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## Original Investigation

# Late Surfactant Administration in Very Preterm Neonates With Prolonged Respiratory Distress and Pulmonary Outcome at 1 Year of Age: A Randomized Clinical Trial

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**IMPORTANCE** Although immature neonate survival has improved, there is an increased risk of developing bronchopulmonary dysplasia, leading to significant respiratory morbidity. Measures to reduce bronchopulmonary dysplasia are not always effective or have important adverse effects.

**OBJECTIVE** To evaluate the effect of late surfactant administration in infants with prolonged respiratory distress on ventilation duration, respiratory outcome at 36 weeks' postmenstrual age, and at 1 year postnatal age.

**DESIGN, SETTING, AND PARTICIPANTS** Double-blind randomized clinical trial at 13 level III French perinatal centers. Participants included 118 neonates at less than 33 weeks' gestation who still required mechanical ventilation on day 14 (SD, 2) with fraction of inspired oxygen of more than 0.30. All survivors were eligible for follow-up. We performed an intent-to-treat analysis.

**INTERVENTIONS** Infants received 200 mg/kg of poractant alfa (surfactant) or air after randomization. At 1 year, after parents' interview, infants underwent physical examination by pediatricians not aware of the randomization.

**MAIN OUTCOMES AND MEASURES** The duration of ventilation was the primary outcome. The combined outcome of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age and respiratory morbidity at 1 year of age were the main secondary outcome measures.

**RESULTS** Of the 118 infants who participated in the study, 65 (55%) were male. Fraction of inspired oxygen requirements dropped after surfactant, but not air, for up to 24 hours after instillation (0.36 [0.11] vs 0.43 [0.18];  $P < .005$ ). Severe bronchopulmonary dysplasia/death rates at 36 weeks' postmenstrual age were similar (27.1% vs 35.6%;  $P = .32$ ). Less surfactant-treated infants needed rehospitalization for respiratory problems after discharge (28.3% vs 51.1%;  $P = .03$ ); 39.5% vs 50% needed respiratory physical therapy ( $P = .35$ ). No difference was observed for weight (7.8 [1.2] kg vs 7.6 [1.1] kg), height (69 [5] cm vs 69 [3] cm), and head circumference (44.4 [1.7] cm vs 44.2 [1.7] cm) measured at follow-up, nor for neurodevelopment outcome.

**CONCLUSIONS AND RELEVANCE** Late surfactant administration did not alter the early course of bronchopulmonary dysplasia. However, surfactant-treated infants had reduced respiratory morbidity prior to 1 year of age.

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← Editorial page 322

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Immature neonate survival has significantly improved, with advances in perinatal care such as prenatal use of corticosteroids,<sup>1,2</sup> continuous positive airway pressure at birth,<sup>3-5</sup> and early use of exogenous surfactant.<sup>6</sup> However, the cost of improved survival is an increased risk of developing bronchopulmonary dysplasia (BPD).<sup>7</sup> Bronchopulmonary dysplasia is responsible for chronic lung disease and abnormal neurodevelopment.<sup>8,9</sup> Different therapeutic approaches have been proposed for treating BPD including postnatal corticosteroids,<sup>1,10</sup> antioxidant treatments,<sup>11</sup> and various strategies of assisted ventilation that aim to reduce barotrauma or volutrauma.<sup>12</sup> However, some of these have been relatively ineffective and others may be related to long-term major adverse effects.<sup>2,12</sup>

Factors associated with severe BPD include the presence of cellular debris in distal airways,<sup>13</sup> cellular dysfunctions in type II pneumocytes,<sup>14,15</sup> episodes of edema and inflammatory bursts,<sup>12,16</sup> alterations in airway compliance, disorders in bronchomotor function,<sup>17</sup> impairments in pulmonary healing and growth,<sup>12,18</sup> and increased oxidative stress.<sup>19</sup> The application of mechanical ventilation alone alters surfactant and growth factor expression.<sup>20</sup> All these factors could theoretically respond to surfactant treatment.

