Oral Azithromycin for Acute Episodic Airway Symptoms in Young Children.

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Summary

In this randomized, double-blind, placebo-controlled trial, the authors recruited children aged 1 to 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 population of Zealand (Denmark). Each episode of asthma-like symptoms lasting at least 3 days was randomly allocated to a 3-day course of azithromycin oral solution (10 mg/kg/d) or placebo after examination by a study physician at the research unit. The primary outcome was duration of the respiratory episode after treatment, verified by prospective daily diaries. Analyses were per protocol (excluding those without a primary outcome measure or who did not receive treatment). Authors randomly allocated 158 asthma-like episodes in 72 children equally to azithromycin or 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 by 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 ($P<0.0001$). Authors concluded that azithromycin reduced the duration of episodes of asthma-like symptoms in young children.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: In recent years, there is increasing evidence for using azithromycin in the management of various respiratory diseases such as acute bacterial bronchitis [1], Mycoplasma pneumonia [2], bronchial asthma [3], bronchiolitis [4,5] and bronchiolitis obliterans syndrome [6]. Investigators have also explored the potential of azithromycin for preventing lower respiratory infection (LRI) among high-risk children with underlying diseases [7], decreasing recurrent wheezing following Respiratory syncytial virus (RSV) bronchiolitis [8], and reducing viral load during episodes of severe bronchiolitis caused by RSV [9]. A recent well-designed multi-centric trial [10] in the USA reported that a short course (5 days) of azithromycin administered at the onset of a respiratory infection in toddlers and young children reduced the progression to severe disease by about one-third.

Longer durations of azithromycin therapy have been reported to decrease acute pulmonary exacerbations in cystic fibrosis [11], non-cystic fibrosis bronchiectasis [12], chronic suppurative lung disease [13], bronchial asthma [14], surfactant protein deficiency [15], and chronic obstructive pulmonary disease [16,17] in adults. This therapeutic and prophylactic diversity suggests that the effects of azithromycin may not be mediated by antimicrobial action alone. Serial measurement of IL-8 in nasal fluid and serum of infants admitted for RSV bronchiolitis [8] showed that azithromycin treatment decreased the levels after two weeks of therapy. Similarly, in a group of adult patients with chronic obstructive lung disease, azithromycin resulted in decreased sputum neutrophils and the neutrophil chemokine CXCL8. These findings suggest an anti-inflammatory and/or immunomodulatory effect of azithromycin [19].

Despite the availability of several pieces of relatively high quality evidence highlighted above, it should be noted that azithromycin is still not included in management guidelines for most of these conditions as a standard of care. The recent trial [20] comparing azithromycin versus placebo for treatment of acute episodic airway symptoms in infants and young children, has to be examined against this backdrop.

Critical appraisal: ***Table*** **I** summarizes a critical appraisal of the study [20]. One of the major difficulties with this trial [20] is that the investigators' definition of

