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The Randomized, Controlled Trial of Late Surfactant: Effects on Respiratory Outcomes at 1-Year Corrected Age

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Objective To determine the effects of late surfactant on respiratory outcomes determined at 1-year corrected age in the Trial of Late Surfactant (TOLSURF), which randomized newborns of extremely low gestational age (≤28 weeks' gestational age) ventilated at 7-14 days to late surfactant and inhaled nitric oxide vs inhaled nitric oxide-alone (control).

Study design Caregivers were surveyed in a double-blinded manner at 3, 6, 9, and 12 months' corrected age to collect information on respiratory resource use (infant medication use, home support, and hospitalization). Infants were classified for composite outcomes of pulmonary morbidity (no PM, determined in infants with no reported respiratory resource use) and persistent PM (determined in infants with any resource use in ≥3 surveys).

Results Infants (n = 450, late surfactant n = 217, control n = 233) were 25.3 ± 1.2 weeks' gestation and 713 ± 164 g at birth. In the late surfactant group, fewer infants received home respiratory support than in the control group (35.8% vs 52.9%, relative benefit [RB] 1.28 [95% CI 1.07-1.55]). There was no benefit of late surfactant for No PM vs PM (RB 1.27; 95% CI 0.89-1.81) or no persistent PM vs persistent PM (RB 1.01; 95% CI 0.87-1.17). After adjustment for imbalances in baseline characteristics, relative benefit of late surfactant treatment increased: RB 1.40 (95% CI 0.89-1.80) for no PM and RB 1.24 (95% CI 1.08-1.42) for no persistent PM.

Conclusion Treatment of newborns of extremely low gestational age with late surfactant in combination with inhaled nitric oxide decreased use of home respiratory support and may decrease persistent pulmonary morbidity. *(J Pediatr 2016;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT01022580

Extreme prematurity carries a risk of ongoing pulmonary morbidity (PM) and resource use following hospital discharge.[1-4] Interventional trials of both drugs and respiratory support strategies in extremely low gestational age newborns (ELGANs) focus on decreasing the rate of bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age (PMA).[5-8] Although BPD is an imperfect

BD	Bronchodilator
BPD	Bronchopulmonary dysplasia
ELGAN	Extremely low gestational age newborn
GA	Gestational age
ICS	Inhaled corticosteroids
iNO	Inhaled nitric oxide
NO CLD	Inhaled Nitric Oxide to Prevent Chronic Lung Disease
PM	Pulmonary morbidity
PMA	Postmenstrual age
RB	Relative benefit
TOLSURF	Trial of Late Surfactant

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predictor of later PM,[1,4,9] clinical trials have not reported broadly accepted later respiratory outcomes. Outcomes previously evaluated at 1-2 years of age include respiratory symptoms, medication use, respiratory exacerbations, and hospitalizations due to respiratory disease.[2-4,10-12]

The Trial of Late Surfactant (TOLSURF) was a randomized, controlled, masked clinical trial in which ELGANs at high risk for BPD who remained intubated in the second week of life were randomized to late surfactant (up to 5 doses) and inhaled nitric oxide (iNO) vs iNO alone.[13] We found no difference in the primary outcome of survival without BPD at 36 weeks' PMA. A potential benefit of treatment with late surfactant, however, emerged with a later respiratory assessment at 40 weeks' PMA (term). Data on respiratory resource use after hospital discharge were collected. We sought to determine whether there were effects of late surfactant on several clinically relevant respiratory outcomes determined through 1-year corrected age. We hypothesized that late surfactant and iNO would improve respiratory outcomes compared with iNO alone.

