Research Article

Pulmonary Circulation

Survey of practices in relation to chronic pulmonary hypertension in neonates in the Canadian Neonatal Network and the National Institute of Child Health and Human Development Neonatal Research Network

Michelle Baczynski[1], Edward F. Bell[2], Emer Finan[3,4,5], Patrick J. McNamara[2,6] and Amish Jain[3,4,5]

[1]Respiratory Therapy, Mount Sinai Hospital, Toronto, Canada; [2]Division of Neonatology, University of Iowa Stead Family Children's Hospital, Iowa City, IA, USA; [3]Department of Pediatrics, Mount Sinai Hospital, Toronto, Canada; [4]Lunnenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada; [5]Department of Paediatrics, University of Toronto, Toronto, Canada; [6]Physiology, University of Toronto, Toronto, Canada

Abstract

Current knowledge gaps pertaining to diagnosis and management of neonatal chronic pulmonary hypertension (cPH) may result in significant variability in clinical practice. The objective of the study is to understand cPH management practices in neonatal intensive care units affiliated with the Canadian Neonatal Network (CNN) and National Institute of Child Health and Human Development Neonatal Research Network (NRN). A 32-question survey seeking practice details for cPH evaluation, diagnostic criteria, conservative measures, pharmacotherapeutics, and follow-up was e-mailed to a designated physician at each center. Responses were described as frequency (percentage) and compared between CNN and NRN, where appropriate. Overall response rate was 67% (CNN 20/28 (71%), NRN 9/15 (60%)). While 8 (28%) centers had standardized management protocols, 17 (59%) routinely evaluate high-risk patients; moderate-severe chronic lung disease being the commonest indication. While interventricular septal flattening on echocardiography was the commonest listed diagnostic criterion, several adjunctive indices were also identified. Asymptomatic neonates with cPH were managed expectantly (routine care) in 50% of sites, and using various conservative measures in others. Pulmonary vasodilators were prescribed for symptomatic cases, with 60% of sites using them early (86% reporting any use). Seventy-five percent of sites use inhaled nitric oxide and sildenafil citrate as first- and second-line agents, respectively. Use of standard protocols, cardiac catheterization, and conservative measures for asymptomatic cases was more common in NRN units ($p < 0.05$). While there is relative homogeneity in patient identification and diagnostic criteria used for neonatal cPH, significant interunit inconsistencies still exists in routine evaluation, use of additional investigations, management of asymptomatic cases, frequency and type of conservative measures, and choice of pulmonary vasodilators.

Keywords

chronic lung disease, pulmonary vascular disease, prematurity

Date received: 11 May 2020; accepted: 3 June 2020

Pulmonary Circulation 2020; 10(3) 1–9
DOI: 10.1177/2045894020937126

Introduction

Chronic pulmonary hypertension (cPH) is a serious secondary complication of chronic lung disease (CLD) among preterm infants and is associated with increased morbidity and mortality.[1–4] Various pharmacotherapies developed for older patients with pulmonary arterial hypertension are

Corresponding author:
Amish Jain, Department of Pediatrics, Room 19-231P, Mount Sinai Hospital, 600 University Ave, Toronto, ON M5G 1X5, Canada.
Emails: amish.jain@sinaihealth.ca; amishjain@gmail.com

currently being used in tertiary neonatal intensive care units (NICUs) despite a paucity of data regarding their efficacy and safety.[5–9] Knowledge gaps exist regarding day-to-day care of neonates with cPH, specifically, diagnostic practices and criteria, the role of echocardiography and optimal time of screening, post-diagnostic care and disease management, the role of invasive diagnostic testing, and follow-up practices. Although expert consensus guidelines have been published,[10–12] a lack of robust evidence evaluating the role of various therapeutics for cPH associated with CLD may result in inconsistency and variance of cPH management across NICUs. Ascertaining and understanding practice variability is an important first step toward the design of systematic research studies and quality improvement initiatives to improve the care of these neonates. A survey including 12% of neonatology members affiliated with the American Academy of Pediatrics (AAP) highlighted variability in broad categories of cPH management.[13] Specific practices such as diagnostic thresholds and pharmacotherapeutics employed at the patient level were not evaluated, needing further investigation. In addition, whether such variability exists in Canadian tertiary NICUs is not known.

Our primary objective was to ascertain and describe the areas of commonality and divergence in specific diagnostic and management practices in relation to cPH in premature neonates across centers. For this, we conducted a unit-level survey of all tertiary NICUs affiliated with the Canadian Neonatal Network (CNN) in Canada and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) in the United States. Our secondary objective was to compare practices in centers affiliated with CNN to those in NRN. We hypothesized that there would be significant variation in management of cPH in premature neonates across centers.

