11 Viral Disease, Air Pollutants, Nanoparticles, and Asthma

Bruce Ryhal, MD

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KEY POINTS

- Viral respiratory tract infections are the most common triggers of significant asthma exacerbations.
- "Upper respiratory tract infections" (URIs) do not just involve the upper respiratory tract.
- Human rhinovirus (HRV), which causes the common cold, is the virus most likely to trigger an asthma exacerbation.
- In contrast to the usual spring and summer temperate zone pollen season, viral infections begin to peak in the fall.
- The number, species, and typical course of viral respiratory tract infections that trigger asthma vary with a person's age.
- Both acute sinusitis and asthma exacerbations are associated with viral respiratory tract infection and therefore antibiotics are rarely needed in uncomplicated cases.
- Sulfur dioxide, nitrogen dioxide, ozone, and particulate matter in air pollution may exacerbate asthma, and patients should be cautioned to stay indoors when levels of these irritants are high.
- Indoor air pollution, especially from tobacco smoke, can be reduced with benefit to the asthma patient.

INTRODUCTION

Health care providers who treat patients with respiratory disease are often asked by their patients, "What caused my asthma? And what causes my asthma suddenly to become worse?" These questions have always been difficult to answer, and moving directly to a discussion of the management of asthma is a much easier road to take. In recent years, though, enough information has accumulated about the causes of asthma that one can weave a story containing useful advice that may help patients participate in the management of their disease. And there are also recent studies that can provide answers to the questions posed by physicians who have watched in puzzlement as their previously well-controlled asthma patients have spiraled rapidly out of control. This story has been growing increasingly complex, with an ever-expanding cast of players that sometimes creates a tangled web of interactions.

This chapter will look at how viral infections, air pollution, and possibly nanoparticles may act as causal agents of asthma. The concept of causal agent, though, has a variety of different interpretations. In general, agents may act on the respiratory tract to initiate asthma or to exacerbate it. Initiation (or inception or development) of asthma refers to the start of asthma in a patient who was previously entirely free of this problem. An exacerbation (or trigger or precipitating event) means the significant and often sudden worsening of an established chronic asthmatic condition. Avoidance of a proven initiating factor, if possible, could permit the primary prevention of asthma. In contrast, avoidance of triggering events will not halt the disease but only decrease the number of exacerbations in someone who already has chronic illness. In studying and treating asthma, identification of a specific trigger is usually much easier than trying to prove an initiating cause.

VIRAL DISEASE AND ASTHMA

Conceptual Framework for Viewing the Virus–Asthma Interaction

Viruses that affect asthma are acting on a complex and varied phenotype, and therefore the outcome of each infection can be quite varied. A simple linear cause-and-effect relationship between a viral infection and an asthmatic episode usually does not exist. Koch's modified postulates for infection-caused disease are:

- The microorganism must be present in every case of the disease.
- The microorganism must be isolated from a diseased organism and grown in pure culture.
- The cultured microorganism should cause disease when introduced into a healthy organism.
- The microorganism must be recovered from an inoculated, diseased experimental host.

This linear way of looking at viral-induced disease is not comprehensive enough to allow sufficient insight into the relationship between viral illness and asthma. No one viral infection consistently causes asthma in all or even most individuals. Systems biology, though, can provide a conceptual framework for better understanding of the virus–asthma interaction. Systems biology looks at the web of factors in the initial state of the individual patient and then examines how one or more external or internal influences perturb this state *(1)*.
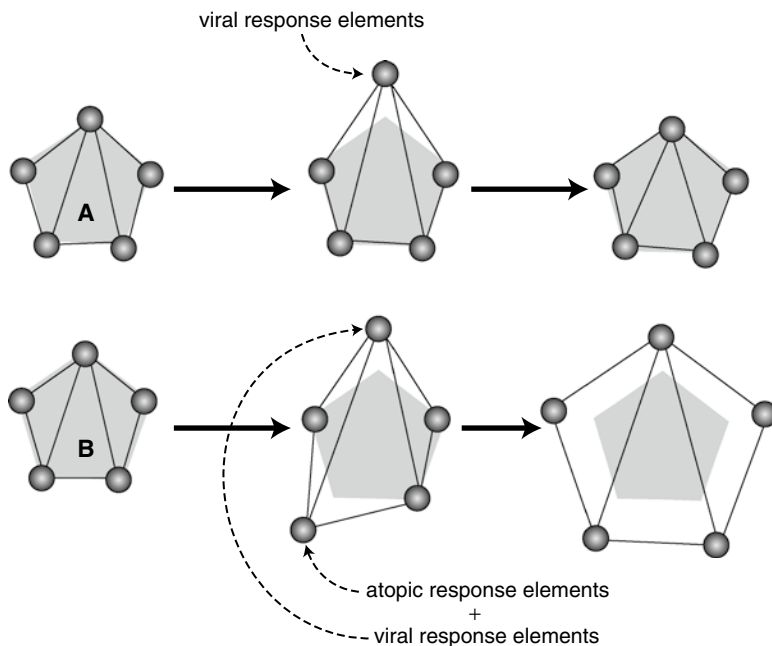
Fig. 1. The system regulating mucosal immune inflammation has many connecting elements. Perturbation of these elements may boost inflammation to a persistently high level.

