

Journal Pre-proof

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PII: S1081-1206(19)31192-5

DOI: <https://doi.org/10.1016/j.anai.2019.09.014>

Reference: ANAI 3027

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 22 August 2019

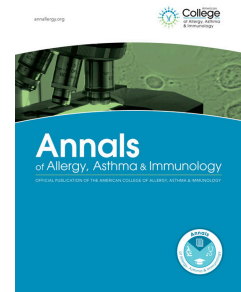
Revised Date: 14 September 2019

Accepted Date: 17 September 2019

Please cite this article as: Peden DB, The “envirome” and what the practitioner needs to know about it, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.09.014>.

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Title Page

The “envirome” and what the practitioner needs to know about it

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Grant Support: US EPA CR 83578501, NIEHS ES025124

No conflicts of interest

INTRODUCTION

The “envirome” is a term which encompasses the overall environmental and extrinsic agents to which an individual is exposed, either constantly, seasonally or episodically. It has become increasingly recognized that such exposures may have significant impact on development of biological characteristics of an individual. This is especially notable in the development of allergic diseases. For example, the term “extrinsic asthma” refers to asthma driven by exposure to airborne allergens to which individuals have developed an IgE-mediated sensitization. “Environmental control” in allergic diseases has historically focused on decreasing exposure to allergens associated with airway allergy, including house dust mites, pet allergens, rodent and cockroach allergens in the indoor environment as well as minimizing exposure (usually by timing of outdoor activity) to outdoor allergens. However, in addition to allergen exposure, other extrinsic factors impact development of allergic disease. This review will focus on a number of non-allergenic environmental influences in asthma and atopy

Pollutants, including outdoor ambient pollutants such as ambient air O₃, NO_x (oxides of nitrogen), particulate matter (PM) that is either 0.5-2.5 microns (PM_{2.5}) or 2.5-10 microns (PM₁₀), as well as indoor PM_{2.5} (usually encountered in much higher concentrations than ambient outdoor pollutants) resulting from tobacco smoking and use of biomass fuels clearly impact exacerbation and likely development of allergic diseases¹⁻³. As outlined below, bacterial and viral exposures induce host responses which influence risk for development of atopic disease. Such exposures include overt infections as well as colonization with microbes resulting in microbial populations being residually present on skin and various mucosal sites which modulate immune response (the microbiome). It is likely that use of antibiotics also impacts these populations with subsequent influences on allergic disease. Social and psychological factors have also been shown to impact development and exacerbation of allergic disease. This review will touch on pollutant, microbial, and stress elements of the envirome which impact

allergic disease, with emphasis of items that can be addressed by clinicians or policy approaches.

Pollutant impacts on asthma incidence:

Air pollutants are well known causes of exacerbation of asthma, with O₃, ambient PM_{2.5} and PM₁₀ and indoor PM_{2.5} (such as those from tobacco smoke) being well-established triggers for asthma exacerbation. However, there is increasing evidence that pollutant exposures are associated with incidence of asthma as well³. As the impact of pollutants on exacerbation of asthma has been extensively reviewed, this section will emphasize representative studies which explores the role of pollutants on development of airway disease.

McConnell et al, published a seminal article demonstrating that children playing high activity outdoor sports in high O₃ areas had increased asthma incidence compared to children in low ozone areas or who did not play outdoor sports (likely a surrogate for decreased respiratory exposure)⁴. More recently, a birth cohort study of 14,000 Dutch, German and Swedish children which followed disease progression from birth through ages 14-16 years demonstrated that increased exposure to NO₂ and PM_{2.5} at birth was associated with increased asthma incidence through adolescence⁵. A 2015 meta-analysis of data from several European and US birth cohorts also indicates that traffic related particulate matter (TRAP) is associated with both incident asthma and sensitization to aeroallergens⁶. Thus, there is a growing body of evidence that ambient air pollutants are co-factors in asthma genesis.

Pollutant impacts on eczema exacerbation:

Air pollution also impacts atopic dermatitis. A study from China by Guo et al, examined 157,595 outpatient visits for eczema and dermatitis from April 2012-2014, finding same day increases in outpatient visits per IQR increase in PM_{2.5}, PM₁₀, NO₂ and SO₂ of 3.81% (95% CI: 2.92-

4.7%), 3.18% (95% CI: 2.39-3.97%), 5.43% (95% CI: 4.43-6.43%) and 5.57% (95% CI: 4.55-6.58%) respectively in older individuals and women⁷. Li et al also reported a positive relationship between ambient air pollutants and eczema in western China, with a negative association with increased relative humidity⁸. Consistent with these Chinese reports are those from a German study by Huls et al, which demonstrated that incident eczema in 843 persons over age 55 was associated with increased levels of NO₂, NO_x, PM_{2.5} and PM₁₀⁹. In this German study, the impact of these pollutants was more notable in non-atopic eczema than atopic eczema.

