Predicting Nasal High-Flow Treatment Success in Newborn Infants with Respiratory Distress Cared for in Nontertiary Hospitals

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Objective To evaluate demographic and clinical variables as predictors of nasal high-flow treatment success in newborn infants with respiratory distress cared for in Australian nontertiary special care nurseries.

Study design A secondary analysis of the HUNTER trial, a multicenter, randomized controlled trial evaluating nasal high-flow as primary respiratory support for newborn infants with respiratory distress who were born ≥31 weeks of gestation and with birth weight ≥1200 g, and cared for in Australian nontertiary special care nurseries. Treatment success within 72 hours after randomization to nasal high-flow was determined using objective criteria. Univariable screening and multivariable analysis was used to determine predictors of nasal high-flow treatment success.

Results Infants (n = 363) randomized to nasal high-flow in HUNTER were included in the analysis; the mean gestational age was 36.9 ± 2.7 weeks and birth weight 2928 ± 782 g. Of these infants, 290 (80%) experienced nasal high-flow treatment success. On multivariable analysis, nasal high-flow treatment success was predicted by higher gestational age and lower fraction of inspired oxygen immediately before randomization, but not strongly. The final model was found to have an area under the curve of 0.65, which after adjustment for optimism was found to be 0.63 (95% CI, 0.57-0.70).

Conclusions Gestational age and supplemental oxygen requirement may be used to guide decisions regarding the most appropriate initial respiratory support for newborn infants in nontertiary special care nurseries. Further prospective research is required to better identify which infants are most likely to be successfully treated with nasal high-flow. *(J Pediatr 2020;227:135-41)*.

Trial registration ACTRN12614001203640.

Noninvasive respiratory support is commonly used as first-line therapy for newborn infants with respiratory distress. Nasal high-flow is a newer mode of noninvasive respiratory support, which has been widely adopted as an alternative to continuous positive airway pressure (CPAP) in both tertiary neonatal intensive care units (NICUs), and nontertiary special care nurseries (SCNs) owing to perceived ease of use and comfort.[1-5]

The recent High-flow nasal cannulae use in non-tertiary centres for early respiratory distress in newborn infants (HUNTER) multicenter, randomized controlled trial (RCT) compared nasal high-flow with CPAP in Australian nontertiary SCNs.[6] Infants were less likely to be successfully treated with nasal high-flow compared with CPAP. However, 80% of the infants who received nasal high-flow were successfully treated. In addition, with the use of rescue CPAP in infants in whom nasal high-flow treatment failed, their outcomes, including rates of intubation and mechanical ventilation and transfers to tertiary NICUs, were no worse than infants commenced on CPAP. Therefore, identifying infants

AUROC	Area under the receiver operating characteristic curve
CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
NICU	Neonatal intensive care unit
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
SCN	Special care nursery

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who are likely to be successfully treated with nasal high-flow or would be better treated with CPAP from the outset will aid clinical decision making.

There has been 1 prior study of predictors of nasal high-flow treatment failure in newborn infants. In a secondary analysis of the High-flow nasal cannulae as primary support in the treatment of early respiratory distress (HIPSTER) trial,[3] an international multicenter RCT that enrolled preterm infants born 28-36 weeks of completed gestation who were admitted to tertiary NICUs, lower gestational age and higher fraction of inspired oxygen (FiO_2) before randomization significantly increased the risk of nasal high-flow failure.[7]

In this secondary analysis of the HUNTER trial, we aimed to identify clinical and demographic variables that predicted nasal high-flow treatment success, in infants with respiratory distress cared for in Australian nontertiary SCNs.