Methods

The TOLSURF study (ClinicalTrials.gov: NCT01022580) has been described in detail.[13] Parental informed consent for participation was obtained under institutional review board approval at 25 US hospitals. In brief, 511 infants ≤ 28 0/7 weeks' gestational age (GA) underwent stratified randomization (<26 weeks' GA or ≥ 26 weeks' GA) by site to late surfactant and iNO vs iNO alone at 7-14 days (n = 252 and 259, respectively). Calfactant (Infasurf; ONY Inc, Amherst, New York) was administered in standard doses every 1-3 days for up to 5 doses in the late surfactant group. Control (iNO alone) infants had no intervention (sham procedure behind a screen to maintain blinding). All infants received iNO for a 25-day course, per the protocol of our previous study of Nitric Oxide to Prevent Chronic Lung Disease (NO CLD).[14,15] The primary outcome of TOLSURF was survival without BPD, determined by oxygen/flow reduction challenge at 36.0 ± 1 weeks' PMA. Infants on nasal cannula support with effective fraction of inspired oxygen < 0.30 who remained hospitalized at 40 weeks' PMA had a repeat assessment. No statistically significant differences were identified in primary or secondary outcomes during the neonatal hospitalization.[13] Clinical study personnel and families remained blinded to treatment group assignment through the follow-up period (completed February 2016). Unblinded outcomes were reviewed periodically by a data safety monitoring board appointed by the National Institutes of Health.

Parents/caregivers were surveyed at 3, 6, 9, and 12 months' corrected age (for prematurity) for interval events since discharge or last contact. Responses to questions regarding respiratory medication prescription, hospitalization for respiratory illness, and home respiratory support (supplemental oxygen by nasal cannula or tracheostomy with or without assisted ventilation/oxygen) were collated. Specific respiratory medication categories queried were inhaled bronchodilators (BD), inhaled corticosteroids (ICS), diuretics, systemic steroids, and pulmonary vasodilators. We also asked caregivers if they had been told by a medical professional that their child had wheeze on auscultation. These questions were posed over the same time interval, since the last contact.

Respiratory Outcomes at 1-Year Corrected Age

We focused the analysis of PM following neonatal discharge on caregiver-reported health resource use for respiratory indications in 3 domains (medications, hospitalization, and home support) using a short recall interval. We predetermined several outcomes to quantify the degree and type of morbidity experienced by these infants. Our primary outcomes were PM and persistent PM. We assigned an outcome of no PM to infants whose caregivers reported no medications, hospitalizations, or home respiratory support on any survey through 12 months' corrected age. We assigned an outcome of any PM to all other infants. We defined persistent PM in infants with morbidity on any domain on at least 3 surveys. Infants with morbidity on 2 or fewer surveys were classified as no persistent PM.

A committee of investigators who remained blinded to treatment assignment evaluated 37 infants with incomplete survey data who were unclassified for one or both outcomes, for adjudication of missing outcomes. Using simple imputation when data were missing between 2 other time points (eg, no resource use reported), and additional respiratory resource use data collected during follow-up visits in the second year of life and among infants with prolonged neonatal hospitalizations beyond 3 months' corrected age, we were able to impute either missing PM or persistent PM for 8 infants, and both for 1 infant. Four infants had no follow-up data, 2 had insufficient data for both outcomes (but contributed other data on resource use), and the remainder were unable to be classified for one missing outcome (**Figure 1**; available at www.jpeds.com). Infants were classified as a wheezing phenotype if caregivers reported any ICS or BD use or wheeze (vs no wheezing phenotype). They were subclassified into 4 ordered categories of wheezing phenotype: likely (ICS with/without BD use), probable (BD use with/without wheeze), possible (wheeze without BD/ICS use), or none (no ICS, BD, or wheeze).

Statistical Analyses

To estimate treatment effect, we used generalized estimating equations to account for clustering of siblings. Analyses of baseline characteristics and potential modifiers of infant lung disease did not account for clustering. All analyses were by intent-to-treat, based on initial randomized allocation. Because of the known impact of sociodemographic factors in postdischarge outcomes among infants born extremely preterm, we planned a priori to adjust estimations of treatment effect for our primary outcomes (PM and persistent PM) for differences ($P < .05$) in baseline characteristics noted between groups.

