Surfactant therapy in late preterm infants: respiratory distress syndrome and beyond

Özge Sürmeli-Onay, Ayşe Korkmaz, Şule Yiğit, Murat Yurdakök
Division of Neonatology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Sürmeli-Onay Ö, Korkmaz A, Yiğit Ş, Yurdakök M. Surfactant therapy in late preterm infants: respiratory distress syndrome and beyond. Turk J Pediatr 2012; 54: 239-246.

A significant ratio of late preterm infants receives surfactant therapy (ST) for respiratory distress syndrome (RDS) and for other neonatal lung diseases characterized by surfactant inactivation or dysfunction. We aimed to investigate the clinical and therapeutic characteristics and outcomes of late preterm infants who received ST in the last 10 years in our neonatal intensive care unit. During the 10-year period, 77 late preterm infants received ST. The underlying lung diseases were RDS in 51 (66.2%), congenital pneumonia in 15 (19.5%), congenital diaphragmatic hernia in 4 (5.2%), pulmonary edema due to hydrops fetalis in 4 (5.2%), and acute respiratory distress syndrome (ARDS) in 3 (3.9%) infants. Pulmonary hypertension was a significant predictive factor for mortality. Although RDS was the main cause of respiratory failure in late preterm infants, other lung diseases leading to surfactant dysfunction were not rare; therefore, ST should be considered as a life-saving treatment.

Key words: late preterm infant, surfactant, respiratory distress.

Late preterm infants are especially at increased risk of respiratory distress syndrome (RDS) when compared with term infants[1-4]. However, in addition to RDS, other neonatal lung diseases characterized by inactivated or dysfunctional pulmonary surfactant can cause respiratory failure necessitating surfactant therapy (ST) in these infants. These include meconium aspiration syndrome (MAS), pneumonia, pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), bronchopulmonary dysplasia (BPD), and congenital diaphragmatic hernia (CDH)[5-7]. ST has been established as an effective and safe therapy for immaturity-related surfactant deficiency, and it reduces pulmonary air leaks and mortality. In very preterm infants with RDS, the principles of ST have been well defined and updated in many international guidelines[8,9]. However, in late preterm or term infants, principles and recommendations regarding ST for RDS or non-RDS lung diseases are not so clear, and implementation differs among centers. Before defining the principles of ST in late preterm infants, the clinical characteristics that lead to a need for ST should be identified in this population.

The objective of this retrospective study was to investigate and define the clinical and therapeutic characteristics of late preterm infants who received ST for severe respiratory failure in our neonatal intensive care unit (NICU) in the last 10 years.

Material and Methods

Study Design

We conducted a retrospective study including late preterm infants with gestational ages between $34^{0/7}$ and $36^{6/7}$ weeks, who had respiratory distress severe enough to be intubated and who received positive pressure ventilation (PPV) and ST in our tertiary care NICU at Hacettepe University, İhsan Dogramacı Children's Hospital, Ankara, Turkey, between January 1, 2001 and December 31, 2010. The hospital files and electronic medical records of the patients were evaluated. The study was approved by the Ethics Committee of the University.

Clinical Data

Maternal data included major chronic medical and obstetric diseases and prenatal steroid

