

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Neonatal Respiratory Distress Syndrome: Things to Consider and Ways to Manage

Bitá Najafian and Mohammad Hossein Khosravi

Abstract

Involving more commonly the premature (less than 37 weeks of gestational age) infants, neonatal respiratory distress syndrome is an important clinical syndrome responsible for a high rate of mortality and morbidity. The main progress in respiratory distress syndrome (RDS) management is attributable to prescription of surfactant for fastening pulmonary maturation. Respiratory protection, such as mechanical ventilation and nasal continuous positive airway pressure, and surfactant are building blocks of disease treatment. In this chapter, we are going to have a rapid review on epidemiology, diagnosis and treatments of RDS.

Keywords: respiratory distress syndrome, epidemiology, treatment, etiology

1. Introduction

Involving more commonly the premature (less than 37 weeks of gestational age) infants, neonatal respiratory distress syndrome (NRDS), is an important clinical syndrome responsible for a high rate of mortality and morbidity. Reports have shown that about 12% of infants are preterm in the United States, while the prevalence ranges between 6 and 11% in European countries [1, 2]. NRDS is a leading cause of admission to neonatal intensive care unit (NICU) with estimated incidence rate of 7.8% and mortality rate of 50% in premature infants [3–5]. The severity usually increases during the first 48 hours of birth [6]. The prevalence and the severity of NRDS decrease as the gestational age increases [7–9].

A variety of factors including cesarean section, prematurity, maternal diabetes and genetic variations have been reported to play role in pathogenesis of NRDS [10, 11]. Damage to type II alveolar cells is another considered mechanism for NRDS. Diffuse alveolar capillary injury results in progressive increased permeability as well as pulmonary and alveolar edema, which make the type II alveolar cells nonfunctional. All these processes lead into severe hypoxemia due to abnormal ventilation/perfusion ratio [12, 13].

NRDS is a result of pulmonary immaturity mostly caused by insufficient levels of surfactant [14, 15]. The condition is developed through hypoventilation, hypoxemia and respiratory acidosis [14, 15].

2. Diagnosis

Early diagnosis is of a high importance due to available management methods [15, 16]. A combination of clinical signs and different modalities such as chest radiographies and laboratory tests are needed for diagnosing NRDS [14].

2.1 Clinical signs and symptoms

There are a wide range of clinical signs from nasal flaring and cyanosis to substernal and intercostal retraction, tachypnea and grunting [16]. A risk assessment tool called “Clinical Risk Index for Babies” (CRIB) is used to estimate the need for admission of infants in NICU [17]. Different factors such as gestational age, birth weight and base excess during the first 12 hours of life, fraction of inspired oxygen and presence of congenital malformations are considered in this assessment (Table 1).

2.2 Laboratory tests

Arterial oxygen pressure (PaO_2) is a marker for diagnosis of NRDS. PaO_2 less than 50 mmHg with cyanosis in room air or need for supplementary oxygen for maintaining O_2 level above 50 mmHg are indicators for NRDS [14]. Metabolic and respiratory acidosis are measured through a blood sample.

Gastric aspirate shake test (GAST) is another laboratory measure with reported sensitivity of 100% and specificity of 92% for diagnosis of NRDS [18]. GAST identifies presence or lack of surfactant in the gastric fluid aspirates [19].

Recently published studies have mentioned a new factor for early detection and prediction of NRDS in premature infants. Transforming growth factor $\beta 1$ (TGF- $\beta 1$) is a cytokine, which has the responsibility for regulating and differentiating different cell lines [20, 21]. These studies have marked the role of TGF- $\beta 1$ in development of various acute and chronic lung injuries and concluded that this factor can be used as a diagnostic and prognostic one [22]. The same role has been considered for interleukin-6, which is a glycoprotein secreted mostly from T cells and mononuclear macrophages causing inflammatory reactions [23, 24].

2.3 Chest radiographs

Previous studies have reported a remarkable diagnostic value for chest radiographs [25]. Features such as reduced lung expansions, air bronchograms and dilated bronchioles can be seen in NRDS [15]. In addition to diagnostic use, chest radiographs have another application to confirm endotracheal tube position. Premature infants receive continuous positive airways pressure (CPAP) for augmenting oxygenation in addition to simplifying intra-tracheal administration of surfactants [14]. The precise adverse effects of radiation have not been yet determined; however, some efforts are being done to find an alternative method for chest radiography [26–28].

