

New Invasive and Non-Invasive Ventilation Strategies for RDS Treatment of Preterm Babies

Citation for published version (APA):

Salvo, V. (2018). *New Invasive and Non-Invasive Ventilation Strategies for RDS Treatment of Preterm Babies*. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20180912vs>

Document status and date:

Published: 01/01/2018

DOI:

[10.26481/dis.20180912vs](https://doi.org/10.26481/dis.20180912vs)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Valorization

Relevance

Preterm labor is a common complication of pregnancies because of its consequences, prematurity, is a public health problem worldwide. Every year, 15 million babies are born prematurely (more than 60% of preterm births occur in Africa and South Asia, 500.000 in Europe) [1,2]. Since the early 1980s, the rate of prematurity is increasing in industrialized countries. This evolution can mostly be attributed to a) a better measurement, b) increase of maternal age and underlying maternal health problems such as diabetes and high blood pressure, c) greater use of infertility treatments leading to increased rates of multiple pregnancies, and d) changes in obstetric practices such as more caesarean births before term [1,3,4].

Prematurity is the leading cause of child death, responsible for 35% of the world's 3.1 million deaths a year, the second most common cause of deaths, under-5 years of age, after pneumonia [5].

The survival chances of preterm babies vary dramatically around the world: more than 90% of extremely preterm babies (less than 28 weeks) born in low-income countries die within the first few days of life, yet less than 10% of extremely preterm babies die in high-income settings [2].

Over the last four decades, survival rates for preterm infants have greatly improved, although these infants remain at risk of developing a broad range of short/long-term complications, and in later life they are also at risk of lung dysfunction, motor and sensory impairment, learning difficulties and behavioral problems [4].

Most of the costs related to preterm birth include acute neonatal intensive care, ongoing long-term health care needs and the requirement for special education services [1]. Preterm birth-related costs added up to \$26.2 billion (\$16.9 billion for medical and health care cost for the baby) in the United States in 2005; and the first-year medical costs for preterm infants (\$32,325) were on average roughly ten times higher than the costs for term ones (\$3,325) and vary inversely with birth-weight and gestational age (GA) [1]. The cost of neonatal intensive care unit (NICU) hospitalizations for the very low birth-weight (VLBW) infants (<1500 g) ranks them among the most expensive of all patients. These costs are roughly \$13.4 billion per year, accounting for 30% of newborn health care costs in the US [6,7]. Overall, these numbers indicate that preterm birth can be considered as a serious global health policy problem if we think that the survival of preterm infants and the incidence of associated chronic diseases is constantly increasing [1,9].

In industrialized countries, the problems are related to the very high costs of managing ELBW infants in terms of expensive drugs, human and technological resources. Conversely, in the low- or middle-income countries, the critical problem of prematurity is represented by the high mortality rate, so also the World Health Organization (WHO) has implemented since 2012 an investment plan to improve the survival, at least of the infants >30-32 weeks, requiring minimal and sustainable care [1].

Despite progresses in perinatal medicine, Respiratory Distress Syndrome (RDS) and its long-term complications such as BPD remain the most important causes of morbidity and mortality of VLBW infants [10,11]. Indeed, premature birth and the VILI due to MV remain the major risk factors for the development of BPD in the newborn. Several studies showed that the high costs of support for extremely preterm infants are parallel to their requirements for MV and the presence or not of BPD [12]. Thus, by definition, infants who develop BPD require more costly resources (eg, oxygen, continuous positive airway pressure, MV), especially for infants with BW <750 g and for the multiple readmissions due to respiratory conditions [7,13]. Moreover, RDS and BPD, impair lung function in later life, resulting in airway hyper-reactivity, fewer alveoli with reduction of the surface area for gas exchange, predisposing to the development of chronic respiratory disease in adulthood, such as asthma, chronic obstructive pulmonary disease (COPD) and hyperinflation [14]. The cost of the first 2 years of life of a preterm baby with BPD and no other major prematurity-related complications ranged between 45,049.81 € and 118,760.43 €, in Spain, depending on BW and GA. If the baby required home oxygen therapy or developed pulmonary hypertension, this cost could add up to 181,742.43 € [13].

The development of new therapies and preventive strategies to decrease the incidence of BPD and other morbidities associated with prematurity should be a priority [13]. For these reasons, in recent years, the efforts of scientific and technological research have focused on trying to identify which ventilation strategy was the best in order to limit the VILI and BPD. In this context, the aim of this thesis was to evaluate which ventilation techniques, invasive or non-invasive, were more effective to reduce the need of MV. The goal was to avoid BPD and VILI, and therefore the costs related to the use of MV in terms of device and equipment used, analgesia, central intravenous lines, parenteral nutrition, time of hospitalization, etc. [15-17].

