



Infections in Children with Asthma

Reza Farid Hossaini¹

Javad Ghaffari^{2*}

Alireza Ranjbar³

Mohammad Reza Haghshenas⁴

Houshang Rafatpanah⁵

^{1,5}Allergy Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

²Molecular and Cell Biology Research Center, Department of Pediatric Immunology and Allergy, Faculty of Medicine, Mazandaran University of Medical Sciences Sari, Iran

³Research Institute of Interventional Allergology and Immunology, Bonn, Cologne, Germany

⁴Molecular and Cell Biology Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

ARTICLE INFO

Article type:

Review Article

Article history:

Received: 15 Aug 2012

Revised: 1 Dec 2012

Accepted: 20 Dec 2012

Keywords:

Children, Asthma, Viruses, Bacteria

<http://jpr.mazums.ac.ir>

ABSTRACT

Asthma is a common chronic inflammatory and complex disease in children with many contributing (including genetic and environmental) factors. This study aims to review the impact of infections in children with asthma.

Different websites including Google Scholar, Yahoo, Pubmed, SID.IR, MAGIRAN, IRANDOC, IRANMEDEX, Embase and Hand searching were searched for pertinent articles with keywords asthma, pediatric, infection, virus, bacteria, and fungus. Out of the results, full articles relevant to pediatric asthma were selected.

Acute respiratory infections caused by Chlamydia pneumoniae and Mycoplasma pneumoniae are involved in 5%-30% of wheezing events and asthma attacks. Viral infections were previously found in 24%-34% of asthmatic children, but technological advancements have revealed them to be present in 77%-81% of cases, with rhinovirus found in 47%, Respiratory Syncytial Virus in 21%, and the rest (including influenza, parainfluenza, adenovirus, coronavirus, and enterovirus) accounting for 2%-5% each.

Viral respiratory infections are basically the major trigger for asthma symptoms and attacks in children. No causal relationship has been established between asthma and viruses and bacteria.

Introduction

Asthma is one of the most common chronic and complicated inflammatory disease in children involving numerous genetic and environmental factors such as allergens inside and outside the

house, irritating factors like air pollutants, cold, tobacco smoke and respiratory infections. It afflicts upper and lower airways and imposes a tremendous financial burden on families and the

*Corresponding Author: Javad Ghaffari MD, Associate professor of allergy and clinical immunology

Mailing Address: Department of pediatric Immunology and Allergy, Bou Ali Sina Hospital, Pasdaran Boulevard, Sari, Iran

Tel: +98 151 2233011-15

Fax: +98 151 2234506

Email: javadneg@yahoo.com

society. Moreover, it impacts the quality of life in patients and their families and is an important cause of morbidity and even mortality.^{1,2} The etiology of asthma is not well understood. More than 300 million people suffer from asthma worldwide, and it is more common in children compared to adults.

Respiratory infections constitute an important environmental factor in asthma. Viral infections are involved in half the cases of asthma development or exacerbation.^{3,4}

Acute respiratory infections caused by *Chlamydia pneumoniae* (C.Pneumoniae) and *Mycoplasma pneumoniae* (M.Pneumoniae) are involved in 5%-30% of wheezing and asthma attacks. These factors may be involved in development of the disease or particularly its exacerbation, which remains to be settled. Some studies consider C.Pneumoniae to be more important than M.Pneumoniae in developing and exacerbating asthma symptoms, and vice versa.⁵ It is believed that many individuals are asymptomatic or only mildly symptomatic and thus unaware of their disease, when an infection intensifies their symptoms. Most studies concur that viral respiratory infections exacerbate asthma symptoms and that avoiding contact with people with common cold may prevent asthma exacerbation. Asthma is not a contagious disease and cannot be transmitted from one person to another.

The present study aims to review the role of different microbial agents in developing and exacerbating asthma in children.

Method

In order to obtain the articles, different websites including Google Scholar, Yahoo, Pubmed, SID.IR, MAGIRAN, IRANDOC, and IRANMEDEX, Embase and Hand search were searched for keywords of asthma, children, infection, virus, bacteria, fungus. Among the

results returned, full articles relevant to the issue of pediatric asthma were selected.

Discussion

Viral Infections

Previously, viral infections were documented in 24%-32% of asthmatic children, which has risen to 77%-81% with development of new techniques.⁵

Many different viruses may exacerbate asthma symptoms, including rhinoviruses, coronavirus, influenza, parainfluenza, adenovirus, enterovirus and Respiratory Syncytial Virus (RSV). Viral agents are basically transmitted in close contact. Viral infections endure longer in crowded environments and are more easily transmitted. Rhinoviruses, RSV and parainfluenza are among the most common infections. Rhinovirus is responsible for 47%, RSV for 21%, and the rest, i.e. influenza, parainfluenza, adenovirus, coronavirus, and enterovirus are each responsible for 2%-5%. RSV-C is more common in winter while rhinovirus is present throughout the year.