TABLE I: CRITICAL APPRAISAL OF THE TRIAL

Research question	Does a short course of oral Azithromycin *(I=Intervention)* administered to infants having a history of recurrent respiratory symptoms, and presenting with an acute episode *(P=Population)*, change the duration of the episode (*O=Outcome)*, compared to placebo *(C=Comparator)*?
Study design	Randomized controlled trial (RCT)
Study setting	Single-centre Danish birth cohort.
Participants	Infants (1-3y) with recurrent respiratory symptoms (labeled as 'recurrent troublesome lung symptoms') presenting with an acute episode (defined as three consecutive days of cough, wheezing or dyspnea) and confirmed by a pediatrician. A composite score of the 'troublesome lung symptoms' was interpreted as 'asthma-like symptoms' based on a previous validation.
Study procedures	Each enrolled infant underwent thorough physical examination, serum C-reactive protein (CRP), hypopharyngeal aspirate (HPA) for bacterial culture, and nasopharyngeal aspirate (NPA) for viral PCR studies (RSV, rhinovirus, enterovirus). Treatment protocol consisted of inhaled salbutamol (delivered by metered dose inhaler with spacer), optional additional montelukast (4mg at night), and oral prednisolone @1-2 mg/kg for 3 days (at the discretion of treating physicians).
Interventions	Azithromycin @ 10mg/kg/d for 3 days.
Outcomes	Placebo (nature, dose, and duration not described)
Sample size	Sample size of 86 episodes per group was calculated for an effect size of one day reduction in duration of episode with alpha 0.05 and beta 0.01, at 5% significance level. However, only 79 episodes were randomized to each arm. Sample sizes were not calculated for secondary outcomes.
Outcomes	Duration of episode (however the criteria for considering end of an episode are not given); Time to subsequent episode; Number of episodes becoming severe; Requirement or steroid (oral) therapy or hospitalization; Duration of rescue treatment with salbutamol; Serious adverse event (SAE); adverse events (AE); other infections; gastro-intestinal symptoms.
Randomization	The random sequence was generated at the study Pharmacy by a computer program with fixed block sizes of 10. The procedure is judged as Adequate.
Allocation concealment	Allocation was concealed using sealed envelopes (opacity not mentioned) stored at the Pharmacy and study site. The procedure is judged as Adequate.
Blinding (masking)	The intervention and comparator had similar physical appearance and properties.The primary outcome assessor, trial investigators, and families of participating infants were blinded to the allocation, until the time of data analysis. It is unclear whether treating physicians were also blinded. The trial report does not state whether assessment of success of blinding was done at any time during the trial. Overall, blinding is judged as Adequate.
Statistical methods	Detailed statistical methods have been described. However, the analysis of the primary outcome was per protocol and not by intention-to-treat. Adverse events were recorded in all infants who received the intervention.
Incomplete outcome reporting	Although the total sample size was calculated as 172 episodes, only 158 (92%) were randomized. Primary outcome was assessed in 148 (94%) of the randomized episodes. The missing episodes were similar in the two groups (6% each).
Selective outcome reporting	The authors have reported only the primary outcome with multiple post hoc analyses. Data on other outcomes have been sketchily presented. Antibacterial resistance pattern was not studied.
Overall assessment of methodological quality	Low risk of bias
Similarity of groups at baseline	Curiously, the two groups have not been compared for baseline characteristics. Instead, the trial participants (72 infants) have been compared to those from the birth cohort who did not participate in the trial (135 infants).
Salient Results	Azithromycin *vs* Placebo : Mean duration of episode: 3.4 *vs* 7.7 d (standard deviations or confidence intervals not presented). Time to subsequent episode: Data not presented, but statistically insignificant result mentioned. Number of episodes becoming severe: Data not presented. Requirement or steroid (oral) therapy or hospitalization: Data not presented. Duration of rescue treatment with salbutamol: 8.9 *vs* 10.1 d (standard deviations not presented). SAE, other infections, gastro-intestinal symptoms: All nil in either group. AE 18/78 *vs* 24/79

Contd....

Interpretation of results	The results appear to suggest that azithromycin is associated with reduction in the duration (and perhaps severity) of episodes of "troublesome lung symptoms" in infants with recurrent symptoms of similar nature. However, caution must be exercised in interpreting these data for asthma or asthma-like symptoms (see text).
Overall impression	*Validity*: Well-designed and well-conducted RCT with a low risk of bias. *Results*: Statistically and clinically meaningful results for the primary outcome. *Applicability*: Please see text for caveats to applicability among infants/children with episodic asthma.

'troublesome lung symptoms' are used interchangeably with 'asthma-like symptoms.' The intention is probably to use the evidence in the latter condition. But the hallmark sign of asthma-like episodes – wheeze auscultable by physicians – is missing in the majority of enrolled infants. In fact, objective wheeze was present in only 18% of the randomized episodes, although (given the age group of the enrolled participants) wheeze would be expected to be a dominant sign. This is also perhaps why the number of infants who required beta-2 agonist as well as those prescribed oral steroids, are not presented. In these circumstances, it is difficult to accept that the enrolled infants in this trial truly represent 'asthma-like' episodes.

What other clinical condition(s) could manifest with the symptoms and signs described in this study? Bronchiolitis can be ruled out for the same reason as above. The authors themselves tried to exclude pneumonia (although their definition with high specificity could have compromised sensitivity). One wonders whether the majority of infants could have had upper respiratory tract infections rather than an episode of asthma. This is indirectly supported by the fact that infants without wheeze who received placebo had a mean duration of illness of 13 days in contrast to 8.8 days in those with wheeze.