therapy. In the family history, the presence of a sibling who had similar respiratory symptoms, signs or diagnoses was investigated. Neonatal data included gender, gestational age (according to last menstrual period), birth weight, intrauterine growth (based on growth curve of Fenton et al.[10]), mode of delivery, 5th minute Apgar score, presence of aggressive resuscitation at birth (bag and mask PPV, PPV through an endotracheal tube, chest compression, or drug administration), complete blood count and peripheral blood smear, blood and tracheal aspirate cultures, serum C-reactive protein (CRP) and procalcitonin levels on the first day of life or on the day of ST, arterial blood gas analysis before ST, chest X-ray findings before and after ST, the type of neonatal lung disease, the type, timing, dosing, and frequency of ST, complications, accompanying neonatal morbidities such as patent ductus arteriosus (PDA), pulmonary hypertension and neonatal sepsis (culture-proven), echocardiographic findings if available, durations of mechanical ventilation, supplemental oxygen, hospital stay, and rate of mortality. ST was defined as "early ST" if it was given in the first two hours of life and as "late ST" if it was given after the second hour of life. The indications for ST were the need of mechanical ventilation with a fractional inspired oxygen concentration (FiO_2) of >0.4, mean airway pressure (MAP) ≥7 cm H_2O, oxygenation index (OI) >15, and abnormal arterial blood gas analysis showing hypoxia (P_aO_2 <50 mmHg), hypercapnia (P_aCO_2 >50 mmHg) or acidosis (pH <7.2) combined with the radiological signs of RDS on the chest X-ray. OI was calculated by the formula: $OI = (MAP \times FiO_2 \times 100)/P_aO_2$. The response to ST was evaluated according to the same defined parameters. Chest X-rays of the patients were obtained from hospital files or from the hospital electronic Picture Archiving and Communication System (PACS) if available and re-evaluated by a senior neonatologist for the confirmation of the diagnoses.

Diagnostic criteria for various neonatal lung diseases were as follows: (1) RDS: The presence of clinical signs of respiratory distress, supplemental oxygen and/or PPV requirement, and typical chest X-ray findings with reticulogranular patterns, air bronchograms and ground glass appearance in the absence of all signs of suspected/proven infection, such as: a) history of maternal chorioamnionitis or maternal urinary tract infection, b) elevated or decreased leukocyte count (>25000/mm^3 or <5000/mm^3), or c) elevated serum CRP or procalcitonin level and positive blood or tracheal aspirate culture that was obtained on the first day of life[11]. (2) Congenital pneumonia: The presence of clinical signs of respiratory distress, supplemental oxygen and/or PPV requirement, extra-pulmonary clinical signs of sepsis beginning from birth, and typical chest X-ray findings in the *presence of* any suspected/proven infection such as: a) history of maternal chorioamnionitis or maternal urinary tract infection, b) elevated or decreased leukocyte count (>25000/mm^3 or <5000/mm^3), or c) elevated serum CRP or procalcitonin level and positive blood or tracheal aspirate culture that was obtained on the first day of life. (3) Transient tachypnea of the newborn (TTN): Mild-to-moderate respiratory distress occurring usually after elective cesarean section (CS) without labor and mainly characterized by tachypnea and need for supplemental oxygen or at most positive airway pressure with nasal continuous positive airway pressure (CPAP), and mild-to-moderate cardiomegaly, perihilar streaking and fluid-filled interlobar fissures on the chest X-ray, which usually resolve in 48-72 hours. (4) MAS: Respiratory distress in an infant born through meconium-stained amniotic fluid whose respiratory and radiological signs cannot be otherwise explained. (5) CDH: Respiratory distress accompanied by the presence of typical chest X-ray and/or abdominal ultrasonography findings: thoracal location of gastric/intestinal loops and/or other abdominal organs such as liver or spleen. (6) Pulmonary edema: Accumulation of fluid in the pulmonary interstitial tissue and/or pleural effusion leading to respiratory distress and typical radiological findings with interlobar fissure fluid accumulation and opacification of lung parenchyma, which usually develops due to hydrops fetalis or heart failure. (7) ARDS: Acute inflammation of the lung parenchyma leading to impaired gas exchange and hypoxic respiratory failure, which is caused by a catastrophic pulmonary or non-pulmonary event, such as asphyxia, shock, sepsis, or disseminated intravascular coagulation[12]. Echocardiography is a routine procedure in our NICU for the patients suffering from severe respiratory

failure. Pulmonary hypertension was defined as elevated right ventricular and pulmonary artery pressure leading to right-to-left ductal or foramen shunt detected by echocardiography.