Method

Study population, survey and distribution

A 32-question detailed survey was developed and distributed using electronic mail (e-mail) attachment to each of the 28 tertiary NICUs in Canada affiliated with the CNN and the 15 clinical centers of the NRN in 2018; only one survey was e-mailed for each eligible unit. In units with a known targeted neonatal echocardiography (TNE) program, its lead physician was preferentially contacted in light of the expertise and likely involvement in the diagnosis and management of cPH. In units without a TNE program, the NICU clinical director was contacted to complete the survey or designate a physician with in-depth knowledge of relevant unit practices. The e-mail sent to physicians outlined the purpose of the study and instructions for survey completion. Two reminder e-mails with the attached survey were re-sent after one and two weeks, respectively. Respondents were required to acknowledge their participation in the research study (survey question #1) in order for their responses to be reviewed. All of the surveys were completed anonymously, and no identifiers were used. This project was approved by the Research Ethics Board at the primary site, Mount Sinai Hospital, Toronto, Canada.

Survey

The survey was prepared by study investigators who have well-known expertise in neonatal cardiovascular physiology and TNE. Independent feedback for our survey was sought from two non-TNE neonatologists not involved in the study, and based on their feedback, the survey was revised. The survey, comprising 32 questions, was organized into six categories: (i) participant information and unit demographics, (ii) patient identification and screening, (iii) diagnostic criteria, (iv) management principles, (v) pulmonary vasodilators and other agents, and (vi) monitoring and follow-up. The participant information and unit demographics section was developed to appraise the professional background of physicians providing survey responses and to understand the demographics of each participating unit. Questions regarding patient selection and screening were included to determine whether sites performed routine screening for cPH and on what basis, or in the absence of routine screening, how patients were identified for targeted evaluation. We also sought to understand what screening tools were used, i.e. echocardiography, electrocardiogram, brain natriuretic peptide (BNP), etc. In the section for diagnostic criteria, the specific echocardiography criteria used for cPH identification were listed for ranking. Questions were also developed to understand other investigations that were being employed in patients diagnosed with cPH, to evaluate for other contributory diagnoses such as aspiration and gastroesophageal reflux. The section pertaining to management principles sought to explore different therapeutic and pharmacological strategies, whether standardized, prophylactic, or targeted, and the use of conservative treatment measures (diuretics, adjustment of oxygen saturation targets, bronchodilators, etc.) for symptomatic or asymptomatic neonates with a diagnosis of cPH. Further, our aim was to describe the use of specific pulmonary vasodilator therapy and the clinical features leading to their prescription. The last section on monitoring and follow-up examined the frequency and nature of in-hospital and postdischarge follow-up practices.

Data analysis

We decided a priori to include only the returned surveys that had at least 85% of fields completed. For included surveys, results are presented as frequency (percentage), unless stated otherwise. To calculate percentage, the denominator consisted only of the completed fields. For example, if a question was unanswered in one of the returned surveys, it was not included in the denominator to calculate percentage. The survey

responses are collated and described by category of questions, as stated above. Responses from the CNN and NRN were compared, when appropriate, using Fischer's exact test. A p value < 0.05 was considered statistically significant.

Results

Unit demographics and cPH evaluation practices

In total, 29 (67%) of the 43 surveys were returned (20/28 (71%) and 9/15 (60%) for CNN and NRN, respectively); all returned surveys had greater than 85% of responses completed. Sixteen (55%) surveys were completed by delegated neonatologists, 11 (38%) by site TNE physician-leads, and 2 (7%) by site clinical directors. The majority of participating centers care for both inborn and outborn patients, and all but three CNN sites are either moderate or high-volume units (Table 1). Screening for cPH in high-risk neonates was reported as a routine practice by 17 (59%) sites, while the remaining 12 sites perform evaluations only if clinically indicated. Moderate to severe CLD was the most commonly reported screening criterion, while worsening or lack of expected progress in respiratory status is the most common clinical indication for cPH evaluation in "non-screening" sites. Five sites reported screening high-risk patients sequentially on more than one occasion, while one site reported rarely evaluating any neonate for cPH. The investigation of choice for cPH evaluation is echocardiography in all but one center. Echocardiography service is provided by both cardiology and TNE service in 13 (45%) sites, cardiology only or TNE only in 14 (48%) and 2 (7%) site(s), respectively.

