Incidence and Outcome of CPAP Failure in Preterm Infants

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abstract

BACKGROUND AND OBJECTIVES: Data from clinical trials support the use of continuous positive airway pressure (CPAP) for initial respiratory management in preterm infants, but there is concern regarding the potential failure of CPAP support. We aimed to examine the incidence and explore the outcomes of CPAP failure in Australian and New Zealand Neonatal Network data from 2007 to 2013.

METHODS: Data from inborn preterm infants managed on CPAP from the outset were analyzed in 2 gestational age ranges (25–28 and 29–32 completed weeks). Outcomes after CPAP failure (need for intubation <72 hours) were compared with those succeeding on CPAP using adjusted odds ratios (AORs).

RESULTS: Within the cohort of 19 103 infants, 11 684 were initially managed on CPAP. Failure of CPAP occurred in 863 (43%) of 1989 infants commencing on CPAP at 25–28 weeks' gestation and 2061 (21%) of 9695 at 29–32 weeks. CPAP failure was associated with a substantially higher rate of pneumothorax, and a heightened risk of death, bronchopulmonary dysplasia (BPD) and other morbidities compared with those managed successfully on CPAP. The incidence of death or BPD was also increased: (25–28 weeks: 39% vs 20%, AOR 2.30, 99% confidence interval 1.71–3.10; 29–32 weeks: 12% vs 3.1%, AOR 3.62 [2.76–4.74]). The CPAP failure group had longer durations of respiratory support and hospitalization.

CONCLUSIONS: CPAP failure in preterm infants is associated with increased risk of mortality and major morbidities, including BPD. Strategies to promote successful CPAP application should be pursued vigorously.

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Dr Dargaville conceptualized and designed the study, assisted with data cleaning and statistical analysis, and drafted the initial manuscript; Drs Gerber and Johansson carried out the data cleaning and processing, assisted with statistical analysis, and reviewed and revised the manuscript; Drs De Paoli, Kamlin, and Davis and Ms Orsini assisted with study design and approach to statistical analysis, and reviewed and revised the manuscript; the Australian and New Zealand Neonatal Network oversaw the collection of data at source, performed first-stage data cleaning and verification, provided the data to the study group, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Results of large clinical trials favor continuous positive airway pressure (CPAP) for initial respiratory management in preterm infants. However, for infants with significant respiratory distress syndrome, intubation is sometimes required secondarily because of CPAP failure, and adverse outcomes may follow.

WHAT THIS STUDY ADDS: In a population-based study of preterm infants of gestational age 25 to 32 weeks, failure of initial CPAP was relatively frequent, especially at <29 weeks. CPAP failure was associated with adverse outcomes, including death, bronchopulmonary dysplasia, other major morbidities, and prolonged hospitalization.

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The optimal approach to the early respiratory management of the preterm infant remains contentious.[1,2] The results of randomized controlled trials (RCTs), considered both individually[3–5] and collectively,[6,7] suggest that initiation of nasal continuous positive airway pressure (CPAP) is at least as good, if not better than early intubation and exogenous surfactant therapy. These findings have recently led to an American Academy of Pediatrics recommendation that application of CPAP at the outset should be considered as a worthy alternative to intubation, including at the lower extremes of gestation.[8]

A concern in the universal application of CPAP to preterm infants is that those with significant respiratory distress syndrome (RDS) will be inadequately supported by CPAP, ultimately require intubation, and receive exogenous surfactant at a later than ideal time. On consideration of the RCT evidence, the American Academy of Pediatrics statement concluded that management with early CPAP alone does not confer an increased risk of adverse outcome if treatment with surfactant were delayed or not given.[8] However, none of the RCTs examined outcomes differentially for infants succeeding or failing on initial CPAP support. Data from several hospital-based cohort studies strongly suggest that CPAP failure is primarily caused by untreated surfactant deficiency, and is associated with adverse outcomes, including increased risk of mortality as well as morbidities, including air leak, bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage (IVH).[9–14]

Reported studies of CPAP failure have involved relatively small cohorts of infants managed at 1 or 2 centers.[9–14] Examination of the effects of initial CPAP support and CPAP failure within large-scale neonatal databases has been hampered by difficulty in identifying the exact sequence of respiratory management in early life within the reported data.[15] Population-based data on the incidence of, and outcomes after, CPAP failure would give clarity on the magnitude of the problem, both overall and within gestation strata. The confounding of adverse outcomes by factors overrepresented among infants with CPAP failure (eg, low birth weight, male sex, and incomplete antenatal steroid exposure) could also be dealt with more effectively. Finally, the potential impact of CPAP failure on duration of mechanical respiratory support and/or length of stay could be determined.