Studies dealing with the role of viruses have yielded diverse results. Some report a positive relationship between viruses, such as rhinovirus, adenovirus, or RSV, with asthma exacerbation^{6,7} while others have failed to demonstrate any association.⁸

Severe bronchiolitis caused by RSV in early childhood may be associated with recurrent wheezing and asthma later on.⁹⁻¹¹ The relationship between RSV infection in early childhood and development of atopy is still controversial.⁹ Rhinovirus is one of the most common viruses found to be involved in asthma attacks in older children.¹²

A study on children with high risk of atopy indicated a significant relationship between rhinovirus and RSV infection in the first year of life with persistent wheezing and asthma at 5 years of age; particularly in children

hospitalized for rhinovirus respiratory infection, the risk of developing asthma at 6 years of age is higher.¹³

Rhinoviruses are often quickly spread in autumn when children go to school. Some studies have shown a strong relationship between respiratory infection and inflammation caused by atopy and persistent asthma.^{14,15}

The relationship between respiratory infections and development of persistent asthma and wheezing is of a complex nature and probably involves an interaction between host factors such as age, development stage of innate and specific immune system, and pathogenic factors such as the frequency and severity of infection. Viral infections in general and RSV infection in particular, are capable of modifying immune system functions after birth. Infants hospitalized for wheezing are at higher risk of developing persistent asthma or wheezing throughout their first decade of life.⁹⁻¹¹

Diagnosis of viral infections is nowadays accomplished by PCR on sputum samples. It is more efficient than traditional methods of serology or immunofluorescence.

Among viral agents accompanying wheezing in children, RSV is more common in children aged below 3 years while rhinoviruses are more frequent in children aged above 3. 100% of children contract RSV by the age of 3. Sometimes RSV may cause severe bronchiolitis with recurrent wheezing and asthma. However, the association between RSV and development of asthma is controversial. It is not clear whether the virus causes asthma directly, or the disease is the result of allergic sensitizations caused by the infection. For instance, one study reported RSV infection during the first 3 years of life to be associated with increased wheezing at 6 years of age¹⁶, but did not show any increase after the age of 13. On the other hand, another study reported that severe bronchiolitis caused by RSV in the first year of life was

associated with increased asthma at 7 and 13 years of age, compared to children with mild infection.⁹ RSV increases sensitivity to allergens through stimulation of TH2, increased IL-4 levels and increased IgE production, whereas mild inflammation is associated with increased gamma-interferon production.

Moreover, RSV causes neurogenic inflammation of respiratory tract mediated by substance P secreted from the end of non-myelinated fibers. This pathogenesis has been confirmed in rats, and Palivizumab, anti-viral F protein, is shown to reduce inflammation and improve symptoms.¹⁷

One study reported 60% of upper respiratory infections in asthma attacks to be related to HRV.¹⁸ Certain strains, including HRV-16, are more prominently involved in developing allergies.¹⁹ The virus increased ICAM-1 via NK-F in respiratory tract. In addition, it stimulates TH2 to produce IL-4, IL-6, IL-8, and IL-16 associated with an increase in fibroblasts, neutrophils, eosinophils and monocytes. The levels of eotaxin and ranteschemokines also rise to improve neutrophil infiltration, whereas gamma-interferon lowers their level.

Animal models suggest that influenza and parainfluenza infections increase pulmonary sensitivity through increased eosinophils, lymphocytes and macrophages. Furthermore, they increase the tone of bronchi via M2 muscarinic receptors and increase the parasympathomimetic bronchospasm reflex through inhibition of acetylcholine release.²⁰ In any case; these viruses increase inflammation, bronchial responsiveness, epithelial damages and bronchial fibrosis (through increased TGF- β).²¹

In infants, RSV-caused bronchiolitis manifests as acute asthma attack, and 30% of them may develop recurrent wheezing later on.²² Severe cases of bronchiolitis may be associated with asthma. One study indicated that children aged

7.5 years with positive family history of asthma and bronchiolitis had a higher rate of asthma (38%) compared to those who had asthma without bronchiolitis (0%).⁹

In any case, respiratory infections with wheezing caused by RSV in young age are associated with recurrent, persistent wheezing and asthma in school years.^{23,24} Other studies, however, did not show this relationship at 11 years of age.^{16,25} A higher load of Human rhinovirus (HRV) is more probable to cause asthma attacks.²⁶ One study reported 48% of wheezing patients positive for HRV and 21% positive for RSV. The study indicated that the risk of asthma is higher when the RSV or HRV caused wheezing occurs at 3 years of age rather than 1 year.²³ In any rate, sensitivity to airborne allergens without wheezing in the first year of life, and wheezing without sensitivity to airborne allergens were associated with increased risk of asthma at 6 years of age.²³

The greatest impact is observed when HRV-caused wheezing is simultaneous with airborne allergens: these two factors have synergistic effect for asthma, although they are independent risk factors.

Exacerbation of asthma symptoms and its attacks are the main cause of morbidity in these patients at all ages. Another study indicated that some 50% of asthma attacks are associated with respiratory infections such as HRV.²⁷ Although PCR has high sensitivity and specificity for diagnosis of infectious agents; it is not a quantitative method.

Influenza virus and RSV are involved in asthma exacerbation with even higher pathogenicity compared to HRV.

HRV has 99 serotypes, classified as A, B, or C.²⁶ Of course, the clinical significance of these groups requires further studies.

There is not strong evidence to suggest that asthma patients catch common cold more²⁸; some studies, however, indicate that the

symptoms of common cold are more severe and last longer in asthma patients.

Infection in patients with allergic asthma results in poorer control compared to those with non-allergic asthma. Thus, patients with allergic asthma experience more severe symptoms when contracting viral infections.

