

Pulmonary Hemorrhage Management Practices in Extremely Preterm Infants: A Global Survey

Pratibha Thakkar¹, Venkata Raju², Prasanth Raju³, Vinayak Govande⁴, Chintan Gandhi⁵, Kartikeya Makker⁶, Ranjit Torgalkar⁷, Rani A Bashir⁸, Sharada Gowda⁹, Naveed Hussain¹⁰, Kaashif Ahmad¹¹

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ABSTRACT

Background: Pulmonary hemorrhage (PHEM) can be life-threatening in extremely premature infants, with only supportive treatment available. Little is known regarding specific management strategies for PHEM because of the rarity of its occurrence and significant associated mortality.

Materials and methods: A multi-institutional working group of physicians was created with the common goal of expanding knowledge about PHEM. We designed a 14-question survey around our experience and current controversies reported in the literature. The survey was circulated via neonatal listservs (MEDNAX neonatology forum, nicu99, Envision Physician Services, and the AAP Training and Early Career neonatologists' group) to capture the management strategies of various neonatologists practicing under different settings and resources. Smartphone Apps for the Global Newborn Society were also used to reach neonatal providers around the world. The data were collected in REDCap software, and statistical analysis was conducted using SPSS version 27.

Results: There were 360 responses from 73 countries. Most neonatologists (79.2%) managed PHEM without unit-based guidelines. For the management of PHEM, there was a consensus on using endotracheal (ET) epinephrine, blood products and high-frequency oscillatory ventilation after acute PHEM. More participants responded using surfactant replacement after (55.6%) rather than during (33.1%) the management of PHEM. Post PHEM, most neonatologists obtain echocardiograms (66%) and consider treatment for patent ductus arteriosus (PDA) (65%), with the majority using acetaminophen (56.4%). Comparative analysis of practices in North America and other NICUs are also reported.

Conclusions: Our study provides a global overview of experience, and opinion-based practices used in the management of PHEM and reflects on the lack of available algorithms. Creating high-quality, evidence-based guidelines is necessary to provide appropriate care and reduce heterogeneity in the management.

Keywords: Management, Neonates, Patent ductus arteriosus, Pulmonary hemorrhage, Preterm infants, Risk factors, Surfactant.

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INTRODUCTION

Pulmonary hemorrhage (PHEM) is a rare but catastrophic complication associated with prematurity.¹ Clinical criteria used to define PHEM have included a combination of findings, including, blood or blood-tinged secretions in the lower respiratory tract, clinical deterioration that prompts escalation of respiratory support, and associated radiographic findings of pulmonary edema.^{2,3} However, there remains a lack of consensus for an objective definition of PHEM.

The incidence of PHEM is inversely proportional to gestational age, with an occurrence rate of 0.1% in all infants and 8–9% in extremely preterm infants.⁴ No definitive treatment is available for PHEM.⁵ Supportive treatment modalities used are based on anecdotal evidence and lack consensus among providers and institutions. Furthermore, limited clinical trial evidence exists regarding strategies for prevention and treatment of PHEM. As a result, care-providers have to rely on information gleaned from retrospective studies and case series.²

In this study, we sought to survey neonatal care-providers worldwide to better understand contemporary strategies used for preventing and treating PHEM. These results, in combination with existing data, may help shape treatment algorithms and design clinical trials for which equipment still remains.

MATERIALS AND METHODS

Questionnaire Development

We created a “PHEM work group” comprising neonatologists from multiple institutions in the US and abroad to expand our understanding

¹Department of Pediatrics-Neonatal/Perinatal Section, University of Oklahoma Health Sciences Centre, Oklahoma City, Oklahoma, United States

^{2–4}Department of Pediatrics, Division of Neonatology, Baylor Scott and White Health, Texas, United States

⁵Department of Pediatrics, Penn State University College of Medicine, Hershey, Pennsylvania, United States

⁶Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland, United States

⁷Department of Pediatrics, University of Kentucky, Lexington, Kentucky, United States

⁸Department of Neonatology, Renai Medicity, Kochi, Kerala, India

⁹Department of Pediatrics, Texas Children's Hospital/Baylor College of Medicine, Houston, Texas, United States

¹⁰Department of Pediatrics, Connecticut Children's/UCONN School of Medicine, Connecticut, United States

