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Fetal and Neonatal Research

Continuous Positive Airway Pressure Failure in Preterm Infants: Incidence, Predictors and Consequences

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Information for the Health Care Professional

It is important to note that the infants may vary markedly in the severity of respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care.

Rapid extubation after surfactant administration may not be achievable or desirable in the most immature infants. Extubation should be performed when the infant is stable at the discretion of the clinician.

Indication

CUROSURF® (poractant alfa) Intratracheal Suspension is indicated for the rescue treatment of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

Important Safety Information

CUROSURF is intended for intratracheal use only. The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of preterm infants.

Transient adverse reactions associated with administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

Pulmonary hemorrhage, a known complication of premature birth and very low birth-weight, has been reported with CUROSURF. The rates of common complications of prematurity observed in a multicenter single-dose study that enrolled infants 700-2000g birth weight with RDS requiring mechanical ventilation and FiO2 ≥ 0.60 are as follows for CUROSURF 2.5 mL/kg (200 mg/kg) (n=78) and control (n=66; no surfactant) respectively: acquired pneumonia (17% vs. 21%), acquired septicemia (14% vs. 18%), bronchopulmonary dysplasia (18% vs. 22%), intracranial hemorrhage (51% vs. 64%), patent ductus arteriosus (60% vs. 48%), pneumothorax (21% vs. 36%) and pulmonary interstitial emphysema (21% vs. 38%).

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Abstract
Background: Preterm infants ≤32 weeks' gestation are increasingly being managed on continuous positive airway pressure (CPAP), without prior intubation and surfactant therapy. Some infants treated in this way ultimately fail on CPAP and require intubation and ventilation. **Objectives:** To define the incidence, predictors and consequences of CPAP failure in preterm infants managed with CPAP from the outset. **Methods:** Preterm infants 25–32 weeks' gestation were included in the study if inborn and managed with CPAP as the initial respiratory support, with division into two gestation ranges and grouping according to whether they were successfully managed on CPAP (CPAP-S) or failed on CPAP and required intubation <72 h (CPAP-F). Predictors of CPAP failure were sought, and outcomes compared between the groups. **Results:** 297 infants received CPAP, of which 65 (22%) failed, with CPAP failure being more likely at lower gestation-

al age. Most infants failing CPAP had moderate or severe respiratory distress syndrome radiologically. In multivariate analysis, CPAP failure was found to be predicted by the highest FiO_2 in the first hours of life. CPAP-F infants had a prolonged need for respiratory support and oxygen therapy, and a higher risk of death or bronchopulmonary dysplasia at 25–28 weeks' gestation (CPAP-F 53% vs. CPAP-S 14%, relative risk 3.8, 95% CI 1.6, 9.3) and a substantially higher risk of pneumothorax at 29–32 weeks. **Conclusion:** CPAP failure in preterm infants usually occurs because of unremitting respiratory distress syndrome, is predicted by an FiO_2 ≥0.3 in the first hours of life, and is associated with adverse outcomes.

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Introduction

Widespread uptake of nasal continuous positive airway pressure (CPAP) as the initial means of respiratory support for preterm infants has fundamentally changed their management in early life [1, 2]. Large clinical trials in preterm infants ≤29 weeks' gestation have indicated that CPAP started soon after birth, without prior intuba-

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tion for surfactant therapy, is associated with equivalent or superior respiratory outcomes compared to a group that are intubated primarily [3–5]. At gestations beyond 29 weeks, most preterm infants with signs of respiratory distress syndrome (RDS) now receive an initial trial of CPAP [6].

A significant proportion of preterm infants managed on CPAP from the outset go on to require intubation in the first days of life. Several reports have suggested that CPAP failure is associated with a higher risk of adverse outcomes, including pneumothorax, bronchopulmonary dysplasia (BPD) and intraventricular haemorrhage (IVH), than the group for whom CPAP successfully avoids intubation [7–10]. The respiratory course for infants failing CPAP needs further clarification, as does the incidence and severity of complications and comorbidities in this group.

Several demographic risk factors for CPAP failure are discernible from previous reports [7–10], including immature gestation, lower birth weight and male gender, but the possibility that clinical indices of respiratory function, in particular early oxygen requirement, might predict CPAP failure requires further examination. Two recent observational studies examining the value of highest FiO_2 in the first hours of life as a predictor of later CPAP failure have yielded disparate results [9, 10]. The product of CPAP level (in cm H_2O) and FiO_2 has also been proposed as a potential predictor of CPAP failure [11], but this index may overestimate the effect of an incremental change in airway pressure on oxygenation.

This study examines the incidence, predictors and outcome of CPAP failure. Our aims were to (a) define the incidence and immediate antecedents of CPAP failure, (b) search for early predictors, including combinations of FiO_2 and CPAP level in early life, and (c) explore any adverse consequences of CPAP failure. We hypothesised that CPAP failure would be associated with prolonged need for respiratory support and oxygen therapy, and an increased risk of adverse outcomes, including severe IVH and BPD.

Methods

The study was conducted at the Royal Hobart Hospital (RHH) and the Royal Women's Hospital, Melbourne (RWH). Management of preterm infants 25–32 weeks' gestation in the two Units is described in detail in the 'online supplement'. Both units initially use CPAP by preference for infants with respiratory distress, with a maximum CPAP pressure of 8 cm H_2O and FiO_2 0.45–0.50. Infants exceeding these limits are intubated, and exogenous surfactant is administered soon after if clinically indicated.

Study Group
Study infants were of gestational age 25 weeks 0 days to 32 weeks 6 days by best obstetric estimate, inborn in the maternity unit of the two hospitals or at a colocated private maternity unit, admitted to the NICU for respiratory support in the first 24 h of life, and managed initially with CPAP. Infants requiring intubation primarily, either in the delivery room or shortly after arrival in the NICU, were excluded. Cases complicated by premature rupture of membranes for 14 days or more, or a congenital anomaly likely to affect respiratory function or alter standard management, were also excluded.