2.4 Ultrasound

Previously, lung ultrasound (LUS) was not used for infant chest imaging due to interference of air levels. This modality has its own potential adverse effects including thermal and mechanical tissue damage [27, 29]. Recently, lung ultrasound

Factor	Score
Birth weight (gr)	
>1350	0
851–1350	1
701–850	4
≤700	7
Gestation (week)	
>24	0
≤24	1
Congenital malformations*	
None	0
Not actually life-threatening	1
Actually life threatening	3
Maximum base excess in first 12 h (nmol/L)	
>−7	0
−7 to −9.9	1
−10 to 14.9	2
≤−15	3
Minimum appropriate FIO₂ in first 12 h	
≤40%	0
41–60%	2
61–90%	3
91–100%	4
Maximum appropriate FIO₂ in first 12 h	
<40%	0
41–80%	1
81–90%	3
91–100%	5

*Excluding inevitably lethal malformations.

Table 1.
 CRIB score.

has been widely used as an accurate diagnostic tool according to published clinical studies [4, 7, 16, 30–34]. Lack of normal air-filled levels and presence of fluid level is a diagnostic clue for NRDS.

A meta-analysis of six studies comparing LUS to chest x-ray for diagnosing NRDS reported a high diagnostic sensitivity (97%) and specificity (91%) for LUS [35]. They have also reported that transthoracic technique is superior to transabdominal approach for diagnosing NRDS.

On the other hand, some researchers believe that lung ultrasound can be helpful only as a complementary diagnostic tool rather than a diagnostic method [36]. They have mentioned in a letter-to-editor that only chest radiographs and CT scan can be reliable for diagnosing neonatal respiratory distress syndrome.

3. Management

3.1 Mechanical ventilation

Mechanical ventilation is the most commonly applied treatment method for NRDS in clinical practice [37–39]; although mechanical ventilation and continuous oxygen therapy are independent risk factors for development of NRDS to bronchopulmonary dysplasia (BPD) [40, 41]. Noninvasive respiratory support methods such as nasal intermittent positive pressure ventilation (NIPPV), high flow nasal cannula (HFNC) and nasal continuous positive airway pressure (NCPAP) are being used more commonly as the initial ways of management, which may decrease need for intubation in up to 50% of infants [42–44]. On the other hand, the failure of noninvasive respiratory support results in delayed administration of surfactant and prolonged mechanical ventilation. Also, this may be associated with higher incidence of bronchopulmonary dysplasia (BPD), major morbidity or even death [45, 46]. So, it seems that a combination of early respiratory support and prescription of surfactant may improve the treatment results. Administration of surfactant during NCPAP, less-invasive (LISA) and minimal-invasive surfactant administration (MISA) have shown convenient results in management of NRDS [47].

Recently published studies have introduced the aerosolized surfactant as a safe and efficient method of drug delivery [47]. It has been claimed that vibrating and ultrasonic mesh nebulizers have the ability to make surfactant aerosols without interfering with biochemical composition of medication [48–50]. It has been reported that aerosolized surfactant can be delivered using nasal cannula in noninvasive respiratory support [51–55].

3.2 Surfactant

Pathophysiology of NRDS (inadequate production of pulmonary surfactant in premature infants) was first discovered by Avery and Mead in 1959, which resulted in changing the former name of the disease “hyaline membrane disease” [56]. This was a window to surfactant replacement therapy.

Lung surfactant is a mixture of phospholipids and some specific proteins secreted by epithelium of alveoli, which lines the small airways. It primarily reduces the surface tension of liquid presented in terminal air spaces [57]. Lack of pulmonary surfactant is the main result of NRDS; so, prescription of pulmonary surfactant can augment respiratory function and pulmonary compliance resulting in elevated oxyhemoglobin level [58–61]. Lack of surfactant results in a chain of problems from collapsed lung, tissue damage, reduced oxygenation and impaired function of alveolar epithelium, resulting in altered production of surfactant [62]. Fujiwara et al. reported the very first application of surfactant-TA in preterm infants with respiratory distress syndrome in 1980 [63].

