

Exposure to Endotoxin in Household Dust To Wheeze or Not to Wheeze

Endotoxin is the term used for lipopolysaccharides, large molecules consisting of a lipid and a polysaccharide composed of O-antigen found in the outer membrane of Gram-negative bacteria. Humans have evolved to have strong, programmed, innate immune responses to endotoxin. Endotoxin recognition and signal amplification occur through a series of endotoxin-protein and protein-protein interactions, leading to activation of Toll-like receptor-4, with resulting inflammation (1). Because of this inflammatory response, considerable research has addressed whether inhalational exposure to this agent contributes to the burden of asthma. Although there is a reasonable body of epidemiological evidence that endotoxin exposure increases the risk of wheeze, it is less clear that it increases the risk for asthma (2). The timing of exposure during critical windows of development may be one reason why conflicting results have been reported. Endotoxin exposure in early life (e.g., as an infant living with a dog or cat) appears to be protective against developing childhood asthma (3). Later in childhood, although endotoxin exposure has been shown to be protective in some studies (4), it also appears to be associated with increased risk for wheeze and greater asthma severity, except for those who live on a farm, where it continues to be protective (5–7). The effect of domestic endotoxin exposure on adults is less well characterized than in children, and the potential mediating effect of allergic sensitization is also unclear. Thus, further research on the effect of endotoxin on asthma onset and exacerbation is needed.

In this issue of the *Journal*, Thorne and colleagues (pp. 1287–1297) report the results of the largest study of the relationship between domestic endotoxin exposure and asthma outcomes to date in children and adults (8). These investigators used data from almost 7,000 participants in the 2005–2006 round of the National Health and Nutritional Examination Survey (NHANES), a study designed to be representative of the general US population, but also to allow analyses of susceptible subgroups, that included measurements of endotoxin and allergen levels in dust from participant homes, as well as specific IgE to a battery of common allergens. They hypothesized that the relationship between the endotoxin concentration in house dust and prevalence of asthma or wheeze could be modified by both sociodemographic factors and sensitization to specific allergens.

Although endotoxin levels were associated with all asthma-related outcomes studied, only current wheezing, exercise-induced wheeze, and use of prescription medication for wheezing were significantly associated with elevated endotoxin concentrations in house dust. Somewhat surprisingly, given a previous report from this research group (9), asthma was not significantly associated with endotoxin levels in house dust. In a logistic regression analysis, a 10-fold increase in endotoxin concentration was associated with the wheeze-related outcomes listed above plus a visit to a doctor

or emergency department for wheeze, all in the past 12 months. These results remained essentially unchanged after adjusting for age, sex, race/ethnicity, and income-to-poverty ratio. Stratification by allergy status showed that these relationships were not dependent upon sensitization status but were enhanced among those living in poverty. In effect modification testing, endotoxin was strongly positively associated with asthma at low levels of specific IgE against dog, mouse, and rat, but negatively at high levels of IgE against mouse and rat.

The relationships of endotoxin with wheeze did not exhibit a threshold effect, but showed a positive exposure-response association over the range of values measured. In addition, with generalized additive modeling, the investigators demonstrated a positive exposure-response relationship between log-transformed endotoxin concentration and asthma diagnosis, current asthma, and wheeze in the past 12 months. The geometric mean of the endotoxin concentrations in the NHANES dust samples, ~15 endotoxin units/mg, is lower than most previously reported studies (5, 10), which probably reflects the large sample size distributed throughout the United States, including regions of the country that likely have lower levels in homes (e.g., Northern states). Endotoxin assay quality control data demonstrated a high degree of reliability from assay to assay, with blind endotoxin repeat samples having an r^2 of 0.93. Significant predictors of higher endotoxin exposures were lower family income, Hispanic ethnicity, younger age, an older home, and the presence of dogs, cats, cockroaches, smokers, and a carpeted floor in the home.

Despite its large sample size, which was representative of the U.S. general population and its careful endotoxin assay methods, this study does have some limitations. The most important is the cross-sectional study design, which does not allow causal inference. Given the uncertainty regarding the role of endotoxin in the development of asthma, especially in adults, a properly designed prospective study would be a major contribution. Asthma and wheeze outcomes were also self-reported, leading to probable measurement error. Recurrent wheeze appeared to be a more sensitive outcome measure than asthma. As the authors suggest, participants reactive to endotoxin exposures in the absence of an allergy phenotype may not have been diagnosed with asthma. Another limitation is the lack of genetic data. Key molecules for the endotoxin recognition pathway include lipopolysaccharide-binding protein, CD14, and MD-2 (1). A number of polymorphisms have been identified that affect expression of molecules involved in endotoxin signaling pathways, which may play a role in responsiveness to endotoxin (11). It is unfortunate, given the comprehensive nature of the endotoxin exposure data in this round of the NHANES, that the opportunity to study gene-environment interactions was missed.