¹¹Pediatrix Neonatology of Houston, Houston, Texas, United States

Corresponding Author: Pratibha Thakkar, Department of Pediatrics-Neonatal/Perinatal Section, University of Oklahoma Health Sciences Centre, Oklahoma City, Oklahoma, United States, Phone: +91 9172912776, e-mail: pratibha-thakkar@ouhsc.edu

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of PHEM. The group is conducting collaborative projects and scoping reviews of the literature to enhance our knowledge about different aspects of PHEM in neonates. For this study, we created a 14-question survey based on our group's experience and various management practices enlisted in the literature. The survey was created, compiled, and circulated electronically. This study was deemed exempt by the Institutional Review Board of the Methodist Healthcare System, San Antonio, Texas.

Design of Survey

Various domains of the survey included (Supplement #1 for a Complete Survey):

- Demographics – practice location, the incidence of PHEM, level of NICU services provided.
- Risk factor assessment – gestational age, time of extubation
- Management.
 - Ventilator strategies – the type of ventilator and ventilator strategies used.
 - Use of blood products – a product used.
 - Medications – prophylactic use, endotracheal (ET) route, repeat surfactant use.
 - Consideration for patent ductus arteriosus (PDA) closure – pharmacotherapy or surgical intervention if PDA present.

Survey Dissemination

The survey was distributed as an embedded link within emails or WhatsApp and responses were collected with a RedCAP database. Various international neonatal listservs were used to reach neonatologists working under different resources and settings. MEDNAX, Neonatology Forum, Nicu99 online forum, and Envision Physician Services mailing lists were used to capture the private-practice neonatologist opinions, and the American Academy of Pediatrics Training and Early Career Neonatologists' Group (AAP TeCAN) was used to assess the academic neonatologists' opinions. Smartphone Apps for the Global Newborn Society were also used to reach neonatal care-providers around the world. The survey was disseminated in November 2021 and again in August 2024, and >80% complete responses obtained within a 4-week period of dissemination were used in data analysis.

Data Analysis

Statistical analyses were conducted using SPSS software version 27. Descriptive statistics were reported as frequency and percentage. Comparisons were performed using unpaired t-tests or Chi-square tests as appropriate. Statistical significance was reported at *p*-values < 0.05.

RESULTS

Study Participant Characteristics (Table 1)

A total of 360 complete responses were received in two rounds of questionnaire responses solicited via emails and WhatsApp® messages. All responses were gathered via online responses collected in a RedCap® database. Most respondents were from North America (53.3%), followed by Australia and Asia (24.7%). More than 90% of providers reported practicing at a level III or a higher NICU (63.9% at Level III; 31.7% at Level IV). Less than 60% of participants had 4 or fewer cases of PHEM annually, and the occurrence of more than 10 cases per year was reported from 11% of the units.

Table 1: Demographics of survey participants (total 360 responders)

<i>Demographic variable</i>	<i>N (%)</i>
Practice location	
North America	192 (53.3)
Australia-Asia	89 (24.7)
Europe	48 (13.3)
South and Central America	16 (4.4)
Africa	13 (3.6)
Unmarked	2
Level of NICU	
Level I	3 (0.8)
Level II	8 (2.2)
Level III	230 (63.9)
Level IV	114 (31.7)
Unmarked	5
Incidence of PHEM at their practicing site	
None	37 (10.3)
1–4	213 (59.2)
5–9	68 (18.8)
≥10	40 (11.1)
Unmarked	1

PHEM, pulmonary hemorrhage

Table 2: Risk factors considered to be important for PHEM by (N = 360) survey responders

<i>Gestational age as a risk factor</i>	<i>N (%)</i>
<25 weeks	212 (58.9)
26–28 weeks	94 (26.1)
29–30 weeks	23 (6.4)
>30 weeks	27 (7.5)
Unanswered	4
<i>Selection for PHEM occurrence scenarios (from 4 choices)</i>	<i>Top selection</i>
Presence of hemodynamically significant PDA	200
Culture-positive early onset sepsis	97
After extubation in the first week of life	64
After the second dose of surfactant	53

PHEM, pulmonary hemorrhage. The top risk scenarios of each respondent are shown in the table. Even when averaged out for second, third, and fourth choices, the same order of concern was noted.