In Fig. 1, the path taken by system A illustrates how one factor, for example a simple rhinovirus infection, may have very little long-term effect on mucosal inflammation in an individual with no atopic stressors and no genetic propensity toward asthma. This individual will return quickly to equilibrium and a low inflammatory state. The path of system B illustrates how multiple stressors, including genetic factors and atopic immune development, may interact with a viral infection to cause a long lasting or perhaps permanent change in the level of mucosal inflammation. Some details of risk factors will be outlined and discussed in this chapter, but systems biology or systems medicine cannot yet specify each feature of the set of interactions in a way that leads to firm predictions about asthma. Out of the complexity of the systems approach, though, some simple and compact principles do emerge, so that every precondition does not have to be known to predict the outcome of intervention or treatment.

Some general factors that appear to be important in the asthmatic response to viral infection include:

- Age
- Sex
- Genetic inheritance
- Immune status
- Asthma phenotype
- Viral genotype
- Local environmental effect on atopic development

Table 1
Types of Respiratory Viral Infections

Respiratory virus	Relative frequency of infection
Human rhinovirus (HRV)	+++
Influenza virus	++
Coronavirus	++
Parainfluenza virus	+
Respiratory syncytial virus (RSV)	+
Adenovirus	+
Metapneumovirus	+
Other viruses	+

Though two-dimensional paper does not allow multidimensional maps, we can walk down a branching path in a narrative fashion to show the interaction of factors important in viral-caused asthma.

Advances in Viral Respiratory Disease

In most of the twentieth century, the office or hospital diagnosis of viral respiratory infection was most often a good guess, a probability statement. Common and more affordable viral molecular diagnostics, especially reverse transcriptase PCR (RT-PCR), and viral culture can now improve the accuracy of the guess when precision is needed. Viruses may be detected in symptomatic or in asymptomatic patients.

Two thirds or more of acute respiratory tract infections (RTIs) occurring in the community can be identified as viral. Traditionally, these have been divided into upper and lower RTI, but the difference between upper and lower infection seems to be more indistinct than previously believed. Human rhinovirus (HRV), for example, replicates initially in the upper respiratory tract yet may cause extensive lower respiratory tract illness. The frequently used term viral upper RTI (URTI) is somewhat of a misnomer.

The most commonly occurring respiratory virus is HRV, which accounts for nearly half of cases of viral respiratory illness, followed by influenza virus and coronavirus, with lesser contributions from parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, metapneumovirus, and other miscellaneous viral species *(2)* (*see* Table 1).

The three main types of viruses that are known to affect asthma are HRV, RSV, and influenza. The peak periods of viral infection tend to vary from year to year, but generally in North America rhinovirus peaks in the fall and early spring, influenza in the early winter, and RSV in midwinter (Fig. 2). Many communities can monitor the progress of these annual epidemics with viral culture and molecular diagnostics, thereby giving physicians a higher probability of knowing in advance what virus a patient may have. A molecular diagnostic panel is commercially available for identifying acute viral respiratory infection, though the cost-effectiveness of this type of testing for routine clinical use is yet to be determined.

More details of the immunobiology of the major asthmogenic viral infection, HRV, have been revealed in the past several years *(3)*. The intercellular adhesion molecule ICAM-1 found on nasal epithelial cells is the attachment point for the majority of serotypes of HRV*(4)*. HRV is divided into clades or strains HRV-A, HRV-B, and HRV-C. HRV-C has proven extremely difficult to culture. There are over 100 different serotypes *(5)*.
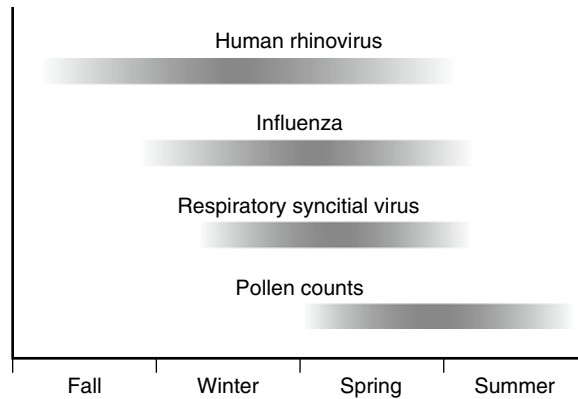
Fig. 2. Respiratory virus peaks compared with pollen counts for a typical year in a Northern California inland valley area. These may vary from year-to-year in this location. Data is compiled from community monitoring.

Age and Virus–Asthma Interactions

Viral species influence asthma in the various age groups in different ways. Age is a marker for the development and maturation of the immune system, which diversifies greatly over time. As the human body ages, the immune system molds itself to the environment to become a mirror image of specific, usually protein, molecules in the external local surroundings. Age also has an important effect on the physics of scaling in the respiratory system. Airway resistance is inversely proportional to the fourth power of diameter, which enlarges with age until young adulthood and then slowly declines. Small increases in airway diameter therefore lead to huge reductions in airway resistance and give more "breathing room."

School-Age Children

VIRAL TRIGGERS OF ASTHMA

About 80% of significant, prolonged wheezing episodes in children are triggered by respiratory viruses and HRV is most often involved *(3)*. The common rhinovirus cold accounts in large part for the fall seasonal peak of asthma in school-age children. Epidemiologic evidence combined with viral molecular diagnosis has suggested that this peak is a consequence of children returning to the classroom with the subsequent spread of respiratory viruses, mainly rhinoviruses *(6)*.

Viral exacerbations of asthma tend to be prolonged and severe. Triggers such as a gust of pollen-laden breeze may be ameliorated by moving the young patient indoors, and exercise triggers can be removed by stopping the exercise, but a viral trigger is usually steady and persistent and replicates within the body. A study of children aged 6–8 years with asthma concluded that an asthma exacerbation was of a greater severity if a viral infection was present as opposed to a nonviral illness *(7)*. Airway hyperreactivity and a corresponding cough and wheeze may be noted for well over 4 weeks after a rhinovirus infection in the asthmatic child.