There are different kinds of animal-derived as well as first- and second-generation synthetic surfactants [64]. As a natural surfactant, Curosurf is taken from pig lung, which is consisted of 41–48% lecithin and 51–58% of hydrophobin and other phospholipids. Liquid gel layer has the responsibility to absorb the Curosurf after its administration to the lungs [65]. Also, this medication has some adverse effects including respiratory discomforts and bucking [66, 67]. Administration of surfactant involves frequent endotracheal intubation (INSURE: INTubation-SURfactant-Extubation) and mechanical ventilation, which is associated with inevitable comorbidities [68, 69].

Recently, in addition to the common INSURE method, a new method has come up and is getting more popular. This method is called a less-invasive surfactant administration (LISA), which has been reported to be more effective in prevention of bronchopulmonary dysplasia and reducing preterm infants' mortality. In this method, surfactant is delivered through a thin catheter while the infant is under continuous positive airway pressure (CPAP) treatment. However, more large-scale randomized clinical trials are needed to make this method accepted as a routine in clinical practice [70].

3.3 Ambroxol hydrochloride

As an active metabolite of bromhexine, ambrotherxol or ambroxol hydrochloride has a mucolytic activity. A wide range of advantages have been reported for ambroxol hydrochloride from reducing production of hydrogen peroxide, stimulating secretion of pulmonary surfactant, reducing lung damage and alleviating the inflammatory response to relieving pulmonary edema and interstitial exudation. As a low-cost and high-efficacy medication, ambroxol hydrochloride is being used in clinical treatment of NRDS [71, 72]. There are reports about satisfactory results of combination of high-dose ambroxol hydrochloride and surfactant [37].

3.3.1 Nitric oxide (NO)

About 2% of all live births are involved with respiratory failure, which is responsible for more than one-third of neonatal mortalities [73]. Inhaled NO (iNO) reduces pulmonary vascular resistance, edema, lung inflammation and hypoxia, which makes the respiratory difficulties easier for infants [74]. Previous researches have also shown that iNO improves pulmonary angiogenesis and protects pulmonary system against infections with no remarkable adverse effects on growth or neurodevelopmental status [75].

Neonatal respiratory distress syndrome (NRDS), as a result of inadequate surfactant production, leads to atelectasis and ventilation-perfusion (V/Q) mismatching. Beside notable response to exogenous surfactant, it has been reported that iNO transiently improves oxygenation in infants with NRDS. Previous studies have shown that iNO therapy alone reduces mortality rate in preterm infants [76]. iNO improves V/Q matching, selectively dilates the pulmonary vasculature and decreases pulmonary inflammatory response. The most convenient advantage of iNO is reducing incidence of chronic lung disease in premature infants with RDS [77]. In other researches, premature infants with suboptimal response to exogenous surfactant showed beneficial clinical responses to combination therapy with iNO [78].

4. Prognosis

Neonatal respiratory distress syndrome is one of the major causes of premature death; however, a notable part of the survivors may develop bronchopulmonary dysplasia and suffer from chronic pulmonary diseases [67]. Prognosis of RDS is highly related to the treatment and management methods, which have been being developed since their discovery. The efficacy of each method for prognosis is under investigation. Also, gestational age has an important role in determining the prognosis, where late preterm infants usually have a better prognosis in comparison with early preterm infants.

5. Conclusion

According to high prevalence and clinical importance of NRDS, seeking new methods of diagnosis and treatment is of a high importance. Available knowledge approves efficacy of surfactant as the stumbling block of medical NRDS management; however, various methods of drug delivery are under development. It seems that a combination of respiratory support and surfactant is the ideal method of management.

Conflict of interest

There are no conflict of interests in terms of the present chapter.