Risk Factors for PHEM and Preventive Strategies (Table 2)

Most respondents (59.8%) considered extreme prematurity, with gestational age <25 weeks, at the highest risk for developing PHEM. Perceived risk for PHEM among respondents decreased with increasing gestational age, with very few considering gestational age beyond 28 weeks as a risk factor. When queried regarding the scenarios that make them most worried about PHEM, of the 4 scenarios offered, the situation considered most at-risk was the presence of hemodynamically significant patent ductus arteriosus (hsPDA), followed by the presence of culture positive sepsis and the period immediately after extubation in the first week of life. The scenario with the least concern was after administering a second dose of surfactant.



Table 3: Diagnostic studies done concerning PHEM

Diagnostic modalities	N (%)
Clinical decline in respiratory status	323 (90)
Chest imaging	336 (93)
Hematocrit	
• ET fluid	75 (21)
• Hemogram and coagulation profile	264 (73)
Sepsis screen	160 (50)
Echocardiogram	237 (66.0)

When asked if any prophylactic management strategy was considered to prevent PHEM in the scenario of risk, only 27 (7.5%) responded in the affirmative using multiple strategies. Within those who considered prophylactic therapy, 21 used prophylactic indomethacin or ibuprofen, and 24 used high PEEP as strategies. Hemocoagulase was considered for prophylaxis by 4 respondents.

Diagnostic Modalities Used (Table 3)

For establishing the diagnosis of PHEM and initiating specific management plans, most of the respondents used the presence of blood in the upper airway along with the clinical findings of a rapid deterioration of respiratory status, which were mostly confirmed by finding diffuse changes in chest radiographs. In some situations, a drop in blood hematocrit was used as contributing evidence. Endotracheal fluid hematocrit was rarely done to establish a diagnosis. Obtaining a hemogram and coagulation profile tests were also commonly used to evaluate the need for supportive therapy. Interestingly, only about half considered doing a sepsis screen following an acute PHEM event. Most respondents performed an echocardiogram soon after the control of PHEM to evaluate the contributions of an hsPDA.

Management – During the Acute PHEM Event (Table 4)

- *Ventilator type and increase in PEEP:* High-frequency oscillatory ventilator was the preferred mode of providing respiratory support during rapid deterioration from PHEM, followed by conventional mode and high-frequency jet ventilator. The change in respiratory management during the PHEM event was one of the most consistent management strategies, with increasing PEEP to tamponade the bleeding being close to unanimous. Most respondents avoided suctioning the ETT during the event, although about a third of responders considered giving a dose of surfactant during the PHEM event.
- *Use of ET medication to stop bleeding:* Using an intra-tracheal vasoconstrictor is widely accepted. Intra-tracheal epinephrine is the most commonly used agent, but cold saline and cocaine are other less frequently considered options. Use of local coagulation agents such as hemocoagulase has also been used.
- *Transfusion of blood products:* The use of pRBCs and fresh-frozen-plasma (FFP) were the most common strategies used for hemodynamic and coagulation support during the bleeding event. Platelets were also commonly used (46.9%) followed by the use of cryoprecipitate (24.2%) to help with hemostasis. The use of recombinant factor VII a way less common, although a few centers used this product as the first line of therapy for PHEM.

Table 4: Treatment strategies for PHEM used by study responders (N= 360)

Immediate treatment during PHEM event	
Mode of ventilatory support	
High-frequency oscillator ventilator (HFOV)	197 (54.7)
Conventional Ventilator	122 (33.9)
High-frequency jet ventilator (HFJV)	38 (10.6)
Respiratory support	
Increasing PEEP	348 (96.7)
Avoid ET suctioning	256 (71.1)
Using surfactant during PHEM	119 (33.1)
ET administration of drugs	
Epinephrine	267 (74.2)
Cold saline	71 (11.8)
Hemocoagulase	14 (3.9)
Cocaine	6 (1.7)
Blood products	
Packed red blood cells (pRBCs)	305 (84.7)
FFP	259 (71.9)
Platelets	169 (46.9)
Cryoprecipitate	87 (24.2)
Recombinant factor VIIa	26 (7.2)
Treatment strategies (Post PHEM event)	
Repeating surfactant after PHEM	200 (55.6)
Attempting PDA closure after PHEM	234 (65.0)
PDA treatment	
Indomethacin	70 (19.4)
Ibuprofen	116 (32.2)
Acetaminophen	203 (56.4)
Surgical ligation	42 (11.7)
Transcatheter device closure	45 (12.5)
Availability of unit-based clinical practice guidelines for PHEM	75 (20.8)