Pollutant impacts on eczema incidence:

There is also a growing appreciation for the effect of pollutants on development of eczema in children. In a French study of 4907 children, the lifetime risk for eczema was associated with the 3-year averaged levels of PM₁₀ (odds ratio=1.13), NO₂ (OR=1.23), NO_x (OR=1.06) and CO (OR=1.03)¹⁰. Likewise, a German birth cohort study demonstrated that location near a heavily traveled road and NO₂ levels were both associated with a diagnosis of eczema¹¹. Another study examined the effect of prenatal exposure and to PM_{2.5} and early post-natal exposure to second hand tobacco smoke. Individually, there was no clear effect of either agent, but when infants are exposed to both pollutants there is a significantly increased risk for eczema (OR=2.39)¹². A number of studies from China also support the idea that ambient air pollutants are associated with development of pediatric eczema. Deng, et al, analyzed data from 3167 three to six-year old children recruited from 12 kindergartens in Hubei, China, comparing parental report of eczema with NO₂, PM_{2.5} and PM₁₀ levels assessed at monitoring stations near these facilities. They found a strong relationship between high levels of NO₂, PM_{2.5}, and PM₁₀ exposures during gestation and the first year of life and risk of childhood eczema¹³. The risk of eczema associated with the third (29.64–54.48 ug/m³) and fourth quartile (>54.48 ug/m³) levels of measured NO₂ during gestation. In the first year of life, NO₂ exposures of 29.55–53.66

and >53.66 ug/m³ were associated with a risk of eczema with ORs of 1.371 and 1.335, respectively.

Genetic variants for a number of inflammatory response mediators, including molecular sensors (e.g. CD14, TLR2, TLR4) which modulate response to microbial agents in the environment, agents which neutralize oxidative stress and cellular toxicants produced with xenobiotic pollutant exposure (e.g. Glutathione-S-Transferase variants,) and inflammatory cytokines (TNF) have been linked with development or exacerbation of airway allergic disease associated with pollutant exposure¹⁴. Huls et al also examined the impact of nine alleles for genetic polymorphisms to GSTP1, TNF, TLR2 and TLR4 on eczema development in 5685 infants from six birth cohorts, developing a genetic risk score for these alleles to assess the role of TRAP on AD development¹⁵. They observed that there was a marginal increase in eczema risk due to TRAP linked to these genes, most notably the TNF rs 1800629 minor allele. Likewise, Wang et al¹⁶ examined the effect of GSTM1 and GSTP1 alleles in risk for eczema development comparing 34 children with eczema to 106 unaffected control infants, with an examination of smoking exposure assessed by cord blood cotinine. Overall, the GSTM1 null and GSTP1 Ile homozygote state was associated with increased eczema risk (OR 3.61 and 3.11 respectively). In children with low tobacco smoke exposure (cotinine <0.1 ng/mL), eczema risk was 6.63 in those with 2 GSTP1 Ile-105 alleles. In children with increased tobacco exposure (cotinine >0.1 ng/mL) and the GSTM1 null genotype, there was increased risk of eczema (OR 5.21). Collectively, these results suggest that gene X environment interactions are important factors in considering the role of the pollutant components of the envirome in mediating allergic type disease.

A number of human studies explore mechanisms by which pollutants modulate atopy. In persons with existing airway allergy, ozone¹, a combination of NO₂ and SO₂¹⁷, endotoxin¹⁸, environmental tobacco smoke¹⁹, and diesel exhaust particles²⁰ have all been shown to augment IgE mediated response to allergens. Additionally, Diaz-Sanchez et al published seminal work in which exposure to diesel exhaust particles rich in polyaromatic hydrocarbons promote IgE production²¹ and enhance development of novel IgE responses to nasal challenge with keyhole limpet hemocyanin (KLH), a neoantigen rarely encountered incidentally as an allergen in the US²². This study in human volunteers demonstrated the biological proof of concept that an air pollutant could modulate primary IgE response to an encountered allergen. As DEP is somewhat similar to tobacco smoke and biomass particles, this effect is likely generalizable to a relatively wide variety of particulates. Indeed, Nadeau et al, examined T regulatory cell function of cells recovered from asthmatic and non-asthmatic children living in a high pollution area (Fresno, CA) and a low pollution area (Stanford, CA)²³. They found strong correlations between T regulatory cell function and FEV₁ and FoxP3 when the entire recruited cohort was assessed as a group. They also observed decreased T regulatory cell function in the cells from asthmatics from Fresno, also linked to worsened GINA asthma scores and decreased FoxP3 expression. They concluded that pollutant exposure was linked to epigenetic suppression of FoxP3 expression and loss of T regulatory cell function with notably worsened asthma outcomes in these children. In addition to these selected studies, additional reviews outline on innate immune²⁴, mucosal, and acquired immune²⁵ mechanisms which mediate pollutant modulation of atopy.