In this study, we analyzed data on initial respiratory management in preterm infants sourced from a large binational database. We aimed (1) to examine the incidence and timing of CPAP failure, (2) to compare neonatal outcomes within the CPAP failure group with those of infants succeeding on CPAP, and (3) to compare resource consumption between the groups.

METHODS

The Australian and New Zealand Neonatal Network (ANZNN) is a binational neonatal database receiving data from all NICUs in Australia and New Zealand. Since 2007, an extended dataset has been kept, documenting the exact timing of key aspects of neonatal management and complications, including respiratory management. The dataset thus allows identification of infants managed on CPAP in early life, and, within this group, those for whom CPAP fails and intubation is required. Data are collected prospectively by audit officers at each site, and de-identified information is sent in a standardized format to the ANZNN headquarters. Collection of data is approved at each site by local ethics committees, and this study was approved by the Tasmanian Health Research Ethics Committee.

For the calendar years 2007 to 2013, we identified preterm infants born at 25 to 32 completed weeks' gestation who were inborn in a tertiary center or colocated private facility, and were admitted to a level III NICU within 60 minutes after birth. Data for infants born at 32 weeks' gestation were incomplete; such infants are reported to ANZNN only if they require respiratory support or major surgery. Outborn infants, in whom respiratory management might have been affected or dictated by the needs of safe retrieval, were not included in the study population. Further exclusions were of infants with (1) a congenital anomaly likely to affect respiratory function or early management, (2) prolonged premature rupture of membranes (>14 days), (3) no requirement for respiratory support in the first 24 hours, and (4) insufficient information regarding early respiratory management.

Among the cohort thus assembled, infants were categorized based on early respiratory management into a group intubated primarily (either in the delivery room or shortly after arrival in the NICU), and a group receiving a CPAP trial of at least 30 minutes' duration. Infants managed on CPAP were further divided into those in whom CPAP was successfully applied (CPAP-S), and those for whom CPAP failed and intubation was required within 72 hours of birth (CPAP-F).[10,13]

Within these groups, the requirement for and timing of surfactant therapy, and the incidence and timing of pneumothorax requiring drainage were determined. Pneumothorax was considered to have been a possible contributor to CPAP failure if it was first noted either before or within an hour after intubation. The incidence of the following outcomes

was ascertained in the 2 groups: BPD (need for respiratory support and/or supplemental oxygen at 36 postmenstrual weeks),[15,16] severe intraventricular hemorrhage (IVH, grades III and IV),[17] necrotizing enterocolitis (modified Bell stage II or greater),[18] retinopathy of prematurity greater than stage 2, and survival to hospital discharge. The presence of a major morbidity (at least 1 of severe IVH, cystic brain injury, retinopathy greater than stage 2, or BPD) was ascertained.[19] The cumulative duration of all episodes of intubation and CPAP was recorded, as well as the length of hospital stay, both overall and for survivors.

The approach to respiratory management was examined by week of completed gestation, and within 2 gestational age ranges (25–28 weeks and 29–32 weeks). Data were further analyzed within these gestation ranges. Comparisons were made between infants succeeding and failing on CPAP by using χ^2 test for dichotomous variables and Mann-Whitney test for continuous variables. Comparisons also were made with the group of infants intubated primarily.

Logistic regression models were used to further investigate the impact of CPAP failure on adverse outcomes during hospitalization, adjusted by demographic and clinical factors, including gestation, birth weight <10th percentile, sex, mode of delivery (vaginal birth or Cesarean delivery), plurality (singleton/multiple), antenatal glucocorticoid exposure (incomplete versus complete), and 5-minute Apgar score (<7 / ≥7). Adjusted odds ratios were derived to describe the association of CPAP failure with adverse outcomes, comparing with both the CPAP-S group, and those intubated primarily. The intubated and CPAP groups were also compared. Given that the dataset is representative of an entire population, we set the probability of a type I error at 0.01.

TABLE 1 Early Respiratory Management by Gestational Age Range

	25–28 wk Gestation	29–32 wk Gestation	All Infants
Total	6771	12 332	19 103
Intubated	4782	2637	7419
CPAP	1989	9695	11 684
CPAP-S (% of all CPAP)	1126 (57)	7634 (79)	8760 (75)
CPAP-F (% of all CPAP)	863 (43)	2061 (21)	2924 (25)

RESULTS

For the 7-year study period, a total of 24 212 infants were reported to ANZNN having been born at 25 to 32 weeks' gestation in 1 of 25 ANZNN tertiary centers. Of these, 962 had a congenital anomaly and 1294 had prolonged membrane rupture. A further 2074 infants did not require respiratory support in the first 24 hours, and 779 had insufficient data on early respiratory management.