HRV reduces γ and interferon in mononuclear cells. An increased TH1 response (ratio of gamma-interferon to IL-5) is associated with milder symptoms and faster viral cleaning.²⁹ Asthma patients have diminished γ and interferon response in their epithelial cells.³⁰

Increased level of TH2 cytokines such as IL-4, IL-5 and IL-13 are among risk factors for allergy and HRV infection. It has been said that allergic sensitization, at least in children, is an important risk factor for HRV-caused wheezing and the IgE-mediated response may be associated with common cold wheezing.³¹

In school season, the elevated stress level, accumulation of airborne allergens and viral respiratory infections all contribute to exacerbation of asthma attacks. Respiratory infections and allergens both harm the respiratory epithelium. Respiratory infections weaken the epithelium and increase inflammation through increased absorption of allergens and stimulants.³²

Moreover, toxic agents like tobacco smoke or nitrogen dioxide increase the risk of wheezing caused by viral infections.

As mucus-secreting goblet cells are more frequent in asthma patients, inflammation is more severe because HRV proliferates preferably in these cells.³³

There are studies that indicate a mutual relationship between allergic inflammation and antiviral immunity. Allergic inflammation may suppress the interferon response of innate immunity under certain circumstances.³⁴ Some studies believe young age infection with viral agents as a factor for increase allergy and asthma.³⁵

Other studies suggest that rhinovirus plays a role in exacerbation of asthma symptoms and reduction of pulmonary function (reduced FEV1 and PEF) in children.³⁶ The viral load on BAL is directly proportional to the severity of symptoms and compromise of pulmonary function.³⁷ The virus prolongs the response of respiratory tract to allergens (38). This harms the epithelium via increase pre-inflammatory mediators. Increased levels of IL-11, IL-8, IL-6, ECP and ICAM-1 are involved in asthma exacerbation with rhinovirus infection.³⁹⁻⁴¹

ICAM-1 improves viral adhesion to human epithelial cells, and also plays a role in allergy through leukocyte infiltration. HRV reduces TH1 response and improves TH2 response which leads to incomplete virus cleaning.²⁹ and interferon production is compromised; these interferons have antiviral properties and their concentration is inversely related to viral load on BAL, severity of symptoms and inflammation of respiratory tract. Metapneumovirus, bocavirus, coronavirus (HKU1, SARS, NL63) and poliovirus may cause exacerbate asthma attacks and wheezing in children.⁴² HRV-C strain is more involved with asthma attacks and wheezing in children.

Some studies have indicated that wheezing caused by virus in infancy is associated with higher risk of recurrent wheezing later on^{9,23} and even higher risk of asthma. Another study shows that RSV does not have a causal relationship with asthma.²⁵ In any case, the type of virus plays an important role in development of respiratory symptoms and asthma.^{23,24}

Other studies show that host factors are crucial in development of wheezing and asthma following viral infections, including:

- 1- Low lung volume on birth, especially in preterm children
- 2- Atopy status of the infant
- 3- Intensity of mucus production in response to infection

4- Response of neurotrophic pathways to airway hypersensitivity by infection

5- The capability of an infant with wheezing to provide immune response to viruses, including -interferon, interferon 1 and 3⁴³

Some studies show that after 3 years of age, viral respiratory infections and allergies increase wheezing and asthma attacks in a synergistic manner.^{24,44-45}

HRV is the main trigger for asthma attack in all ages, and it is also responsible for development of asthma. Li CZ conducted a study in asthmatic children to demonstrate that in 48% of them, antibodies were against non-bacterial respiratory agents, including 25% for MP, 9% for adenovirus, and 9% for influenza B. In some patients, multiple factors were found simultaneously. The most common age of involvement was 1-6 months (67%). The pathogens were more common in patients with asthma compared to those with bronchitis, and more common in the latter compared to patients with bronchiolitis. Infected patients had lower eosinophil levels but higher IgE levels.⁴⁶ Similar to other studies, Benitez demonstrated that respiratory infections exacerbate asthma symptoms.⁴⁷

Holt PG et al reported that increased respiratory infections are associated with exacerbated symptoms, prolongation of the disease, and poor control of asthma in atopic patients compared to non-atopic asthma patients. FCR1 is expressed to a greater extent on dendritic cells and monocytes of patients with atopic asthma, indicating greater allergic inflammation of respiratory tract. Type C HRV causes greater wheezing.⁴⁸

Another study by the same author mentions that early in life, allergic sensitivity is converted to atopic asthma when atopy is accompanied by viral respiratory infections. Thus, the immune response in allergic individuals may have protective or aggravating properties for asthma

depending on other conditions and even infections. Controlling allergy in young age may lower the risk of asthma.⁴⁹

Bacterial infection

Infections such as *M. pneumoniae* and *C. pneumoniae* (especially in chronic and stable asthma) play a pivotal role in asthma pathophysiology (3,4). They are found in 53% of cases, and thus it is said that chronic asthma accompanies chronic infection.

