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Asthma and the host-microbe interaction

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Activity Objectives

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1. To understand the influence that early microorganism exposure and infection can have on the development of asthma and the atopic phenotype.
2. To appreciate that the respiratory and gastrointestinal tracts are populated with a diverse number of microorganisms that might play a role in asthma pathogenesis and progression.
3. To identify the role of microbes in asthma exacerbations and chronic disease burden.
4. To understand the role antimicrobial therapy might have in the management of asthma exacerbations and uncontrolled disease.

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CLINICAL VIGNETTE

A 34-year-old woman with moderate persistent asthma presents for evaluation of increased cough, wheezing, and shortness of breath with chest tightness. These symptoms began approximately 4 days ago after 5 days of nasal congestion and sore throat that resolved. She reports that her 4-yearold daughter had a similar “cold” recently but improved much more quickly than she did. Before her daughter began day care 1 year earlier, the patient’s symptoms were well controlled with an inhaled corticosteroid only. At her last clinic visit, 3 months prior, she denied nocturnal symptoms and only required her short-acting bronchodilator about once a week with a medium-dose inhaled glucocorticoid and long-acting β-agonist. She is currently using her short-acting bronchodilator 3 times daily with this recent illness. Despite these efforts, her peak expiratory flow measurements remain less than 70% of her personal best. She calls requesting prescriptions for prednisone and an antibiotic and is scheduled for a same-day appointment. She denies fevers, chills, or chest pain but reports minimal yellow sputum.

The patient was given a diagnosis of asthma as an infant after a hospitalization for respiratory syncytial virus (RSV) bronchiolitis but has not been hospitalized for asthma since that time. She believes that throughout her life it has generally taken her longer to recover from colds and has been frequently treated with antibiotics in addition to steroids for “bronchitis” complicating her asthma exacerbations but denies receiving a clear diagnosis of recurrent pneumonias, sinusitis, or otitis media. She has a history of eczema and known triggers for asthma symptoms, including upper respiratory tract infections, tobacco smoke, cats, and some tree pollens but denies these other exposures recently.

Her physical examination is remarkable for a temperature of 37.1°C, a heart rate of 92 beats/min, a respiratory rate of 22 breaths/min, and oxygen saturations of 96% while breathing ambient air. There are diffuse end-expiratory wheezes on examination but an otherwise unremarkable auscultatory examination and no dullness to chest percussion or increased work of breathing at rest. Spirometry reveals an FEV_1 of 62% of predicted value that increased to 69% of predicted value after inhaled bronchodilator therapy in the clinic. A chest radiograph appears normal.

The patient's most recent exacerbation is believed likely secondary to a previously resolved upper respiratory tract viral infection and not complicated by a bacterial cause. The indications for antibiotics during an asthma exacerbation are reviewed with the patient, as well as the potential adverse effects of antibiotics, including allergic and adverse reactions, increased antibiotic resistance, and its potential role in driving further atopy. The patient is given a 7-day course of prednisone and reminded to use her inhaled bronchodilator regularly with appropriate technique and monitor her peak flow daily. She is scheduled for a follow-up appointment in 1 week's time and instructed to contact the provider sooner with any clinical concerns.

The full version of this article, including a review of relevant issues to be considered, can be found online at www.jacionline.org. *If you wish to receive CME or MOC credit for this article, please see the instructions above*.

REVIEW

Overview

Although the causes are clearly multifactorial, evidence supports an association between host-microbe interactions and the development, exacerbation, and chronic stable course of asthma. The association between asthma exacerbations and acute viral and bacterial infections is well established; however, the relationship between host-microbe interactions and the development and chronic stable course of asthma is only recently emerging. Recognition of a relationship between microorganism exposure and immune system development, along with the identification of diverse microbiota inhabiting the respiratory and gastrointestinal tracts in health and disease, guide many of these developing ideas and inquiries. The implications of these findings remain unclear but pose new directions for research and management of the asthmatic patient.