In the present thesis, we investigated the effectiveness of invasive and non-invasive respiratory support strategies as first intention in the RDS treatment. In particular, we showed that early HFOV in VLBW infants who did not receive corticosteroid prophylaxis allowed to reduce: a) the days of MV and NIV, b) the doses of surfactant, and c) the length of hospitalization in NICU. The findings are of relevance in terms of reducing costs related to preterm assistance.

Secondly, in the thesis, we investigated the best NIV strategy as first intention for RDS treatment throughout three studies among BiLevel-CPAP, (BiPAP), Nasal Synchronized Intermittent Positive Pressure Ventilation (N-SIPPV) and N-CPAP. The results suggest that BiPAP and N-SIPPV are both equally effective and superior to N-CPAP.

Given the premise on the incidence of prematurity worldwide and on the costs related to it, this thesis evidences the effectiveness of new ventilation techniques, reducing the need of MV and the costs. Anyway, the limitation of a small sample size, in our series, does not allow to draw any conclusions on long-term respiratory outcome such as BPD. Further investigations in wider population are needed to empower results reported by a recent meta-analysis [18-20].

Target groups

The present thesis also offers several interesting aspects for the parents of preterm infants. In particular, the adoption of non-invasive respiratory support, without pharmacological sedation, the improvement in VLBW infants care, the empowerment of the dyad mother-newborn provided evidence of a great impact on the families, reducing parental stress, anxiety and uncertainty [1,21]. The psychosocial and emotional impact on the family, such as psychological distress and maternal depression, mainly depends on the severity of the infant's health condition [21]. The so-called "gentle treatment" during the NIV support in which no sedation, early mother milk feeding (when possible) and bonding (kangaroo care) are promoted, surely represent an important issue. Conversely, the invasive ventilation, with neurological sedation, without the possibility of a contact with the newborn, represents a stress factor with a higher negative impact on the mother's psyche. The advantages, in terms of the reduction of the stress and of the psychological impairment, would be even more important if the long-term complications (neurological and respiratory chronic disease) could be reduced.

Moreover, in VLBW infants, requiring MV support and whose mother did not receive antenatal prophylaxis with steroids, HFOV as first intention seems to be more effective than other invasive ventilation strategies. These encouraging results open the way to a more extensive use of HFOV in the RDS treatment of VLBW infants, in particular of E/VLBW who did not receive antenatal glucocorticoid prophylaxis.

Finally, the possibility to use the simple and cheap NIV devices for RDS treatment can significantly improve the quality of neonatal care and the outcomes of newborns, especially in low- or middle-income countries. In this regard, the WHO in a recent document "*Born too soon*" suggests the use of N-CPAP or other NIV support, for preterm babies with RDS, as a priority intervention to reduce the mortality in low-income countries. This model of lower intensity can be used for middle-income countries and for some low-income countries.

Activities/products

Increased use of NIV may therefore reduce hospital costs as well as the number of hospital days. Reducing short and long-term morbidity in patients receiving NIV, instead of mechanical ventilation, might enhance these economic effects. In the light of the promising results of the thesis and of the other studies in Literature, in the near future there will be an increase of use of NIV. Therefore, it is desirable that the NIV culture could be spread in NICUs, with adequate training of the medical and nursing staff, who play a leading role in the management of newborns on NIV (comfort care) and on the effectiveness of the respiratory support. Moreover, for healthcare institutions it is important to invest

on NIV equipment in order to offer to the neonatologist the opportunity to apply the more gentle and the most appropriate respiratory support to the needs of the newborn.

Innovation

Currently HFOV is not used routinely but often only as a rescue modality; as for the NIV techniques, BiPAP and N-SIPPV, they are not yet widespread because the devices are not always available in the NICUs. In this context, this thesis offers encouraging results on the effectiveness of these innovative methods, HFOV and for the NIV, BiPAP and N-SIPPV, compared to the conventional MV or to the common nasal-CPAP respectively. Therefore, it is desirable that these new methods of invasive and non-invasive ventilation support for RDS treatment can be increasingly used and widespread in the near future, also to be able to evaluate their effectiveness in larger populations of preterm newborns.

Schedule and implementation

For the future, it is very important that there is a synergic effort between the clinical, experimental and technological research, involving manufacturers, to develop new devices, new interfaces and new synchronization systems able to minimize the need of MV and the VILI.

