Curr Allergy Asthma Rep (2017) 17: 34
DOI 10.1007/s11882-017-0701-6

ALLERGIES AND THE ENVIRONMENT (M HERNANDEZ, SECTION EDITOR)

Microbes and the Role of Antibiotic Treatment for Wheezy Lower Respiratory Tract Illnesses in Preschool Children

Christina G. Kwong[1] · **Leonard B. Bacharier**[1]

Published online: 29 April 2017

Abstract
Purpose of Review Antibiotics are commonly used to treat wheezy lower respiratory tract illnesses in preschoolers, although these infections have been traditionally thought to be predominantly of viral origin. Our purpose is to review recent research pertaining to the role of antibiotics in lower respiratory tract illnesses and on subsequent asthma development, as well as the possible mechanisms of their effects.
Recent Findings Increasing evidence suggests that asthma pathogenesis is associated with events during infancy and early childhood, particularly respiratory tract infections. While viruses are frequently detected in children with lower respiratory tract infections, the presence of potentially pathogenic bacteria is also often detected and may play a role in asthma pathogenesis. Recent evidence suggests that use of macrolides, particularly azithromycin, may decrease the risk of and duration of lower respiratory tract illnesses and prevent future episodes in specific high-risk populations.
Summary Infants and preschoolers who have wheezy lower respiratory tract illnesses have a higher risk of asthma development. Alterations in the microbiome are thought to be influential. While several recent studies identify azithromycin as a therapeutic option in these illnesses, additional research is needed.

This article is part of the Topical Collection on *Allergies and the Environment*

✉ Leonard B. Bacharier
bacharier_L@wustl.edu

[1] Division of Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine in St. Louis, St. Louis Children's Hospital, One Children's Place, St. Louis, MO 63110, USA

Keywords Recurrent wheezing · Bronchiolitis · Asthma pathogenesis · Antibiotics · Macrolides · Preschool children

Introduction

Lower respiratory tract illnesses are a frequent occurrence for preschoolers, often accompanied by wheezing, and associated with increased risks of recurrent wheezing and subsequent asthma diagnosis. Approximately one third of children will experience at least one episode of wheezing during the first 3 years of life, and approximately half of these children will continue to experience wheezing episodes until at least 6 years of age [1]. These episodes are often severe and exert substantial morbidity, including unscheduled visits to physician offices, urgent care centers, and emergency departments. Many of these young children have been diagnosed with asthma, and among them, 20.9% seek emergency department care and 6.5% are hospitalized each year [2]. There is mounting evidence that asthma pathogenesis is linked to events during early childhood, particularly viral respiratory tract infections and their interactions with the recently identified and characterized respiratory tract microbiome [3, 4]. Since asthma is a disease with substantial health care costs and morbidity, advancing our knowledge of potential treatments that reduce the frequency, severity, and sequelae of these early-in-life lower respiratory tract illnesses could make a significant impact. In this review, we will examine the role of antibiotics in the management of these episodes, with a focus on recent developments.

Impact of Lower Respiratory Tract Infections on Recurrent or Persistent Wheezing

Bronchiolitis is an important cause of morbidity in young children, particularly infants. A study of U.S. hospital

discharges between 1988 and 1996 found that 47% of lower respiratory tract discharges and 16% of overall discharges were due to bronchiolitis [5]. A subsequent study found that on average each year, respiratory syncytial virus (RSV) bronchiolitis in particular accounts for an estimated two million outpatient visits and 57,527 hospitalizations among children 5 years old and younger [6]. The occurrence of viral respiratory tract infections with wheezing increases the risk of subsequent asthma development, particularly when underlying atopy is present [7, 8], and the wheezing illnesses are triggered by human rhinovirus. Preschoolers with wheezing during rhinovirus respiratory tract infections are at increased risk of asthma [9] and have lower lung function at age 8 years compared with those who do not have rhinovirus wheezing illnesses during the first 3 years of life [10]. The severity of the respiratory tract infection and the specific viral pathogen (e.g., rhinovirus C) causing the illness also influence the risk of subsequent asthma [11–13].

