

Respiratory management of extremely low birth weight infants: survey of neonatal specialists

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Background: To investigate strategies used for the management of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) in extremely low birth weight (ELBW) infants.

Methods: A survey of neonatal specialists working in US academic institutions with fellowship training programs.

Results: Eighty percent (72/89) of the identified academic institutions had at least one physician who responded to the survey. Among respondents, 85% (171/201) agreed or strongly agreed to use continuous positive airway pressure (CPAP) initially for the management of RDS, and the majority agreed or strongly agreed to use a fraction of inspired oxygen (FiO_2) ≥ 0.4 and a mean airway pressure (MAP) ≥ 10 cm H_2O as a criteria for surfactant therapy; and 73% (146/200) sometimes or always used caffeine to prevent BPD. Only 25% (50/202) sometimes or almost always used steroids to prevent or treat BPD. Identified indications to use steroids were 3 or more extubation failures or inability to extubate beyond 8 weeks of age.

Conclusions: Variability in treatment strategies of ELBW is common among neonatal specialists. However, the majority of the respondents agreed or strongly agreed to use early CPAP for the management of RDS, consider a $\text{FiO}_2 \geq 0.4$ and a $\text{MAP} \geq 10$ cm H_2O as criteria for surfactant therapy, and sometimes or almost always used caffeine to prevent BPD. Steroids continue to have a role in the management of BPD in infants who are difficult to extubate.

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Introduction

Preterm birth affects approximately 10% of live births worldwide and it is responsible for an estimated cost of US\$51 600 per infant annually.^[1] Preterm infants often develop respiratory distress syndrome (RDS) as a result of their immature lungs. Therefore, artificial oxygenation and ventilation are needed, which often leads to long term morbidities such as bronchopulmonary dysplasia (BPD) and frequent rehospitalizations especially during the first two years of life.^[2,3] Volutrauma, atelectrauma, and biotrauma have been incriminated as potential risk factors for the development of BPD in mechanically ventilated premature infants;^[4] therefore, a less invasive mode of ventilation, such as nasal continuous positive airway pressure (CPAP), might be beneficial.^[5] However, in early studies prophylactic nasal CPAP did not reduce the incidence of BPD,^[6] but prophylactic use of surfactant reduced the incidence of air leak, interstitial emphysema, and mortality in preterm infants less than 30-32 weeks gestation.^[7] Recently, early CPAP to reduce BPD has regained interest.^[8-11] Decreasing oxygen supplementation to reduce lung injury is another strategy that has regained interest, however it has neither resulted in a lower incidence of BPD among survivors nor a lower incidence of BPD or death at 36 weeks post menstrual age.^[12] Short-term treatment with corticosteroid suppresses pulmonary inflammation and improves pulmonary function in ventilator-dependent premature infants with BPD.^[13] However, steroid is associated with short-term morbidities such as intestinal perforation, hypertension, hypertrophic cardiomyopathy, failure to thrive, and long-term morbidities such as cerebral palsy,^[14-17] although there was no difference in death or BPD at 36 weeks postmenstrual age between infants treated with early low dose of dexamethasone and their controls in one study.^[18] When inhaled steroid was used as an alternative strategy to prevent and treat BPD, there was no beneficial effect.^[19,20] Infants with BPD have elements of fluid retention and reactive airways; however diuretics,^[21,22] and bronchodilators,^[23] do not prevent the development of BPD. The use of caffeine has recently emerged as a new strategy. Use of caffeine for apnea of prematurity was recently shown to be

associated with a reduction in BPD.^[24,25]

With the recent advances, and expanding literature regarding the management of RDS and BPD, we sought to investigate, in this survey, the current therapeutic strategies for the management of RDS and BPD in ELBW infants among neonatal specialists working in academic institutions with fellowship training programs in the United States.

Methods

A survey was conducted to assess the opinion of neonatal specialists regarding management of RDS and prevention and management of BPD. The response of the neonatal specialists was measured with a 5-point Likert scale questionnaire (ranging from strongly disagree to strongly agree).

The survey consisted of 13 questions (Supplementary). Respondents were allowed to choose more than one answer to most of the questions. A series of questions addressed the initial management of RDS with invasive versus non invasive mechanical ventilation and use of surfactant. Another series of questions addressed fraction of inspired oxygen (FiO₂) and mean airway pressure (MAP) criteria to guide surfactant therapy. Two questions addressed opinions regarding the use of caffeine to prevent BPD, and three questions addressed opinions regarding the use steroids to prevent and or treat BPD. The last questions of the survey inquired about the physicians' demographics. Physicians were asked about their age, gender, if they were board certified, the number of years of practice, and about the size of their NICU.