The objectives of this study were to evaluate the effect of late surfactant administration at the age of first extubation in infants with severe respiratory distress that required prolonged invasive ventilation and to evaluate the effect of late surfactant administration on the respiratory outcome of the infants at 36 weeks' postmenstrual age (PMA) and 1 year of age.<sup>21,22</sup>

## Methods

This prospective, randomized, controlled, double-blinded, multicenter trial was conducted in 13 level III French Perinatal Centers from December 2009 to November 2012. It was approved by the Comité de Protection des Personnes de Lorraine Ethics Committee (see study protocol in [Supplement 1](#)). Written consent from the parents or legal guardian was obtained before randomization.

### Inclusion Criteria

Neonates were eligible if they were born before 33 weeks' gestation and still needed conventional mechanical ventilation or high-frequency oscillatory ventilation at 14 days of life (SD, 2) with a fraction of inspired oxygen (FiO<sub>2</sub>) of more than 0.30 and/or an oxygenation index (FiO<sub>2</sub> multiplied by mean airway pressure per arterial oxygen pressure) of 8 or more for at least 6 hours (based on arterial or percutaneous blood gases and measured with a sensor in the postductal position).

### Exclusion Criteria

Infants were excluded if they had an active infection, defined as a C-reactive protein (CRP) level of more than 30 mg/L (to convert to nanomoles per liter, multiply by 9.524), that was not controlled with an antibiotic treatment that targeted an identified microbe at the time of randomization; if they had

## Key Points

**Question:** Could surfactant administration at 2 weeks of age in very preterm infants with prolonged respiratory distress reduce ventilation duration and respiratory morbidity?

**Findings:** In this randomized clinical trial, there was no difference in ventilation duration; there was a significant decrease in rehospitalization rate for respiratory problems after discharge within the first year postnatal age (28.3% vs 51.1%).

**Meaning:** Late surfactant administration is associated with better pulmonary outcome than controls at 1 year of age.

undergone a surgical intervention within the past 72 hours; or if they presented with a disease (chromosomal or neurological) that might contraindicate extubation.

### Blinding Procedure

A practitioner not involved in the child's care contacted the coordinator center and received the number of an opaque, sealed envelope available in the centers. The envelope contained the notification of the assigned treatment. According to the assignment, the practitioner proceeded to instill either poracant alfa (surfactant group) at 2.5 mL/kg (200 mg/kg) or the same volume of air (control group), without knowledge of the personnel (medical and nursing) involved in the child's care. Care was then continued according to the unit's routine without knowledge of the treatment allocation.

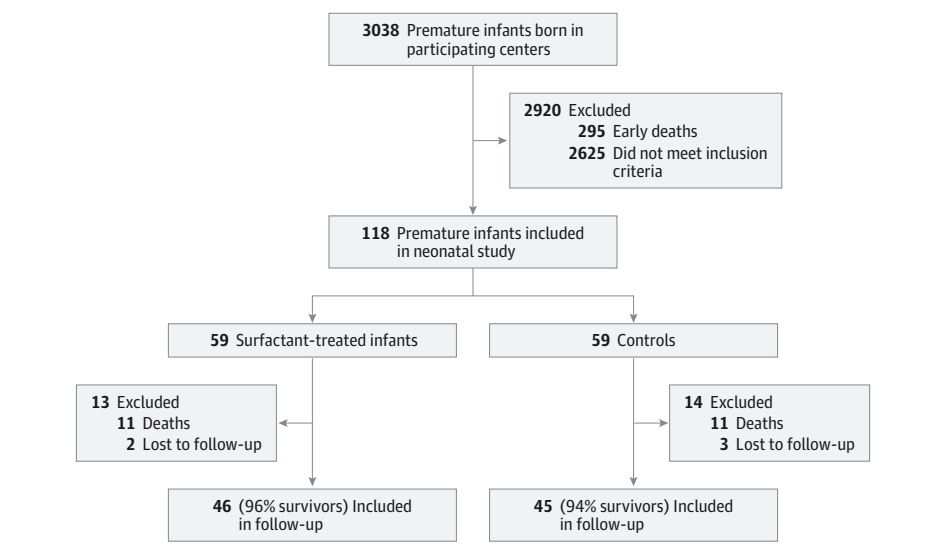
### Measures of Outcome

The primary outcome was the time to first successful extubation. Predefined extubation criteria included: FiO<sub>2</sub> less than 0.30 for arterial oxygen percent saturation between 88% and 92% and partial pressure of carbon dioxide between 40 and 55 mm Hg for at least 6 hours. Extubation was considered successful when adequate spontaneous respiration was maintained for at least 72 hours. Criteria for reintubation included 6 episodes of apnea and/or bradycardia that required stimulation over a 6-hour period; 1 episode of apnea and/or bradycardia that required resuscitation with positive pressure; FiO<sub>2</sub> greater than 0.60; or partial pressure of carbon dioxide greater than 60 mm Hg for at least 6 hours.<sup>3</sup>