Assessing the role of RSV infection with subsequent asthma risk is particularly important, as RSV infection is almost universally acquired during the first 2 years of life [14]. The Tucson Children's Respiratory Study reported that children under 3 years of age with predominantly mild RSV lower respiratory tract infections were at increased wheezing risk at age 11 years but not at age 13 years, suggesting that the risk after mild RSV infection may diminish with time [15]. Recently, additional studies strengthened the evidence supporting the association between severe RSV infection during infancy and subsequent wheezing risk. A large retrospective cohort study of over 70,000 children in Northern California showed that mild and severe RSV infections during infancy, defined as requiring outpatient evaluation or prolonged hospitalization, respectively, were associated with increased risk of wheezing at both ages 3 and 5 years, with an escalating risk linked to increasing RSV illness severity [16]. Infants with a severe RSV infection were at higher risk for future recurrent wheezing even when compared with premature infants born at 32–33 weeks of gestation. In addition to being associated with greater risk of subsequent recurrent wheezing, severe RSV infection is also linked to greater asthma risk. Several studies have found positive associations between severe RSV infection during infancy and subsequent development of asthma [17, 18], with the RSV Bronchiolitis in Early Life (RBEL) cohort reporting that severe RSV bronchiolitis requiring hospitalization during infancy is followed by an approximately 50% likelihood of developing physician-diagnosed asthma by 7 years of age [19].

The exact mechanisms responsible for the association between bronchiolitis during infancy and subsequent increased recurrent wheezing or asthma risk remain uncertain, but recent studies have identified potential associations and pathways. Increased nasal epithelial cell expression of the chemokine CCL5, a chemoattractant for inflammatory cells such as T-lymphocytes, during RSV bronchiolitis was found to be a predictor of physician-diagnosed asthma [19]. Higher levels of IL-3 and IL-12p40 in bronchoalveolar lavage fluid during hospitalization for RSV bronchiolitis were associated with increased risk of recurrent wheezing [20]. Rare non-synonymous genetic variants, notably in *ADRB2*, have been found to contribute to asthma development following severe RSV bronchiolitis [21]. Another potential association has been reported between the *TLR9* rs1870084 gene polymorphism and wheezing after bronchiolitis [22].

The Role of the Microbes and the Microbiome on Recurrent or Persistent Wheezing

Recent work highlights the frequent co-presence of bacteria during viral respiratory tract infections, and the presence of certain bacteria impacts the outcomes of such illnesses. Suarez-Arrabal et al. assessed RSV-infected infants requiring hospitalization compared with healthy aged-matched controls who were enrolled either at primary care offices or prior to scheduled non-respiratory tract surgical procedures such as hernia repairs [23]. Compared with controls, infants with RSV infection were more likely to be culture positive for the potentially pathogenic organisms *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis* (81% in RSV-positive infants vs 65% in controls) in samples obtained via nasopharyngeal swab and nasal wash. Thirty-two percent of RSV-positive infants versus 4% of controls had growth of more than one potentially pathogenic bacterial species, and RSV-positive infants had increased numbers of white blood cells in nasopharyngeal fluid. Their analysis was limited by high rates of antibiotic use in the prior 2 weeks, which resulted in a significant decrease in bacterial recovery. A study from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) cohort found that the presence of pathogenic bacteria or viruses in the hypopharynx during a wheezy episode was not associated with the duration of the episode [24•].

There is evidence that children who develop recurrent or persistent wheezing have differences in their upper airway microbial composition compared with those who do not. In the COPSAC study, Bisgaard and colleagues found that one-month old infants with hypopharyngeal colonization with *S. pneumoniae*, *M. catarrhalis*, and/or *H. influenzae* were at increased risk of recurrent wheezing and later diagnosis of asthma at 5 years of age [25]. A retrospective study assessed bronchoalveolar lavage samples from children aged 4 to 38 months with persistent wheezing despite treatment with inhaled corticosteroids and found that 48.5% of the children had positive lower airway cultures for potentially pathogenic bacteria, with non-typeable *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* being the most common [26].

