathogens *H influenzae*, *S pneumoniae*, and *M catarrhalis*. We obtained a nasopharyngeal aspirate for viral identification with PCR. The viral airway pathogens analysed were rhinoviruses, respiratory syncytial virus (RSV), and enteroviruses.

We treated episodes of troublesome lung symptoms with the β2 agonist salbutamol (Airomir; Teva, Kongens Lyngby, Denmark) inhaled from a pressurised metered dose inhaler delivered via a spacer (AeroChamber; Trudell Medical International, London, ON, Canada) as needed. We added 4 mg of montelukast in the evening for 2 weeks in children who had previously benefited from this treatment. We added prednisolone 1–2 mg/kg per day for 3 days for severe episodes at the discretion of the attending paediatricians in the COPSAC research unit.

Recurrent troublesome lung symptoms were diagnosed if a child had: daily diary recordings of five episodes of troublesome lung symptoms within 6 months; 4 weeks of continuous symptoms; or a severe acute episode needing oral prednisolone or hospital admission. This diagnosis algorithm had previously been validated in our at-risk $COPSAC_{2000}$ birth cohort.[19,20] At diagnosis of recurrent troublesome lung symptoms, we gave children a 3-month course of 2×50 μg fluticasone (Flixotide; GlaxoSmithKline, UK) inhaled from a pressurised metered dose inhaler delivered via a spacer twice daily. If a second relapse of troublesome lung symptoms occurred after cessation of inhaled corticosteroids, we initiated a 6-month course of inhaled corticosteroids.

Children diagnosed with recurrent troublesome lung symptoms and participating in this trial were prescribed azithromycin or placebo at the COPSAC research unit when subsequent acute episodes of troublesome lung symptoms occurred after diagnosis. We gave azithromycin as an oral solution of 10 mg/kg per day in closed bottles (Teva) for 3 consecutive days or a matching placebo of similar look and taste (Pharmacy of Glostrup).

Outcomes

The primary outcome was diary-verified duration of episodes of troublesome lung symptoms after initiation of treatment. Secondary outcomes were the time from treatment to the next episode of troublesome lung symptoms, the number of episodes that turned into severe exacerbations (need for oral steroids or admission to hospital), and the duration of β2 agonist use after treatment. Serious adverse events, any adverse events, gastrointestinal symptoms, or other infections were documented with daily diary cards and hospital records.

Statistical analysis

We based our power calculations on the duration of episodes of troublesome lung symptoms at age 1–3 years in the children of the previous $COPSAC_{2000}$ cohort.[18,19,21] 86 independent episodes were needed to detect a difference of 1 day duration of episodes with a power of 90%, a p value of 0·05, and an SD of the duration of an episode of 1·4 days.[18,19,21]

We analysed the duration of an episode of troublesome lung symptoms and β2 agonist use after treatment with Poisson regression with a log link. This type of regression is ideal for modelling counts because it captures both skewness and variance heterogeneity and provides an easy-to-interpret quantification of effects as relative change in mean counts. The model includes fixed effects of the categorical variable episode number and an effect of treatment. We included a random effect of child to account for heterogeneity between children. We analysed factors potentially modifying the treatment effect with robust Poisson regression to account for within-child correlation. We obtained inference by means of the generalised estimating equations procedure with a working independence assumption.

We analysed gap times between episodes with Cox regression, including γ-distributed frailties shared by gap times within each child to account for between-child heterogeneity. We included fixed effects of treatment at the preceding episode in the model and stratified baseline hazards by episode number. We obtained estimates with maximum likelihood estimation with Wald 95% CIs and a 0·05 p value cutoff. We did analyses using R version 3.2.2 and the add-on package lme4.

Primary analyses were per protocol (excluding those without a primary outcome measure or who did not receive treatment). Safety analyses included those

without a primary outcome measure but who did receive the study treatment.

This trial was monitored by the Good Clinical Practice unit at Copenhagen University Hospital (Copenhagen, Denmark). This trial is registered with ClinicalTrials.gov, number NCT01233297.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JS, CBP, and HB had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

207 (30%) of the 700 children enrolled in the main cohort were diagnosed with recurrent troublesome lung symptoms during the first 3 years of life; between Nov 17, 2010, and Jan 28, 2014, we randomly allocated 158 episodes for trial treatment (79 [50%] to azithromycin and 79 [50%] to placebo; figure 1) from 72 (35%) of these children. Before analyses, we excluded ten (6%) episodes from the analysis (five [6%] in each group), nine (6%) because of missing diary information (azithromycin four [5%]; placebo five [6%]) and one (1%; in azithromycin group) because the treatment was never given to the child.

