



Maintenance of Certification-CME Review

Air pollution and asthma: how can a public health concern inform the care of individual patients?



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Learning Objectives:

At the conclusion of this activity, participants should be able to:

- Describe the established connection between exposure to air pollution and exacerbation of existing asthma
- Develop approaches to identifying air pollution sources, beyond environmental tobacco smoke, that may be contributing to the exacerbation of a patient's asthma
- Discuss exposure-reduction measures that can be incorporated into asthma action plans, in cases where air pollution may be involved in an exacerbation, and counsel patients to reduce exposure to air pollution in order to maintain optimal asthma control

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Clinical Vignette

A 38-year-old woman presented to the clinic reporting wheezing near the end of her 30-minute commute by bicycle. The patient was a professor who had long enjoyed bicycling to work and had recently moved from a rural community to a dense urban environment, where her new route took her along streets with prominent vehicular traffic. The professor had childhood asthma but had been asymptomatic throughout adulthood. A referral to an allergist disclosed sensitization to birch pollen. Her physician recommended that she obtain peak expiratory flow rate readings 4 times daily for 4 weeks. She complied, and the readings were consistently above 500 L/m on the weekend and in the early mornings. However, peak expiratory flow rates of 400 L/m associated with wheezing were recorded midmorning and early afternoon on weekdays. Her physician suspected that traffic-related air pollution was exacerbating her asthma. This case was described elsewhere.¹

Introduction

Air Pollution and Asthma Exacerbation

Asthma is characterized by airway inflammation, intermittent bronchoconstriction, and airway hyperresponsiveness to different triggers.² Air pollution is a complex mixture of gasses, such as ozone, particulate matter (PM), diesel exhaust particles (DEPs), and biomass and biological constituents.^{1,2} During the past few decades, air pollution has become a clear public health concern, and the evidence is sufficient to confirm that it exacerbates pre-existing asthma.³ Less confirmatory but suggestive is newer evidence that air pollution may contribute to new-onset or new-onset asthma.² It is estimated that more than 120 million people in the United States live in areas where air pollution regularly exceeds accepted levels.¹

Much research has been carried out at the public health level, but has our understanding evolved to the level that physicians can identify air pollution as a contributor to exacerbations in individual patients? In the preceding case study, a geographic change increased the patient's exposure levels, coincident with enhanced asthma exacerbations after a long period of quiescence. Here, we review current knowledge of the effects of air pollution on airway biology, bring to light some potential exposure sources that clinicians may find useful to consider, and argue that exposure-decreasing interventions can be an important part of asthma action plans for individual patients. We also briefly discuss air pollution and incident asthma and the interaction between air pollution and virus-induced asthma exacerbations.

Effects on Airway Biology

Ozone is a secondary pollutant formed through redox reactions involving volatile organic compounds, nitrogen dioxide, and sunlight.³ Ozone has long been known to produce

pulmonary effects, mediated by oxidative stress and activation of nociceptive nerves.³ Several epidemiologic studies and meta-analyses have pointed to an increase in emergency department visits for asthma after ozone peaks.¹ Controlled human exposure studies have shown that patients with asthma and healthy participants develop decreased lung function in response to ozone exposure.⁴ Those with atopy, with or without asthma, show increased sputum neutrophils and interleukin (IL)-8.⁴ Patients with asthma also exhibit increased IL-6 and IL-1 β in sputum.⁴ Gene expression studies have shown that patients with asthma upregulate proinflammatory pathways after ozone exposure and that those without asthma show increased expression of genes that mitigate oxidative stress.⁵ Exposure studies also have shown that certain people may be more sensitive than others. Exposure studies have allowed the designation of responders and non-responders based on ozone-induced sputum neutrophilia. Those with a robust response also have increased innate immune markers (CD16, CD11b, CD80) on sputum macrophages, whereas nonresponders do not.⁶ Distinct responses may allow further dissection of how exposure-induced inflammation interacts with genetics on the individual level.^{2,6} A study by Fry et al⁶ showed that subject stratification based on airway inflammatory cell responses rather than on the presence or absence of disease may be useful. For the clinician, this may reveal certain patients who are exquisitely sensitive to the effects of air pollution, although currently there is no protocol that has been validated for this purpose in the standard clinical setting.

