

Asthma, Atopy, and Airway Inflammation What Does It Mean in Practice?

Pediatricians have long realized that “asthma” is not one disease but many. The classic phenotypes of transient (present, age 0–3 yr only), persistent (present, age 0–3 and 3–6 yr), and late-onset (not present, age 0–3 yr; present, age 6 yr) wheeze described in the Tucson study (1) have been very helpful in understanding disease patterns, although less useful to the practicing clinician, since by definition transient wheeze is diagnosed retrospectively, and indices that try prospectively to determine prognosis have reasonable negative predictive value, but only very poor positive predictive value (2–4). Recently, phenotyping of preschool wheeze has been refined by analyzing data collected more frequently than by the Tucson group, using sophisticated mathematical modeling (5). A different approach is to describe patterns and precipitants of symptoms: episodic (viral), present only in association with viral upper respiratory tract infection; and multitrigger, in which symptoms are present with and between viral infections.

Phenotyping older children with asthma also needs to progress. The simple division into “atopic” and “nonatopic” wheeze is easy to make, but can be deceptive. The tacit assumption is that atopic wheeze is synonymous with eosinophilic airway inflammation, but many atopic children wheeze only with viral colds, and the evidence for airway eosinophilia and a response to inhaled corticosteroids in this group is weak at best. Conversely, the nonatopic child may in fact subsequently become atopic. Furthermore, it is likely that, in the developing world, the nonatopic phenotype may be very different from that seen in the developed world. Recent data suggest that, in the developing world, nonatopic asthma may be the commonest phenotype, associated with early viral bronchiolitis and poverty (6). These data challenge the assumption that phenotypes should be allowed uncritically to cross geopolitical boundaries.

Adult studies have shown no significant differences in the airway pathology of extrinsic and intrinsic (or better, atopic and nonatopic) asthma (7). In this issue of the *Journal* (pp. 476–482), Turato and colleagues have extended these studies into atopic and nonatopic children with asthma, using endobronchial biopsy to study airway pathology (8), and showed no structural or functional differences between atopic and nonatopic multitrigger wheezers. As with all pediatric bronchoscopy studies, they were unable to study a truly healthy control group of children, and this may have influenced comparisons. However, it is likely that the absence of ideal control subjects would obscure differences between control subjects and subjects with asthma, rather than lead to reporting of differences that do not exist.

The interpretation of these data needs careful thought. There is a real danger that the superficial reader will conclude that, after all, all wheeze is the same, all wheeze is associated with airway eosinophilia, and, by implication, all wheeze is a symptom of airway steroid deficiency. What in fact do these data actually *mean*?

It is important to be clear that the group studied by Turato and colleagues falls symptomatically into the multitrigger phenotype; they have not studied any children with episodic (viral) wheeze, and are careful not to claim that the pathology is the same (8). Indeed, the evidence for the eosinophil having a

role in episodic (viral) wheeze is scant; this is a neutrophil-predominant disease (9).

The findings showing similar airway pathology in both atopic and nonatopic children with a similar pattern of wheeze should also be interpreted bearing in mind that the median age of all children was 5 years, so at least half of each group were too young to have a confirmed diagnosis of asthma, and to have completely manifested atopy. Only time will tell whether some children currently in the nonatopic group will subsequently become atopic, although the older the child, the less likely is this switch to happen. Finally, there are no data on treatment response; although the implication is that atopic and nonatopic multitrigger wheeze will respond equally well to inhaled corticosteroids, this awaits further studies.

Ultimately, we need to deliver better treatment to the child with wheezing. So we surely need to move from understanding of asthma phenotypes to the study of biomarkers (another trendy concept) predictive of treatment response. Turato and coworkers have shown that atopy in the setting of multitrigger wheeze is not a marker of a particular airway pathology and, by implication, of response to treatment (8). In an adult setting, eosinophilic airway disease has been described both in asthma and chronic obstructive pulmonary disease (COPD) (10), and the suggestion has been made that a better discrimination should be between eosinophilic versus noneosinophilic airway disease, rather than asthma and COPD. However, the mere presence of an eosinophil in the airway is not sufficient for a prescription of some form of steroid; eosinophilic airway wall inflammation has been described in asthma in apparent complete remission (11). Perhaps the more sound view is that the absence of airway eosinophilia should strongly militate against the use of steroids.