Environmental microbe exposure has also been linked to an altered risk of recurrent wheezing, with more diverse

bacterial exposures being associated with a decreased risk for recurrent wheezing. In an urban population at high risk for asthma, children who were exposed to the highest diversity of bacterial content in house dust were at lower risk of recurrent wheezing at age 3 years. Additionally, lower exposure to *Firmicutes* and *Bacteriodetes* in house dust during the first year of life was associated with atopic wheeze [27]. Similarly, environmental exposure to a wide range of microbes [28] and higher endotoxin levels [29] in house dust found in houses from certain farming communities has been associated with lower asthma rates.

Increasing evidence has highlighted a critical time window for establishing protective or detrimental microbiota compositions. Alterations in the infant microbiome, specifically reflected by the presence and/or abundance of specific organisms and the overall degree of microbiome diversity, may be uniquely protective. Cardenas et al. assessed microbiota composition in oropharyngeal swabs from infants who were 10.2 months old on average [30]. This population from rural Ecuador was unique in that they had minimal antibiotic exposure and no inhaled corticosteroid exposure. This case control study found that compared with controls, oropharyngeal samples from infants who wheezed had increased *Streptococcus* spp. and *Haemophilus* spp., similar to the findings of Bisgaard et al. [25], as well as increased *Staphylococcus* spp. The Canadian Healthy Infant Longitudinal Development (CHILD) Study found that the abundance of four bacterial species, specifically *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*, was transiently decreased in stool samples of children with early onset atopic wheezing when compared with controls at 3 months of age [31••]. By 1 year of age, these differences were much less apparent. A study by Abrahamsson et al. found that a lack of microbial diversity during early infancy appeared to be detrimental, as lower microbial diversity in stool samples from the first week and month of life was associated with increased asthma rates at 7 years of age [32].

Role of Antibiotics in the Treatment of Bronchiolitis and Wheezing in Young Children

Despite the unequivocal role of viral infections in the pathogenesis of acute bronchiolitis, antibiotics are often used clinically in this condition, being prescribed during nearly one third of emergency department visits for bronchiolitis [33] despite limited evidence for this practice. A 2014 Cochrane Report assessing the use of antibiotics for bronchiolitis in children under 2 years of age included seven studies with 824 participants [34]. The primary outcome was duration of symptoms, including wheezing in some studies. They found insufficient evidence to support the use of antibiotics, although they comment that perhaps a subgroup would benefit from antibiotic treatment. The 2014 American Academy of Pediatrics bronchiolitis guidelines recommend that antibiotics should not be used for routine treatment of bronchiolitis in infants and children, and should only be prescribed if there is a concomitant bacterial infection or a strong suspicion of one [35•]. Another 2014 Cochrane Report comparing antibiotics with no antibiotics for children aged 2–59 months with non-severe pneumonia and wheeze found no studies that completely fulfilled their inclusion criteria [36]. A 2012 Cochrane Report assessed the use of antibiotics for persistent cough or wheezing following acute bronchiolitis in children. Only one study met their inclusion criteria, and it did not find a therapeutic effect [37].

Macrolide antibiotics, in particular, have been the focus of recent clinical studies, as they have anti-inflammatory properties and reduce neutrophil numbers [38, 39]. Macrolides have been demonstrated to be beneficial in inflammatory airway diseases such as cystic fibrosis, diffuse panbronchiolitis, COPD, and in some cases, asthma, although studies have yielded mixed results [39]. The mechanism of action, anti-inflammatory and/or antimicrobial, in these conditions remains uncertain. Several studies assessing the impact of antibiotic use on the duration of hospitalization for bronchiolitis have been consistently negative (Table 1). A Dutch study assessed the impact of azithromycin use by infants 2 years old and younger hospitalized with RSV bronchiolitis, and found no differences in mean hospitalization duration or RSV symptom score improvement when compared with placebo [40]. A randomized controlled trial in Brazil assessed the use of a 7-day course of azithromycin in infants less than 12 months of age who were hospitalized with acute bronchiolitis [41]. A virus was detected in 63–64% of patients, of which 90–95% were positive for RSV. There was no difference in duration of either hospitalization or supplemental oxygen use. McCallum et al. performed two studies of azithromycin use in the setting of acute bronchiolitis, neither of which found an association between macrolide use and bronchiolitis symptom improvement. The use of one dose of azithromycin in children 18 months and younger hospitalized for bronchiolitis was not associated with significant differences in supplemental oxygen requirement or rehospitalization [42]. Nasopharyngeal bacterial carriage was found to be reduced among the azithromycin-treated children. In another study, 219 infants who were 24 months of age and younger and hospitalized for bronchiolitis were randomized to receive three once-weekly doses of azithromycin or placebo, and no differences in time receiving supplemental oxygen, symptoms, or need for rehospitalization within 6 months were found between the treatment groups [43•].