Hospital secondary outcomes included BPD or death at 36 weeks' PMA according to the Jobe and Bancalari definition.<sup>16</sup> We also recorded short-term changes in FiO<sub>2</sub> requirements after instillation of surfactant or air. Similarly, general inflammation, defined as CRP level of more than 10 mg/mL, was measured before and 48 hours after instillation. Finally, neonatal morbidities such as late-onset sepsis (defined as clinical deterioration, elevated CRP, and bacteria isolated in blood culture); cerebral intraventricular hemorrhage or ventricular dilatation; feeding tolerance; and necrotizing enterocolitis were evaluated.

Infants that remained intubated at 28 days of age had echocardiographic evaluation. Associated pulmonary hypertension was defined as the presence of tricuspid regurgitation and/or a ratio less than 0.54 of the time-to-peak velocity/

Figure 1. CURDYS Study Diagram Flow



right ventricular ejection time.<sup>23-25</sup> To treat associated pulmonary hypertension, 10 ppm inhaled nitric oxide (iNO) were added for 1 to 3 weeks, depending on weekly hemodynamics evaluations.

All surviving infants were eligible for follow-up at 1 year of age. After a parents' interview recording all events that occurred since discharge, the infants underwent complete physical examination by certified, trained pediatricians not aware of the randomization. Uses of health care resources were recorded, including rehospitalization for respiratory problems with the need for reintubation, invasive ventilation, and oxygen supplementation; corticosteroid use after discharge; outpatient visits for respiratory or any problem; and home chest physical therapy. Parents will remain blinded for randomization until the end of the follow-up scheduled at 7 years of age. Neurodevelopment was evaluated with selected items of the Brunet-Lezine test<sup>26</sup> including motor, coordination, language, and socialization subtests.

### Permitted Associated Treatments

Hydrocortisone was allowed in cases of corticotrophic axis immaturity, and short-term betamethasone treatment was allowed at the sole discretion of the clinical team in charge of the infant for extubation.<sup>10</sup>

### Statistics

Sample size was calculated based on a previous study with a neonate population similar to the population of this study.<sup>27</sup> We considered a difference of 10 days of mechanical ventilation between the groups to be clinically significant in a 2-sided test with an a risk of 5% and a power of 90%. The calculated number of patients required was at least 43 per group (Power and Precision software, 2001; Biostat Ed). Considering an estimated 20% risk of losing patients to follow-up, a sample size of at least 50 children per group was expected to be sufficient. We performed an intent-to-treat analysis.

General neonate characteristics were compared between groups with a  $\chi^2$  test for categorical variables and a comparison of means test for continuous variables. A *t* test was used to compare the mean duration of ventilation between groups and among subgroups of different ages (in days). A  $\chi^2$  test (or a Fisher exact test, when appropriate) was used to compare percentages, and a *t* test (or a rank test, when necessary) was used to compare means of quantitative variables between groups. Mann-Whitney *U* test was used for neurodevelopment subscores comparison at 1 year of age. Analyses were performed with SAS software, version 9.1 (SAS Institute Inc).

## Results

### Patients

Thirteen centers included 118 infants from December 2009 to November 2012 (Figure 1). They and their mothers were similar in perinatal characteristics. There was no significant pathology of pregnancy in only 9 (15%) vs 7 (12%) mothers of infants in the control (*n* = 59) vs surfactant (*n* = 59) groups, respectively (*P* = .59) (Table 1). Early-onset sepsis was present in 25 (44%) vs 26 (41%) infants (*P* = .58). All infants had received Curosurf for respiratory distress prophylaxis before 1 hour of life. There were no differences in respiratory support or  $\text{FiO}_2$  at randomization.

