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Spectrum of Current Management of Pediatric Pulmonary Hypertensive Crisis

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Objectives: Pulmonary hypertension is a growing pediatric problem and children may present with pulmonary hypertensive crisis—a life-threatening emergency requiring acute interventions. The aim of this study was to characterize the broad spectrum of care provided in North American PICUs for children who present with pulmonary hypertensive crisis.

Design: Electronic cross-sectional survey. Survey questions covered the following: demographics of the respondents, institution, and patient population; pulmonary hypertension diagnostic modalities; pulmonary hypertension-specific pharmacotherapies; supportive therapies, including sedation, ventilation, and inotropic support; and components of multidisciplinary teams.

Setting: PICUs in the United States and Canada.

Subjects: Faculty members from surveyed institutions.

Interventions: None.

Measurement and Main Results: The response rate was 50% of 99 identified institutions. Of the respondents, 82.2% were pediatric intensivists from large units, and 73.9% had over a decade of experience beyond training. Respondents provided care for a median of 10 patients/yr with acute pulmonary hypertensive crisis. Formal echocardiography protocols existed at 61.1% of institutions with varying components reported. There were no consistent indications for cardiac catheterization during a pulmonary hypertensive crisis admission. All institutions used inhaled nitric oxide, and enteral phosphodiesterase type 5 inhibitor was the most frequently used additional targeted vasodilator therapy. Milrinone and epinephrine were the most frequently used vasoactive infusions. Results showed no preferred approach to mechanical ventilation. Fentanyl and dexmedetomidine were the preferred sedative infusions. A formal pulmonary hypertension consulting team was reported at 51.1% of institutions, and the three most common personnel were pediatric cardiologist, pediatric pulmonologist, and advanced practice nurse.

Conclusions: The management of critically ill children with acute pulmonary hypertensive crisis is diverse. Findings from this survey may inform formal recommendations - particularly with regard to care team composition and pulmonary vasodilator therapies - as North American guidelines are currently lacking. Additional work is needed to determine best practice, standardization of practice, and resulting impact on outcomes.

Key Words: cardiology; intensive care unit, pediatric; pediatrics; pulmonary hypertension; pulmonary medicine; vasodilator agent

Despite recent advances in the targeted treatment of pulmonary vascular disease, pulmonary hypertension (PH) remains a progressive and often fatal disease (1, 2). In pediatrics, the burden of disease continues to grow. PH is associated with substantial morbidity and mortality, and the financial cost is significantly higher than that for other chronic illnesses (3–5). The etiologies and pathophysiology of pediatric PH vary from those most often encountered in adult PH patients and are often related to developmental disorders and diseases of the lung (2, 3). Chronic PH may lead to right ventricular (RV) failure as a result of maladaptive mechanisms and ultimately death (6). Some PH patients may present in extremis with pulmonary hypertensive crisis—an abrupt and sustained increase in pulmonary vascular resistance with often suprasystemic elevations in pulmonary arterial pressure. These changes result in fulminant RV failure and low cardiac output syndrome with immediate need for emergency intervention (6, 7). Management of acute alterations in pulmonary hemodynamics includes optimization of preload, afterload, and contractility with well-integrated adjustments of fluid status, pulmonary vasomotor tone, and circulotropic support of the right

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ventricle. These priorities are most commonly managed by multidisciplinary teams in ICUs (7, 8). Additional vital adjunctive therapies for the critically ill patient in the ICU with pulmonary hypertensive crisis may include management of sedation, airway, and ventilation with strategies that optimize systemic and pulmonary vascular resistance and cardiopulmonary interactions (7). Historically, in children who developed acute pulmonary hypertensive crisis after congenital heart surgery, the mortality has been found to be as high as 22% and 55% (9, 10). Improvements in overall care and pulmonary vasodilator therapy have reduced the mortality risk, and contemporary single-center studies of patients with PH undergoing noncardiac surgical procedures have reported a mortality rate of ~1% when pulmonary hypertensive crisis occurred postoperatively (11, 12).

