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Respiratory Management of Extremely Preterm Infants: An International Survey

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Keywords
Practice variation · Bronchopulmonary dysplasia · Preterm infants · Ventilation

Abstract
Background: There are significant international variations in chronic lung disease rates among very preterm infants yet there is little data on international variations in respiratory strategies. ***Objective:*** To evaluate practice variations in the respiratory management of extremely preterm infants born at <29 weeks' gestational age (GA) among 10 neonatal networks participating in the International Network for Evaluating Outcomes (iNeo) of Neonates collaboration. ***Methods:*** A web-based survey was sent to the representatives of 390 neonatal intensive care units from Australia/New Zealand, Canada, Finland, Illinois (USA), Israel, Japan, Spain, Sweden, Switzerland, and Tuscany (Italy). Responses were based on

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See online supplementary Appendix A for a full list of the investigators (International Network for Evaluating Outcomes of Neonates).

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practices in 2015. ***Results:*** Overall, 321 of the 390 units responded (82%). The majority of units within networks (40–92%) mechanically ventilate infants born at 23–24 weeks' GA on continuous positive airway pressure (CPAP) with 30–39% oxygen in respiratory distress within 48 h after birth, but the proportion of units that offer mechanical ventilation for infants born at 25–26 weeks' GA at similar settings varied significantly (20–85% of units within networks). The most common respiratory strategy for infants born at 27–28 weeks' GA on CPAP with 30–39% oxygen with respiratory distress within 48 h after birth used by units also varied significantly among networks: mechanical ventilation (0–60%), CPAP (3–82%), intubation and surfactant administration with immediate extubation (0–75%), and less invasive surfactant administration (0–68%). ***Conclusions:*** There are marked variations but also similarities in respiratory management of extremely preterm infants between networks. Further collaboration and exploration is needed to better understand the association of these variations in practice with pulmonary outcomes.

Introduction

Bronchopulmonary dysplasia (BPD) is a highly prevalent morbidity affecting approximately 40% of extremely preterm infants born at <29 weeks' gestational age (GA) [1]. It is associated with short- and long-term adverse consequences [2, 3]. Advances in medical care including prenatal corticosteroids, surfactant, and noninvasive ventilation have altered the pathophysiology of BPD [4, 5]. Practice guidelines and national/international quality improvement initiatives supported by strong levels of evidence have contributed to disseminating and improving these practices [6, 7]. However, high-quality evidence is lacking to guide other practices like choosing the mode of mechanical ventilation and criteria for intubation and extubation [8]. Consequently, neonatal intensive care units (NICUs) and regional neonatal networks formulate their own protocols based on experience and interpretation of the literature, potentially leading to justified variations in practice between regional networks [1].

Recent studies have found marked variations in the incidence of BPD between neonatal networks, and variations in care practices may contribute to this [9, 10]. A better understanding of the variations in practice between neonatal networks can help identify best practices and opportunities for improvement. The International Network for Evaluating Outcomes (iNeo) of Neonates is a multinational collaboration of population-based national neonatal networks including 11 countries and aims to provide a platform for comparative evaluation of outcomes of extremely preterm infants and very low birth weight infants at the national, site, and individual level to improve outcomes of these infants. The structure, design, and overall objectives of the iNeo collaboration have been previously described [11]. In this study, our objective was to survey and compare the variations in clinical practices for the management of respiratory conditions in extremely preterm infants born at <29 weeks' GA among 10 neonatal networks participating in iNeo. We hypothesized there would be significant variations between networks in practices where high-quality evidence was lacking and less variation in practices where high-quality evidence was available.

Methods

Study Design

A web-based survey was designed following the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines [12]. It was composed of 8 questions with predefined answer options related to respiratory management of extremely preterm infants born at <29 weeks' GA. Questions were reviewed by the directors of the 10 networks to reach a consensus on content, relevance, and appropriateness of possible responses. The question and questionnaire design were developed following recommendations to minimize biases in surveys [13]. The survey addressed five domains: (1) maximum settings used before intubation, (2) respiratory strategies for infants with persistent respiratory distress based on GA and fraction of inspired oxygen (FiO_2) requirement, (3) modes of invasive and noninvasive ventilation practiced, (4) evaluation of extubation readiness, and (5) use of medications to prevent and treat respiratory morbidities. For survey questions asking frequencies, the choices included routine (90–100%), often (50–90%), sometimes (10–49%), and rarely/never (0–10%). The full survey is provided as a supplementary file and was distributed in English (see online suppl. Appendix B).

