

Artemisia species pollen (mugwort) as a major vector for ambient LPS: Brothers in harm?



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LPS, also known as endotoxin, from gram-negative bacteria is well described as causing immune-mediated inflammation related to clinical conditions, such as asthma, on inhalation. However, the vast majority of research on LPS has been either experimental or as observed in the indoor environment. Therefore the article by Oteros et al¹ in this issue of the *Journal* is an advance in that it focused on the outdoor setting and, importantly (because outdoor characterization of LPS itself is rare but not novel), asks whether LPS levels are associated with a specific ambient allergen and furthermore with particular microbial species.

How did the authors do this, and what exactly did they find? Focusing on airborne LPS in the Munich and Davos areas, the authors collected daily LPS and pollen data over the course of 4 years and identified *Artemisia* species pollen (mugwort) as a major vector for ambient LPS. In fact, 70% of airborne endotoxin was dispersed with only *Artemisia* species pollen. Furthermore, through biochemical and next-generation sequencing, they identified specific bacteria (*Pseudomonas* and *Pantoea* species) as primary sources of LPS. Furthermore, in an attempt to show clinical relevance, they deepened the discovery by using an asthma mouse model to show that the effect of *Artemisia* species pollen on asthma was dependent on coexposure to LPS. They also demonstrated that endotoxin was not a simple surrogate for pollution levels, although this was demonstrated only indirectly (eg, by noting that levels of particulate matter [sized at $\leq 10 \mu\text{m}$] and endotoxin were not correlated).

Even recognizing that the claim of *Artemisia* species as the vector for LPS is based on a model that is subject to interpretation, the suggestion that it is LPS specifically rather than broader elements of air pollution is important given the well-described synergy between allergens and air pollution demonstrated to have low LPS content in driving a spectrum of inflammatory phenomena.² Accordingly, the authors are commended for the significant effort necessary to connect the dots between LPS and *Artemisia* species in such a creative manner with attention

to detail and rigor, illuminating allergy-relevant immunology through this unique perspective.

Still, there are a number of caveats and limitations of which the reader should be aware. First, in terms of clinical relevance, it is important to recognize (as these authors did) that the direct link to asthma was made in a mouse model with all its inherent pitfalls, such that adverse effects of *Artemisia* species–LPS coexposure remain to be elucidated in the human subject. Even in the mouse model, the authors were unable to test for *Artemisia* species-specific IgE, although their documentation of *Artemisia* species-specific IgG₁ clearly demonstrates an immunologic effect. Apparently, no commercial test for mouse specific IgE against *Artemisia* species is available, and alternative attempts to measure specific IgE by using a standard ELISA and trying to optimize ImmunoCAP ISAC with a mouse-specific anti-IgE antibody for detection were unsuccessful because of poor sensitivity for mouse samples (personal communication from the authors). Also, it is difficult to be certain that microbial growth did not occur after sampling (eg, in the storage phase of the study, where samples were at 4°C) because the precise effects of specific storage conditions on low-level but potentially active microbiome is poorly understood. Finally, it is difficult to know how specific the mouse-derived results are to *Artemisia* species because other pollens or other triggers, such as house dust mite, are known adjuvants to LPS.^{3,4}

Ultimately, where does this leave us, and where might future work proceed? Although likely premature to conclude, one wonders whether these results could lead to increased focus on control of mugwort as a priority for environmental remediation. *Artemisia* species reportedly comprise the most common airborne allergen in some countries, including China.⁵ There is also a suggestion of *Artemisia* species' potency in terms of "allergenic power," which can be derived by dividing the exposure to *Artemisia* species pollen by the percentage of sensitization to *Artemisia* species in the population of a given geographic area (personal communication from the authors, data not shown). Given Davos' reputation as a therapeutic environment, one wonders whether low LPS levels and possibly allergen in that region could be partly responsible for its salutary effect. Surely this is highly speculative, and although this study's narrow geographic focus produced attendant and advantageous high-resolution data, it can also be seen as a limitation because it is not certain that these results would be replicated in other settings with differing humidity, for example. Furthermore, although these insights into the outdoor environment are welcome (because, as noted earlier, LPS is most often studied indoors), it remains true that many or even most global citizens now (and increasingly frequently) spend the majority of their time indoors; this is true even in countries like China, which was formerly more rural,⁶ and it is not clear how much *Artemisia* species pollen typically penetrates indoors. Regardless, the results do prompt the question of whether such features of outdoor air can significantly affect allergic disease at the clinical level, and only future innovative research efforts will likely be able to shed light on that.

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In summary, Oteros et al¹ have used a novel study design combining ambient air sampling and a murine experiment to link airborne endotoxin to *Artemisia* species pollen and to show that these exposures together enhance allergic sensitization in mice. If indeed endotoxin in particular (rather than other factors associated with the endotoxin-producing gram-negative bacteria) is driving similar immune phenomena in human subjects, this paves the way for intervention trials either at the community or individual levels.

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