The groups were similar in the detection and treatment of associated pulmonary hypertension. In the control vs surfactant groups, respectively, 27 vs 20 infants received iNO (*P* = .20) at mean (SD) 28.5 (0.5) days vs 28.7 (1.9) days, for 11.1 (9.3) days vs 12.3 (4.9) days.

### Primary Outcome

The mean (SD) age at first successful extubation was not different between groups (control, 38.3 [18.5] days vs surfactant, 35.7 [20.0] days; *P* = .29). All extubation criteria were

Table 1. Perinatal Characteristics of Mothers and Neonates

Characteristic	Poractant Alfa (n = 59)	Control (n = 59)
Maternal characteristics, No. (%)		
Nephropathy of pregnancy	17 (29)	18 (31)
Premature rupture of membranes	21 (36)	14 (24)
Oligohydramnios	15 (26)	11 (19)
Chorioamnionitis	5 (8)	5 (8)
Other infection at delivery	5 (8)	6 (10)
Diabetes	2 (3)	4 (7)
Prenatal steroids (any)	53 (89)	49 (83)
Steroid maturation (complete)	38 (65)	38 (65)
Cesarean section	27 (46)	34 (57)
Infants characteristics		
Gestational age, mean (SD, range), wk	26.2 (1.5, 24-31)	26.6 (1.3, 23-30)
Birth weight, mean (SD), g	814 (157)	770 (174)
Severe IUGR (<3rd percentile)	9 (15)	8 (14)
Male, No. (%)	33 (56)	32 (54)
CRIB score, mean (SD, median)	5.3 (2.8, 5)	6.0 (3.0, 7)
Apgar scores (medians: 1/5 min)	4/6	3.5/7
Age at randomization, mean (SD), d	14.6 (1.3)	14.4 (1.3)
FiO <sub>2</sub> at randomization, mean (SD)	0.40 (0.13)	0.42 (0.15)
Conventional mechanical ventilation, No.	28	33
Airway pressure in cm H <sub>2</sub> O, mean (SD)	10.4 (2.0)	10.1 (2.7)
High frequency oscillation, No.	31	26
Airway pressure in cm H <sub>2</sub> O, mean (SD)	13.0 (2.3)	13.5 (1.8)

Abbreviations: CRIB, Clinical Risk Index for Babies; FiO<sub>2</sub>, fraction of inspired oxygen; IUGR, interuterine growth restriction.

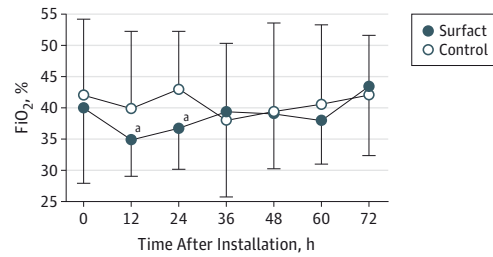
present before extubation in 26.5% and 26.8% ( $P = .98$ ), and extubation failed at least once in 22 (37.3%) control and 18 (30.3%) surfactant infants ( $P = .45$ ). On day 28, 17 (31%) control and 23 (41%) surfactant infants ( $P = .27$ ) were extubated.

### In-Hospital Secondary Outcomes

After instillation, FiO<sub>2</sub> requirements dropped significantly in the surfactant group compared with the control group for 24 hours, but after 36 hours, the groups no longer showed a difference (Figure 2). No adverse events were associated with surfactant administration. No difference was observed in inflammation between groups; CRP was greater than 10 mg/mL in 3 control and 7 surfactant infants before instillation, and in 7 control and 6 surfactant infants 48 hours after instillation. Negative baseline CRP rose to more than 10 mg/mL at 48 hours in 6 control and 1 surfactant infants.

Eleven infants died in each group. Bronchopulmonary dysplasia severity levels were similar: 8 vs 3 mild, 30 vs 40 moderate, and 21 vs 16 severe BPD/death for control and surfactant infants, respectively ( $P = .11$ ). The rate of the composite outcome, severe BPD, or death were not different at 36 weeks' PMA (Table 2). Of note, infants who received iNO required respiratory support longer in the control (median, 82 days; range, 41-191 days) than in the surfactant group (median, 65 days;

Figure 2. Changes in Fraction of Inspired Oxygen (FiO<sub>2</sub>) Requirements for 72 Hours After Surfactant (Surfact) or Air (Control) Instillation (Mean [SD])



<sup>a</sup>  $P < .05$ .

range, 38-263 days;  $P = .15$ ). Three infants that had received iNO died in each group.