Asthma onset and the role of microbes

Viral respiratory tract infections in infancy and airway colonization with previously presumed bacterial pathogens might predict the development of asthma early in life.[E1] Nearly all children have serologic evidence of RSV infection in their first 2 years of life, but only 40% will have clinical symptoms of bronchiolitis. In a cohort of children hospitalized for RSV bronchiolitis, those with this infection in infancy were more likely to have asthma at 18 years old (33% vs 7%) and to have positive skin test responses to perennial allergens (41% vs 14%) than healthy control subjects.[E2] The Tucson Children's Respiratory Study followed 1200 infants from birth and found that children with RSV bronchiolitis were 3 to 4 times more likely to wheeze at 6 years of age. This relationship significantly decreased with

age and was almost nonsignificant by age 13 years. Unfortunately, neither study distinguishes whether RSV bronchiolitis directly causes asthma or is the result of a shared defective immune response presenting as a clinically significant infection. The best clinical evidence regarding a causal link comes from a prospective study of premature infants receiving the mAb palivizumab for RSV prophylaxis.[E3] Palivizumab prophylaxis in infancy was protective against recurrent wheezing but only in those without a family history of atopy. Disputing a causal link, Chawes et al[E4] showed that in a cohort of children born to mothers with asthma, bronchial hyperresponsiveness to methacholine in neonates 1 month of age using a thoracoabdominal compression technique predicted acute severe viral bronchiolitis regardless of the viral species, including RSV. These findings and others support an increasing acceptance that the relationship between early infections, wheezing, and asthma is likely more complex than previously considered. Individual host and genetic factors clearly contribute because not all patients with RSV bronchiolitis or wheezing during infancy have asthma.

In the Copenhagen Prospective Study on Asthma, hypopharyngeal colonization at 1 month with *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* in infants of mothers with asthma was associated with persistent wheezing, acute severe exacerbations of wheeze, hospitalization for wheezing, airway reversibility to a β_2-agonsist, blood eosinophilia, and total IgE later in childhood.[E5] This relationship was lost in hypopharyngeal cultures taken at 12 months because colonization patterns changed and were not predictive. Regarding the seemingly conflicting results from the Tuscon and Copenhagen studies, there might be more than 1 mechanism that results in the presentation of asthma. The presence of bacteria in early life outside of acute infection can be associated with derangements of mucosal immunity, allowing colonization of these organisms and an association with chronic inflammation at a later time in life. The mechanism driving acute respiratory illnesses caused by RSVand subsequent asthma up to the age of 11 years (not 6 years) might be that patients with asthma or a subphenotype prone to exacerbations have a defect in viral responses that predisposes both to RSV and subsequent asthma, such as bronchial hyperresponsiveness or narrow airways, or that RSV triggers an abnormal response to viruses in predisposed subjects that begets subsequent asthma. Thus the presentation of asthma later in childhood might be due to chronic colonization of bacteria, deranged responses to viral infections, or both. These processes are not mutually exclusive.

Host microbes and the hygiene hypothesis

The previous 5 decades were marked by an increase in the incidence of asthma and allergic disease in the industrialized world. During this same time period, the increased use of antibiotics, improved hygiene, and urbanization presumably decreased childhood exposure to previously common infections, diverse environmental microorganisms, and their products.[E6,E7] These events, along with other population studies, suggest an inverse relationship between microbiologic diversity and atopic disease, which is also known as the hygiene hypothesis. An early and prolonged imbalanced expression of the T_H2 allergic phenotype can persist in those without an appropriate T_H1-directed response to infection in early life. This is supported by mouse models in which pathogen exposure before allergic sensitization favors decreased airway inflammation, airway hyperresponsiveness, and T_H2-

related cytokines with allergen re-exposure.[E8] Recognition of the human microbiome and its systemic immunomodulatory effects further contribute to the hygiene hypothesis. When taken with evidence that diverse gut and lung microbiota can favor a balanced T_H response, some have proposed the "microbiota hypothesis."

Asthma and the host microbiome

Seventy percent of all bacterial species that inhabit bodily surfaces cannot be cultured by using currently available techniques. New culture-independent techniques aimed predominately at PCR amplification of the highly conserved 16s rRNA gene allow identification of these previously unappreciated broad populations of microorganisms.[E9] The gut mucosa microbiome might represent our most significant source of immune stimulation, and changes in this ecosystem resulting in imbalanced T-cell and cytokine responses are increasingly associated with autoimmune and atopic disease.[E10] Early and frequent interactions between gut microbial antigens and mucosal immune systems might promote immune tolerance and a shift away from a T_H2 phenotype.[E11] One early influence of the gut microbiome is the mode of delivery at childbirth. The intestinal microbiota of babies delivered vaginally are more frequently populated with *Lactobacillus* species, whereas the intestinal microbiota of those born by means of cesarean delivery are more frequently populated with potential pathogens, such as *Staphylococcus* and *Acinetobacter* species. Furthermore, although the mechanisms remain unclear, cesarean delivery is associated with a significant increase in the rate of asthma.