A total of 19 103 infants were thus included in the analysis (15–295 infants per center per year), with 11 684 of them managed with CPAP initially (Table 1). Considerable differences in both the use of initial CPAP (29% vs 79%) and the incidence of CPAP failure (43% vs 21%) were noted between the 2 gestational age ranges (Table 1). Analysis by week of gestation showed a steady increase in the proportion managed with initial CPAP from 25 to 32 weeks' gestation (Fig 1). Incidence of CPAP failure remained close to 50% for infants at 25 to 27 weeks' gestation, and decreased steadily with each week of additional gestation thereafter. Nonetheless, given the progressively larger numbers starting CPAP, more mature infants made a substantially greater numerical contribution to the CPAP-F group overall. No major trends in application of initial CPAP or rate of CPAP failure were discernible between 2007 and 2013 for infants of 25 to 28 weeks' gestation (data not shown). For those at 29 to 32 weeks, rate of application of CPAP remained unchanged but failure rate increased marginally, from 20% to 22% during the first 5 years to 23% in 2012 and 2013 ($P = .036$, χ^2 test for trend).

In the CPAP-F group, intubation occurred at a median of 4.4 hours (interquartile range [IQR] 2.3–12.0 hours) in the 25- to 28-week gestation range, and at 5.9 (2.8–20.0) hours at 29 to 32 weeks. In the CPAP-S group, intubation at some time beyond 72 hours occurred in 12.0% and 2.0% in the 2 gestation ranges, respectively.

Compared with infants for whom CPAP was successful, infants in the CPAP-F group at 25 to 28 weeks' gestation were smaller and less likely singletons, with lesser incidence of complete steroid exposure, a higher rate of delivery by Cesarean without labor, and somewhat lower Apgar score at 5 minutes (Table 2). These latter 3 factors were also associated with CPAP failure at 29 to 32 weeks, with additional significant finding at this gestation range being a slight male preponderance (Table 2). For both gestation ranges, compared with all infants commencing on CPAP, those intubated primarily were smaller, less likely to have complete steroid exposure, and in worse condition at birth (Supplemental Table 6).

For infants at 25 to 28 weeks' gestation, 97% of those intubated primarily received exogenous surfactant, at 0.30 (0.13–0.67) hours of age. By contrast, for the 97% of