In contrast, two recent trials have shown the efficacy of azithromycin in preschool children with recurrent lower respiratory tract illnesses (Table 2). A large, multicenter trial by the NHLBI's AsthmaNet explored the preemptive use of azithromycin in an effort to prevent severe episodes. This trial assessed if azithromycin, when started at the earliest signs of a

Table 1 Summary of referenced studies of the role of azithromycin in children with bronchiolitis

Reference	Study design	Study population and location	Sample size	Population characteristics	Intervention	Outcome
Kneyber et al. 2008 [40]	RDBPC	2 years old and younger Netherlands	71 children	Hospitalized for confirmed diagnosis of mild-moderate RSV bronchiolitis	3-day course of azithromycin during RSV bronchiolitis vs placebo given within 24 h of hospital admission Dose 10 mg/kg/day	No difference in mean hospitalization duration or RSV symptom score improvement
McCallum et al. 2013 [42]	RDBPC	18 months of age or younger Australia	97 children	Hospitalized for bronchiolitis	Single dose of azithromycin or placebo within 24 h of hospitalization Dose 30 mg/kg/dose	No difference in hospital length-of-stay, supplemental oxygen duration, or rehospitalization rates
McCallum et al. 2015 [43•]	RDBPC	2 years of age and younger Australia and New Zealand	219 children	Hospitalized for a clinical diagnosis of bronchiolitis Indigenous ethnicity	3 once-weekly doses of azithromycin or placebo given within 24 h of hospitalization. Dose 30 mg/kg/dose	No difference in hospital length-of-stay, supplemental oxygen duration or rehospitalization rates
Pinto et al. 2012 [41]	RDBPC	<12 months of age Brazil	184 infants	Hospitalized for clinical diagnosis of acute viral bronchiolitis	7-day course of azithromycin vs placebo within 72 h of initial clinical symptoms Dose 10 mg/kg/day	No difference in hospital length-of-stay or supplemental oxygen duration

RDBPC randomized, double-blinded, placebo-controlled trial, *RSV* respiratory syncytial virus

respiratory tract illness and before the development of lower respiratory tract symptoms, in high-risk children aged 12–71 months, could prevent progression to severe episodes [44••]. The duration of the study was 12–18 months for each participant, with a maximum of four treated illnesses per participant. Children had histories of recurrent severe lower respiratory tract illnesses but were not receiving daily asthma controller therapy. Four hundred forty-three children were included in the primary outcome analysis, and these children experienced a total of 937 treated respiratory tract illnesses, 80–83% of which had a virus detected in nasal wash samples. Compared with placebo, a 5-day course of azithromycin resulted in a significant reduction in the risk of progression to a severe episode, with a hazard ratio of 0.64 (95% CI, 0.41–0.98, $p = 0.04$) and less rescue albuterol use during severe illnesses. Azithromycin-resistant organisms in oropharyngeal samples were infrequently acquired, occurring in six of 36 participants treated with azithromycin and four of 37 treated with placebo.