Atopy confers additional risk on asthmatic children who become ill with respiratory virus infection *(10)*. School-aged children with atopic asthma, as opposed to those with

nonatopic asthma, have been noted in a number of studies to experience more frequent symptomatic colds, more episodes of viral-triggered asthma, and more prolonged airway hyperreactivity after the colds (*7–9*). The tendency to have higher numbers of symptomatic RTIs and a longer duration of illness was also noted for allergic children in general, with and without asthma (*9*). Parents of children with atopy and asthma tend to be frustrated by the prolonged recovery time compared with their nonatopic siblings, and school absences are more problematic.

Treatment and Prevention of Viral-Triggered Wheezing in School-Age Children

Inhaled corticosteroids and leukotriene receptor antagonists (LTRAs) are well known to control the number of wheezing exacerbations in school-age children with chronic persistent asthma, an effect that appears to encompass those episodes caused by viral illness. A survey of school children in Ontario found that children presenting in September to the emergency department for asthma exacerbations, presumably mostly viral triggered, were less likely to have used preventive anti-inflammatory medications than their counterparts who did not have such severe exacerbations (*12*). A retrospective study suggested that inhaled fluticasone and salmeterol administered prior to and during the fall could reduce the morbidity of the fall viral season in patients with asthma (*13*). A trial of a montelukast added to usual asthma therapy was able to attenuate the fall asthma peak in one study (*14*) though this effect did not reach statistical significance in a later trial (*15*). Inhaled corticosteroids might be expected to prevent viral-induced wheezing in children with minimal chronic disease as well. A preventive effect, though, has not been consistently shown in clinical trials. A study conducted in school-aged children without persistent disease but with a history of viral-triggered wheezing demonstrated that inhaled beclomethasone dipropionate was not superior to placebo in reducing future episodes. The inhaled steroid failed to reduce days with symptoms, or the frequency, severity, or duration of episodes of upper or lower respiratory illness (*11*). Preventive medication should therefore be targeted especially to those patients with persistent chronic asthma.

For acute treatment of a viral-provoked asthma exacerbation, oral systemic corticosteroids continue to be the most effective choice (*16*) and are part of the current therapy protocols (*17*). Use of high-dose acute corticosteroid inhalers continues to be studied with varying success.

Whether vaccination can prevent asthma exacerbations is unclear. The Expert Panel Report concluded that influenza vaccine does not reduce the frequency or severity of asthma exacerbations during the influenza season (*17*). Many patients in the community with asthma experience severe complications from an influenza infection, so all reasonable means of prevention should still be taken, including vaccination. The influenza virus appears to be a less potent trigger of asthma than HRV, and influenza peaks are not as well correlated with childhood asthma peaks as in the case of HRV.

An oral influenza antiviral (oseltamivir) improved pulmonary function and reduced exacerbation frequency in one randomized, placebo-controlled trial in school-age asthmatic children who had influenza (*18*). Unfortunately, increasing resistance of the influenza virus to antiviral agents limits their use as a long-term strategy to reduce illness in asthmatic children. The concept of using antivirals to reduce asthma morbidity in children seems theoretically promising.

Infants and Preschool Children 0–4

The preschool years can lay the groundwork for the later asthma issues of the type that have been discussed. Diagnosing viral-triggered asthma in infants and preschool children, though, must be done with caution. Asthma is defined as a chronic disease, and several, or even many, self-limited acute wheezing illnesses do not necessarily add up to a chronic illness. Often children in this age group will experience wheezing in association with a variety of viral infections. Parents are naturally anxious about treatment and prognosis in these children.

Preschool children who experience RSV- and HRV-induced wheezing are more likely to develop asthma in later years. The Childhood Origins of Asthma study (COAST) showed that viral wheezing illnesses in infancy and early childhood caused by HRV were the most significant predictors of the subsequent development of asthma at age 6 *(19)*. A bidirectional causation has been proposed with RSV: severe RSV was associated with a short-term increase in bronchial hyperresponsiveness, and, in turn, the presence of asthma was associated with long-term increased susceptibility for severe RSV disease *(20)*.

INCEPTION OF ASTHMA

Whether early childhood viral infection initiates a series of events that lead to asthma has been an area of much interest and study. One analysis showed that infants reaching 4 months of age at the winter virus peak had a 29% increased risk of developing later asthma compared with those reaching age 1 year at the winter peak *(21)*. If viruses do initiate asthma in some patients, then prevention of RSV or HRV or a similar illness in a critical time period might prevent or reduce the frequency of asthma in later years. Nonatopic infants who had received palivizumab (a humanized MAb against RSV) for prevention of RSV infection showed an 80% reduction in risk of recurrent wheezing from ages 2 to 5 *(22)*, though no effect was noted in atopic children.

The hypothesis that early viral infections lead to asthma is made less convincing by epidemiologic studies showing that frequent exposure to viral RTIs throughout early childhood may actually decrease the risk of later asthma. Studies in the United States and in the United Kingdom have shown that day care attendance and other factors that increase the frequency of viral RTIs reduce the risk of later (after 5–6 years) frequent wheezing *(23, 24)*. One interesting medical editorial on this topic was subtitled with tongue-in-cheek, "Please sneeze on my child" *(25)*. That strategy may not be practical, but clinicians should be able to reassure worried parents that day care exposure does not seem to result in a long-term risk of asthma.

