PEDIATRIC ALLERGY, IMMUNOLOGY, AND PULMONOLOGY
Volume 29, Number 2, 2016

DOI: 10.1089/ped.2016.0663

Macrolides for Acute Wheezing Episodes in Preschool Children

Hengameh H. Raissy, PharmD,[1] and Kathryn Blake, PharmD BCPS, FCCP[2]

The National Asthma Education and Prevention Program's Expert Panel Report 3, Guidelines for the Diagnosis and Management of Asthma does not recommend antibiotics for the management of acute episodes of asthma exacerbation. Macrolides seem to have some potential effect beyond or in addition to their antibacterial effect. It has been reported that macrolides may potentially benefit patients with chronic inflammatory airway diseases due to their antibacterial, antiviral, and/or anti-inflammatory effects. This review presents recent data on use of azithromycin in prevention and management of acute exacerbation of respiratory symptoms in infants and young children.

Asthma remains the most common chronic disease among children in the United States. About 50% of patients with asthma have been reported to have one or more asthma exacerbations.[1] Preschool children seem to have a greater healthcare use and morbidity compared with older children.[2] Preschool children have their own age criteria for severity and management of asthma in The National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3), Guidelines for the Diagnosis and Management of Asthma[3] and the decision about when to start long-term controller medication remains difficult. In addition, these children have high rate of spontaneous remission of symptoms. Low dose of inhaled corticosteroids (ICSs) has been shown to decrease the likelihood of exacerbations, requiring oral corticosteroids by 35% compared with placebo. However, the rate of exacerbations in children on daily ICSs still remains at 57.4/100 child-years, which warrants identification of alternative management approaches.[4] This may explain why wheezing exacerbations are not universally prevented by ICSs[5] nor do they completely respond to oral corticosteroids[6] as corticosteroids more effectively reduce T helper 2/eosinophilic inflammation.

The use of antibiotics for management of wheezing in children remains controversial. The EPR3 does not recommend routine use of antibiotics for management of acute asthma[3] since respiratory viruses are detected in 80% of asthma exacerbations.[7–9] A recent meta-analysis in children under 2 years of age with bronchiolitis did not find sufficient evidence to support use of antibiotics.[10] Interestingly, the rate of antibiotics prescribed within 7 days of wheezing is reported as 1,309 prescriptions per 1,000 children.[11] About 30% of preschool children had immediate dispensing of antibiotic with an increased use of broad spectrum macrolides (azithromycin and clarithromycin) in wheezing.[11]

Use of macrolides in other respiratory diseases such as cystic fibrosis[12–14] and diffuse panbronchiolitis[15,16] has provided clinical benefits; although the precise mechanism is not known, the effect is suggested to be unrelated to macrolides antimicrobial activity but to its anti-inflammatory activity. Studies suggest that macrolides attenuate neutrophilic airway inflammation; neutrophils play a predominant role at the onset of most infections including rhinovirus infection.[17,18] Respiratory tract infections caused by viruses, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, seem to play a role in the pathogenesis of asthma.[19] Hence macrolides, especially azithromycin, have been investigated for the management of chronic inflammatory airway diseases based on their antibacterial,[20–22] antiviral,[23] and/or anti-inflammatory effects.

In a recent publication, Bacharier and colleagues reported a randomized, double-blind, placebo-controlled, parallel group trial to evaluate early administration of azithromycin in preschool children with recurrent severe lower respiratory tract illness (LRTI).[24] The outcome was the number of respiratory tract illnesses (RTI) not progressed to a severe LRTI defined as use of oral corticosteroids. Nine academic U.S. medical centers in the National Heart, Lung and Blood Institute's AsthmaNet network enrolled children aged 12–71 months old with histories of recurrent severe wheezing defined as requiring oral corticosteroids, an unscheduled visit to physician office, an emergency room or urgent care visit,

[1]Department of Pediatrics, University of New Mexico, School of Medicine, Albuquerque, New Mexico.
[2]Department of Biomedical Research, Nemours Children's Clinic, Jacksonville, Florida.