Author details

Bitra Najafian^{1*} and Mohammad Hossein Khosravi²

1 Department of Pediatrics, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

2 International Otorhinolaryngology Research Association (IORA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

*Address all correspondence to: dr.najafian@yahoo.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Glass HC, Costarino AT, Stayer SA, Brett C, Cladis F, Davis PJ. Outcomes for extremely premature infants. *Anesthesia and Analgesia*. 2015;**120**(6):1337
- [2] Zeitlin J, Szamotulska K, Drewniak N, Mohangoo A, Chalmers J, Sakkeus L, et al. Preterm birth time trends in Europe: A study of 19 countries. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2013;**120**(11):1356-1365
- [3] El HE-DGM, Hany S, Mahmoud MK, Ali AM. Lung ultrasonography in evaluation of neonatal respiratory distress syndrome. *The Egyptian Journal of Radiology and Nuclear Medicine*. 2015;**46**(2):469-474
- [4] Liu J, Cao H-Y, Wang H-W, Kong X-Y. The role of lung ultrasound in diagnosis of respiratory distress syndrome in newborn infants. *Iranian Journal of Pediatrics*. 2014;**24**(2):147
- [5] Zhou B, Zhai J-F, Wu J-B, Jin B, Zhang Y-Y. Different ventilation modes combined with ambroxol in the treatment of respiratory distress syndrome in premature infants. *Experimental and Therapeutic Medicine*. 2017;**13**(2):629-633
- [6] British Association of Perinatal Medicine. *Guidelines for Good Practice in the Management of Neonatal Respiratory Distress Syndrome*. London: BAPM; 1999
- [7] Lovrenski J. Lung ultrasonography of pulmonary complications in preterm infants with respiratory distress syndrome. *Upsala Journal of Medical Sciences*. 2012;**117**(1):10-17
- [8] Euro-Peristat. *European perinatal health report health and care of pregnant women and babies in Europe* in 2010. Available from: www.premup.org/. [2013, Accessed: 27 March 2016]
- [9] Khosravi MH, Najafian B, Bigham P, Torkaman M, Shohrati M. Comparison of intravenous dexamethasone and budesonide nebulizer in the treatment of infantile respiratory distress syndrome; A randomized clinical trial. *Razavi International Journal of Medicine*; **13**(23)
- [10] Liszewski MC, Stanescu AL, Phillips GS, Lee EY. Respiratory distress in neonates: Underlying causes and current imaging assessment. *Radiologic Clinics*. 2017;**55**(4):629-644
- [11] Tochie JN, Choukem S-P, Langmia RN, Barla E, Koki-Ndombo P. Neonatal respiratory distress in a reference neonatal unit in Cameroon: An analysis of prevalence, predictors, etiologies and outcomes. *Pan African Medical Journal*. 2016;**24**(1)
- [12] Tabit CE, Chung WB, Hamburg NM, Vita JA. Endothelial dysfunction in diabetes mellitus: Molecular mechanisms and clinical implications. *Reviews in Endocrine & Metabolic Disorders*. 2010;**11**(1):61-74
- [13] Speer CP. Neonatal respiratory distress syndrome: An inflammatory disease? *Neonatology*. 2011;**99**(4):316-319
- [14] Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants-2013 update. *Neonatology*. 2013;**103**(4):353-368
- [15] Agrons GA, Courtney SE, Stocker JT, Markowitz RI. Lung disease in premature neonates: Radiologic-pathologic correlation. *Radiographics*. 2005;**25**(4):1047-1073