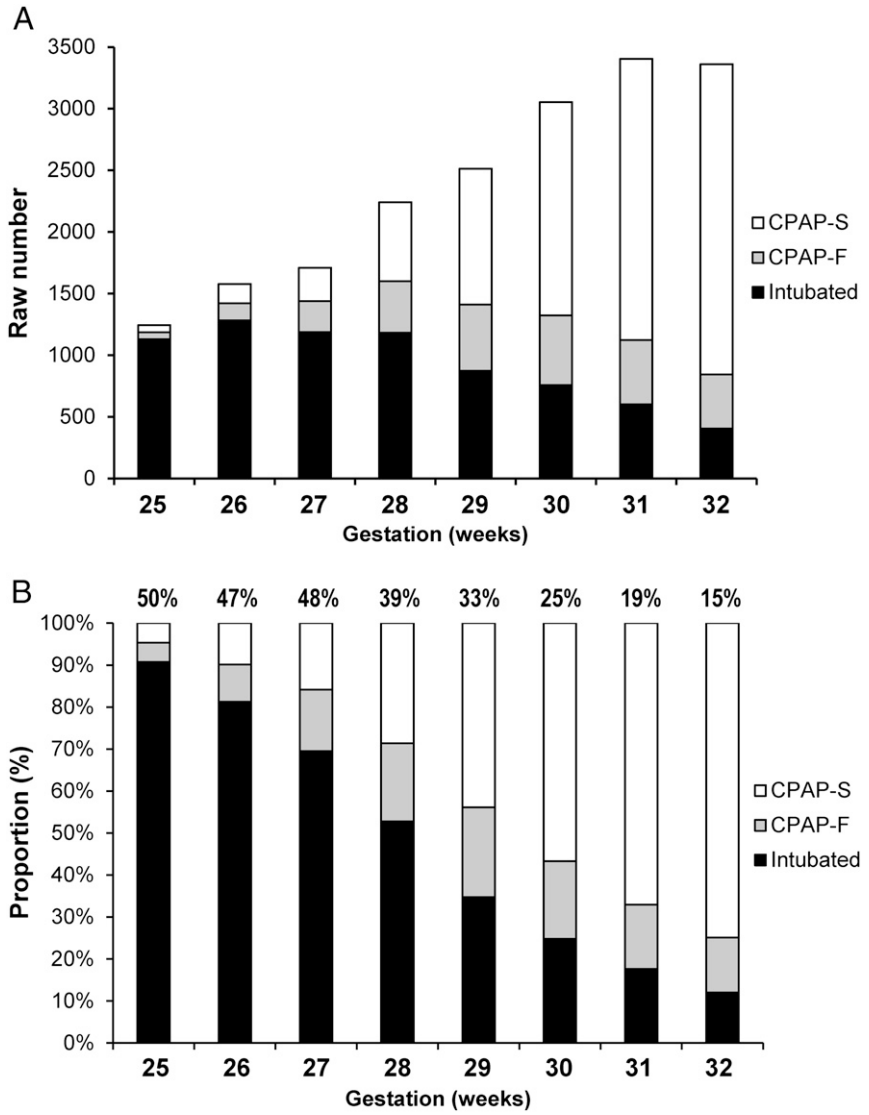

FIGURE 1

Initial respiratory support by gestation. Cumulative histograms showing respiratory support initiated at each gestational age (completed weeks) for the entire ANZNN cohort (n = 19 103). A, Raw values. B, Proportions in relation to total number receiving respiratory support, with the rate of CPAP failure in those commencing on CPAP indicated above each column. Black bars: intubated primarily; white bars: initial CPAP, successful; gray bars: initial CPAP, but failed and required intubation before 72 hours.

infants in the CPAP-F group receiving surfactant, administration was considerably later, at 4.7 (2.6–12.0) hours. Findings were similar in the 29- to 32-week infants: intubation group: 88% received surfactant, administration time 0.55 (0.20–1.2) hour; CPAP-F: 95%, time 6.1 (3.1–19.0) hours.

Within both gestational age ranges, the incidence of adverse outcomes other than pneumothorax was higher in infants intubated primarily compared with infants commencing on CPAP (Supplemental Table 7). Within the CPAP group, there was a clear difference in risk profile for adverse outcomes depending on whether CPAP failed or succeeded in preventing intubation in the first 72 hours (Table 3). Rate of pneumothorax was substantially higher in the CPAP-F group than those succeeding on CPAP. For infants at 25 to 28 weeks, pneumothorax was a preintubation event in 37% of cases, and was a contributing factor to the failure of CPAP and need for intubation in 2.7% of the CPAP-F group overall. For the more mature infants, 48% of pneumothoraces occurred before intubation, with this complication contributing to CPAP failure in 4.9% of the group overall. Risk of BPD (both gestation ranges) and severe IVH (25–28 weeks) was higher in the CPAP-F infants compared with the CPAP-S group (Table 3). The incidence of at least 1 major morbidity was also substantially increased after CPAP failure (Table 3), and approached that of infants intubated primarily (Supplemental Table 7).

After adjustment for demographic and clinical factors in multiple logistic regression, the apparent advantage of commencing CPAP at the outset remained, with higher rates of BPD and major morbidity in the group intubated primarily (Table 4). For those commencing on CPAP, the odds of major adverse outcomes in the CPAP-F group were found to be twofold to threefold higher than the CPAP-S group at 25 to 28 weeks' gestation, and higher still at 29 to 32 weeks (Table 5). For both gestation ranges, in logistic regression analysis, the odds of adverse outcomes in those failing CPAP were similar to the group intubated primarily (Supplemental Table 8). Covariates in the logistic regression models that were consistently associated with adverse outcomes were lower gestation and birth weight <10th percentile.

In association with the differences in incidence of adverse outcomes, there were differences in the duration of mechanical respiratory support and length of hospital stay between groups (Fig 2). Within both gestation ranges, infants commencing on CPAP had a shorter duration of respiratory