Another intriguing issue is that azithromycin started early (*i.e.* prior to day 6 of the acute episode) had greater effect. However, the trial was designed with a stringent daily diary monitoring of infants in the birth cohort to detect eligible infants having three consecutive days of symptoms, at which point they were examined by physicians. Under these circumstances, it is unclear how/ why an unspecified number of the infants were enrolled after 6 days of symptoms.

Subgroup analyses (although under-powered) suggested that azithromycin was superior to placebo in those with C-reactive protein (CRP) <8mg/L, temperature <38 ^{0}C, and absence of pathogenic bacteria in hypopharyngeal aspirate. Although these could be statistical artefacts, the anti-bacterial effect of azithromycin (as proposed by the authors) would be expected to work in the exact opposite circumstances. This raises the question whether the effects are related to non-antimicrobial actions of azithromycin. But, azithromycin was superior in those colonized by *H. influenzae*, and in those without respiratory viruses.

The authors of this study were cognizant of the risks of fostering antimicrobial resistance, although they did not examine the issue. This is a significant limitation, especially as there is data showing that children treated with azithromycin show resistance as early as 4-7 days after initiating therapy, and this persists for several weeks to months [21,22]. In this study, bacterial cultures were performed, but somehow antimicrobial sensitivity was not reported. The authors have rightly concluded that their results cannot be applied to clinical practice.

Extendibility: As elucidated above, it is difficult to extrapolate the data to infants/toddlers with asthma/ asthma-like symptoms based on the data presented here. For this reason, it cannot be extended to our setting, even though infants may have similar clinical presentations.

Conclusion: Azithromycin appears to reduce the duration of respiratory episodes in infants presenting with a combination of symptoms and signs suggesting an acute respiratory illness (although it is not similar to an acute asthma or bronchiolitis episode).

REFERENCES

1. Laopaiboon M, Panpanich R, Swa Mya K. Azithromycin for acute lower respiratory tract infections. Cochrane Database Syst Rev. 2015;3:CD001954.
2. Gardiner SJ, Gavranich JB, Chang AB. Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. Cochrane Database Syst Rev. 2015;1:CD004875.
3. Liu L, Wang GZ, Han D, Li MX. Effectiveness and safety of azithromycin in the treatment of bronchial asthma: a meta-analysis. Nan Fang Yi Ke Da Xue Xue Bao. 2015;35:83-7.
4. Farley R, Spurling GK, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev. 2014;10:CD005189.
5. Pinto LA, Pitrez PM, Luisi F, de Mello PP, Gerhardt M, Ferlini R, *et al.* Azithromycin therapy in hospitalized infants with acute bronchiolitis is not associated with better clinical outcomes: a randomized, double-blinded, and placebo-controlled clinical trial. J Pediatr. 2012;161: 1104-8.

6. Kingah PL, Muma G, Soubani A. Azithromycin improves lung function in patients with post-lung transplant bronchiolitis obliterans syndrome: a meta-analysis. Clin Transplant. 2014;28:906-10.
7. Onakpoya IJ, Hayward G, Heneghan CJ. Antibiotics for preventing lower respiratory tract infections in high-risk children aged 12 years and under. Cochrane Database Syst Rev. 2015;9:CD011530.
8. Beigelman A, Isaacson-Schmid M, Sajol G, Baty J, Rodriguez OM, Leege E, *et al.* Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2015;135:1171-8.
9. Beigelman A, Bacharier LB, Baty J, Buller R, Mason S, Schechtman KB, *et al.* Does azithromycin modify viral load during severe respiratory syncytial virus bronchiolitis? J Allergy Clin Immunol. 2015;136:1129-31.
10. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, *et al.* Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. JAMA. 2015;314:2034-44.
11. Southern KW, Barker PM, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. Cochrane Database Syst Rev. 2012;11:CD002203.
12. Haworth CS, Bilton D, Elborn JS. Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. Respir Med. 2014;108:1397-1408.
13. Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, *et al.* Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2013;1:610-20.
14. Brusselle GG, Vanderstichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, *et al.* Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax. 2013;68:322-9.
15. Thouvenin G, Nathan N, Epaud R, Clement A. Diffuse parenchymal lung disease caused by surfactant deficiency: dramatic improvement by azithromycin. BMJ Case Rep. 2013; pii:bcr2013009988.
16. Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, *et al.* Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomized, double-blind, placebo-controlled trial. Lancet Respir Med. 2014;2:361-8.
17. Ni W, Shao X, Cai X, Wei C, Cui J, Wang R, *et al.* Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. PLoS One. 2015;10:e0121257.
18. Simpson JL, Powell H, Baines KJ, Milne D, Coxson HO, Hansbro PM, *et al.* The effect of azithromycin in adults with stable neutrophilic COPD: a double blind randomized, placebo controlled trial. PLoS One. 2014;9:e105609.
19. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. Eur J Clin Pharmacol. 2012;68:479-503.
20. Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, *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.
21. Kastner U, Guggenbichler JP. Influence of macrolide antibiotics on promotion of resistance in the oral flora of children. Infection. 2001;29:251-6.
22. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomized, double-blind, placebo-controlled study. Lancet. 2007;369:482-90.