VIRAL TRIGGERS OF ASTHMA IN PRESCHOOL CHILDREN

While the factors that contribute to the development of asthma are still unclear, there is little doubt that viral infections act as potent triggers of asthma in preschool children. As noted, HRV is the most potent of triggers, though all HRVs do not seem to be alike. Pathogenicity of HRV appears to vary among groups A, B, and C. HRV-C was found in a study of hospitalized preschool children to be associated with asthma more often than HRV-A *(26)*, and HRV-C was noted to be the most frequent type found in patients presenting to the emergency department *(27)*. In contrast, experimental infection with a type of HRV-A resulted in no worse illness in allergic than in nonallergic subjects *(28)*.

Table 2
Classification Systems for Wheezing Preschool Children

Wheezing type (retrospective)	Trigger type	Asthma risk type (Asthma Predictive Index)

Transient early wheezers
• Wheezing in the interval from 0–3 years old, not at 6 years
Late-onset wheezers
• Wheezing at 6 years but not in the interval from 0 to 3 years old
Persistent wheezers
• Wheezing in the interval 0–3 years old and at 6 years old
Ref. Martinez et al. (60)
	Episodic, viral-triggered wheeze
	Multitrigger wheeze
	Ref. European Respiratory Society (61)
		High risk
		• Has recurrent wheezing during 0–3 years old and
		  – Parent with asthma[a] or
		  – Eczema in child[a]
		  Or
		  – 2 of 3: allergic rhinitis,[a] wheezing without colds, eosinophilia
		Low risk
		• Wheezing present but
		  – Criteria above not met
		Ref. Castro-Rodriguez (30)

[a] Physician diagnosis.

Knowledge of a circulating virulent HRV strain in the community could put clinicians on the alert for more serious symptoms in their asthmatic patients with colds.

TREATMENT OF VIRAL-TRIGGERED WHEEZING IN INFANTS AND PRESCHOOL CHILDREN

There are several competing classification systems for the wheezing preschool child that aim to help with prognosis and treatment (Table 2). As a conceptual model, one can create two opposing poles. At one pole is the small child who experiences rare mild wheezing with acute viral illness, has no wheezing or cough between episodes, and has no atopy or parental asthma. These children appear to benefit very little or not at all from acute or chronic corticosteroid therapy for viral-triggered wheezing illness (29). At the other pole are children who wheeze daily or weekly, have an atopic history, have a parental history of asthma, and may be on chronic controller therapy. A viral infection in these children appears to be a trigger that requires a step up in asthma therapy, perhaps to a burst of oral corticosteroids. Between these poles of severity are many children whose therapy must be individualized. The criteria from the National Asthma Education and Prevention Program help select preschool children who may benefit from acute and/or chronic corticosteroids. These guidelines use the Asthma Predictive Index (30) to specify which wheezy small children have or likely will have chronic asthma and could benefit from various forms of inhaled and oral corticosteroid therapy.

Owing to concerns about oral corticosteroids, other forms of treatment for viral wheezing have been examined in preschool children. A study in 1- to 6-year-old children showed a benefit of episodic high-dose inhaled steroids with viral RTI and wheezing (31), though some adverse effects on growth were noted. The effectiveness
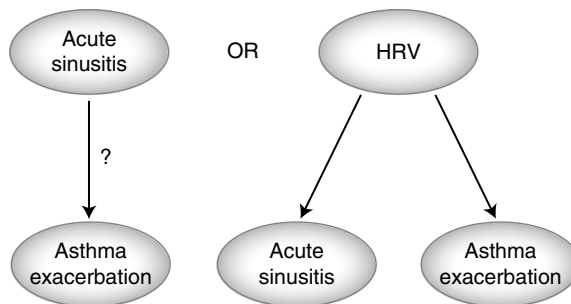
Fig. 3. Diagram illustrating the links between sinusitis, HRV, and asthma.

of a LTRA, montelukast, was examined in a study of 2–5 year olds with a history of intermittent asthma. This study showed a reduction of typically viral-induced asthma exacerbations in children given the LTRA as a daily controller *(32)*. Both inhaled corticosteroids and LTRAs are options to control chronic asthmatic wheezing in this age group *(17)*.

Prolonged or chronic cough after viral RTI may be a problem. Preschool children, whether asthmatic or not, spend a considerable percentage of the year with viral RTI symptoms that are distressing to patient and parent.

Teens and Young Adults

The years from teen through young adulthood tend to be the healthiest years of an individual's life. An expanded antiviral immunologic repertoire helps in reducing the number of annual viral RTIs. While childhood is the time of most frequent viral RTIs, young adults who are exposed to their own small children may have a secondary peak near their 30s.

Acute sinusitis is a common problem in this age group. Sinusitis has been known to precede a worsening of asthma, and episodes of acute sinusitis have often been the occasion for a course of antibiotics. The entity of viral rhinosinusitis, though, is far more common than previously believed. A viral RTI can produce a week or more of purulent discharge and radiographic abnormalities of the sinus cavities on CT scans *(33)*. Most acute sinusitis is not predominantly initiated by bacteria nor, at least in the first week or so, antibiotic-responsive *(34, 35)*. The mechanism by which acute viral sinusitis becomes linked with worsening asthma is generally through the association of both diseases with viral infection (Fig. 3).

The adult group of patients with asthma diverges into several different phenotypes, likely representing various diseases. Asthma is often said to be a syndrome rather than one disease. Different phenotypes may have varying responses to viral infection. A cluster analysis divided asthma patients into five different groups. One group, "benign asthma" seemed to have well-controlled symptoms regardless of triggers, viral or otherwise. Another group that was female preponderant, "obese nonesosinophilic," had minimal atopy or eosinophilic inflammation yet a high level of symptoms in response to typical triggers *(36)*.