Inclusion Criteria

Online questionnaires were sent by e-mail to the directors of 9 population-based national or regional neonatal networks participating in iNeo that chose to participate in this survey and the Illinois Neonatal Network (who joined the iNeo collaboration for the purpose of survey responses at this time). The network directors forwarded an e-mail containing the web link and a unique access code (one per unit) to each unit director or representative of each NICU participating within their network. The unit director or representative was responsible for completing the survey and was instructed to provide answers based on common unit-level practice rather than their personal opinions/practices alone. None of the questions asked were mandatory questions and they were allowed to choose not to answer (any question). The survey was distributed to 390 NICUs participating in Australia/New Zealand (n =

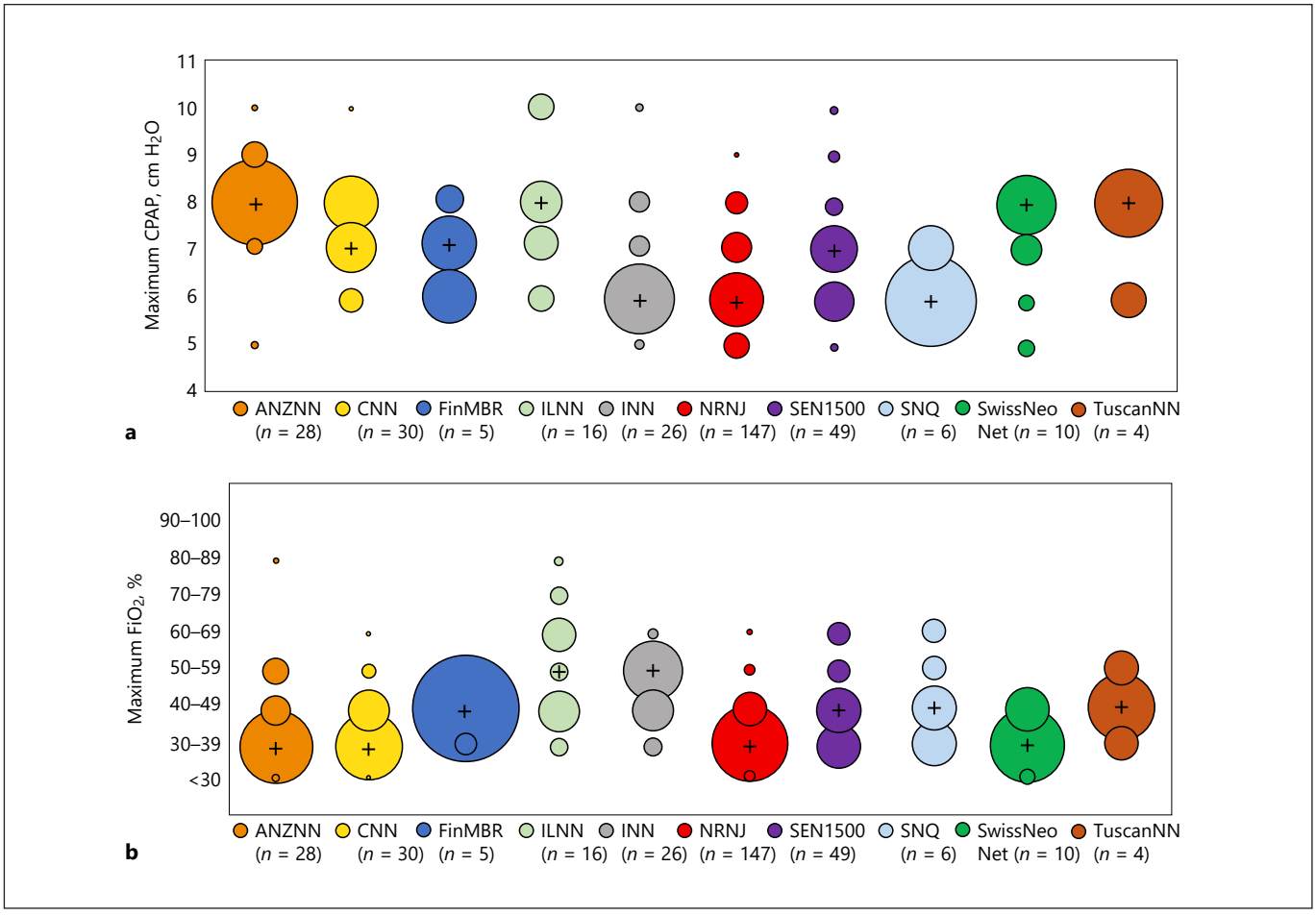

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Fig. 1. Maximum continuous positive airway pressure (CPAP) (**a**) and fraction of inspired oxygen (FiO_2) (**b**) used before intubating infants born at <29 weeks' GA in participating networks. The size of circles corresponds to the percentage of units within each network; a larger circle denotes a higher percentage. The median value for each network is indicated with a plus sign. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane on-line.

28), Canada (n = 30), Finland (n = 5), Illinois in the USA (n = 18), Israel (n = 26), Japan (n = 204), Spain (n = 57), Sweden (n = 6), Switzerland (n = 12), and Tuscany in Italy (n = 4). All of these units are level 3 NICUs or mixed level 3 and level 2 NICUs and provide specialized care for infants born at <29 weeks' GA. The response rate to questionnaires was monitored on a weekly basis. A reminder questionnaire was sent twice (at a monthly interval) to units that did not respond. The survey was first sent in August 2016 and was closed by December 2016. Responders were instructed to answer based on their practices in the year 2015 to allow retrospective queries of unit-specific data on care practices if required.

Data Analysis

Data are reported using descriptive statistics. The distributions of survey answers within each network are described in absolute numbers and percentages for categorical variables and medians (ranges) for continuous variables. No statistical comparison between networks with regard to answers was planned. Since the objective of the study was to describe variations in practice between networks, surveys were sent to all units within each network and no sample size was calculated.

Ethics

All participating networks obtained ethics/regulatory approval or the equivalent from their local granting agencies as part of the protocol for collaborative comparisons of international health services for quality improvement in neonatal care [11]. Specific approval for this project was obtained from the Research Ethics Board at Mount Sinai Hospital, Toronto (ON, Canada) where the coordination of the project was conducted. The responders were asked to proceed to survey only if they provided consent for data assimilation and anonymous reporting.