Infections and Microbial Colonization:

One of the first suggestions that microbes impacted the development of atopy was the development of the “hygiene hypothesis” by David Strachan, who suggested that increases in allergic diseases were associated with decreased occurrences of infection²⁶. Indeed, with

smaller family sizes, use of antibiotics and modern sanitation, there does appear to be increases in allergic disease. The hygiene hypothesis has inspired a number of studies which demonstrate that microbial exposures impact development of asthma and atopy.

In 1999, Martinez et al reported that the C-T -159 polymorphism for CD14, a co-receptor for endotoxin that acts in conjunction with TLR4, was associated with IgE levels²⁷. TT homozygotes, who produce greater amounts of CD14 than those with the CC or CT genotypes, have increased response to endotoxin and decreased levels of IgE. In 2002, Braun-Fahrlander, et al²⁸, reported that levels of endotoxin in bedding from children living in farm environments was higher than that in urban settings, and that the bedding endotoxin level was inversely associated with development of allergic rhinitis, allergic asthma and allergic sensitization yet positively associated with TH1 cytokine production from circulating immune cells. In addition to the farm environment, there are other animal exposures that impact microbial populations. Dog ownership is associated with both increased levels of endotoxin²⁹ and richer and more diverse bacterial communities compared to homes without pets³⁰, with early life exposure to pets associated with decreased asthma³¹. Extrapolating these observations, it seems plausible that decreased response to microbes, either due to decreased host ability to respond, or decreased exposure to microbes would result in increased IgE production and occurrence of allergic disease.

Building on these and other studies, Stein et al, examined differences between Hutterite and Amish families, who despite similar genetic and cultural backgrounds, have markedly differing incidence of asthma and atopy³². The Amish population had a 4-6-fold lower incidence than the Hutterites, with 6.8-fold higher levels of endotoxin, likely associated with animal-based farming practices. There were also notable differences in peripheral blood immune cell characteristics in these populations. Additionally, Kirjavainen, et al³³ compared microbial composition of dust

collected in studies of Finnish cohorts to the GABRIELA cohort, and has observed similarities in dusts collected from suburban homes in which children were protected from asthma development and those present in the GABRIELA rural cohort, suggesting that the farm effect might be transferred to a non-farm environment.

However, there is growing recognition that indoor endotoxin may also increase asthma symptoms, especially in adults or regardless of atopy status. In a series of studies, Thorne and Zeldin and colleagues examined endotoxin levels in houses and examined the relationship of these levels to asthma events. In a 2005 report assessing endotoxin in 2552 dust samples from 831 homes and assessing symptoms in 2456 people, there were clear correlations between increasing endotoxin levels and asthma symptoms, diagnosis, and medication use in this cohort³⁴. They later expanded these results with data from 7,450 dust samples and 6,963 subjects from the National Health and Nutrition Examination Survey, again showing that endotoxin levels strongly correlated with asthma and wheezing events³⁵. This was true regardless of atopy status. They reported that indoor endotoxin augmented response to PM_{2.5}, and that having dogs and cats in the household increased the effect of endotoxin on asthma outcomes³⁶. Factors which predicted endotoxin levels in household dust included increased poverty, people, pets, and decreased household. Using the Northeast as a reference region, indoor endotoxin levels were significantly higher in the West, Midwest and South. Taken together, studies of endotoxin exposure and asthma and atopy suggest that endotoxin exposure in early life skews people away from developing IgE mediated responses. Conversely, in non-atopic persons, indoor endotoxin appears to increase airway disease. This may reflect the effect of endotoxin on two distinctly different inflammatory processes in the lung.

Viral infections are a clear cause of bronchiolitis and asthma exacerbation. The role of viral infections in asthma has been recently reviewed in the *Annals* by Mikhail and Grayson³⁷.

Respiratory Syncytial Virus (RSV) clearly induces lower airway disease and is frequently associated with asthma development. Rhinovirus (RV) is likely the leading viral cause of asthma exacerbation and also linked with disease development. It remains unclear if viral infections cause asthma, though they do cause epithelial injury and may cause remodeling. There are indications that RSV is more often associated with non-atopic asthma and RV is more important for exacerbation of allergic (T2) asthma.