Chronic adult diseases of previously unknown cause have occasionally been found, in whole or in part, to have an infectious etiology. These include peptic ulcer disease (*Helicobacter pylori*), polyarteritis nodosa (hepatitis B and C), reactive arthritis (*Shigella* and *Chlamydia*), and Lyme arthritis (*Borrelia burgdorferi*). A survey of asthma patients, of mean age 38, suggested that 45% of initial attacks started after an illness suggestive of a respiratory infection *(37)*. This subset tended to be nonatopic and may represent a distinct phenotype. Viral and nonviral initiating infectious agents have been proposed for adult "infectious asthma," including mycoplasma, chlamydia, adenovirus, and adult RSV, but reasonable proof of an infectious mechanism is still pending.

Regardless of initiating cause, asthma is exacerbated in adults, as in children, by viral respiratory infections. Respiratory virus is found at least 50% of the time in adults with asthma exacerbations, but not as frequently as in childhood acute significant wheezing episodes *(3)*.

Older Adults and the Elderly

Older and elderly adults experience some degree of immune senescence but also have expanded specific antiviral immunity. The types of viral illness that exacerbate asthma are slightly different than in younger years. The peak of ED visits and asthma admissions for adults over 50 tends not to be in the fall but rather from December to January, suggesting a broader range of viral triggers than in the fall rhinovirus peak *(38)*.

The contribution of influenza to excess morbidity in older adults is well known, but less generally appreciated is the contribution of rhinovirus to serious illness. Concomitant heart disease, chronic obstruction pulmonary disease, and hypertension can make viral-exacerbated asthma a more complicated and serious illness in older adults. A rhinovirus outbreak in a nursing home for elderly patients resulted in two thirds of the affected patients having lower respiratory tract symptoms, nearly one-third requiring corticosteroid or bronchodilator therapy, and three individuals having serious morbidity including one death *(39)*. A peak of rhinovirus RTI may be seen in grandparents who care for small children.

Consistently effective treatments for viral-caused respiratory disease have been frustratingly slow to arrive in the modern pharmacopoeia. Despite these obstacles, however, a proactive approach, including vaccination and respiratory hygiene, can improve the care of the patient at risk for viral illness and bronchospasm and avert complications.

AIR POLLUTANTS AND NANOPARTICLES

Air Gases and Particles

Since the time of Albert Einstein, scientists have known to be wary of "spooky action at distance." Particles that affect the respiratory tract must first be dispersed into the air and enter and contact the respiratory tissue to have an effect. These particles vary in size from molecules in the angstrom range (1×10^{-10} m), to so-called nanoparticles ($1–100 \times 10^{-9}$ m), to large pollen grains (50×10^{-6} m), on up to the largest dust particles that can remain suspended in air (about 100×10^{-6} m).
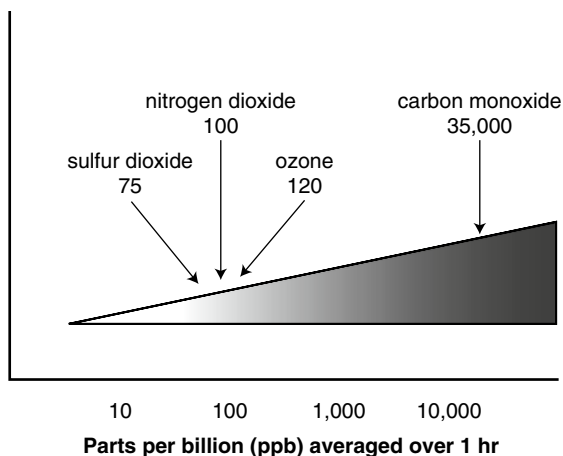
Fig. 4. Exposure limits for gases from the US National Ambient Air Quality Standards for 2010.

Air particles are divided into several common ranges for study purposes:

- *PM10* – particulates of an aerodynamic diameter of less than 10 μm or 10,000 nm
- *Fine particles* of diameters below 2.5 μm or 2,500 nm
- *Ultrafine particles or nanoparticles* of diameters below 0.1 μm or 100 nm

Study of the real-world, clinical effects of the individual components of air pollution is challenging since most or all components tend to be released into the air at about the same time.

Air Pollution Outdoors

Unwanted and/or unhealthy gases and particles make up the components of air pollution. Outdoor air quality issues vary to great extent by specific location and depend on weather and climate, the level of vehicle traffic, and the type of fuel used for energy and manufacture. In the United States, the Office of Air Quality Planning and Standards (OAQPS) has established the National Ambient Air Quality Standard (NAAQS) for each of the several pollutants. Carbon monoxide, lead, nitrogen dioxide (NO_2), ozone, sulfur dioxide (SO_2), and particulate matter in the air have maximum exposure standards (Fig. 4).

Studies of the effect of air pollution on health attempt to use statistical analysis to separate the individual contribution of each component of pollution. Additionally, provocation/exposure testing can be performed in the laboratory.

Many of the same questions that can be asked about viral disease can be asked about air pollution – does it initiate asthma and does it trigger asthma? Clearly not everyone breathing air pollution gets asthma or wheezing, but exposure does seem to increase the risk.

Clinical Effects of Pollution in Outdoor Air

INCEPTION OF ASTHMA BY AIR POLLUTANTS

A population study in the Netherlands found that children with higher exposure to traffic-related pollutants (NO_2, particulate matter) were more likely to develop asthma *(40)*. Data from the Taiwan Children Health Study showed an increased prevalence

of bronchitic symptoms among children with long-term exposure to outdoor air pollutants *(41)*.