Results

Patients were enrolled between January 2010 and September 2013. Of 471 infants alive at 36 weeks' PMA, 455 who remained in the study were discharged alive and 5 infants died

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Table I. Baseline characteristics and neonatal respiratory outcomes of infants discharged alive by treatment group (late surfactant vs control)

Characteristics	Follow-up cohort (n = 450)	Late surfactant (n = 217)	Control (n = 233)	*P* value
GA, wk	25.3 ± 1.2	25.3 ± 1.2	25.3 ± 1.2	.90
<26 0/7 wk	310 (68.9)	148 (68.2)	162 (69.5)	.76
Birth weight, g	713 ± 164	715 ± 174	711 ± 154	.81
Intrauterine growth restriction	73 (16.2)	40 (18.4)	33 (14.2)	.22
Antenatal steroids	388 (86.2)	184 (84.8)	204 (87.6)	.11
Male sex	248 (55.1)	124 (57.1)	124 (53.2)	.40
Multiple gestation	139 (30.9)	56 (25.8)	83 (35.6)	.02
Multiple siblings enrolled	102 (22.7)	41 (18.9)	61 (26.2)	.07
Maternal characteristics				
Race/ethnicity				.47
White, non-Hispanic	220 (48.9)	101 (46.5)	119 (51.1)	
African American	159 (35.3)	82 (37.8)	77 (33.0)	
Hispanic	50 (11.1)	21 (9.7)	29 (12.4)	
Asian	13 (2.9)	5 (2.1)	8 (3.7)	
Other	8 (1.8)	5 (2.3)	3 (1.3)	
Age, y	28.8 ± 6.4	27.8 ± 6.1	29.8 ± 6.6	.0007
Education				.06
High school not complete	56 (12.4)	23 (10.6)	33 (14.2)	
High school graduate or some college	227 (50.4)	123 (56.7)	104 (44.6)	
College graduate ± graduate school	166 (36.9)	71 (32.7)	95 (40.8)	
Unknown	1 (0.2)	0	1 (0.4)	
Neonatal respiratory outcomes				
BPD at 36 wk PMA	291 (64.7)	140 (64.5)	151 (64.8)	.95
BPD at 40 wk PMA	165 (36.7)	71 (32.7)	94 (40.3)	.09
Duration of mechanical ventilation (d)	41.9 ± 30.4	42.3 ± 30.6	41.4 ± 30.3	.77

Data are mean ± SD or n (%).
P value by *t* test or χ^2.
Intrauterine growth restriction ≤ 10th percentile for GA per fetal growth curves derived from Fenton and Kim.[16]

after discharge without further follow-up data collected (**Figure 1**). Consistent with characteristics of the original study participants, infants with 1-year follow up were predominantly male and averaged 25.3 ± 1.2 weeks' gestation, with birth weight 713 ± 164 g (**Table I**).[13,16] The duration of mechanical ventilation was prolonged; 65% of infants had a diagnosis of BPD at 36 weeks' PMA, and 37% had a diagnosis of BPD at 40 weeks' PMA. Eleven infants had undergone tracheostomy, 6 were receiving assisted ventilation at home, and 1 was lost to follow-up. There were significant baseline differences between late surfactant-treated and control infants. Namely, infants in the late surfactant group had mothers who were 2 years younger (with a trend to lower educational attainment), and there were fewer products of multiple gestation.

We also evaluated for differences in potential modifiers of infant lung disease identified from the caregiver discharge survey. These included potential environmental exposure to tobacco smoke, anticipated breast milk feeding, exposure to furry pets, private insurance status, and parental history of asthma. There were no significant differences by treatment group, although there was a trend toward a lower proportion of parents with asthma in the late surfactant group (14.5% vs 21.9%, *P* = .05) (**Table II**; available at www.jpeds.com).