Mean age at randomisation was 2·0 years (SD 0·6). The mean number of randomisations for each child was 2·2 treatments (SD 1·5). In 121 (82%) of the 148 episodes analysed (62 [84%] in the azithromycin-treated episodes and 59 [80%] in the placebo-treated episodes), the child received concurrent treatment with inhaled corticosteroids. In 89 (60%) episodes, the child received concurrent treatment with montelukast (47 [64%] in the azithromycin-treated episodes and 42 [57%] in the placebo-treated episodes). Treatment was complied with in 154 (97%) of 158 episodes: one (1%) azithromycin treatment was never given and three (2%) treatments were discontinued after initiation; one (1%) in the azithromycin group and two (1%) in the placebo group. 71 (99%) of 72 children had complete clinical follow-up from inclusion in the study until age 3 years.

Baseline characteristics did not differ significantly between participants in the trial and other children diagnosed with recurrent troublesome lung symptoms from the COPSAC$_{2010}$ cohort who did not participate in the

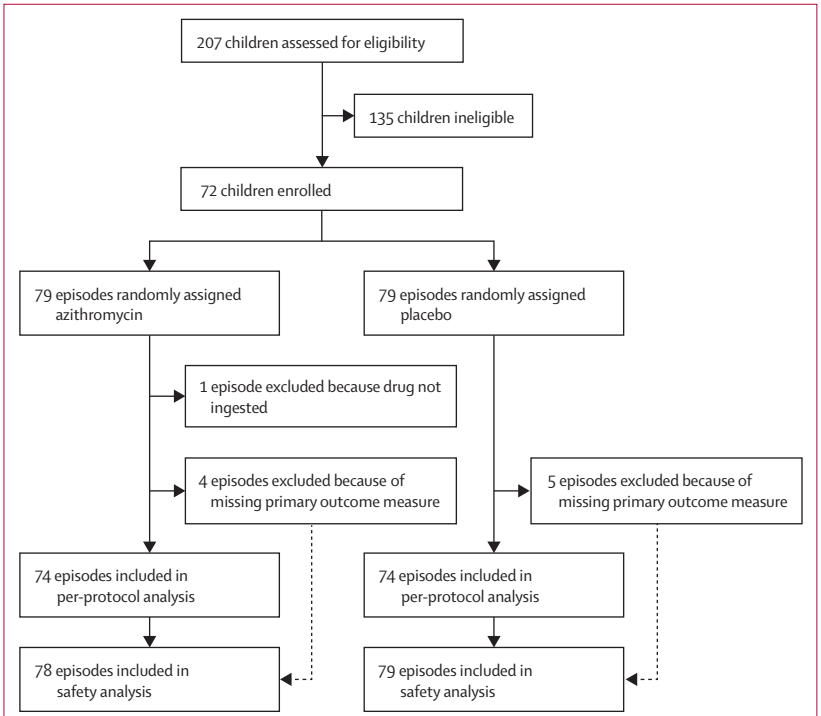

Figure 1: **Trial profile**
Each episode after inclusion was randomly allocated individually.

	RCT participants (n=72)	Non-RCT participants (n=135)
Child		
Male sex	47 (65%)	74 (55%)
White	70 (97%)	130 (96%)
Older children in the home at birth	39 (54%)	70 (52%)
Sensitisation (SPT or specific IgE)	8 (11%)	20 (15%)*
Atopic dermatitis	21 (30%)*	39 (30%)†
17q21 risk variant (RS2305480)	26 (41%)‡	46 (39%)§
Smoking in pregnancy	9 (13%)	16 (12%)
Cat or dog at birth	26 (36%)	48 (36%)
Antibiotics in pregnancy	31 (43%)	50 (37%)
Term birth >37 weeks	67 (93%)	127 (94%)
Caesarean section	18 (25%)	31 (23%)
Season of birth		
Winter	25 (35%)	38 (28%)
Spring	17 (24%)	37 (27%)
Summer	12 (17%)	29 (21%)
Autumn	18 (25%)	31 (23%)
Mother		
Maternal age at birth (years)	31·9 (4·7)	32·2 (4·5)
Maternal asthma¶	31 (44%)*	38 (28%)
Maternal educational level		
Low‖	9 (13%)	15 (11%)
Medium**	53 (74%)	83 (61%)
High††	10 (14%)	37 (27%)
Household annual income		
Low‡‡	4 (6%)	17 (13%)
Medium§§	45 (63%)	73 (54%)
High¶¶	23 (32%)	45 (33%)

