remain with patients who spontaneously generate large tidal volumes, we agree with this recommendation that ICU clinicians should rarely set or target a tidal volume much above 6 ml/kg PBW.

The issue of timing of treatment is familiar to critical care physicians in sepsis, trauma, acute myocardial infarction, and acute cerebrovascular accidents. It should not be surprising that timely recognition and treatment of ARDS should also be important. With this study, Needham and colleagues have brought the issue to forefront and started the clock. ■

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Toward Improved Diagnosis of Early Asthma

A well-known adage among clinicians is that “all that wheezes is not asthma,” which invites the question, Which wheezing is asthma? This is an especially difficult question to answer in the preschooler, but it is an important one. Wheezing is very common in children younger than 6 years, with almost half of children having at least one episode early in life (1). However, wheezing resolves by age 6 years in the majority of these children, so they are diagnosed in retrospect as having “transient wheeze of childhood” (2). However, most of the children who are eventually diagnosed with asthma report wheezing early in life (3), so the challenge is to identify the subset of

children who will eventually go on to develop persistent wheezing.

The tools currently available to clinicians and researchers to predict asthma in young children are generally easy to use, but they have relatively poor positive predictive value. The Asthma Predictive Index (API) developed from the Tucson Children's Respiratory Study is a well-studied and simple tool for use in children who wheeze, incorporating information on child eczema, parental asthma, child rhinitis, and blood eosinophilia (4). In multiple studies, the API performs best as a negative predictive tool (i.e., a negative API indicates very low asthma risk), but the

positive predictive value remains modest (i.e., many children with a positive score will not go on to develop asthma) (5). Although children with a positive API are clearly at risk for asthma (or already have asthma), relying on the API will result in a high proportion of children without asthma receiving inappropriate treatment.

In this issue of the *Journal*, Klaassen and colleagues (pp. 201–207) present the results of the Asthma Detection and Monitoring (ADEM) study, which prospectively tested whether four biomarkers improved on the API for early asthma diagnosis (6). The investigators recruited 202 children aged 2–4 years with a history of recurrent wheeze and followed them until age 6 years. At the time of recruitment, the researchers measured airway resistance, collected exhaled breath condensate for volatile organic compounds (VOCs) and cytokines, and obtained blood for gene expression. Inhaled steroids were stopped at least 4 weeks before these studies to avoid biasing the results. Asthma was diagnosed at age 6 years, using symptoms, asthma medication use, and response to bronchodilator and/or airway hyperresponsiveness to methacholine. The investigators tested whether adding baseline biomarkers at age 2–4 years to a logistic regression model with API improved the ability to predict asthma diagnosis at age 6 years. What they found was that although airway resistance and exhaled breath condensate cytokine levels did not improve the model, both VOCs and gene expression independently and in combination dramatically improved the positive predictive value of the API. In this cohort, the API classified 60% of children accurately, whereas the API plus VOCs and gene expression classified 89% of children accurately.

One of the reasons making a diagnosis of asthma in young children is so difficult is because of the unreliability of spirometry at that age (7). Without this tool, and with only a subset of children going on to have persistent wheeze at age 6 years, many clinicians are reluctant to make a diagnosis of asthma in the preschooler. The results presented here suggest that pathogenic features of asthma (as represented by VOC and gene expression patterns) can be detected in preschoolers. In contrast, it is important to note that the biomarkers identified by Klaassen and colleagues do not identify children at risk for asthma, which was a major goal identified by a recent National Heart, Lung, and Blood Institute workshop (8). The children enrolled in the current study already had a history of wheezing, and were therefore not presymptomatic. At least for inhaled steroids, once a child is wheezing and at high risk for asthma, intervention is unlikely to prevent the disease (9). Instead, these biomarkers, similar to the API, likely help identify children who already have asthma. This early diagnosis is important because, although they will not cure asthma, early treatment with inhaled corticosteroids and environmental modifications may reduce asthma severity and prevent asthma exacerbations (7). A logical next step is to test whether VOCs and gene expression patterns can be used to identify presymptomatic children who are at risk for asthma. This includes children who are very young (younger than 1 yr), as well as nonwheezing preschoolers.

Although the results from this study are compelling, they are from a single cohort study recruited in a local geographic area. The authors split the sample into discovery and replication cohorts, reducing the likelihood these findings are a result of chance. To be generalizable, however, replication in diverse populations

is needed. This is no easy feat for prospective studies, so ideally replication could be performed in conjunction with early intervention clinical trials, which could then be used to extend the results of the current study.

Finally, although the results here significantly improve on the API as an early diagnostic tool, the use of gene expression and exhaled VOCs adds complexity and cost to an otherwise simple tool. For example, the collection, measurement, and interpretation of VOCs is in its early stages, and not easily applicable to the clinical setting (10). As commercial companies step forward to provide user-friendly clinical systems that simplify collection and analysis, we can expect that the complexity and cost will improve. Whether they will improve enough to justify their use in a clinical setting is unclear, but from a research perspective, the use of these biomarkers holds great promise in advancing our understanding of early asthma pathogenesis, and potentially in developing novel therapies. ■

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