Published in final edited form as:

J Allergy Clin Immunol Pract. 2019 February ; 7(2): 616–617. doi:10.1016/j.jaip.2018.10.003.

Growing concerns with *Staphylococcus aureus* and asthma: new territory for an old foe?

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Staphylococcus aureus is a common bacterium that colonizes the upper airway, primarily the nares. While this opportunistic pathogen is best known for its role in skin and soft-tissue infections, it is of increasing interest as a potential driver of respiratory disease. In this issue of *JACI In Practice*, Kim *et al.* offer a timely systematic review and meta-analysis of a growing body of epidemiologic studies that assess linkages between *S. aureus* nasal carriage in adults and asthma prevalence with consideration of the presence of chronic rhinosinusitis (CRS).⁽¹⁾ The authors identified that nasal *S. aureus* carriage was positively associated with asthma prevalence in meta-analysis of five cross-sectional studies (Odds Ratio (OR) 1.19, 95% Confidence Interval (CI): 1.06, 1.34) in the general adult population, and it also was positively associated with asthma in meta-analysis of 11 studies of CRS patients (OR 1.86, 95% CI: 1.18, 2.95); however, the CRS studies had substantial statistical heterogeneity and higher potential for publication bias, and therefore reporting an overall estimate may not be appropriate. Methodologic heterogeneity among the studies of CRS patients was reflected in variable sample sizes, specimens studied (surgical tissue, swab samples), and study populations.⁽¹⁾ Despite this, the authors did identify much stronger associations with asthma prevalence for *S. aureus* recovery from surgical tissue specimens from CRS patients (OR 40.4, 95% CI: 10.5, 155) than for *S. aureus* recovery from swab samples (OR 1.21, 95% CI 0.99, 1.48).⁽¹⁾ While this could be attributable to bias given the relatively smaller sample sizes for studies of surgical patients, it is also possible that incorporation of *S. aureus* into nasal tissue could be a mechanism by which exposure contributes to disease, as some have suggested.⁽²⁾

The current work builds on two systematic reviews and meta-analyses of associations between *S. aureus*-related exposures and asthma; these studies included both adults and children, assessed host serum response to staphylococcal enterotoxins (via SE-IgE) as the marker of exposure with or without adjustment for atopic status, and identified overall strong positive associations between SE-IgE and asthma on meta-analyses.^(3, 4) SEs are bacterial proteins produced by *S. aureus* and related bacteria that may be present on or in nasal tissue,

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Conflict of Interest: Nothing to declare.

contributing to Th2-biased immune responses, including the production of IL-5.⁽⁵⁾ Not all *S. aureus* strains will harbor SEs,⁽⁶⁾ and a limitation of the literature reviewed by Kim *et al.* is that detection of SEs typically was not performed for cultured *S. aureus* isolates. If SEs are responsible for initiation of inflammatory pathways that drive asthma (with or without a role for other intrinsic or secreted components of *S. aureus*), then misclassification bias could contribute to the weaker associations noted in the reviewed literature since some *S. aureus* nasal carriage would be expected to be SE negative. Further, SE-IgE is a product of an atopic host immune response, and little is known regarding the relationship between *S. aureus* exposure and asthma according to atopic status. It is not yet clear whether host responsiveness (sensitization measured via SE-IgE production) is necessary for disease pathogenesis given exposure to SE proteins, and most studies typically measure either nasal *S. aureus* carriage or SE-IgE production as the marker of exposure—not both.

The growing coherence in the literature of an association between *S. aureus* and asthma is tempered by substantial concerns for reverse causation, and (regardless of whether SEs are or are not involved in a mechanism of association) this limits immediate clinical utility of the findings. In the cross-sectional studies included by Kim *et al.*, it is possible that adults with asthma, including those with worse disease, have higher contact with healthcare settings. Healthcare contact is a known risk factor for acquisition of *S. aureus*, and so *S. aureus* nasal carriage could result from healthcare exposures related to asthma rather than drive the disease. While the authors appropriately note that four studies identified no independent associations between healthcare contact and *S. aureus*,^(7–10) and that we ourselves adjusted for hospital visits in the study we conducted using U.S. population data from NHANES,⁽¹⁰⁾ longitudinal studies will be needed to advance evidence for *S. aureus* to play a causal role in the development of asthma. It is possible that *S. aureus* colonization may not be on the causal pathway but instead be associated with atopy, which is a known risk factor for asthma. In addition, given that *S. aureus* is known to be associated with exacerbations of eczema, it will be important to determine whether the bacterium worsens disease among those with existing asthma. Regardless, concurrent assessment of the atopic status of the host is critical to unpack the interplay between exposure, host sensitization, and respiratory outcomes.

The literature provides evidence of a modest association between *S. aureus* nasal carriage and asthma prevalence. If more targeted, longitudinal studies support a potential causal relationship between *S. aureus* and asthma development or morbidity, then this raises the question of whether such exposures could be prevented or reduced, starting with randomized controlled trials. Whether decolonization can and should be attempted to intervene on *S. aureus* nasal carriage is controversial, even for infection outcomes where the causal relationship between nasal colonization and subsequent infection is more established. First, *S. aureus* may occupy multiple host niches: nares, pharynx, and moist skin sites. Typical decolonization protocols include use of nasal mupirocin ointment to target nasal colonization and chlorhexidine or bleach-based body washes to reduce skin carriage; while pharyngeal carriage is more rare, it may be associated with failure to decolonize.⁽¹¹⁾ Second, increased uses of decolonization drugs may contribute to antimicrobial resistance and limit the utility of the drugs in the long-term. Therefore, any intervention studies that are attempted should assess both the effectiveness of any decolonization protocol to improve

outcomes as well as assess selection for drug-resistant strains of *S. aureus* through treatment. Household members may serve as reservoirs to recolonize patients following decolonization.⁽¹²⁾ In addition, growing evidence, including our own work, suggests that *S. aureus* strains persist on environmental surfaces, including in the home,⁽¹³⁾ and that exposure to environmental staphylococcal enterotoxins may be associated with asthma morbidity.⁽¹⁴⁾ No current standard protocols exist for household decontamination for *S. aureus* outcomes related to infection, and it is not yet clear if environmental control protocols that target allergen reduction hold promise to reduce microbial exposures. Further, the interplay between host colonization and environmental contamination is dynamic: people with asthma may shed *S. aureus* into the home environment, and they also may pick up *S. aureus* from the home environment, including after decolonization or other treatment.^(13, 15) Finally, any decolonization protocol to eradicate *S. aureus* carriage could have impacts on the nasal microbiome, which is suspected to contribute to respiratory outcomes; attention should be paid to both the benefits and unintended consequences of decolonization protocols.

The Kim *et al.* review and meta-analysis draws attention to the potential role of *S. aureus*, which is one of a growing number of pathogens associated with respiratory outcomes. It also helps clarify research steps needed to advance the literature. For *S. aureus* carriage among CRS patients, larger, well-designed studies are necessary to address concerns with the heterogeneity of the current literature. For *S. aureus* in the general adult population, targeted longitudinal studies are needed to provide evidence for a casual role of *S. aureus* in asthma development and exacerbation. Given how common exposures to *S. aureus* are, even a modest association could be expected to contribute to a population burden of disease, and therefore better understanding of the role of this bacterium in respiratory disease has important implications for both research and practice.

Sources of Funding:

Investigators were supported by NIH NIEHS (R01ES023447 to E.C.M. and P50ES018176 to M.C.M.); NIH NIAID (K24AI114769 to E.C.M.; R21AI133492 to M.F.D.); and NIH OD (K01OD019918 to M.F.D.).

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