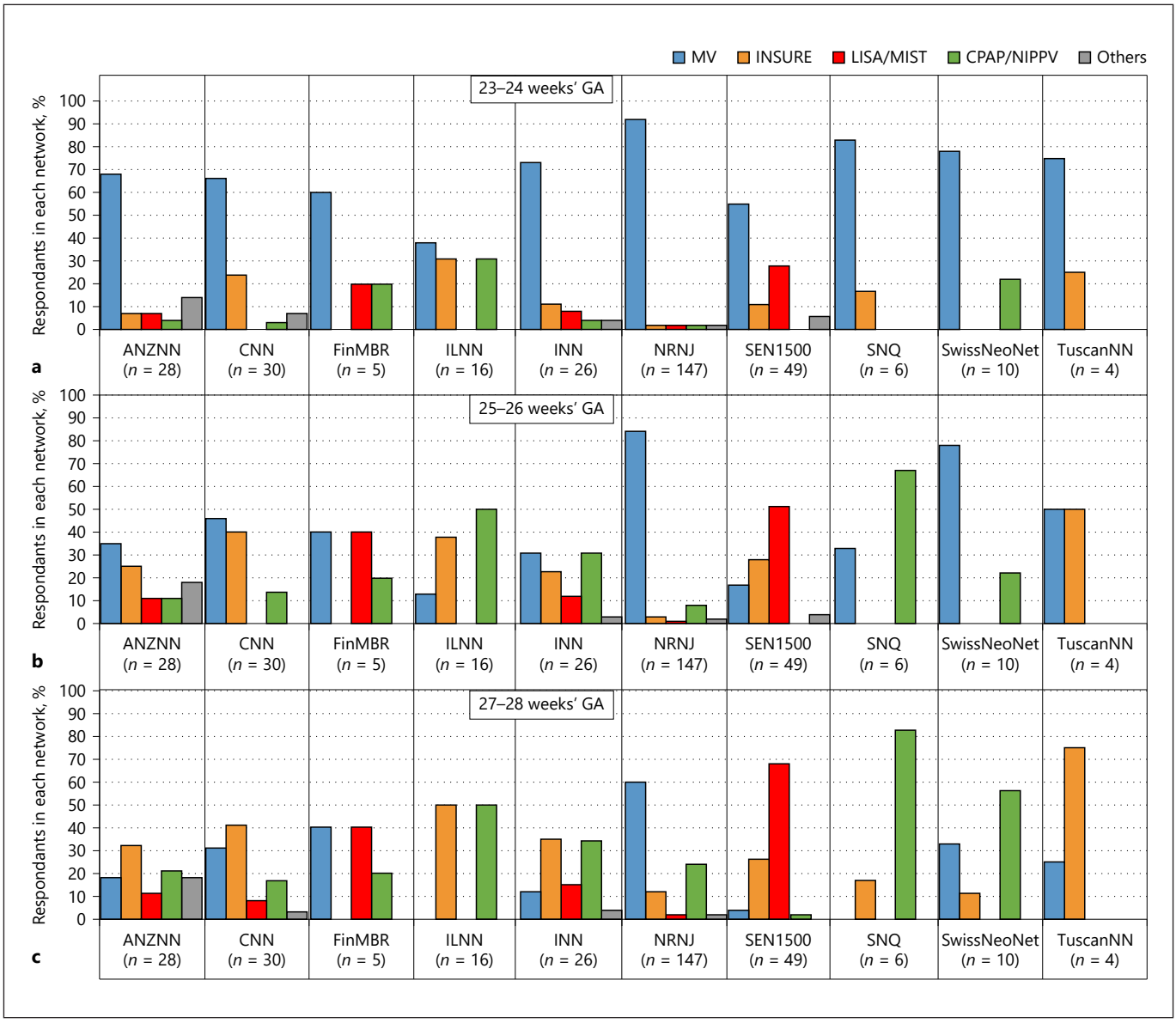

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Fig. 2. Most common respiratory strategies for preterm infants who are on CPAP and have respiratory distress within 48 h after birth and are needing 30–39% oxygen by gestational age: 23–24 weeks' GA (**a**), 25–26 weeks' GA (**b**), and 27–28 weeks' GA (**c**). All numbers indicate the percentage of units within each network. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane on-line. MV, mechanical ventilation; CPAP, continuous positive airway pressure; INSURE, intubation and surfactant administration followed by immediate extubation; LISA, less invasive surfactant administration; NIPPV, noninvasive positive pressure ventilation.

Results

Overall, 321 of the 390 contacted units responded (82%). The survey response varied from 72 to 100% among participating networks: 28/28 (100%) from Australia/New Zealand, 30/30 (100%) from Canada, 5/5 (100%) from Finland, 16/18 (89%) from Illinois, 26/26 (100%) from Israel, 147/204 (72%) from Japan, 49/57 (86%) from Spain, 6/6 (100%) from Sweden, 10/12 (83%) from Switzerland, and 4/4 (100%) from Tuscany. Only

Table 1. Initial most common invasive ventilation modes and methods used to evaluate extubation readiness in infants born at <29 weeks' gestation

