Upfront Combination Therapy: Growing the Case to Get Ahead of Pediatric Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a rare, life-limiting disease marked by progressive remodeling of the pulmonary vascular bed that affects patients of all ages (1). Over the past two decades, the advent and increased use of pulmonary-specific vasodilator therapies has improved lung transplant–free survival in children with PAH (2–4). These therapies modulate vasoactive signaling to relax the pulmonary arterial bed through three distinct pathways: the nitric oxide, endothelin, and prostacyclin pathways (5). In recent years, much research has focused on optimization of timing, dosing, and defining the advantages of combination therapy in the treatment of PAH (6). Despite these improved therapeutic opportunities, the timing of drug initiation, transition, dosing, and benefits of additive therapy specific to the pediatric population remains incompletely understood.

Credence for early aggressive pulmonary vasodilator therapy in patients with PAH started with clinician experience and observational data but was subsequently propelled by adult studies suggesting beneficial response (7). Over 15 years ago, the small BREATHE-2 (Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH) trial was the first upfront combination randomized clinical trial, using intravenous epoprostenol and bosentan in some subjects and finding a nonsignificant improvement in hemodynamics for those on combination therapy (8). In 2015, the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial, a double blinded randomized control trial in adult patients with functionally mild PAH (World Health Organization class I and II), studied the efficacy of monotherapy versus a more aggressive upfront dual therapy regimen with both ambrisentan and tadalafil. Results from the primary and associated studies demonstrated decreased death, disease progression, and hospitalization, and significant improvements in NT-proBNP and 6-minute-walk distance in patients treated with upfront dual therapy compared with either monotherapy alone (9–12). These publications, buoyed by clinical experience, supported the concept that instead of a sequential therapy approach, early synergistic targeting of multiple vasoactive pathways using existing FDA-approved therapeutics improves the care of patients with PAH, even those with mild disease. Subsequent adult studies evaluating the benefits of early implementation of three pulmonary hypertension–specific vasodilators ("upfront triple combination therapy") suggested that adults with severe PAH showed a better clinical response, including improved hemodynamics, functional status, and long-term outcomes (13, 14).

Although this increasingly robust adult data suggests an overall benefit from aggressive early upfront therapy with a two or three drug regimen at time of diagnosis, the optimal approach for the treatment of pediatric PAH remains unclear. Given the relative paucity of pediatric clinical trials in PAH in general, the issue of upfront combination therapy versus a sequential therapy approach has yet to be investigated in a formal randomized clinical trial. This leaves clinicians to approach pediatric care by extrapolating data and experience from adult patients, a process with both risks and benefits (15). Current pediatric guidelines distinguish between low and high-risk disease, suggesting a treatment strategy that may result in the avoidance of parental prostacyclin/prostacyclin derivatives (hereafter called "prostanoids") in patients with less severe disease despite possible functional and survival benefits with early, aggressive treatment (6, 16). In addition, current recommendations lack direction for goal prostanoid dosing and safe parameters for therapy deescalation from parental to oral/inhaled prostanoid. Intriguingly, a recent small retrospective observational study of 21 children with severe PAH by Haarman and colleagues reported improved survival among individuals treated with upfront triple combination therapy, but the results were confounded by a large percentage of patients (43%) undergoing Potts shunt during the study period (17).

In this issue of *AnnalsATS*, Douwes and colleagues (pp. 227–237) (18) for the first time provide a relatively large scale, international, multiinstitutional retrospective analysis of the long-term outcomes of children with varying baseline PAH severity treated with intravenous or subcutaneous (IV/SQ) prostanoid therapy and aggressive dual and triple combination therapy. Notably, results demonstrate improved transplant-free survival with high dose (>25 ng/kg/min epoprostenol and approx. 45 ng/kg/min treprostinil) and early initiation of prostanoids in addition to dual or triple combination PAH therapy, including a prostanoid regardless of baseline disease severity, functional class, age, sex, and presence of cardiac shunt. The authors provide an additional contribution, exploring the predictors for successful transition from IV/SQ

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to oral or inhaled prostanoid therapies in a subset of patients for whom IV/SQ therapies were discontinued, finding favorable outcomes in patients with mean pulmonary artery pressure <35 mm Hg and pulmonary vascular resistance index <4.4 WU/m^2 in addition to a better World Health Organization functional class at time of transition.