Methods

The HUNTER trial (Australian and New Zealand Clinical Trials Registry ACTRN12614001203640) was conducted in nine Australian SCNs, and compared nasal high-flow delivered at flows of 6-8 L/min with CPAP delivered at pressures of 6-8 cm H_2O as primary respiratory support for newborn infants with respiratory distress.[6,8] The peripheral oxygen saturation target range was 91%-95% for all infants receiving supplemental oxygen. Infants were eligible to be enrolled in the trial if they were born at ≥31 weeks of gestation and had a birth weight of ≥1200 g, were <24 hours of age, and required noninvasive respiratory support for respiratory distress, as determined by the treating clinician, or because they had received supplemental oxygen for >1 hour, or both. Because CPAP was the standard treatment in this setting, infants were permitted to receive up to 2 hours of CPAP therapy before randomization while consent was sought from parents. Infants were excluded from the trial if, before randomization, they received >2 hours of CPAP, had undergone endotracheal intubation, had a known major congenital abnormality, or the treating clinician had already determined that the infant would require endotracheal intubation or transfer to a NICU. Parents provided prospective, written informed consent. Ethics approval (No. 34222) was obtained for the trial from The Royal Children's Hospital, Melbourne, along with site-specific approval at each participating center.

The primary outcome of the HUNTER trial was treatment failure within 72 hours. Treatment failure was defined as the infant receiving the maximal respiratory support (nasal high-flow gas flow of 8 L/min or CPAP pressure of 8 cm H_2O), plus any one of the following criteria: FiO_2 of ≥0.4 for >1 hour to maintain target peripheral oxygen saturations of 91%-95%; a pH of <7.2 with a partial pressure of carbon dioxide of >60 mm Hg on 2 samples of arterial or capillary blood obtained ≥1 hour after commencement of nasal high-flow and 1 hour apart; or apnea, defined as ≥2 episodes requiring positive-pressure ventilation within a 24-hour period, or ≥6 episodes requiring any intervention within a 6-hour period. Treatment failure was also considered to have occurred if an infant received endotracheal intubation and mechanical ventilation or was transferred to a NICU (as ordered by the treating clinician). Infants who experienced nasal high-flow treatment failure were subsequently managed with CPAP, if not already intubated and mechanically ventilated. Infants in whom CPAP treatment failed and/or who required intubation were transferred to a tertiary NICU. After intubation, surfactant could be administered at the discretion of the treating clinician.

Baseline data were collected, including maternal demographics and information regarding the labor and delivery, infant demographics, including the need for advanced resuscitation and indication for respiratory support, respiratory support settings and duration, and results of blood gas analysis.

Predictors of Nasal High-Flow Treatment Success

Infants who were randomized to nasal high-flow but never received it (owing to a protocol violation) were excluded from this secondary analysis. Demographic and clinical data of infants who received nasal high-flow were compared for those in whom nasal high-flow treatment was successful and those in whom nasal high-flow failed. Variables chosen for this analysis were agreed upon by the investigators of this current project a priori, based on their clinical experience and on previous studies of predictors of noninvasive respiratory support success.[7,9-24]

Admission between 7:00 p.m. and 7:00 a.m. was included to assess the impact of admission during a period of potentially lower clinical resources. Caffeine therapy in the first 24 hours was not included as a predictive variable, because caffeine was only received by a small number of infants (10%); the majority of the cohort were late preterm or term. The final respiratory diagnosis (eg, respiratory distress syndrome [RDS], transient tachypnea of the newborn) was also not included as a predictive variable, because it was assigned at discharge rather than admission, and therefore was not known at the time of randomization. In addition, these diagnoses were not objectively defined for the trial.

Statistical Analyses

All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

Univariable Screening. For the univariable prediction analysis, the statistical significance of the difference between groups was measured using the appropriate statistical test for categorical (χ^2 test) or continuous parametric (t test) or nonparametric (Wilcoxon rank-sum test) data. Where exact binomial confidence limits were calculated, the Clopper-Pearson method was used.

Continuously distributed variables were examined visually to determine the appropriate form for logistic modelling (eg, linear, binary, categorical). Where continuous variables were categorized, cut-points were created to balance theoretical

considerations with practical needs for sufficient sample size within each category and to facilitate easy interpretation for the clinician. For example, FiO_2 before randomization was categorized as 0.21, 0.22-0.30, and >0.30 because many infants were found to have received exactly 0.30. Age at nasal high-flow commencement was categorized as <1 hour, 1-2 hours, or ≥3 hours.