FFP, fresh frozen plasma; PDA, patent ductus arteriosus; PEEP, positive end-expiratory pressure; PHEM, pulmonary hemorrhage

Management – Post PHEM Event

Since PDA is one of the common risk factors identified to be associated with PHEM, the respondents were surveyed regarding evaluating for PDA post-PHEM event. About 2/3rd of all respondents reported obtaining a screening echocardiogram after the event. Most respondents would consider PDA closure after acute PHEM, with acetaminophen being the most commonly used drug (56.4%). Some centers would consider surgical ligation or trans catheter closure of a PDA after PHEM.

Open-ended Questions in the Survey

At the end of our survey, we had a few open-ended questions to capture further comments from the respondents. Approximately 10% of the individuals commented on highlighting the practices not covered in the survey questions. The majority supported fluid restriction in the first week of life to limit volume overload, considering it a risk factor leading to PHEM. Few respondents reported obtaining a head ultrasound after the hemorrhagic event. Controversy regarding the use of surfactants in the management of PHEM was underlined in these comments, where some supported its use to control hypoxemia. In contrast, others questioned if PHEM



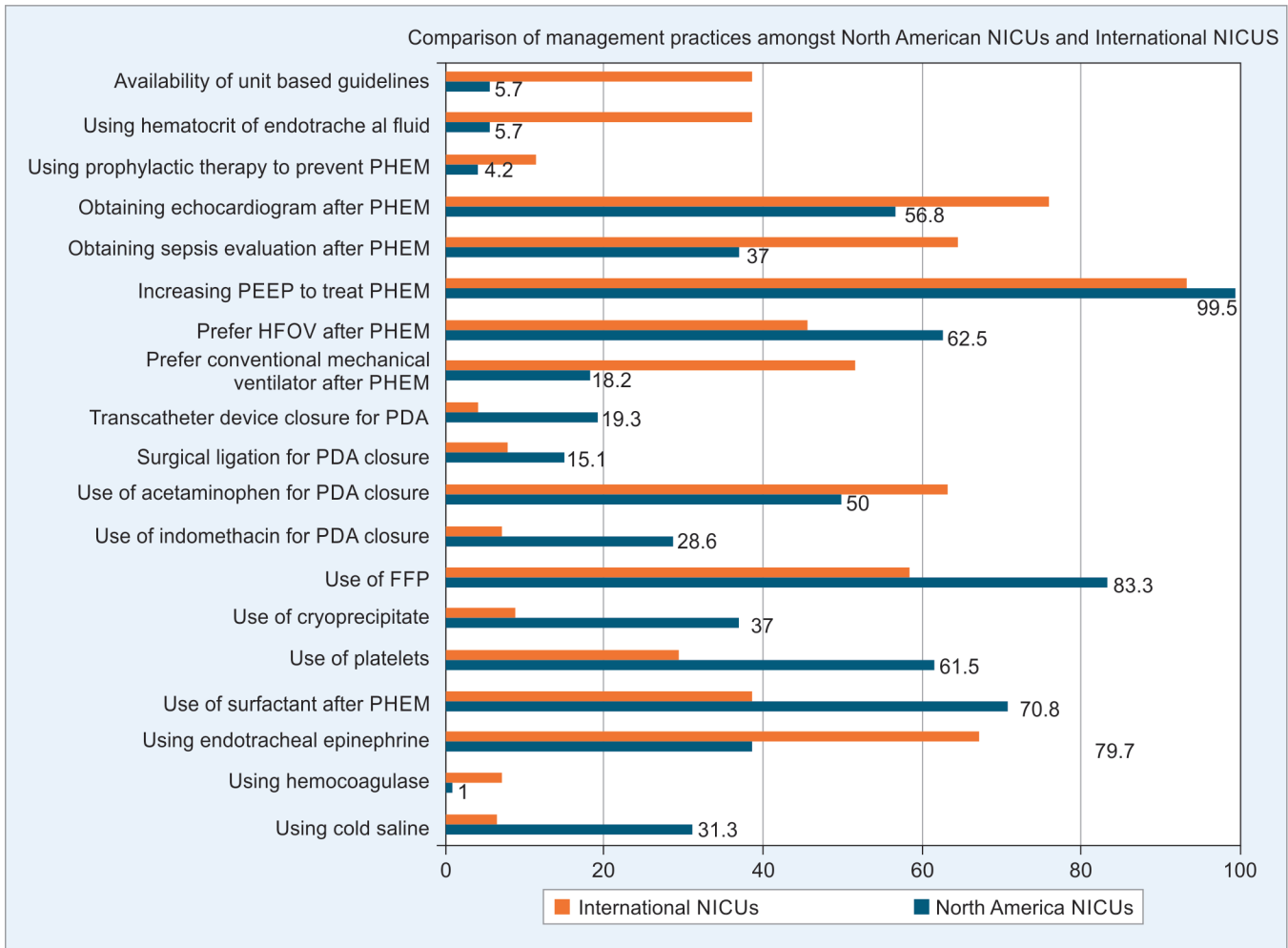


Fig. 1: Management practices in North America vs International NICUs for acute PHEM and post-PHEM * (N = 358)
 FFP, fresh frozen plasma; HFOV, high-frequency oscillatory ventilator; PDA, patent ductus arteriosus; PEEP, positive end expiratory pressure; PHEM, pulmonary hemorrhage. *All values are statistically significant with $p < 0.05$

was the consequence of surfactant use. Interestingly, one provider reported their practice of performing bronchoalveolar lavage with diluted surfactant followed by administration of surfactant bolus.

Variation in Practices based on Location – North America vs International NICUs

When responses were stratified based on practice location, comparing centers in North America and other parts of the world, some striking differences were noted (Fig. 1). These differences in the management of PHEM were statistically significant ($p < 0.05$). Though most of the respondents were from North America ($n = 192, 53.3\%$), other centers also collectively