In addition to irritant properties, air pollution may contain immunologically active particles. Nanoparticles, including particles of diesel exhaust, which are suspended in air are especially interesting to immunologists studying the development of asthma. They have been proposed to act as adjuvants and immunomodulators *(42)*. Most diesel particulates have sizes of less than 1 μm and represent a mixture of fine particles and nanoparticles.

TRIGGERING OF ASTHMA BY AIR POLLUTANTS

Acute wheezing may be triggered by exposure to high levels of pollutant gases including nitrogen dioxide, sulfur dioxide, and carbon monoxide. Burning of fossil fuels is the main source of these pollutants in most locations. Nitrogen dioxide and sulfur dioxide gases diffuse rapidly and impact upon the wet respiratory tract to produce highly irritating acids. Sulfur dioxide can cause respiratory constriction in asthmatic patients at concentrations of 0.1 ppm when exercising *(44)*. Healthy adults begin experiencing increased airway resistance at 5 ppm, and even nonasthmatic adults will develop bronchospasm at 20 ppm, though these levels would be highly unusual in outdoor air pollution. Nitrogen oxides, and especially NO_2, are also irritating to the upper and lower respiratory tracts at low levels, and patients with asthma are more susceptible to these adverse effects. Higher concentrations of outdoor NO_2 were associated with more asthma symptoms in a study of inner city children *(45)*. Though the mechanism of action is uncertain, exposure to carbon monoxide in city air was found in one European study to worsen lung function in adult patients with asthma *(43)*.

Ozone, while of critical importance to global health in the upper atmosphere, is an especially noxious chemical when generated at or near ground level. Ozone (O_3) is not produced directly by traffic or by hydrocarbon burning. Instead, the combination of NO_2 and hydrocarbons with air and sunlight form the secondary pollutant ozone. High average ozone and airborne particulate matter were associated with more frequent asthma symptoms and ED visits and hospital stays in a study of asthma sufferers in the San Joaquin Valley in California *(46)*. Ozone from air pollution has been shown to exacerbate asthma in children and adults, though this effect may be greater in children *(47)*. A study of over 90,000 emergency department visits in Atlanta for pediatric asthma showed a relationship to ozone and primary pollutant concentrations from traffic sources. These pollutants increased ED visits even at relatively low concentrations *(48)*.

The study of particulate matter in the air is quite complex, since the exact composition varies geographically. In general, high levels of particulate matter have long been associated in epidemiological studies with increased levels of respiratory disease. Ongoing research is examining the importance of particle size, fine versus more coarse, in asthma and chronic respiratory illness. One study in Turkey showed an 18% rise in asthma admissions when air contained high levels of coarse particles *(49)*. In contrast, a US study did not find increased hospitalizations for respiratory disease during those periods with high coarse particle levels *(50)*. The evidence for a negative effect on health from suspended fine particles is stronger *(51)*.

Genetic and phenotype differences may be important in the sensitivity of the asthma patient to air pollution. The risk of childhood asthma in Mexico City was modulated in some children by genes controlling the response to oxidative stress, such as might occur while breathing ozone *(52)*.

Avoidance and Treatment Issues

Advice on how to avoid high concentrations of air pollutants is important for asthma patients. Air pollution, like pollens and viruses, follows a seasonal pattern, and knowledge of the local pattern can help the primary physician with diagnosis and treatment. In the United States, a daily Air Quality Index (AQI) is computed and distributed for most large population areas. The AQI, which is determined on the basis of the highest pollutant of the day, may be considered safe for patients with chronic respiratory disease if less than 50 (green zone). On days with poor air quality, asthma sufferers should come inside where pollutant levels are typically much lower. Indoor ozone levels vary from 10 to 80% of outdoor concentrations, depending on the size of outdoor air flows into a building *(53)*.

Although asthma patients should continue their controller therapy during periods of high air pollution, pretreatment with controller medications may not always be successful. Budesonide treatment in one study was not successful in preventing ozone-triggered functional airways impairment in test subjects with mild persistent asthma *(54)*.

Indoor Air Pollution

While outdoor air pollution rightly receives a great deal of media and government attention, indoor air pollution can make living inside hazardous as well. Fortunately, indoor air problems are usually amenable to personal control and behavioral advice. Air quality issues may occur in both home and work environments. The field of occupational medicine examines workplace concerns and is reviewed in another chapter. Home air quality is typically not regulated, though pollution may result from several indoor sources.

Hydrocarbon fuels are, of course, burned inside as well as outdoors. Indoor gas cooking and heating stoves may produce NO_2, high levels of which have been associated with increased asthma symptoms in children *(55)*. Good ventilation is essential if natural gas is to be burned indoors. Indoor nitrogen oxides are also produced by wood-burning stoves, especially if not well vented.

The most serious and prevalent type of home air pollution is secondhand or environmental tobacco smoke (ETS). The risk from this indoor pollutant begins in utero. Maternal smoking during pregnancy is associated with increased infant wheezing *(56)*. This risk of respiratory morbidity continues to increase with postnatal parental smoking *(57)*. Laws regulating indoor tobacco smoking in one European country were followed by improved quality-of-life scores in a group of asthmatic indoor workers *(58)* and also by a reduction in the overall rate of hospitalizations for childhood asthma *(59)*.

As noted previously, indoor ozone is usually much less than outdoor levels. In recent years, though, indoor ozone generators have been marketed to the public for odor control and purported heath benefits. A US EPA review has warned the public about the potential hazards of adding an additional amount of a measured air pollutant to the indoor air.