Because birth weight and gestation are collinear, after assessment of the distributions, a decision was made to model gestation as a linear variable with weight for sex and gestational age modelled as a set of dummy variables (small, normal, or large). Thresholds for small and large were drawn from Australian norms published separately for male and female singleton and twin births at thresholds of 10% and 90%.[25,26]

Multivariable Prediction Analysis. Variables with differences between groups that produced a *P* value of <.20 on univariable screening were included in a multivariable logistic regression model, where the dependent variable was nasal high-flow treatment success within 72 hours of randomization. A manual stepwise, variable addition technique commencing with the most statistically significant variable in univariate analysis and adding each variable to assess significance; variables that remained statistically significant at a *P* value of <.05 in the multivariable model were retained, subject to adequate fit of the model as assessed by the overall Hosmer-Lemeshow test. ORs and 95% CIs were computed for the retained variables, as was the area under the receiver operating characteristic curve (AUROC).

The AUROC is a measure of the capacity of the model to distinguish between nasal high-flow infants who had successful vs failed treatment; an AUROC of 0.5 indicates no capacity for differentiation and 1.0 indicates perfect differentiation. AUROC is known to be overestimated in the population used for model development. To preserve the limited sample size, model overestimation of the AUROC was assessed using a standard bootstrap procedure (**Appendix**; available at www.jpeds.com), and the AUROC was adjusted accordingly.[27]

Results

Of the 381 infants randomized to nasal high-flow treatment, 18 infants who never received nasal high-flow were excluded, leaving 363 infants in the analysis (337 singletons and 26 from twins). The cohort (**Table I**; available at www.jpeds.com) had a mean gestational age of 36.9 ± 2.7 weeks and birth weight of 2928 ± 782 g; 177 infants (49%) were born preterm (<37 weeks of gestation) and 232 (64%) were male. The median age at high-flow treatment commencement was 1.4 hours (IQR, 0.9-2.5 hours), and 55 (15%) infants received CPAP before randomization. Almost one-half (48%) of the infants were not receiving supplemental oxygen before randomization.

Predictors of Nasal High-Flow Treatment Success

Of the 363 infants who received nasal high-flow, 290 infants (80%) were treated successfully.

Univariable Screening. **Table II** shows the results of univariable analyses comparing success rates for the demographic and clinical variables of infants. On univariable analysis, variables found to be significantly different ($P < .05$) between the nasal high-flow treatment success and failure groups included: FiO_2 category (21%, 22%-30%, and >30%; $P = .006$); a linear term for gestation ($P = .01$) and the recording of oxygen requirement as a reason for respiratory support ($P = .02$). More mature infants without an oxygen requirement were more likely to be successfully treated with nasal high-flow. **Figure 1** shows the actual success rates, with 95% confidence limits, by FiO_2 category and gestation.

Several other variables met the screening threshold for assessment in multivariable models: infants who had blood gas performed before randomization ($P = .06$), who were male ($P = .07$), or who had ruptured membranes for >24 hours ($P = .18$) had higher rates of treatment success, whereas exposure to corticosteroids <7 days before birth ($P = .08$) was associated with a lower success rate of nasal high-flow. A higher proportion of infants who succeeded commenced treatment at 1-2 hours of age, compared with those commenced at <1 or >2 hours of age ($P = .16$ overall).

Small and large for sex and gestational age were not predictive of treatment success ($P = .43$). Neither admission between 7:00 p.m. and 7:00 a.m. ($P = .46$) nor CPAP before randomization ($P = .73$) were predictive.

Although not included in the predictive analysis, transient tachypnea of the newborn was diagnosed in 52% of infants with nasal high-flow success compared with 10% with nasal high-flow failure. In comparison, RDS was diagnosed in 36% of infants with nasal high-flow success and 70% of infants with nasal high-flow failure.

Multivariable Analysis. Because FiO_2 was the strongest predictor on univariable screening, 2 infants (both with treatment success) were removed from this analysis because their FiO_2 before randomization was unknown, leaving 361 infants for analysis. As shown in **Table III**, the final model comprised only 2 variables: FiO_2 before randomization (21%, 22%-30%, and >30%) and gestation in weeks ($P = .007$ and $P = .01$, respectively). The probability of success was associated with increased maturity, and was markedly reduced when FiO_2 was >0.3 before randomization (**Figure 2**). The interaction between the 2 terms was assessed and found to be nonsignificant ($P = .37$). The final model was adequate as assessed by the Hosmer-Lemeshow test ($\chi^2 = 7.6$; $P = .47$) and the AUROC was 0.65 in the full dataset; after bootstrap adjustment for optimism this value decreased to 0.63 (95% CI, 0.57-0.70).

