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Trends, Characteristic, and Outcomes of Preterm Infants Who Received Postnatal Corticosteroid: A Cohort Study from 7 High-Income Countries

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Keywords
Infant · Preterm · Bronchopulmonary dysplasia · Postnatal steroid

Abstract
Introduction: Our objective was to evaluate the temporal trend of systemic postnatal steroid (PNS) receipt in infants of 24–28 weeks' gestational age, identify characteristics associated with PNS receipt, and correlate PNS receipt with the incidence of bronchopulmonary dysplasia (BPD) and BPD/death from an international cohort included in the iNeo network. ***Methods:*** We conducted a retrospective study using data from 2010 to 2018 from seven international networks participating in iNeo (Canada, Finland, Israel, Japan, Spain, Sweden, and Switzerland). Neonates of 24 and 28 weeks' gestational age who survived 7 days and who received PNS were included. We assessed temporal trend of rates of systemic PNS receipt and BPD/death. ***Results:*** A total of 47,401 neonates were included. The mean (SD) gestational age was 26.4 (1.3) weeks and birth weight was 915 (238) g. The PNS receipt rate was 21% (12–28% across networks) and increased

The list of investigators for iNeo is provided in the online supplementary file, available at www.karger.com/doi/10.1159/000530128.

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over the years (18% in 2010 to 26% in 2018; $p < 0.01$). The BPD rate was 39% (28–44% across networks) and remained unchanged over the years (35.2% in 2010 to 35.0% in 2018). Lower gestation, male sex, small for gestational age status, and presence of persistent ductus arteriosus (PDA) were associated with higher rates of PNS receipt, BPD, and BPD/death. ***Conclusion:*** The use of PNS in extremely preterm neonates increased, but there was no correlation between increased use and the BPD rate. Research is needed to determine the optimal timing, dose, and indication for PNS use in preterm neonates.

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Introduction

The past few decades have seen significant improvement in the survival of extremely low gestational age (GA) infants, but morbidities such as bronchopulmonary dysplasia (BPD) have not decreased. Incidence of BPD has either remained static or increased in most countries [1]. Infants born before 29 weeks' GA are at a higher risk of developing BPD compared to those born after 29 weeks [2, 3]. Antenatal steroids and postnatal surfactant replacement therapy have improved survival by accelerating fetal lung maturation and preventing or treating respiratory distress syndrome, but their overall impact in reducing BPD has been less impressive [4, 5].

The pathogenesis of BPD is believed to be due to an imbalance between pulmonary inflammation and repair [6, 7]. To counter inflammatory effects, systemic and topical postnatal corticosteroids (PNS) are utilized. The incidence of BPD varied from 10.2% to 24.8% in 10 European regions, and PNS use varied from 3% to 50% among neonates from 19 regions in 11 European countries [8, 9]. The guidelines for the use of systemic postnatal steroids for BPD differs among academic bodies and networks [10–12]. Most of these bodies and studies warn against the early use of systemic corticosteroids in the first week after birth [13–15]. Currently, suggestions are to use low-dose steroid after the first week of birth who remain ventilated and have increasing oxygen requirements and worsening lung disease [16, 17]. However, the use of systemic hydrocortisone on postnatal days 14–28 was not associated with higher survival without moderate or severe BPD [18]. The NEUROSIS trial reported that early use of inhaled corticosteroids significantly decreased BPD, but increased mortality at 36 weeks postmenstrual age [19, 20]. With these conflicting reports, the practice of PNS use differs among neonatal intensive care units (NICU) across the world, as well as within a single NICU.

The International Network for Evaluation of Outcomes (iNeo) of neonates is a collaborative effort involving neonatal networks from 11 high-income countries/regions to identify care practices that improve neonatal outcomes [21]. We reported that while mortality decreased between years 2007 and 2015 in most countries, BPD increased for neonates born very preterm [22]. The use of systemic PNS use has swung from extremely restricted use in 2010 to a slowly increasing trend in the current era, accompanying more active perinatal care of infants born at 22–24 weeks of GA [23]. However, this changing trend in increasing use of PNS has not been clearly documented and various practices across different countries provide a good platform to evaluate contemporary practices [24]. Our aim was to evaluate and compare the temporal trend of systemic PNS use among infants 24–28 weeks' GA, identify characteristics of patients for whom PNS are used, and correlate PNS use with the incidences of BPD or composite of BPD/death.

Material and Methods

Design and Setting

In this retrospective cohort study, we included neonates admitted to the participating NICU in 7 national neonatal networks included in iNeo. Neonates born between January 1, 2010, and December 31, 2018 with GA between 24^0 and $28^{6/7}$ weeks were included. Neonates born ≥29 weeks' GA with major congenital malformations and those who received palliative care in the delivery room were excluded. Neonates who died in the first 7 days were excluded, as it was less likely that they would be exposed to PNS for the purpose of preventing or treating evolving BPD.