Statistical Analysis

Statistical data were analyzed by using the Statistical Package for the Social Sciences (SPSS) 16.0 software on a personal computer. Continuous variables were compared by using two-tailed *t* test for parametrically distributed data or Mann-Whitney for non-parametrically distributed data. Categorical variables were analyzed by χ^2 test or Fisher's exact test. Relative risks (RR) of mortality with 95% confidence interval (CI) were calculated by univariate and multivariate logistic regression analysis. A p value of <0.05 was accepted as statistically significant.

Results

During the 10-year period, 2437 late preterm infants were born in our hospital, and among them, 77 infants (3.2%) received ST. Prenatal, natal and postnatal demographic characteristics of the infants are given in Table I.

None of the infants had primary lung disease diagnosed as TTN, MAS or pulmonary hemorrhage. Among 4 patients with CDH, 3 (75.0%) had prenatal diagnoses. In 2 infants, ARDS developed due to severe sepsis and multiorgan failure, while it was due to severe postnatal hypoxia in 1 infant with BPD.

In all infants, natural, animal-derived surfactant preparations were used. In 52 (67.5%) infants, beractant (Survanta ®, Abbott Laboratories, USA, 4 ml/kg) and in 25 (32.5%) infants, poractant alfa (Curosurf, Chiesi Pharmaceuticals, Italy, 2.5 ml/kg) were used. The second product has been available in our hospital's pharmacy for four years. All infants received ST after endotracheal intubation and with bolus administration in 1 or 2 divided doses.

In infants with RDS (n=51), 19 (37.3%) received ST in the first 2 hours of life, 14 (27.4%) between 2-6 hours of life and 18 (35.3%) after the 6th hour of life. In this group, 30 (58.8%) received only 1 dose, while 15 (29.4%) received 2 doses, and 6 (11.8%) received 3 doses of ST.

In infants with non-RDS lung disease (n=26), 8 (30.8%) received ST in the first 2 hours of

Table I. Prenatal, Natal and Postnatal Demographic Characteristics of All Late Preterm Infants Who Received ST (n=77)

Demographic characteristics	
Gestational age (wk)*	35.1±0.8 (34-36.5)
Birth weight (g)*	2476±466 (930-3540)
Gender (M/F), n (%)	49 (63.6)/28 (36.4)
Intrauterine growth restriction, n (%)	4 (5.2)
Cesarean section (CS), n (%) Urgent CS Elective After labor	64 (83.1) 42 (65.6) 13 (20.3) 9 (14.1)
Family history of a similar sibling, n (%)	12 (15.6)
Maternal diabetes, n (%)	6 (7.8)
Preeclampsia, n (%)	16 (20.8)
PPROM, n (%)	18 (23.4)
Chorioamnionitis, n (%)	13 (16.9)
Prenatal steroids, n (%)	12 (15.6)
Apgar score (5th minute)*	7.4±1.9 (3-10)
Aggressive resuscitation at birth, n (%)	43 (58.9)
Perinatal asphyxia, n (%)	14 (18.2)

* Mean±SD (range).
PPROM: Preterm premature rupture of membranes.

life, 4 (15.4%) in 2-6 hours of life and 14 (53.8%) after the 6th hour of life. Eighteen (69.2%) infants received only 1 dose, while 8 (30.8%) received 2 doses of ST.

Pulmonary air leak syndrome (pulmonary interstitial emphysema and/or pneumothorax) occurred in 4 (5.2%) infants before ST and in 8 (10.4%) infants after ST, for a total of 12 (15.6%) infants. Pulmonary hemorrhage occurred in 4 (5.2%) infants; 3 (75.0%) of them developed after ST in infants with RDS and were treated with a second dose of ST, while in 1 infant, it developed due to ARDS, multiple organ failure and disseminated intravascular coagulation. Clinical characteristics of all late preterm infants who received ST are given in Table II, and a comparison of the clinical characteristics of late preterm infants with RDS and with non-RDS lung disease is given in Table III.