Table 1. Demographic details of participating units ($n = 29$) and practices related to evaluation for chronic pulmonary hypertension (cPH) in neonates in units affiliated to Canadian Neonatal Network (CNN) and Neonatal Research Network (NRN).

Variable	Frequency (percentage)
Type of center	
Mixed inborn and outborn	21 (72)
Predominantly inborn	7 (24)
Predominantly outborn	1 (3)
Patient type and volume	
Mixed medical and surgical patients	19 (66)
Predominantly medical patients	10 (34)
High volume (>100 VLBW neonates/year)	15/28 (54)
Moderate volume (50–100 VLBW neonates/year)	10/28 (36)
Low volume (25–49 VLBW neonates/year)	3/28 (11)
Screening criteria followed ($n = 17$)	
Moderate or severe chronic lung disease	16 (94)
Birth weight <1 kg	8 (47)
Gestational age at birth <28 weeks	9 (53)
Prior episode of acute pulmonary hypertension	4 (24)
Timing of first cPH screen	
>36 weeks postmenstrual age	12 (71)
34 to 36 weeks postmenstrual age	3 (18)
<34 weeks postmenstrual age	2 (12)
Clinical signs prompting evaluation in "non-screening" sites ($n = 12$)	
Worsening/lack of progress in respiratory status	11 (92)
Signs of congestive heart failure	8 (67)
Poor growth	4 (33)
Difficulty feeding	1 (8)
Physician speciality primarily leading the ongoing management of cPH	
Neonatology	17 (59)
Pediatric cardiology	12 (41)
TNE trained neonatologists	5 (17)
Pulmonary hypertension teams	5 (17)
Respirologists/pulmonologists	4 (14)

VLBW: very low birth weight (<1500 grams at birth); TNE: targeted neonatal echocardiography.

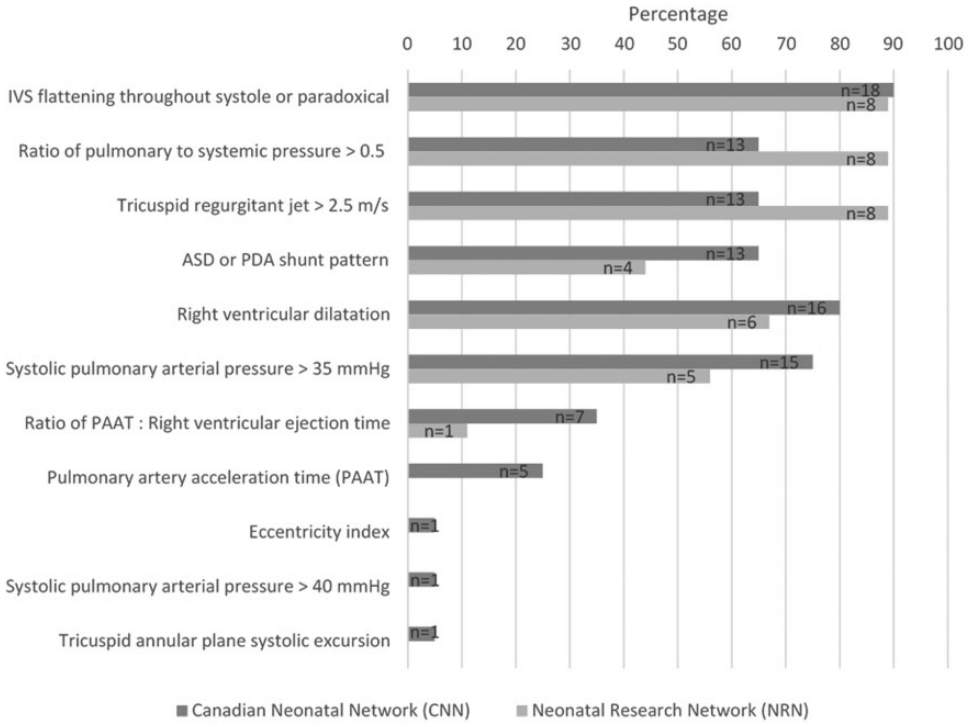

Fig. 1. Echocardiography criteria employed for diagnosis of chronic pulmonary hypertension (cPH), responses from Canadian Neonatal Network (CNN) and Neonatal Research Network (NRN) sites. Responses are graphed as percentage of total respondents from CNN ($n = 20$) and from NRN ($n = 9$). The differences between CNN and NRN sites with respect to type of diagnostic criteria used were not statistically significant; p value > 0.05 for all comparisons.
IVS: interventricular septum; >: greater than; m/s: meters per second; ASD: atrial septal defect; PDA: patent ductus arteriosus; mmHg: millimeters mercury; PAAT: pulmonary artery acceleration time.