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Microbiologist's Perspective

In the present study [1], the researchers made two groups, one in which azithromycin was administered and a placebo group. However, did they actually isolate the mentioned group of implicated organisms from the placebo group? Did the authors document if at all and how many patients were immunized for *H.influenzae* and Pneumococcus in the azithromycin group, especially when both vaccines are given under the national immunization program of Denmark? It may be possible that azithromycin may have some bronchodilator effect in the alveoli of patients in a country with lower pollution [2], but then how and why would azithromycin act against respiratory viruses? Besides, colonization may be an established risk factor for infection but not for bronchoconstriction. Once such questions are introspected, why should anyone replace a simple bronchodilator with azithromycin? Without establishing answers to these questions, it would be unfair to prescribe azithromycin, especially when there are reports of high minimum inhibitory concentrations of azithromycin in Salmonella in India and also considering the side effect of prolonged QT interval with azithromycin [3].

REFERENCES

1. Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, *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.
2. Daenas C, Hatziefthimiou AA, Gourgoulianis KI, Molyvdas PA. Azithromycin has a direct relaxant effect on precontracted airway smooth muscle. Eur J Pharmacol. 2006;553:280-7.
3. Rai S, Jain S, Prasad KN, Ghoshal U, Dhole TN. Rationale of azithromycin prescribing practices for enteric fever in India. Indian J Med Microbiol. 2012;30:30-3.

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Pediatric Asthma Experts' Viewpoint

Acute episodes of asthma-like symptoms are truly troublesome in children less than 5 years and account for major morbidity and health care expenses. Thus, all research directed towards elucidation of underlying cause and appropriate treatment is as much needed as appreciated. The current double blind randomized controlled trial (RCT) on the use of azithromycin for episodes of asthma-like symptoms in children 1-3 years of age concluded that those who received azithromycin for such episodes had significantly shorter duration of episodes compared to the placebo group, more so with early initiation of treatment [1].

Very few studies have been done to demonstrate a beneficial effect of macrolides in amelioration of 'acute asthma exacerbations', especially in children, and overall they show a favourable response to their use [2-5]. The postulated mechanism have been antibacterial, immunomodulatory and potential anti-viral properties of the macrolides, but no conclusive evidence of the same is available [6]. Much more literature exists for use of azithromycin in 'persistent asthma', both in adults and children, but the results are conflicting [7,8]. The reason for such incongruous results is the heterogeneous nature of asthma itself. Macrolides have shown to be effective in severe neutrophilic asthma but this effect was lost when non-severe non-neutrophilic cases were analyzed together [4]. Children with moderate to severe asthma did not respond to macrolides [9]. In fact, certain studies have shown that wheezing and asthma may be enhanced by macrolide use in early childhood [10]. Thus, it is imperative to search for targeted groups amongst the children with acute-asthma like symptoms, to minimize antibiotic resistance, drug toxicity and an unnecessary economic burden.

Another important issue is to identify bacterial pathogens as the possible cause of asthma-like episodes. Though the study by Stockholm, *et al*. [1] has identified the commoner bacteria, no isolation of the atypical bacteria was done. Studies have shown Chlamydia and Mycoplasma to be triggers of acute asthma-like symptoms in all age groups [11-15]. It is possible that a higher presence of these organisms in the response group confounded the results. Moreover, detection of these atypical bacteria is challenging and requires a combination of PCR and serology, despite which the sensitivity of detection is variable [16].