The studied population consisted of neonatal specialists who worked in hospitals with a neonatology fellowship program (an academic institution) in the U.S. Hospitals with a neonatology fellowship program were found on the fellowship and residency electronic interactive database (FREIDA) website that is available on line at <https://freida.ama-assn.org> which is part of the American medical association (AMA) website. The names and available e-mails of the neonatal specialists were obtained from the websites of different hospitals with fellowship programs.

The electronic mail survey was conducted using Survey Monkey that is available at www.surveymonkey.com. The emails had a unique link to the survey. The survey was initiated on March 20, 2012 and ended on May 8, 2012.

The survey was approved by the institution review board (IRB) at Metro Health Medical Center.

Statistical analysis

The data were expressed as mean±standard deviation, median and interquartile range, and as percentages. A chi square test was used for comparison. For statistical significance, a *P* value <0.05 was used. To investigate the degree of agreement amongst physicians belonging

to the same institution, a kappa agreement coefficient was calculated for each unit that has two or more respondents. For units with more than two respondents, a kappa agreement coefficient was calculated between two randomly chosen respondents. To be able to conduct a kappa coefficient calculation, the answers to the survey were converted into two categories, disagreement or neutral as one category and agreement as another category. Therefore we converted the 5 point Likert scale into two categories (one category as strongly disagree/disagree/neutral, and the other category as agree/strongly agree). We also converted the 5 point response of never, rarely, every once in a while, sometimes and almost always to two categories (one category as never/rarely/every once in a while, and the other category as sometimes/almost always).

Results

A total of 89 academic institutions were identified, and 80% (72/89) of the identified institutions had at least 1 physician who responded to the survey. A total of 247 physicians responded to the survey.

Assessment of the initial management of RDS in ELBW

In response to the question regarding the initial management of RDS, majority of the respondents, 85% (171/201) agreed or strongly agreed to use CPAP at delivery followed by intubation and surfactant therapy only if there was an increase in FiO₂ requirement, CO₂ retention or hemodynamic instability; 40% (75/187) agreed or strongly agreed to use the INSURE approach (intubation followed by surfactant and extubation within one hour); and 49% (94/191) agreed or strongly agreed to use the approach of intubation at birth plus surfactant therapy and extubation once the infant was hemodynamically stable and on a low ventilator's setting.

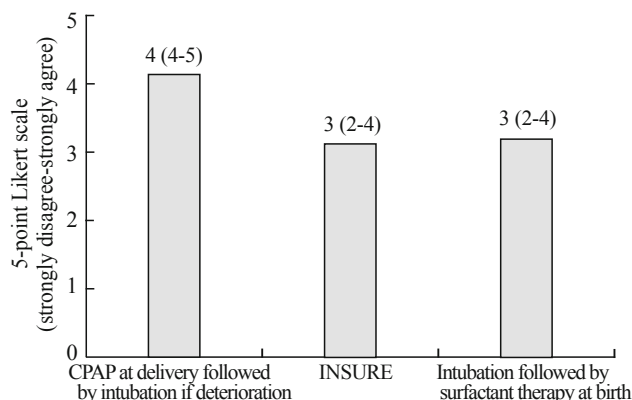


Fig. 1. Agreement (on a 5-point-Likert scale) regarding the initial management of respiratory distress syndrome in extremely low birth weight infants among neonatal specialists. Data are expressed as median (interquartile range). CPAP: continuous positive airway pressure; INSURE: intubation-surfactant-extubation.