Diagnostic and management principles

Several echocardiography criteria were reported as being employed for diagnosis of cPH across surveyed sites, with no significant difference between sites from CNN and NRN (Fig. 1). Interventricular septal flattening in systole and right ventricular dilatation are the most common echocardiography diagnostic criteria. Twenty-six sites reported performing additional investigations for neonates diagnosed with cPH including chest X-ray (17; 65%), electrocardiogram (15; 58%), BNP (6; 23%), and cardiac catheterization (5; 19%). In terms of management, while it was reported that asymptomatic neonates with cPH are more likely to be managed expectantly, symptomatic neonates with cPH are more likely to receive cPH-related conservative measures (adjustment of oxygen saturation targets, restriction of total fluid intake, diuretic therapy), pulmonary vasodilatory therapies, and more frequent echocardiography monitoring (Table 2). The following are the oxygen saturation target adjustments reported by sites ($n = 25$): > 95% (18; 72%), 90%–94% (5; 20%), > 92% (1; 4%), and 92%–96% (1; 4%). The sites employing diuretics in cPH management ($n = 23$) often used multiple agents, including hydrochlorothiazide and spironolactone (Aldactazide) (15; 65%), oral furosemide (12; 52%), intravenous furosemide (10; 43%), hydrochlorothiazide (4; 17%), and spironolactone (2; 9%). The indications reported for using diuretics were signs of congestive heart failure (20; 87%) and presence of moderate to severe CLD (14; 61%). Only seven sites reported frequently evaluating neonates with cPH for oropharyngeal or gastroesophageal dysfunction, and only six sites reported frequently evaluating for upper airway anomalies. The remaining sites seldom perform any of these evaluations for neonates with a diagnosis of cPH.

Use of pulmonary vasodilator therapy

A number of therapies were reported as being in use across both networks, of which inhaled nitric oxide (iNO) and sildenafil citrate were listed as the most common first- and second-line agents (Table 3). Overall, 25 (86%) sites reported any use of pulmonary vasodilator therapy at some point, of which 15 (60%) reported prescribing it for initial management in neonates with cPH deemed to be symptomatic. One site reported prescribing pulmonary vasodilator agents in asymptomatic cPH neonates. Pulmonary vasodilator therapies were being prescribed based on echocardiography features (22; 88%), symptoms of congestive heart failure (13; 52%), and serum biomarkers (5; 20%).

Follow-up arrangements for neonates with cPH

Of the 27 sites who completed the post-discharge follow-up section of the survey, 19 (70%) sites reported organizing

Table 2. Management principles employed for neonates with a diagnosis of chronic pulmonary hypertension (cPH) deemed to be asymptomatic versus symptomatic in units to Canadian Neonatal Network (CNN) and Neonatal Research Network (NRN).

	Asymptomatic neonates with cPH, $n = 28$	Symptomatic neonates with cPH $n = 28$	p value
Management practices			
Expectant	14 (50)	0 (0)	<0.01
Conservative	13 (46)	21 (75)	0.05
Use of conservative measures			
Oxygen saturation targets adjusted	14 (50)	25 (89)	<0.01
Restricted total fluid intake	5 (18)	13 (46)	0.04
Increased caloric intake	10 (36)	17 (61)	0.11
Inhaled corticosteroids	2 (7)	5 (18)	0.42
Systemic corticosteroids	3 (11)	5 (18)	0.70
Inhaled bronchodilator, therapy	0 (0)	4 (14)	0.11
Diuretic therapy	5 (18)	16 (57)	<0.01
Gastroesophageal reflux treatment	2 (7)	10 (36)	0.02
Use of specific pulmonary vasodilator therapy	1 (4)	15 (54)	<0.01
Frequency of echocardiography surveillance			
Weekly	4/27 (15)	14 (50)	<0.01
Biweekly	8/27 (30)	7 (25)	0.77
Monthly	11/27 (41)	2 (7)	<0.01
No fixed frequency	4/27 (15)	5 (18)	1.0

Values are listed as frequency (percentage). Expectant management indicates no specific changes made to clinical management based on a diagnosis of cPH. Conservative measures indicate the use of supportive treatment targeted toward a diagnosis of cPH. One site was excluded from analysis as it left this section of the survey unanswered. One additional site was excluded from the frequency of echocardiography surveillance of asymptomatic neonates with cPH as it left this section of the survey unanswered.

