2. Younger children, especially infants receiving APRV, may demonstrate fatiguability with inconsistent and variable spontaneous breathing rates and efforts.
3. Given the higher airway resistance and compliant chest walls causing a lower driving force for recoil and exhalation, infants and young children are likely to experience higher and highly variable intrinsic positive end-expiratory pressures with APRV.
4. In young children, collateral channels of ventilation, such as pores of Kohn, may not be well developed. This may impede the recruitment and redistribution of alveolar volume (and pressure) throughout the lung.

One of the relatively underappreciated aspects of APRV is its dependence on the delivery system (3, 7–10). The mechanical profile of the APRV breath may vary significantly across ventilators from different manufacturers (7–10). We agree completely that the type of ventilator is a key factor in APRV research and should not be overlooked, but we do not know whether one ventilator is superior to another for providing this mode of ventilation.

We think that the APRV debate needs to focus on Plow and prevention of repetitive lung injury during release. Zhou and colleagues used a personalized-APRV approach with Plow of 5 cm H_2O (6), and the two RCTs by Varpula and Putensen used a fixed-APRV approach with a nonzero Plow (11, 12). The only adult RCT (13) that used a personalized-APRV approach with a Plow of zero similar to the one used in the recent pediatric trial (1) showed a trend toward worse secondary outcomes in the APRV arm with increased ventilator days, ICU length of stay, and ventilator-associated pneumonia. The worse outcomes seen with the personalized-APRV approach using a Plow of zero could be mediated through repeated alveolar collapse or right ventricular dysfunction secondary to abrupt deflation. Therefore, future clinical research should evaluate personalized-APRV with nonzero Plow or a fixed-APRV strategy in both adults and children with ARDS.

In summary, it is possible that applications of APRV truly differ between adults and children, as is true for several aspects of mechanical ventilation and critical care. Given the small number of studies to date, we do not have a clear understanding of APRV strategies that will work in either group. ■

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Selection of Biologics for Type 2–High Asthma

To the Editor:

We read with great interest the review article by McGregor and colleagues. The authors have reviewed the mechanism of action, indications, expected benefits, and adverse effects of each of the currently approved biologics for severe uncontrolled asthma (1). We would like to thank McGregor and colleagues for their contribution to literature with such a valuable review.

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The authors say that "a recent pragmatic trial of omalizumab demonstrated similar benefits in T2-high and -low patients (AEC $<$300 or $\geq$300 cells/μl and fractional exhaled nitric oxide [F_{ENO}] $<$25 or $\geq$25 ppb)." However, we think that describing the patient population of this study as type 2 (T2)-high and -low patients may cause confusion because we should not evaluate the atopic asthma (in which asthma is clinically allergen driven) independently from T2-high asthma. Allergic (atopic) asthma is also part of the T2-high asthma (2). The authors of the study have already described the patient groups as high-biomarker subgroups and low-biomarker subgroups, not T2 high and low (2).

Another point the authors have mentioned is that omalizumab has no biomarker that has been useful for predicting or monitoring response. However, some potential predictors of good response to omalizumab have been recommended in the GINA (Global Initiative for Asthma) severe asthma guidelines such as blood eosinophils $\geq$ 260/μl, F_{ENO} $\geq$ 20 ppb, childhood-onset asthma, and clinical history suggesting allergen-driven symptoms (3).

In conclusion, current biologics for T2-high severe asthma should be chosen wisely according to some logical recommendations, which can be made at this time on the basis of the mechanisms of the action of the drugs and the underlying pathophysiology of various asthma phenotypes, until validated biomarkers are detected for the selection of biologics. ■

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Reply to Yilmaz

From the Authors:

We thank Dr. Yilmaz for the thoughtful comments in his letter to the editor regarding our review, "Role of Biologics in Asthma" (1).

Dr. Yilmaz makes an important point when discussing atopic asthma as a type 2 (T2)-high condition. The PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) study we referenced demonstrates similar benefits of omalizumab in patients with both high and low absolute blood eosinophil counts and fractional exhaled nitric oxide levels (2). Although these are important biomarkers of T2 inflammation, allergic (atopic) asthma is also driven by T2 inflammation, and thus it is better to describe these subgroups of allergic asthma as high- and lower-biomarker groups rather than T2-high and -low groups. The important takeaway point from the PROSPERO trial was that patients who were deemed candidates for omalizumab in a real-world setting responded irrespective of their biomarker profile, and thus omalizumab should be considered in patients with allergic asthma regardless of the biomarker levels. However, if the patients have asthma that is severe enough to require high-dose maintenance corticosteroids, anti-IgE therapy is unlikely to be effective even if the patients are atopic (3), implying that IgE may not be the main driver of symptoms in those patients.

The recently updated 2019 GINA (Global Initiative for Asthma) guidelines (4) do suggest that blood eosinophils $\geq$ 260/μl, fractional exhaled nitric oxide $\geq$ 20 ppb, allergen-driven symptoms, and childhood-onset asthma may be predictors of response to anti-IgE therapy. As noted in our review, although retrospective analyses have suggested that patients with high biomarker profiles treated with omalizumab may have a greater reduction in exacerbation rates (5), this difference may be a result of the higher rate of exacerbation in the high biomarker group. Future studies that prospectively evaluate factors that predict response to omalizumab and other biologics are paramount in the era of precision medicine. ■

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