No other variables were statistically significant at $P = .05$ in the final model. Some variables had substantial overlap with

Table II. Nasal high-flow treatment success and failure by maternal and infant characteristics

Characteristics	Failed (n = 73)	Succeeded (n = 290)	*P* value
Exposure to any antenatal corticosteroid <7 days before birth*	27 (37.0)	77 (26.6)	.08
Ruptured membranes >24 hours*	4 (5.5)	31 (10.7)	.18
Labor*	48 (65.8)	202 (69.7)	.52
Chorioamnionitis*	3 (4.1)	11 (3.8)	.90
Cesarean delivery	41 (56.2)	156 (53.8)	.72
Gestational age in weeks†	36.1 ± 2.7	37.0 ± 2.7	.01
Birth weight small and large for sex and gestation (10%)			
Small for gestational age (<10%)	4.0 ± 5.5	29.0 ± 10.0	.43
Normal	59.0 ± 80.8	217.0 ± 74.8	
Large for gestational age (>90%)	10.0 ± 13.7	44.0 ± 15.2	
Male sex	40 (54.8)	192 (66.2)	.07
Multiple birth	7 (9.6)	19 (6.6)	.37
5-Minute Apgar‡	8.0 (8.0-9.0)	8.0 (7.0-9.0)	.60
CPAP, IPPV, or external cardiac massage in the delivery room	49 (67.1)	213 (73.4)	.28
Admitted after 7:00 p.m. and before 7:00 a.m.	24 (32.9)	109 (37.6)	.46
Indication for respiratory support (multiple selections permitted)			
Clinical signs	64 (87.7)	267 (92.1)	.24
Acidosis	9 (12.3)	47 (16.2)	.41
Oxygen requirement	38 (52.1)	107 (36.9)	.02
Apnea	6 (8.2)	18 (6.2)	.54
Other	1 (1.4)	2 (0.7)	.57
CPAP before randomization	12 (16.4)	43 (14.8)	.73
Blood gas before randomization	35 (47.9)	174 (60.0)	.06
FiO_2 before randomization in categories§			
0.21	28 (38.4)	146 (50.7)	.006
0.22-0.30	25 (34.2)	106 (36.8)	
>0.30	20 (27.4)	36 (12.5)	
Age at treatment commencement in hours			
<1	22 (30.1)	74 (25.5)	.16
1-2	19 (26.0)	110 (37.9)	
>2	32 (43.8)	106 (36.6)	
Final respiratory diagnosis at discharge¶			
Transient tachypnea of the newborn	7 (9.6)	152 (52.4)	<.001
RDS	51 (69.9)	104 (35.9)	
Other	15 (20.5)	34 (11.7)	

IPPV, intermittent positive pressure ventilation.
Values are number (%), mean ± SD, or median (IQR).
*Of the 363 infants, 26 were twins. Two pairs of twins were both randomized to nasal high-flow and included in the study population (one pair both failed and the other pair both had treatment success). In calculating percentages for these maternal characteristics (ie, antenatal corticosteroid, ruptured membranes, labor, and chorioamnionitis), 2 mothers were therefore counted twice.
†Calculated in days and divided by 7.
‡One record missing (treatment success).
§Two records missing (both treatment success).
¶Data not included in the prediction analysis.

stronger predictors that were included (eg, oxygen requirement as a documented indication for respiratory support vs FiO_2 before randomization).

Discussion

This study examined predictors of nasal high-flow treatment success in newborn infants enrolled in an RCT of early noninvasive respiratory support in Australian nontertiary SCNs.

In this secondary analysis of the HUNTER trial, predictors of nasal high-flow treatment success on univariable analysis and multivariable analysis included higher gestational age and lower FiO_2 immediately before randomization. Nasal high-flow treatment success was not strongly predicted by a model that included these variables. Infants who experienced nasal high-flow success were more mature and required less supplemental oxygen than those who failed, on average about 64% of the time. It seems that other factors also influence treatment success, but the current study has not measured them, or lacks the sample sizes to identify their smaller contributors with statistical confidence.