Examination of this commensal relationship suggests that diet might play a role. Small-chain fatty acids, a product of gut microbe metabolism of fermentable dietary fiber, are known ligands for GPR43, a G protein–coupled receptor. Mice deficient in GPR43 had exacerbated inflammation in an allergic airway model.[E12] Efforts to treat allergic disease with prebiotics and probiotics remain largely unsuccessful but are limited by our understanding of these populations and their interactions with the immune system.[E13]

Early characterization of the airway microbiome in asthmatic patients demonstrates broad populations different from healthy control subjects that might have clinical significance.[E9] Hilty et al first characterized this population through 16s rRNA in asthmatic patients and healthy control subjects.[E9] A mean of 2000 bacterial genomes per cubic centimeter surface sample were identified. Asthmatic patients were more likely to have pathogenic Proteobacteria, including *Haemophilus* species. Healthy control subjects were more frequently colonized with Bacteroidetes, such as *Prevotella* species, a commonly identified oral flora. Most recently, Huang et al showed that patients with suboptimally controlled asthma had greater lung microbiome diversity than healthy control subjects.[E9] Additionally, bronchial hyperresponsiveness was correlated with population diversity and, in particular, the presence of Proteobacteria. The significance of these findings remains unclear and is further clouded by concomitant use of inhaled corticosteroids in many subjects.

Immune mechanisms of host-microbe interactions in asthma

Attempts to examine the host-microbe interaction in asthmatic patients have expanded on earlier ideas of T_H1-T_H2 imbalance and suggest additional mechanisms of

immunoregulation and promotion of allergen tolerance. Through interactions with innate immune receptors, such as Toll-like receptors and pathogenassociated molecular patterns, the adaptive allergic response might be limited.[E14] For example, binding of LPS to Toll-like receptor 4 generates cytokines, such as IL-10, IL-12, and IFN-γ, that inhibit allergic sensitization; however, after allergeninduced sensitization, LPS can amplify production of T_H2 cytokines. In murine models, when dendritic cells from mice infected with *Schistosoma japonicum*, *Chlamydia muridarum*, or BCG were transferred to noninfected mice, allergic airway inflammation was inhibited, demonstrating the significance of innate immunity in infection-mediated inhibition of the allergic response.[E15]

Regulatory T (Treg) cells are known for their ability to suppress other immune cells, including those responsible for T_H1 and T_H2 responses. Increasingly, microbes are recognized for their ability to induce Treg cells. Again, in murine models stimulation of dendritic cells with pathogen-associated molecular patterns led to the development of Treg cells through an IL-10–dependent pathway, and adoptive transfer of these cells stimulates Treg cell development in the recipient.[E14] Additionally, *Lactobacillus reuteri*, a frequent inhabitant of healthy mammalian gastrointestinal tracts, induces Treg cells and attenuates the allergic airway response in mice.[E15] In germ-free mice oral tolerance cannot be established because of impaired Treg cell function and the associated cytokines IL-10 and TGF-β. In human subjects maternal stool colonization with common commensal gut microbes, such as gram-positive anaerobes (lactobacilli and bifidobacteria) and gram-negative anaerobes (*Bacteroides* and *Prevotella* species), correlates with IL-10 secretion from cord blood mononuclear cells.

Atypical bacteria and asthma

The role of atypical bacterial infections in asthmatic patients deserves particular attention because they are associated with asthma exacerbations, chronic stable asthma, and disease severity.[E16] In 2001, Martin et al found PCR-positive evidence by means of bronchoscopy of *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* in 56% of patients with chronic stable asthma compared with 9% of healthy control subjects, along with a greater number of tissue mast cells in PCR-positive asthmatic patients.[E16] In 2005, Martin and Johnston found that 9 of 12 studies examining a role for atypical bacteria in acute asthma flares demonstrated an association among *M pneumoniae*, *C pneumonia*, and exacerbations.[E16] Various *in vitro* studies support an increase in MUC5AC (an airway mucin) mRNA expression with atypical bacterial infection of asthmatic epithelial cells, a hallmark of asthma exacerbations.