Surveys were completed near the target dates (3.2 ± 0.6, 6.2 ± 0.7, 9.1 ± 0.6, and 12.3 ± 0.8 months' corrected age), with 421, 423, 413, and 414 fully completed surveys at 3, 6, 9, and 12 months' corrected age, respectively. We were able to classify 439 infants (97.6%) for PM (no PM vs any PM) and 426 infants for persistent PM (no persistent PM vs persistent PM); 25% (110/439) of the infants had no PM, and 36% (153/426) had persistent PM. Of infants who reported resource use, 96 had morbidity at only 1 survey, 80 at 2 surveys, 73 at 3 surveys, and 80 at 4 surveys. The distribution of respiratory outcomes of interest at 1-year corrected age by treatment group is shown (**Table III**). No benefits of late surfactant on composite outcomes were seen in unadjusted analyses: relative benefit (RB) of treatment with late surfactant was 1.27 (95% CI 0.89-1.81; *P* = .19) for no PM and 1.01 (95% CI 0.87-1.17; *P* = .91) for no persistent PM. After adjustment for baseline imbalances (maternal age and multiple gestation status), the RB of treatment with late surfactant increased to RB 1.40 (95% CI 0.96-2.04; *P* = .08) for no PM, and RB 1.24 (95% CI 1.08-1.42; *P* = .003) for no persistent PM. With adjustment for parental history of asthma in sensitivity analyses, there were no significant benefits of treatment for either no PM nor no persistent PM. There also was no difference between groups for our definition of wheezing phenotype.

To further describe the relationship of treatment to postdischarge domains of PM, we plotted overall resource use and use in each domain (medications, home support, and hospitalizations) at each survey time point by treatment group (**Figure 2**, A-D). Resource use was greater in the control group at all time points except 9 months. The treatment effect on these domains was limited. The overall proportion of infants in the late surfactant group that received home respiratory support (predominantly home oxygen use) over the follow-up period,

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Table III. Respiratory outcomes at 1-year corrected age by treatment group

Treatment groups	Follow-up cohort	Late surfactant	Control	RB (95% CI)
No PM	110/439 (25.1)	59/210 (28.1)	51/229 (22.3)	1.27 (0.89-1.81)
Persistent PM	153/426 (35.9)	74/208 (35.6)	79/218 (36.2)	1.01 (0.87-1.17)
Wheezing phenotype				
Dichotomous				
Any	291/436 (66.7)	140/210 (66.7)	151/226 (66.8)	0.99 (0.74-1.31)
Ordered*				
ICS ± BD	134/436 (30.7)	66/210 (31.4)	68/226 (30.1)	
BD ± wheeze	108/436 (24.8)	51/210 (24.3)	57/226 (25.2)	
Wheeze only	49/436 (11.2)	23/210 (11.0)	26/226 (11.5)	
None	145/436 (33.3)	70/210 (33.3)	75/226 (33.3)	
Postdischarge morbidity domains				
Respiratory hospitalization	121/428 (28.3)	60/205 (29.3)	61/223 (27.4)	0.97 (0.85-1.10)
Home respiratory support	198/431 (45.9)	80/208 (38.5)	118/223 (52.9)	1.28 (1.07-1.55)
Any respiratory medication exposure	277/438 (63.2)	132/211 (62.6)	145 (63.9)	1.07 (0.82-1.40)
Postdischarge medication use				
Diuretic	89/430 (20.7)	40/207 (19.3)	49/223 (22.0)	1.04 (0.94-1.15)
BD	221/435 (50.8)	110/210 (52.4)	111/225 (49.3)	0.95 (0.77-1.16)
ICS	134/430 (31.2)	66/208 (31.7)	68/222 (30.6)	0.99 (0.87-1.13)
Systemic steroid	70/430 (16.3)	37/208 (17.8)	33/222 (16.3)	0.97 (0.89-1.06)

Data are n/N (%) and RB (95% CI).
RB by generalized estimating equation, accounting for clustering of siblings.
*P value .97 by χ^2.

however, was lower (RB 1.28, 95% CI 1.07-1.55; **Table III**), consistent with the observed pattern of less support at each time point. We also evaluated the relationship of reported exposures to respiratory medication classes (diuretics, BD, ICS, systemic steroids) and treatment group, at each survey (**Figure 2**, E-H). Diuretic use tended to be greater in controls and BD use tended to be greater in the late surfactant group. Only 9 infants reported pulmonary vasodilator therapy, so this exposure was not evaluated further.