Several studies have reported the effects of traffic-related air pollution and diesel exhaust (DE) on asthma. Meta-analyses have concluded that residential proximity to traffic-related air pollution is associated with asthma morbidity, particularly in children.^{1,3} In animals, DEPs have been shown to enhance IgE production and T-helper cell type 2 cytokines at allergen challenge.¹ Controlled human DE exposure studies also have been conducted to assess effects in people with asthma. Nordenhall et al⁷ exposed patients with asthma on inhaled corticosteroid treatment to 300 $\mu\text{g}/\text{m}^3$ of DE or filtered air for 1 hour on 2 occasions separated by 3 weeks. Compared with filtered air exposures, DE exposure was associated with a significant increase in methacholine responsiveness 24 hours after exposure.⁷ This study showed that even in the presence of inhaled corticosteroid therapy, short-term exposure to DEPs is associated with clinically relevant effects in patients with asthma.⁷

Other crossover studies using DEPs plus nasal ragweed challenge have shown the importance of the glutathione-S-transferase (GST) genotype.² The GSTs are a family of phase II isozymes that catalyze the conjugation of glutathione to xenobiotics for detoxification and elimination. Crossover studies have shown that in individuals with decreased-function GST genotypes (eg, *GSTM1* null), DEP exposure enhances nasal responses to allergen,² whereas ozone exposure induces persistent airway neutrophilia⁸ and lipopolysaccharide enhances airway and

systemic neutrophil responses.⁹ Because mutations in *GST* are fairly common, these studies have identified a large proportion of people who may be more susceptible to adverse effects.² It also has been suggested that supplementation with antioxidants may have protective value,² and one controlled human study has recently reported this.¹⁰

In addition to outdoor air pollution, important exposures originate inside the home. Biomass is used by approximately 2.4 billion people worldwide for cooking and heating.¹ Common biomass materials include wood, charcoal, dung, and crop residues but also can include cigarettes, campfires, wildfires, garbage incineration, smokestack emissions from coal plants, and other sources.¹ Low-efficiency combustion leads to smoke that is high in fine PM and elemental carbon.³ Meta-analyses have shown that children exposed to biomass PM are at increased risk for acute respiratory infections.¹ Although pooled studies of asthma diagnoses are inconclusive, respiratory infections are known to be associated with asthma exacerbations. The problem of biomass emissions is not isolated to less-developed countries. Residential wood burning is an important source of ambient PM during the winter heating season in many communities across the United States.^{11,12} Recently, the same group that reported an association between wood smoke and forced expiratory volume in 1 second in children with asthma in Seattle found that an air filter intervention decreased concentrations of inflammatory biomarkers.¹² Thus, wood smoke and other biomass combustion may play a significant role in exacerbation of asthma.

Air pollution is often viewed as a mixture of inert particles and irritating gasses. However, various biological components, bacterial constituents, and pollens can have important effects, such as activating innate immunity or eliciting or enhancing an allergic response.¹ Inhalation of endotoxin is known to induce bronchospasm in those with and without asthma.¹³ Double-blinded exposures of patients with asthma to particle-associated endotoxin (500 ng/m³ for 4 hours) showed significantly increased airways responsiveness to allergen.¹³ In rats, vitamin E supplementation significantly decreased the infiltration of neutrophils elicited by endotoxin.¹⁴ A crossover study in humans recently yielded similar results. Participants were treated with vitamin E or placebo for 7 days before undergoing an inhaled lipopolysaccharide challenge.¹⁴ Vitamin E treatment significantly decreased sputum neutrophils.¹⁴ Thus, allergens and endotoxin are important constituents of polluted air and may act synergistically with air pollutants.