Data Collection
This was a retrospective analysis of data prospectively collected by neonatal audit nurses and bedside nursing staff during hospitalisation. The data collection periods were June 2006 to June 2009 (RHH) and May 2009 to April 2010 (RWH). The study was approved by Ethics Committees at both sites as an audit of clinical practice. The respiratory course for all infants managed initially on CPAP was defined from the intensive care charts. Data recorded included highest FiO_2 (sustained for at least 15 min), CPAP pressure and CPAP-FiO_2 product (= CPAP level in cm H_2O × FiO_2) [11] in the first 2 h (25–28 weeks) or first 6 h (29–32 weeks), as well as highest PCO_2 in the first 6 h. For those failing CPAP, defined as the need for intubation before 72 h [7], the most recent physiological parameters prior to intubation were documented, and the radiological severity of RDS was categorised by one of the authors as mild, moderate or severe [12].

Demographic and clinical details were collected from the Unit databases, including need for intubation and mechanical ventilation in the first 72 h (and thereafter), surfactant therapy, pneumothorax, BPD (need for supplemental oxygen at 36 weeks corrected gestational age) [13], severe IVH (grades III and IV) [14], necrotising enterocolitis (NEC; modified Bell stage II or greater) [15], ROP >stage 2, and survival to hospital discharge. The presence of a major morbidity (at least one of severe IVH, periventricular leucomalacia, NEC, ROP >stage 2 and BPD) was ascertained [16]. The cumulative duration of all episodes of intubation and CPAP was recorded, along with the total number of days receiving any form of respiratory support (intubation, CPAP or high flow nasal cannula), and the total days of oxygen therapy.

Data Analysis and Statistical Comparison
Amongst infants admitted to NICU in the first 24 h, the proportions treated initially with CPAP, failing CPAP, and intubated primarily were determined in total and by gestational age group (25–28 and 29–32 weeks).

Logistic regression models were used to investigate the effects of FiO_2 and CPAP level in early life in prediction of CPAP failure, coupled with potential demographic predictors. Highest values for FiO_2 and CPAP in the first 2 h (25–28 weeks) or 6 h (29–32 weeks) were used. Demographic variables included in the analysis were gestation, birth weight, plurality (singleton, multiple) and delivery mode (vaginal, Caesarean). Two multivariate models were generated. Model 1 included the above demographic variables along with FiO_2; model 2 added CPAP level as an additional predictive variable. The effect of the CPAP-FiO_2 product (interaction term) was examined in each model. The value of clinical variables in prediction of CPAP failure was also examined using receiver operating characteristic (ROC) curves, plotting sensitivity (true positive

Table 1. Demographic and clinical details

| | 25–28 weeks | | 29–32 weeks | |
	CPAP-S (n = 36)	CPAP-F (n = 30)	CPAP-S (n = 196)	CPAP-F (n = 35)
Gestation, weeks	27.5 (26–28)	27 (26–27)	31 (30–31)	30 (29–31)
Birth weight, g	1,045 (930–1,251)*	915 (784–1,054)	1,508 (1,289–1,764)	1,484 (1,325–1,655)
Male	20 (56)	19 (63)	95 (48)	21 (60)
Singleton	27 (75)	17 (57)	107 (55)	20 (57)
2nd or subsequent multiple	5 (14)	7 (23)	47 (24)	9 (26)
Antenatal corticosteroids, any	35 (97)	27 (90)	154 (79)	30 (86)
Caesarean delivery	16 (44)*	24 (80)	138 (70)	30 (86)
Apgar score at 5 min	8 (8–9)	8 (7–9)	9 (8–9)	8 (8–9)

Summary data for infants succeeding and failing CPAP (CPAP-S, CPAP-F), by gestation. Median (IQR) or n (%). * Differs from CPAP-F group, $p < 0.05$, Mann-Whitney test or χ^2 test, as appropriate.

rate) against 1 – specificity (false-positive rate) at different thresholds. Area under the ROC curve was determined as a measure of predictive power.

Outcome variables were compared between infants succeeding and failing on CPAP using the Mann-Whitney test for continuous variables, and χ^2 or Fisher's exact tests, as appropriate, for dichotomous outcomes. All reported p values are two-sided.

Results

A total of 297 infants 25–32 weeks' gestation were treated initially with CPAP (online suppl. table 1; for all online supplementary material, see www.karger.com/doi/10.1159/000346460). Overall, CPAP failure occurred in 65 infants commencing on CPAP (22%), and was more likely to occur at 25–28 than at 29–32 weeks' gestation (45 vs. 15%, OR 4.7, 95% CI 2.6, 8.5). The proportion offered CPAP primarily, and the CPAP success rate, steadily increased with each week of gestation (online suppl. fig. 1).

Among infants of 25–28 weeks' gestation, those failing CPAP were of lower birth weight than the CPAP-S group (table 1), and were more likely to have been born by Caesarean delivery. At 29–32 weeks, the effect of Caesarean delivery was less prominent (p = 0.061), and birth weight did not differ between the two CPAP groups (table 1).