Although these agents do not act via IgE to create asthma symptoms, previous studies indicate an increase in mast cells in the respiratory tract, suggesting the relationship between infection and sensitization to allergens.⁸ Inhalational steroids may help reduce inflammation and the microorganism count.⁵⁰ *C. pneumoniae* and *M. pneumoniae* each account for 2%-5% of infectious etiologies in asthmatic children.⁵¹ But the rate of finding the organism is reportedly 4.5%-25% for *C. pneumoniae*, and 5%-22.5% for *M. pneumoniae* in other studies.⁵¹⁻⁵³ Some studies fail to establish the relationship.⁵⁴

It is said that acute *C. pneumoniae* and *M. pneumoniae* infections are associated with acute asthma attacks, while their chronic infections lead to persistent and stable asthma. Antibiotic therapy is not recommended in acute asthma attack, unless there is evidence of bacterial infection.⁵⁵

It is said that in allergic inflammation increases after *C. pneumoniae* infection, which may result in exacerbation of asthma symptoms.^{56,57} Children hospitalized with asthma attacks following *C. pneumoniae* and *M. pneumoniae* infection have longer and more resilient symptoms.⁵²

Antibacterial therapy for *M. pneumoniae* and *C. pneumoniae* has yielded different results in terms of asthma symptoms. Some studies report negligible effect⁵⁸, while other show excellent improvement in symptoms.⁵⁹

C. pneumoniae

C. pneumoniae is a Gram-negative, obligate intracellular bacterium targeting monocytes, macrophages, and epithelial and endothelial cells in the respiratory system, resulting in upper and lower respiratory infection. Repeated and chronic infection with *C. pneumoniae* exacerbates asthma.⁶⁰ Genetic and environmental factors, including other diseases, smoking and steroids, render an individual susceptible to persistent *C. pneumoniae* infection. The symptoms are more severe in asthmatic patients with *C. pneumoniae* infection requiring higher steroid doses.⁵⁸ Whether the relationship between *C. pneumoniae* and asthma is causal or simultaneous is not clear yet. Some studies have reported that treatment with macrolides improves PEF and FEV1 and reduces respiratory tract response.^{58,61} On the other hand, other studies have reported no impact on respiratory symptoms and function.⁶² In most individuals, *C. pneumoniae* is asymptomatic or with mild symptoms only. Repeated infection is common leading to chronic intracellular inflammation.⁶³ Chronic and stable infection may exacerbate asthma. Some researchers believe that *C. pneumoniae* infection is not different in asthmatic and normal individuals (64, 65). Other studies indicate that *C. pneumoniae* is positive in 33% of patients with wheezing compared to 17% of patients without wheezing, whereas the related figures in asthmatic patients are 80% and 53%, respectively.^{66,67} *C. pneumoniae* causes wheezing in asthmatic children and its treatment improves the symptoms.³ Patients with recurrent asthma attacks experience longer and more frequent *C. pneumoniae* infection compared to the normal population.⁶⁸ IL-5 levels are higher in these patients. One study reported *C. pneumoniae* infection in 4.5% of children hospitalized for severe asthma using PCR.⁵¹

Therefore, previous studies indicate that *C. pneumoniae* infections are associated with asthma and lowered FEV1/FVC ratio.⁶⁷⁻

⁶⁹Children with *C. pneumoniae* and *M. pneumoniae* infection on their first asthma attack are more liable to recurrent attacks (62% versus 27%).⁵³ Some studies do not demonstrate this relationship and even suggest a protective effect for asthma.^{64,70} Acute *C. pneumoniae* and *M. pneumoniae* infections cause 5%-30% wheezing or asthma attacks in children.⁷¹

Chronic *C. pneumoniae* infection is associated with more severe asthma.⁷² Via an increasing level of IgA and Heat Shock Proteins, *C. pneumoniae* infection is associated with lower pulmonary function, more severe symptoms and more severe asthma.^{72,73} *C. pneumoniae* infection causes respiratory symptoms in atopic children⁷⁴; another study, however, did not find a significant difference between asthmatic and normal children.⁶⁴

M. pneumoniae

M. pneumoniae is an intra- and extracellular microbe and basically infects ciliated epithelial cells and alveolar macrophages. It may be isolated from sputum weeks or even months after infection. It jeopardizes cilia, epithelium, and the physiology of respiratory tract. It is involved in many diseases including rhinitis, pharyngitis, otitis, atypical pneumonia, bronchitis, lung cancer and even chronic obstructive pulmonary disease (COPD) in different age groups.^{75,76}

M. pneumoniae exacerbates asthma in children and even adults greater than *C. pneumoniae*. It is sometimes involved in development of asthma in children.⁵³ Other studies show that it prolongs asthma symptoms or creates resistance to steroids.⁷⁷ Others believe that asthmatic patients are more susceptible to this infection.

Previous studies reported 25%-40% wheezing in *M. pneumoniae* infection in children.⁷⁸ In

children hospitalized with severe asthma, *M. pneumoniae* was positive in 2.2% of cases with PCR⁵¹, while another study reported 20% of children hospitalized with asthma to be positive for *M. pneumoniae*, with 50% positive *M. pneumoniae* in children experiencing their first asthma attack.⁵³ Many studies have demonstrated the relationship between *C. pneumoniae* and *M. pneumoniae* infection and acute asthma attacks.^{66,68,79}

Other studies pose the possibility of *C. pneumoniae* and *M. pneumoniae* involvement in development and exacerbation of asthma symptoms in children.⁶⁸ *M. pneumoniae* is asymptomatic in 20% of cases.⁸⁰ It is more frequent in children than adults, and exacerbates asthma symptoms more in children than adults.⁸¹ No chronic carrier of the microbe has been observed in immunocompetent individuals, thus its chronic infection has no role in exacerbating asthma. *M. pneumoniae* colonization and infection is more common in asthmatic patients than others.⁶¹