Data are n (%) or mean (SD). RCT=randomised controlled trial. SPT=skin prick test. *One child has missing information. †Seven children have data missing. ‡Nine children have missing information. §17 children have data missing. ¶History of doctor-diagnosed asthma. ‖Primary school, secondary school, or college graduate. **Tradesman or Bachelor degree. ††Masters degree. ‡‡Less than €50 000. §§€50 000–110 000. ¶¶More than €110 000.

Table 1: **Baseline characteristics**

trial, except for a higher proportion of mothers of RCT participants being asthmatic (31 [44%] of 71) than of mothers of non-participants (38 [28%] of 135; p=0·03; table 1). The mean total duration of respiratory episodes was 13·7 days. The episode duration after randomisation was unrelated to sex, mother's smoking status, allergic sensitisation to inhalant or food allergens at 6 months or 18 months, atopic dermatitis, or 17q21 genetic risk variant (appendix).

Figure 2 shows the proportion of symptomatic children day-by-day during the 30 days after treatment, showing a shortening of the symptomatic period after treatment with azithromycin. The average number of symptom days after azithromycin treatment was 3·4 days versus 7·7 days after placebo, corresponding to a calculated reduction in episode length of 63·3% (95% CI 56·0–69·3; p<0·0001) within a child due to azithromycin treatment (table 2). Restriction of the analysis to the first randomised treatment in each child substantiated a significant reduction of symptom duration by 44·4% (30·9–55·2; p<0·0001) after treatment with azithromycin, corresponding to a mean duration of 4·0 days after azithromycin versus 7·1 days after placebo.

The effect of azithromycin was increased when the duration of symptoms before treatment was shorter, showing a reduction in episode duration of 83% if treatment was initiated before day 6 of the episode compared with 36% if initiated on or after day 6 (p<0·0001). Figure 3 shows the reduction of episode duration after azithromycin treatment as a function of episode duration before treatment (less than or more than the median value of 6 days). We noted no differential effect for episodes presenting with fever of ≥38°C or with increased CRP concentration of ≥76·19 nmol/L (≥8 mg/L), and treatment was equally effective in episodes with and without objective wheeze during examination in the research clinic (table 2).

Presence of any pathogenic bacteria did not significantly modify the treatment effect compared with episodes without detection of bacteria, but azithromycin was more effective in episodes positive for *H influenzae* (table 2). Presence of any virus did not modify the treatment effect of azithromycin. None of the detected viruses significantly modified treatment effects (table 2). Concurrent treatment with inhaled steroids (p value for interaction=0·57) or montelukast (p value for interaction=0·69) did not significantly modify the treatment effect, and responses were equal (appendix).

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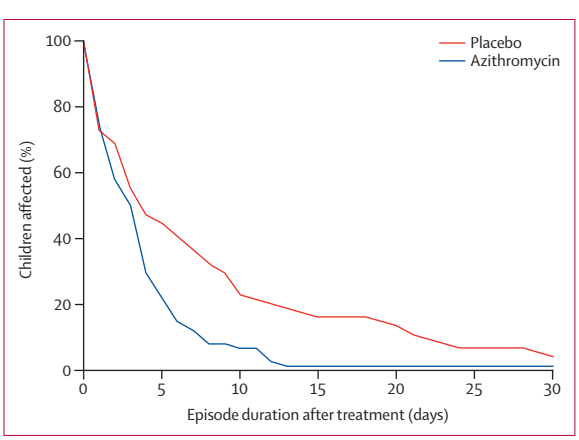

