Reconstructing Phenotypes in Recurrent Severe Wheeze in Young Children

Recurrent wheeze in preschool children is troublesome for patients and providers alike. Almost half of young children wheeze by age 6 years (1) and preschool children have the highest rate of emergency department visits for asthma symptoms (2). Clinicians are often challenged to make a diagnosis, choose therapy, and discuss prognosis with families amid great heterogeneity of recurrent wheeze. Several clinical categorizations, including episodic viral wheeze (EVW) and multitrigger wheeze (MTW) (3), that reflect some combination of pattern of wheeze and similarity to childhood asthma have been used to help clinical decision-making, but fall short of truly capturing the heterogeneity of the condition (4). Fortunately, most young children with recurrent wheeze improve over time (1) or respond well to available asthma therapies (5, 6).

One of the fundamental limitations to advancing our understanding of preschool wheeze is the limited access to airway samples and functional assessments of underlying lung pathophysiology in the context of the symptoms and inflammatory phenotype. Children in this age group are frequently unable to produce high-quality pulmonary function tests, and there is a high threshold for subjecting a young child to the risk of anesthesia and bronchoscopy until many medical interventions have been exhausted. Research bronchoscopy in children is unethical.

In this issue of the *Journal*, Robinson and colleagues (pp. 523–535) aimed to identify the pathophysiologic underpinnings of severe respiratory disease in young children (7). They evaluated clinical symptoms, blood inflammatory markers, allergic sensitization, and BAL samples for cytology and microbes in 105 preschool children with recurrent severe wheeze (RSW) and 31 with nonwheeze respiratory disorders (NWRD) (i.e., recurrent croup, stridor, recurrent pneumonia) presenting for clinically indicated bronchoscopy. The authors examine the phenotypic and endotypic differences between the RSW and NWRD groups, then among the RSW group, based on the European Respiratory Society–endorsed wheezing phenotypes of EVW and MTW (3). Finally, an unbiased cluster analysis segregates a combination of eight clinicopathologic features and prescription of inhaled corticosteroid therapy to create four phenotypic clusters.

Surprisingly, there were no differences between neutrophils, eosinophils, or presence of bacteria in BAL samples between the RSW and NWRD groups; only blood eosinophil count was higher in the RSW group. Similarly, among children with RSW, there were no differences in lower airway pathology identified between those identified as EVW and MTW by medical record review. These data challenge the assumptions that clinical designations of wheezing phenotypes are related to distinct pathological entities (that necessitate different treatment approaches), at least in the most severe cases. Most wheezing participants were treated with inhaled corticosteroids at the time of bronchoscopy, so a treatment effect must be considered in the interpretation of the differential BAL findings, particularly in regard to airway eosinophils; nevertheless, the participants were clinically symptomatic despite this treatment.

The most innovative portion findings of this work are the use of BAL cytology, culture data (bacterial culture and viral PCR), along with clinical phenotyping (blood leukocyte counts, atopy, and inhaled corticosteroids [ICS] prescription) to inform the clusters. It is important to note that participants were clinically stable at the time of procedure, which suggests the findings are likely reflective of the underlying airway condition rather than an acute exacerbation.

The resulting four clusters were primarily differentiated by atopy, microbial presence, and treatment with inhaled steroids: *1*) atopic; *2*) nonatopic, low infection rate, high ICS; *3*) nonatopic, high infection rate; and *4*) nonatopic, low infection rate, no ICS. Notably, participants with RSW were equally distributed across the four clusters, and there was no difference in cluster membership between those with preclassified EVW and MTW. This finding suggests that the framework of differentiating MTW from EVW based on clinical observations lacks airway pathologic foundation, at least among children with severe recurrent wheeze, consistent with recent data that found inconsistency in these categorizations (4). Not surprisingly, those with nonwheezing respiratory disease predominately fell into the nonatopic, low infection rate, no ICS cluster—these are patients who didn't wheeze. The clusters remained unchanged when the control group was excluded from analysis, indicating that there was no dilutional effect of including nonwheezing children.

The high proportion of common respiratory pathogens detected during a period of stability is consistent with other preschool wheeze cohorts (8, 9) and may explain the successful antibiotic approach to exacerbation prevention (10, 11).

Although remarkable, the findings from this study must be viewed in context of the severely affected cohort of children available for inclusion. The authors acknowledge that few children with recurrent wheeze are referred for bronchoscopy, cautioning the generalizability of the findings to the broader population of preschool children with recurrent wheeze. As the majority of children with recurrent wheeze are reasonably managed with medical therapies (ICS, bronchodilators) or have spontaneous remission with age, the tertiary referral population may represent a clinically and pathologically unique subset of children with wheeze refractory to ICS.

The four distinct clusters identified in this cohort with equal RSW representation is provocative. The aggregation of distinct clinical and pathologic features with discriminatory variables of blood eosinophils,

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BAL neutrophils, allergic sensitization, and different bacterial detection may lay the foundation for therapeutic decisions for this difficult-to-manage population. Unbiased phenotype clustering has helped redefine the framework of severe asthma (12), although even "unbiased" approaches are constrained by the selection of variables (13). Acknowledging the difficulty in procuring airway samples in preschool children, validation of these findings in similar cohorts is needed. Although these clusters have face validity, baseline and predictive validity (i.e., association with important health outcomes), long-term prognosis, or differential treatment response in the clinical setting is needed. Longer-term follow-up of this unique cohort will be critical to answer many of these questions.

Fully understanding the mechanisms and optimal treatment approaches for preschool children with recurrent wheeze remains a significant research challenge. Robinson and colleagues begin to chart a different course highlighting the discordance between current clinical labels and airway pathology and identifying clusters of clinical–pathologic features that may lay the foundation for future prognostic studies and therapeutic trials in this heterogenous condition. ■

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Place Matters: Residential Racial Segregation and Chronic Obstructive Pulmonary Disease

The combination of the striking racial disparities in coronavirus disease (COVID-19) outcomes and the tragic series of the deaths of Black people caused by police violence during the pandemic has brought unprecedented attention to the structural racism that persists in the United States (1). Segregation by race and ethnicity is a prominent feature of American cities that has not diminished over time despite civil rights laws (2). Black-segregated neighborhoods have been disproportionately burdened by many adverse social, economic, and environmental factors. Historical "redlining" was a federally promoted program during the 1930s and 1940s that inflicted severe and permanent economic harm to communities of color by systematically denying residents home mortgage loans (3). This overtly racist policy deprived Black families of legacy wealth as home property has been the primary vehicle for accumulating such wealth and is one of the major reasons for the Black–White income gap in the United States (4). Despite enactment of legislation to prevent segregation-promoting real estate practices, many formerly redlined neighborhoods remain very segregated. These neighborhoods are more likely to be characterized by poverty, greater exposures to air pollution, less green space, less access to

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