This study has multiple strengths, including its comparatively large sample size from an international cohort, well-phenotyped patient demographics, and inclusion of the full range of PAH disease severity. The authors took expert advantage of provider-based differences in dosing, uptitration and weaning, and multidrug strategies to complete thoughtful subgroup analysis. However, the study is innately limited by its retrospective nature and lack of randomized assignment to a given treatment approach, potentially exposing the study to significant selection bias. In addition, authors describe improved survival with high dose prostanoids and multidrug therapy regardless of PAH disease severity. However, it is important to note that prostanoids were only initiated " … in patients at high risk for death or with insufficient response to non-parenteral therapy" (18). Parenteral prostanoids did require discontinuation because of complications or severe side effects in five children but it is not clear the extent to which therapeutic complications and/or side effects impacted the group of patients overall. Although likely generalizable, it is notable that the field has seen a shift in prostanoid use since the close of the study's data collection period (2000–2010); that is, in the last decade, clinical practice has favored use of subcutaneous over intravenous prostanoids. Also, although still strongly center dependent, there is an ongoing movement toward treatment of refractory severe PAH with Potts shunt placement to unload the right ventricle and decrease the need for high dose, side effect-inducing vasodilators (17, 19). In this study, only 11% of patients used subcutaneous treprostinil for over 3 months and no patients underwent Potts shunt. The ever-evolving treatment advances, including novel drug delivery modalities and implementation of new advanced interventional and surgical techniques in the care for patients with PAH, stresses the importance of use of more current data when possible if conclusions hope to direct future clinical care recommendations.

Despite these limitations, the current study highlights the potential benefit of early implementation of high dose prostanoid therapy with aggressive upfront combination therapy in improving transplant-free survival in children with PAH. These results align with previously reported adult data. Given the relative paucity of evidence informing pediatric-specific dosing and therapeutic strategies in PAH, this work should serve as preliminary evidence to support future prospective studies in children with PAH. One such example is MoD ("Mono versus Dual Therapy for Pediatric Pulmonary Arterial Hypertension") (NCT NCT04039464), a multicenter randomized controlled trial evaluating the efficacy and long-term safety of early, upfront combination therapy for the treatment of precapillary pulmonary hypertension in children, which will hopefully soon launch in North America. However, additional prospective trials of upfront triple combination therapy, and alternative approaches, are needed as well. The contributions from these authors and others have nicely paved the way for such trials. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Should We Be Permissive with Hypercapnia?

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Protective lung ventilation, focusing on low tidal volumes and low alveolar pressures, reduces mortality in patients with acute respiratory distress syndrome (ARDS) (1). Such ventilator strategies implemented to reduce lung stretch and lung injury led to an improvement in patient outcomes, albeit with a higher incidence of hypercapnia (2). This was deemed to be an acceptable tradeoff, given the clinical improvement observed. Hypercapnia, now routinely seen and tolerated, triggered an interest in understanding the impact of CO_2 itself in critically ill patients.

Animal and preclinical studies revealed that hypercapnia influences multiple organ systems and causes various physiologic effects (3). Although hypercapnia can increase local alveolar ventilation, improving ventilation–perfusion ($\dot{V}/\dot{Q}$) matching, it can worsen pulmonary vasoconstriction, aggravating cor pulmonale and precipitating right ventricular failure (4, 5). Hypercapnia reduces myocardial contractility, but through vasodilation and reflex sympathoadrenal activation, cardiac output is maintained (6). The impact on the immune system is wide, ranging from reducing cytokines (such as interleukin [IL]-5, IL-6, and tumor necrosis factor-α) to inhibiting neutrophils and phagocytosis (3). This was used to justify observations that early in the course of sepsis, hypercapnia can be beneficial by attenuating the inflammatory response (7). However, late exposure to hypercapnia could accelerate bacterial growth (8).

These observations made from preclinical studies were difficult to replicate at the bedside. The few clinical studies examining the impact of hypercapnia and hypercapnic acidosis are observational and offered different, sometimes conflicting results. Some have shown hypercapnia to be independently associated with increased mortality, but others have not (9–11).

In this issue of *AnnalsATS*, Tiruvoipati and colleagues (pp. 245–254) investigate the association between hypercapnia and mortality in a large cohort of 3,153 patients with 84,819 arterial carbon dioxide tension/pressure (Pa_{CO_2}) measurements (12). In this multicenter observational study, the investigators attempted to answer the following: *1*) What is the impact of hypercapnia on patient outcomes, and is the impact of hypercapnic acidosis different?; *2*) Is there a CO_2 "dose" effect, estimated from the length of stay in the intensive care unit (ICU)?; and *3*) Could CO_2 effect differ between ventilated and nonventilated patients and for pulmonary versus nonpulmonary sources of sepsis?

The investigators found that, in their large population of critically ill patients with sepsis, hypercapnia ($Pa_{CO_2} \geq 45$ mm Hg) and severe hypercapnia ($Pa_{CO_2} > 55$ mm Hg) were common, well tolerated, and not associated with increased mortality. This was in contrast to prolonged exposure to hypercapnic acidosis, which was associated with increased mortality in patients with nonpulmonary sepsis and in mechanically ventilated patients. Perhaps to the surprise of the investigators, there was also a strong signal for increased mortality due to prolonged exposure to hypocapnia.

These results are in line with another recently published multicenter observational study that similarly showed no evidence for benefit or harm from hypercapnia (11). That study also highlighted that sustained hypocapnia in patients with ARDS was associated with increased ICU mortality. These results are in sharp contrast to earlier studies showing hypercapnia to increase mortality (8, 9).

To better interpret this conflicting data, one should understand the pathophysiology

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