Median age at the time of CPAP failure was 7.9 and 18 h in the two gestation groups (table 2), with overall only 4 infants failing before 2 h. Infants failing CPAP had relatively high CPAP levels and oxygen requirements at the time of intubation. By contrast, PCO_2 was only modestly elevated, with few infants having PCO_2 values above 60 mm Hg prior to intubation (table 2). Prior to intuba-

Table 2. Condition at CPAP failure

	25–28 weeks (n = 30)	29–32 weeks (n = 35)
Time of intubation, h	7.9 (3.8–19)	18 (6.9–34)
FiO_2	0.50 (0.41–0.60)	0.44 (0.40–0.50)
CPAP pressure, cm H_2O	8 (7–8)	8 (7–8)
CPAP × FiO_2	3.6 (3.2–4.4)	3.5 (2.6–3.9)
PCO_2, mm Hg	52 (47–56)	52 (44–59)
PCO_2 >60 mm Hg	4 (14)	6 (17)
Radiological severity of RDS		
Mild	2 (7)	7 (20)
Moderate	22 (73)	23 (66)
Severe	6 (20)	5 (14)
Pneumothorax prior to intubation	3 (10)	8 (23)

Median (IQR) or n (%), as appropriate.

tion, at least 80% of infants had moderate or severe RDS radiologically, and a number had pneumothoraces. There were no cases of proven congenital pneumonia. Exogenous surfactant therapy was given after intubation to 97 and 89% of infants in the two gestation ranges, respectively, and mechanical ventilation continued for at least 2 h thereafter in all cases.

For infants at 25–28 weeks' gestation, univariate logistic regression analyses confirmed a strong association between Caesarean delivery and risk of CPAP failure (table 3), and some evidence of increased risk at lower gestation and birth weight. Amongst infants with gestational ages of 29–32 weeks, these demographic variables were not

Table 3. Prediction of CPAP failure at 25–28 weeks' gestation

Predictor	Univariate logistic regression			Multivariate logistic regression model 1			Multivariate logistic regression model 2		
	OR	p value	95% CI	OR	p value	95% CI	OR	p value	95% CI
Gestational age	0.61	0.044	0.38, 0.99	0.41	0.087	0.15, 1.14	0.48	0.193	0.16, 1.45
Birth weight	0.99	0.018	0.99, 0.99	0.99	0.265	0.99, 1.00	0.99	0.387	0.99, 1.00
Multiple birth	2.63	0.069	0.93, 7.43	1.62	0.555	0.32, 8.12	2.59	0.305	0.42, 16.03
Caesarean delivery	5	0.004	1.65, 15.17	11.12	0.024	1.37, 90.10	14.77	0.022	1.47, 148.55
FiO_2 by 2 h	1.21	<0.001	1.10, 1.33	1.20	0.001	1.08, 1.33	1.19	0.002	1.06, 1.33
CPAP level	3.21	0.001	1.57, 6.56	–	–	–	3.04	0.054	0.98, 9.40

Logistic regression analysis examining prediction of CPAP failure at 25–28 weeks' gestation (n = 66). OR, p values and 95% CI for univariate analysis, and multivariate logistic regression using model 1 (excluding CPAP level) and model 2 (with CPAP level included).

Table 4. Prediction of CPAP failure at 29–32 weeks' gestation

Predictor	Univariate logistic regression			Multivariate logistic regression model 1			Multivariate logistic regression model 2		
	OR	p value	95% CI	OR	p value	95% CI	OR	p value	95% CI
Gestational age	0.76	0.115	0.55, 1.07	0.91	0.685	0.57, 1.44	0.97	0.902	0.60, 1.57
Birth weight	1	0.229	0.99, 1.0	0.99	0.435	0.99, 1.0	0.99	0.376	0.99, 1.00
Multiple birth	0.89	0.765	0.43, 1.85	0.81	0.613	0.36, 1.82	0.78	0.557	0.35, 1.76
Caesarean delivery	2.58	0.062	0.95, 6.98	2.59	0.085	0.88, 7.65	2.53	0.094	0.85, 7.52
FiO_2 by 6 h	1.11	<0.001	1.06, 1.16	1.11	<0.001	1.06, 1.16	1.10	<0.001	1.05, 1.15
CPAP level	1.71	0.008	1.15, 2.54	–	–	–	1.28	0.279	0.82, 2.02

Logistic regression analysis examining prediction of CPAP failure at 25–28 weeks' gestation (n = 66). OR, p values and 95% CI for univariate analysis, and multivariate logistic regression using model 1 (excluding CPAP level) and model 2 (with CPAP level included).

predictive of CPAP failure by the univariate analyses (table 4). For both gestation ranges, higher oxygen requirement in the first hours of life was strongly predictive of CPAP failure, as was CPAP level at 25–28 weeks' gestation.

In multivariate logistic analysis, FiO_2 in early life had the strongest predictive effect on CPAP failure in both gestational age groups, with Caesarean delivery remaining as an independent predictor (model 1, tables 3, 4). Addition of CPAP level to the multivariate regression model (model 2) enhanced prediction of CPAP failure for 25–28 weeks' gestation (goodness of fit 0.5 vs. 0.45 for model 1), but not at 29–32 weeks. There was no evidence that the CPAP-FiO_2 product provided any further predictive value for CPAP failure (data not shown). At both gestation ranges, ROC curves showed that FiO_2 in early life appeared to be a good predictor of CPAP failure, with an area under the curve of at least 0.8 (fig. 1).