Treatment of children with PH is directed toward controlling the underlying condition, if identifiable and if possible, and involves therapies that augment pulmonary vasodilatation and reduce vascular remodeling. However, for patients who acutely present with hemodynamic compromise with pulmonary hypertensive crisis, it is paramount to control and stabilize the pulmonary vasculature while maintaining function of other vital organs. Therapeutic options for children are mainly extrapolated from adult trials, as evidence in the pediatric population is limited and largely based on expert opinion (13). Algorithms have been published for the management of pulmonary hypertensive crisis in adults, but adherence to the recommendations is low, despite evidence from other cardiovascular diseases that standardization improves outcomes (14–18). Furthermore, the recommendations for PH management in adults are of limited utility in children, given the divergence in pathogenesis, anatomy, and pathophysiology.

There is a paucity of literature on emergency interventions for pediatric patients with acute pulmonary hypertensive crisis and associated RV failure. As medical care in the PICU encompasses the whole of the patient, elucidating a complete description of patient care, including commonalities and differences in management, is vital to developing comprehensive standardized treatment plans. In this study, we sought to characterize the current spectrum of management practices for children with acute pulmonary hypertensive crisis in the United States and Canada. We hypothesized that we would document considerable variability in the demographics of patients admitted, overall management, and provider team composition.

MATERIALS AND METHODS

We administered an electronic cross-sectional survey to physicians who provide care to children with acute pulmonary hypertensive crisis in PICUs in the United States and Canada. The survey was developed by a team at the Johns Hopkins Hospital and edited for clarity. The study was approved by the Johns Hopkins Institutional Review Board, and survey response served as participant consent.

The survey was administered to academic and research-orientated hospitals with PICUs between June 2015 and February 2016. Publicly available databases were used to identify academic institutions as hospitals with a fellowship training program in pediatric cardiology and/or pediatric critical care medicine (19, 20). Research-orientated institutions were identified as members of the Pediatric Pulmonary Hypertension Network (PPHNet)—core centers of North American pediatric PH care and investigation—and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI)—a multi-institutional research collaborative of pediatric critical illness (21, 22). We collected publicly available email addresses and distributed the 37-question survey electronically in English using the secure institution-sponsored survey application Qualtrics (Qualtrics, Provo, UT). No identifying information was collected from survey respondents. The survey included five content areas: demographics of the respondents, institution, and patients; PH diagnostic modalities; PH-specific pharmacotherapies; supportive therapies, including sedation, ventilation, and inotropic support; and components of multidisciplinary care teams. The questions were closed-ended with multiple choice answers, and many included "other" as an option where respondents could enter a free-text response. A single open-ended question at the end of the survey encouraged comments on the future of pediatric PH care. The survey was distributed directly to the senior member at PPHNet institutions. It was directed to the PICU medical director or fellowship program director at institutions that do not participate in PPHNet, with a request that it be forwarded to the institution-specific physician with the most experience in treating patients with acute pulmonary hypertensive crisis. After initial disbursement, six survey reminders were sent out to nonrespondents; no incentive was offered for participation.

After the survey closed, data were exported into STATA 11.2 (College Station, TX). A survey was evaluated if at least one question was answered. We performed descriptive data analysis to examine specific practice characteristics and summarized free-text responses according to themes.

RESULTS

Institution and Patient Demographics

We identified 99 survey sites: 73 classified as academic with fellowship training programs and 26 classified as research-oriented based on membership in PALISI. All 10 programs identified in PPHNet were academic sites. We received 49 responses to the survey (50% response rate) including 80% of PPHNet sites. Demographic data for respondents regarding specialty and years in practice are shown in **Table 1**, along with data about the PICUs. The respondents were predominantly pediatric intensivists with more than 10 years of practice beyond training who worked in large PICUs of more than 20 patient beds. Respondents were from all geographic locations in the United States and Canada. The median number of critically ill children with pulmonary hypertensive crisis admitted to a PICU yearly was 10, with ranges from "a few" or "uncertain/unknown" to greater than 100. Neonates (0–28 d old) and infants (1 mo to 12 mo old) represented 52.4% of the admissions for pulmonary hypertensive crisis. The three most common precipitating causes for pulmonary hypertensive crisis requiring ICU level care were perioperative crisis (24.8%), new diagnosis of PH (22%), and intercurrent infection (17.7%) (**Fig. 1*A***). Nearly two-thirds of patients with pulmonary hypertensive crisis were admitted to definitive care areas from the emergency department (22.4%),