Another randomized controlled trial found that azithromycin use during an episode of lower respiratory tract symptoms resulted in a shorter duration of asthma-like episodes. This trial, from the COPSAC cohort, assessed 72 children aged 1–3 years with a history of recurrent asthma-like symptoms who were randomly assigned to receive either a 3-day course of azithromycin or placebo during asthma-like episodes, which were physician-evaluated and defined as having at least 3 consecutive days of troublesome lung symptoms prior to starting study medication [45••]. Hypopharyngeal aspirates were cultured for selected bacteria (*H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*). Nasopharyngeal aspirates were assessed for rhinoviruses, RSV, and enteroviruses via PCR. 60% of samples collected were positive for at least one of the bacterial species, with *M. catarrhalis* being the most common (47%). Forty-three percent of the samples collected were PCR-positive for a virus, with an incidence of 16–20% for each type of virus. One hundred fifty-eight asthma-like episodes occurred in the two groups, and the average duration of each episode after treatment initiation was significantly shorter in the azithromycin group compared with placebo (3.4 vs 7.7 days). They found that early treatment with azithromycin, prior to day 6 of symptoms, resulted in the greatest reduction in the episode duration (83%).

There is considerable evidence that antibiotic use contributes to the development of antimicrobial resistance and may also negatively alter the microbiome. A study by Korpela et al. of antibiotic use in 2–7-year old Finnish children found that early antibiotic use was associated with altered intestinal microbiota composition and increased risk of asthma [46•]. The altered microbiota composition was notable for decreased *Actinobacteria*, increased *Bacteroidetes* and *Proteobacteria*, and increased rates of macrolide resistance. A retrospective population-based cohort study found that antibiotic use during the first year of life was associated with an increased risk of

Table 2 Summary of referenced studies of the role of azithromycin in children with recurrent wheezing

Reference	Study design	Study population and location	Sample size	Population characteristics	Intervention	Outcome
Bacharier et al. 2015 [38]	RDBPC	12–71 months of age USA	443 children 937 treated RTIs	History of recurrent severe LRTIs	5-day course of azithromycin vs placebo at earliest signs of a RTI Dose 12 mg/kg/day	Azithromycin treatment group had reduced risk of progression to a severe episode Hazard ratio 0.64
Stokholm et al. 2016 [39]	RDBPC	1–3 years of age COPSAC cohort Denmark	72 children 158 asthma-like episodes	History of recurrent asthma-like symptoms	3-day course of azithromycin vs placebo after at least 3 days of asthma-like episodes Dose 10 mg/kg/day	Azithromycin treatment group had a shorter subsequent episode duration: 3.4 vs 7.7 days

COPSAC Copenhagen Prospective Study on Asthma in Childhood, *LRTI* lower respiratory tract illness, *RDBPC* randomized, double-blinded, placebo-controlled trial, *RTI* respiratory tract illness

asthma development by 3 years of age, with a positive relationship between number of antibiotic courses received and risk of asthma [47]. A cross-sectional study showed that bronchiolitis during the first 2 years of life and antibiotic exposure during infancy were associated with asthma development during adolescence [48]. While these studies suggest that antibiotic use and subsequent asthma development are related, the cause of this relationship is still unknown. Furthermore, this association is likely to be complicated by confounding by indication. Children with significant lower respiratory tract illnesses are more likely to receive antibiotics for treatment of these illnesses, and thus it is possible that while antibiotics could be causative of subsequent asthma development, antibiotic use could also be a marker of an underlying predisposition for, or a comorbidity associated with, asthma.

Role of Antibiotics for the Prevention of Asthma

While macrolide use does not significantly alter the course of acute bronchiolitis, recent studies suggest that azithromycin may have a role in the prevention of recurrent wheezing following bronchiolitis. The first was a randomized trial of 21 infants with RSV bronchiolitis which compared clarithromycin to placebo for 3 weeks, and reported that clarithromycin use was associated with a shorter length of hospital stay, shorter duration of supplemental oxygen requirement, lower amount of β2 agonist use, and lower rates of readmission to hospital over the ensuing 6 months [49]. However, subsequent communications have questioned the validity of these findings [50, 51]. The second study was a proof-of-concept, randomized, placebo-controlled trial involving 40 children 1–18 months of age without a prior wheezing history who were hospitalized with RSV bronchiolitis [52••]. A unique aspect of this study was inclusion of a homogeneous population of otherwise healthy full-term infants. When added to routine bronchiolitis care, azithromycin treatment for 14 days resulted in a lower risk of recurrent wheezing in the subsequent year when compared to placebo. It is interesting to note that wheezing outcomes between the treatment and placebo group were similar at 6 months, suggesting that the effect of azithromycin therapy may be predominantly on illnesses occurring more than 6 months after treatment [53]. Additionally, nasal lavage fluid IL-8 levels, a marker of neutrophilic airway inflammation, were reduced, although serum IL-8 levels were not [52••]. The upper airway microbiome was also assessed, and treatment with azithromycin for acute RSV bronchiolitis was found to result in changes in airway microbiome composition, particularly a reduction in *Moraxella* [54]. Azithromycin was well-tolerated, with mild gastrointestinal adverse events including diarrhea, vomiting, and abdominal pain reported at similar rates in the placebo group compared with the treatment group [52••]. These studies were limited by their small sample size. Larger studies are required to determine if this therapy provides clinically important and durable effects on recurrent wheezing and asthma as well as the consequences of this therapy on the microbiome.