The iNeo dataset contains anonymized individual data for neonates admitted to 10 independent network or registries. Data from 7 of these registries were used for this study, including 33 units from the Canadian Neonatal Network unit (CNN), 28 units from the Finnish Medical Birth register units (FinMBR), 27 units from the Israel Neonatal network units (INN), 159 units from the Neonatal Research Network Japan units (NRNJ), 50 units from the Spanish Neonatal Network units (SEN1500), 37 units from the Swedish Neonatal Quality Register units (SNQ), and 10 units from the Swiss Neonatal Network units (SwissNeoNet). The characteristics of included units have been reported previously [25]. The study was approved by the Research Ethics Board at Mount Sinai Hospital and by iNeo Directors. Informed consent was waived due to retrospective nature of the study.

Data Source and Definitions

Data harmonization and data collection at each participating unit were described previously [21]. GA was determined based on information available in each country, typically using either early

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Table 1. Characteristics of infants included in the study from various networks

Characteristic	CNN	FinMBR	INN	NRNJ	SNQ	SNN	SEN1500	Total
Number of infants	12,585	1,222	4,399	15,925	3,303	2,044	7,916	47,394
Antenatal steroids, *n* (%)	11,115 (90.2)	1,165 (96.1)	3,625 (82.4)	10,047 (64.4)	2,832 (88.8)	1,902 (93.5)	6,557 (90.1)	37,243 (80.9)
GA, weeks mean (SD)	26.4 (1.3)	26.5 (1.4)	26.6 (1.3)	26.3 (1.4)	26.4 (1.4)	26.5 (1.3)	26.6 (1.3)	26.4 (1.3)
Birth weight, g mean (SD)	950 (242)	947 (247)	936 (215)	865 (228)	935 (249)	901 (224)	937 (242)	915 (238)
Birth weight, Z score (SD)	0.04 (0.92)	−0.02 (0.92)	0.02 (0.88)	−0.17 (1.00)	−0.04 (0.93)	−0.14 (0.84)	0.04 (1.05)	−0.05 (0.97)
SGA, *n* (%)	981 (7.8)	120 (9.8)	353 (8.0)	2,208 (13.9)	336 (10.2)	210 (10.3)	745 (9.4)	4,953 (10.4)
Male *n* (%)	6,826 (54.3)	637 (52.1)	2,396 (54.5)	8,478 (53.3)	1,785 (54.0)	1,089 (53.3)	4,190 (52.9)	25,401 (53.6)
PDA, *n* (%)	6,975 (55.7)	467 (38.2)	2,353 (51.5)	8,263 (52.4)	1,583 (47.9)	945 (46.1)	4,213 (54.3)	24,799 (52.7)
Other characteristics								
Cesarean birth, *n* (%)	7,546 (60.1)	792 (65.8)	3,140 (71.4)	12,678 (80.1)	2,247 (68.6)	1,640 (80.3)	5,119 (64.7)	33,162 (70.2)
Apgar <7 at 5 min	4,814 (38.7)	588 (49.1)	651 (15.2)	6,137 (38.9)	1,113 (34.5)	889 (43.6)	1,434 (18.2)	15,626 (33.4)
Surfactant, *n* (%)	8,765 (69.6)	1,039 (89.0)	3,374 (76.7)	12,644 (80.6)	2,208 (66.9)	1,516 (74.0)	5,378 (68.4)	34,924 (73.7)

GA, gestational age; SD, standard deviation; PDA, Patent Ductus Arteriosus; SGA, small for gestational age; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network, NRNJ, Neonatal Research Network Japan; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; SEN1500, Sociedad Espanola de Neonatologia.

ultrasound or last menstrual period. Birth weight z-scores were calculated using a country-specific birth weight standard [26]. BPD was defined as a receipt of supplemental oxygen or positive pressure ventilation (including mechanical ventilation, continuous positive airway pressure, and high-flow nasal cannula) at 36 weeks postmenstrual age or at the time of discharge or transfer from the NICU if it occurred earlier [7]. Mortality was defined as death during the NICU stay. A composite parameter of death or BPD was also investigated due to competing nature of these outcomes.