The mortality rate in our study group was 24.7% (n=19). Mortality rates were 100% (4/4) in CDH, 33.3% (1/3) in ARDS, 25% (1/4) in pulmonary edema, 20% (3/15) in congenital pneumonia, and 19.6% (10/51) in RDS. In infants with accompanying pulmonary hypertension, the mortality rate was 42.3%. When the clinical characteristics of infants who

Table II. Clinical Characteristics of All Late Preterm Infants Who Received ST (n=77)

Clinical characteristics	
Lung diseases, n (%)	
RDS	51 (66.2)
Non-RDS	26 (33.8)
Congenital pneumonia	15 (19.5)
Congenital diaphragmatic hernia	4 (5.2)
Pulmonary edema (hydrops fetalis)	4 (5.2)
Acute respiratory distress syndrome	3 (3.9)
Arterial blood gas analysis before ST, n (%)	
Acidosis (pH <7.2)	29 (37.7)
Hypoxia (P_aO_2 <50 mmHg)	46 (59.7)
Hypercarbia (P_aCO_2 >50 mmHg)	40 (51.9)
Type of respiratory support before clinical deterioration and ST, n (%)	
O_2 with nasal cannula	7 (9.1)
nCPAP	41 (53.2)
Mechanical ventilation	29 (37.7)
(SIMV, PTV, HFOV)	
The timing of ST (hr)**	5 (0.5-77)
Early (≤2 hr), n (%)	27 (35.0)
Late (>2 hr), n (%)	50 (65.0)
Surfactant dose*	1.5±0.6 (1-3)
Accompanying diseases, n (%)	
Patent ductus arteriosus	35 (45.6)
Secondary pulmonary hypertension	26 (33.8)
Sepsis	15 (19.5)
Necrotizing enterocolitis	4 (5.2)
Bronchopulmonary dysplasia	3 (3.9)
Duration of mechanical ventilation (day)*	3.9±4.1(0.08-29.0)
Duration of oxygen support (day)*	6.9±5.3 (0.08-30.0)
Duration of hospitalization (day)*	10.8±7.8 (0.08-43.0)
Mortality, n (%)	19 (24.7)

*Mean±SD (range), **Median (range).

ST: Surfactant therapy. RDS: Respiratory distress syndrome. nCPAP: Nasal continuous positive airway pressure. SIMV: Synchronized intermittent mandatory ventilation. PTV: Patient triggered ventilation. HFOV: High frequency oscillatory ventilation.

Table III. Comparison of Clinical Characteristics of Late Preterm Infants with RDS and with Non-RDS Lung Disease

	Infants with RDS (n=51)	Infants with non-RDS lung disease (n=26)	p
Gestational age (wk)*	35.0±0.8 (34-36.5)	35.2±0.8 (34-36.5)	0.267
Birth weight (g)*	2352±436 (930-3500)	2719±431 (2000-3540)	0.001
IUGR, n (%)	4 (7.8)	-	0.150
Resuscitation at birth, n (%)	31 (60.0)	12 (46.1)	0.100
The timing of ST (hr)**	4.0 (1-43)	7.8 (0.5-77)	0.030
Multiple doses of surfactant, n (%)	21 (41.1)	8 (30.7)	0.373
Arterial blood gas analysis before ST, n (%)			
Acidosis (pH <7.2)	15 (29.4)	14 (53.8)	0.036
Hypoxia (P_aO_2 <50 mmHg)	28 (54.9)	18 (69.2)	0.225
Hypercapnia (P_aCO_2 >50 mmHg)	24 (47.0)	16 (61.5)	0.229
Pulmonary hypertension, n (%)	12 (23.5)	14 (53.8)	0.008
Duration of mechanical ventilation (day)*	3.9±4.5 (0.25-29.0)	3.9±3.5 (0.08-12.0)	0.926
Duration of oxygen support (day) *	7.2±5.5 (0.25-30.0)	5.9±4.8 (0.08-15.0)	0.337
Duration of hospitalization (day)*	11.1±6.8 (0.25-31.0)	10.2±9.7 (0.08-43.0)	0.650
Mortality, n (%)	10 (19.6)	9 (34.6)	0.149

* Mean±SD (range), ** Median (range).