TABLE 2 Demographic and Clinical Data by Gestational Age Range

	25–28 wk			29–32 wk		
	CPAP, all, *n* = 1989	CPAP-S, *n* = 1126	CPAP-F, *n* = 863	CPAP, all, *n* = 9695	CPAP-S, *n* = 7634	CPAP-F, *n* = 2061
Gestation, wk, median (IQR)	28 (27–28)	28 (27–28)	27 (27–28)[a]	31 (30–32)	31 (30–32)	30 (29–31)[a]
Birth weight, g, median (IQR)	1060 (890–1210)	1090 (920–1230)	1010 (860–1170)[a]	1550 (1330–1780)	1560 (1330–1790)	1520 (1290–1770)[a]
Birth weight, *z* score, median (IQR)	0.22 (−0.43–0.77)	0.32 (−0.29–0.84)	0.059 (−0.62–0.69)[a]	0.06 (−0.60–0.64)	0.05 (−0.63–0.63)	0.11 (−0.50–0.69)[a]
Birth weight <10th percentile	145 (7.3)	66 (5.9)	79 (9.2)[a]	920 (9.5)	775 (10)	145 (7.0)[a]
Boys, *n* (%)	1067 (54)	579 (51)	488 (57)	5391 (56)	4138 (54)	1253 (61)[a]
Plurality, *n* (%)						
Singleton	1351 (68)	818 (73)	533 (62)[a]	6128 (63)	4777 (63)	1351 (66)
First-order multiple	326 (16)	169 (15)	157 (18)	1747 (18)	1427 (19)	320 (16)[a]
Second/higher-order multiple	311 (16)	139 (12)	172 (20)[a]	1814 (19)	1425 (19)	389 (19)
Antenatal steroids, *n* (%)						
Complete	1419 (72)	842 (75)	577 (67)[a]	6377 (66)	5100 (67)	1277 (62)[a]
Incomplete	489 (25)	248 (22)	241 (28)[a]	2503 (26)	1919 (25)	584 (29)[a]
None	72 (3.6)	31 (2.8)	41 (4.8)	738 (7.7)	550 (7.3)	188 (9.2)[a]
Delivery mode, *n* (%)						
Vaginal birth	749 (38)	535 (48)	214 (25)[a]	2990 (31)	2549 (34)	441 (21)[a]
Cesarean delivery in labor	433 (22)	250 (22)	183 (21)	1930 (20)	1545 (20)	385 (19)
Cesarean delivery, no labor	792 (40)	332 (30)	460 (54)[a]	4712 (49)	3477 (46)	1235 (60)[a]
Apgar scores, median (IQR)						
1 min	7 (5–8)	7 (5–8)	6 (5–8)[a]	7 (6–8)	7 (6–8)	7 (6–8)[a]
5 min	9 (8–9)	9 (8–9)	8 (8–9)[a]	9 (8–9)	9 (8–9)	9 (8–9)[a]

Shows data for infants managed with CPAP primarily, with subdivision into CPAP-S and CPAP-F groups depending on whether CPAP was successful or failed (intubation required in the first 72 hours).

[a] Differs from CPAP-S group, $P < .01$.

TABLE 3 In-Hospital Outcomes: Binary Variables

	25–28 wk			29–32 wk		
	CPAP, all, *n* = 1989	CPAP-S, *n* = 1126	CPAP-F, *n* = 863	CPAP, all, *n* = 9695	CPAP-S, *n* = 7634	CPAP-F, *n* = 2061
Pneumothorax	73 (3.7)	4 (0.36)	69 (8.1)[a]	257 (2.7)	28 (0.37)	229 (11)[a]
BPD	499 (25)	208 (18.5)	291 (34)[a]	439 (4.5)	226 (3.0)	213 (10)[a]
Home oxygen	110 (5.6)	41 (3.7)	69 (8.1)[a]	78 (0.8)	39 (0.5)	39 (1.9)[a]
Grade III or IV IVH	62 (3.1)	18 (1.6)	44 (5.1)[a]	57 (0.6)	38 (0.5)	19 (0.9)
Cerebral cystic change	36 (1.8)	18 (1.6)	18 (2.1)	80 (0.8)	61 (0.8)	19 (0.9)
Retinopathy of prematurity stage ≥3	68 (3.4)	35 (3.1)	33 (3.8)	38 (0.4)	24 (0.3)	14 (0.7)
Necrotizing enterocolitis	84 (4.2)	39 (3.5)	45 (5.2)	64 (0.7)	45 (0.6)	19 (0.9)
Major morbidity	588 (30)	250 (22)	338 (39)[a]	571 (5.9)	321 (4.2)	250 (12)[a]
Died	77 (3.9)	25 (2.2)	52 (6.0)[a]	40 (0.4)	14 (0.2)	26 (1.3)[a]
Died or survived with BPD	564 (28)	229 (20)	335 (39)[a]	476 (4.9)	238 (3.1)	238 (12)[a]
Died or survived with major morbidity	632 (32)	268 (24)	364 (42)[a]	602 (6.2)	330 (4.3)	272 (13)[a]

All values are *n* (%).

[a] Differs from CPAP-S group, $P < .01$.