Respiratory strategy	ANZNN (n = 28)	CNN (n = 30)	FinMBR (n = 5)	ILNN (n = 16)	INN (n = 26)	NRNJ (n = 147)	SEN1500 (n = 49)	SNQ (n = 6)	SwissNeoNet (n = 10)	TuscanNN (n = 4)
Most common initial mode of ventilation in mechanically ventilated infants										
HFOV or HFJV	0	7	0	0	12	12	0	33	11	25
SIPPV										
Volume-targeted	86	66	40	31	15	8	77	17	33	0
Pressure-controlled	7	17	20	69	61	72	19	50	56	75
IPPV										
Nonsynchronized, volume-targeted	0	7	0	0	4	1	2	0	0	0
Nonsynchronized, pressure-controlled	0	0	0	0	4	6	0	0	0	0
NAVA	0	0	40	0	0	0	0	0	0	0
Other	7	3	0	0	4	1	2	0	0	0
Method used to evaluate extubation readiness										
Protocol/guideline	7	13	20	15	19	5	9	0	22	25
Spontaneous breathing trial or CPAP test	19	13	0	15	6	8	15	0	0	25
Use of respiratory function test	4	0	0	0	0	9	34	33	0	0
Clinical judgment of attending team	59	67	80	70	75	77	42	67	78	50
Other	11	7	0	0	0	1	0	0	0	0

All numbers indicate the percentage of units within each network. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane on-line. CPAP, continuous positive airway pressure; HFJV, high-frequency jet ventilation; HFOV, high-frequency oscillation ventilation; IPPV, intermittent positive pressure ventilation; NAVA, neurally adjusted ventilatory assist; SIPPV, synchronized intermittent positive pressure ventilation.

one questionnaire was incomplete (section on use of medications was skipped).