TABLE 1. Demographic Data of Respondents and Respondent ICUs

Characteristic	No. of Respondents (%)
Field of practice	
Pediatric critical care	37 (82.2)
Pediatric cardiology	5 (11.1)
Combined pediatric critical care and cardiology	2 (4.4)
Other	1 (2.2)
Years of practice after training	
0–4	2 (4.4)
5–9	10 (21.8)
10–19	15 (32.6)
≥ 20	19 (41.3)
Practice location	
Northeast	13 (28.3)
Southeast	7 (15.2)
Northwest	6 (13)
Southwest	4 (8.7)
Midwest	10 (21.7)
South	2 (4.4)
Intermountain West	4 (8.7)
Size of PICU, beds	
< 10	0 (0)
10–19	8 (17.4)
20–39	30 (65.2)
≥ 40	8 (17.4)

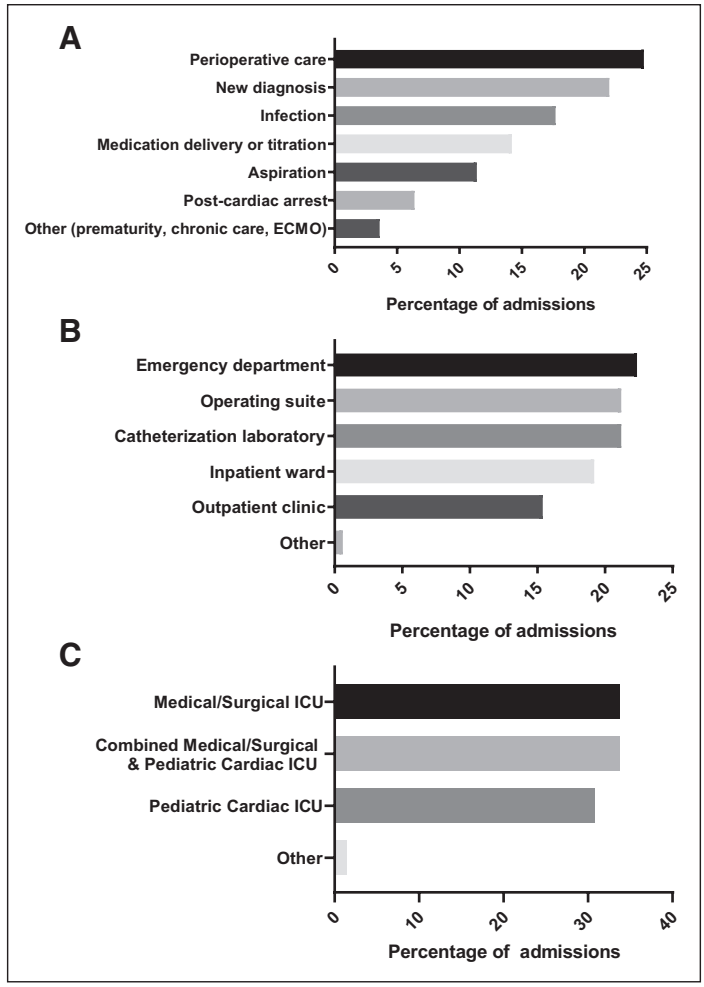

Figure 1. Pulmonary hypertensive crisis admission characteristics. **A**, Precipitating causes of pulmonary hypertensive crisis requiring intensive care, percentage of respondents stating each as a cause for admission. **B**, Locations from which patients were admitted to the ICU. **C**, Type of ICU to which patients were admitted. ECMO = extracorporeal membrane oxygenation.