Table 3. Specific pulmonary vasodilator therapy prescribed to neonates with a diagnosis of chronic pulmonary hypertension (cPH) in units affiliated to Canadian Neonatal Network (CNN) and Neonatal Research Network (NRN).

	Inhaled nitric oxide	Sildenafil citrate	Milrinone	Bosentan
CNN, $n = 17$				
First line	13 (76)	3 (18)	1 (6)	0 (0)
Second line	2/16 (13)	12/16 (75)	1/16 (6)	1/16 (6)
NRN, $n = 8$				
First line	6 (75)	2 (25)	0 (0)	0 (0)
Second line	0 (0)	6 (75)	0 (0)	2 (25)

Values are listed as frequency (percentage). Centers were asked to only rank therapies currently in use in their respective site. Seventeen out of 20 CNN sites and 8 out of 9 NRN sites ranked each of the four listed therapies. One CNN site selected only one therapy being in use. p value > 0.05 for all CNN versus NRN comparisons.

specific follow-up for all neonates diagnosed with cPH during NICU stay, while 6 (22%) sites organize follow-up only for neonates with cPH who receive treatment while admitted to NICU. The specialist services receiving referrals include pediatric cardiology (25; 93%), pediatric respirology/pulmonology (20; 74%), community pediatrics (14; 52%), and pulmonary hypertension specialists (10; 37%). All but three sites refer infants to more than one specialist service at discharge. The timing of first follow-up appointment varies from < 6 weeks postdischarge (13; 48%), > 6 weeks (6; 22%) postdischarge, and being decided on a case-by-case basis (8; 27%).

Comparison between CNN and NRN

While the use of echocardiography as a screening tool was almost universal between sites in both networks, NRN sites were more likely to have a standardized management approach, employ cardiac catheterization in the diagnostic work-up, and prescribe conservative treatment measures in

Table 4. Comparison of management principles of chronic pulmonary hypertension (cPH) between Canadian Neonatal Network (CNN) and Neonatal Research Network (NRN) sites.

	CNN, $n = 20$	NRN, $n = 9$	p value
Performance of routine screening for cPH	10 (50)	7 (78)	0.32
Echocardiography as screening tool	20 (100)	8 (89)	0.31
Additional investigation using cardiac catheterization	1 (5)	4 (44)	0.04
Standardized management approach	3 (15)	5 (56)	0.07
Management principles for asymptomatic infants			
Expectant	12/19 (63)	2 (22)	0.10
Use of conservative measures	6/19 (32)	7 (78)	0.06
Use of specific pulmonary vasodilator therapy	1/19 (5)	0 (0)	1.0
Management principles for symptomatic infants			
Expectant	0/19 (0)	0 (0)	1.0
Use of conservative measures	16/19 (84)	5 (56)	0.24
Use of specific pulmonary vasodilator therapy	10/19 (53)	5 (56)	1.0

Values are listed as frequency (percentage). Expectant management indicates no specific changes made to clinical management based on a diagnosis of cPH. Conservative measures indicate the use of supportive treatment targeted toward a diagnosis of cPH, including oxygen saturation limits adjusted, restricted total fluid intake, increased caloric intake, inhaled corticosteroids, systemic corticosteroids, diuretic therapy, and/or gastro-esophageal reflux treatment. One site was excluded from analysis as it left this section of the survey unanswered.

management of neonates with cPH deemed asymptomatic (Table 4). The management of symptomatic neonates with cPH was similar in sites from both networks.

Discussion

Knowledge that neonates who develop cPH in association with CLD have a significant risk of adverse outcomes is a matter of concern for neonatal clinicians.[1–4] The risk is further compounded by lack of good quality evidence to guide day-to-day diagnostic and management practices, including the role of various conservative and specific pharmacological therapies. This paucity of data may in part explain the variability in management practices observed across NICUs, as clinicians may feel compelled to employ different strategies in attempt to mitigate the additional burden of illness imposed by cPH in neonates with CLD. Analogous to a recent clinician-level survey of AAP affiliated neonatologists broadly examining cPH-related management practices,[13] our unit-level survey of two neonatal networks found comparable rates of utilization of routine screening for cPH (AAP: 46% vs. CNN & NRN: 66%), any use of pulmonary vasodilator therapy (AAP: 90% vs. CNN & NRN: 86%), and use of cardiac catheterization (AAP: 11% vs. CNN & NRN: 17%). We further expanded our survey to examine the details of various specific aspects of day-to-day care of neonates with cPH in tertiary NICUs, the purpose of which was to provide granularity and important insight toward advancing knowledge in this field. We identified the following practices almost universally reported across all participating NICUs, moderate or severe CLD as screening criteria, timing of the first screening ≥ 34 weeks postmenstrual age (PMA), echocardiography as the diagnostic tool of choice, presence of flat interventricular septal motion in end-systole as diagnostic criteria, use of conservative measures and specific pharmacotherapies in neonates with cPH deemed symptomatic, and post-discharge follow-up of those receiving therapeutic interventions in NICU. Conversely, routine screening versus clinically indicated evaluation, adjunctive echocardiography diagnostic criteria, additional investigations for those with a diagnosis of cPH, evaluation for contributory diagnoses in cPH, use of expectant management versus conservative measures in asymptomatic neonates with cPH, types of conservative measures, and use of pulmonary vasodilator therapies were identified as areas of significant unit-to-unit variability.