Maximum Continuous Positive Pressure and FiO_2 Used before Intubating

The median maximum nasal continuous positive airway pressure (CPAP) used before intubating was higher in Australia/New Zealand, Illinois, Switzerland, and Tuscany (8 cm H_2O) than in the other networks (6–7 cm H_2O) (Fig. 1a). Most of the units in each network (50–100%) reported using CPAP of 5–8 cm H_2O. The majority of units in each network reported intubating extremely preterm infants when FiO_2 was 30–39% or 40–49% (Fig. 1b). Generally, there was little variation of the maximum FiO_2 used within each network except for Illinois, Spain, and Sweden.

Respiratory Strategies for Infants with Persistent Respiratory Distress within 48 h after Birth

The most common respiratory strategies within 48 h after birth for infants on CPAP with respiratory distress requiring 30–39% oxygen are reported by GA in Figure 2. The majority of units in each network (55–92%) reported to mechanically ventilate infants born at 23–24 weeks' GA. As the GA increased, the proportion choosing noninvasive ventilation strategies increased, although in 2 networks (Japan and Switzerland) the majority (78 and 84%, respectively) still chose mechanical ventilation for infants born at 25–26 weeks' GA. The choice of noninvasive strategies (CPAP/NIPPV [noninvasive positive pressure ventilation]; INSURE [intubation and surfactant administration followed by immediate extubation], LISA [less invasive surfactant administration]) varied widely. The most common noninvasive strategy in each network was CPAP/NIPPV in Japan, Sweden, and Switzerland, INSURE in Australia/New Zealand, Canada, and Tuscany, and LISA in Finland and Spain. In Illinois and Israel, CPAP/NIPPV and INSURE were similarly common. The proportions of units choosing mechanical ventilation were higher for infants requiring 40–60% oxygen than those requiring 30–39% in all networks (see online suppl. Appendix C Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000487987).

Modes of Invasive Ventilation

The most common initial mode of ventilation in intubated infants was synchronized intermittent positive pressure ventilation (SIPPV) in 60–100% of units in each net-