contributed significantly ($n = 166, 46.3\%$). Two respondents did not comment on their site of practice and were excluded from this analysis. More centers outside North America reported having access to unit-based guidelines (38.6 vs 5.7%). Cumulative use of blood products was significantly lower in the units outside North America (FFP 58.4 vs 83.3%; cryoprecipitate 9% vs 37%; platelets 29.5 vs 61.5%). Providers outside North America were more likely to screen for sepsis (64.5 vs 37%) and PDA (75.9 vs 56.8%) after an acute PHEM event. Interestingly, providers in other units outside

North America were less likely to consider PDA treatment despite increased echocardiography use for screening for PDA after PHEM.

DISCUSSION

In this work, we sought to better understand contemporary prevention and management strategies for PHEM in neonates by surveying practicing neonatologists and neonatal trainees. Despite a lack of clinical trials focusing on this high mortality condition, we found some areas of consensus in management. These included use of high-frequency ventilation, escalating PEEP, ET epinephrine, and the use of packed red blood cells and fresh frozen plasma. However, there were many important differences in how this condition is approached within vs outside to North America.

The incidence of PHEM varies in different regions of the world, and the regional incidence and availability of resources may impact the management strategies used. Reports from Asia show a relatively high incidence of PHEM and a more aggressive management strategy.⁶⁻¹⁰ In our study, we found that prophylaxis was significantly more common used by non-North American responders. Some centers have shown effectiveness of using



hemocoagulase as prophylaxis and treatment in lowering the incidence, duration and mortality associated with PHEM.^{11,12}

We found broad agreement that extremely low gestational age at birth (<25 weeks) and the presence of a hemodynamically significant PDA were important risk factors. However, there was less agreement on the importance of sepsis and the role of surfactant therapy or post-extubation changes in alveolar pressure in the genesis of PHEM. Available published literature yields no insight into these risk factors, and there is a need for further experimental studies to clarify these issues.