Infants failing CPAP had considerably prolonged durations of respiratory support and oxygen therapy compared to the CPAP-S group (online suppl. fig. 2). Within both gestation ranges, incidence of adverse outcomes was higher in infants failing CPAP (fig. 2). At 25–28 weeks' gestation, rates of BPD, death or BPD, major morbidity and NEC were considerably higher in CPAP-F infants compared to the CPAP-S group. Incidence of BPD was 40 and 14% in the two groups, respectively (RR 2.9, 95% CI 1.1, 7.3), and of death or BPD 53 and 14% (RR 3.8, 95% CI 1.6, 9.3). The risk of these outcomes in CPAP-F infants was comparable with those intubated primarily, in whom the incidence of BPD was 28% (p = 0.23 compared with CPAP-F group) and of death or BPD 43% (p = 0.35). For infants with gestational age 29–32 weeks, CPAP failure was associated with a substantially higher risk of pneumothorax than the CPAP-S group (fig. 2) (RR 90, 95% CI 12, 650).
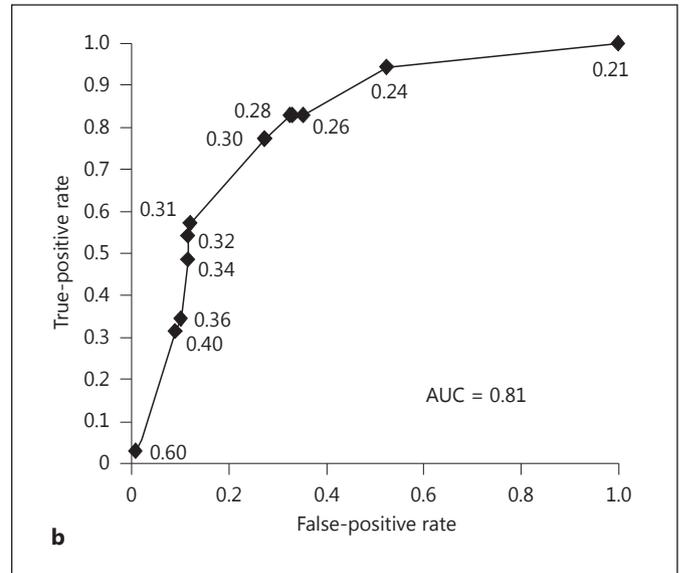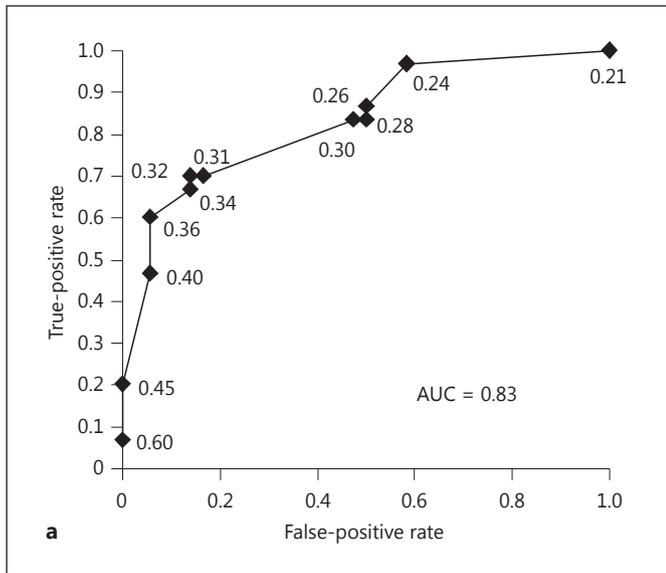
Fig. 1. Prediction of CPAP failure with FiO_2 in early life. ROCs plotting the true-positive (sensitivity) against the false-positive rate (1 – specificity) for prediction of CPAP failure with FiO_2, using the highest value in the first 2 h (25–28 weeks) or 6 h (29–32 weeks). **a** 25–28 weeks' gestation. **b** 29–32 weeks' gestation. Each data point represents the true- and false-positive rates for predic-

tion of CPAP failure at a given threshold value of FiO_2 (shown on the graph). The curvilinearity of the relationship and the area under the curve (AUC) provide an indication of the predictive ability of FiO_2 in identifying CPAP failure. The area under the curve is shown in each panel; a value of 0.5 would indicate no predictive power, and a value of 1.0 perfect prediction.
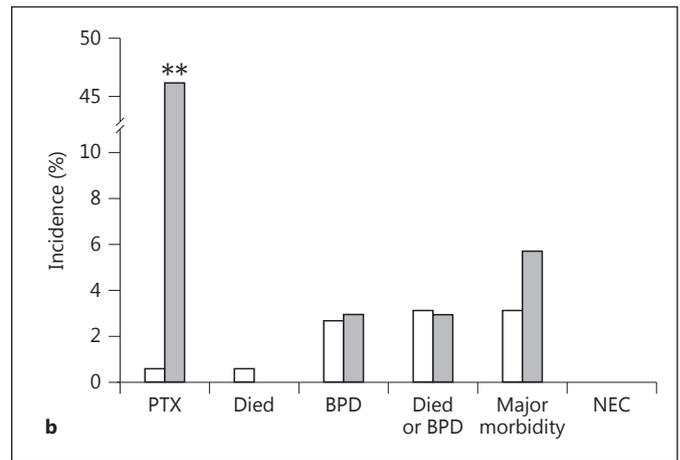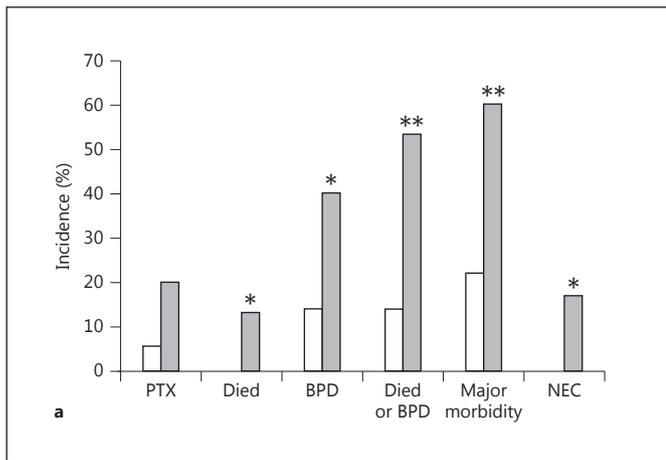

Fig. 2. Neonatal outcomes in the CPAP groups. **a** 25–28 weeks' gestation. **b** 29–32 weeks' gestation. White bars = Initial CPAP, successful; grey bars = initial CPAP, failed; PTX = pneumothorax. Higher incidence in infants failing CPAP, * $p < 0.05$. ** $p < 0.01$.