RDS: Respiratory distress syndrome. IUGR: Intrauterine growth restriction. ST: Surfactant therapy.

survived and who died after ST were compared, the incidences of resuscitation at birth, acidosis, hypoxia, hypercapnia in arterial blood gas analysis before ST, CDH, and pulmonary hypertension were higher in infants who died (p values: 0.025, 0.000, 0.012, 0.029, 0.003, and 0.010, respectively). In addition, due to early death, duration of oxygen support and hospitalization were significantly shorter in infants who died (p values: 0.016 and 0.000, respectively). In the evaluation of risk factors for mortality, CDH, pulmonary hypertension and ARDS had the highest RRs for mortality (RR: 18.4, 3.9 and 1.6, respectively) (Table IV).

Discussion

Since the first application of ST in 1980, many systematic reviews of randomized, controlled trials have led to the development of international guidelines for optimal ST strategy. However, these guidelines have mostly focused on the treatment of RDS in very preterm infants and included less evidence-based recommendations for late preterm or term infants with respiratory failure requiring ST[8,9]. Late preterm infants have a considerable risk of developing RDS; however, the clinical presentation and the response to ST may be different than that seen in very preterm infants. Apart from RDS, the risk of other neonatal lung diseases is higher in late preterm infants than in term infants, and in severe cases, ST may be necessary to improve oxygenation and ventilation, as it has been proven to decrease secondary surfactant inactivation or dysfunction[5-7]. However, before developing evidence-based guidelines for ST in late preterm infants, the clinical characteristics of the patients should be investigated in detail. Therefore, in this study, we tried to define the clinical and therapeutic characteristics of late preterm infants who received ST for severe respiratory failure in our NICU in the last 10 years.

In our study, the main lung disease leading to respiratory failure and requirement of ST in late preterm infants was RDS. The most important clinical characteristics of these infants were high (83.1%) CS and low antenatal steroid therapy rates. A significant

number of late preterm infants would develop RDS if delivered electively before the onset of labor. Labor tends to protect against RDS as it decreases lung liquid secretion and increases surfactant[13]. In our study, only 22 (28.6%) infants (including vaginal deliveries) could be delivered after the onset of the labor. The rest of the infants (55, 71.4%) were delivered by urgent and elective CS. This was mostly due to high-risk pregnancies. In high-risk late preterm pregnancies, elective delivery should be indicated after balancing the risks of continuing. In our study, this high rate of CS without labor should have contributed to the dominance of RDS in late preterm infants with respiratory failure.

Antenatal steroid therapy decreases the risk of RDS (RR: 0.66, 95%CI: 0.59-0.73), and it is recommended in all pregnancies with threatened preterm labor before 35 weeks' gestation. However, according to available evidence, antenatal steroids in late preterm pregnancies do not offer a statistically significant protection from RDS[14,15]. In our study, only a minority (15.6%) of the patients received antenatal steroids, as it was not a policy of the Perinatology Unit of our hospital to give antenatal steroids after the 34th week of gestation. However, the high incidence of RDS in our study group could not be explained by this low rate of antenatal steroid therapy. Antenatal steroid therapy beyond the 35th week of pregnancy requires substantial evidence and cannot be recommended routinely.