Discussion

We demonstrated no substantial benefit of late surfactant as administered in TOLSURF on novel respiratory outcomes determined at 1-year corrected age; however, there was significantly less use of home respiratory support over the first year in infants in the late surfactant group, consistent with the trend shown previously toward decreased need for oxygen at 40 weeks' PMA.[13] Because no substantial adverse effects of late surfactant were found during the neonatal hospitalization, the current data further support the safety of late surfactant therapy in high-risk ELGAN.

Many randomized trials in ELGAN aim to improve infant respiratory status during the neonatal hospitalization. A number of these have failed to identify benefit in the neonatal period but subsequently have demonstrated advantage in at least one measure of respiratory status at follow-up.[4-6,10,12,17] Although Zivanovic et al[17] found no difference in symptomatic lung disease at follow-up, measures of air flow obstruction and diffusing capacity were less compromised in children who were randomized to primary high-frequency ventilation compared with conventional mechanical ventilation. Davis et al[10] demonstrated a trend toward fewer respiratory exacerbations requiring asthma medications by 1-year corrected age in infants born preterm receiving antioxidant therapy with recombinant human superoxide dismutase compared with controls. Similarly, Stevens et al[4] demonstrated fewer respiratory exacerbations by 22 months' corrected age in children randomized at birth to primary nasal continuous positive airway pressure vs intubation with surfactant administration and mechanical ventilation. Akin to our findings, infants who were intubated and mechanically ventilated at 14 days of age and received a single dose of poractant alfa (Curosurf; Chiesi USA, Inc, Cary, North Carolina) had lower rates of respiratory hospitalization by 9.5 months' corrected age, although there were

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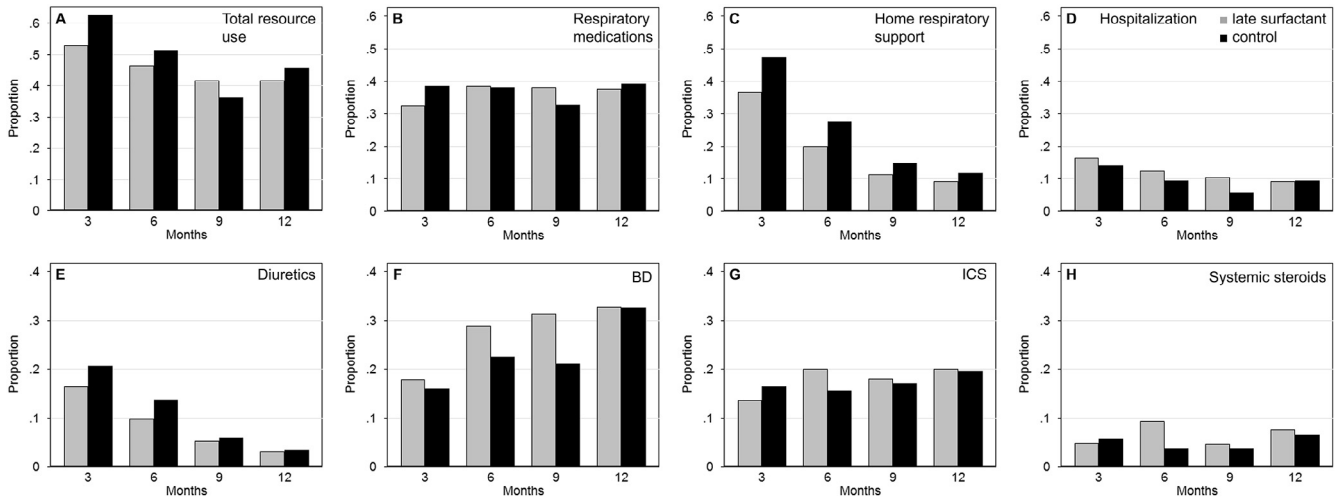

Figure 2. Proportion of infants with respiratory resource use at each survey time point, 3, 6, 9, and 12 months' corrected age, in late surfactant and control groups: **A**, Total resource use, **B**, respiratory medication exposure, **C**, home respiratory support, **D**, hospitalization for respiratory cause, and **E**, diuretics, **F**, BD, **G**, ICS, and **H**, systemic steroid exposure.