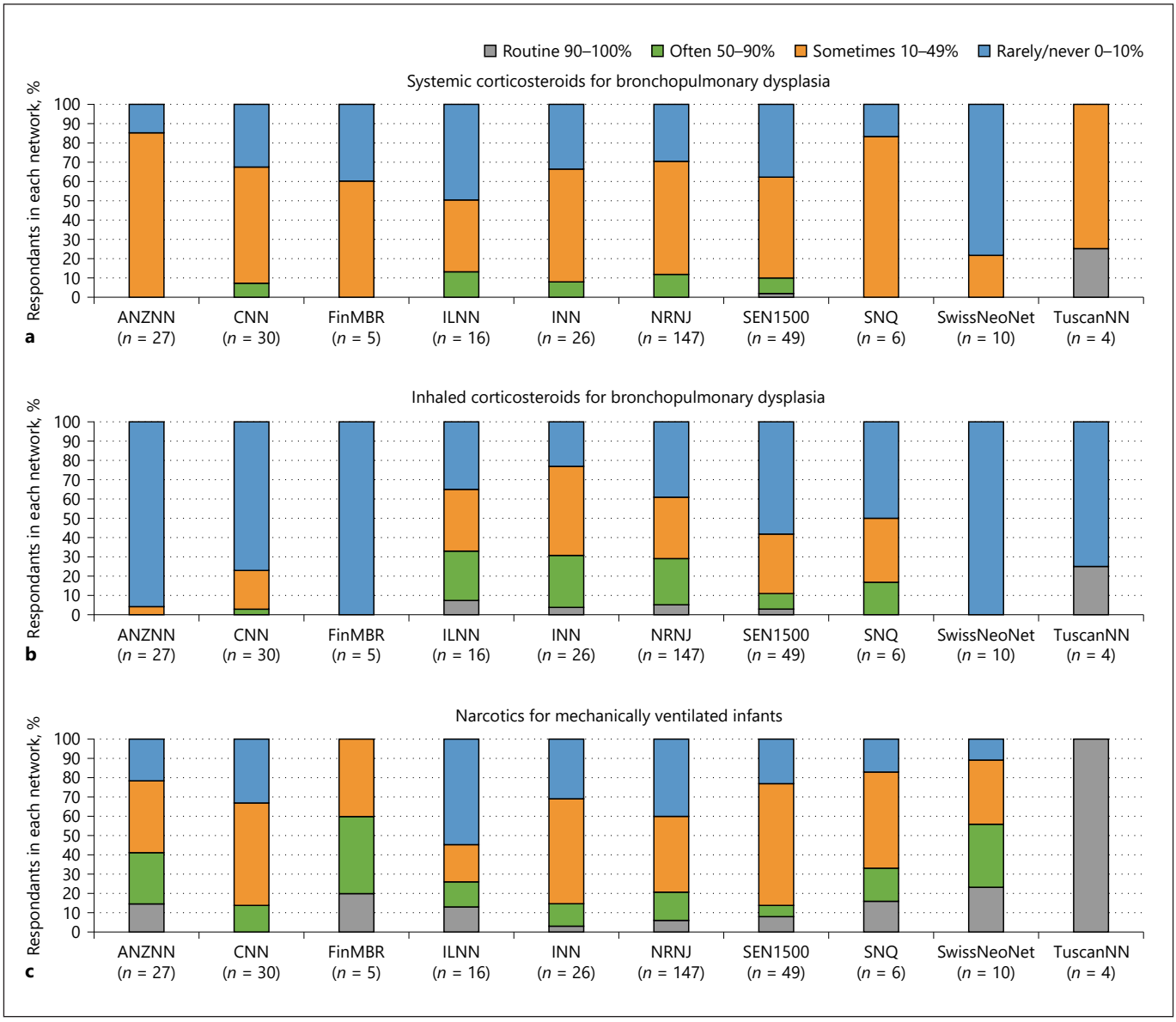

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Fig. 3. Use of medication for respiratory management of infants born at <29 weeks' GA in each network. **a** Systemic corticosteroids for bronchopulmonary dysplasia. **b** Inhaled corticosteroids for bronchopulmonary dysplasia. **c** Narcotics for mechanically ventilated infants. All numbers indicate the percentage of units within each network. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane on-line.

work (volume-targeted or pressure-controlled; Table 1). However, the choice of volume-targeted or pressure-controlled ventilation varied significantly between networks. Among units choosing SIPPV, volume-targeted SIPPV was more common (>50% of units) in 4 networks (Australia/New Zealand, Canada, Finland, and Spain) while pressure-targeted SIPPV was more common in others.

Assessment of Extubation Readiness

The majority of units in each network (43–80%) reported using the clinical judgment of the attending team to determine extubation readiness (Table 1). The use of a protocol/guideline was low in all networks (<25% of units).

Use of Medication

A minority of units in all the networks reported routinely or often using systemic steroids (0–25% of units; Fig. 3). However, the majority of units used systemic corticosteroids at least sometimes in all the networks (52–85%) except for Illinois (37%) and Switzerland (22%). The majority of units from Finland, Switzerland, and Tuscany (56–100% in each network) routinely or often used narcotics for sedation in mechanically ventilated infants born at <29 weeks' GA, while a minority of units in the other networks routinely or often used narcotics (14–41% in each network). Most units reported rarely using nonnarcotic sedatives (56–84% of units in each network) except for Japan (39% of units; see online suppl. Appendix D). Caffeine was used often or routinely in infants born at <29 weeks' GA in all networks (90–100% of units). Routine use of intramuscular vitamin A was low in all networks (0–12% of units).

Discussion

In this international survey on respiratory management of extremely preterm infants born at <29 weeks' GA across 10 neonatal networks, we found significant variations but also similarities in respiratory management. Significant variations in practices included the respiratory strategy within 48 h of birth for infants of ≥25 weeks' GA in respiratory distress. Similarities in practice between networks included using 30–49% FiO_2 before intubating, the use of SIPPV as the initial mode of ventilation in mechanically ventilated infants, and the routine use of caffeine.

Previous survey-based and epidemiological studies have documented significant variations in noninvasive ventilator settings used prior to intubation in the NICU [14, 15]. Our findings of variations in maximum CPAP pressure used before intubation may be due to variations in interfaces used for noninvasive ventilation. Also, we did not differentiate between CPAP and NIPPV that can be used to increase the mean airway pressure above the customary CPAP level. Also, lack of strong evidence concerning maximum CPAP pressure and maximum FiO_2 to predict CPAP failure and indicate intubation is likely another contributor that justifies practice variation [16, 17]. How this variation in unit practices is associated with outcomes requires further investigation.