Bisgaard et al ³⁸, reported that infants colonized in the nasopharyngeal region at 1 month of age with *S. pneumoniae*, *M. catarrhalis*, *H. influenzae*, or a combination of these organisms were at increased risk for persistent wheeze, increased total IgE and increased blood eosinophil counts. *S. aureus* colonization was not associated with this risk. Ege et al ³⁹, reported on the relationship between farm and non-farm house dust microbial exposures assessed by measuring bacterial DNA and occurrence of asthma in samples obtained in the large PARSIFAL and GABRIELA cohorts. They found a marked increase in levels of bacteria and fungi in farm samples that were associated with decreased occurrence of asthma and atopy (assessed by threshold levels of specific allergens). Specific species which were associated with asthma were the fungal species *euotium* (OR=0.37) and a number of bacteria, including *Listeria monocytogenes*, *bacillus species*, and *corynebacterium species*. Intriguingly, the bacterial airway microbiome also modifies the impact of viruses in asthma. In a recent study of 413 children (ages 6-17) assessing seasonal use of omalizumab to decrease asthma exacerbation in the fall, McCauley et al, ⁴⁰ examined the relationship between the nasal microbiome and asthma exacerbation. They observed that bacterial populations dominated by *Moraxella* were associated with increased risk of disease and eosinophil activation and that when *Streptococcus* species dominant, there was increased risk of RV infection. *Staphylococcus* or *Corynebacterium* were associated with reduced acute asthma.

Antibiotics:

A number of recent studies have revealed a relationship between early life use of antibiotics and development of asthma. Mulder et al, used a case control and case sibling study design to explore use of antibiotics in the third trimester and risk for subsequent development of asthma, finding adjusted odds ratios of 1.4 and 1.37 respectively for asthma in preschool children⁴¹. Yamamoto-Hanada explored the impact of antibiotic use in 1,196 children at age 2 with occurrence of allergic diseases at age 5, finding increased risks for asthma (OR=1.72), eczema (OR=1.4) and allergic rhinitis (OR=1.65) associated with antibiotic use⁴². Fishman et al,⁴³ examined the relationship between frequency of antibiotic use (measured as number of prescriptions filled) and incidence of asthma in a cohort of 79,582 children in a Medicaid program. New asthma was reported in 2381 children, and after adjustment, the absolute risk of developing asthma by age 4.0 years was 2.7% in children with no antibiotics, 3.6% in children with 1-2 antibiotics, and 4.5% in those who had ≥ 3 antibiotics prescriptions filled. Donovan et al, assessed the impact of antibiotic use in 152,622 singleton, full term, healthy infants covered in the Tennessee Medicaid Program on development of asthma using multivariable logistic regression models⁴⁴. Seventy-nine percent of these children had at least one antibiotic prescription filled. The odds of childhood asthma increased with antibiotic use in a dose-dependent manner, with a 20% increase in odds (adjusted odds ratio [aOR] 1.20, 95% confidence interval [CI] 1.19-1.20) for each additional antibiotic prescription filled.

A number of recent studies have focused on the effect of azithromycin on wheezing disease and asthma. Bacharier et al,⁴⁵ examined the ability of 5-day treatment with azithromycin to prevent development of a lower respiratory tract infection in children age 12-72 months who develop acute respiratory tract infection, finding that azithromycin significantly prevented development of severe LRTI. Stockholm et al,⁴⁶ made similar observations comparing azithromycin to placebo in acute treatment of asthma like events in 1-3-year-old children. Gibson, et al⁴⁷ examined the

effect of 48 weeks of azithromycin on asthma events in the AMAZES study of severe asthmatics and reported significant improvements in a broad array of asthma outcomes. This macrolide has both antibiotic and anti-inflammatory actions, and it remains unclear which of these actions accounts for its effect in asthma. There is concern that change in the microbiome and development of microbial resistance may result from this treatment. To assess this, a second analysis of paired sputum samples from 61 patients of the AMAZES study was performed⁴⁸. There was no effect in overall bacterial load but there was decreased load of *H Influenza* and microbial diversity. Molecular analysis identified 89 antibiotic resistance genes, in which five macrolide and two tetracycline resistance genes were significantly increased.

Of note, it is increasingly recognized that agricultural and community antibiotic use changes resistance patterns in regional microbial communities. Such changes in communal microbes are likely to be reflected in personal microbiota. Taken together, environmental exposures to microbes and items which impact microbes (antibiotics) likely impact development and exacerbation of asthma, likely due to change in resident microbiome.