no other significant differences in respiratory status during the neonatal hospitalization or among other follow-up outcomes.[12]

The choice of respiratory outcomes after neonatal discharge in these and other studies has varied broadly and has included symptoms, respiratory resource use (medications, hospitalization, and home respiratory support), and measures of pulmonary function. Early and persistent decreases in pulmonary function are likely to have repercussions throughout life, even in the absence of symptoms.[18,19] Thus, pulmonary function testing can yield data that are relevant to clinicians and families; however, there is also a burden on children and families associated with persistent clinically symptomatic lung disease, related to repeated hospitalizations, exposures to multiple medications with potentially adverse effects, cost, and other effects.[1-4]

For some clinical trials, multiple single areas (domains) of symptoms or resource use have been evaluated.[2,4] The NO CLD trial, for instance, showed benefit of iNO therapy in high-risk infants born preterm both with neonatal respiratory outcomes and in multiple domains of postdischarge respiratory resource use at 1-year corrected age, including medication use and home respiratory support.[2] The Surfactant Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) trial, however, which investigated primary delivery room management with continuous positive airway pressure, did not show an effect on diagnosis of BPD at 36 weeks' PMA but did demonstrate lower rates of wheeze and respiratory exacerbations at 6-22 months' corrected age.[4] Composite outcomes of respiratory status have had limited application in neonatal clinical trials, and prospective data collection toward outcomes as we have developed and analyzed in the current study have not been used.[9] Although both resource use and symptom reporting can be affected by socioeconomic status, biological variables also demonstrate associations with these later outcomes, making them plausible primary or secondary trial outcomes.[20-25] This is analogous to the use of neurodevelopmental impairment as an outcome, which often is assessed at 18-24 months' corrected age and also is influenced by socioeconomic status.[26]

Given the young age of our cohort at the time of analysis, we explored a limited "wheezing phenotype" in this study, derived only from reported inhaled medication exposure and wheeze. We did not see a signal for treatment effect on this outcome, nor for the medication components of the outcome. This observation suggests that any effect of late surfactant with iNO on persistent lung disease may be distinct from wheezing illness commonly present in former infants born preterm (which occur across the spectrum of preterm birth).[27] Previous studies evaluating childhood respiratory outcomes before and after the advent of surfactant replacement therapy showed mild improvements or no change in prevalence of wheezing illness or airway obstruction in the surfactant era, despite an increase in survival of more immature infants.[28,29] These findings are in contrast to our previous findings with iNO alone, wherein beneficial effects of iNO in the NO CLD study were seen on both classes of inhaled medications.[2] Finally, although data supporting the association of parental asthma and preterm respiratory outcomes are variable, we did plan a sensitivity analysis because this characteristic is of interest with respect to childhood wheezing illness.[30,31]

With lack of effect on our wheezing phenotype, it is of interest that the treatment effect we did demonstrate was on the use of home respiratory support. In contrast to wheezing illness, the use of home oxygen is more specific to infants born extremely preterm than to the broader population of preterm infants as a whole.[32] Thus, the effect of late surfactant may be more specific to the perturbed lung development of ELGAN. Diuretics similarly are more common is this population, although we failed to show a significant benefit of late surfactant on diuretic exposure.[33] Notably, the results of the current study represent the effects of late surfactant in infants receiving

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iNO, which, when administered by this protocol in the NO CLD study, decreased home oxygen use and respiratory medication exposure from all drug classes. Thus, the effects of late surfactant administration alone (without iNO), as administered by Hascoët et al,[12] may differ from the effects seen in the current study.

The data for the current study were collected by caregiver recall, which may raise concerns regarding its accuracy. Previous studies, however, have shown that parents can report important events from the last 12 months (such as hospitalizations and medical visits for asthma and bronchitis), with moderate-to-substantial (85%-95%) agreement with medical records.[34,35] In addition, test-retest reliability for questions related to respiratory illness administered to parents of preterm infants at 6 months' corrected age revealed substantial-to-perfect agreement over the 2 tests, and strong internal consistency.[36] Thus, within the short time frame of surveys for the current study, we would expect good accuracy and reliability of parent responses.