or hospitalization. Patients were excluded if they had significant daily symptoms or had inadequate compliance with diary card completion. Patients were randomly assigned to either oral azithromycin 12 mg/kg once daily for 5 days or matching placebo. Parents and study team developed an individual care plan to start the study medication as soon as a child developed the starting signs and symptoms of respiratory tract illness (RTI). Parents were also instructed to start albuterol inhalation treatment four times daily for the first 48 h of RTI followed by as needed use and to collect nasal secretion during each treated RTI identified by the parents. Nasal secretions were also collected at each study visit. Patients were followed up to 52 weeks and could use study treatment for maximum of three treated RTIs not progressing to severe LRTI. A year after the start of the study, the follow-up period was increased to 78 weeks and patients were allowed a maximum of four treated RTIs due to a lower-than-expected RTI episodes/year. Primary outcome was reached and patients completed the study if they had ≤3–4 RTIs in 52–78 weeks or at least one severe LRTI. Severe LRTI was defined as (a) having more than mild symptoms after three albuterol treatments over 1 h, (b) need for albuterol more than once every 4 h, (c) need for albuterol treatment more than six times over a 24-h period, or (d) having moderate to severe cough or wheeze for five or more days after initiation of study medication. Patients were also terminated if they (a) required emergent care visit due to respiratory symptoms, (b) use of oral corticosteroids, (c) symptoms consistent with uncontrolled persistent asthma, or (d) withdrawal from the study by physician discretion due to respiratory-related problems. A total of 708 participants were enrolled in the study and 607 were randomized to treatment arms. During the study, 164 participants did not have any RTI (no difference between the treatment arms). A total of 937 RTIs occurred during the study: 473 in azithromycin group and 464 in placebo group. When compared with placebo group, the azithromycin group experienced significantly lower risk of progression to LRTI (hazard ratio, 0.64 [95% CI, 0.41–0.98], $P = 0.04$; absolute risk for first RTI: 0.05 for azithromycin, 0.08 for placebo; risk difference, 0.03 [95% CI, 0.00–0.06]); the result was adjusted for study site, age, modified Asthma Predictive Index status, season when RTI occurred, and the follow-up phase (52 weeks versus 78 weeks). Furthermore, the overall severity of symptoms during LRTI was significantly reduced in the azithromycin group. Nasal wash swabs were collected for 95% of all treated RTI. Interestingly, viral pathogens were detected in 47% of children in the azithromycin group compared with 43% in the placebo group at randomization visit. During the study, viral pathogens were detected in 83% of RTIs in the azithromycin group compared with 80% in the placebo group. There was no difference in the time to the second treated RTI in the treatment groups. The most common virus at randomization and during RTIs and severe LRTI was rhinovirus. To assess antibiotic resistance with use of azithromycin, one clinical site performed deep oropharyngeal swab samples at randomization and at study completion at least 14 days after the final dose of study medication. An azithromycin-resistant organism was identified in 5 of 41 participants in the azithromycin group and 4 of 45 in the placebo group at randomization visit (12.2% versus 8.9%, correspondingly). At the end of the trial, 6 of 36 participants treated with azithromycin and 4 of 37 participants not treated by azithromycin acquired azithromycin resistance organisms, mainly *Staphylococcus aureus*. The authors concluded that azithromycin started at the earliest signs of an RTI can reduce the risk of progression to severe LRTI in addition to a significant reduction in severity of LRTI in preschool children. This study is the first to evaluate use of azithromycin for prevention of severe LRTI.

Use of macrolides for management of asthma or wheezing illness has also been investigated; however, interpretation of the results and their general applicability are difficult due to difference in study design, patient population, outcome, and treatment protocols. Chronic use of clarithromycin in adult patients with stable moderate-severe asthma was investigated; 6 weeks treatment with clarithromycin improved FEV1 in a subgroup of patients with evidence of infection with *M. pneumoniae* or *C. pneumoniae*.[25] Use of clarithromycin was also evaluated in adult patients with mild to moderate asthma, not well controlled on low dose of ICSs. Addition of clarithromycin for 16 weeks did not change asthma control but it significantly improved airway hyperresponsiveness.[26] In a similar study,[27] adult patients with severe asthma on high dose of ICSs and long acting beta agonist and history of at least two asthma exacerbations in the previous year were randomized to azithromycin (250 mg capsule) or placebo; patients took study medications for 5 days at randomization visit and then one capsule 3 days per week for 26 weeks. The primary outcome was the rate of asthma exacerbation during 26 weeks, and it was not different between azithromycin and placebo groups, 0.75 versus 0.81 per subject correspondingly ($P = 0.682$).

