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

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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

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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. Various pharmacotherapies developed for older patients with pulmonary arterial hypertension are...
of practices in relation to cPH in neonates in CNN and NICHD NRN
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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 volume units 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.
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
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
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, any use of pulmonary vasodilator therapy, and use of cardiac catheterization (AAP: 46% vs. CNN & NRN: 66%, 90% vs. 89%, 11% vs. 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 logistical 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.\(^8\) 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
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 practices 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.

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 (≥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

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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.

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Conflict of interest

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

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Supplemental material

Supplemental material for this article is available online.

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