Exposure to corticosteroids <7 days before birth was associated with lower treatment success rates on univariable analysis, but not in the multivariable model. Table I shows that out of 363 infants who received nasal high-flow, only 104 (29%) were exposed to antenatal corticosteroids. However, when restricted to the 177 preterm infants born at <37 weeks of gestation, 100 (57%) were exposed to antenatal corticosteroids. We have shown that more immature infants are more likely to have treatment failure with nasal high-flow, but were also more likely to be exposed to antenatal corticosteroids.

One other study investigated predictors of nasal high-flow treatment success and failure in newborn infants, albeit in more immature infants who were admitted to tertiary NICUs, and were more likely to have a diagnosis of RDS. The secondary analysis of the HIPSTER trial by Manley et al

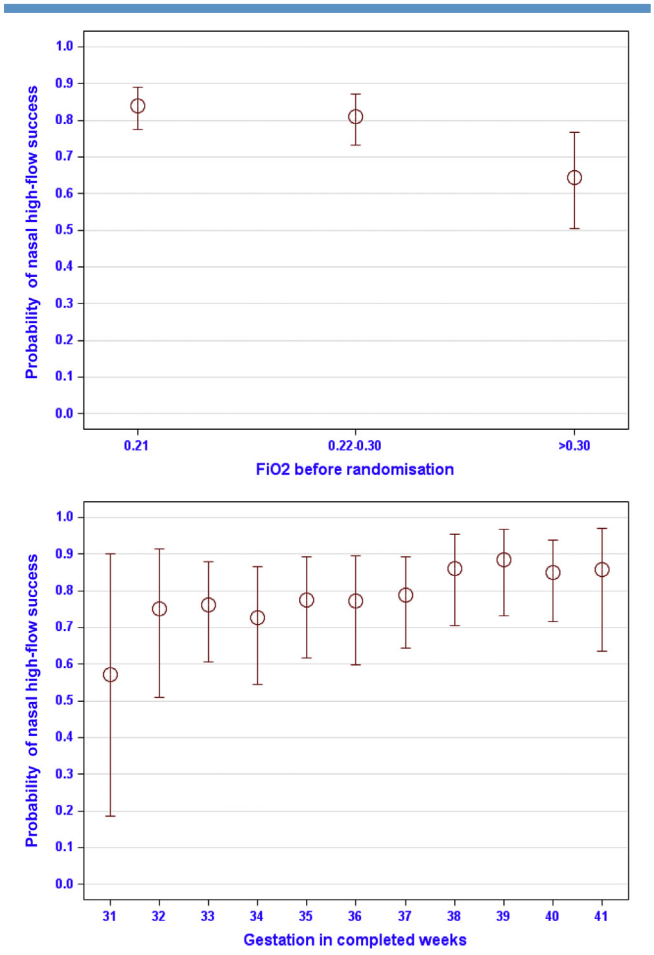

Figure 1. Success rates, and 95% CIs, by FiO_2 category and gestational week. Circle represents point estimate of treatment success, error bars represent 95% CI.

Table III. Final model of predictors of nasal high-flow treatment success

Variables	OR (95% CI)	*P* value
FiO_2 before randomization		.007
21%	Reference group	
22-30%	0.80 (0.44-1.46)	
>30%	0.34 (0.17-0.67)	
Gestational age, per week	1.13 (1.03-1.24)	.01

also identified that lower gestational age and higher FiO_2 before randomization significantly increased the risk of nasal high-flow failure.[7] Despite the differences in the study populations, Manley et al used similar methodology to our study, and had similar objective failure criteria.

Higher gestational age and lower FiO_2 predicted nasal high-flow treatment success in this study, which is broadly consistent with Manley et al, and other studies predicting CPAP failure.[7,9-24] The HIPSTER study included infants born at 28-36 weeks' completed gestation and found an AUROC of 0.76 (not adjusted for overestimation) in that population, higher than that found in the current study, likely reflecting the greater contribution of infants at 28-30 weeks gestation (included in HIPSTER but not in HUNTER) rather than at 37-41 weeks (included in HUNTER but not HIPSTER).[6,7] The finding of increasing immaturity predicting nasal high-flow treatment failure is not surprising to clinicians. Because nasal high-flow produces inconsistent distending pressures,[28-30] preterm infants suffering RDS may require more consistent and higher airway pressures to hold open their poorly compliant lungs.