Following *M. pneumoniae* infection, tissue mast cells increase.⁸² *M. pneumoniae* infection is also associated with increased IL-1B, IL-6, IL-8, TNF- α , RANTES, and TGF- β .⁸³

Previous studies indicate that treating *M. pneumoniae* infection with macrolides and steroids reduces inflammation in the respiratory tract and improves clinical symptoms and respiratory function.⁷² Other studies show that macrolides may improve symptoms in asthmatic patients as anti *C. pneumoniae* and *M. pneumoniae*, as well as anti-inflammatory agents.⁸⁴

Conclusion

There is not enough evidence to support a causal role for *C. pneumoniae* and *M. pneumoniae* in developing pediatric asthma. Most studies indicate a significant relationship between *M. pneumoniae* and *C. pneumoniae* infections and

chronic, persistent asthma; however, it remains to be discovered whether this reflects a causal relationship or simultaneous susceptibility.

Hygiene theory

Contracting infections in childhood reinforces TH1 and reduces TH2, thus lowering the risk of allergic diseases. Microbes direct lymphocytes towards TH1 through stimulation of gamma-interferon, IL-12, and IL-18.⁸⁵ Delayed hypersensitivity to TB (*Mycobacterium tuberculosis*) reduces the risk of atopy (86). Other studies, however, do not corroborate these reports.⁸⁷ Overall, this theory still has certain challenges to answer.^{88,89}

Other infections

Helicobacter pylori (*H. Pylori*) enter human body early in life and remains there for almost the entire lifetime. It is transmissible unless eradicated by medication. Some studies indicate a relationship between *H. pylori* and asthma. One study demonstrated an inverse relationship between *H. pylori* infection and prevalence of asthma, allergic rhinitis (AR) and atopy.⁹⁰

Other studies, however, have reported controversial results⁹¹ with OR=0.41, 95% CI: 0.24-0.69.

Other studies indicate that treating non-respiratory infections in the first year of life is associated with increased risk of asthma, revealing the protective role of *H. pylori* in asthma.⁹²

In other studies, hepatitis A virus, Herpes Simplex Virus type 1 (HSV-1), and toxoplasma have been incriminated as possible risk factors for asthma.⁹³

Holster IL reported that in children aged 7-9 with allergic symptoms, *H. pylori* prevalence was significantly lower in children with wheezing compared to others, while the prevalence of *H. pylori* was not significantly different in allergic patients, including asthma.⁹⁴

A study by Capili CR indicated that patients with asthma had a higher risk of pertussis infection compared to the control group (38% versus 26%). They recommended DTap reaction in older children as booster vaccination.⁹⁵

Brar T et al reported that an ensemble of risk factors, including allergens and infections, are involved in the pathogenesis of asthma. Microbes play a role in asthma exacerbation and may even be involved in its development.⁹⁶

Sinusitis and Asthma

Half of patients with moderate to severe asthma suffer from chronic sinusitis. Sinus infection affects asthma symptoms. Sinusitis is associated with more severe asthma and poorer asthma control. Treating either asthma or sinusitis will improve the symptoms of the other.⁹⁰ Thus; respiratory infections exacerbate symptoms more in patients with uncontrolled asthma. It must be remembered that bacterial infections have little role in asthma exacerbation and antibiotic therapy is not indicated for asthma management.

Conflict of Interest

None declared.

Funding/Support

None declared.

References

- Centers for Disease Control and Prevention. Asthma mortality and hospitalization among children and young adults—United States, 1980-1993. *MMWR Morb Mortal Wkly Rep* 1996;45(17):350-3.
- National Asthma Education and Prevention program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Institutes of Health; 1997. National Institutes of Health publication No. 97-4051.
- Emre U, Roblin PM, Gelling M, Dumornay W, Rao M, Hammerschlag MR, et al. The association of *Chlamydia pneumoniae* infection and reactive airway