Statistical Analysis

Annual data for PNS use and the incidence of BPD across all networks were obtained from iNeo dataset. Baseline characteristics were reported as frequency (percentage) or mean (standard deviation) for continuous and categorical variables, respectively. The rates of PNS use, BPD, and BPD/death were calculated for each network stratified by characteristics of patients (GA, sex, small for GA, receipt of antenatal steroid, and presence/absence of patent ductus arteriosus). Rates with 95% confidence interval (CI) were reported. Rates of BPD and BPD/death were calculated for each network according to receipt of PNS, and the risk ratio with 95% CI was estimated. Furthermore, duration of respiratory support was presented for each network according to receipt of PNS, and median (IQR) was reported. The trend of PNS use and incidence of BPD were plotted graphically by birth year and assessed by the Cochrane-Armitage trend test. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) with a two-sided significance level of 0.05.

Results

A total of 47, 401 infants were eligible for this study. The baseline characteristics of neonates were similar across networks (Table 1). The mean (SD) GA and birth weight were 26.4 (1.3) weeks and 915 (238) g, respectively. Antenatal steroids were received by 81%, birth via cesarean section occurred in 70%, surfactant was received by 74% of neonates, and PDA was diagnosed or treated in 53% of neonates (Table 1).

Overall, the PNS receipt rate was 21.2% (varying between 12% and 28% across different networks), which increased over years (18% in 2010–26% in 2018; $p < 0.01$). The rate of receipt of PNS varied from 30% to 76% at 24 weeks and from 3% to 11% at 28 weeks' gestation between networks (Table 2). The rate of BPD among networks was 35.3% (varying between 24% and 41% across different networks), which remained unchanged over years (35.2% in 2010 and 35.0% in 2018). The rate of BPD/death was 38.7% (varying between 28 and 41% across different networks) (Table 2). The rates of PNS receipt, BPD, and BPD/deaths are reported by infant characteristics in Table 3. There was a significantly higher rate of BPD and BPD/death among those who received steroid compared to those who did not receive steroids

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Table 2. Rates of steroid use, BPD, and BPD/death by GA in the iNeo network

GA	Outcome	CNN	FinMBR	INN	NRNJ	SNQ	SNN	SEN 1500	Total, *n* (%), 95% CI
24 weeks, *n* (%)	Steroid use	650 (46.2)	109 (76.2)	181 (49.3)	1,173 (52.9)	189 (46.1)	60 (30.3)	263 (39.9)	2,625 (48.6) (47.3, 50.0)
Total = 5,399	BPD	883 (72.7)	74 (58.3)	153 (59.5)	1,369 (65.1)	228 (62.8)	89 (53.6)	244 (54.8)	3,040 (65.0) (63.7, 66.4)
	BPD/death	1,074 (76.4)	90 (62.9)	264 (71.9)	1,493 (67.3)	278 (67.8)	119 (61.0)	460 (69.7)	3,778 (70.0) (68.8, 71.2)
25 weeks, *n* (%)	Steroid use	764 (36.1)	84 (49.7)	227 (37.2)	1,047 (40.0)	157 (29.9)	69 (23.6)	329 (28.5)	2,677 (35.8) (34.7, 36.8)
Total = 7,488	BPD	1,119 (58.0)	63 (39.9)	203 (40.3)	1,393 (55.1)	266 (53.9)	108 (40.2)	386 (40.4)	3,538 (51.7) (50.5, 52.9)
	BPD/death	1,309 (61.8)	74 (43.8)	312 (51.2)	1,488 (56.8)	297 (56.6)	132 (44.6)	584 (50.7)	4,193 (56.0) (54.9, 57.1)
26 weeks, *n* (%)	Steroid use	572 (22.6)	60 (27.5)	244 (27.6)	924 (28.9)	113 (16.8)	52 (11.7)	294 (19.3)	2,259 (23.8) (23.0, 24.7)
Total = 9,471	BPD	1,154 (47.9)	61 (28.6)	253 (31.2)	1,372 (43.9)	254 (39.4)	108 (26.0)	450 (32.8)	3,652 (40.6) (39.6, 41.7)
	BPD/death	1,288 (50.8)	66 (30.3)	328 (37.1)	1,454 (45.5)	284 (42.2)	132 (29.9)	600 (39.5)	4,152 (43.8) (42.8, 44.8)
27 weeks, *n* (%)	Steroid use	360 (12.1)	57 (18.0)	201 (17.5)	577 (15.7)	72 (9.8)	36 (7.1)	260 (12.7)	1,563 (13.7) (13.1, 14.3)
Total = 11,405	BPD	950 (32.8)	75 (24.1)	230 (20.9)	1,118 (30.7)	212 (29.7)	85 (17.3)	418 (21.7)	3,088 (27.9) (27.0, 28.7)
	BPD/death	1,029 (34.6)	81 (25.6)	283 (24.6)	1,163 (31.6)	232 (31.6)	98 (19.4)	539 (26.4)	3,425 (30.0) (29.2, 30.9)
28 weeks, *n* (%)	Steroid use	205 (5.8)	28 (7.5)	148 (10.7)	323 (7.7)	28 (2.9)	29 (4.7)	149 (5.9)	910 (6.7) (6.3, 7.1)
Total = 13,631	BPD	808 (23.1)	56 (15.1)	175 (12.9)	877 (21.0)	182 (19.3)	84 (13.7)	373 (15.1)	2,555 (19.0) (18.4, 19.7)
	BPD/death	858 (24.2)	61 (16.3)	210 (15.1)	911 (21.7)	202 (21)	94 (15.1)	450 (17.7)	2,786 (20.4) (19.8, 21.1)
All gestation, *n* (%)	Steroid use	2,551 (20.3)	338 (27.7)	1,001 (22.8)	4,044 (25.4)	559 (16.9)	246 (12.0)	1,295 (16.4)	10,034 (21.2) (20.8, 21.5)
Total = 47,394	BPD	4,914 (41.1)	329 (27.9)	1,014 (25.2)	6,129 (39.3)	1,142 (36.2)	474 (24.3)	1,871 (26.1)	15,873 (35.3) (34.8, 35.7)
	BPD/death	5,558 (44.2)	372 (30.4)	1,397 (31.8)	6,509 (40.9)	1,293 (39.2)	572 (28.1)	2,633 (33.3)	18,334 (38.7) (38.3, 39.1)