Stress Exposures:

There is a growing body of evidence that prenatal and early life maternal stressors have a marked impact on development of asthma, indicating that stress and social environmental factors should be considered as an important element of the envirome⁴⁹. Sternthal et al⁵⁰, used multilevel logistic regression models to estimate asthma risk in 2071 children age 0-9 in Chicago, accounting for personal factors (age, sex, race/ethnicity, maternal asthma, socioeconomic status and domestic violence) and neighborhood factors (social disorder) as potential confounders, and found that medium and high level community violence were linked to increased asthma risk (OR 1.6 and 1.56. respectively). Cohen et al,⁵¹ undertook a household survey of 1213 children in San Juan and Caguas, Puerto Rico. While neighborhood

violence was not associated with asthma, a history of physical or sexual abuse was linked to increased asthma (OR=2.52), health care visits for asthma (OR=1.95) and medication use for asthma (OR=2.53). In a Norwegian study of 63,626 children born from 2000-2007, it was reported that maternal lifetime major depressive symptoms, as well as depression during and 6 months after pregnancy increased risk for asthma (relative risk of 1.19, 1.17 and 1.17 respectively)⁵².

Suglia et al,⁵³ examined the impact of poor housing and intimate partner violence on asthma diagnosis by age 36 months in a birth cohort of 2013 children. They reported a 1.8-fold increased risk of asthma associated with intimate partner violence and a 1.5-fold increase associated with living with housing disarray. While housing stress was explored as a cofactor for asthma in this study, poor housing in general may be a risk factor for asthma morbidity. Supporting this idea are observations by Hughes et al⁵⁴, who examined housing quality and home ownership as independent factors in asthma morbidity in a secondary analysis of data from the 2011 American Housing Survey of 33,201 households with children age 6-17 years. They reported that poor housing quality increased risk for asthma diagnosis (OR=1.45), ED visits for asthma (ED=1.59) and home ownership decreased risk for asthma-related ED visits (OR=0.62).

There are additional indications that stress modifies response to environmental pollutants as well. Shankardass et al⁵⁵, examined incidence of asthma over 3 years (using doctor-diagnosed asthma as the endpoint) in a group of 2,497 children aged 5-9 with asthma at time of enrollment into the Children's Health Study in 2002-2003. They examined the relationship between traffic related particulate exposure, maternal smoking during pregnancy, socioeconomic status (using parental education level as a proxy) and parental stress. Particulate exposure increased asthma risk 1.51-fold in the context of high parental stress vs. only 1.05-fold in low stress families,

Similar observations were made regarding the impact of maternal smoking on asthma. SES was also a notable modifier of particulate and *in utero* tobacco exposure on asthma development. This group reported similar impact of stress on the effect of traffic related pollution (oxides of nitrogen) on lung function in children. In New York, Lee et al,⁵⁶ observed that increased prenatal PM_{2.5} exposure was associated with increased risk of asthma in boys, but not girls, born to women with high levels of stress. Bose et al from this same group found that prenatal exposure to ambient air nitrites (derived from oxides of nitrogen produced by both stationary and mobile pollution sources) also impacted asthma development in boys, but not girls, both to mothers experiencing high stress⁵⁷.

There are additional data supporting the biological plausibility of the effect of stress on asthma and allergy. In studies of lower income mothers, cord blood mononuclear cells were recovered and stimulated with innate or adaptive immune stimuli. In women with higher stress levels, tetanus, dust mite, and cockroach stimuli which activate adaptive immune processes resulted in increased IL-13 responses, which would be expected to promote asthma and atopy⁵⁸. There are also both animal and some emerging human data to suggest that corticosteroid response and methylation of the corticosteroid receptor may be induced by prenatal and early life stress. Brehm et al⁵⁹, reported that stress is associated with a 10.2% reduction in bronchodilator response in a study of 234 Puerto Rican children (age 9-14) with asthma. This reduced response was associated with a polymorphism in ADCYAP1R1, which reduces expression the beta-2 adrenergic receptor. With a growing appreciation that stress impacts cytokines, HPA axis biology and beta-adrenergic response, stress, SES, domestic and neighborhood violence and housing stock should all be considered part of the “envirome”.

CONCLUSIONS:

The major reason for examining the role of the envirome in development and expression of allergic disease is to identify actions at the medical and public health level that can prevent and mitigate many of these impacts. One general observation is that perinatal and early life exposure to pollutants, various infections and microbial populations, and stressors have a disproportionate impact on development of allergic disease when compared to such stressors later in life. This suggests that early life represents an important immune developmental period, in which specific environmental exposure may have lifelong impact in an individual.