- disease in children. *Arch Pediatr Adolesc Med* 1994;148(7):727-32.
4. Hahn DL, McDonald R. Can acute Chlamydia pneumonia respiratory tract infection initiate chronic asthma? *Ann Allergy Asthma Immunol* 1998;81(4):339-44.
 5. Pattermore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. *ClinExpAllergy* 1992;22(3):325-36.
 6. Folkerts G, Busse WW, Nijkamp FP, Sorkness R, Gern JE. Virus-induced Airway hyperresponsiveness and asthma. *Am J Respir Crit Care Med* 1998;157(6pt 1):1708-20.
 7. Marin J, Jeler-Kacar D, Levstek V, Macek V. Persistence of viruses in upper respiratory tract of children with asthma. *J Infect* 2000;41(1):69-72.
 8. Richard JM, Monica K, Hong WC, Eric AB, Gail HC. A link between chronic asthma and chronic infection. *J Allergy Clin Immunol* 2001;107(4):595-601.
 9. 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(5):1501-7.
 10. 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(9178):541-5.
 11. Kneyber MCJ, Steyerberg EW, de Groot R, Moll HA. Long term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. *Acta Paediatr* 2000;89(6):654-60.
 12. Johnston SL, Pattermore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ* 1995;310(6989):1225-8.
 13. Kotaniemi-Syrjanen A, Vainionpaa R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111(1):66-71.
 14. Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M. Differential immune responses to acute lower respiratory illness in early life and subsequent development of persistent wheezing and asthma. *J Allergy Clin Immunol* 1998;102(6pt 1):915-20.
 15. Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy and breastfeeding on childhood asthma. *Eur Respir J* 2002;19(5):899-905.
 16. Stein RT, Sherril 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(9178):541-5.
 17. Piedimonte G, King KA, Holmgren NL, Bertrand PJ, Rodriguez MM, Hirsch RL. A humanized monoclonal antibody against respiratory syncytial virus (paviluzumab) inhibits RSV-induced neurogenic-mediated inflammation in rat airways. *Pediatr Res* 2000;47(3):351-6.
 18. Tan WC. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005;11(1):21-6.
 19. Peebles RS Jr, Hartert TV. Respiratory viruses and asthma. *Curr Opin Pulm Med* 2000;6(1):10-4.
 20. Barnes PJ. Modulation of neurotransmission in airways. *Physiol Rev* 1992;72(3):699-729.
 21. Pelaia G, Cuda G, Vatrella A, Fratto D, Grembiale RD, Tagliaferri P, et al. Effects of transforming growth factor- and budesonide on mitogen-activated protein kinase activation and apoptosis in airway epithelial cells. *Am J Respir Cell Mol Biol* 2003;29(1):12-8.
 22. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009; 360(6): 588-98.
 23. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; 178(7): 667-72.
 24. Kusel MM, de Klerk NH, Keadze 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(5): 1105-10.
 25. Thomsen SF, van der Sluis S, Stensballe LG, Posthuma D, Skytthe A, Kyvik KO, et al. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med* 2009; 179(12): 1091-97.
 26. Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PA, Bartlett NK, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; 12(9): 1023-26.
 27. Minor TE, Dick EC, DeMeo AN, Ouellette JJ, Cohen M, Reed CE. Viruses as precipitants of asthmatic attacks in children. *JAMA* 1974; 227(3): 292-98.
 28. Horn ME, Gregg I. Role of viral infection and host factors in acute episodes of asthma and chronic bronchitis. *Chest* 1973; 63 (suppl): 44s-48s.
 29. Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus

- infection. *Am J Respir Crit Care Med* 2000; 162(6): 2226–31.
30. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005; 201(6): 937–47.
 31. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002; 324(740): 763.
 32. Sakamoto M, Ida S, Takishima T. Effect of influenza virus infection on allergic sensitization to aerosolized ovalbumin in mice. *J Immunol* 1984; 132(5): 2614–17.
 33. Lachowicz-Scroggins ME, Boushey HA, Finkbeiner WE, Widdicombe JH. Interleukin-13 induced mucous metaplasia increases susceptibility of human airway epithelium to rhinovirus infection. *Am J Respir Cell Mol Biol* 2010; 43(6): 652–61.
 34. Tversky JR, Le TV, Bieneman AP, Chichester KL, Hamilton RG, Schroeder JT. Human blood dendritic cells from allergic subjects have impaired capacity to produce interferon-alpha via Toll-like receptor 9. *Clin Exp Allergy* 2008; 38(5): 781–88.
 35. Benoit LA, Holtzman MJ. New immune pathways from chronic post-viral lung disease. *Ann N Y Acad Sci* 2010; 1183: 195–210.
 36. Lemanske RF Jr, Dick EC, Swenson CA, Vrtis RF, Busse WW. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. *J Clin Invest*. 1989; 83(1): 1–10.
 37. Message SD, Laza-Stanca V, Mallia P, Parker HL, Zhu J, Kebabdzic T, et al. Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci U S A*. 2008; 105(36): 13562–13567.
 38. Cheung D, Dick EC, Timmers MC, de Klerk EP, Spaan WJ, Sterk PJ. Rhinovirus inhalation causes long-lasting excessive airway narrowing in response to methacholine in asthmatic subjects in vivo. *Am J Respir Crit Care Med* 1995; 152(5pt 1): 1490–1496.
 39. Staunton D E., V. J. Merluzzi, R. Rothlein, R. Barton, S. D. Marlin, and T. A. Springer. 1989. A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. *Cell* 56: 849–853.
 40. Johnston S L, Papi A, Bates P J, Mastrorade J G, Monick M M, Hunninghake G W. Low grade rhinovirus infection induces a prolonged release of IL-8 in pulmonary epithelium. *J Immunol*. 1998; 160(12): 6172–6181.
 41. Stellato C, Beck L A, Gorgone G A, Proud D, Schall T J, Ono S J. Expression of the chemokine RANTES by a human bronchial epithelial cell line. *J Immunol*. 1995; 155(1): 410–418.
 42. Rosenthal LA, Avila PC, Heymann PW, Martin RJ, Miller EK, Papadopoulos NG. Viral Respiratory Infections and Asthma: the Course Ahead. *J Allergy Clin Immunol*. 2010; 125(6): 1212–1217.
 43. Tortorolo L, Langer A, Polidori G, Vento G, Stampachiachere B, Aloe L, et al. Neurotrophin over expression in lower airways of infants with respiratory syncytial virus infection. *Am J Respir Crit Care Med* 2005; 172(2): 233–7.
 44. Heymann PW, Carper HT, Murphy DD, Platts-Mills TA, Patrie J, McLaughlin AP, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. *J Allergy Clin Immunol* 2004; 114(2): 239–47.
 45. Wu P, Dupont WD, Griffin MR, Carroll KN, Mitchell EF, Gebretsadik T, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. *Am J Respir Crit Care Med* 2008; 178(11): 1123–9.
 46. Li CZ, Rao JJ, Wang R, Sun H, Ai HW. Analysis of non-bacterial respiratory pathogen infection in children with asthmatic diseases. *Zhongguo Dang Dai ErKeZaZhi*. 2012; 14(11): 834–7.
 47. Fernández-Benítez M. The role of infection in asthma. *Allergol Immunopathol (Madr)*. 2001; 29(3): 147–51.
 48. Holt PG, Strickland DH, Sly PD. Virus infection and allergy in the development of asthma: what is the connection? *Curr Opin Allergy Clin Immunol*. 2012; 12(2): 151–7.
 49. Holt PG. Infection and the development of allergic disease. *Allergy*. 2011; 66(Suppl 95): 13–5.
 50. Bowden JJ, Schoeb TR, Lindsey JR, McDonald DM. Dexamethasone and oxytetracycline reverse the potentiation of neurogenic inflammation in airways of rats with *Mycoplasma pulmonis* infection. *Am J Respir Crit Care Med* 1994; 150(5pt): 1391–401.
 51. Freymuth F, Vabret A, Brouard J, Toutain F, Verdon R, Petitjean J, Gouarin S, Duhamel JF, Guillois B. Detection of viral, Chlamydia pneumoniae and Mycoplasma pneumoniae infections in exacerbations of asthma in children. *J Clin Virol* 1999; 13(3): 131–139.
 52. Thumerelle C, Deschildre A, Bouquillon C, Santos A, sardet A, scalbet M, et al. Role of viruses and atypical bacteria in exacerbations of asthma in hospitalized children: a prospective study in the Nord-Pas de Calais region (France). *Pediatr Pulmonol* 2003; 35(2): 75–82.