Use of macrolides for management of acute asthma exacerbation has also been investigated. Recently, Stockholm and colleagues reported a randomized, double-blind, placebo-controlled trial in children 1–3 years of age with recurrent troublesome lung symptoms.[28] Recurrent troublesome lung symptoms were defined as (a) five episodes of daily diary recorded troublesome lung symptoms (consisting of cough, wheeze, dyspnea severely affecting the well-being of the child for at least 3 days, and confirmed by study physician's examination) in the last 6 months, (b) 4 weeks of continuous symptoms, and (c) severe acute episode requiring oral steroid or hospitalization. A total of 207 children were enrolled and 158 episodes were randomly assigned to a 3-day course of azithromycin (10 mg/kg) or placebo for acute troublesome lung symptoms episode lasting at least 3 days and confirmed by the study physician. Patients remained in the study for up to seven treated episodes or age of 3. The primary outcome was duration of the episodes after starting the treatment. There was no difference in baseline characteristics between the treatment groups. The mean duration of episodes was 13.7 days (median 6 days) as reported in daily diary cards. The duration of the episodes was 63.3% shorter for azithromycin group than placebo, 3.4 days versus 7.7 days, correspondingly (95% CI 56.0–69.3: $P < 0.0001$). Interestingly, the duration of episodes was reduced by 83% in the subset of patients whose treatment was initiated before day 6 of the episode compared with only 36% reduction if it was started after day 6 ($P < 0.0001$). Duration of beta agonist treatment was reduced by 22% in the azithromycin group (8.9 days versus 10.1 days, 95% CI 7.0–34.6; $P = 0.006$). Concurrent treatment with ICS or montelukast and or presence of any virus or bacteria did not modify the treatment effects. Oral

corticosteroid use or hospital admission was reported for three episodes (4%) in the azithromycin group compared with two (3%) episodes in the placebo group. Treatment with azithromycin did not affect the time to the next acute episode. Authors suggested that azithromycin could have a role in acute management of physician-confirmed asthma exacerbation by reducing the duration of episodes in children with history of recurrent asthma-like symptoms. This study is the first to investigate clinical benefit of azithromycin for the management of acute asthma-like symptoms. However, it is important to note that these episodes were confirmed by a physician.

Fonseca-Aten and colleagues[29] investigated the effect of clarithromycin on serum and nasopharyngeal cytokine and chemokine concentrations in children 4–17 years old with an acute asthma exacerbation and history of recurrent wheezing or asthma. Forty-three patients were randomized within 72 h of the onset of acute exacerbation to clarithromycin (15 mg/kg) or placebo for 5 days. All patients received beta agonists and systemic corticosteroids. Patients were evaluated in 3–5 days (28 patients) and then 3–8 weeks (19 patients) after randomizations. Although clarithromycin reduced nasopharyngeal concentration of tumor necrosis factor-α, interleukin-1β, and interleukin-10 significantly and persistently in both follow-up visits, there was no difference in clinical outcome of the patients in 3–5 days follow-up and they all had complete resolution. In a randomized, double-blind, placebo-controlled study, 278 adult patients with acute asthma were randomized to telithromycin (800 mg/day) or placebo for 10 days.[30] Patients on telithromycin reported a significantly greater reduction in asthma symptoms compared with placebo regardless of evidence of infection with *C. pneumoniae* and or *M. pneumoniae*.

As we learn more about macrolides and their potential efficacy in patients with asthma, we need more data on development of macrolide-resistant organisms and disturbing the lung microbiome especially in children.[31–33] In addition, the rate of exposure to macrolides should be noted in clinical trials. Larger studies are needed to assess the potential increased risk of macrolide resistance when used for management of wheezing illnesses. Nearly 40% of children have intermittent asthma and the need for identifying a novel treatment approach for management of recurrent wheezing in preschool children is well recognized.[34] Bacharier and colleagues reported the first study for prevention of severe LRTI through early intervention with azithromycin; they also reported a reduction in severity of LRTI with this approach. Previous reports have shown that oral prednisone does not reduce the severity of these episodes.[7,35,36] Nor do low dose chronic or high dose intermittent ICS therapies completely prevent them. It is also important to note how the patient population is defined and how the episodes are identified. Bacharier and colleagues allowed the start of azithromycin at home using an individual care plan identified by parents. Stockholm and colleagues managed physician-confirmed acute exacerbation episodes, which may result to a less generalizable approach. The result of these recent studies in the pediatric population is promising; however, it does not auger the widespread use of azithromycin for management of wheezing in clinical practice. More clinical trials are needed to identify patients who would most benefit from this approach. In addition, investigating duration and frequency of macrolide use is paramount. The long-term use of macrolides and its safety and efficacy require continued research.

Acknowledgments

This work was supported by funding from the National Institutes of Health grant # UL1TR001449 and U10 HL098075A (NIH/NHLBI AsthmaNet).

Author Disclosure Statement

No competing financial interests exist.