Differences between CNN and NRN sites

Several expert consensus-based guidelines have consistently recommended routine echocardiography screening of neonates at risk of cPH, having a systematic approach incorporating various conservative measures for those diagnosed with cPH and consideration for cardiac catheterization and pulmonary vasodilator therapies in atypical and progressive cases.[10–12] On the contrary, some authors have argued against routine screening until a particular management strategy is proven to improve outcomes.[14] Our survey results indicate that more participating units affiliated with NRN were in compliance with expert guidelines as compared to CNN sites. Although we did not specifically elucidate the reasons for this disparity, it may indicate a higher prevalence of conflicting viewpoints among Canadian centers. However, these differences may also reflect a relative lack of awareness; of the 20 respondents from CNN, only 3 reported having a unit standardized cPH management approach. A Canadian national guideline issued by a relevant body may help bridge this gap and reduce practice

inconsistencies across CNN. Whether a proactive diagnostic and management approach, as followed more by units in NRN, results in better clinical outcomes needs to be tested in future studies.

cPH diagnostics

The majority of previous studies highlighting the adverse effects of cPH in CLD patients have used qualitative echocardiography diagnostic criteria, namely flat interventricular septum in end-systole and right ventricular dilatation.[2,15,16] These were also the most frequently used clinical diagnostic definitions across surveyed sites. However, several adjunctive quantitative echocardiographic indices are also employed in cPH diagnosis by units across both networks. Interestingly, none of these parameters have a validated diagnostic threshold established for cPH in neonates. Our survey has revealed an interest in the neonatal community for incorporating both qualitative and quantitative echocardiography measures in clinical practice, which may allow for better quantification of disease severity and monitor progression. We have identified several such parameters to help inform future research. There was also variability in the use of additional investigations in neonates with cPH, which likely reflects the non-definitive nature of evidence currently available. A few small observational studies have indicated clinically meaningful alterations in serum levels of BNP, and more recently urinary levels of N-terminal pro-BNP in neonates with cPH[17–19]; however, adequately powered studies are needed to define robust diagnostic thresholds and their clinical application. The use of cardiac catheterization was relatively infrequent in participating centers, particularly in CNN. This may reflect a relative lack of access to relevant facilities and/or a reluctance on the part of clinical teams due to the logistic challenges and side effects associated with invasive procedures in this patient population. Recognizing these issues, the Pediatric Pulmonary Hypertension Network guidelines also urged clinicians to carefully balance the risks associated with cardiac catheterization against the need to obtain critical diagnostic information for clinical decision making in this population.[11]

cPH management

Interesting intraunit differences were identified in the management of cPH. While several units, particularly those affiliated with CNN, reported choosing expectant management (no specific changes made to clinical practice) for neonates with cPH deemed asymptomatic, others prefer a range of conservative measures. This variability likely stems from a lack of understanding of the natural history of cPH when it is not modulated by clinical interventions and the impact of cPH on post-discharge outcomes, highlighting another area for future investigation. Among conservative measures, the most common intervention practiced by participating units was adjustment of oxygen saturation targets to $> 95\%$, suggesting that neonatal physicians are cognizant of the cumulative effect of hypoxic episodes in the pathophysiology of cPH.[20] The impact of higher oxygen saturation on subsequent course in established disease and the target range which provides the optimal balance between avoidance of hypoxia and hyperoxia require further investigation. Several sites also reported prescribing diuretic therapy in the presence of signs and symptoms of congestive heart failure (generalized edema, tachypnea, tachycardia, and diaphoresis), providing further grounds for future physiological and epidemiological investigations.