Previous surveys reported an increased use of LISA in European countries (52% of units assessed) [18] and a wide variation in LISA use between Nordic countries (9–100% of units assessed) [19]. We identified that the use of LISA in the iNeo collaboration was very limited in networks other than Spain and Finland. The overall low use of LISA likely reflects the small number of studies to have been published by 2015 [20]. This illustrates that the uptake of new practices varies significantly based on geographical areas. Furthermore, we showed that the choice of respiratory strategies varied between networks and the selection depended on infants' GA and FiO_2 levels. The use of INSURE and CPAP/NIPPV for preterm infants on CPAP with respiratory distress within 48 h after birth and requiring 30–39% oxygen increased with GA in each network. The high use of CPAP/NIPPV in infants born at 25–28 weeks' GA reflects current evidence suggesting that early CPAP reduces the incidence of BPD compared to mechanical ventilation [21]. The high rate of units in networks using INSURE also reflects evidence from systematic reviews suggesting it reduces BPD compared to mechanical ventilation [22].

We also report that most units (84%) used SIPPV in mechanically ventilated preterm infants. However, among units using SIPPV, most used pressure-controlled ventilation (60% of units using SIPPV) despite evidence published in 2014 that volume-targeted ventilation may reduce mortality and chronic lung disease compared to pressure-controlled ventilation [23]. The variation in the modes of ventilation may be due to a slow uptake and variations in the availability of ventilator devices in each unit, since algorithms and methods used by ventilators for pressure-controlled and volume-targeted ventilation vary according to device [24].

We identified that the use of protocols to evaluate extubation readiness was low in all networks despite the fact that 85% of infants born at <29 weeks' GA are mechanically ventilated at some point during the NICU stay [1]. Although, there is little evidence regarding what is the best method to evaluate extubation readiness, there is increasing evidence that the presence of protocols/guidelines for respiratory management and evaluation of extubation readiness improves outcomes of preterm infants by standardizing care [25]. This highlights the need for more research and the need for standardizing practices within units without protocols or guidelines.

Implications

The incidence of BPD has either remained static or risen in the last decade, yet there are significant variations between centers and networks [1]. Our findings have implications for epidemiological research and quality improvement. First, the variations in practice we identified

highlight the need to study their association with outcomes. Second, we identified areas of important variation within networks due to lack of evidence and guidelines. Although evidence from randomized controlled trials is ideal, prevention of BPD requires a multifaceted approach. There is a need to develop and prospectively study different respiratory care bundles to help standardize care and determine what approach improves outcomes which can be accomplished by comparative effectiveness research strategies. Third, our findings highlight areas needing quality improvement initiatives to implement current best evidence such as reducing routine narcotic use among mechanically ventilated preterm infants.

Strengths and Limitations

There are some limitations to this study. As with other surveys, despite instructions, responder bias could not be ruled out as answers potentially may not be representative of the unit practices. Indeed, we did not survey all neonatologists within each unit and practices are subject to variations between providers within a single unit. However, this risk is likely minimized since surveys were completed by site investigators who are people actively involved in local data collection and quality improvement and were instructed clearly. We did not collect data on the type of device used to deliver respiratory support in each NICU as it is constantly changing in each unit. We did not collect more detailed data on the use of respiratory management protocols in units or detailed information on specific modes of invasive ventilation. This was a cross-sectional survey on respiratory management practices, and consequently we are currently unable to link these variations in practices with outcomes. However, the objective of this study was to describe the variations in practice between networks and to offer insight into areas of international collaboration for research and quality improvement, and encourage all units to look at the linkage between their practices and outcomes.

Conclusions

In summary, we conclude that there are variations in respiratory management of extremely preterm infants among the 10 surveyed neonatal networks, particularly in areas where high-quality evidence is lacking. Whether practice variations in the maximum CPAP pressure or FiO_2 used before intubation and the selection of respiratory strategies contribute to variations in outcomes between networks requires further investigation.

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Statement of Ethics

Specific approval for this project was obtained from the Research Ethics Board at Mount Sinai Hospital, Toronto (ON, Canada).

Disclosure Statement

The authors have no conflicts of interest to declare.

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