Our findings also illustrate the potential usefulness of the need and level of supplemental oxygen requirement to guide the choice of noninvasive respiratory support. Although it is difficult to define an FiO_2 value that reliably distinguishes infants who will respond well to noninvasive respiratory support, including nasal high-flow, in our study infants with an FiO_2 of ≤0.30 before randomization had a significantly higher treatment success rate than infants with an FiO_2 of >0.30 to maintain oxygen saturations between 90% and 95%.

The strengths of this study include the prospective collection of data from infants enrolled in an RCT conducted in nontertiary centers. The trial protocol outlined objective criteria for nasal high-flow treatment failure and the subsequent management of these infants. The variables of interest for analysis were chosen a priori. Because this was a multicenter trial, the results are more likely to be robust in a broad range of nontertiary neonatal care settings.

The study has several limitations. The decision to initiate noninvasive respiratory support was based on the treating clinicians discretion and subjective evidence of respiratory distress. The cohort enrolled in the primary RCT may not be truly representative of the overall population to whom the results may be applied: 59% of eligible infants were enrolled in the trial. Reasons for this may have included the need to rapidly gain prospective parental consent very soon after birth, which may not be possible in some scenarios. Around 15% of infants received CPAP before randomization; therefore, the mean prerandomization FiO_2 may not be an accurate representation of the infant's FiO_2 at admission. Furthermore, all of the centers in the trial had rescue CPAP available for infants who experienced nasal high-flow treatment failure. In addition, 17 infants (23% of those with nasal high-flow treatment failure) had treatment escalation without meeting treatment failure criteria. In some cases, this could have represented clinicians' unfamiliarity with nasal high-flow and may have affected the results of the HUNTER trial. Finally, in the HUNTER trial, treatment failure was defined as failure within 72 hours of randomization; although the majority of failures occurred on the first day, some nasal high-flow failures may have occurred beyond 72 hours and would not have been included as having treatment failure.

The infants in the trial required respiratory support for a variety of diseases. The final respiratory diagnosis was made after randomization and was not objectively defined in the study, and thus was not included in the prediction

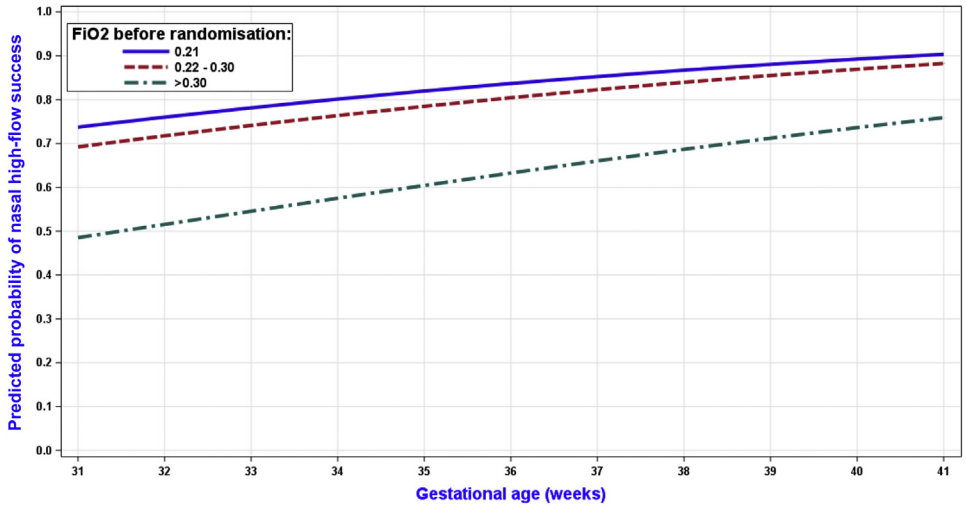

Figure 2. Model prediction of treatment success by FiO_2 category and gestational week.

analysis. RDS was more commonly diagnosed than transient tachypnea of the newborn in infants in whom nasal high-flow treatment failed, and vice versa (**Table II**). Because RDS is more common in preterm infants, this finding may reflect the higher treatment failure rate seen with increasing immaturity, but because the diagnosis was assigned after randomization, could also be influenced by the treatment outcome or other clinical or nonclinical factors. Nevertheless, it is plausible that nasal high-flow is less effective in diseases that require more positive distending pressure, as might be provided by CPAP.