Figure 2: **Duration of episodes of troublesome lung symptoms after treatment**

	n (%)	Mean azithromycin episode duration (days)	Mean placebo episode duration (days)	% reduction (95% CI)	p value	Modification p value
All	148	3·4	7·7	63·3% (56·0 to 69·3)	<0·0001	
Clinical measures						
C-reactive protein concentration (nmol/L)	133 (100%)					0·6350
≥76·19 nmol/L (≥8 mg/L)	23 (17%)	3·6	6·3	45·6% (–53·9 to 80·8)	0·2510	
<76·19 nmol/L (<8 mg/L; lowest detection)	110 (83%)	3·5	8·4	59·4% (15·6 to 80·5)	0·0158	
Fever (°C)	136 (100%)					0·4809
≥38	23 (17%)	3·8	4·9	21·4% (–61·6 to 61·8)	0·5122	
<38	113 (83%)	3·6	7·2	47·3% (2·9 to 71·4)	0·0401	
Objective wheeze	144 (100%)					0·8140
Yes	26 (18%)	3·4	8·8	55·0% (6·3 to 78·4)	0·0330	
No	118 (82%)	3·6	13·0	60·1% (18·3 to 80·5)	0·0120	
Bacterial infection						
Any pathogenic bacteria	135 (100%)					0·2864
Present	90 (67%)	4·2	7·9	41·6% (–8·3 to 68·5)	0·0881	
Not present	45 (33%)	2·0	5·5	64·7% (35·6 to 80·7)	0·0007	
Haemophilus influenzae	135 (100%)					0·0323
Present	32 (24%)	2·7	12·1	77·0% (58·0 to 87·4)	<0·0001	
Not present	103 (76%)	3·8	5·9	33·4% (–28·7 to 65·6)	0·2264	
Moraxella catarrhalis	135 (100%)					0·9062
Present	64 (47%)	4·4	8·7	40·5% (–64·3 to 78·5)	0·3163	
Not present	71 (53%)	2·8	5·2	45·0% (1·7 to 69·3)	0·0436	
Streptococcus pneumoniae	135 (100%)					0·8576
Present	43 (32%)	3·3	6·2	44·4% (–22·1 to 74·7)	0·1436	
Not present	92 (68%)	3·6	7·5	49·6% (3·8 to 73·5)	0·0377	

(Table 2 continues on next page)

	n (%)	Mean azithromycin episode duration (days)	Mean placebo episode duration (days)	% reduction (95% CI)	p value	Modification p value
(Continued from previous page)						
Viral infection						
Any pathogenic virus	135 (100%)					0·7999
Present	58 (43%)	3·8	6·8	44·0% (−32·4 to 76·4)	0·1866	
Not present	77 (57%)	2·7	7·4	50·7% (27·3 to 66·6)	0·0004	
Rhinovirus	135 (100%)					0·5125
Present	26 (19%)	4·6	6·9	26·7% (−172·6 to 80·3)	0·6430	
Not present	109 (81%)	3·1	7·1	54·1% (34·3 to 67·9)	<0·0001	
RSV	135 (100%)					0·8886
Present	22 (16%)	3·3	5·9	42·1% (−71·7 to 80·5)	0·3242	
Not present	113 (84%)	3·6	7·2	46·9% (6·3 to 69·9)	0·0289	
Enteroviruses	135 (100%)					0·1997
Present	27 (20%)	2·1	6·8	66·3% (31·5 to 83·4)	0·0026	
Not present	108 (80%)	4·0	7·1	41·1% (−2·7 to 66·2)	0·0619	

p values correspond to associations and test for effect modification by covariants. RSV=respiratory syncytial virus.

Table 2: **Duration of episodes of troublesome lung symptoms after intervention and effect modification from paraclinical measures**

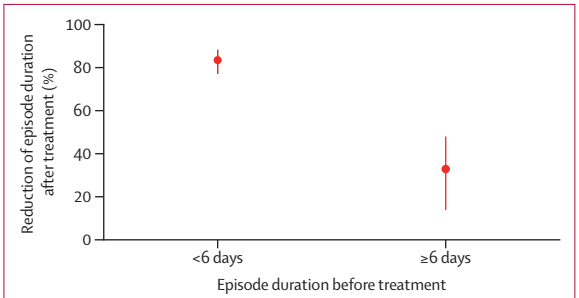

Figure 3: **Reduction of duration of episodes of troublesome lung symptoms after azithromycin treatment as a function of episode duration before treatment**

Circles correspond to estimates and solid lines to 95% pointwise CIs.