GA, gestational age; BPD, bronchopulmonary dysplasia; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; SEN1500, Sociedad Espanola de Neonatologia.

(Table 4). The rates of PNS receipt, BPD, and BPD/death were higher in males compared to females; in SGA neonates compared to non-SGA neonates; and in neonates treated for PDA compared to those not treated for PDA. There was no difference in rates of PNS receipt, BPD, and BPD/death among those who received antenatal steroid and those did not receive them (Table 3).

When evaluated as a longitudinal trend over years, the overall rate of BPD for all networks did not show a significant change from 2010 to 2018, but the PNS receipt rate increased over the years (18% in 2010 to 26% in 2018, $p < 0.01$). With respect to the trends within individual networks, Canada and Spain showed a decreasing trend of BPD and an increasing trend of PNS use. The trend of steroid use and BPD both increased in Japan, while Israel, Finland, Sweden, and Switzerland did not show a significant change in the trends of either BPD or PNS over the study period (Fig. 1). Correspondingly, the durations of receipt of mechanical ventilation (median 32 days vs. 5 days) and supplemental oxygen (median 81 days vs. 34 days) were higher among neonates who received PNS compared to those who did not receive PNS confirming that at-risk neonates received PNS at higher rate (Table 5).

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Table 3. Rates of steroid use, BPD, and BPD/death according to patient characteristics