CONCLUSION

This chapter has examined some of the most significant initiating and exacerbating causes of asthma. Viral respiratory infections, and to a lesser extent air pollution, are common triggers of exacerbations and may interact with individuals to affect the development of some forms of asthma. These causal factors do not exist in isolation but rather interact with the personal attributes of each patient, including his or her genetic and environmental background. The role of viruses and pollutants in asthma is important knowledge that has consequences for prevention, treatment, and avoidance of illness. Helpful education may be given to patients and appropriate treatments selected, and health care providers can avoid the considerable human effort and resources wasted on interventions that are useless or harmful.

Viral and pollutant triggers demonstrate that the highly complex inflammatory asthmatic response is called forth on many more occasions than simply by the contact of pollen grains and other allergens with the respiratory tract. Since so much of immune inflammation seems to have arisen from the need to combat infection, the interaction between asthmatic inflammation and viral infection is a natural topic for further investigation. Some of the most significant advances in medical care have come through the treatment and prevention of viral illnesses, and furthering the understanding of respiratory viruses is a worthy priority for the future study of asthma prevention and treatment. In addition to natural harmful infectious particles, humans in recent decades have added many substances of their own creation, including the molecules and particles that constitute indoor and outdoor air pollution. Control of this problem is very important for overall respiratory health.

Important action and advice is available for each asthma patient. By understanding and anticipating respiratory viral infections and air pollution as important causes of asthma, the health care provider can provide superior care for those who suffer from this chronic disease.

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REFERENCES

1. Ahn AC, Tewari M, Poon C-S, Phillips RS. The clinical applications of a systems approach. PloS Medicine 2006;3:e209.
2. van Gageldonk-Lafeber AB, Heijnen ML, Bartelds AI, Peters MF, van der Plas SM, Wilbrink B. A case-control study of acute respiratory tract infection in general practice patients in The Netherlands. Clin Infect Dis 2005;41:490–7.
3. Friedlander SL, Busse WW. The role of rhinovirus in asthma exacerbations. J Allergy Clin Immunol 2005;116:267–73.
4. Bianco A, Whiteman SC, Sethi SK, Allen JT, Knight RA, Spiteri MA. Expresssion of intercellular adhesion molecule-1 (ICAM-1) in nasal epithelial cells of atopic subjects: a mechanism for increased rhinovirus infection? Clin Exp Immunol 2000;121:339–45.
5. Poland GA, Barry MA. Common cold, uncommon variation. N Engl J Med 2009;360:2245–46.
6. Sears MR, Johnston NW. Understanding the September asthma epidemic. J Allergy Clin Immunol 2007;120:526–9.
7. Olenec JP, Kim WK, Lee W-M, et al. Weekly monitoring of children with asthma for infections and illness during common cold seasons. J Allergy Clin Immunol 2010;125:1001–6.

8. Xepapadaki P, Papadopoulos NG, Bossios A, et al. Duration of postviral airway hyperresponsiveness in children with asthma: Effect of atopy. J Allergy Clin Immunol 2005;116:299–304.

9. Ciprandi G, Tosca MA, Fasce L. Allergic children have more numerous and severe respiratory infections than non-allergic children. Pediatr Allergy Immunol 2006;17:389–91.

10. Busse WW, Lemanske RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet 2010;376:826–34.

11. Doull IJM, Lampe FC, Smith S, Schreiber J, Freezer NJ, Holgate ST. Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children: randomised double blind placebo controlled trial. BMJ 1997;315:858–62.

12. Johnston NW, Johnston SL, Duncan JM, et al. The September epidemic of asthma exacerbations in children: A search for etiology. J Allergy Clin Immunol 2005;115:132–8.

13. Spahn J, Sheth K, Yeh WS, Stempel DA, Stanford RH. Dispensing of fluticasone propionate/salmeterol combination in the summer and asthma-related outcomes in the fall. J Allergy Clin Immunol 2009;124:1197–203.

14. Johnston NW, Mandhane PJ, Dai J, et al. Attenuation of the September epidemic of asthma exacerbations in children: A randomized, controlled trial of montelukast added to usual therapy. Pediatrics 2007;120:e702–e712.

15. Weiss KB, Gern JE, Johnston NW, et al. The Back to School asthma study: the effect of montelukast on asthma burden when initiated prophylactically at the start of the school year. Ann Allergy Asthma Immunol 2010;105:174–81.

16. Spahn JD, Szefler SJ. Steroid therapy for asthma in children. Curr Opin Pediatr 2007;19:300–5.

17. National Asthma Education and Prevention Programs Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Fall Report 2007. National Heart, Lung and Blood Institute.

18. Johnston SL, Ferrero F, Garcia ML, Dutkowski R. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. Pediatr Infect Dis J. 2005;24:225–32.

19. 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.

20. Stensballe LG, Simonsen JB, Thomsen SF, et al. The causal direction in the association between respiratory syncytial virus hospitalization and asthma. J Allergy Clin Immunol 2009;123:131–7.

21. Wu P, Dupont W, Griffin MR, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. Am J Respir Crit Care Med 2008:178:1123–9.

22. Simões EAF, Carbonell-Estrany X, Rieger CHL et al. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. J Allergy Clin Immunol 2010;126: 256–62.

23. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med 2000;343:538–43.

24. Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A. Day-care attendance, position in sibship, and early childhood wheezing: A population-based birth cohort study. J Allergy Clin Immunol 2008;122:500–6.

25. Christiansen SC. Day care, siblings, and asthma-Please, sneeze on my child. N Engl J Med 2000;343:574–75.

26. Miller EK, Edwards KM, Weinberg GA, et al. A novel group of rhinoviruses is associated with asthma hospitalizations. J Allergy Clin Immunol 2009;123:98–104.