Thus, macrolide use for acute asthma-like symptoms in children should be viewed with cautious optimism. More trials are needed to establish its usefulness and identify the cohort of patients who would benefit the most, apart from deciding which macrolide to use, the optimal dose and duration.

REFERENCES

1. Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, *et al.* Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial. Respir Med. 2016;4:19–26.
2. Koutsoubari I, Papaevangelou V, Konstantinou GN, Makrinioti H, Xepapadaki P, Kafetzis D, *et al.* Effect of clarithromycin on acute asthma exacerbations in children: an open randomized study. Pediatr Allergy Immunol. 2012;23 385-90.
3. Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. The effect of telithromycin in acute exacerbations of asthma. N Engl J Med. 2006;354:1589-600.
4. Brusselle GG, Vanderstichele C, Jordens P, Deman R, Slabbynck H, RingoetV, *et al.* Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax. 2013;68:322-9.
5. Fonseca-Aten M, Okada PJ, Bowlware KL, Chavez-Bueno S, Mejias A, Rios AM, *et al.* Effect of clarithromycin on cytokines and chemokines in children with an acute exacerbation of recurrent wheezing: a double-blind, randomized, placebo-controlled trial. Ann Allergy Asthma Immunol. 2006;97:457-63.
6. Ernie H C Wong, James D Porter, Michael R Edwards, Sebastian L Johnston. The role of macrolides in asthma: current evidence and future directions. Lancet Respir Med. 2014,2:657-70.
7. Richeldi L, Ferrara G, Fabbri LM, Lasserson TJ, Gibson PG. Macrolides for chronic asthma. Cochrane Database Syst Rev. 2005;4:CD002997.
8. Reiter J, Demirel N, Mendy A, Gasana J, Vieira ER, Colin AA, *et al.* Macrolides for the long-term management of asthma- a meta-analysis of randomized clinical trials. Allergy. 2013;68:1040-9.
9. Strunk RC, Bacharier LB, Phillips BR, Szefler SJ, Zeiger RS, Chinchilli VM, *et al.* Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderateto-severe

childhood asthma study. J Allergy Clin Immunol. 2008;122: 138-44.
10. Jedrychowski W, Perera F, Maugeri U, Mroz E, Flak E, Perzanowi M, *et al.* Wheezing and asthma may be enhanced by broad spectrum antibiotics used in early childhood. Concept and results of a pharmacoepidemiology study. J Physiol Pharmacol. 2011;62:189-95.
11. Xepapadaki P, Koutsoumpari L, Papaevagelou V, Karagianni C, Papadopoulos NG. Atypical Bacteria and Macrolides in Asthma Allergy, Asthma, and Clinical Immunology. 2008;4:111-6.
12. Bezerra PG, Britto MC, Correia JB, Duarte Mdo C, Fonceca AM, Rose K, *et al.* Viral and atypical bacterial detection in acute respiratory infection in children under five years. Plos One. 2011;6:e18928.
13. Yao MM, Wang KM, Xu QY, Wang GL, Liu XT. Etiology and risk factors of infantile wheezing. Zhongguo Dang Dai Er Ke Za Zhi. 2011;13:195-8.
14. Lehtinen P, Jartti T, Virkki R, Vuorinen T, Leinonen M, Peltola V, *et al.* Bacterial coinfections in children with viral wheezing. Eur J Clin Microbiol Infect Dis. 2006;25:463-9.
15. Esposito S, Blasi F, Arosio C, Fioravanti L, Fagetti L, Droghetti R, *et al.* Importance of acute Mycoplasma pneumoniae and Chlamydia pneumoniae infections in children with wheezing.. Eur Respir J. 2000;16:1142-6.
16. Dowell SF, Peeling RW, Boman J, Carlone GM, Fields BS, Guarner J, *et al.* Standardizing Chlamydia pneumoniae assays: recommendations from the Centers for Disease Control and Prevention (USA) and the Laboratory Centre for Disease Control (Canada). Clin Infect Dis. 2001;33:492-503.

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