Characteristic	Outcome	CNN	FinMBR	INN	NRNJ	SNQ	SNN	SEN 1500	Total, *n* (%)	95% CI
Male, *n* (%) Total = 25,401	Steroid use	1,459 (21.4)	199 (31.2)	597 (24.9)	2,262 (26.7)	362 (20.3)	143 (13.1)	713 (17)	5,735 (22.6)	(22.1, 23.1)
	BPD	2,790 (43.2)	184 (29.9)	586 (26.8)	3,407 (41.1)	675 (40)	288 (27.7)	1,069 (28.5)	8,999 (37.5)	(36.8, 38.1)
	BPD/ death	3,165 (46.4)	207 (32.5)	799 (33.3)	3,616 (42.7)	778 (43.6)	343 (31.5)	1,512 (36.1)	10,420 (41)	(40.4, 41.6)
Female, *n* (%) Total = 21,970	Steroid use	1,088 (18.9)	139 (23.8)	404 (20.2)	1,781 (23.9)	197 (13)	102 (10.7)	582 (15.6)	4,293 (19.5)	(19.0, 20.1)
	BPD	2,120 (38.7)	145 (25.7)	428 (23.3)	2,721 (37.3)	467 (31.8)	185 (20.3)	801 (23.5)	6,867 (32.8)	(32.1, 33.4)
	BPD/ death	2,388 (41.6)	165 (28.2)	598 (29.9)	2,892 (38.9)	515 (33.9)	227 (23.8)	1,120 (30.1)	7,905 (36)	(35.4, 36.6)
SGA, *n* (%) Total = 4,953	Steroid use	304 (31)	49 (40.8)	152 (43.1)	772 (35)	88 (26.2)	45 (21.4)	198 (26.6)	1,608 (32.5)	(31.2, 33.8)
	BPD	571 (64.2)	61 (53)	178 (61)	1,243 (59.2)	170 (56.1)	88 (46.6)	278 (46.9)	2,589 (57.8)	(56.3, 59.2)
	BPD/ death	663 (67.6)	67 (55.8)	239 (67.7)	1,371 (62.1)	204 (60.7)	110 (52.4)	433 (58.1)	3,087 (62.3)	(61.0, 63.7)
Non-SGA, *n* (%) Total = 42,441	Steroid use	2,247 (19.4)	289 (26.2)	849 (21)	3,272 (23.9)	471 (15.9)	201 (11)	1,097 (15.3)	8,426 (19.9)	(19.5, 20.2)
	BPD	4,343 (39.3)	268 (25.1)	836 (22.4)	4,886 (36.2)	972 (34)	386 (21.9)	1,593 (24.2)	13,284 (32.8)	(32.3, 33.2)
	BPD/ death	4,895 (42.2)	305 (27.7)	1,158 (28.6)	5,138 (37.5)	1,089 (36.7)	462 (25.2)	2,200 (30.7)	15,247 (35.9)	(35.5, 36.4)
Any antenatal steroid, *n* (%) Total = 37,243	Steroid use	2,298 (20.7)	323 (27.7)	839 (23.1)	2,738 (27.3)	489 (17.3)	229 (12)	1,049 (16)	7,965 (21.4)	(21.0, 21.8)
	BPD	4,379 (41.4)	320 (28.4)	842 (25.2)	4,139 (41.9)	1,000 (37)	453 (24.9)	1,543 (25.9)	12,676 (35.8)	(35.3, 36.3)
	BPD/ death	4,919 (44.3)	358 (30.7)	1,135 (31.3)	4,331 (43.1)	1,134 (40)	540 (28.4)	2,157 (32.9)	14,574 (39.1)	(38.6, 39.6)
No antenatal steroid, *n* (%) Total = 8,803	Steroid use	216 (17.8)	12 (25.5)	162 (20.9)	1,269 (22.8)	63 (17.5)	17 (12.8)	126 (17.5)	1,865 (21.2)	(20.3, 22.0)
	BPD	446 (39.6)	7 (16.3)	172 (25.1)	1,902 (35.1)	111 (31.9)	20 (16.4)	176 (27.6)	2,834 (33.8)	(32.8, 34.8)
	BPD/ death	535 (44.1)	12 (25.5)	262 (33.9)	2,061 (37.1)	124 (34.5)	31 (23.3)	257 (35.7)	3,282 (37.3)	(36.3, 38.3)
PDA, *n* (%) Total = 24,799	Steroid use	1,888 (27.1)	153 (32.8)	737 (31.3)	2,390 (28.9)	423 (26.7)	157 (16.6)	939 (22.3)	6,687 (27)	(26.4, 27.5)
	BPD	3,536 (54.1)	168 (37.3)	708 (33.9)	3,442 (42.6)	729 (48.7)	310 (35.1)	1,290 (35)	10,183 (43.9)	(43.2, 44.5)
	BPD/ death	3,979 (57)	185 (39.6)	979 (41.6)	3,644 (44.1)	821 (51.9)	373 (39.5)	1,825 (43.3)	11,806 (47.6)	(47.0, 48.2)
No PDA, *n* (%) Total = 22,231	Steroid use	657 (11.8)	185 (24.5)	264 (12.9)	1,639 (21.8)	136 (7.9)	89 (8.1)	327 (9.2)	3,297 (14.8)	(14.4, 15.3)
	BPD	1,366 (25.5)	161 (22)	306 (15.8)	2,658 (36)	413 (24.8)	164 (15.4)	541 (16.2)	5,609 (26.1)	(25.5, 26.7)
	BPD/ death	1,562 (28.2)	187 (24.8)	418 (20.4)	2,803 (37.3)	472 (27.4)	199 (18.1)	749 (21.1)	6,390 (28.7)	(28.2, 29.3)

BPD, bronchopulmonary dysplasia; SGA, small for gestational age; PDA, patent ductus arteriosus; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; SEN1500, Sociedad Espanola de Neonatologia.