operating suite (21.2%), or catheterization laboratory (21.2%) (**Fig. 1*B***). Admission location was nearly equally spread among PICU subtypes: medical/surgical ICUs (33.8%), combined medical/surgical and pediatric cardiac ICUs (33.8%), and pediatric cardiac ICUs (30.8%) (**Fig. 1*C***). One respondent stated that patients were admitted to the cardiac and pulmonary hospital wards. Most institutions (77.8%) reported at least one patient with pulmonary hypertensive crisis requiring extracorporeal membrane oxygenation (ECMO) support in the prior year. Just over one-third of respondents (34.8%) stated that a formal notification or identification mechanism was in place within their electronic health record system to alert clinicians specializing in the care of children with PH that a previously known patient with PH had been admitted to the hospital.

Diagnostic Modalities

Of all respondents, 61.1% stated that a formal echocardiography protocol was used at their institution to evaluate children with pulmonary hypertensive crisis. These protocols focused on common findings in PH: tricuspid valve regurgitation (36.1% of respondents); ventricular septal position (32.8%); tricuspid annular plane systolic excursion (19.7%); and a combination of ventricular size and function, presence of RV dilation and ejection fraction, and presence and direction of intracardiac shunts (11.3%). Procedural indications for cardiac catheterization during an admission for pulmonary hypertensive crisis varied. Evaluation of a patient with new diagnosis of PH was the most frequent indication (23.7%) followed by vasoreactivity testing (21.8%), medication titration (21.8%), and routine testing in all patients for hemodynamic measurements (18.2%). Other indications included patients with conflicting clinical and echocardiogram data, those selected on a case by case basis, specific interventions, and substantial changes in clinical course or PH that was refractory to escalating care (14.6%).

Pharmacotherapy for Pulmonary Hypertensive Crisis

Institutions reported using a full spectrum of medications to manage a pulmonary hypertensive crisis (**Fig. 2**). All respondents reported using inhaled nitric oxide (iNO) therapy with maximum

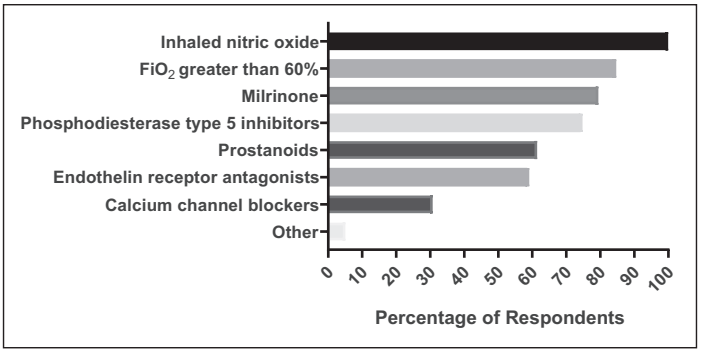

Figure 2. Pharmacologic therapies for pulmonary hypertensive crisis. Percentage of respondents stating institutional use of medication or pharmacotherapy class.

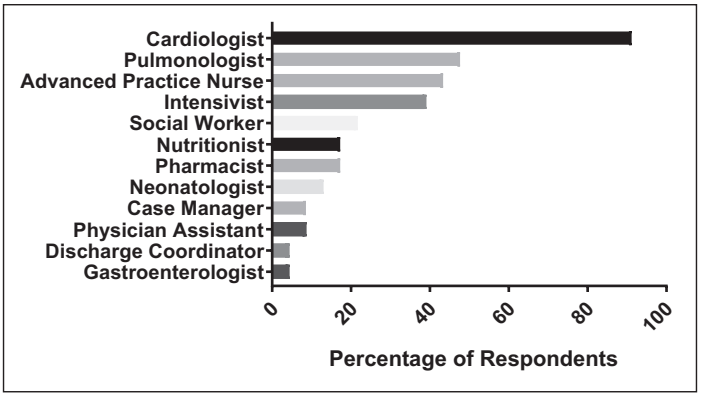

Figure 3. Composition of multidisciplinary care. Percentage of respondents stating discipline participated in the institutional pulmonary hypertension team.