Treatment with azithromycin did not significantly affect the time to next episode of troublesome lung symptoms in individual children (hazard ratio 0·95 [95% CI 0·65–1·40]; p=0·82). Treatment with azithromycin significantly reduced the duration of treatment with β2 agonists after intervention. The mean number of β2 agonist days after azithromycin treatment was 8·9 days versus 10·1 days after placebo, corresponding to a calculated reduction in duration of β2 agonist treatment of 22·0% (95% CI 7·0–34·6; p=0·006). Too few episodes requiring oral steroids or admission to hospital occurred for this secondary outcome to be analysed statistically (azithromycin three [4%] episodes; placebo two [3%] episodes).

We noted no differences between treatment groups during the 30 days after treatment with respect to serious or any adverse events, gastrointestinal symptoms, or other infections, as documented by daily diary cards and hospital records (appendix).

Discussion

Azithromycin significantly reduced the duration of physician-verified episodes of asthma-like symptoms in children aged 1–3 years with a history of recurrent asthma-like symptoms. The duration was decreased by about 63% after azithromycin treatment, with more improvement if treatment was started early in the episode. Azithromycin had no long-term effect on risk of subsequent episodes.

This study is substantially strengthened by the prospective, longitudinal, daily diary recordings of lung symptoms before development of attacks, validated by study paediatricians at 6-monthly and acute visits. COPSAC served as the primary health-care centre for the birth cohort, ensuring a standardised approach to diagnosis and treatment, which improves reliability of diagnoses compared with reporting from community doctors and retrospective information from parents.[18–20,22] Diagnosis was based on an algorithm of symptom quantity, which has been analysed and validated in detail[13] and applied in our previous RCT[19] of inhaled corticosteroids in young children in the at-risk $COPSAC_{2000}$ birth cohort. Such strict diagnostic procedure is paramount to clinical assessments, diagnoses, and treatments, which are otherwise poorly standardised in the community and more difficult in young children than later in life.[13] The in-depth clinical assessment of each respiratory episode by the study paediatrician before randomisation, including a thorough objective examination and CRP concentration measurement in the research clinic, ensured validity and homogeneity of the primary outcome and exclusion of children with clinical signs of pneumonia. This assessment minimised the possibility of the azithromycin effect being driven by treatment of bacterial pneumonia misclassified as an episode of asthma-like symptoms.

Another strength is the centralised longitudinal clinical follow-up of the cohort by a research team with a well established routine of doing clinical cohort studies. This routine ensured a high follow-up of the cohort, with 99% of the randomised children completing full follow-up until 3 years of age and only 6% of randomised treatments being unavailable. We obtained airway samples before treatment in 91% of episodes, with only 13 episodes missed. Our results are generalisable to a similar group of children with a known history of recurrent asthma-like symptoms, with or without concomitant treatment with inhaled steroids and with an episode duration of at least 3 days. An important limitation is that our data pertain to children with a

detailed clinical history and acute worsening judged by the study clinician. They cannot be generalised to a more liberal setting, such as initiation at home by parents or children with mild disease.

This study is the first, to our knowledge, to investigate and show an effect of azithromycin for treatment of acute respiratory episodes in young children with a history of recurrent asthma-like symptoms, in a cohort designed and powered to explore such effects. A third of all children will experience an episode of asthma-like symptoms in relation to airway infections before 3 years of age.[23] Shortening of such episodes by 63% is therefore clinically significant to the child, families, health-care user, and society. We noted that azithromycin had a marked effect in relation to any given type of episode independently of the trigger, clinical presentation, or symptom duration before the intervention, which suggests a broad application. The sensitivity analysis restricting episodes to the first randomisation validated the primary finding.

Asthma-like episodes in young children probably represent a heterogeneous clinical syndrome. Importantly, we excluded typical pneumonia based on predefined clinical criteria. Furthermore, most children (more than 80%) had undetectable concentrations of CRP and no fever at randomisation, and the treatment effect was similar in these children, strongly suggesting that the effect of azithromycin is not due to misclassification of pneumonia. Azithromycin treatment was particularly effective in children who were treated shortly after symptom debut. This finding makes us speculate that azithromycin is mainly acting on the acute inflammatory[24] or infectious[6,25] processes related to exacerbations, rather than a persistent underlying inflammation. This hypothesis is supported by the absence of effect on time to next episode. Alternatively, azithromycin acts by clearing bacterial pathogens indirectly responsible for the respiratory episode through subsequent co-infection by a viral trigger, and therefore the treatment was more effective when initiated early in the episode than when initiated late.[26]