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Table 4. Rate of BPD and BPD/death according to receipt of postnatal steroid

Characteristic	CNN	FinMBR	INN	NRNJ	SEN 1500	SNN	SNQ	Total
BPD								
Received steroid, *n*/*N* (%)	1,680/2,451 (68.5)	189/311 (60.8)	622/946 (65.8)	2,885/3,999 (72.1)	777/1,196 (65.0)	158/228 (69.3)	368/517 (71.2)	6,679/9,648 (69.2)
Not received steroid, *n*/*N* (%)	3,228/9,484 (34.0)	140/870 (16.1)	392/3,077 (12.7)	3,244/11,584 (28.0)	1,094/5,969 (18.3)	323/1,741 (18.6)	774/2,642 (29.3)	9,195/35,367 (26.0)
Ratio (95% CI) of BPD among those who received steroid versus not received steroid	2.0 (1.9–2.1)	3.8 (3.2–4.5)	5.2 (4.7–5.7)	2.5 (2.5–2.7)	3.5 (3.3–3.8)	3.7 (3.3–4.3)	2.4 (2.2–2.6)	2.7 (2.6–2.7)
BPD/death								
Received steroid, *n*/*N* (%)	1,780/2,458 (69.9)	217/338 (64.2)	680/1,001 (67.9)	2,932/4,044 (72.5)	880/1,295 (68.0)	177/247 (71.7)	411/559 (73.5)	7,077/10,032 (70.5)
Not received steroid, *n*/*N* (%)	3,771/10,024 (37.6)	155/884 (17.5)	717/3,398 (21.1)	3,577/11,881 (30.1)	1,753/6,622 (26.5)	402/1,816 (22.1)	882/2,744 (32.1)	11,257/37,369 (30.1)
Ratio (95% CI) of BPD/death among those who received steroid versus not received steroid	1.9 (1.9–2.0)	3.7 (3.1–4.7)	3.2 (3.0–3.5)	2.4 (2.3–2.5)	2.6 (2.4–2.7)	3.2 (2.9–3.6)	2.5 (2.3–2.6)	2.3 (2.3–2.4)

BPD, bronchopulmonary dysplasia; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan, SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; SEN1500, Sociedad Espanola de Neonatologia.

Discussion

In this large international cohort from 7 countries, we identified variations in outcomes of BPD or BPD/death among preterm neonates of <29 weeks' GA between countries. Approximately 1 in 5 neonates of 24^0–28^6 received PNS, and 1 in 3 neonates was diagnosed with BPD. The overall BPD rate for the majority of networks did not show a change between years 2010 and 2018; however, the receipt of PNS increased during the study period. Neonates of lower GA; male neonates compared to female neonates; SGA compared to non-SGA, those diagnosed with PDA compared to those not diagnosed as having PDA received PNS at a higher rate and had higher rates of BPD and BPD/death.

The strengths of our study include the large, multinational cohort of high-risk neonates for whom data were collected using a standardized reporting system within each country. However, our study has limitations. First, we excluded neonates of <24 weeks' GA who may be at very high risk of both exposure to PNS and BPD. Neonates of 22–23 weeks' GA may drive the change in practice over time as resuscitation at 22–23 weeks' GA has become more common. However, in order to keep the cohort homogeneous and not affected by variations in resuscitation practices and active care of neonates at lower GA, we excluded those neonates. It is possible that practices of 22 and 23 weeks' GA neonates may have influenced practice of 24–29 weeks' GA neonates with regard to PNS; however, we do not have data to prove this speculation. Second, we did not include inhaled steroids as the data were not available for most of the networks. Third, we do not have data on indication or threshold each unit or practitioner used or reasons for initiation of PNS. Such thresholds are likely to be highly variable between units and even within units between practitioners. Fourth, we do not have data on the type of steroid, dose of steroid, duration of steroid, and severity of lung disease that prompted initiation of steroid. Again, variations are expected in all these aspects, and this report may just scratch the surface of PNS practice around the world. Based on durations of respiratory support among groups that received steroid versus those that did not receive steroids, it can be suspected that severity of lung disease was higher among exposed groups. Finally, we also do not have data on severity of BPD. It is also