Because the use of nasal high-flow to treat newborn infants with respiratory distress is increasing, and to avoid delaying CPAP initiation in those infants at higher risk of nasal high-flow treatment failure, it is important to identify which infants are likely to be successfully treated with nasal high-flow in SCNs. Results from this study may also help to guide clinicians in their choice of the most appropriate modality of initial noninvasive respiratory support, where they have access to both nasal high-flow and CPAP. Although our model was not highly predictive, nasal high-flow was more likely to be successful in infants with higher gestational age and those with an FiO2 of ≤0.30. Therefore, nasal high-flow may be a reasonable first-line respiratory management option for infants with these characteristics in nontertiary care centers. Furthermore, some clinicians may choose to commence infants on nasal high-flow treatment, knowing that with rescue CPAP available, outcomes are no worse than if infants were commenced on CPAP.

Further prospective research, for example, cohort studies with the potential to generate large sample sizes, is required to help to guide clinicians choosing initial respiratory support for newborn infants in nontertiary centers. Such studies could explore the potential value of pre-treatment respiratory diagnosis or the value of pretreatment scores (eg, Silverman, which is not currently in routine use in Australia), along with other variables considered but not included in the current study which may make small but clinically important contributions to predictions, for subsets of the treatment population. Such studies could help to identify those infants likely to succeed on nasal high-flow, thereby potentially avoiding the harms associated with CPAP. In addition, it allows timely recognition of those infants who are likely to require treatment escalation and may subsequently require transfer to a tertiary NICU. ■

Acknowdements available at www.jpeds.com (Appendix).

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Data Statement

Data sharing statement available at www.jpeds.com.

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Appendix

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Table I. Characteristics of the study population (n = 363)

Characteristics	
Exposure to any antenatal corticosteroid <7 days before birth*	104 (28.7)
Restricted to 177 infants born <37 weeks*	100 (56.5)
Ruptured membranes >24 hours*	35 (9.6)
Labor*	250 (68.9)
Chorioamnionitis*	14 (3.9)
Cesarean delivery	197 (54.3)
Gestational age in weeks†	36.9 ± 2.7
Gestation <37 weeks	177 (48.8)
Gestation <34 weeks	69 (19.0)
Birthweight in grams	2928 ± 782
Male	232 (63.9)
Multiple birth	26 (7.2)
Apgar score at 5 minutes	8.0 (7.0-9.0)
CPAP, IPPV, or external cardiac massage in the delivery room	262 (72.2)
Admitted after 7:00 p.m. and before 7:00 a.m.	133 (36.6)
Indication for respiratory support (multiple selections permitted)	
Clinical signs	331 (91.2)
Acidosis	56 (15.4)
Oxygen requirement	145 (39.9)
Apnea	24 (6.6)
Other	3 (0.8)
CPAP before randomization	55 (15.2)
Duration of CPAP (n = 55) in minutes	60 (30-95)
Blood gas before randomization	209 (57.6)
pH (n = 209)	7.19 ± 0.09
Partial pressure of carbon dioxide (n = 208‡) where recorded	64.55 ± 14.3
FiO_2 before randomisation§	27.0 ± 9.8
FiO_2 before randomisation§	23 (21-30)
Age at treatment commencement in hours	1.4 (0.9-2.5)

IPPV, intermittent positive pressure ventilation.
Values are number (%), mean ± SD, or median (IQR).
*Of the 363 infants, 26 were twins. Two pairs of twins were both randomized to nasal high-flow and included in the study population. In calculating percentages for these maternal characteristics (ie, antenatal corticosteroid, ruptured membranes, labor, and chorioamnionitis), 2 mothers were therefore counted twice.
†Calculated in days and divided by 7.
‡One record missing.
§Two records missing.