Collaboration between allergy/immunology clinicians and those who provide pregnancy care (obstetricians and family medicine practitioners), may provide robust opportunities to impact allergic disease. Additionally, intervention to modify early life postnatal exposures represents another important opportunity for primary prevention of allergic disease. While avoidance of pollutants (tobacco or ambient air) is appropriate general advice, it is especially important in the perinatal period. Indoor biomass burning can be avoided, and if possible, living away from PM sources (roadways, point sources) may reduce risk for asthma. Microbial exposures clearly impact asthma and allergy, and numerous studies already suggest intriguing intervention studies. However, it is likely too soon to make specific recommendations on microbial exposures in the clinic. That said, appropriate use of antibiotics will certainly be an essential element of maintaining a healthy microbiome.

On a public health level, there is good evidence that environmental stewardship can have significant impact on asthma and allergy outcomes. This is perhaps best shown in Southern California, in which gradual improvement of air quality since 1995 has been very clearly associated with improved lung function⁶⁰ and fewer asthma and bronchitis events⁶¹. Likewise, efforts to reduce automobile exhaust are associate with decreased asthma in Japan as well⁶². Extending environmental stewardship to overall climate, it is expected that climate change resulting in increases in global temperatures will cause increases in ambient air pollutants and

allergen levels⁶³. It also seems likely that public policy focused on safe housing stock would have substantial impact on allergic disease. Thus, public health policy actions focused on environmental factors certainly result in reduction of asthma.

In addition to the items discussed in this review, there are a number of environmental factors which also impact development of asthma and atopy. Nutritional factors may influence atopy development as well. For example, the role of Vitamin D in modulation asthma has been an area of intense investigation in recent years. As noted in a recent meta-analysis, supplementation with vitamin D is associated with decreased need for corticosteroids for acute asthma⁶⁴. While nutritional factors are beyond the scope of this review, this is clearly an evolving area of interest for our specialty.

Our understanding of the impact of environmental determinants of allergic disease will clearly evolve over time. Our understanding of the role of specific environmental exposures will also certainly lead to use of specific microbiotic (probiotic) treatments for allergy prevention. Further, our understanding of the role of specific genetic factors which increase risk for atopy due to environmental factors will eventually allow for more precise identification of individuals who will benefit from primary prevention approaches. Overall, practitioners in our specialty are in a unique position to impact patient care and inform policymakers on public health and medical practice policies that can remarkably reduce allergic disease risk⁶⁵.