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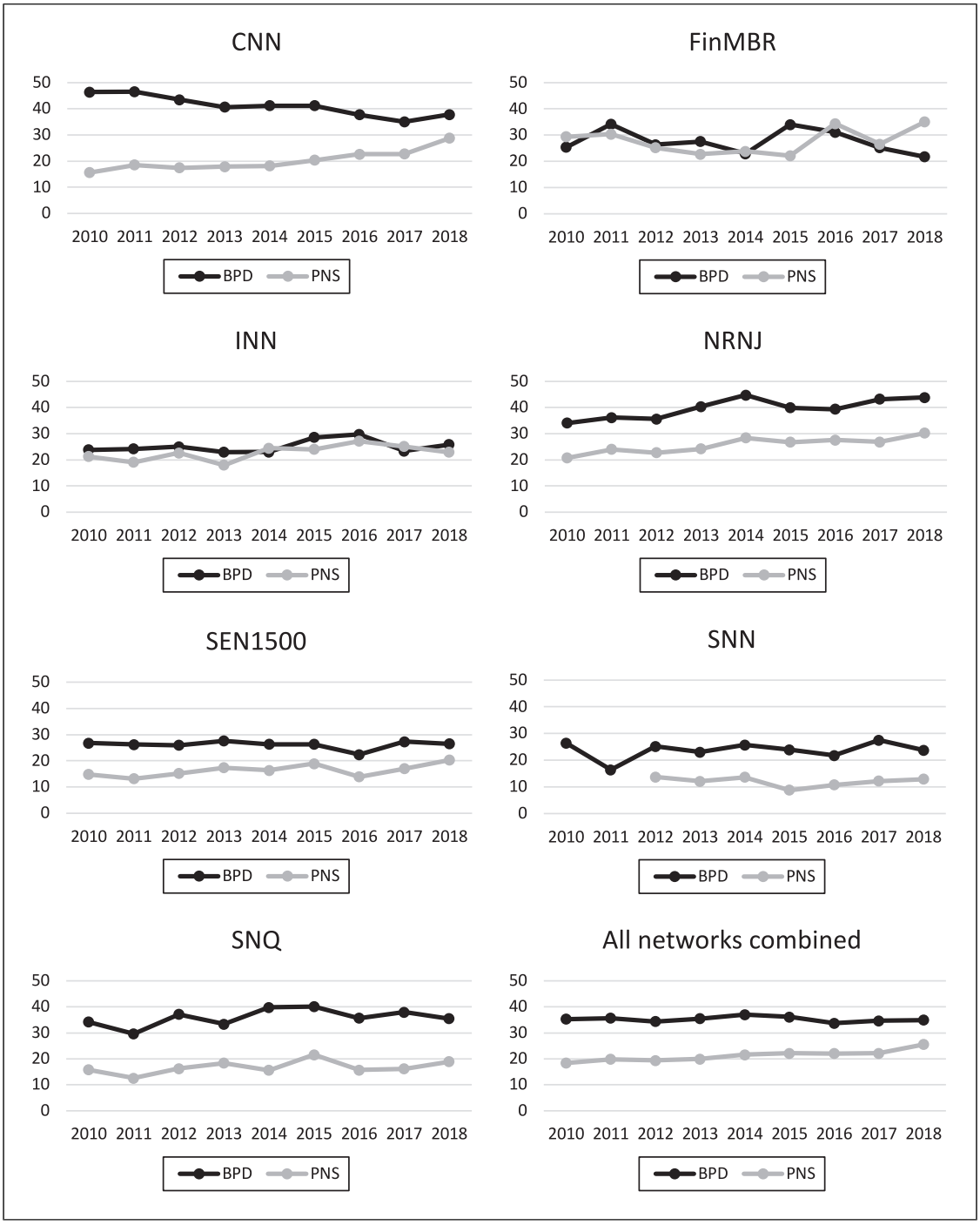

Fig. 1. Trend of postnatal steroid use in various networks over study years. CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; SEN1500, Sociedad Espanola de Neonatologia.

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Table 5. Duration of respiratory support among those who received steroids versus those who did not receive steroid

Respiratory support	Group	CNN	FinMBR	INN	NRNJ	SEN1500	SNN	SNQ	Total
Duration of mechanical ventilation, median (IQR)	Received steroid	31 (15, 46)	19 (11, 34)	25 (10, 44)	41 (27, 57)	25 (13, 39)	18 (10, 27)	21 (13, 32)	32 (18, 49)
	Not received steroid	3 (0, 14)	4 (1, 10)	3 (0, 10)	16 (4, 36)	4 (0, 13)	2 (0, 6)	2 (0, 8)	5 (1, 20)
Duration of oxygen supplementation, median (IQR)	Received steroid	78 (43, 111)	NA	72 (50, 101)	88 (61, 125)	74 (43, 102)	71 (52, 85)	84 (56, 108)	81 (53, 114)
	Not received steroid	22 (4, 51)	NA	24 (8, 45)	50 (25, 72)	25 (6, 50)	31 (7, 53)	40 (15, 63)	34 (9, 60)

NA, not available; IQR, interquartile range; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; SEN1500, Sociedad Espanola de Neonatologia.

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speculated that PNS may have reduced severity of BPD and not actual BPD rate; however, this needs to be evaluated further in other setting.