Discussion

Although nasal CPAP is often effective for initial respiratory support, some preterm infants fail CPAP and require endotracheal intubation in the first 72 h. We

found that most infants failing CPAP had moderate-to-severe RDS radiologically, along with relatively high CPAP levels and oxygen requirements. CPAP failure was predicted by oxygen requirement in the first hours of life. Infants failing CPAP had considerably prolonged dura-

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Kuschel/Kamlin/Orsini/Carlin/Davis

tions of respiratory support and oxygen therapy, and a substantially increased risk in adverse outcomes, including BPD and major morbidity at 25–28 weeks, and pneumothorax at 29–32 weeks.

The proportion of preterm infants 25–28 weeks' gestation managed with CPAP from the outset in our two NICUs (50%) was lower than several previous single-centre studies (65–90% [7–10]), but higher than the reported figure for the calendar year 2007 in two large Neonatal Networks (NICHD Network: 40% [17]; ANZNN Network: 32% [18]). For infants in the 29- to 32-week gestation range, 86% were started on CPAP, a figure comparable with one previous report (~87%) [8], but falling short of the remarkable 100% reported from Columbia, New York [7]. Variation in the approach to initial resuscitation and management, including the use of prophylactic surfactant, will inevitably lead to regional and local differences in the rate of application of CPAP as primary therapy.

Differences in management of infants on CPAP will also have a significant bearing on the likelihood of CPAP failure, and may well affect the risk of adverse outcomes. For most infants failing CPAP, the reason for intubation is that the oxygen requirement exceeds a pre-specified threshold [3, 9, 10]. Our FiO_2 threshold was set at 0.5, with some cases intubated at a lower FiO_2 because of apnoea. Only a small proportion of infants were intubated because of hypercarbia related to hypoventilation, with most having acceptable pH and CO_2 in the first hours of life, a finding consistent with other reports [7, 9]. For the 25- to 28-week gestation range, the CPAP failure rate (45%) was on par with or higher than that reported in previous single-centre studies (25–50%) [7–10], and similar to that reported in a multicentre clinical trial (46% intubated in the first 5 days) [3].

Given the continued enthusiasm for, and uptake of, CPAP as the primary therapy in preterm infants, the prediction of CPAP failure has increasing relevance. The value of demographic predictors is limited by a lack of sensitivity and specificity, as well as a reluctance on the part of clinicians to adjust management strategy based on demographic factors alone. Indices of oxygenation centred around arterial PO_2 [7, 19] have the limitation of reflecting a single point in time, and are impractical in those infants on CPAP managed without an indwelling arterial catheter in situ. Hence, we examined whether a simpler indicator of oxygenation, the highest appropriate FiO_2 in the first hours of life, could predict CPAP failure. We found that early FiO_2 was predictive of those ultimately requiring intubation <72 h, with a threshold of around 0.3

providing a balance between adequate sensitivity and an acceptable false-positive rate on ROC analysis. An FiO_2 threshold of 0.25 was identified as optimal for CPAP failure prediction by De Jaegere et al. [10] in infants <30 weeks' gestation. Another study in which infants on CPAP were intubated at an FiO_2 of 0.6 found that a lower intubation threshold would not have altered the numbers of infants intubated, but only delayed the time of intubation [9]. Despite the long documented observation of better oxygenation with higher airway pressures on CPAP [20], addition of CPAP level into the predictive modelling in the present study, either alone or as a product with FiO_2 [11], only marginally improved the goodness of fit.

A striking difference in the rates of adverse outcomes was noted between infants succeeding and failing on CPAP in the first 72 h. CPAP failure was associated with short-term deleterious effects (increased risk of pneumothorax and severe IVH) but also a 3-fold higher risk of BPD, and a higher mortality. Early complications such as pneumothorax and IVH have long been linked to the severity of RDS [21], and are explicable on this basis in infants failing CPAP. The finding of a protracted influence on lung function, with long-lasting oxygen requirements and a relatively high rate of BPD, reaffirms the value of optimising early respiratory management in preterm infants, in particular administration of surfactant to those with surfactant deficiency. It is also re-emphasises the importance of early (and undertreated) RDS in the development of BPD.

Our study has the limitations of examining relatively small numbers at each week of gestation, and the involvement of only two study sites, both of which have a relatively aggressive approach to the use of CPAP. The results may differ somewhat in units in which a larger proportion of infants are intubated early and given surfactant, and also where lower intubation thresholds are adopted for those starting on CPAP. Similarly, variation in the rate of Caesarean births may have an impact on the subsequent respiratory course. Examination of the risk and outcome of CPAP failure in a larger number of NICUs would help clarify the generalisability of our results.

In conclusion, CPAP failure in preterm infants usually occurs because of unremitting RDS, is predicted by an $FiO_2 \geq 0.3$ in the first hours of life, and is associated with adverse outcomes. Efforts to prevent CPAP failure, including consideration of selective surfactant therapy, appear warranted.

Disclosure Statement

The authors declare no conflict of interest.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CUROSURF® safely and effectively. See full prescribing information for CUROSURF.