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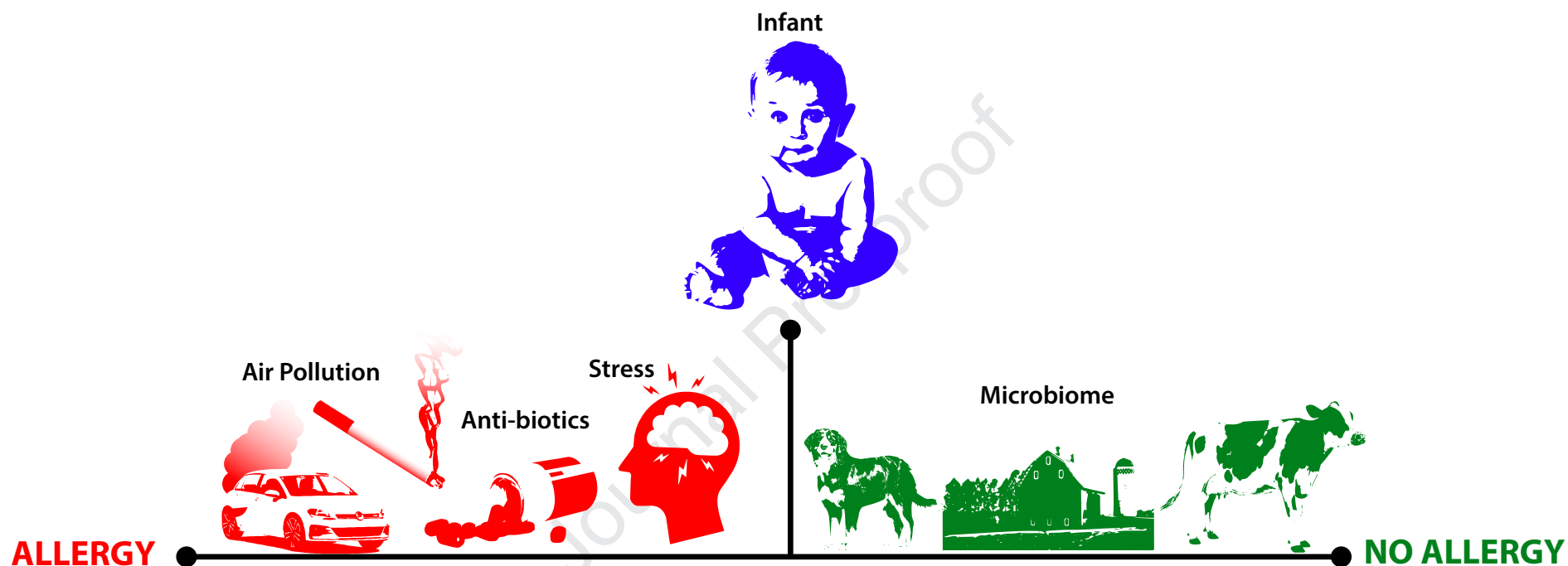
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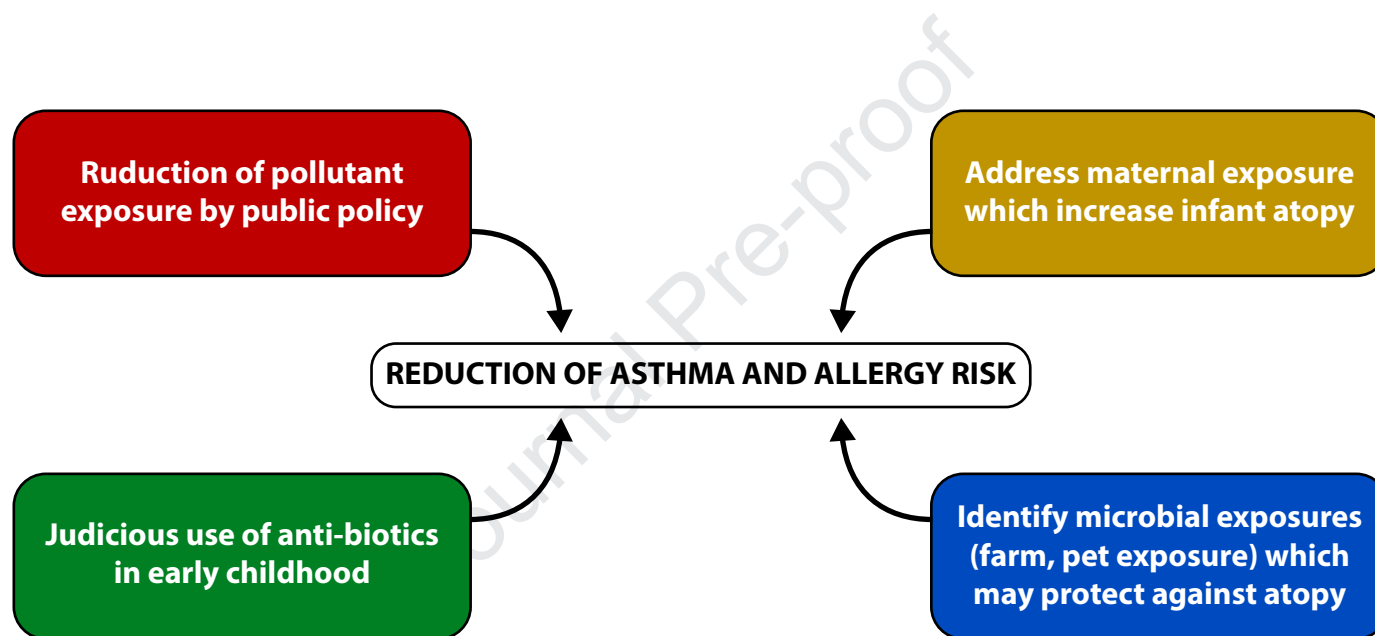
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Figure Legends:

Figure 1: Schematic diagram of the impact of specific environmental factors in the perinatal period on atopy risk.

Figure 2: Actions not focused on allergens that can be undertaken by allergy/immunology practitioners to reduce environmental risks for atopy. Actions may include individual and organizational advocacy efforts for policy change, working with other practitioners to reduce maternal exposure risk factors (pollutants, stress, smoking), judicious use of antibiotics and as new data evolves suggesting beneficial environmental exposures.





CME Material

Learning Objectives:

- Describe the impact of bacterial exposures in infancy in allergic disease.
- Describe the effect of air pollutants and psychosocial stress on development of allergic disease

Q1. Which of the following is true about microbial exposure infancy on asthma risk?