In our study, the majority (53.2%) of the infants had respiratory support by nasal CPAP from admission to NICU until clinical deterioration. Nasal CPAP is used as a substitute for mechanical ventilation to provide respiratory support for many infants with RDS and some can be managed on CPAP without receiving ST. The earlier CPAP is applied, the greater the chance of avoiding mechanical ventilation[8]. Late preterm infants have more physical respiratory capacity and greater lung surfactant pool size when compared with very preterm infants, and this enables them to keep their respiratory stability longer under nasal CPAP in the early hours of life. During this prolonged "honeymoon period", neonatologists may try "avoiding" ST as long as the infant stays clinically and radiologically stable. We think that the "late" median timing of ST (7 hours) in our study indicates this reality. The approach of treating spontaneously breathing infants with evolving RDS with surfactant and then extubating to nasal CPAP has become incorporated in practice[16]. However, none of the infants in our study group could be immediately extubated after ST. In our study, only 37.3% of the late preterm infants with RDS received ST in the first 2 hours of life, while 35.3% of them received ST after the 6th hour of life. This situation was more prominent in late preterm infants with non-RDS lung disease, and the majority (53.8%) of them received ST after the 6th hour of life. However, in most of the infants in this specific group of patients, ST was not the primary therapeutic option. Guidelines have stated that preterm infants with established RDS should be treated as soon as possible, preferably within 2 hours after birth[8,9]. However, in a survey about ST in European countries, even in very preterm infants, the proportion of infants receiving the first dose of ST after 2 hours was 28%. In this survey, in 88% of the NICUs, the indicator for rescue ST was FiO_2 (>0.40), and in many NICUs, the FiO_2 was combined with other variables, such as MAP (36%), signs of RDS on the

Table IV. Risk Factors for Mortality in Late Preterm Infants Who Received ST

Risk factors	RR (95% CI)
Congenital diaphragmatic hernia	18.4 (2.00-169)
Pulmonary hypertension	3.9 (1.33-11.6)
Acute respiratory distress syndrome	1.6 (0.13-18.1)
Pulmonary edema	1.0 (0.10-10.4)
Congenital pneumonia	0.7 (0.18-2.87)
Respiratory distress syndrome	0.5 (0.15-1.33)

ST: Surfactant therapy. RR: Relative risk. CI: Confidence interval.

chest radiograph (15%), the product of FiO_2 and MAP (12%), and OI (9%)[17]. In our unit, especially in very preterm infants, we establish RDS based on the clinical findings of respiratory distress (physical signs and symptoms and need for supplemental oxygen and/or positive pressure) and with radiological findings since arterial blood gas analysis usually does not show marked abnormalities in the first hours of life. However, in our study, significant ratios of late preterm infants with RDS had acidosis, hypoxia and hypercapnia in arterial blood gas analysis just before ST. We thought this result could be a reflection of both disease severity and delayed ST in late preterm infants.

Surfactant inactivation and secondary dysfunction may occur with conditions such as neonatal pneumonia, pulmonary edema and hemorrhage and ARDS[5,9]. As a common pathophysiologic pathway, alveolar inflammation results in disturbed vascular permeability, with leakage of proteins and inflammatory agents into the alveoli, and these proteins disturb surface tension-lowering properties of the surfactant. In our study, 33.8% of late preterm infants were found to receive ST for severe non-RDS lung disease. Although no data from randomized controlled trials exist, ST that counterbalances surfactant inactivation seems to improve oxygenation and lung function in many infants with pneumonia and ARDS[5,18-22]. In our study, the median timing of ST in infants with non-RDS lung disease was significantly later than in infants with RDS. However, in most of these infants, ST was not the primary therapeutic option.

The mortality risk in late preterm infants who received ST seemed to depend on the severity of the underlying lung diseases, as expected, and the existence of pulmonary hypertension also contributed greatly to mortality. Early echocardiographic detection and prompt treatment of pulmonary hypertension in preterm infants with severe respiratory failure could increase the chance of survival.

This study has some limitations resulting from its retrospective structure. First, patient inclusion was based on the need for ST and not on the need for invasive mechanical ventilation. This means that not all mechanically ventilated infants were included in the patient cohort, and the results do not reflect all the patients with respiratory failure. In addition, we are unable to compare the study group with controls who were treated without ST. Second, as the study period is long, ST policies and the actual practices could have changed towards early ST.

