Heliox as Adjunctive Therapy for Pediatric Critical Asthma: Time to Question Its Role?

Critical asthma remains a common indication for admissions into pediatric ICU (PICU) and accounts for significant morbidity in children with asthma.[1] Advances in pediatric respiratory care allowed the use of a wide array of adjunctive therapies such as heliox (helium-oxygen mixture), noninvasive ventilation, and inhaled anesthetics; however, only limited pharmacologic therapies (systemic steroids, nebulized β-agonists and anticholinergics, and intravenous magnesium) have been proven effective.[2] Thus, the search for the most effective current and emerging adjunctive therapy for critical asthma remains of high interest.

Adjunctive therapies are typically reserved for patients with critical asthma; however, recommendations regarding using these therapies are not standardized and remain vague, which results in wide variability in critical care provided for pediatric patients with critical asthma.[3,4] This is secondary to the lack of validated and wildly available critical asthma–specific illness severity scoring and reproducible outcome measures, limiting meaningful conclusions regarding the efficacy of adjunctive therapies.[4] Therefore, most studies examining adjunctive therapies for critical asthma have focused on individualized therapies rather than combination therapy delivered to patients using a standardized pathway and individualized consideration of both response to therapies and severity of illness.[5]

In this issue of Respiratory Care, Lew et al[6] describe chronological prescribing rates of heliox for critical asthma and explore the relationship between heliox use and the frequency and duration of mechanical ventilation. Heliox is a low-cost gas mixture (21% oxygen and 79% helium molecules) that has relatively same viscosity as atmospheric air but 6 times lower density.[7] The lower density of heliox decreases turbulent flow through small airways and results in less flow resistance, making it an attractive therapy for severe asthma. The maximum benefits of heliox are achieved when nebulized bronchodilators, systemic steroids, and intravenous magnesium have been initiated and lower F_{IO_2} is used.[8] This latter point is vital as oxygen has a similar density to the nitrogen replaced by helium, and using a lower F_{IO_2} will result in higher helium concentrations supporting laminar flow and improved delivery of nebulized bronchodilators. The potential benefits of heliox

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in treating critical asthma were first recognized in the 1930s; however, it was not until 1980s that the interest in heliox began to arise secondary to increasing mortality and morbidity from asthma.[9] Although initial studies were promising, the benefits of heliox in managing critical asthma remain unclear, with conflicting supporting literature. In this large multi-center retrospective cohort study using the Virtual Pediatric Systems database, Lew et al[6] studied 43,238 encounters of patients admitted with severe asthma. They found that heliox was prescribed for 1,070 (2.50%) encounters with wide variability of utilization by individual centers (0–36.78%) and United States geographical region, with highest use in the Midwest and South. The mean duration of heliox therapy was 21.4 ± 27.2 h. Moreover, they found that the annual institutional heliox prescribing rates declined over the study period from 4.11 ± 9.86% to 2.37 ± 5.75%. The authors found that 2,064 (4.77%) subjects required support with intermittent mandatory ventilation (IMV), which is a slightly higher intubation rate when compared to recently published literature.[10] In subgroup analysis excluding subjects who either were intubated prior to or within 6 h of PICU admission or who didn't receive heliox prior to mechanical ventilation, only 273 (0.69%) subjects were intubated. Subjects who received noninvasive heliox were at higher risk for intubation, with an odd ratio of 2.34 (95% CI 1.27–4.31, $P < .001$). However, the duration of IMV did not differ between subjects treated with or without heliox during IMV.

Endotracheal intubation and IMV in patients with critical asthma are particularly associated with significant morbidity, and as such, the rapid escalation of pharmacologic and adjunctive therapies is often utilized to avoid intubation.[11] Theoretically, therapies that target primary critical asthma pathophysiology, optimize the delivery of nebulized bronchodilators, and have an instantaneous effect on restricted bronchial gas flow, that is, heliox, should be initiated first. Although few studies showed faster improvement and decreased the need for IMV when heliox was initiated prior to intubation, the variable study designs, exclusion of the

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Correspondence: Kyle J Rehder MD. E-mail: kyle.rehder@duke.edu.

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sickest patients, and implementation timing make it hard to draw definitive conclusions regarding the benefits of heliox to prevent intubation.[12,13] From a physiological standpoint, given that mechanical ventilation may worsen turbulent flow during inspiration secondary to higher airway caliber and velocity of ventilated breath, it is plausible that heliox administration during mechanical ventilation could improve lung mechanics (ie, decrease both peak inspiratory pressure and intrinsic PEEP and increase alveolar ventilation and carbon dioxide elimination).[14,15] Few studies have evaluated the use of heliox during intubation; however, for the same reasons described earlier, it is hard to draw any definitive conclusions from those studies.[16,17]

Noninvasive ventilation, as a widely available adjunctive therapy, has been shown to be safe and efficient in reducing the work of breathing and the use of accessory muscles in patients with asthma and could potentially provide a safer and intermediate alternative to IMV.[18] In addition, noninvasive ventilation may require less monitoring and calibration of delivery devices when compared to heliox.[10,19] Over the last decade, noninvasive ventilation utilization for pediatric critical asthma has increased from 1.5% to 2.1%, whereas the need for IMV decreased to $< 1\%$.[10] Although some studies focused on describing the use of noninvasive ventilation as an alternative to IMV, there are no clear data describing the effect of such a trend on the use of other adjunctive therapies, especially heliox, where such a trend might explain the lower utilization rate of heliox over the last decade. Moreover, there is a paucity of literature describing combining heliox with noninvasive ventilation for critical asthma. Lew et al[6] attempted to address this issue in their article and showed that the use of noninvasively administered heliox was not associated with decreased frequency of intubation; however, the authors were not able to control for severe hypoxemia, asthma-specific severity of illness, or how the variability of practices between centers could potentially affect their outcomes.

One of the largest challenges in this study by Lew et al,[6] and in almost all retrospective studies of therapies for critical asthma, is accounting for severity of illness and other confounders in study subjects. Commonly used scoring systems such as the Pediatric Index of Mortality and Pediatric Risk of Mortality scores focus on multi-organ failure and mortality, yet critical asthma in the PICU is typically single-organ failure and, fortunately, carries a low mortality. Clinical asthma scores have been associated with outcomes[20,21] but are inherently subjective and are not typically included in large registries. The variability in management between centers also adds a separate layer of confounders such that it may be difficult to isolate the effect of any given therapy. For example, the regional variation of heliox use in this study may be reflective of unmeasured factors that affect asthma severity, including access to care or environmental exposures, or may be coupled with other variabilities in therapeutic strategies. The limited ability to account for severity of illness and other confounders results in lack of clarity about a given therapy's efficacy or utility.

This study is welcomed to the current literature as it provides an important insight to the current use of noninvasive and invasive heliox in the PICU and uncovers potential challenges to study the efficacy of heliox in patients with severe asthma. However, practitioners should use caution when interpreting and applying the results of this study to current practices due to the limitations highlighted in this editorial. This descriptive study should be used mainly to support ongoing efforts to design and conduct prospective multi-institutional studies focused on investigating the benefits of standardized asthma management pathways that utilize both evidence- and expert opinion-based combination of adjunctive therapies in patients with critical asthma.

Awni M Al-Subu
Division of Pediatric Critical Care Medicine
Department of Pediatrics
University of Wisconsin School of Medicine
and Public Health
Madison, Wisconsin

Kyle J Rehder
Division of Pediatric Critical Care Medicine
Department of Pediatrics
Duke University Health System
Durham, North Carolina

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