Both groups had high rates of late-onset sepsis. Infants in the surfactant group had better feeding tolerance with less necrotizing enterocolitis and shorter durations of hospitalization among survivors (Table 2). The 2 groups were not significantly different in other morbidities.

### 1-Year Follow-up Outcome

Follow-up was performed at a median of 12.6 months (range, 10.2-15.2 months) vs 12.4 months (range, 10.1-15.9 months) postnatal age ( $P = .44$ ) in the control and surfactant groups, respectively. Parents' education and family social status were similar in the 2 groups (eTable in Supplement 2). There was no difference for the rate of passive smoking exposure (12 of 37 vs 12 of 40,  $P = .82$  in the control and surfactant groups, respectively). More infants were kept at home during the first year of life in the control group, while more infants were kept by a childminder or attended a daycare in the surfactant group (eTable in Supplement 2). Nevertheless, fewer surfactant-treated infants needed rehospitalization for respiratory problems after discharge: 13 surfactant-treated infants (28.3%) vs 23 control-group infants (51.1%) ( $P = .03$ ), with a median of 1 (IQR, 1-3) vs 2 (IQR, 1-8) episodes for the infants needing rehospitalization. There was no difference for infants who had received iNO in the neonatal period: 15 of 24 vs 9 of 17 ( $P = .54$ ) needed at least 1 rehospitalization after discharge in the control and surfactant groups, respectively. Other follow-up data are displayed in Table 3.

### Discussion

This study showed that among very premature infants with severe respiratory distress, late surfactant administration did not significantly shorten the time to extubation compared with controls. The surfactant group of infants had 2.5 days shorter intubations and 10% more extubations on day 28, but that was not significant. Also, we observed no significant difference in the combined outcome of death/BPD between groups at 36 weeks' PMA. However, at 1 year postnatal age, formerly sick, very premature infants treated with

Table 2. Neonatal Outcome

Study Group	No. (%)		OR (95% CI)	P Value
	Poractant Alfa (n = 59)	Control (n = 59)		
Mortality	11 (18.6)	11 (18.6)	1 [Reference]	>.99
Severe BPD or death	16 (27.1)	21 (35.6)	0.673 (0.308-1.474)	.32
Discharged home on oxygen	13 (28)	10 (22)	0.725 (0.280-1.879)	.51
Total days of FiO <sub>2</sub> in survivors, mean (SD), d	105 (35)	108 (46)		.76
Hospitalization in survivors, mean (SD), d	117 (30)	124 (40)		.08
Postnatal steroids in survivors	51 (87)	54 (92)	0.532 (0.145-1.954)	.53
Late-onset sepsis	55 (93)	56 (95)	0.737 (0.158-3.445)	.70
Receiving full feeds on day 28	59 (98)	50 (85)	9.362 (1.130-77.634)	.04
Necrotizing enterocolitis	5 (8)	15 (25)	0.272 (0.092-0.806)	.02
Patent ductus arteriosus	40 (68)	42 (71)	0.852 (0.389-1.868)	.69
Intraventricular hemorrhage in survivors	19 (39)	17 (35)	1.195 (0.523-2.732)	.67
Cerebral ventricular dilatation in survivors	3 (6)	9 (19)	0.289 (0.073-1.142)	.06

Abbreviations: BPD, bronchopulmonary dysplasia; FiO<sub>2</sub>, fraction of inspired oxygen; OR, odds ratio.