Nonetheless, the hospital' investments have to point towards a change of the respiratory approach to the newborns affected by RDS and towards staff training, focused on the use and application of the new techniques and equipment for the ventilation support, and on the care of VLBW during NIV respiratory support. This thesis showed that these new methods of ventilation, HFOV, BiPAP and N-SIPPV, allow to reduce the need of MV and shorten hospital stay with a consequent reduction in hospital costs. Also in our NICUs a reduction of costs was noted after we started routine use of BiPAP or N-SIPPV as first intention strategy for RDS treatment in E/VLBW infants.

It is now known that in recent years the use of NIV methods is increasingly widespread, as well as being recommended by the guidelines, therefore, it is appropriate that the investments of the industries, producing devices, are oriented in this direction, offering greater market opportunities in the sphere of neonatal respiratory support.

Furthermore, the NIV support using simple and very cheap device, represents a sustainable health care model even for the countries with the lowest resources. Therefore, the humanitarian organizations and the health workers operating in developing countries can acquire devices for N-CPAP or NIV, manageable in first-level hospital, that allow survival of children with mild RDS who otherwise would have an unfavorable outcome.

In conclusion, scientific, clinical and technological research must be oriented towards a *“more gentle approach”* for the RDS, that has shown significant benefits in terms of

improving the health of the E/VLBW infants (considering also that in recent years the survival rate of children with lower gestational age improved), better psychological impact on parents and reduction of health expenditure and hospital costs, in addition to even more significant implications for the newborns of countries with lower resource. To summarize, the data reported within this thesis are scientifically, socially and economically relevant. Therefore, the content of this thesis can be of interest to target groups within and outside of the scientific and clinical community.

References

1. March of Dimes, PMNCH, Save the children, WHO. Born Too Soon: The Global action report on preterm Birth. Eds CP Howson, MV Kinney, JE Lawn. World health organization. Geneva, 2012.
2. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional and worldwide estimates of preterm birth rates in the year 2010 with time trends for selected countries since 1990: a systematic analysis and implications. *Lancet*. 2012 Jun 9;379(9832):2162-72.
3. Tucker J, McGuire W. Epidemiology of preterm birth. *BMJ* 2004;329:675-8.
4. Soilly AL, Lejeune C, Quantin C, et al. Economic analysis of the costs associated with prematurity from a literature review. *Public Health* 2014 Jan;128(1):43-62-
5. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet*. 2016 Dec 17; 388(10063): 3027–3035.
6. Schmitt SK, Sneed L, Phibbs CS. Costs of newborn care in California: a population-based study. *Pediatrics*. 2006;117:154-60.
7. Johnson TJ, Patel AL, Jegier BJ, et al. Cost of morbidities in very low birth weight infants. *J Pediatr*. 2013 Feb;162(2):243-49.e1.
8. Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in England and Wales. *Pediatrics* 2009;123(2):e312-27.
9. World Health Organization. Preterm birth. World Health Organization; 2016; Available from: <http://www.who.int/mediacentre/factsheets/fs363/en/>.
10. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med*. 2014 Jan;11(1):e1001596.
11. Patel RM, Kandefer S, Walsh MC, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. *N Engl J Med*. 2015 Jan 22;372(4):331-40.
12. Gilbert WM, Nesbitt TS, Danielsen B. The cost of prematurity: quantification by gestational age and birth weight. *Obstet. Gynecol*. 2003; 102: 488-92.
13. Álvarez-Fuente M, Arruza L, Muro M, et al. The economic impact of prematurity and bronchopulmonary dysplasia. *Eur J Pediatr* (2017) 176:1587–1593
14. Islam JY, Keller RL, Aschner JL, et al. Understanding the Short- and Long-Term Respiratory Outcomes of Prematurity and Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med*. 2015 Jul 15;192(2):134-56.
15. Carlo WA. Gentle ventilation: the new evidence from the SUPPORT, COIN, VON, CURPAP, Colombian Network, and Neocosur Network trials. *Early Hum Dev*. 2012;88(suppl 2):S81–S83
16. DeMauro SB, Millar D, Kirpalani H. Noninvasive respiratory support for neonates. *Curr Opin Pediatr*. 2014 Apr;26(2):157-62.
17. Bhandari V. The potential of non-invasive ventilation to decrease BPD. *Semin Perinatol*. 2013;37:108-14.
18. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. *Neonatology*. 2016 Sep 21;111(2):107-125.
19. Li W, Long C, Zhangxue H, et al. Nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: a meta-analysis and update. *Pediatr Pulmonol*. 2015 Apr;50(4):402-9.
20. Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev*. 2015 Mar 19;(3):CD000104.
21. Ionio C, Colombo C, Brazzoduro V, et al. Mothers and Fathers in NICU: The Impact of Preterm Birth on Parental Distress. *Europe's Journal of Psychology*, 2016, Vol. 12(4), 604–621.