concentrations ranging from 20 to 80 parts per million. When iNO therapy was deemed no longer necessary, most institutions (68.4%) followed a weaning protocol that was driven by either the respiratory therapist (53.1%) or the prescriber (43.8%). One respondent stated that a protocol existed only for neonates. No institution used an iNO-tapering protocol that was driven by beside nurses. The most frequently referenced criteria for weaning were oxygen saturation via pulse oximetry and partial pressure of arterial oxygen (38.1% and 30.2% of respondents, respectively). The two other most frequently prescribed medications were supplemental oxygen at concentrations greater than 60% and milrinone. Additional pulmonary vasodilators included the following (in descending order of frequency in reporting): phosphodiesterase type 5 inhibitors, prostacyclin analogs, and endothelin receptor antagonists. Phosphodiesterase type 5 inhibitors were prescribed enterally by nearly all institutions that used them in the setting of pulmonary hypertensive crisis (96.6%), with 44.8% reporting additional use as scheduled parenteral dosing, and 17.2% using parenteral infusions. Of those who prescribed prostanoid therapies, 87.5% used parenteral IV infusion, 45.8% used a continuous inhaled delivery method, 41.7% employed intermittent inhalation therapy, and 33.3% used subcutaneous delivery (respondents were able to select as many as applied).

Supportive Care

Supportive care for patients in pulmonary hypertensive crisis was addressed by questions regarding vasoactive infusions, mechanical ventilation, and sedation. Milrinone and epinephrine were the two most frequently reported circulotropic medicines prescribed, with 97.3% of respondents using milrinone and 83.3% using epinephrine frequently, very frequently, or always. Use patterns for dopamine were mixed, with 41.2% of respondents stating that it was used frequently, very frequently, or always, but 58.8% reporting that it was rarely or never used. The pattern of dobutamine use was similar to that of dopamine, as 21.9% of respondents reported frequent or very frequent use and 78.1% reported rarely or never using the agent. Over 75% of respondents reported that phenylephrine and vasopressin were rarely or never used, and 93.8% reported never using norepinephrine.

Conventional forms of mechanical ventilation were preferred over high-frequency oscillatory ventilation. However, survey results showed no preference for either volume or pressure control modes (reported by 40.5% and 37.8% of respondents, respectively) during conventional ventilation. Only one respondent (2.7%) stated a preference for high-frequency oscillatory ventilation. The remaining 19% stated "other" for preferred method with the qualifiers "depends on [the] case" or "all can be used and it is physiology-specific." For patients that require sedation for safety, comfort, and alleviation of agitation, the medications of choice were fentanyl (94.7%), dexmedetomidine (79%), and midazolam (73.7%), with 87.2% of respondents preferring continuous infusions over intermittent dosing. Two-thirds of respondents reported using neuromuscular blocking agents frequently, very frequently, or always in patients with pulmonary hypertensive crisis.

Multidisciplinary Teams

A formal PH consulting service/team was reported at 51.1% of institutions. Team composition with regards to included personnel varied (**Fig. 3**). Nearly all institutions (91.3%) reported that a cardiologist was on the team, with pulmonologists and advanced practice nurses representing the second and third most common disciplines, respectively.

Future Directions

Of the 49 respondents, 17 (34.7%) provided free-text responses on next-generation innovations in the management of pulmonary hypertensive crisis. The answers focused on three areas: therapeutics ("more specific pulmonary vasodilators" and "use of ECMO in extubated patients in extreme cases to prepare for lung transplant"); detection and prevention ("better non-invasive monitoring of [pulmonary] pressure and response to therapy," "preventing its occurrence," and "improvement in continues monitoring at the bedside"); and coordination of care ("dedicated treatment teams").