Table 3. Follow-up at 1 Year Postnatal Age

Study Group	Mean (SD)		OR (95% CI)	P Value
	Poractant Alfa	Controls		
No. children (% survivors)	46 (96)	45 (94)		.65
Corrected age at evaluation, mo	9.5 (1.5)	9.6 (1.1)		.69
Weight, kg	7.8 (1.2)	7.6 (1.1)		
Corrected z score	-0.89 (1.05)	-1.14 (1.09)		.38
Length, cm	69.4 (5.2)	68.7 (3.5)		
Corrected z score	-1.12 (1.47)	-1.44 (1.26)		.46
Head circumference, cm	44.4 (1.7)	44.2 (1.7)		.54
Children, No. (%)				
Rehospitalized for respiratory problems	13 (28.3)	23 (51.1)	0.377 (0.158-0.898)	.03
Requiring CMV	1 (2)	5 (11)	0.178 (0.020-1.587)	.12
Requiring O <sub>2</sub> since discharge	7 (15)	10 (22)	0.628 (0.216-1.828)	.39
With steroids since discharge	21 (45)	27 (60)	0.551 (0.235-1.290)	.17
Outpatient visits for respiratory problems, No. (%)	26 (57)	26 (56)	1.040 (0.454-2.380)	.93
Chest physical therapy, No. (%)	18 (39)	23 (50)	0.654 (0.279-.530)	.33
Global neurodevelopment (% maximum score)	73 (21)	74 (21)		.85
Subscore				
Motor	74 (36)	72 (38)		.83
Coordination	92 (26)	97 (10)		.18
Language	76 (30)	78 (27)		.71
Socialization	51 (35)	50 (35)		.94

Abbreviations: CMV, conventional mechanical ventilation; OR, odds ratio.

late surfactant needed significantly less rehospitalization for pulmonary problems than infants in the control group after discharge (OR, 0.377 [95% CI, 0.158-0.898],  $P = .03$ ). We speculate that the absence of significant differences at extubation or 36 weeks' PMA may be caused by too-short time periods for adequate evaluation. In accordance with the National Institutes of Health recommendation that respiratory health care use and respiratory symptoms at 1 year of age are more meaningful indicators of respiratory morbidity than the 36 weeks' PMA evaluation,<sup>21,22</sup> our results at 1 year might better reflect

our infants' respiratory outcome. Of note, the clinical status of the infants at discharge suggests a difference in illness severity between the groups. Surfactant infants had significantly less necrotizing enterocolitis and earlier full enteral feeding; they needed slightly less postnatal steroids and were discharged about 1 week earlier than controls. The numbers are too small to reach statistical significance, but it suggests that surfactant-treated infants had a better clinical status after discharge. However, we cannot exclude unidentified confounding factors leading to the same evolution.

Tremblay et al<sup>28</sup> recalled that, owing to lung heterogeneity, mechanical ventilation is associated with alveolar distension in very premature infants, leading to severe lung injury. Mechanical ventilation prevents healing,<sup>18</sup> and extubation is indeed an issue in these vulnerable infants. Digeronimo et al<sup>20</sup> showed that mechanical ventilation could down-regulate surfactant protein expression. In a randomized trial by Keller et al,<sup>29</sup> 85 very premature infants were administered up to 5 doses of surfactant from 7 to 15 days post natal with iNO compared with iNO alone. They showed that low surfactant protein values increased after surfactant administration, with an improvement in the clinical status of the infants, but the effects waned after 1 day.<sup>29</sup> In a retrospective analysis of 126 infants, Katz et al<sup>30</sup> evaluated 25 infants who received 1 repeated course of surfactant therapy for respiratory failure after 6 days. They found that 70% of them had significant improvement in their lung disease up to 48 hours after instillation. Those results are consistent with our study. However, because of the advances in perinatal care, adding the requirement of at least 30% oxygen to invasive ventilation to prevent the inclusion of infants on ventilation for other reasons than pulmonary disease led to a selected subgroup of about 5% of the newborns presenting with prolonged pulmonary disease. In the study used for sample size calculation,<sup>27</sup> 16% of the infants had more than 14 days of ventilation and 75% developed BPD. Because all our infants had BPD or died at 36 weeks' PMA, we only observed a nonsignificant difference, in favor of surfactant, for severe BPD or death at 36 weeks' PMA (OR, 0.673 [95% CI, 0.308-1.474]).