The use of PNS in neonates with evolving BPD is considered based on their anti-inflammatory properties. Different regimens have been tested, including early prophylactic use (before 1 week of age) [27], use during postnatal weeks 2–4, and later use after the first month of postnatal age. A network meta-analysis concluded that a moderately early initiated (8–14 days after birth) PNS regimen of a cumulative dose of 2–4 mg/kg of systemic dexamethasone may be the most beneficial PNS regimen for preventing BPD or mortality at 36 weeks postmenstrual age [15]. The European guidelines recommended using a small dose of dexamethasone for infants at the highest risk of BPD, such as those who remain ventilator dependent after 1–2 weeks [11]. The American Academy of Pediatrics and the Canadian Pediatric Society position recommend an initial low dose of 0.15–0.2 mg/kg/day, tapered over a period of 7–10 days, and do not recommend the use of hydrocortisone beyond the first week of age for the same group of patients [10]. Thus, most recommendations during our study period warned and advised caution in the use of PNS. The decline in the PNS use after these statements/guidelines could have resulted in an increase in rate of BPD; however, this has not been the case when we see combined data form all networks. However, for the majority of networks, BPD rates either reduced or remained unchanged. Since our data excluded neonates below 24 weeks' gestation, we cannot explain the increase in PNS use as a result of the survival of extremely low GA neonates, as the rate of steroid use is reported to be higher in these neonates [28]. The majority of neonates received steroids between weeks 2 and 6 of postnatal age. It is known that the setup for inflammatory cascade may have been initiated in first few hours after birth and thus, for PNS to be effective they may need to be utilized very early in the disease stage. This will need to be evaluated in future studies. Moreover, recent information on administration of budesonide along with surfactant showing beneficial effects was not known during the study years and, thus, it was not utilized by any units.

Similar to our results, Cheong et al. [29] reported in a regional study of extremely low birth weight and extremely preterm neonates from Victoria, Australia that the use of PNS reduced in 2005 compared to 1991–92 and 1997; however, the rates of BPD increased during the same period. There was no correlation between increased steroid use and BPD as an outcome over the study period. However, this has not been always been the case as reported in Europe [9]. Israel had the lowest rate of steroid receipt among those who did not develop BPD, whereas Canada had the highest. Finland had the lowest rate of steroid receipt among those who developed BPD, while Japan had the highest. Steroids are frequently used to wean babies off respirators to avoid damaging the lungs. However, although this intervention seems to be successful for this purpose, the ongoing damage that leads to BPD, initiated as soon as the smallest babies start breathing, is not modified. Thus, a higher rate among those who finally did not end up getting diagnosed with BPD may be acceptable; however, one would not be able to prove that, had those neonates not received steroid, they could have ended up with a diagnosis of BPD or not. On the other hand, countries with higher rates of steroid receipt among those diagnosed with BPD can be questioned as well. The likely effects of BPD and PNS

exposure on neurodevelopmental outcomes are of a magnitude of odds ratio between 1.5 and 2.5 for both, and thus exposing neonates to a double hit may put them at higher risk of neurodevelopmental adversity. Association between exposure to PNS and autistic spectrum disorder has also been reported [30]. Our result indicates a rather random distribution of PNS receipt probabilities between countries, which supports the idea that the use of PNS remains a largely "nonevidence informed" strategy for the prevention or treatment of BPD. Further research is needed to determine the optimal dosing, regimen, and indication for PNS use. A similar trend of PNS use has also been reported within units participating in Vermont Oxford Network and there is a call to evaluate efficacy and safety of PNS use in extremely preterm neonates [31].

Conclusions

We conclude that there were variations in the rate of PNS receipt, BPD, and BPD/death among networks studied, and that the use of systemic PNS in extremely premature infants has increased, but there is no correlation between increased use and BPD as an outcome. It is clear that PNS use remains a nonevidence-based therapy with respect to the timing, dose, and duration of use. A neurodevelopmental follow-up of this cohort is important to determine whether this increased PNS use as beneficial or adverse effects on brain development.

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Statement of Ethics

Data collection and data transfer from individual networks were approved by the Research Ethics Boards of the participating networks in the respective countries and by the iNeo steering committee. Specific ethics approval for this project was obtained from the Mount Sinai Hospital Research Ethics Board and the iNeo Steering Committee. This study protocol was reviewed and approved by Research Ethics Board (approval number 21-0248-C). Informed consent from individual patients was waived due to retrospective nature of this database study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Drs. Prakesh Shah and Shalin Parikh were involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and revising it critically for important intellectual content. All other authors (Brian Reichman, Satoshi Kusuda, Mark Adams, Liisa Lehtonen, Maximo Vento, Mikael Norman, Laura San Feliciano, Tetsuya Isayama, Stellan Hakansson, Kjell Helenius, Dirk Bassler, and Junmin Yang) were involved in the conception and design of the study, interpretation of results, and revising article critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data Availability Statement

Prakesh S. Shah, Mount Sinai Hospital, Toronto, ON, Canada, has full access to the data. He takes responsibility for the integrity of the data and the accuracy of the data analysis. The data analyses were conducted by Junmin Yang. Data are confidential and not available for public access. Further inquiries can be directed to the corresponding author.

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