CUROSURF (poractant alfa) intratracheal suspension
Initial U.S. Approval: 1999

───────────────INDICATIONS AND USAGE ─────────────────
CUROSURF is a surfactant indicated for the rescue treatment, including the reduction of mortality and pneumothoraces, of Respiratory Distress Syndrome (RDS) in premature infants. (1)

─────────────────DOSAGE AND ADMINISTRATION ────────────────
• Before administering CUROSURF, assure proper placement and patency of endotracheal tube (2.1)
• Administer intratracheally either in (2.1):
   o Two divided aliquots after briefly disconnecting endotracheal tube from ventilator; or
   o A single aliquot through secondary lumen of a dual lumen endotracheal tube without interrupting mechanical ventilation
• Initial recommended dose is 2.5 mL/kg birth weight (2.2)
• Up to two repeat doses of 1.25 mL/kg birth weight may be administered at approximately 12-hour intervals (2.2)
• Maximum total dose (initial plus repeat doses) is 5 mL/kg (2.2)
• See Full Prescribing Information for instructions on preparation and administration of the CUROSURF suspension (2.3, 2.4)

───────────── DOSAGE FORMS AND STRENGTHS───────────────
Intratracheal Suspension: 80 mg poractant alfa (surfactant extract) in 1 mL of suspension includes 76 mg of phospholipids and 1 mg of protein of which 0.45 mg is SP-B and 0.59 mg is SP-C (3)
───────────────── CONTRAINDICATIONS ─────────────────
None. (4)

───────────────WARNINGS AND PRECAUTIONS ─────────────
• Acute Changes in Lung Compliance: Frequently assess need to modify oxygen and ventilatory support to respiratory changes (5.1)
• Administration-Related Adverse Reactions: Transient adverse effects include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition (5.2)

───────────────── ADVERSE REACTIONS ─────────────────
• Common adverse reactions associated with the administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

Revised: 12/2014

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FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1   INDICATIONS AND USAGE

CUROSURF® (poractant alfa) Intratracheal Suspension is indicated for the rescue treatment of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

2   DOSAGE AND ADMINISTRATION

2.1   Important Administration Instructions
For intracheal administration only.

CUROSURF should be administered by, or under the supervision of clinicians experienced in intubation, ventilator management, and general care of premature infants. Before administering CUROSURF, assure proper placement and patency of the endotracheal tube. At the discretion of the clinician, the endotracheal tube may be suctioned before administering CUROSURF. Allow the infant to stabilize before proceeding with dosing.

Administer CUROSURF either:

- Intratracheally by instillation in two divided aliquots through a 5 French end-hole catheter after briefly disconnecting the endotracheal tube from the ventilator; or
- Intratracheally in a single aliquot through the secondary lumen of a dual lumen endotracheal tube without interrupting mechanical ventilation.

2.2   Recommended Dosage
The initial recommended dose is 2.5 mL/kg birth weight (see Table 1), administered as one or two aliquots depending upon the instillation procedure *[see Dosage and Administration (2.3)].*

Up to two repeat doses of 1.25 mL/kg birth weight each may be administered at approximately 12-hour intervals in infants who remain intubated and in whom RDS is considered responsible for their persisting or deteriorating respiratory status. The maximum recommended total dosage (sum of the initial and up to two repeat doses) is 5 mL/kg.

Table 1:   CUROSURF Weight-Based Dosing Chart for Rescue Treatment of RDS

Weight (grams)	Initial Dose 2.5 mL/kg	Repeat Dose 1.25 mL/kg	Weight (grams)	Initial Dose 2.5 mL/kg	Repeat Dose 1.25 mL/kg
	Each Dose (mL)			Each Dose (mL)	
600-650	1.60	0.80	1301-1350	3.30	1.65
651-700	1.70	0.85	1351-1400	3.50	1.75
701-750	1.80	0.90	1401-1450	3.60	1.80
751-800	2.00	1.00	1451-1500	3.70	1.85
801-850	2.10	1.05	1501-1550	3.80	1.90
851-900	2.20	1.10	1551-1600	4.00	2.00
901-950	2.30	1.15	1601-1650	4.10	2.05
951-1000	2.50	1.25	1651-1700	4.20	2.10
1001-1050	2.60	1.30	1701-1750	4.30	2.15
1051-1100	2.70	1.35	1751-1800	4.50	2.25
1101-1150	2.80	1.40	1801-1850	4.60	2.30
1151-1200	3.00	1.50	1851-1900	4.70	2.35
1201-1250	3.10	1.55	1901-1950	4.80	2.40
1251-1300	3.20	1.60	1951-2000	5.00	2.50

2.3   Preparation of the CUROSURF Suspension
1) Remove the vial of CUROSURF suspension from a refrigerator at +2 to +8°C (36 to 46°F) and slowly warm the vial to room temperature before use.
2) Visually inspect the CUROSURF suspension for discoloration prior to administration. The color of the CUROSURF suspension should be white to creamy white. Discard the CUROSURF vial if the suspension is discolored.
3) Gently turn the vial upside-down, in order to obtain a uniform suspension. DO NOT SHAKE.
4) Locate the notch (FLIP UP) on the colored plastic cap and lift the notch and pull upwards.
5) Pull the plastic cap with the aluminum portion downwards.
6) Remove the whole ring by pulling off the aluminum wrapper.
7) Remove the rubber cap to extract content.
8) Unopened, unused vials of CUROSURF suspension that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Do not warm to room temperature and return to refrigerated storage more than once. Protect from light.

2.4   Administration
For endotracheal tube instillation using a 5 French end-hole catheter
1) Slowly withdraw the entire contents of the vial of CUROSURF suspension into a 3 or 5 mL plastic syringe through a large-gauge needle (e.g., at least 20 gauge). Enter each single-use vial only once.
2) Attach the pre-cut 8-cm 5 end-hole French catheter to the syringe. Fill the catheter with CUROSURF suspension. Discard excess CUROSURF through the catheter so that only the dose to be given remains in the syringe.
3) When administering CUROSURF using a 5 French end-hole catheter, administer in two divided aliquots:
   - For the first dose: 1.25 mL/kg (birth weight) per aliquot