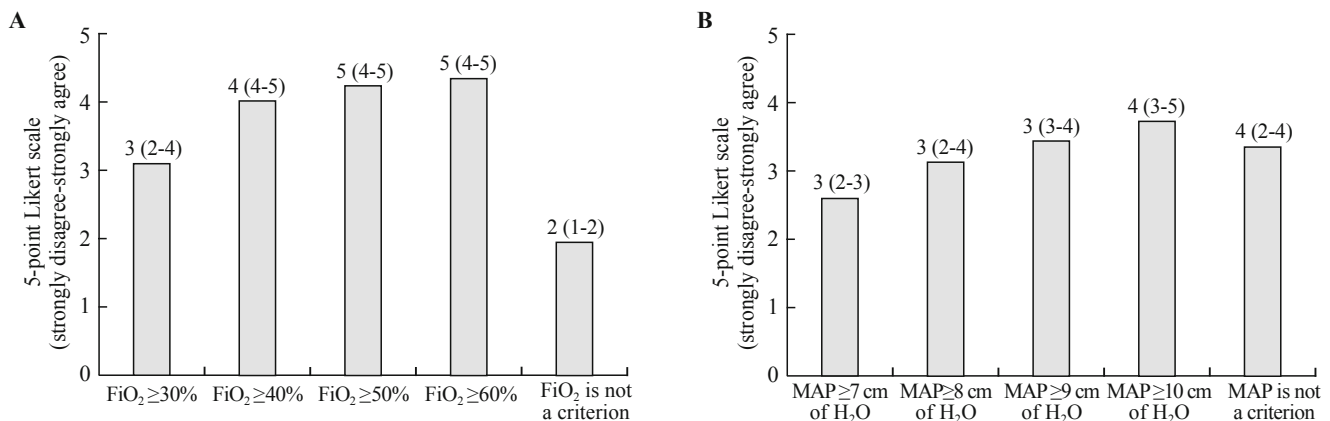


Fig. 2. Agreement (on a 5-point-Likert scale) regarding (A) fraction of inhaled oxygen (FiO₂), and (B) mean airway pressure (MAP) as criteria for surfactant therapy in respiratory distress syndrome in extremely low birth weight infants among neonatal specialists. Data are expressed as median (interquartile range).

Among the respondents, the uses of CPAP at delivery scored the highest on the 5 point Likert scale, followed by intubation at birth/extubation later and INSURE (Fig. 1).

Among the respondents, 45% (83/186) agreed or strongly agreed to use FiO₂ ≥ 30%, 81% (155/190) agreed or strongly agreed to use a FiO₂ ≥ 40%, 85% (152/178) agreed or strongly agreed to use FiO₂ ≥ 50%, and 89% (158/178) agreed or strongly agreed to use a FiO₂ ≥ 60% as a criterion to administer surfactant. And 13% (22/162) did not use FiO₂ as a criterion to administer surfactant; 17% (24/141) agreed or strongly agreed to use a MAP ≥ 7 cm of H₂O, 36% (51/142) agreed or strongly agreed to use a MAP ≥ 8 cm of H₂O, 48% (68/141) agreed or strongly agreed to use a MAP ≥ 9 cm of H₂O, and 63% (90/143) agreed or strongly agreed to use a MAP ≥ 10 cm of H₂O as a criterion to administer surfactant; 58% (101/173) did not use MAP as a criterion to administer surfactant. Among the respondents, the use of a FiO₂ ≥ 60% and a MAP ≥ 10 cm of H₂O scored the highest on the 5 point Likert scale (Fig. 2).

Assessment of physicians' use of caffeine to prevent BPD

In response to the question addressing the usage of early caffeine for prevention of BPD, 73% (146/200) of the respondents sometimes or almost always used caffeine and 23% (47/200) never or rarely used caffeine. When physicians were asked about the reasons for not using caffeine to prevent BPD, 39% (56/142) agreed or strongly agreed that lack of consensus among colleagues was the reason, and 37% (55/147) agreed or strongly agreed that lack of evidence based literature was the reason. Only 15% (21/140) reported that caffeine related side effect was the reason for not using caffeine. On a 5 point Likert scale, lack of evidence based literature, and lack of consensus among colleagues scored the highest as a reason for not using caffeine.

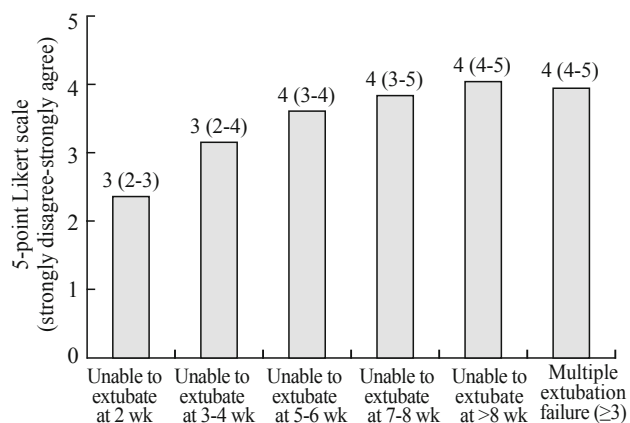


Fig. 3. Agreement (on a 5-point-Likert scale) regarding the indications to use steroids to prevent or treat bronchopulmonary dysplasia in extremely low birth weight infants among neonatal specialists. Data are expressed as median (interquartile range).