53. Biscardi S, Lorrot M, Marc E, Mulin F, Boutonnat-Faucher B, Heilbronner C, et al. Mycoplasma pneumoniae and asthma in children. *Clin Infect Dis* 2004;38(10):1341–6.
54. Mills GD, Lindeman JA, Fawcett JP, Herbison GP, Sears MR, et al. Chlamydia pneumonia serological status is not associated with asthma in children or young adults. *Int J Epidemiol* 2000;29(2):280–4.
55. National Asthma Education and Prevention Program. Use of antibiotics to treat asthma exacerbations. *J Allergy Clin Immunol* 2002;110(5supp):S180–3.
56. Wark PA, Johnston SL, Bucchieri F, Power R, Puddicombe S, Laza-Stance V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005;201(6):937–47.
57. Contoli M, Message SD, Laza-Stanca V, Edward MR, Wark PA, Bartlett NW, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006;12(9):1023–6.
58. Black PN, Blasi F, Jenkins CR, Scicchitano R, Mills GD, Rubinfeld AR, et al. Trial of roxithromycin in subjects with asthma and serological evidence of infection with Chlamydia pneumoniae. *Am J Respir Crit Care Med* 2001;164(4):536–41.
59. Richeldi L, Ferrara G, Fabbri L, Gibson PG, Lasserson TJ, Macrolides for chronic asthma (Cochrane Review). In: *The Cochrane Library* 2008; 4:1-49.
60. von HL. Role of persistent infection in the control and severity of asthma: focus on Chlamydia pneumoniae. *Eur Respir J* 2002;19(3):546–56.
61. Kraft M, Cassell GH, Pak J, Martin RJ. Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. *Chest* 2002;121(6):1782–8.
62. Gotfried MH, Jung R, Messick CR, Rubinstein I, Garey KW, Rodvold KA, et al. Effects of six-week clarithromycin therapy in corticosteroid-dependent asthma: a randomized, double-blind, placebo-controlled pilot study. *Curr Ther Res* 2004;65(1):1–12.
63. Schachter J. Chlamydia as pathogens. Overview of human diseases. In: Barron AL, ed. *Microbiology of Chlamydia*. Boca Raton, Fla, CRC Press, 1988:153-65.
64. Korppi M, Paldanius M, Hyvarinen A, Nevalainen A, Husman T, et al. Chlamydia pneumoniae and newly diagnosed asthma: a case-control study in 1 to 6-year-old children. *Respirology* 2004;9(2):255–9.
65. Tuuminen T, Edelstein I, Punin A, Kisiova N, Stratchounski L, et al. Use of quantitative and objective enzyme immunoassays to investigate the possible association between Chlamydia pneumoniae and Mycoplasma pneumoniae antibodies and asthma. *Clin Microbiol Infect* 2004;10(4): 345–8.
66. Hahn DL, Golubjatnikov R. Asthma and chlamydial infection: a case series. *J Fam Pract* 1994;38(6):589–95.
67. Esposito S, Blasi F, Arosio C, Fioravati L, Façetti L, Droghetti R, et al. Importance of acute Mycoplasma pneumoniae and Chlamydia pneumoniae infections in children with wheezing. *Eur Respir J* 2000;16(6):1142–6.
68. Hahn DL, Dodge RW, Golubjatnikov R. Association of Chlamydia pneumoniae (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. *JAMA* 1991;266(2):225–30.
69. tenBrinke A, van Dissel JT, Sterk PJ, Zwinderman AH, Rabe KF, Bel EH, et al. Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of Chlamydia pneumoniae infection. *J Allergy Clin Immunol* 2001;107(3):449–54.
70. Schmidt SM, Muller CE, Wiersbitzky SK. Inverse association between Chlamydia pneumoniae respiratory tract infection and initiation of asthma or allergic rhinitis in children. *Pediatr Allergy Immunol* 2005;16(2):137–44.
71. Gern JE, Lemanske RF Jr. Infectious triggers of pediatric asthma. *Pediatr Clin North Am* 2003;50(3):555–75.
72. Black PN, Scicchitano R, Jenkins CR, Blasi F, Allegra L, Wlodarczyk J, et al. Serological evidence of infection with Chlamydia pneumoniae is related to the severity of asthma. *Eur Respir J* 2000;15(2):254–9.
73. Huittinen T, Hahn D, Anttila T, Wahlstrom E, Saikku P, Leinonen M, et al. Host immune response to Chlamydia pneumoniae heat shock protein 60 is associated with asthma. *Eur Respir J* 2001;17(6):1078–82.
74. Ferrari M, Poli A, Olivieri M, Verlatto G, Tardivo S, Nicolis M, et al. Respiratory symptoms, asthma, atopy and Chlamydia pneumoniae IgG antibodies in a general population sample of young adults. *Infection* 2002;30(4):203–7.
75. Littman AJ, Jackson LA, Vaughan TL. Chlamydia pneumoniae and lung cancer: epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev* 2005;14(4):773–8.
76. von Hertzen L, Isoaho R, Leinonen M, Koskinen R, Laippala P, Toyryla M, et al. Chlamydia pneumoniae antibodies in chronic obstructive pulmonary disease. *Int J Epidemiol* 1996;25(3):658–64.
77. Thumerelle C, Deschildre A, Bouquillon C, Santos C, Scardet A, Scalbert M, et al. Role of viruses and