Recently, the study of the effects of air pollution on asthma has been affected by new developments in fields such as epigenetics. MicroRNAs (miRNAs) are epigenetic regulators of the response to environmental stimuli. The first study to examine miRNAs in sputum after controlled human exposure to ozone showed upregulation of 10 miRNAs.¹⁵ Pathway analyses showed that their predicted targets were associated with inflammation, which has implications for asthma.¹⁵

The interaction between known exacerbating factors, such as viral infections, and air pollution are not often considered but may be important for individual patients. Asthma admission rates have been shown to positively correlate with influenza and SO₂ level.¹⁶ The enhanced inflammatory response to ozone in patients with asthma may play a role.^{4,5} A recent *in vitro* study has shown that ozone disrupts the protease–antiprotease balance, leading to increased influenza susceptibility, whereas antioxidants significantly decrease viral replication.¹⁷ Hackett et al¹⁸ recently reported that asthmatic epithelial cell cultures released greater concentrations of IL-6, IL-8, and granulocyte–macrophage colony-stimulating factor in response to environmental challenges, such as infection with respiratory syncytial virus or exposure to PM. Thus, there is evidence that patients with asthma may exhibit

intrinsic phenotypic differences that affect interactions between viruses and air pollution.

Air Pollution and New-Onset Asthma

Evidence has recently emerged that air pollution may contribute to the development of asthma. Studies have shown that high air pollution levels increase the risk of new-onset asthma.^{1,3} Jerrett et al¹⁹ determined individual estimates of traffic-related air pollution and found an association with new-onset asthma. The Traffic, Asthma and Genetics study recently showed that the *GST* genotype is associated with asthma and that children carrying minor alleles are at increased risk of asthma associated with air pollution.²⁰ Previously, evidence for a causal relationship between air pollution and the development of asthma was classified as in between “suggestive but not sufficient” and “sufficient.”³ As new studies have strengthened the evidence, the consensus is becoming “sufficient.”

Case Revisited

The physician instigated an intervention based on the suspicion that traffic-related air pollution was exacerbating the patient's asthma. The professor's cycling route was analyzed for the proportion of time she spent within 300 m of major roadways, and it was determined that 70% of her commute was in such proximity. An alternative route was mapped out by which only 15% of her time was within 300 m of high-traffic roads. By following this new route over the next month, the frequency of her wheezing and peak expiratory flow rate readings below 400 L/m decreased dramatically.

The Precautionary Principle

Although we acknowledge that it is difficult to isolate air pollution as an exacerbating factor for an individual patient, we argue that our knowledge of this pressing public health issue has evolved to the point where physicians can integrate it into primary practice. This presents challenges because, unlike environmental tobacco smoke, with an easily identifiable source, the assessment of air pollution exposure may require a more detailed interview with the patient. We suggest it might be helpful to focus on changes in routine, such as travel to a community or other country with high ambient levels of air pollution (eg, this was a concern during the Olympic games in China), outdoor smoke exposure (eg, camping, wildfires), the beginning of the home heating season, a new ozone-generating air purifier, increased exposure to endotoxin (eg, swine dust, animal caging), or increased time spent on or near major roadways.

We advocate for adhering to the “precautionary principle” even without direct evidence that air pollution exposure has increased. Because there appears to be no threshold below which air pollution has no adverse effects, decreased exposure can benefit the patient.¹¹ Interventions that increase overall wellness, such as improved nutrition, antioxidant supplementation, and increased exercise, also likely shore up defenses against the effects of air pollution.¹¹ Expert opinion dictates that rather than discouraging patients from exercising outdoors, the best approach is to encourage them to exercise in outdoor areas that are as far removed from sources of air pollution as possible,¹¹ as the physician did by mapping out an alternate cycling route in this case.

Conclusion

Air pollution is known to be associated with asthma exacerbations on a population level and can have an impact on individual patient health. We assert that it is time for better integration of our knowledge of the effects of air pollution into individual patient care and specifically into asthma action plans. Physicians are in a position to suggest exposure-decreasing strategies to patients and to

document their clinical effects with objective measurements such as peak expiratory flow rate, sputum cell counts, and quality-of-life questionnaires.