TABLE 4 Odds Ratios for Association of Primary Intubation With Adverse Outcomes, Compared With Infants Commencing on CPAP

Outcome	25–28 wk		29–32 wk	
	Crude Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)	Crude Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
BPD	1.95 (1.67–2.27)	1.30 (1.09–1.54)	2.36 (1.91–2.91)	1.57 (1.23–1.99)
Died	2.71 (1.96–3.75)	1.40 (0.98–2.01)	7.27 (4.38–12.0)	3.17 (1.78–5.63)
Died or survived with BPD	2.37 (2.04–2.75)	1.36 (1.15–1.62)	2.86 (2.36–3.47)	1.77 (1.42–2.21)
Major morbidity	2.07 (1.79–2.40)	1.30 (1.10–1.53)	2.59 (2.15–3.10)	1.74 (1.41–2.14)
Died or survived with major morbidity	2.36 (2.05–2.73)	1.36 (1.15–1.60)	2.92 (2.45–3.48)	1.87 (1.54–2.29)

Crude and adjusted odds ratios with 99% CIs for adverse outcomes, comparing odds in the intubated group with those of the CPAP group. Adjusted odds ratio derived from multiple logistic regression modeling, with the following covariates: gestation, birth weight <10th percentile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, and 5-minute Apgar score (<7 / ≥7).

TABLE 5 Odds Ratios for Association of CPAP Failure With Adverse Outcomes

Outcome	25–28 wk		29–32 wk	
	Crude Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)	Crude Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
BPD	2.25 (1.72–2.95)	1.94 (1.44–2.61)	3.78 (2.93–4.87)	3.32(2.51–4.39)
Died	2.83 (1.49–5.35)	2.82 (1.40–5.65)	6.95 (2.95–16.4)	6.04 (2.47–14.8)
Died or survived with BPD	2.49 (1.92–3.24)	2.30 (1.71–3.10)	4.05 (3.17–5.18)	3.62 (2.76–4.74)
Major morbidity	2.26 (1.75–2.92)	2.03 (1.53–2.70)	3.14 (2.50–3.95)	2.77 (2.16–3.54)
Died or survived with major morbidity	2.34 (1.82–3.01)	2.20 (1.65–2.93)	3.36 (2.69–4.20)	2.99 (2.35–3.81)

Crude and adjusted odds ratios with 99% CIs for adverse outcomes, comparing odds in the CPAP-F group with those of the CPAP-S group. Adjusted odds ratio derived from multiple logistic regression modeling; covariates as for Table 4.