While the majority of centers reported using pulmonary vasodilator therapies only for symptomatic cases, and iNO and sildenafil citrate were the most commonly used agents, it was surprising to note that most units across both networks selected iNO as their favored first-line agent. While there is no randomized control trial for the management of cPH in neonates, sildenafil citrate is the most frequently described therapeutic agent in case series.[5–7] A recent systematic review presented pooled data from 5 such reports, including 101 neonates with cPH, demonstrating the wide range of age at treatment initiation and dosing schedule being used in clinical practice.[9] While there was no significant acute side effect noted, and a reduction in pulmonary pressures was described after one to six months of therapy in three-fourths of cases, the pooled mortality rate was high at 28%. This likely reflects the illness severity of cases selected for treatment, and the role of sildenafil citrate in neonatal cPH management remains unanswered. Although there is some evidence that iNO may acutely improve oxygenation and indices of pulmonary vascular resistance in neonates with CLD,[21–23] iNO as a treatment for cPH in neonates has not been described. Further, iNO is an inhaled medication with a short half life and requires a cumbersome delivery apparatus making it less suitable for medium to long-term use. Our survey did not examine the specific rationale for a unit's choices of therapeutic agents; it is possible that physicians' familiarity with iNO, its proven safety profile in neonates, and in-patient nature of NICU practice may be contributing factors in its selection as the first-line pulmonary vasodilator agent. There is an urgent need for randomized control trials in pharmacotherapeutic management of cPH in neonates. Our data may help establish equipoise for undertaking such investigations and its design. Further, our survey provides granular data for various aspects of clinical care in neonatal cPH, which may facilitate consensus building and plan quality improvement initiatives to improve short- and long-term outcomes of this vulnerable patient population.

Limitations

There are some important limitations to our study. *First*, we did not have responses from all CNN and NRN sites, and while this is a common complication of this study design, our overall response rate was comparable with similar

studies.[24,25] Further, the majority of units that responded had high patient volumes, likely accounting for a large proportion of cPH-related practices within the network. *Second*, while CNN includes all tertiary centers in Canada, NRN is one of the several major neonatal networks existing in the United States and may not reflect management practices on a national scale. Nevertheless, it provided meaningful regional data and allowed comparison between two similar-sized neonatal networks. *Third*, our survey was conducted at the unit-level and relied on the knowledge of unit practices of the designated individual. Although, we preferentially contacted the relevant administrative leaders for delegation of the task to suitable representatives, we cannot be certain that we were able to capture all practice variation, at the physician-level, from participating units. *Lastly*, although our survey provided many details pertaining to the day-to-day care of neonates with cPH in tertiary NICUs, the themes covered were not exhaustive. For instance, topics such as evaluation of cPH infants for possible structural lesions such as pulmonary vein stenosis or the rationale for various management choices were not explored.

Conclusion

Significant unit-level variability exits in the management of neonates at risk of adverse outcomes from cPH in tertiary NICUs affiliated with CNN and NRN. Patient selection (moderate to severe CLD), diagnostic method (qualitative echocardiographic measures) and timing ($\geq$34 weeks PMA), and overarching principles of management in symptomatic cPH cases were similar, while the type of specific conservative measures and selection of pulmonary vasodilator therapies, and management of asymptomatic neonates with cPH varied widely. Despite published recommendations from expert bodies, half of Canadian tertiary NICUs do not practice routine evaluation of high-risk neonates for cPH. Inhaled nitric oxide and sildenafil citrate are the most commonly employed pharmacotherapies in the care of symptomatic neonates with cPH. There is an urgent need for observational and trial data to inform various aspects of day-to-day clinical care of cPH neonates. Our survey provides the granular details of current practice which may help consensus building and designing future quality improvement and research endeavors.

Disclaimer

This work was not endorsed or supported by the NICHD or CNN. The member sites who participated in the survey did so of their own accord.

Author contributions

AJ conceived the research question, conceptualized the initial study and survey design, and revised the final draft of the manuscript. MB participated in the conceptualization of the initial study and survey design, collated the survey responses, and produced the first draft of the manuscript. PJM, EFB, and EF made significant intellectual contributions to the study and survey design and reviewed the manuscript and provided critical feedback. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgements

We would like to thank individuals from CNN and *Eunice Kennedy Shriver* NICHD NRN sites for participating to our survey. We would also like to thank Dr A. Mukerji and Dr Y. Diambomba for their constructive feedback toward the development of our survey.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

This project is conducted as a part of Amish Jain's "Improving Management of Pulmonary hypertension and Right heart function In NeonaTes (IMPRINT)" research program, supported by funding from the Heart & Stroke Foundation of Canada and operating New Investigator Research grant from the SickKids Foundation and Canadian Institute of Health Research.

Supplemental material

Supplemental material for this article is available online.