References

- [1] Alexis N, Carlsten C. Asthma triggers—air pollutants. In: Bernstein JA, Levy ML, eds. *Clinical Asthma: Theory and Practice*. Boca Raton, FL: CRC Press; 2014.
- [2] Gilliland FD. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. *Pediatrics*. 2009;123(suppl 3):S168–S173.
- [3] Health Effects Institute Panel on the Health Effects of Traffic Related Air Pollution. *Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects*. Special Report 17. Boston, MA: Health Effects Institute; 2010.
- [4] Hernandez ML, Lay JC, Harris B, et al. Atopic asthmatic subjects but not atopic subjects without asthma have enhanced inflammatory response to ozone. *J Allergy Clin Immunol*. 2010;126:537–544.e1.
- [5] Hernandez M, Brickey WJ, Alexis NE, et al. Airway cells from atopic asthmatic patients exposed to ozone display an enhanced innate immune gene profile. *J Allergy Clin Immunol*. 2012;129:259–261.e1–2.
- [6] Fry RC, Rager JE, Zhou H, et al. Individuals with increased inflammatory response to ozone demonstrate muted signaling of immune cell trafficking pathways. *Respir Res*. 2012;13:89.
- [7] Nordenhall C, Pourazar J, Ledin MC, Levin JO, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. *Eur Respir J*. 2001;17:909–915.
- [8] Alexis NE, Zhou H, Lay JC, et al. The glutathione-S-transferase Mu 1 null genotype modulates ozone-induced airway inflammation in human subjects. *J Allergy Clin Immunol*. 2009;124:1222–1228.e5.
- [9] Dillon MA, Harris B, Hernandez ML, et al. Enhancement of systemic and sputum granulocyte response to inhaled endotoxin in people with the GSTM1 null genotype. *Occup Environ Med*. 2011;68:783–785.
- [10] Carlsten C, Macnutt MJ, Zhang Z, Sava F, Pui MM. Anti-oxidant N-acetylcysteine diminishes diesel exhaust-induced increased airway responsiveness in person with airway hyper-reactivity. *Toxicol Sci*. 2014;139:479–487.
- [11] Giles LV, Barn P, Kunzli N, et al. From good intentions to proven interventions: effectiveness of actions to reduce the health impacts of air pollution. *Environ Health Perspect*. 2011;119:29–36.
- [12] Allen RW, Carlsten C, Karlen B, et al. An air filter intervention study of endothelial function among healthy adults in a woodsmoke-impacted community. *Am J Respir Crit Care Med*. 2011;183:1222–1230.
- [13] Boehlecke B, Hazucha M, Alexis NE, et al. Low-dose airborne endotoxin exposure enhances bronchial responsiveness to inhaled allergen in atopic asthmatics. *J Allergy Clin Immunol*. 2003;112:1241–1243.
- [14] Hernandez ML, Wagner JG, Kala A, et al. Vitamin E, gamma-tocopherol, reduces airway neutrophil recruitment after inhaled endotoxin challenge in rats and in healthy volunteers. *Free Radic Biol Med*. 2013;60:56–62.
- [15] Fry RC, Rager JE, Bauer RN, et al. Air toxics and epigenetic effects: ozone altered microRNAs in the sputum of human subjects. *Am J Physiol Lung Cell Mol Physiol*. 2014;306:L1129–L1137.
- [16] Liao CM, Hsieh NH, Chio CP. Fluctuation analysis-based risk assessment for respiratory virus activity and air pollution associated asthma incidence. *Sci Total Environ*. 2011;409:3325–3333.
- [17] Kesic MJ, Meyer M, Bauer R, Jaspers I. Exposure to ozone modulates human airway protease/antiprotease balance contributing to increased influenza A infection. *PLoS One*. 2012;7:e35108.
- [18] Hackett TL, Singhera GK, Shaheen F, et al. Intrinsic phenotypic differences of asthmatic epithelium and its inflammatory responses to respiratory syncytial virus and air pollution. *Am J Respir Cell Mol Biol*. 2011;45:1090–1100.
- [19] Jerrett M, Shankardass K, Berhane K, et al. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect*. 2008;116:1433–1438.
- [20] MacIntyre EA, Brauer M, Melen E, et al. GSTP1 and TNF Gene variants and associations between air pollution and incident childhood asthma: the Traffic, Asthma and Genetics (TAG) study. *Environ Health Perspect*. 2014;122:418–424.