Conclusion

In summary, early-in-life lower respiratory tract infections are strongly associated with augmented risks of persistent wheezing and asthma development. Most research on this topic has focused on viral causes of lower respiratory tract disease, particularly RSV and rhinovirus. However, increasing knowledge about the infant microbiome and effects of environmental exposure on expression of respiratory disease suggests that subsequent asthma development is also associated with alterations in microbiome composition. Current evidence indicates that while macrolides do not impact the immediate course of illness for infants hospitalized with bronchiolitis, azithromycin may have a role in the prevention of future post-bronchiolitis wheezing episodes in high-risk children with severe RSV bronchiolitis. Furthermore, recent evidence suggests that azithromycin use early during respiratory episodes in high-risk preschoolers with recurrent wheeze can

shorten episode duration and lower the risk of progression to severe lower respiratory tract illnesses. More research is needed to confirm these beneficial effects, to better characterize azithromycin's mechanism of action in these disorders, to further define the risk of antibiotic resistance, as well as to explore the potential roles for other antibiotics in the management of early life recurrent wheezing.

Compliance with Ethical Standards

Conflict of Interest Dr. Kwong has nothing to disclose. Dr. Bacharier reports grant support from NIH; serving as a consultant to Aerocrine, GlaxoSmithKline, Genentech/Novartis, Cephalon, Teva, Circassia, and Boehringer Ingelheim; serving on advisory boards for Merck, Sanofi, and Vectura; serving on data and safety monitoring boards for DBV Technologies; and receiving honoraria for lectures or continuing medical education development from Aerocrine, GlaxoSmithKline, Genentech/Novartis, Merck, Cephalon, Teva, AstraZeneca, WebMD/Medscape, and Boehringer Ingelheim.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Declaration of Helsinki and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of Particular Interest, Published Recently, Have Been Highlighted as:
- • Of importance
- •• Of major importance