Assessment of physicians' use of steroids to prevent or treat BPD

In response to the question addressing the use of steroids to prevent or treat BPD, 48% (98/202) never or rarely used steroids, 27% (55/202) used every once in a while steroids, and only 25% (50/202) of the physicians sometimes or almost-always used steroids to prevent or treat BPD. Among responders, 74.5% (137/184) reported intravenous dexamethasone, 40% (73/184) reported intravenous hydrocortisone, 31% (58/184) reported inhaled steroids, and 25% (46/184) reported oral steroids as steroids that they would use.

In response to the question addressing the indications to use steroids, 81% (141/173) agreed or strongly agreed to use steroids if they were unable to extubate an infant at >8 weeks of age, and 79% (138/175) agreed or strongly agreed to use steroids if an infant had failed extubation ≥ 3 times. On a 5 point Likert scale, unable to extubate at >8 weeks of age and multiple extubation failure scored the highest; of interest, 50% of the respondents

Table. Physicians' demographics

Age (y)	47±10
Gender (% male)	108/199 (54%)
Board certification (%)	175/201 (87%)
Years of practice (y)*	15 (6-25)
NICU beds*	54 (40-80)

*: Data expressed as median (interquartile range). NICU: neonatal intensive care unit.

reported that they would use steroids if unable to extubate a patient at 5 to 6 weeks (Fig. 3).

Assessment of physicians' agreements belonging to the same institution

To investigate the degree of agreement amongst physicians belonging to the same institution, a kappa agreement coefficient was calculated for each unit that had two or more respondents. Our findings showed that the median (range) kappa coefficient between two respondents from each unit was 0.38 (-0.67 to 0.86), with 72% (37/51) of the kappa agreement coefficients being fair or better (Kappa >0.20). Our findings indicated that the majority of the units had a fair agreement amongst their respondents.

Assessment of physicians' demographics and intensive care units' sizes

The physicians' demographics and NICU sizes are summarized in Table.

To determine the relationship between the professional experiences of the physicians and the size of the units and the given answers, we divided the respondents based on the number of years of practice and the size of their units. There were no differences in the rating of questions between physicians who had 10 years or more versus less than 10 years of practice. When we divided the respondents based on the size of their units, there were also no differences in the rating of the questions between physicians who practice in units with 40 beds or less or greater than 40 beds, except for the use of caffeine in the first few days. Physicians practicing in smaller units use more caffeine to prevent BPD than the ones practicing in larger units [5 (4-5) vs. 5 (2-5); $P=0.04$ on a scale of 1 to 5 with 1 being never, and 5 being almost always].

Discussion

The current survey has shown that neonatal specialists from the majority of US academic institutions agreed and strongly agreed to use early CPAP for the management of RDS, and $FiO_2 \geq 0.4$ and a MAP ≥ 10 cm of H_2O as criteria for surfactant therapy. The majority also sometimes or almost always uses caffeine

to prevent BPD, and consider lack of consensus among colleagues and lack of evidence based literature as barriers for not using routinely such therapy. Steroids remain a therapeutic agent that is limited to infants who remain ventilation dependent for more than 8 weeks and who had failed extubation three or more times during their NICU stay.

The increase use of CPAP amongst neonatal specialists noted in this survey was in accordance with the favorable outcome seen in recent studies. For instance, in one study, there was a trend, although not statistically significant at 36 weeks post menstrual age, toward a lower rate of BPD or death in 25 to 28 week premature infants treated with early CPAP versus early intubation.^[9] In another study, there was also a trend toward a lower risk, although insignificant for BPD or death in infants treated with CPAP.^[8] In this study, infants treated with CPAP had fewer days of mechanical ventilation and less frequently required post-natal steroids than infants who were intubated and received surfactant within one hour of birth.^[8] In a randomized trial comparing different approaches to the initial management of RDS, 48% of infants treated with nasal CPAP were managed without intubation or mechanical ventilation, and 54% were managed without surfactant therapy. Infants treated with nasal CPAP also had a trend toward a lower rate of BPD than infants who received prophylactic surfactant at birth followed by a period of mechanical ventilation but this difference was not statistically significant.^[10] In another trial, where infants 25 to 28 weeks gestational age, were randomized to prophylactic surfactant versus nasal CPAP, there was no difference in BPD or death between the two groups.^[26] A recent meta-analysis has shown that early stabilization with nasal CPAP and selective surfactant administration to infants requiring mechanical ventilation decrease the risk of BPD and mortality.^[11]