DISCUSSION

To our knowledge, this was the first survey to characterize the care of children with acute pulmonary hypertensive crisis in PICUs in the United States and Canada. Our results revealed variability among institutions in the frequency of patients who require PICU-level care, in the therapies prescribed both for specific pulmonary vasodilation and general PICU care, and in the composition of medical teams that care for these patients. Similarly, imaging and diagnostic modalities were heterogeneous. Almost

two-thirds of institutions had formalized echocardiographic protocols but with differences in reported metrics. Indications for cardiac catheterization during an admission for pulmonary hypertensive crisis were even more disparate. iNO was used universally in children with pulmonary hypertensive crisis but at no standard dose, and weaning protocols, when used, were driven with nearly equal frequency by respiratory therapists or prescribers. At institutions that used phosphodiesterase type 5 inhibitors and prostanoids, the routes of administration varied. Epinephrine was the preferred vasoactive infusion after milrinone, and no one mode of mechanical ventilation was more prevalent than others. Fentanyl was the overwhelmingly preferred medication for sedation when needed. Last, only half of the institutions surveyed had a formalized PH consulting service. In those that did have one, a cardiologist was the most frequent team member followed by a pulmonologist. The findings of this survey support the conclusion that variability is wide in the overall care of pediatric patients with acute pulmonary hypertensive crisis admitted to a PICU in North America.

Pulmonary hypertensive crisis consists of an acute increase in pulmonary arterial pressure and vascular resistance leading to RV failure and the potential for total cardiovascular collapse (arrest) and death (23, 24). Triggers vary and include intercurrent infections, periprocedural events, vasodilator therapy manipulation, systemic noxious stimuli, and physiologic imbalances such as hypoxia and acidosis (25, 26). In this survey study, the most common reason reported for admission of a patient with pulmonary hypertensive crisis to a PICU was perioperative crisis, and multiple single-center studies have shown substantial increases in morbidity and mortality in children with PH after both heart disease- and non-heart disease-related procedures (9–12, 25). In a large multicenter prospective cohort, children admitted to an ICU with PH had higher mortality rates, longer hospitalizations, and required more invasive therapies than children admitted without PH (27). Published North American guidelines for the care of children with PH direct little attention to ICU-specific care (28, 29). Additional focus is needed on ICU-specific therapies and on pulmonary hypertensive crisis as a consequence of another primary disease process (25, 28). European guidelines do directly discuss care of pulmonary hypertensive crisis in the ICU, yet rely on expert consensus rather than clinical studies because there are very few data for children (5).

Pulmonary vasodilator therapy during pulmonary hypertensive crisis varies from the algorithms that are presented in existing pediatric guidelines from the American Heart Association/American Thoracic Society and the European Paediatric Pulmonary Vascular Disease Network (5, 29). Although iNO and prostanoids are widely used for direct vasodilator therapy during acute crisis, we found considerable variation in administration practices (5, 25, 28, 30, 31). All institutions reported the use of iNO but without consensus on prescribed dose. Furthermore, there was limited consensus on how to wean iNO therapy when no longer indicated. In this survey, phosphodiesterase type 5 inhibitors were used with greater frequency than prostanoids during acute pulmonary hypertensive crisis. This greater use of phosphodiesterase type 5 inhibitors mirrors findings from surveys on the management of PH in adults. The less frequent use of prostanoids than phosphodiesterase type 5 inhibitors also diverges from consensus recommendations for prostanoid therapy as a first line targeted pulmonary vasodilator during pulmonary hypertensive crisis. It is important to note that recommendations for prostanoid use include the presence of capability and experience monitoring and mitigating the systemic arterial hypotension that may occur with the initiation and titration of prostacyclin analogs (5, 14, 15).

Although focused on the management of acute postoperative pulmonary hypertensive crisis, North American pediatric guidelines specifically recommend fentanyl for sedation, and this was the agent preferred by our respondents (25, 28). Muscle relaxants are also recommended, along with adequate analgesia and sedation, to prevent sympathetic stress that may acutely raise pulmonary vascular resistance. In this survey, most respondents reported the use of neuromuscular blocking agents. No specific directions have been published regarding the use of inotropes and vasopressors, a fact that was reflected in our study by a preference for epinephrine, but also wide variability in the use of all agents. Finally, adequate oxygenation and ventilation are recommended to ameliorate pulmonary vasoconstriction, and most respondents reported using high concentrations of supplemental oxygen acutely without a consistently preferred method of mechanical ventilation.

