Under Pressure: The Pulmonary Vasculature and Its Role in the Pediatric Cardiac ICU

Pediatric patients with severe pulmonary hypertension (PH) represent one of the most challenging patient populations for clinicians to take care of, as their pulmonary vascular disease makes their propensity for rapid changes in hemodynamics quite high. In patients with underlying congenital or acquired heart disease who already have a myriad of anatomic and physiologic challenges, pulmonary vascular disease can be the "icing on the cake" when it comes to making their medical management particularly harrowing.

To better characterize this particular cohort, in this issue of the *Journal*, Morell and colleagues (pp. 454–461) provide a thoughtful and systematic analysis of risk of mortality in 1,709 neonates, children, and young adults (2,602 medical admissions) with PH who received care in 38 North American pediatric cardiac ICUs (PCICU) between 2014 and 2019 (1). Their findings lend granularity, a new venue, and eye-opening follow up to previous cautionary notes in the literature regarding the fragility of children with pulmonary vascular diseases of various etiologies (2, 3). The current work isolates some specific factors that help to organize thinking about risk assessment and reduction in this unique patient subset by drilling down into clinical scenarios involved and into constellations of interventions that may cause or be associated with increased mortality.

One striking finding in this study is that the use of vasoactive infusions on the second day of the PCICU stay was the dominant factor for increased mortality. However, details of the specific vasoactive agents that were used in the cases under study are not listed in detail. Given this finding, some challenges in the use of these drugs in the setting of cardiac dysfunction with PH are worthy of note. α-adrenergic agents provide benefit by increasing systemic vascular resistance, diastolic pressure, and coronary perfusion, but a parallel increase in pulmonary vascular resistance may present an ailing right ventricle with increased afterload. β-adrenergic agents may increase cardiac output by increasing left ventricular contractility, but the effects of increased chronotropy on a hypertrophied and stiff right ventricle may be counterproductive, as filling time is cut short. Alternatively, avoidance of adrenergic receptor stimulation by using vasopressin infusions in the setting of cardiac dysfunction with PH in children has been shown to increase aortic pressure and improve systemic hemodynamics while avoiding increased pulmonary vascular resistance that challenges the right ventricle (4, 5). Milrinone is a particular pharmacologic agent that inspires heated debate in the PH population. Although some use it frequently in nearly all patients with PH, others tend to avoid it with equal veracity. In the current study, milrinone did not appear to add to mortality risk. This finding is both reassuring and potentially misleading and may be partially attributable to its frequent use as a tonic support rather than an acute rescue agent. However, it is important to keep in mind that this phosphodiesterase-3 inhibitor is a relatively long-acting vasoactive drug that inhibits platelet activation. It can compromise coronary perfusion of the vulnerable right ventricle by decreasing systemic diastolic pressure in the setting of increased right ventricle wall tension owing to hypertrophy and dilatation. Milrinone may also complicate interventricular interactions by dropping systemic vascular resistance.

It is interesting that patients with chronic PH that had been on home therapy with treprostinil before their PCICU admission fared better than those for whom it was initiated as an acute ICU intervention. This experience both underscores the viability of long-term home treprostinil infusions (as recently reported in a case series from Germany with over 260 patient-years) (6) and highlights the high-risk nature of care for acutely ill children with PH, in whom rapid increases in intravenous treprotinil to effective doses may be fraught with concomitant exacerbation of systemic hypotension.

Disparities in health outcomes related to race and ethnicity are being appropriately more closely scrutinized. In pediatric patients with PH, Ong and colleagues recently published their analysis of the Pediatric Pulmonary Hypertension Network Registry, demonstrating that those in minority groups had higher mortality rates when compared with white non-Hispanic patients (7). A similar finding was reported following a well-conducted study by Lopez and colleagues looking at the interplay between race and outcomes in the congenital heart disease population (8). However, this particular disparity was not apparent in the current study's findings, and this issue therefore represents an area for further investigation.

Co-opting of the Pediatric Cardiac Critical Care Consortium (PC4) database (originally designed as a quality-improvement tool) for clinical research, as is done by Morell and colleagues, presents a novel opportunity for much-needed "big data" in a small niche population but also raises some important caveats related to data interpretation. As expected, the population is skewed heavily toward the congenital heart disease cohort, with a marked difference in that population's representation compared with published registry cohorts (9). There is also a lack of precision about the diagnosis of "pulmonary vascular obstructive disease," a somewhat nebulous term that could represent some particularly difficult-to-manage conditions that made up a substantial segment (12%) of the study cohort.

Additionally, patients with PH and lung or airway disease, such as those with bronchopulmonary dysplasia or congenital diaphragmatic hernia, are not readily identified in this study but often experience significant morbidity and mortality (10). Information about mortality risk for patients with PH with these comorbidities in an ICU setting, and particularly its interplay with underlying heart disease, would further inform providers and families regarding risk and expectations for recovery.

Originally Published in Press as DOI: 10.1164/rccm.202104-1044ED on June 21, 2021

It is unfortunate that pulmonary vein stenosis was only available as a diagnostic designation for a subset of the cohort in the PC4 database so that this diagnosis could not be included in the multivariate model. This disorder, although uncommon, can be extraordinarily difficult to manage, with a high risk of mortality (up to 30%) as described by the authors.

In summary, Morell and colleagues, in what is a first look at patients with PH admitted to PCICUs, bring to light the challenges and risks these patients face as a result of their PH. This work shows the formidable effect pulmonary vascular disease can have on outcomes and the role various therapeutic interventions may have on mortality risk. It's an exciting first start for providing insight into patient stratification for mortality in the PCICU and opens the door for future studies looking at patients following cardiac surgery, cardiac transplant, and other interventions. ■

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

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Innate Immune Training for Prevention of Recurrent Wheeze in Early Childhood

Severe lower respiratory tract infections (sLRIs) in early childhood with accompanying wheezing symptoms represent significant causes of hospital admission, particularly during infancy and the preschool years, and moreover, the repeated occurrence of these episodes in individual children is associated with markedly enhanced risk for their subsequent development of persistent asthma (1). Treatments to protect against these infections are extremely limited given the low availability of vaccines against relevant viral pathogens and the generally modest clinical benefits that appear achievable in this age group with currently available antiinflammatory drugs (2). The paucity of such treatment options has impeded the development of effective preventive strategies targeting the long-term sequelae of these infections, particularly asthma. However, recent findings, including clinical trial data published in this issue of the *Journal* by Nieto and colleagues (pp. 462–472), point toward a new therapeutic approach based on the principle of "Innate Immune Training (IIT)," which could radically impact this picture (3). This phenomenon was first recognized in infectious disease animal models as

Originally Published in Press as DOI: 10.1164/rccm.202103-0698ED on April 12, 2021