Historically, caffeine has been used to treat apnea of prematurity and prevention of extubation failure, but evidence has shown that caffeine can also prevent the development of BPD.^[24,25] In a randomized controlled study comparing caffeine used for prevention of apnea of prematurity to placebo, caffeine reduced the duration of mechanical ventilation and the rate of BPD,^[24] and improved survival without neurodevelopmental disability at 18 to 21 months of age in very low birth weight (VLBW) infants.^[27] When the same cohort of patients was followed up to the age of 5 years, caffeine did not have an ongoing effect on survival without disability at 5 years of age.^[28] In our survey, the majority of respondents use caffeine to prevent BPD; and consider lack of consensus among colleagues and lack of evidence based literature as barriers to use routinely early caffeine to prevent BPD. Our results reflect the literature. The landmark study showing that caffeine reduces the

incidence of BPD was not originally designed to study BPD, but to study the short-term and long-term benefits and risks of methyxanthines as a treatment for apnea of prematurity in VLBW infants in preparation for extubation.

Steroids mainly dexamethasone has been used to facilitate extubation and decrease the incidence of BPD; however it has been associated with significant side effects such as growth failure and neurodevelopmental disabilities.^[14,15,17,29] The effect of postnatal corticosteroids on the combined outcome of death or cerebral palsy varies with the level of risk of developing chronic lung disease.^[30] For instance, when infants are stratified based on their risk of developing chronic lung disease; steroids increase the incidence of death or cerebral palsy in infants at low risk for developing chronic lung disease, and decrease the incidence of cerebral palsy and developmental delay in infants at high risk for developing chronic lung disease.^[30] Few studies have shown lack of neurodevelopmental disabilities related to dexamethasone.^[31-33] In a study evaluating the incidence of death or neurodevelopmental disability at 18-22 months of age in ELBW infants who were enrolled in a trial of early dexamethasone treatment to prevent death of BPD in ELBW, the risk of death or neurodevelopmental disability and rate of poor growth were high but similar between the dexamethasone and the control group.^[18] Different studies have used different dosage regimens that were initiated at different times and used for different periods. Few studies have shown an improvement in survival without BPD in infants treated with hydrocortisone,^[34,35] while other studies have shown equivocal results.^[36,37] Few long term follow up studies have shown no difference in neurodevelopmental outcome in infants treated with hydrocortisone.^[38,39] The results of the current survey were consistent with the literature. Neonatal specialists use steroids in high risk infants who are unable to be liberated from mechanical ventilation and who have failed extubation multiple times. Our survey has limitations. Many aspects of the respiratory management of premature infants have not been incorporated in our survey. Future surveys are needed to address the different options of the initial respiratory support at early postnatal life, such as use of nasal CPAP versus mandatory mechanical ventilation, and the different criteria used to assess CPAP failure or readiness for extubation following mandatory mechanical ventilation. Future surveys are also necessary to address the type of surfactant used and the number of doses used, since it would affect the clinical outcome and frequency of intra-tracheal intubation and mechanical ventilation. Definition of co-morbidities and complications of aggressive ventilation is another topic that needs to be addressed also in future surveys.

One of the limitations of our study is that we did not differentiate between "old" and "new" BPD in our questionnaire. In contrast to the old BPD,^[3] the most important risk factor of the new BPD is immaturity which has an impact on the treatment strategies.^[40] Unfortunately we did not ask in our survey about the percentage of ELBW infants who are at risk for the new BPD in each unit.

Variability in treatment strategies of ELBW is common among neonatal specialists working in academic institutions in the US. However, the majority of the respondents agree or strongly agree to use early CPAP for the management of RDS, consider a $FiO_2 \geq 0.4$ and a $MAP \geq 10$ as criteria for surfactant therapy, and sometimes or almost always use caffeine to prevent BPD. Steroids continue to have a role in the management of BPD in infants who are difficult to extubate or who have multiple extubation failures.

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Competing interest: None.

Contributors: PS was involved in literature search, study design, data collection, and manuscript preparation. MMJ was involved in study design, analysis of data, manuscript preparation, and review of manuscript.

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