27. Bizzintino J, Lee WM, Laing IA, et al. Association between human rhinovirus and severity of acute asthma in children. Eur Respir J 2010: Aug 6 ePub.

28. Avila PC, Abisheganaden JA, Wong H, et al. Effects of allergic inflammation of the nasal mucosa on the severity of rhinovirus 16 cold. J Allergy Clin Immunol 2000;105:923–32.

29. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med 2009;329–38.

30. Castro-Rodriguez JA. The Asthma Predictive Index: A very useful tool for predicting asthma in young children. J Allergy Clin Immunol 2010;126:212–6.

31. Ducharme FM, Lemire C, Noya FJ et al. Preemptive use of high-dose fluticasone for virus induced wheezing in young children. N Engl J Med 2009;360:409–10.

32. Bisgaard H, Zielen S, Garcia-Garcia ML, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005;171:315–22.

33. Gwaltney JM, Phillips DC, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med 1994;330:25–30.

34. Bucher HC, Tschudi P, Young J, et al. Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis. Arch Intern Med 2003;163:1793–98.

35. Ahovuo-Saloranta A, Borisenko OV, Kovenen N, et al. Antibiotics for acute maxillary sinusitis. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.:CD000243. DOI:10.1002/14651858. CD000243.pub2.

36. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008;178:218–24.

37. Hahn, DL. Infectious asthma: a reemerging clinical entity? J Fam Prac 1995;41:153–7.

38. Sears MR. Epidemiology of asthma exacerbations. J Allergy Clin Immunol 2008;122:662–8.

39. Wald TG, Shult P, Krause P, Miller BA, Drinka P, Gravelstein S. A rhinovirus outbreak among residents of a long-term care facility. Ann Intern Med 1995;123:588–93.

40. Gehring U, Wijga AH, Brauer M, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med 2010;181:530–1.

41. Hwang BF, Lee Yl. Air pollution and prevalence of bronchitic symptoms among children in Taiwan. Chest 2010;138:956–64.

42. Chang C. The immune effects of naturally occurring and synthetic nanoparticles. J Autoimmunity 2010;34:234–246.

43. Canova C, Torresan S, Simonato L, et al. Carbon monoxide pollution is associated with decreased lung function in asthmatic adults. Eur Resp J 2010;35:266–72.

44. Medical Management Guidelines for Sulfur Dioxide (SO$_2$): Agency for Toxic Substances and Disease Registry. (http://www.atsdr.cdc.gov/MMG/MMG.asp?id=249&tid=46). Accessed October 31, 2010.

45. O'Connor GT, Neas L, Vaughn B, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 2008;121:1133–9.

46. Meng YY, Rull RP, Wilhelm M, Lombardi C, Balmes J, Ritz B. Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California. J Epidemiol Community Health 2010;64:142–7.

47. Mar TF, Koenig JQ. Relationship between visits to emergency departments for asthma and ozone exposure in greater Seattle, Washington. Ann Allergy Asthma Immunol 2009;103:474–9.

48. Strickland MJ, Darrow LA, Klein M, et al. Short-term associations between ambient air pollutants and pediatric emergency department visits. Am J Respir Crit Care Med 2010;182:307–16.

49. Tecer LH, Alagha O, Karaca F, Tuncel G, Eldes N. Particulate matter (PM(2.5), PM(10-2.5), and PM(10))and children's hospital admissions for asthma and respiratory diseases: a bidirectional case-crossover study. J Toxicol Environ Health A 2008;71:512–20.

50. Peng RD, Chang HH, Bell ML, et al. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among Medicare patients. JAMA 2008;299:2172–79.

51. Brunekreef B, Forsberg B. Epidemiological evidence of effects of coarse airborne particles on health. Eur Respir J 2005;26:309–18.

52. David GL, Romieu I, Sienra-Monge JJ, et al. Nicotinamide adenine dinucleotide (phosphate) reduced:quinone oxidoreductase and glutathione S-transferase M1 polymorphisms and childhood asthma. Am J Respir Crit Care Med 2003;168:1199–204.

53. Ozone and Your Health:Indoor Ozone: North Carolina Public Health Epidemiology. (http://www.epi. state.nc.us/epi/oee/ozone/indoor.html). Accessed October 23, 2010.

54. Vagaggini B, Taccola M, Conti I, et al. Budesonide reduces neutrophilic but not functional airway response to ozone in mild asthmatics. Am J Resp Crit Care Med 2001;164:2172–6.

55. Kattan M, Gergen PJ, Eggleston P, Visness CM, Mitchell HE. Health effects of indoor nitrogen dioxide and passive smoking on urban asthmatic children. J Allergy Clin Immunol 2007;120:618–24.

56. Garcia-Marcos L, Mallol J, Sole' D, et al. International study of wheezing in infants:risk factors in affluent and non-affluent countries during the first year of life. Pediatric Allergy Immunol. 2010;21: 878–88.

57. Kuiper S, Muris JWM, Dompeling E, et al. Interactive effect of family history and environmental factors on respiratory tract-related morbidity in infancy. J Allergy Clin Immunol 2007;120:388–95.

58. Menzies D, Nair A, Williamson PA, et al. Respiratory symptoms, pulmonary function, and markers of inflammation among bar workers before and after a legislative ban on smoking in public places. JAMA 2006;296:1742–8.
59. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free legislation and hospitalizations for childhood asthma. N Engl J Med 2010;363:1139–45.
60. Martinez FD, Wright AC, Taussig LM et al. Asthma and wheezing in the first 6 years of life. N Engl J Med 1995;322:133–8.
61. Brand PLP, Baraldi E, Bisgaard H, et al. Definition, assessment, and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008;32:1096–110.