- [16] Grappone L, Messina F. Hyaline membrane disease or respiratory distress syndrome? A new approach for an old disease. *Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)*. 2014;**3**(2):e030263
- [17] Cockburn F, Cooke R, Gamsu H, Greenough A, Hopkins A, Mcintosh N, et al. The CRIB (clinical risk index for babies) score. *The Lancet*. 1993;**342**(8865):193-198
- [18] NooriShadkam M, Lookzadeh MH, Taghizadeh M, Golzar A, NooriShadkam Z. Diagnostic value of gastric shake test for hyaline membrane disease in preterm infant. *Iranian Journal of Reproductive Medicine*. 2014;**12**(7):487
- [19] Ahuja CK, Saxena AK, Sodhi KS, Kumar P, Khandelwal N. Role of transabdominal ultrasound of lung bases and follow-up in premature neonates with respiratory distress soon after birth. *The Indian Journal of Radiology and Imaging*. 2012;**22**(4):279
- [20] Gaede KI, Amicosante M, Schürmann M, Fireman E, Saltini C, Müller-Quernheim J. Function associated transforming growth factor- β gene polymorphism in chronic beryllium disease. *Journal of Molecular Medicine*. 2005;**83**(5):397-405
- [21] Kinnula V. Focus on antioxidant enzymes and antioxidant strategies in smoking related airway diseases. *Thorax*. 2005;**60**(8):693-700
- [22] Chen F, Huang F, Zhan F. Correlation between serum transforming growth factor β 1, interleukin-6 and neonatal respiratory distress syndrome. *Experimental and Therapeutic Medicine*. 2019;**18**(1):671-677
- [23] Iannuzzi MC, Rybicki BA. Genetics of sarcoidosis: Candidate genes and genome scans. *Proceedings of the American Thoracic Society*. 2007;**4**(1):108-116
- [24] Rincon M, Irvin CG. Role of IL-6 in asthma and other inflammatory pulmonary diseases. *International Journal of Biological Sciences*. 2012;**8**(9):1281
- [25] Vergine M, Copetti R, Brusa G, Cattarossi L. Lung ultrasound accuracy in respiratory distress syndrome and transient tachypnea of the newborn. *Neonatology*. 2014;**106**(2):87-93
- [26] Harbron RW. Cancer risks from low dose exposure to ionising radiation—is the linear no-threshold model still relevant? *Radiography*. 2012;**18**(1):28-33
- [27] Lichtenstein DA, Mauriat P. Lung ultrasound in the critically ill neonate. *Current Pediatric Reviews*. 2012;**8**(3):217-223
- [28] Pereda MA, Chavez MA, Hooper-Miele CC, Gilman RH, Steinhoff MC, Ellington LE, et al. Lung ultrasound for the diagnosis of pneumonia in children: A meta-analysis. *Pediatrics*. 2015;**135**(4):714-722
- [29] Sande RK, Kiserud T. Ultrasound safety, power and image quality: What do we know? *Fetal and Maternal Medicine Review*. 2013;**24**(4):260-276
- [30] Raimondi F, Migliaro F, Sodano A, Ferrara T, Lama S, Vallone G, et al. Use of neonatal chest ultrasound to predict noninvasive ventilation failure. *Pediatrics*. 2014;**134**(4):e1089-e1e94
- [31] Bober K, Swietliński J. Diagnostic utility of ultrasonography for respiratory distress syndrome in neonates. *Medical Science Monitor*. 2006;**12**(10):CR440-CR446
- [32] Federici M, Federici P, Feleppa F, Gizzi C, Agostino R, Bellelli A, et al. Pulmonary ultrasonography in the follow-up of respiratory distress

- syndrome on preterm newborns. Reduction of X-ray exposure. *Journal of Ultrasound*. 2011;**14**(2):78-83
- [33] Sawires HK, Ghany EAA, Hussein NF, Seif HM. Use of lung ultrasound in detection of complications of respiratory distress syndrome. *Ultrasound in Medicine & Biology*. 2015;**41**(9):2319-2325
- [34] Pang H, Zhang B, Shi J, Zang J, Qiu L. Diagnostic value of lung ultrasound in evaluating the severity of neonatal respiratory distress syndrome. *European Journal of Radiology*. 2019;**116**:186-191
- [35] Hiles M, Culpan A-M, Watts C, Munyombwe T, Wolstenhulme S. Neonatal respiratory distress syndrome: Chest X-ray or lung ultrasound? A systematic review. *Ultrasound*. 2017;**25**(2):80-91
- [36] Quarato CMI, Verrotti dPV, Sperandeo M. Transthoracic ultrasound in neonatal respiratory distress syndrome (NRDS): Complementary diagnostic tool. *European Journal of Radiology*. 2019;**120**:108664
- [37] Xiang J, Wang P. Efficacy of pulmonary surfactant combined with high-dose ambroxol hydrochloride in the treatment of neonatal respiratory distress syndrome. *Experimental and Therapeutic Medicine*. 2019;**18**(1):654-658
- [38] Najafian B, Esmaili B, Khosravi MH. Comparison of fentanyl and midazolam for the sedation of infants under mechanical ventilation; a randomized clinical trial. *Hospital Practices and Research*. 2017;**2**(3):63-67
- [39] Najafian B, Eyvazloo H, Khosravi MH. Effects of different doses of fentanyl on the sedation of infants under mechanical ventilation; A randomized clinical trial. *Hospital Practices and Research*. 2017;**2**(4):109-112
- [40] Lassi ZS, Middleton PF, Crowther C, Bhutta ZA. Interventions to improve neonatal health and later survival: An overview of systematic reviews. *eBioMedicine*. 2015;**2**(8):985-1000
- [41] Khosravi MH, Najafian B, Ansari-Benam I, Torkaman M. Comparing the efficacy of NCPAP and NIPPV in infants with RDS after extubation; A randomized clinical trial. *Razavi International Journal Medicine*; **13**(26)
- [42] Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet J-M, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. *The New England Journal of Medicine*. 2008;**358**(7):700-708
- [43] Bancalari E, Claure N. The evidence for non-invasive ventilation in the preterm infant. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2013;**98**(2):F98-F102
- [44] Kugelman A, Riskin A, Said W, Shoris I, Mor F, Bader D. A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS. *Pediatric Pulmonology*. 2015;**50**(6):576-583
- [45] Miall L, Wallis S. The management of respiratory distress in the moderately preterm newborn infant. *Archives of Disease in Childhood-Education and Practice*. 2011;**96**(4):128-135
- [46] Dargaville PA, Gerber A, Johansson S, De Paoli AG, Kamlin COF, Orsini F, et al. Incidence and outcome of CPAP failure in preterm infants. *Pediatrics*. 2016;**138**(1):e20153985
- [47] Sood BG, Cortez J, Kolli M, Sharma A, Delaney-Black V, Chen X. Aerosolized surfactant in neonatal respiratory distress syndrome: Phase