Antimicrobial agents and asthma

The most recent National Asthma Education and Prevention Program guidelines from 2007 recommended against empiric antibiotics in the treatment of asthma exacerbations because many exacerbations are not due to respiratory tract infections and most infections were attributed to viruses.[E17] These recommendations were supported by 2 small, randomized, double-blind, placebo-controlled trials that enrolled patients hospitalized for asthma exacerbations believed not likely caused by a bacterial infection. Both used penicillin-based antibiotics and demonstrated no improvement in asthma outcomes.[E7]

Observations of the potential relationship between atypical bacterial organisms in chronic and exacerbated asthma led to recent trials with macrolide antibiotics.[E16] In 2002, Kraft et al showed that bronchoalveolar lavage fluid *M pneumoniae* or *C pneumoniae* PCR-positive asthmatic patients experienced an increase in FEV_1 compared with levels seen in PCR-negative asthmatic patients and control subjects, as well as reduced pulmonary inflammatory cytokine levels in PCR-positive and PCR-negative subjects when treated with clarithromycin.[E16] These relationships did not hold when cultures or serologic results were used for diagnosis. Similar studies in asthmatic patients with serologic evidence of *C pneumoniae* showed transient improvement in mean peak expiratory flows and FEV_1 levels with macrolide therapy. This benefit might not only be present in those with presumed atypical bacterial infections, as recently shown in a population of patients with severe, refractory, noneosinophilic asthma without known *Mpneumoniae* or *C pneumoniae*. Patients treated with 8 weeks of clarithromycin reported an improvement in quality-of-life scores and had reduced sputum IL-8 levels. These findings might be attributable to the direct anti-inflammatory effects of macrolides and might make them an attractive add-on therapy in the neutrophilic asthma phenotype.

There have been several studies evaluating the utility of antibiotics in patients with chronic asthma with variable results.[E18–E20] A Cochrane analysis was published in 2005 in which 95 studies were initially evaluated, and 20 potentially met entry criteria requiring that they be randomized placebo-controlled trials of more than 4 weeks' duration.[E21] However, only 5 studies met these criteria and were included in the analysis. Although a positive effect on symptoms was noted, the numbers of subjects were considered too small to draw further conclusions. A recent study by Brusselle et al[E18] demonstrated that azithromycin did not improve exacerbations overall in a cohort of 109 subjects with severe asthma who were exacerbation prone, but a subgroup analysis did demonstrate an improvement in the group with noneosinophilic asthma, as determined based on induced sputum. The authors concluded that evaluating macrolides in this particular inflammatory phenotype of asthma warrant further study.

As for acute exacerbations, TELICAST investigated the efficacy of telithromycin in acute asthma flares and demonstrated a small but statistically significant 0.3-point improvement in asthma symptom scores but no change in morning peak expiratory flow rates. These findings were independent of *M pneumoniae*, *C pneumoniae*, or both infection status. Most recently, in an open-labeled, randomized, prospective study of 40 children with asthma exacerbations, Koutsoubari et al[E22] demonstrated that a 3-week course of clarithromycin was associated with an increase in symptom-free days, decreased duration of exacerbation, and decrease in severity of symptoms. Despite these favorable findings, difficulty in making a rapid noninvasive diagnosis of atypical bacterial infections, heterogeneity across studies, uncertainty about who might clearly benefit, and lack of durable clinical improvement compared with placebo continue to make it unclear who would best benefit from macrolide therapy.

THE CASE REVISITED

Our patient with a long-standing history of asthma first considered after viral bronchiolitis during infancy and atopy presents with a recent change in asthma control. She reports increased cough, wheezing, dyspnea, and decreasing pulmonary function test results characteristic of her usual asthma exacerbation and requests antibiotics in addition to corticosteroids given her history of similar therapy and a preceding upper respiratory tract infection that has now resolved. This case highlights many of the emerging concepts indicating that the host-microbe interaction might play in the development, exacerbation, chronic stable course, and management of asthma.

Early severe infections with the ubiquitous RSV might suggest a future risk for asthma in early adulthood; however, this risk appears most significant for those with an atopic phenotype, and a causative role cannot be established at this time. Efforts to identify the abundant and varied populations of microbiota colonizing the gastrointestinal and respiratory tracts suggest differences in the airway microbiome between asthmatic patients and healthy control subjects. Whether these differences are the result of early microbial exposures, antimicrobial therapies, inhaled corticosteroids, or chronic inflammatory airways disease is unclear. Even more uncertain is the significance of these differences and our ability to alter them in a clinically beneficial manner. Perhaps the best evidence for our ability to positively affect the host-microbe interaction in asthmatic patients remains in treating atypical bacteria with macrolide therapies. Despite the difficulty in making a rapid diagnosis of *M pneumoniae* or *C pneumoniae*, evidence suggests increased rates of colonization, acute infection, or both with these microorganisms in patients with chronic stable asthma and acute exacerbations. Viral infections remain the most common recognized infectious cause of an asthma exacerbation, and antibiotic therapy is generally not indicated; however, when antibiotic therapy is prescribed, macrolides should be considered.

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