For each repeated dose: 0.635 mL/kg (birth weight) per aliquot

4) First aliquot of CUROSURF suspension:
   a) Position the infant in a neutral position (head and body in alignment without inclination), with either the right or left side dependent.
   b) Immediately before CUROSURF administration, change the infant's ventilator settings to a rate of 40-60 breaths/minute, inspiratory time 0.5 second, and supplemental oxygen sufficient to maintain $SaO_2 > 92\%$.
   c) Briefly disconnect the endotracheal tube from the ventilator.
   d) Insert the pre-cut 5 French catheter into the endotracheal tube and instill the first aliquot of CUROSURF suspension.
   e) After the first aliquot is instilled, remove the catheter from the endotracheal tube and manually ventilate the infant with 100% oxygen at a rate of 40-60 breaths/minute for one minute.
5) Second aliquot of CUROSURF suspension:
   a) When the infant is stable, reposition the infant such that the other side is dependent.
   b) Administer the remaining aliquot using the same procedures as the first aliquot.
6) After completion of the dosing procedure, resume usual ventilator management and clinical care. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur. Post dosing, consider maintenance of PaO_2 of about 55 mmHg, $PaCO_2$ of 35-45, and pH > 7.3 *[see Clinical Studies (14.1)].*

For endotracheal instillation using the secondary lumen of a dual lumen endotracheal tube
1) Slowly withdraw the entire contents of the vial of CUROSURF suspension into a 3 or 5 mL plastic syringe through a large-gauge needle (e.g., at least 20 gauge). Do not attach 5 French end-hole catheter. Remove the needle and discard excess CUROSURF so that only the dose to be given remains in the syringe.
2) Keep the infant in a neutral position (head and body in alignment without inclination).
3) Administer CUROSURF suspension through the proximal end of the secondary lumen of the endotracheal tube as a single dose, given over 1 minute, and without interrupting mechanical ventilation.
4) After completion of this dosing procedure, ventilator management may require transient increases in FiO_2, ventilator rate, or PIP. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur.

3   DOSAGE FORMS AND STRENGTHS

CUROSURF (poractant alfa) is an intratracheal suspension available in vials:

- 1.5 mL [120 mg poractant alfa (surfactant extract)], or
- 3 mL [(240 mg poractant alfa (surfactant extract)].

CUROSURF is a white to creamy white suspension. Each mL of suspension contains 80 mg poractant alfa (surfactant extract) that includes 76 mg of phospholipids and 1 mg of protein of which 0.45 mg is SP-B and 0.59 mg is SP-C.

4   CONTRAINDICATIONS

None.

5   WARNINGS AND PRECAUTIONS

5.1   Acute Changes in Oxygenation and Lung Compliance

The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of pre-term infants.

5.2   Administration-Related Adverse Reactions

Transient adverse reactions associated with administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

6   ADVERSE REACTIONS

6.1   Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Studies in Premature Infants with Respiratory Distress Syndrome

The safety data described below reflect exposure to CUROSURF at a single dose of 2.5 mL/kg (200 mg/kg), in 78 infants of 700-2000 grams birth weight with RDS requiring mechanical ventilation and a $FiO_2 \geq 0.60$ (Study 1) [*see clinical studies (14.1)*]. A total of 144 infants were studied after RDS developed and before 15 hours of age; 78 infants received CUROSURF 2.5 mL/kg single dose (200 mg/kg), and 66 infants received control treatment (disconnection from the ventilator and manual ventilation for 2 minutes).

Transient adverse effects seen with the administration of CUROSURF included bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. The rates of the most common serious complications associated with prematurity and RDS observed in Study 1 are shown in Table 2.

Table 2: Most Common Serious Complications Associated with Prematurity and RDS in Study 1

	CUROSURF 2.5 mL/kg n=78	CONTROL* n=66
Acquired Pneumonia	17%	21%
Acquired Septicemia	14%	18%
Bronchopulmonary Dysplasia	18%	22%
Intracranial Hemorrhage	51%	64%
Patent Ductus Arteriosus	60%	48%
Pneumothorax	21%	36%
Pulmonary Interstitial Emphysema	21%	38%

*Control patients were disconnected from the ventilator and manually ventilated for 2 minutes. No surfactant was instilled.

Seventy-six infants (45 treated with CUROSURF) from study 1 were evaluated at 1 year of age and 73 infants (44 treated with CUROSURF) were evaluated at 2 years of age to assess for potential long-term adverse reactions. Data from follow-up evaluations for weight and length, persistent respiratory symptoms, incidence of cerebral palsy, visual impairment, or auditory impairment was similar between treatment groups. In 16 patients (10 treated with CUROSURF and 6 controls) evaluated at 5.5 years of age, the developmental quotient, derived using the Griffiths Mental Developmental Scales, was similar between groups.

6.2   Immunogenicity
Immunological studies have not demonstrated differences in levels of surfactant-anti-surfactant immune complexes and anti-CUROSURF antibodies between patients treated with CUROSURF and patients who received control treatment.

6.3   Postmarketing Experience
Pulmonary hemorrhage, a known complication of premature birth and very low birth-weight, has been reported both in clinical trials with CUROSURF and in postmarketing adverse event reports in infants who had received CUROSURF.

8   USE IN SPECIFIC POPULATIONS

8.4   Pediatric Use

CUROSURF is indicated for the rescue treatment, including the reduction of mortality and pneumothoraces, of Respiratory Distress Syndrome (RDS) in premature infants [*see Indications and Usage (1) and Dosage Administration (2)*].

The safety and efficacy of CUROSURF in the treatment of full term infants or older pediatric patients with respiratory failure has not been established.

10   OVERDOSAGE

There have been no reports of overdosage following the administration of CUROSURF.

In the event of accidental overdosage, and if there are clear clinical effects on the infant's respiration, ventilation, or oxygenation, aspirate as much of the suspension as possible and provide the infant with supportive treatment, with particular attention to fluid and electrolyte balance.

11   DESCRIPTION

CUROSURF (poractant alfa) is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. CUROSURF is an extract of natural porcine lung surfactant consisting of 99% polar lipids (mainly phospholipids) and 1% hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C).