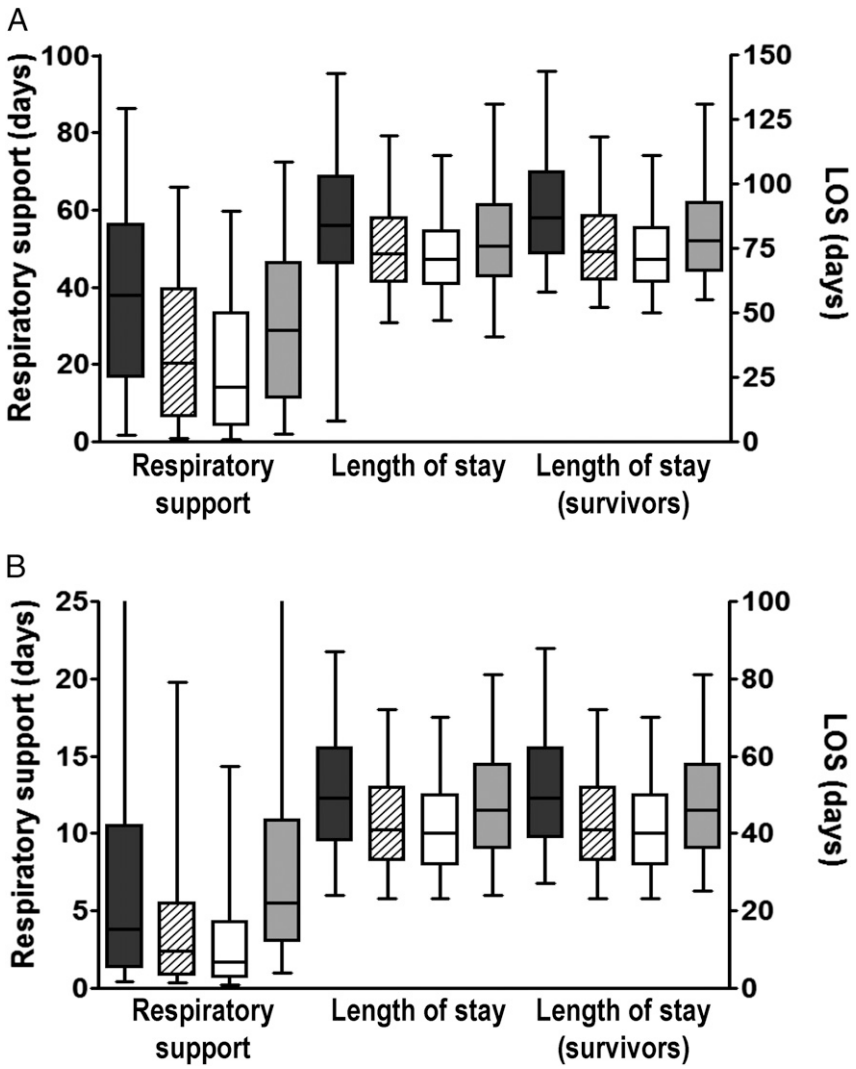

FIGURE 2
Outcomes: respiratory support and length of stay. Box and whisker plots of cumulative duration of respiratory support (intubation + CPAP), length of hospital stay, and length of stay (LOS) for survivors. Whiskers denote 5th and 95th centiles. A, 25–28 weeks' gestation; B, 29–32 weeks. Black bars: intubated primarily; hatched bars: all CPAP; white bars: CPAP-S; gray bars: CPAP-F. Within both gestation ranges, all values differ between the intubated and CPAP groups, and among the intubated, CPAP-S, and CPAP-F groups ($P < .01$).

support and length of stay than those intubated primarily. However there was divergence within the CPAP group depending on whether CPAP succeeded or failed, in particular for duration of respiratory support (25–28 weeks: CPAP-S median 14 days [IQR 4.3–33] vs CPAP-F 29 [11–46] days, $P < .001$; 29–32 weeks: 1.7 [0.67–4.3] days vs 5.5 [3.0–11.0] days, $P < .001$). This discrepancy remained when infants who died were excluded: 25–28 weeks: CPAP-S median 14 days (IQR 4.1–33) vs CPAP-F 30 (13–47) days, $P < .001$; 29–32 weeks: 1.7 (0.67–4.3) days vs 5.5 (3.0–10) days, $P < .001$. Median length of hospital stay was ~1 week greater for the CPAP-F infants compared with the CPAP-S group (Fig 2).

DISCUSSION

The approach to early respiratory management of the preterm infant continues to evolve, with enthusiasm for initial CPAP tempered by concern regarding the consequences of delay in surfactant administration and the potential failure of CPAP support, especially for the extremely preterm group. In this population-based study, we found CPAP failure to be relatively prevalent, with a gestation-dependent decrease in risk at 28 weeks and beyond. Characteristics overrepresented among infants failing CPAP included incomplete exposure to antenatal glucocorticoids and Cesarean delivery without labor. Compared with those successfully managed on CPAP, CPAP failure was associated with a marked increase in the rate of pneumothorax, and a heightened risk of BPD and major morbidity even after correction for potential confounders. Finally, infants

failing CPAP had a longer duration of respiratory support, and a 1 week longer length of hospital stay.

Several uncontrolled observational studies,[20,21] as well as large RCTs,[3–5] have noted better outcomes for preterm infants commencing on CPAP compared with those intubated. Our study had a similar finding, with higher odds of adverse outcomes among infants intubated primarily, even after adjustment for confounding factors. Caution is needed in interpretation of this result, as our study design was purely observational, with no control exercised over selection of infants for inclusion, nor the intervention applied. The intubated group is undoubtedly heterogeneous, and includes infants requiring intubation in the delivery room for resuscitation, for whom initial CPAP would not have been an option, and in whom risk of adverse outcome is greater.

The clinical trials and meta-analyses comparing initial CPAP with primary intubation do not clarify whether infants destined to fail CPAP and require intubation are compromised as a result. We examined this notion by division of the CPAP group into those successfully managed on CPAP for the first 3 days (and usually thereafter), and those for whom CPAP failed, and intubation and mechanical ventilation was required. To our knowledge, this is the first large population-based study in which the timing of CPAP and intubation were known with sufficient precision to conduct such an analysis.

The adverse respiratory and general outcomes that we observed after CPAP failure were not explicable by demographic or clinical factors alone, with odds ratios adjusted for these confounders clearly showing a heightened vulnerability to adverse outcome in those failing CPAP. We postulate that both the respiratory antecedents of CPAP failure, as well as the interventions imposed on infants after it has occurred, contribute to the burden of morbidity and the development of serious complications. The ANZNN database gives limited detail about clinical condition in the individuals commencing on CPAP, and does not allow meaningful comparison between the CPAP-F and CPAP-S groups in this respect. Similarly, no data on radiologic severity of RDS are recorded. Smaller cohort studies in which analysis of such data has been performed concur that the presence of RDS is the single most important antecedent to CPAP failure in preterm infants, with both clinical and radiologic indicators suggesting more severe disease in those destined to fail CPAP.[13,14] The ANZNN data provide circumstantial evidence in favor of this, in that 96% of infants failing CPAP were given surfactant shortly after being intubated.