References

1. http://www.cdc.gov/asthma/most_recent_data.htm.
2. Akinbami L. The state of childhood asthma, United States, 1980–2005. Adv Data. Number 381, December 12, 2006; 1–24.
3. National Asthma Education and Prevention Program. Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda, MD: US Department of Health and Human Services, 2007.
4. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006; 354:1985–1997.
5. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, et al. CARE Network of the National Heart, Lung, and Blood Institute. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med. 2011; 365:1990–2001.
6. Beigelman A, King TS, Mauger D, et al. Childhood asthma research and education network of National Heart, Lung, and Blood Institute. Do oral corticosteroids reduce the severity of acute lower respiratory tract illnesses in preschool children with recurrent wheezing? J Allergy Clin Immunol 2013; 131:1518–1525.
7. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 1995; 310:1225–1229.
8. Heymann PW, Carper HT, Murphy DD, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. J Allergy Clin Immunol 2004; 114:239–247.
9. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. Pediatr Infect Dis J 2005; 24:S217–22.
10. 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.
11. Kozyrskyj AL, Dahl ME, Ungar WJ, et al. Antibiotic treatment of wheezing in children with asthma: what is the practice? Pediatrics 2006; 117:e1104–10.
12. Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomized, placebo controlled crossover trial. Lancet 2002; 360:978–984.
13. Saiman L, Anstead M, Mayer-Hamblett N, et al. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA 2010; 303:1707–1715.
14. Gaylor AS, Reilly JC. Therapy with macrolides in patients with cystic fibrosis. Pharmacotherapy 2002; 22:227–239.
15. Nagai H, Shishido H, Yoneda R, et al. Long-term low-dose administration of erythromycin to patients with diffuse panbronchiolitis. Respiration 1991; 58:145–149.

16. Sakito O, Kadota J, Kohno S, et al. Interleukin 1 beta, tumor necrosis factor alpha, and interleukin 8 in bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis: a potential mechanism of macrolide therapy. Respiration 1996; 63:42–48.
17. Lacy P, Eitzen G. Control of granule exocytosis in neutrophils. Front Biosci 2008; 13:5559–5570.
18. Bentley JK, Newcomb DC, Goldsmith AM, et al. Rhinovirus activates interleukin-8 expression via a Src/p110beta phosphatidylinositol 3-kinase/Akt pathway in human airway epithelial cells. J Virol 2007; 81:1186–1194.
19. Guilbert TW1, Denlinger LC. Role of infection in the development and exacerbation of asthma. Expert Rev Respir Med 2010; 4:71–83.
20. Freymuth F, Vabret A, Brouard J, et al. Detection of viral, *Chlamydia pneumoniae* and m*ycoplasma pneumoniae* infections in exacerbations of asthma in children. J Clin Virol 1999; 13:131–139.
21. Biscardi S, Lorrot M, Marc E, et al. *Mycoplasma pneumoniae* and asthma in children. Clin Infect Dis 2004; 38:1341–1346.
22. Esposito S, Blasi F, Arosio C, et al. Importance of acute-*Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections in children with wheezing. Eur Respir J 2000; 16:1142–1146.
23. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J 2010; 36:646–654.
24. Bacharier LB, Guilbert TW, Mauger DT, et al. National Heart, Lung, and Blood Institute's AsthmaNet. 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; 314:2034–2044.
25. Kraft M, Cassell GH, Pak J, Martin RJ. Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. Chest 2002; 121:1782–1788.
26. Sutherland ER, King TS, Icitovic N, et al; National Heart, Lung and Blood Institute's Asthma Clinical Research Network. A trial of clarithromycin for the treatment of suboptimally controlled asthma. J Allergy Clin Immunol 2010; 126:747–753.
27. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 2013; 68:322–329.
28. Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, 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.
29. Fonseca-Aten M, Okada PJ, Bowlware KL, 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; 97:457–463.
30. Johnston SL, Blasi F, Black PN, et al. TELICAST Investigators. The effect of telithromycin in acute exacerbations of asthma. N Engl J Med 2006; 354:1589–1600.
31. Wickens K, Ingham T, Epton M, et al. New Zealand Asthma and Allergy Cohort Study Group. The association of early life exposure to antibiotics and the development of asthma, eczema, and atopy in a birth cohort: confounding or causality? Clin Exp Allergy 2008; 38:1318–1324.
32. Su Y, Rothers J, Stern DA, et al. Relation of early antibiotic use to childhood asthma: confounding by indication? Clin Exp Allergy 2010; 40:1222–1229.
33. Penders J, Kummeling I, Thijs C. Infant antibiotic use and wheeze and asthma risk: a systematic review and meta-analysis. Eur Respir J 2011; 38:295–302.
34. http://www.cdc.gov/asthma/asthma_stats/severity_child.htm.
35. Oommen A, Lambert PC, Grigg J. Effi cacy of a short course of parentinitiated oral prednisolone for viral wheeze in children aged 1–5 years: randomised controlled trial. Lancet 2003; 362:1433–1438.
36. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med 2009; 360:329–338.

Address correspondence to:
Hengameh H. Raissy, PharmD
Department of Pediatrics
University of New Mexico
School of Medicine
Albuquerque, NM 87131-0001

E-mail: hraissy@salud.unm.edu

Received for publication April 24, 2016; accepted after revision May 2, 2016.