References

1. Choi EK, Shin SH, Kim EK, et al. Developmental outcomes of preterm infants with bronchopulmonary dysplasia-associated pulmonary hypertension at 18-24 months of corrected age. *BMC Pediatr* 2019; 19: 26.
2. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007; 120: 1260–1269.
3. Weismann CG, Asnes JD, Bazzy-Asaad A, et al. Pulmonary hypertension in preterm infants: results of a prospective screening program. *J Perinatol* 2017; 37: 572–577.
4. Baker CD, Abman SH and Mourani PM. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. *Pediatr Allergy Immunol Pulmonol* 2014; 27: 8–16.
5. Kadmon G, Schiller O, Dagan T, et al. Pulmonary hypertension specific treatment in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 2017; 52: 77–83.
6. Trottier-Boucher MN, Lapointe A, Malo J, et al. Sildenafil for the treatment of pulmonary arterial hypertension in infants with bronchopulmonary dysplasia. *Pediatr Cardiol* 2015; 36: 1255–1260.
7. Tan K, Krishnamurthy MB, O'Heney JL, et al. Sildenafil therapy in bronchopulmonary dysplasia-associated pulmonary hypertension: a retrospective study of efficacy and safety. *Eur J Pediatr* 2015; 174: 1109–1115.
8. Wardle AJ, Wardle R, Luyt K, et al. The utility of sildenafil in pulmonary hypertension: a focus on bronchopulmonary dysplasia. *Arch Dis Child* 2013; 98: 613–617.
9. van der Graaf M, Rojer LA, Helbing W, et al. EXPRESS: sildenafil for bronchopulmonary dysplasia and pulmonary

hypertension: a meta-analysis. *Pulm Circ* 2019; 9: 2045894019837875.
10. Abman SH, Ivy DD, Archer SL, et al. Committee AAJGfPPH. Executive summary of the American Heart Association and American Thoracic Society Joint Guidelines for Pediatric Pulmonary Hypertension. *Am J Respir Crit Care Med* 2016; 194: 898–906.
11. Krishnan U, Feinstein JA, Adatia I, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. *J Pediatr* 2017; 188: 24–34.e1.
12. Hilgendorff A, Apitz C, Bonnet D, et al. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016; 102(Suppl 2): ii49–ii56.
13. Altit G, Lee HC, Hintz S, et al. Practices surrounding pulmonary hypertension and bronchopulmonary dysplasia amongst neonatologists caring for premature infants. *J Perinatol* 2018; 38: 361–367.
14. Suresh G, King BC and Jain SK. Screening for pulmonary hypertension in preterm infants-not ready for prime time. *J Perinatol* 2018; 38: 206–210.
15. Mourani PM, Sontag MK, Ivy DD, et al. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009; 154: 379–84, 384 e1-2.
16. Bhat R, Salas AA, Foster C, et al. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. *Pediatrics* 2012; 129: e682–e689.
17. Xiong T, Kulkarni M, Gokulakrishnan G, et al. Natriuretic peptides in bronchopulmonary dysplasia: a systematic review. *J Perinatol* 2020; 40: 607–615.
18. Naeem B, Ayub A, Aly AM, et al. Urinary NT-proBNP as a potential noninvasive biomarker for screening of pulmonary hypertension in preterm infants: a pilot study. *J Perinatol* 2020; 40: 628–632.
19. Behere S, Alapati D and McCulloch MA. Screening echocardiography and brain natriuretic peptide levels predict late pulmonary hypertension in infants with bronchopulmonary dysplasia. *Pediatr Cardiol* 2019; 40: 973–979.
20. Tuder RM, Yun JH, Bhunia A, et al. Hypoxia and chronic lung disease. *J Mol Med* 2007; 85: 1317–1324.
21. Banks BA, Seri I, Ischiropoulos H, et al. Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia. *Pediatrics* 1999; 103: 610–618.
22. Berkelhamer SK, Mestan KK and Steinhorn RH. Pulmonary hypertension in bronchopulmonary dysplasia. *Semin Perinatol* 2013; 37: 124–131.
23. Mourani PM, Ivy DD, Gao D, et al. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2004; 170: 1006–1013.
24. Finan E, Sehgal A, Khuffash AE, et al. Targeted neonatal echocardiography services: need for standardized training and quality assurance. *J Ultrasound Med* 2014; 33: 1833–1841.
25. Pugh ME, Hemnes AR, Trammell A, et al. Variability in hemodynamic evaluation of pulmonary hypertension at large referral centers. *Pulm Circ* 2014; 4: 679–684.