- A. Increased antibiotic use is associated with decreased risk for asthma
- B. Streptococcus colonization of the nasopharynx is associated with decreased risk for asthma
- C. Moraxella colonization of the nasopharynx is associated with increased risk for asthma
- D. Staphylococcal colonization for the nasopharynx is associated with increased risk for asthma
- E. Corynebacterium colonization for the nasopharynx is associated with increased risk for asthma

Q1 ANS: C. Moraxella colonization of the nasopharynx is associated with increased risk for asthma

Rationale:

Antibiotic use is associated with increased risk for asthma. Colonization with Streptococcus, Moraxella, and H. Influenza are all associated with increased asthma risk. Corynebacterium colonization was protective against asthma development

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1. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med.* 2007;357(15):1487-95. Epub 2007/10/12. doi: 10.1056/NEJMoa052632. PubMed PMID: 17928596.
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Q2. Which of the following air pollutants has been shown to promote IgE response to a neoantigen in humans?

- A. Ozone

- B. Endotoxin
- C. Sulfur Dioxide
- D. Environmental Tobacco Smoke
- E. Diesel exhaust particles

Q2 ANS: E. Diesel exhaust particles

Rationale:

Ozone, endotoxin, sulfur dioxide, environmental tobacco smoke and diesel exhaust particle have all been shown to augment response to allergens in sensitized persons. Only diesel exhaust particles has been shown to augment IgE response to a neoantigen.

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2. Eldridge MW, Peden DB. Allergen provocation augments endotoxin-induced nasal inflammation in subjects with atopic asthma. J Allergy Clin Immunol. 2000;105(3):475-81.
3. Diaz-Sanchez D, Rumold R, Gong H, Jr. Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings. J Allergy Clin Immunol. 2006;118(2):441-6.

Q3: Which of the following is statements is correct regarding reported aspects of the effect of endotoxin in asthma?

- A. Increased levels of endotoxin in house dust are have been reported to be associated with increased wheeze in children
- B. Acute endotoxin inhalation decreases response to inhaled allergen
- C. Endotoxin exposure is associated with increased incidence of atopy in children
- D. Persons with the CC genotype for C-T -159 polymorphism for CD14 have decreased IgE response relative to those with the TT genotype.
- E. Higher levels of income were associated with increased levels of domestic endotoxin

Q3 ANS: D

Rationale: Thorne and Zeldin have reported in studies from nationwide surveys of indoor endotoxin that wheeze and asthma symptoms are increased with increased exposure. Endotoxin challenge has been reported to increase response to allergen in adults, while environmental endotoxin (especially in farm settings) is associated with lowewr risk for atopy in children. Persons with the CC genotype for C-T -159 polymorphism for CD14 have decreased expression of CD14 (a co-receptor for endotoxin) and increased IgE response relative to those with the TT genotype. Poverty, not increased income, correlates with increased endotoxin levels in homes.

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Q4: Which of the following has been reported regarding the effect of azithromycin use in airway disease?

- A. Azithromycin when given early for 5 days for a respiratory tract infection in younger children had little effect on risk of developing a LRTI
- B. Azithromycin use does not reduce asthma like symptoms in 1-3 year olds
- C. In the AMAZES study, 48 weeks of azithromycin use in adults with severe asthma yielded significant improvements in a number of asthma outcomes vs. placebo
- D. Sputum recovered from 61 adults with severe asthma treated with azithromycin in the AMAZES study revealed decreased overall bacterial load
- E. Sputum recovered from 61 adults with severe asthma treated with azithromycin in the AMAZES study revealed no change in bacterial resistance gene expression.

Q4 ANS: C

Rationale: Young children treated early for respiratory tract infection had lower occurrence of LRTI and acute asthma. In the AMAZES study, there was significant improvement in asthma. Overall bacterial load in samples from these volunteers was not changed, though there was evidence of increased expression of antimicrobial resistance genes.

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Q5: Which of the following factors has been reported in studies of stress on asthma risk or outcomes?

- A. Stress has been associated with increased airway response to beta adrenergic agonists
- B. Peripheral blood mononuclear cells recovered from women who are stressed have similar levels of IL-13 secretion following biological stimuli as those who are not stressed
- C. Home ownership was associated with increased risk for acute asthma
- D. Neighborhood violence is associated with increased asthma risk
- E. High parental stress was not found to increase PM2.5 induced asthma events

Q5 ANS: D

Rationale: Stress has been associated with decreased response to beta adrenergic agonists. It has also been reported that there is increased IL-13 production by peripheral blood mononuclear cells recovered from women under stress, increased asthma risk for children exposed to neighborhood violence and increased asthma events related response to PM2.5 exposure in stressed children. Home ownership is associated with decreased asthma risk.

1. Rosa MJ, Lee AG, Wright RJ. Evidence establishing a link between prenatal and early-life stress and asthma development. *Curr Opin Allergy Clin Immunol*. 2018;18(2):148-58. Epub 2018/01/26. doi: 10.1097/aci.0000000000000421. PubMed PMID: 29369067; PMCID: PMC5835351.
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