- atypical bacteria in exacerbations of asthma in hospitalized children: a prospective study in the Nord-Pas de Calais region(France). *PediatrPulmonol* 2003;35(2):75–82.
78. Principi N, Esposito S. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* cause lower respiratory tract disease in paediatric patients. *Curr Opin Infect Dis* 2002;15(3):295–300.
 79. Allegra L, Blasi F, Centanni S, Cosentini R, Denti F, Raccanelli R, et al. Acute exacerbations of asthma in adults: role of *Chlamydia pneumoniae* infection. *EurRespir J* 1994;7(12):2165–8.
 80. Clyde WA Jr. Clinical overview of typical *Mycoplasma pneumoniae* infections. *ClinInfect Dis* 1993; 17(suppl):S32-6
 81. Gil JC, Cedillo RL, Mayagoitia BG, Paz MD. Isolation of *Mycoplasma pneumoniae* from asthmatic patients. *Ann Allergy* 1993; 70(1):23-5.
 82. Martin RJ, Kraft M, Chu HW, Berns EA, Cassell GH. A link between chronic asthma and chronic infection. *J Allergy ClinImmunol* 2001;107(4):595–601.
 83. Yang J, Hooper WC, Phillips DJ, Talkington DF. Regulation of proinflammatory cytokines in human lung epithelial cells infected with *Mycoplasma pneumoniae*. *Infect Immun* 2002;70(7):3649–55.
 84. Blasi F, Johnston SL. The role of antibiotics in asthma. *Int J Antimicrob Agents* 2007;29(5):485–93.
 85. PJ Barnes. Pathophysiology of asthma. *British journal of clinical pharmacology* 1996;42(1):3-10
 86. Hopkin JM. Atopy, asthma, and the mycobacteria. *Thorax* 2000;55(6):443–5.
 87. Ota MO, van der Sande MA, Walraven GE, Jeffres D, Nyan OA, Marchant A, et al. Absence of association between delayed type hypersensitivity to tuberculin and atopy in children in The Gambia. *ClinExp Allergy* 2003;33(9):731–6.
 88. Svanes C, Jarvis D, Chinn S, Omenaas E, Gulsvik K, Burney P, et al. Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey. *Thorax* 2002;57(11):945–50.
 89. Maitra A, Sherriff A, Griffiths M, Henderson J; Avon longitudinal study of parents and children study team. Pertussis vaccination in infancy and asthma or allergy in later childhood: birth cohort study. *BMJ* ;2004;328(7445): 925–6.
 90. Chen Y, Blaser MJ. *Helicobacter pylori* Colonization Is Inversely Associated with Childhood Asthma. *J Infect Dis*, 2008; 198(4):553– 60.
 91. Matricardi PM, Rosmini F, Riondino S, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; 320(7232):412–7.
 92. Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. *Chest* 2007; 131(6):1753–9.
 93. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy ClinImmunol* 2002; 110(3):381–7.
 94. Holster IL, Vila AM, Caudri D, den Hoed CM, Perez-Perez GI, Blaser MJ. The impact of *Helicobacter pylori* on atopic disorders in childhood. *Helicobacter*. 2012;17(3):232-7.
 95. Capili CR, Hettlinger A, Rigelman-Hedberg N, Fink L, Boyce T, Lahr B. Increased risk of pertussis in patients with asthma. *J Allergy ClinImmunol* 2012;129(4):957-63.
 96. Brar T, Nagaraj S, Mohapatra S. Microbes and asthma: the missing cellular and molecular links. *Curr OpinPulm Med*. 2012 Jan;18(1):14-22.