This study is based on our previous birth cohort study[6] in which we discovered that pathogenic airway bacteria and respiratory viruses are equally closely associated with acute episodes of asthma-like symptoms in young children and mostly occur together. Our finding in this study that the treatment effect was strong, even in episodes for which no bacterial pathogen was detected, suggests that the effect of azithromycin is not only antibacterial. Macrolide antibiotics are active against both common airway pathogenic bacteria and atypical bacteria,[27–29] but also have anti-inflammatory activity[24] and, possibly, antiviral effects.[30] Studies of macrolides in adults with severe asthma episodes are ambiguous,[31,32] and macrolides reportedly reduce exacerbations in adults with an asthma type characterised by chronic neutrophilic inflammation.[33,34] Indeed, recurrent asthma-like symptoms in young children are also characterised by neutrophilic inflammation,[25,35,36] which, in particular, might be present for episodes triggered by *H influenzae*.[34] This corresponds with our finding of a stronger azithromycin effect in episodes triggered by *H influenzae*. Viral infection in general did not predict an altered effect of azithromycin treatment. Low numbers in some viral species groups limit the conclusions drawn about effect modification by specific viruses. Thus, the antibacterial, anti-inflammatory, and antiviral pathways of azithromycin could have contributed to the shortening of episode length observed in this study. We cannot rule out that the effects noted are mainly anti-inflammatory because episodes triggered by *H influenzae* induce neutrophilic inflammation[34] and azithromycin also reduced episode duration in children without any evidence of bacterial infection. An RCT[37] of treatment with azithromycin in RSV-positive children showed a reduction of the neutrophilic marker interleukin 8 at day 14 after azithromycin treatment. This finding could point towards an anti-inflammatory effect as the primary mediator of our findings and also explain why findings from previous RCTs[38,39] have failed to show treatment effects of non-anti-inflammatory antibiotics in acute exacerbations of childhood asthma.

Present guidelines do not recommend antibiotics for treatment of episodes of asthma-like symptoms in young children[10] and yet they are among the most commonly prescribed drugs for such episodes in both the USA and Europe.[4] Our data suggest an effect of azithromycin on acute asthma-like episodes and thereby identify a potential future treatment, but do not provide sufficient evidence to recommend this treatment in clinical practice. How the effect of azithromycin compares with narrow-spectrum antibiotics and whether any long-term effects are associated with recurrent use need to be investigated. We are keenly aware of the potential ecological issues relating to use of antibiotics in terms of bacterial ecology and resistance. Macrolide resistance in organisms causing respiratory illness in children is already an issue.[40] Future research should establish the choice of antimicrobial treatment and criteria for treatment, taking societal aspects into consideration. We did not identify strong effect modifiers from the objective clinical measures, concomitant treatments, or the microbiological profile other than the presence of *H influenzae*. Our data suggest that the effect increases by starting early in the episode. Future studies might help to identify specific disease phenotypes or biomarkers directing the treatment to specific groups of young children.

The results of this study identify a potential treatment for a common childhood disease for which better treatment options are needed than are currently available. Better treatments might help to alleviate a substantial disease burden for children, families, and society.

Contributors

HB conceived, designed, and carried out the study, acquired, analysed, and interpreted data, and wrote the report. JS, BLC, and KB contributed

to design of the study. JS acquired, analysed, and interpreted data and drafted the report. CBP did the statistical analyses. SS and KAK cultured and identified the bacteria. TKF identified the viruses. BLC, NHV, EB, TMP, RKV, A-MMS, HMW, ST, HWH, LA, and KB collected and interpreted data and wrote the report. All coauthors have contributed substantially to the analyses or interpretation of the data and have provided important intellectual input and approval of the final version of the manuscript.

Declaration of interests

HB has received funds for research and for members of research staff and been paid as a consultant for Chiesi. All other authors declare no competing interests.

Acknowledgments

Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) is funded by private and public research funds all listed on www.copsac.com. The Lundbeck Foundation, Danish Ministry of Health, Danish Council for Strategic Research, and Capital Region Research Foundation have provided core support for COPSAC. We express our gratitude to the children and families of the $COPSAC_{2010}$ cohort for all their support and commitment. We likewise acknowledge and appreciate the unique efforts and teamwork of the COPSAC research team. Steffen Lynge Jørgensen is thanked for microbiological technical assistance.

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