I study. *Early Human Development*. 2019;**134**:19-25

[48] Schermuly R, Schmehl T, Gunther A, Grimminger F, Seeger W, Walmrath D. Ultrasonic nebulization for efficient delivery of surfactant in a model of acute lung injury: Impact on gas exchange. *American Journal of Respiratory and Critical Care Medicine*. 1997;**156**(2):445-453

[49] Ellyett K, Broadbent R, Fawcett E, Campbell A. Surfactant aerosol treatment of respiratory distress syndrome in the spontaneously breathing premature rabbit. *Pediatric Research*. 1996;**39**(6):953

[50] Marks L, Notter R, Oberdorster G, McBride J. Ultrasonic and jet aerosolization of phospholipids and the effects on surface activity. *Pediatric Research*. 1983;**17**(9):742

[51] Bhashyam AR, Wolf MT, Marcinkowski AL, Saville A, Thomas K, Carcillo JA, et al. Aerosol delivery through nasal cannulas: An in vitro study. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. 2008;**21**(2):181-188

[52] Sunbul FS, Fink JB, Harwood R, Sheard MM, Zimmerman RD, Ari A. Comparison of HFNC, bubble CPAP and SiPAP on aerosol delivery in neonates: An in-vitro study. *Pediatric Pulmonology*. 2015;**50**(11):1099-1106

[53] DiBlasi RM. Clinical controversies in aerosol therapy for infants and children. *Respiratory Care*. 2015;**60**(6):894-916

[54] Ari A. Aerosol drug delivery through high flow nasal cannula. *Current Pharmaceutical Biotechnology*. 2017;**18**(11):877-882

[55] Al-Subu AM, Hagen S, Eldridge M, Boriosi J. Aerosol therapy through high flow nasal cannula in pediatric patients.

Expert Review of Respiratory Medicine. 2017;**11**(12):945-953

[56] Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *AMA Journal of Diseases of Children*. 1959;**97**(5_PART_I):517-523

[57] Johansson J, Curstedt T. Synthetic surfactants with SP-B and SP-C analogues to enable worldwide treatment of neonatal respiratory distress syndrome and other lung diseases. *Journal of Internal Medicine*. 2019;**285**(2):165-186

[58] Fan Y-Z, Wen Z-L. Efficacy of different dosages of ambroxol hydrochloride in the prevention of neonatal respiratory distress syndrome. *Chinese Journal of Contemporary Pediatrics*. 2009;**11**(9):771-772

[59] Wu X, Li S, Zhang J, Zhang Y, Han L, Deng Q, et al. Meta-analysis of high doses of ambroxol treatment for acute lung injury/acute respiratory distress syndrome based on randomized controlled trials. *The Journal of Clinical Pharmacology*. 2014;**54**(11):1199-1206