CUROSURF is a white to creamy white suspension of poractant alfa. Each milliliter of suspension contains 80 mg of poractant alfa (surfactant extract) that includes 76 mg of phospholipids and 1 mg of protein of which 0.45 mg is SP-B and 0.59 mg is SP-C. The amount of phospholipids is calculated from the content of phosphorus and contains 55 mg of phosphatidylcholine of which 30 mg is dipalmitoylphosphatidylcholine. It is suspended in 0.9% sodium chloride solution. The pH is adjusted with sodium bicarbonate to a pH of 6.2 (5.5 to 6.5).

CUROSURF contains no preservatives.

12   CLINICAL PHARMACOLOGY

12.1   Mechanism of Action

Endogenous pulmonary surfactant reduces surface tension at the air-liquid interface of the alveoli during ventilation and stabilizes the alveoli against collapse at resting transpulmonary pressures. A deficiency of pulmonary surfactant in preterm infants results in Respiratory Distress Syndrome (RDS) characterized by poor lung expansion, inadequate gas exchange, and a gradual collapse of the lungs (atelectasis).

CUROSURF compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

12.2   Pharmacodynamics

In vitro - CUROSURF lowers minimum surface tension to ≤ 4mN/m as measured by the Wilhelmy Balance System.

12.3   Pharmacokinetics

CUROSURF is administered directly to the lung, where biophysical effects occur at the alveolar surface. No human pharmacokinetic studies have been performed to characterize the absorption, biotransformation, or elimination of CUROSURF.

13   NONCLINICAL TOXICOLOGY

13.1   Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess potential carcinogenic effects of CUROSURF have not been conducted.

Poractant alfa was negative for genotoxicity in the following assays: bacterial reverse mutation assay (Ames test), gene mutation assay in Chinese hamster V79 cells, chromosomal aberration assay in Chinese hamster ovary cells, unscheduled DNA synthesis in HELA S3 cells, and in vivo mouse micronucleus assay.

No studies to assess reproductive effects of CUROSURF have been performed.

14   CLINICAL STUDIES

14.1   Rescue Treatment of Respiratory Distress Syndrome

The clinical efficacy of CUROSURF in the treatment of established Respiratory Distress Syndrome (RDS) in premature infants was demonstrated in one single-dose study (Study 1) and one multiple-dose study (Study 2) involving approximately 500 infants. Each study was randomized, multicenter, and controlled.

In study 1, premature infants 700 to 2000 grams birth weight with RDS requiring mechanical ventilation and a $FiO_2 \geq 0.60$ were enrolled. CUROSURF 2.5 mL/kg single dose (200 mg/kg) or control (disconnection from the ventilator and manual ventilation for 2 minutes) was administered after RDS developed and before 15 hours of age. The results from Study 1 are shown below in Table 3.

Table 3:   Study 1 Results in Premature Infants with Respiratory Distress Syndrome

Efficacy Parameter	Single Dose CUROSURF n=78	Control n=67	p-Value
Mortality at 28 Days (All Causes)	31%	48%	≤0.05
Bronchopulmonary Dysplasia*	18%	22%	N.S.
Pneumothorax	21%	36%	≤0.05
Pulmonary Interstitial Emphysema	21%	38%	≤0.05

*Bronchopulmonary dysplasia (BPD) diagnosed by positive x-ray and supplemental oxygen dependence at 28 days of life.
N.S.: not statistically significant

In Study 2, premature infants 700 to 2000 g birth weight with RDS requiring mechanical ventilation and a $FiO_2 \geq 0.60$ were enrolled. In this two-arm trial, CUROSURF was administered after RDS developed and before 15 hours of age, as a single-dose or as multiple doses. In the single-dose arm, infants received CUROSURF 2.5 mL/kg (200 mg/kg). In the multiple-dose arm, the initial dose of CUROSURF was 2.5 mL/kg followed by up to two 1.25 mL/kg (100 mg/kg) doses of CUROSURF. The results from Study 2 are shown below in Table 4.

Table 4:   Study 2 Results in Premature Infants with Respiratory Distress Syndrome

Efficacy Parameter	Single Dose CUROSURF n=184 Rate (%)	Multiple Dose CUROSURF n=173 Rate (%)	p-Value
Mortality at 28 Days (All Causes)	21	13	0.048
Bronchopulmonary Dysplasia*	18	18	N.S.
Pneumothorax	17	9	0.03
Pulmonary Interstitial Emphysema	27	22	N.S.

*Bronchopulmonary dysplasia (BPD) diagnosed by positive x-ray and supplemental oxygen dependence at 28 days of life.
N.S.: not statistically significant

There is no controlled experience on the effects of administering initial doses of CUROSURF other than 2.5 mL/kg (200 mg/kg), subsequent doses other than 1.25 mL/kg (100 mg/kg), administration of more than three total doses, dosing more frequently than every 12 hours, or initiating

therapy with CUROSURF more than 15 hours after diagnosing RDS. Adequate data are not available on the use of CUROSURF in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation or extracorporeal membrane oxygenation.

16   HOW SUPPLIED/STORAGE AND HANDLING

CUROSURF (poractant alfa) intratracheal suspension is available in sterile, rubber-stoppered clear glass vials containing (one vial per carton):

- 1.5 mL [120 mg poractant alfa (surfactant extract)] of suspension: NDC Number: 10122-510-01
- 3 mL [(240 mg poractant alfa (surfactant extract)] of suspension. NDC Number: 10122-510-03

Store CUROSURF intratracheal suspension in a refrigerator at +2 to +8°C (36 to 46°F). PROTECT FROM LIGHT. Do not shake. Vials are for single use only. After opening the vial discard the unused portion *[see Dosage and Administration (2.3)]*.

Manufactured for:
Chiesi USA, Inc.
Cary, NC 27518

Manufactured by and licensed from:
Chiesi Farmaceutici, S.p.A.
Parma, Italy 43100

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