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med. 1995;332:133–8.
2. Moorman J, Akinbami L, Bailey C. National surveillance of asthma: United States, 2001–2010. Vital Heal Stat. 2012;3(35):1–67.
3. Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe. 2015;17:704–15.
4. Sullivan A, Hunt E, MacSharry J, Murphy DM. The microbiome and the pathophysiology of asthma. Respir Res. 2016;17:163.
5. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. JAMA. 1999;282:1440–6.
6. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360:588–98.
7. Kusel MMH, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol. 2007;119:1105–10.
8. Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Pappas TE, Lee WM, et al. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. Am J Respir Crit Care Med. 2012;185:281–5.
9. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med. 2008;178:667–72.
10. Guilbert TW, Singh AM, Danov Z, et al. Decreased lung function after preschool wheezing rhinovirus illnesses in children at risk to develop asthma. J Allergy Clin Immunol. 2011;128:532–538.e10.
11. Bochkov YA, Watters K, Ashraf S, Griggs TF, Devries MK, Jackson DJ, et al. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. Proc Natl Acad Sci U S A. 2015;112:5485–90.
12. Drysdale SB, Alcazar M, Wilson T, et al. Respiratory outcome of prematurely born infants following human rhinovirus A and C infections. Eur J Pediatr. 2014;173:913–9.
13. Miller EK, Khuri-bulos N, Williams JV, et al. Human rhinovirus C associated with wheezing in hospitalized children in the Middle East. J Clin Virol. 2009;46:85–9.
14. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child. 1986;140:543–6.
15. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet. 1999;354:541–5.
16. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. BMC Pediatr. 2013;13:97.
17. Carroll KN, Wu P, Gebretsadik T, Griffin MR, Dupont WD, Mitchel EF, et al. The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma. J Allergy Clin Immunol. 2009;123:1055–1061.e1.
18. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med. 2000;161:1501–7.
19. Bacharier LB, Cohen R, Schweiger T, Yin-Declue H, Christie C, Zheng J, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2012;130:91–100.e3.
20. Bertrand P, Lay MK, Piedimonte G, Brockmann PE, Palavecino CE, Hernández J, et al. Elevated IL-3 and IL-12p40 levels in the lower airway of infants with RSV-induced bronchiolitis correlate with recurrent wheezing. Cytokine. 2015;76:417–23.
21. Torgerson DG, Giri T, Druley TE, et al. Pooled sequencing of candidate genes implicates rare variants in the development of asthma following severe RSV bronchiolitis in infancy. PLoS One. 2015;10:1–15.
22. Nuolivirta K, Tormanen S, Terasjarvi J, Vuononvirta J, Koponen P, Korppi M, et al. Post-bronchiolitis wheezing is associated with toll-like receptor 9 rs187084 gene polymorphism. Sci Rep. 2016;6:1–9.
23. Suárez-Arrabal MC, Mella C, Lopez SM, et al. Nasopharyngeal bacterial burden and antibiotics: influence on inflammatory markers and disease severity in infants with respiratory syncytial virus bronchiolitis. J Inf Secur. 2015;71:458–69.
24.• Carlsson CJ, Vissing NH, Sevelsted A, Johnston SL, Bonnelykke K, Bisgaard H. Duration of wheezy episodes in early childhood is independent of the microbial trigger. J Allergy Clin Immunol. 2015;136:1208–14. **A large prospective cohort study of infants at high-risk for asthma. Nasopharyngeal and hypopharyngeal aspirates were obtained during acute wheezy episodes. Duration of wheezy episodes was found to be independent of the presence of potentially pathogenic bacteria or viruses**
25. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med. 2007;357:1487–95.
26. De Schutter I, Dreesman A, Soetens O, De Waele M, Crokaert F, Verhaegen J, et al. In young children, persistent wheezing is