Some progress has already been made in addressing inflammatory biomarkers, with studies using exhaled nitric oxide to predict the success of changes in treatment, and as an early warning of impending treatment failure, having been published (12). However, there is still no clear consensus of what should be done in practice, although there is clear proof of concept that measuring some inflammatory biomarker improves the outcome for older children with asthma. The situation is even less clear in children with preschool wheeze, where we are largely stuck at the level of clinical history to guide treatment, with little in the way of biomarker research to help us. Turato and colleagues' article (8) highlights the importance of assessing structural changes together with airway inflammation in making a diagnosis. Therefore, biomarkers that reflect changes in both airway remodeling and inflammation in response to therapy are the ideal, but not yet obviously within sight.

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Pseudomonas aeruginosa An Uninvited Guest Refuses to Leave

Pseudomonas aeruginosa has long been an unwelcome guest in the intensive care unit. Both a frequent and serious cause of ventilator-associated pneumonia (VAP), this organism causes infections that are especially difficult to treat. For example, VAP caused by *P. aeruginosa* is associated with attributable mortality rates of 40%, higher than the corresponding rates for most other causes of VAP (1–4). Even patients who recover with the aid of appropriate antimicrobial therapy have an 18% chance of experiencing a relapse (1). These alarming figures are no doubt partly due to this bacterium's propensity to develop resistance to commonly used antibiotics, but the intrinsic virulence of *P. aeruginosa* has also been hypothesized to play a role.

Clues as to why *P. aeruginosa* is associated with such poor outcomes in the context of VAP are beginning to emerge. For example, studies have shown that, even when treated with antimicrobial agents to which it was initially susceptible, *P. aeruginosa* persisted in the lungs of some patients with VAP for up to 15 days, a finding not as frequently observed with other causes of VAP, such as *Staphylococcus aureus* and *Escherichia coli* (2, 3). These observations provided a scientific rationale for current American Thoracic Society/Infectious Diseases Society of America guidelines recommending that VAP caused by *P. aeruginosa* be treated with longer courses of antibiotics than VAP caused by many other bacterial pathogens (4). But what is the mechanism responsible for the persistence of *P. aeruginosa*?

In this issue of the *Journal* (pp. 513–519), El Solh and colleagues add an important piece to the puzzle of *P. aeruginosa* persistence in VAP (5). Their findings suggest that type III secretion plays a major role in this aspect of infection. The *P. aeruginosa* type III secretion system is a complex syringe-like apparatus on the bacterial surface that injects proteins (called effector proteins) directly into host cells (6). Two effector proteins, ExoU and ExoS, are particularly virulent in animal models of acute pneumonia (7). Importantly, VAP isolates of *P. aeruginosa* differ in the complement of type III effector proteins they secrete, with some strains lacking functional type III secretion systems altogether (8, 9).

El Solh and colleagues performed noninvasive bronchoscopy on 34 patients with VAP caused by *P. aeruginosa*. All patients received antimicrobial therapy to which their isolates were initially susceptible. Despite this, in 13 of 24 patients infected with type III secretion–positive strains, *P. aeruginosa* was recovered from the lungs after 8 days of therapy. In contrast, *P. aeruginosa* did not persist in the lungs of any of the 10 patients infected with type III secretion–negative strains. Persistence appeared to be clinically significant in that relapse occurred in 8 of 13 patients with *P. aeruginosa* still present in their lungs at the completion of antimicrobial therapy. Also, the survival rate for patients infected with nonsecreting strains was 66%, compared with only 32% in patients infected with secreting strains. These findings are intriguing and suggest that type III secretion may be acting in a way that allows bacterial persistence in the harsh pulmonary environment consisting of immune responses and antibiotics; this persistence may account for previous reports that type III secretion is associated with poor outcomes in *P. aeruginosa* acute respiratory infections (8, 9).

How might functional type III secretion lead to bacterial persistence in the lungs? One possibility is that *in vivo* induction of type III secretion decreases susceptibility to antimicrobial agents. In this regard, it is interesting that ExoU⁺ strains have been reported to be more resistant to certain antibiotics than other strains (10). El Solh and colleagues, however, provide evidence supporting another explanation: type III secretion targets neutrophils, rendering this important component of the immune system less capable of eradicating *P. aeruginosa*. Secretion of type III toxins was associated with apoptotic changes in neutrophils and increased release of neutrophil elastase in the lungs. These *in vivo* results fit well with earlier *in vitro* observations demonstrating that type III secretion causes apoptosis and death of neutrophils and macrophages (11–14). Thus, type III secretion may tilt the precarious balance between the host immune response (aided by antimicrobial therapy) and bacterial survival mechanisms in favor of the bacterium. If this is indeed the case, immunotherapies that block type III se-