In conclusion, ST may be of significant benefit in late preterm infants with serious respiratory failure secondary to a number of insults. However, the best preparation, technique, and optimal timing and dose of administration are not so clear in this group. Additional randomized, controlled studies and evidence-based guidelines are needed for optimal ST in late preterm infants.

REFERENCES

1. Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 2006; 118: 1207-1214.
2. Engle WA, Tomashek KM, Wallman C, and the Committee on Fetus and Newborn. Late preterm infants: a population at risk. Pediatrics 2007; 120: 1390-1401.
3. Teune MJ, Bakhuizen S, Bannerman CG, et al. A systematic review of severe morbidity in infants born late preterm. Am J Obstet Gynecol 2011; 205: 374. e1-9.
4. Consortium on Safe Labor, Hibbard JU, Wilkins I, Sun L, et al. Respiratory morbidity in late preterm births. JAMA 2010; 304: 419-425.
5. Finer NN. Surfactant use for neonatal lung injury: beyond respiratory distress syndrome. Pediatr Resp Rev 2004; 5 (Suppl): S289-S297.
6. Been JV, Zimmermann LJ. What's new in surfactant? A clinical view on recent developments in neonatology and paediatrics. Eur J Pediatr 2007; 166: 889-899.
7. Sweet DG, Halliday HL. The use of surfactants in 2009. Arch Dis Child Educ Pract Ed 2009; 94: 78-83.
8. Sweet DG, Carnielli V, Greisen VG, et al. European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants-2010 Update. Neonatology 2010; 97: 402–417.
9. Engle WA, Committee on Fetus and Newborn. Surfactant replacement therapy for respiratory distress in the preterm and term neonate. Pediatrics 2008; 121: 419-432.
10. Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr 2003; 16: 3-13.
11. Hamvas A. Pathophysiology and management of respiratory distress syndrome. In: Martin RJ, Fanaroff AA, Walsh MC (eds). Fanaroff and Martin's Neonatal-Perinatal Medicine (9th ed). Vol. 1. St. Louis: Elsevier Mosby; 2011: 1106-1116.

12. Abu-Shaweesh JM. Respiratory disorders in preterm and term infants. In: Martin RJ, Fanaroff AA, Walsh MC (eds). Fanaroff and Martin's Neonatal-Perinatal Medicine (9th ed). Vol. 2. St. Louis: Elsevier Mosby; 2011: 1141-1170.
13. Hallman M, Peltoniemi O, Kari MA. Enhancing functional maturity before preterm birth. Neonatology 2010; 97: 373-378.
14. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006; 3: CD004454.
15. Porto AM, Coutinho IC, Correia JB, Amorim MM. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ DOI 2011; 342: d1696.
16. Soll RF. Current trials in the treatment of respiratory failure in preterm infants. Neonatology 2009; 95: 368-372.
17. Van Kaam AH, De Jaegere AP, Borensztajin D, Rimensberger PC. Surfactant replacement therapy in preterm infants: a European survey. Neonatology 2011; 100: 71-77.
18. Donn SM, Dalton J. Surfactant replacement therapy in the neonate: beyond respiratory distress syndrome. Respir Care 2009; 54: 1203-1208.
19. Rüdiger M, Friedrich W, Rüstow B, Schmalisch G, Wauer R. Disturbed surface properties in preterm infants with pneumonia. Biol Neonate 2001; 79: 73-78.
20. Ramanathan R. Surfactant therapy in preterm infants with respiratory distress syndrome and in near-term or term newborns with acute RDS. J Perinatol 2006; 26: S51-S56.
21. Wirbelauer J, Speer CP. The role of surfactant treatment in preterm infants and term newborns with acute respiratory distress syndrome. J Perinatol 2009; 29 (Suppl): S18-22.
22. Nkadi PO, Merritt TA, Pillers DA. An overview of pulmonary surfactant in the neonate: genetics, metabolism and the role of surfactant in health and disease. Mol Genet Metab 2009; 97: 95-101.