In conclusion, endotoxin levels in house dust from beds and bedroom floors were lower than those reported in previous studies

of the U.S. population, farmhouses, and inner city homes. Despite these lower levels, endotoxin in dust samples was associated with active wheezing requiring medication and healthcare use. Sensitization status did not appear to play a major role. Because poverty, younger age, carpeting, pets, cockroaches, or a smoker in the household predicted higher endotoxin levels, strategies to reduce exposure could be devised. The crux of a preventive strategy would need to involve societal efforts to reduce poverty and improve the quality of education and housing for the lower-income strata in the United States. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

John R. Balmes, M.D.
Department of Medicine
University of California, San Francisco
San Francisco, California
and

School of Public Health
University of California
Berkeley, California

References

1. Doreswamy V, Peden DB. Modulation of asthma by endotoxin. *Clin Exp Allergy* 2011;41:9–19.
2. Rennie DC, Lawson JA, Senthilselvan A, Willson PJ, Dosman JA. Domestic endotoxin exposure and asthma in children: epidemiological studies. *Front Biosci (Elite Ed)* 2012;4:56–73.
3. Campo P, Kalra HK, Levin L, Reponen T, Olds R, Lummus ZL, Cho SH, Khurana Hershey GK, Lockett J, Villareal M, et al. Influence of dog ownership and high endotoxin on wheezing and atopy during infancy. *J Allergy Clin Immunol* 2006;118:1271–1278.
4. Gehring U, Strikwold M, Schram-Bijkerk D, Weinmayr G, Genuneit J, Nagel G, Wickens K, Siebers R, Crane J, Doekes G, et al.; ISAAC Phase Two Study Group. Asthma and allergic symptoms in relation to house dust endotoxin: phase two of the International Study on Asthma and Allergies in Childhood (ISAAC II). *Clin Exp Allergy* 2008;38:1911–1920.
5. Perzanowski MS, Miller RL, Thorne PS, Barr RG, Divjan A, Sheares BJ, Garfinkel RS, Perera FP, Goldstein IF, Chew GL. Endotoxin in inner-city homes: associations with wheeze and eczema in early childhood. *J Allergy Clin Immunol* 2006;117:1082–1089.
6. Celedón JC, Milton DK, Ramsey CD, Litonjua AA, Ryan L, Platts-Mills TA, Gold DR. Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. *J Allergy Clin Immunol* 2007;120:144–149.
7. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D, Gerlach F, Bufe A, et al.; Allergy and Endotoxin Study Team. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–877.
8. Thorne PS, Mendy A, Metwali N, Salo P, Co C, Jaramillo R, Rose KM, Zeldin DC. Endotoxin exposure: predictors and prevalence of associated asthma outcomes in the United States. *Am J Respir Crit Care Med* 2015;192:1287–1297.
9. Thorne PS, Kulhánková K, Yin M, Cohn R, Arbes SJ Jr, Zeldin DC. Endotoxin exposure is a risk factor for asthma: the national survey of endotoxin in United States housing. *Am J Respir Crit Care Med* 2005;172:1371–1377.
10. Thorne PS, Cohn RD, Mav D, Arbes SJ Jr, Zeldin DC. Predictors of endotoxin levels in U.S. housing. *Environ Health Perspect* 2009;117:763–771.
11. Lau MY, Dharmage SC, Burgess JA, Lowe AJ, Lodge CJ, Campbell B, Matheson MC. CD14 polymorphisms, microbial exposure and allergic diseases: a systematic review of gene-environment interactions. *Allergy* 2014;69:1440–1453.

Copyright © 2015 by the American Thoracic Society

Continuous β -Lactam Infusion to Optimize Antibiotic Use for Severe Sepsis A Knife Cutting Water?

It is well known that the survival of patients with severe sepsis or septic shock depends on early initiation of effective antimicrobial treatment; that is, the etiologic microbe is sensitive to the therapeutic agent, and the dose is optimal, as are the administration route and infusion duration (1, 2). However, optimal dose and administration modalities for a given broad-spectrum β -lactam depend on several factors, including the infection-causing pathogen, the host, and the antibiotic itself, and thus are not easily determined. Although originally highly successful, β -lactams are now becoming increasingly limited in terms of efficacy and risk of failures (3, 4), not only because of the emergence of very high-level resistant microorganisms (against which the antibiotic is completely ineffective) but also because of moderately but significantly decreased bacterial susceptibility (low-level resistance) that sharply reduces the antibiotics' efficacy margin. In that setting, even when the antibiotic is still active against the pathogen, killing it often requires reaching a very high concentration at the infection site that is close to the breakpoint (i.e., the antibiotic

concentration that separates susceptible from resistant strains, with respective likelihood of therapeutic success or failure).

For time-dependent antibiotics, such as β -lactams and carbapenems, pharmacokinetic–pharmacodynamic (PK–PD) studies have consistently shown that maximum killing occurs at concentrations three to four times the antibiotic's minimum inhibitory concentration (MIC) against the microorganism, with higher concentrations offering little additional bactericidal benefit (5). Therefore, the time during which the free-drug concentration (unbound fraction) exceeds the MIC is the dominant PK–PD index associated with bacterial killing ($fT > MIC$) (6, 7). However, the exact PK–PD target that must be reached remains speculative and requires additional studies for validation. Although most experts target a free-antibiotic concentration above the MIC throughout 100% of the dosing interval (100% $fT > MIC$), some require up to 100% $fT > 4 \times MIC$, whereas others target only 70% $fT > MIC$, arguing that more prolonged exposure might not be necessary.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.