More than 40% of infants in each group were treated for inflammation, giving rise to a suspicion of materno-fetal infection. Paananen et al<sup>31</sup> studied 128 very premature infants and found that infants with inflammation and high concentrations of inflammatory cytokines in cord blood were at high risk of BPD. Schneibel et al<sup>32</sup> examined the tracheal aspirates of 27 very low-birth-weight neonates and showed that high levels of inflammatory mediators increased the risk of developing BPD. In addition, Marshall et al<sup>33</sup> investigated chronic lung disease risk factors among 1224 very low-birth-weight infants. They showed that, among 423 infants who received more than 48 hours of ventilation, nosocomial infection was significantly associated with an increased risk of BPD.<sup>33</sup>

In our study, more than 90% of the infants presented with late-onset sepsis. This is consistent with the status of the highly vulnerable group of patients included in the study and the overall rate of late-onset sepsis, ranging from 14% to 24% in the participating centers for infants below 33 weeks' gestation. Gronck et al<sup>12</sup> demonstrated an association between pulmonary inflammation and increased microvascular permeability during BPD development, which is consistent with our study.

Two studies raised concern that poractant alfa might contribute to elevated CRP.<sup>34,35</sup> el Hanache et al<sup>34</sup> retrospectively studied 150 premature infants treated with or without surfactant, and mean CRP rose significantly in infants treated with poractant alfa. However, the groups were not comparable at baseline, and the authors did not report more infants with positive CRP, only a higher mean CRP in the treated group, which is not an appropriate indicator.<sup>34</sup> Kukkonen et al<sup>35</sup> found

that 45% of infants treated with poractant alfa vs 12% treated with Exosurf had CRP values above the threshold for risk of infection. However, some infants had documented infections, and no blood control had been obtained before instillation. Therefore, no conclusion could be drawn from that study. In our randomized study, the groups were not different either before or 48 hours after instillation. Therefore, a direct inflammatory effect of poractant alfa is highly unlikely.

We had hypothesized that iNO might be synergistic with surfactant. Vascular abnormalities associated with BPD may lead to pulmonary arterial hypertension.<sup>23</sup> We and others have shown that iNO may be used safely in neonates for prevention<sup>27</sup> or treatment of BPD.<sup>24,36</sup> Nitric oxide does not have any adverse effects on surfactant,<sup>37</sup> but evidence for iNO efficacy remains insufficient to recommend its use for BPD. However, it may be considered when respiratory distress is associated with pulmonary hypertension.<sup>23,29,36</sup> We found that when iNO was added to surfactant in cases of associated pulmonary hypertension, the median duration of respiratory support was 17 days shorter than when iNO was applied without surfactant. However, our study was not powered to answer that question. Other studies have shown that combined iNO and surfactant decreased morbidity at follow-up,<sup>38</sup> despite no significant benefit at 36 weeks' PMA. In our study, we did not find a significant effect of iNO on the respiratory outcome at 1 year postnatal age.

Our study had limitations. First, the extubation criteria were not strictly fulfilled for all infants. Practitioners sometimes judged the infants ready for extubation even though they did not meet the protocol criteria. This discrepancy may have been caused by the predefined study criteria that had been validated for acute situations but not for chronic respiratory disease.<sup>3</sup> Nevertheless, the groups were not significantly different in the number of extubation failures. Thus, this protocol violation was unlikely to have biased the results. Second, we had intended to restrain postnatal corticosteroid use to improve the evaluation of the effects of surfactant. Hydrocortisone was only allowed when infants exhibited corticotropic axis immaturity and short-term betamethasone treatment for extubation support only.<sup>10</sup> However, about 90% of the infants eventually received postnatal steroid throughout the neonatal period. This high rate of corticosteroid use may have blunted an effect of surfactant, despite the lack of difference in steroid use between the 2 groups. Finally, despite most confounding factors for respiratory morbidity, such as parents' education, family social status, or passive smoking, exposure was similar between the groups, although more infants were kept by a childminder or attended a daycare in the surfactant group. Because an increased incidence in respiratory infections and morbidity is associated with daycare attendance,<sup>39</sup> this discrepancy in favor of the control group may have blunted an effect of surfactant.

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## Conclusions

Late surfactant administration showed an acceptable safety profile and was associated with a better pulmonary outcome than controls at 1 year of age. Evaluation at 36 weeks' PMA or

discharge did not show a significant improvement, but because the infants involved in the study had a severe prolonged pulmonary disease at baseline, these times may have

been too early to appreciate a significant effect. However, we cannot exclude that other clinical factors may also be responsible for part of the observed differences.

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**Study concept and design:** Hascoët.

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