In conclusion, compared with iNO alone, late surfactant decreases the use of home respiratory support following initial hospital discharge. Unfortunately, we did not demonstrate a substantial benefit of late surfactant on our novel, composite respiratory outcomes. One possible explanation for the lack of benefit is that we didn't treat with late surfactant frequently enough to achieve a persistent effect on lung function.[13,37] Regardless, these novel respiratory outcomes are clinically relevant and should be considered for the assessment of the effects of interventions in neonatal clinical trials. Neurodevelopmental outcomes for this trial will be reported separately; however, from the current data, late surfactant with iNO appears to be a safe intervention, with no adverse effects demonstrated at 1-year corrected age. These data are reassuring as we consider using surfactant as a vehicle for instillation of local corticosteroids to the lung, which may prove an effective therapy to prevent BPD in high-risk ELGAN.[38] ■

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Appendix

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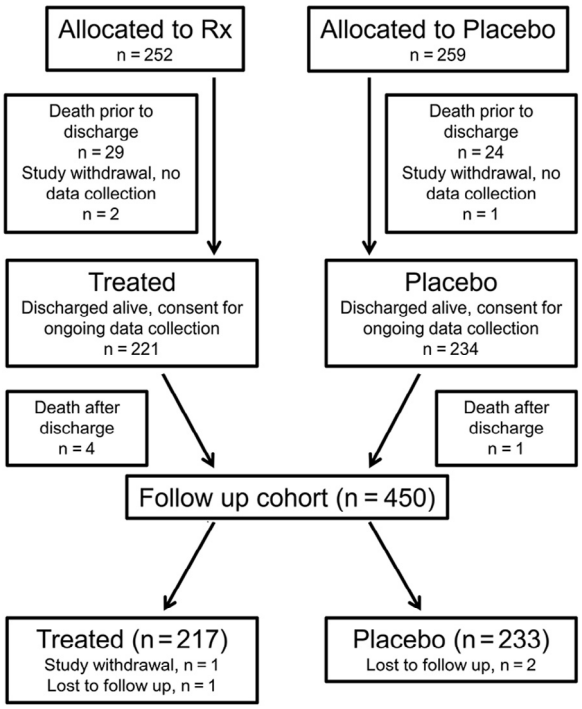

Figure 1. Patient flow diagram. Deaths and study withdrawals before neonatal discharge detailed in Ballard et al.[13] *Rx*, treated.

Table II. Potential modifiers of postdischarge PM by treatment group (late surfactant vs control)

Modifiers	Follow-up cohort (n = 432)*	Late surfactant (n = 211)	Control (n = 221)	*P* value
Breast milk (full or partial) anticipated	195 (45.1)	91 (43.1)	104 (47.1)	.41
Furry pet in home	178 (41.2)	85 (40.3)	93 (42.1)	.70
Young child exposure anticipated	228 (52.8)	115 (54.5)	113 (51.1)	.48
Potential ETS exposure	105 (24.3)	51 (24.2)	54 (24.4)	.95
Private insurance	170/430 (39.5)	78/210 (37.1)	92/220 (41.8)	.32
Asthma in parent	77/422 (18.2)	30/207 (14.5)	47/215 (21.9)	.05

ETS, environmental tobacco smoke.
Data are n/N (%).
P value by χ^2.
"Young child exposure anticipated" was classified as yes if caregiver reported another child <5 years in the home or anticipated a young child at day care.
"Potential ETS exposure" was classified as yes if caregiver reported (1) a parent smokes, (2) there is a smoker living in the home, (3) smoking is allowed in home, or (4) the child will travel in vehicle where smoking is permitted.
"Breast milk anticipated" was classified as yes if caregiver reported either a breast milk only diet or combination of breast milk and formula at discharge.
*Missing data for infants not discharged to their biological parents' care (family history) and those discharged from nonstudy hospitals.

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