No published guidelines discuss the use of multidisciplinary and multiprofessional teams in the care of children with PH or acute pulmonary hypertensive crisis, despite the multisystem nature of the acute physiologic derangements in these patients. Collaboration among multidisciplinary programs in other forms of pediatric critical illness has yielded improvements in patient care with respect to guideline adherence and outcomes (32–34). Half of the respondents to this survey reported having a multidisciplinary team, and a pediatric cardiologist was the most frequently represented subspecialist. Pediatricians with interests in treating children with PH come from several different backgrounds and training programs that may inform their varying perspectives on therapeutics. Harnessing these unique perspectives on complex patient care may provide creative solutions to multifaceted patient problems including approaches to acute sedation and management of mechanical ventilation.

Although all respondents reported that patients with pulmonary hypertensive crisis are admitted to an ICU setting at their institutions, less than half of the respondents reported that an intensivist was a member of the multidisciplinary PH team. Intensivists may serve as crucial links between other PH experts and the expertise and dynamics of the PICU team. Furthermore, comprehensive care of critically ill children often includes expertise from other professions, including advanced practice providers, social workers, pharmacists, nutritionists, and case managers who assist in providing care for the child and family. Advanced practice nurses were noted to be present on 40% of PH teams. Opportunities exist to integrate multiprofessional and multidisciplinary expertise to improve outcomes for these patients (31).

In 2012, the Pulmonary Hypertension Association's Scientific Leadership Council recognized the need for standardization of

PH care and developed criteria for PH Care Centers (35). Since then, over 55 programs have received accreditation, but only eight currently exist for pediatric patients (36). Additionally, the process is currently voluntary and smaller programs may not meet the accreditation criteria, despite ongoing programs for the care of these patients (36). This notion is mirrored in the comments section of our survey in which respondents stated that creation of dedicated PH treatment teams was an important next step in the care of children with pulmonary hypertensive crisis. Standardized evidenced-based guidelines with adaptation for local implementation are needed. Given the wide-ranging number of critically ill children with pulmonary hypertensive crisis admitted at institutions, specific guidelines could benefit all by providing a framework of care. The creation and integration of pediatric PH networks and registries may provide insight into these best practices (37).

This study had some noteworthy limitations. First, the low survey response rate of 50% and varying rates of completion within those responses may affect the generalizability of results. However, 80% of PPHNet sites completed the survey which provided a high rate of expert responses. Additionally, selection bias may exist if the nonrespondents had limited experience in treating children with acute pulmonary hypertensive crisis. Second, we do not know if survey respondents were the institutional experts in acute pulmonary hypertensive crisis care—the survey was sent to the PICU medical director or institutional fellowship training program director with instructions to forward to the individual with the most experience in treating acute pulmonary hypertensive crisis in a PICU. We were unable to track whether this forwarding actually occurred and this factor may have had an impact on some respondents' interpretation of the term "pulmonary hypertensive crisis." A small subset of the surveys were sent directly to the institutional contact member for PPHNet, and this individual was most often not an intensivist. Although nearly three-quarters of the respondents had over a decade of experience after fellowship training, it is unclear if this duration correlated with experience in treating children with pulmonary hypertensive crisis. Additionally, only one survey was sent to each institution, and we therefore cannot account for intra-institutional practice variations among providers of PH and pulmonary hypertensive crisis care. Finally, as the responses were self-reported and based on recall of patterns, the stated behaviors and patient management may not completely reflect the day-to-day practice occurring at the bedside.

CONCLUSIONS

Children with acute pulmonary hypertensive crisis receive heterogeneous care in the United States and Canada. Disease management varies widely, from the location of patient admission and members of the care team to the direct pulmonary vasodilators prescribed and supportive therapies used. Currently, North American guidelines for the care of pediatric patients with acute pulmonary hypertensive crisis are lacking, and data regarding best practices are sparse. Additional investigation is needed to derive algorithms for optimal care by studying patient outcomes after standardized changes in guidelines are tested.

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