associated with bronchial bacterial infection: a retrospective analysis. BMC Pediatr. 2012;12:83.
27. Lynch SV, Wood RA, Boushey H, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. J Allergy Clin Immunol. 2014;134:593–601.e12.
28. Ege MJ, Mayer M, Normand A-C, Genuneit J, Cookson W, Braun-Fahrlander CB, et al. Exposure to environmental microorganisms and childhood asthma. N Engl J Med. 2011;364:701–9.
29. Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in Amish and Hutterite farm children. N Engl J Med. 2016;375:411–21.
30. Cardenas PA, Cooper PJ, Cox MJ, Chico M, Arias C, Moffatt MF, et al. Upper airways microbiota in antibiotic-naïve wheezing and healthy infants from the tropics of rural Ecuador. PLoS One. 2012; doi:10.1371/journal.pone.0046803.
31.•• Arrieta M-C, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med. 2015;7:307ra152-307ra152. **Analysis of the gut microbiome of 319 infants showed that a transient decrease in certain gut bacteria was associated with increased asthma risk**
32. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. Clin Exp Allergy. 2014;44:842–50.
33. Johnson LW, Robles J, Hudgins A, Osburn S, Martin D, Thompson A. Management of bronchiolitis in the emergency department: impact of evidence-based guidelines? Pediatrics. 2013;131:S103–9.
34. Farley R, Spurling GKP, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age (review). Cochrane Database Syst Rev. 2014:1–42.
35.• Ralston SL, Lieberthal A, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis 2014. Pediatrics. 2014; doi:10.1542/peds.2014-2742. **These are the current guidelines for bronchiolitis management**
36. Lassi ZS, Kumar R, Das JK, Salam RA, Bhutta ZA. Antibiotic therapy versus no antibiotic therapy for children aged two to 59 months with WHO-defined non-severe pneumonia and wheeze. Cochrane Database Syst Rev. 2014;5:CD009576.
37. McCallum GB, Morris PS, Chang AB. Antibiotics for persistent cough or wheeze following acute bronchiolitis in children. Cochrane Database Syst Rev. 2012;12:CD009834.
38. Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. Am J Respir Crit Care Med. 2008;177:148–55.
39. Cameron EJ, Mcsharry C, Chaudhuri R, Farrow S, Thomson NC. Long-term macrolide treatment of chronic inflammatory airway diseases: risks, benefits and future developments. Clin Exp Allergy. 2012;42:1302–12.
40. Kneyber MCJ, van Woensel JBM, Uijtendaal E, Uiterwaal CSPM, Kimpen JLL. Azithromycin does not improve disease course in hospitalized infants with respiratory syncytial virus (RSV) lower respiratory tract disease: a randomized equivalence trial. Pediatr Pulmonol. 2008;43:142–9.
41. Pinto LA, Pitrez PM, Luisi F, 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.
42. McCallum GB, Morris PS, Chatfield MD, Maclennan C, White AV, Sloots TP, et al. A single dose of azithromycin does not improve clinical outcomes of children hospitalised with bronchiolitis: a randomised, placebo-controlled trial. PLoS One. 2013;8:e74316.
43.• McCallum GB, Morris PS, Grimwood K, et al. Three-weekly doses of azithromycin for indigenous infants hospitalized with bronchiolitis: a multicentre, randomized, placebo-controlled trial. Front Pediatr. 2015;3:32. **Study of indigenous children from Australia and New Zealand with RSV assessing the effect of azithromycin use on their subsequent hospital course**
44.•• Bacharier LB, Guilbert TW, Mauger DT, 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. **Large multicenter trial demonstrating that the use of azithromycin at the beginning of a respiratory tract illness decreases the risk of progression to a severe episode in high risk children**
45.•• Stokholm J, Chawes BL, Vissing NH, 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. **Azithromycin use was associated with a reduced duration of asthma-like symptoms in children with a prior history of asthma-like symptoms, with the greatest reduction noted with early azithromycin initiation**
46.• Korpela K, Salonen A, Virta LJ, Kekkonen RA, Forslund K, Bork P, et al. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. Nat Commun. 2016;7:10410. **Study of Finnish children demonstrating that early-onset antibiotic use is associated with long-lasting alterations in the intestinal microbiome**
47. Ong MS, Umetsu DT, Mandl KD. Consequences of antibiotics and infections in infancy: bugs, drugs, and wheezing. Ann Allergy, Asthma Immunol. 2014;112:441–445.e1.
48. Lee E, Kwon J-W, Kim H-B, et al. Association between antibiotic exposure, bronchiolitis, and TLR4 (rs1927911) polymorphisms in childhood asthma. Allergy Asthma Immunol Res. 2015;7:167–74.
49. Tahan F, Ozcan A, Koc N. Clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomised, placebo-controlled trial. Eur Respir J. 2007;29:91–7.
50. Korrpi M. To the editors: macrolides and bronchiolitis in infants. Eur Respir J. 2007;29:1283–4.
51. Tahan F. From the authors: macrolides and bronchiolitis in infants. Eur Respir J. 2007;29:1284.
52.•• Beigelman A, Isaacson-Schmid M, Sajol G, 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;135:1171–1178e1. **Proof-of-concept trial of otherwise healthy infants who were hospitalized for RSV bronchiolitis. Use of azithromycin was associated with a reduction in the risk of recurrent wheezing in the following year**
53. Beigelman A, Bacharier LB. Reply. J Allergy Clin Immunol. 2015;136:1135–6.
54. Zhou Y, Bacharier LB, Isaacson-Schmid M, Baty J, Schechtman KB, Sajol G, et al. Azithromycin therapy during respiratory syncytial virus bronchiolitis: upper airway microbiome alterations and subsequent recurrent wheeze. J Allergy Clin Immunol. 2016;138:1215–1219.e5.