Beyond the presence and severity of RDS, other elements of respiratory dysfunction undoubtedly contribute to CPAP failure in some cases, and may have longer-term effects in their own right. Both intractable apnea and respiratory acidosis can be the precipitant for intubation in this setting,[3,12,13] perhaps accounting for ∼20% of all instances of CPAP failure. Both clearly have the potential to contribute to neurologic complications. Similarly, the destabilization related to intubation of the deteriorating patient, the sedative medications that may be administered during and after, as well as the lung injury associated with mechanical ventilation, may all contribute to the outcome for an individual preterm infant.

Notwithstanding the contribution of other factors, given the impact of RDS on the destiny of preterm infants managed on CPAP from the outset, the obvious conclusion is to interrupt the chain of events by timely administration of exogenous surfactant. The intubate, surfactant, extubate approach is advocated and widely practiced in this setting. The disadvantages are plain: subjecting an infant to a full intubation, exposure to positive pressure ventilation even if only briefly, and the difficulty with extubation. Evidence from clinical trials suggests no advantage of the intubate, surfactant, extubate approach over CPAP alone when applied universally in the delivery room,[5,22] but some advantages (decreased air leak and need for ventilation) when applied selectively to infants showing an oxygen requirement.[23]

Another approach to bolster the surfactant pool in an infant on CPAP has been the use of techniques of minimally invasive surfactant therapy,[24] with observational studies[25,26] and several RCTs[27,28] suggesting that CPAP failure can be averted in up to 50% of cases. Whether the downstream consequences of CPAP failure are ameliorated remains to be proven definitively, and further, larger trials are needed, including with follow-up in infancy. Individual patient data on the use of less invasive methods of surfactant administration are not currently collected by the ANZNN, and it may be that some infants who received surfactant by such methods were coded as having been intubated when in fact they were not. The impact of any resultant misclassification is likely to be negligible, as techniques of minimally invasive surfactant therapy were not widely practiced in Australia and New Zealand during the period of the study (∼1.0% of all infants at 25 to 28 weeks' gestation, ∼0.36% at 29–32 weeks; data on file, ANZNN 2016).

Beyond consideration of surfactant therapy, optimization of an infant's condition in general and CPAP support in particular may play a role in preventing CPAP failure. Adding noninvasive positive pressure inflations may improve functional residual capacity in those languishing

on CPAP with surfactant deficiency, but this mode of noninvasive support was not found to improve outcomes in a recent large trial.[29] By contrast, early use of caffeine for infants <1250 g may help regularize breathing patterns and prevent CPAP failure related to apnea, and may reduce the incidence of BPD by other mechanisms.[30]

Undoubtedly the approach to respiratory management within individual units is likely to have an impact on outcomes for preterm infants in this study, as has been seen previously.[20,31] As an example, compared with the figures reported herein, we recently found the incidence of pneumothorax to be higher in 2 Australian units with an ethos of applying CPAP at the outset whenever possible, without substantial effects on other complications of prematurity.[13] An investigation of the effect of center-specific patient volumes and management practices on outcomes was beyond the scope of the present analysis, but may well assist in understanding the complex interplay of factors that contribute to the destiny of the preterm infants we look after.

An important strength of our study is that the analysis is of a large and complete dataset from all NICUs in Australia and New Zealand. Beyond those already stated, several limitations are evident, including the observational design, and the restrictions associated with reporting data to a network registry, meaning that detailed information on chest radiography, noninvasive positive pressure ventilation, caffeine therapy, and other relevant interventions was not available. The imprecision associated with adjusting for risk profile within the study groups by using the demographic and clinical data items available in the ANZNN database is also acknowledged.

CONCLUSIONS

CPAP failure occurs frequently in preterm infants, especially in those at <29 weeks' gestation, and is associated with heightened risk of mortality and major morbidities, and a more protracted duration of ventilation and length of stay. Strategies to avoid CPAP failure, including less invasive approaches to surfactant therapy, should be strenuously investigated.

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ABBREVIATIONS

ANZNN: Australian and New Zealand Neonatal Network
AOR: adjusted odds ratio
BPD: bronchopulmonary dysplasia
CI: confidence interval
CPAP: continuous positive airway pressure
CPAP-F: failed CPAP and required intubation <72 hours
CPAP-S: successfully managed on CPAP for the first 72 hours
IQR: interquartile range
IVH: intraventricular hemorrhage
RCT: randomized controlled trial
RDS: respiratory distress syndrome

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