[60] Najafian B, Karimi-Sari H, Khosravi MH, Nikjoo N, Amin S, Shohrati M. Comparison of efficacy and safety of two available natural surfactants in Iran, Curosurf and Survanta in treatment of neonatal respiratory distress syndrome: A randomized clinical trial. *Contemporary Clinical Trials Communications*. 2016;**3**:55-59

[61] Najafian B, Khosravi MH, Setayesh F, Shohrati M. Comparing the effect of Inhaler N-acetyl cysteine and intravenous dexamethasone on respiratory distress syndrome in premature infants: A randomized clinical trial. *Thrita*. 2017;**6**(1)

[62] Sardesai S, Biniwale M, Wertheimer F, Garingo A,

Ramanathan R. Evolution of surfactant therapy for respiratory distress syndrome: Past, present, and future. *Pediatric Research*. 2017;**81**(1-2):240

[63] Fujiwara T, Chida S, Watabe Y, Maeta H, Morita T, Abe T. Artificial surfactant therapy in hyaline-membrane disease. *The Lancet*. 1980;**315**(8159):55-59

[64] Jeon GW. Surfactant preparations for preterm infants with respiratory distress syndrome: Past, present, and future. *Korean Journal of Pediatrics*. 2019;**62**(5):155

[65] K Ketko A, M Donn S. Surfactant-associated proteins: Structure, function and clinical implications. *Current Pediatric Reviews*. 2014;**10**(2):162-167

[66] Gortner L, Schüller SS, Herting E. Review demonstrates that less invasive surfactant administration in preterm neonates leads to fewer complications. *Acta Paediatrica*. 2018;**107**(5):736-743

[67] Zhang C, Zhu X. Clinical effects of pulmonary surfactant in combination with nasal continuous positive airway pressure therapy on neonatal respiratory distress syndrome. *Pakistan Journal of Medical Sciences*. 2017;**33**(3):621

[68] van Bel F, de Winter PJ, Wijnands HB, van de Bor M, Egberts J. Cerebral and aortic blood flow velocity patterns in preterm infants receiving prophylactic surfactant treatment. *Acta Paediatrica*. 1992;**81**(6-7):504-510

[69] Durrmeyer X, Danan C. Neonatal intubation. In: Rimensberger PC, editor. *Pediatric and Neonatal Mechanical Ventilation*. Berlin Heidelberg: Springer-Verlag; 2015

[70] Lista G, Bresesti I, Fabbri L. Is less invasive surfactant administration necessary or “only” helpful or just

a fashion? *American Journal of Perinatology*. 2018;**35**(06):530-533

[71] Baranwal AK, Murthy AS, Singhi SC. High-dose oral ambroxol for early treatment of pulmonary acute respiratory distress syndrome: An exploratory, randomized, controlled pilot trial. *Journal of Tropical Pediatrics*. 2015;**61**(5):339-350

[72] Elsayed HF, Elkhaiouby MI, Elsharkawey SM, Elnemr MA. Evaluation of the role of postnatal ambroxol in the prevention and treatment of respiratory distress syndrome in preterm neonates. *Sultan Qaboos University Medical Journal*. 2006;**6**(2):41

[73] Steinhorn RH. Neonatal pulmonary hypertension. *Pediatric Critical Care Medicine*. 2010;**11**(2 Suppl):S79

[74] Ghanta S, Leeman KT, Christou H. An update on pharmacologic approaches to bronchopulmonary dysplasia. In: *Seminars in Perinatology*. WB Saunders; 1 Apr 2013;**37**(2):115-123

[75] Akter F, Coghlan G, de Mel A. Nitric oxide in paediatric respiratory disorders: Novel interventions to address associated vascular phenomena? *Therapeutic Advances in Cardiovascular Disease*. 2016;**10**(4):256-270

[76] Dzierba AL, Abel EE, Buckley MS, Lat I. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2014;**34**(3):279-290

[77] Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *The New England Journal of Medicine*. 2003;**349**(22):2099-2107

[78] Uy IP, Pryhuber GS, Chess PR, Notter RH. Combined-modality therapy with inhaled nitric oxide and exogenous surfactant in term infants with acute respiratory failure. *Pediatric Critical Care Medicine*. 2000;1(2):107-110

IntechOpen

IntechOpen