There appears to be confusion regarding the role of surfactant therapy in PHEM. Some consider it a risk factor, especially after the second dose of surfactant.^{13–15} Others consider surfactant therapy important as part of the management of PHEM, both during the acute event and post-event in the replacement of surfactant deactivated by the presence of blood in alveolar spaces.¹⁶ Published reports on this topic show that the period when surfactant use was in its early phases had suggested an association with PHEM, but later studies have not confirmed this finding.¹⁴ As we have become more selective and proficient at surfactant therapy, the association with PHEM has not been an issue. Moreover, an understanding of the physiology of surfactant deactivation has led credence to its use as a therapy during and after PHEM.^{17–19} Clarification of this issue is critical if a commonly agreed upon algorithm is to be developed for the management of PHEM.

There appears to be a consensus of opinion that the diagnosis of PHEM could be established based on the following:

- Presence of blood in the lower respiratory tract (usually identified via the ET tube) in conjunction with
- An acute deterioration of respiratory and general clinical status of the infant.^{20,21} The use of ET tube fluid hematocrit or the concurrent presence of coagulopathy, is not necessary for the diagnosis. However, the evaluation of hemodynamic status (blood loss) and coagulation profile (platelet and coagulation cascade dysfunction) is important in the management of the acute PHEM event. There is also general agreement among responders in our survey that the presence of a hemodynamically significant PDA should be evaluated by an echocardiogram soon after managing the acute PHEM bleed. The opinion regarding medical or interventional treatment of this PDA is, however, variable in different regions. The reluctance to treat the post-PHEM diagnosed PDA among the non-North American responders in our study is interesting.

There is evidence from the literature that systemic sepsis is one of the risk factors for PHEM.^{20,21} The role that sepsis plays in the development of PHEM is not well recognized, and many responders would not routinely evaluate for sepsis after the event. Increased capillary permeability in the presence of circulating endotoxins has been suggested as one of the possible etiologies of PHEM in patients with sepsis.⁷ In addition, a few case studies have shown an association between viral infections (SARS-CoV-2, cytomegalovirus and coxsackievirus) and the development of PHEM.^{22–25} The risks vs benefits of screening and treating for presumed sepsis after a PHEM event may favor treatment until sepsis can be definitely ruled out.

Treatment provided for an acute PHEM event varies among responders, but there are some strategies that are almost universally applied. These near-consensus strategies could be clustered into four strategies clustered in the acronym–PHEM that stands for: (1) physical tamponade: can be achieved by endotracheal intubation

or an increase in positive end-expiratory pressure (PEEP) or mean airway pressure (MAP). The most widely used method for consistently applying high pressure while limiting lung injury was the use of HFOV; (2) hemodynamic support: using blood products based on laboratory findings—mostly pRBCs or FFP or platelet transfusion, or a combination of these to replenish the losses; (3) ET medications: use of ET epinephrine or another agent that can cause vasoconstriction to limit the bleeding. The use of cold saline, hemocoagulase or cocaine intratracheally has been reported by the respondents and has some support from small reports in the literature;^{11,26} (4) monitoring for risk factors, such as sepsis (sepsis work-up) and PDA (echocardiography evaluation).

Another point of controversy and variation was the use of ET suction during the event. Many responders indicated that they would avoid ET suctioning during the bleed, but at the same time some reported that they would give intra-tracheal medications or surfactant. This discrepancy may be due to the timing of the suctioning as the acute event develops. Initially, there may be reluctance to perform suction until the alveolar tamponade is established. Later, when there is a need for airway epinephrine or the instillation of another agent, suction may be needed to clear the airway and ensure that the agent reaches the site of action.⁷ The construction of our question in the survey may not have been adequate to address this issue. There is also a lack of clarity in the published literature regarding this issue.

The use of blood products for hemodynamic and coagulation support also has wide consensus among the responders, with the use of pRBCs, FFP, and platelets being the most common. However, there are a not insignificant number of responders who have indicated that they would use cryoprecipitate and recombinant Factor VIIa. In 1 center, the use of Factor VIIa was part of the standard order set for an infant following PHEM. There are reports in the literature of the use of factor VIIa, but its primacy in management of PHEM in some centers but not in others is worth investigating.^{5,27–29}

In summary, this questionnaire survey highlights the areas where the management of PHEM is similar among neonatologists practicing in different parts of the world. However, there are also many areas of controversy and differences in management of PHEM for which there are no clear explanations. Based on this information, we believe that there is an urgent need to develop rational guidelines based on clinical consensus.

SUPPLEMENTARY MATERIAL

The supplementary file is available online on the website www.jnb.org.

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