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ORIGINAL ARTICLE

Less invasive ventilation in extremely low birth weight infants from 1997 to 2011: survey versus evidence

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Abstract Evidence for target values of arterial oxygen saturation (SaO_2), CO_2, and pH has changed substantially over the last 20 years. A representative survey concerning treatment strategies in extremely low-birth-weight infants (ELBW) was sent to all German neonatal intensive care units (NICUs) treating ELBW infants in 1997. A follow-up survey was conducted in 2011 and sent to all NICUs in Germany, Austria, and Switzerland. During the observation period, NICUs targeting SaO_2 of 80, 85, and 90 % have increased, while units aiming for 94 and 96 % decreased (all $p<0.001$). Similarly, NICUs aiming for pH 7.25 or lower increased, while 7.35 or higher decreased (both $p<0.001$). Furthermore, more units targeted a CO_2 of 50 mmHg (7.3 kPa) or higher ($p<0.001$), while fewer targeted 40 or 35 mmHg ($p<0.001$). Non-invasive ventilation (NIV) was used in 80.2 % of NICUs in 2011. The most frequently used ventilation modes were synchronized intermittent mandatory ventilation (SIMV) (67.5 %) and intermittent positive pressure ventilation (IPPV) (59.7 %) in 1997 and SIMV (77.2 %) and synchronized intermittent positive pressure ventilation (SIPPV) (26.8 %) in 2011. NICUs reporting frequent or always use of IPPV decreased to 11.0 % ($p<0.001$). SIMV (77.2 %) and SIPPV (26.8 %) did not change from 1997 to 2011, while high-frequency oscillation (HFO) increased from 9.1 to 19.7 % ($p=0.018$). Differences between countries, level of care, and size of the NICU were minimal.

Conclusions: Target values for SaO_2 decreased, while CO_2 and pH increased significantly during the observation period. Current values largely reflect available evidence at time of the surveys.

What is Known:

- *Evidence concerning target values of oxygen saturation, CO_2, and pH in extremely low-birth-weight infants has grown substantially.*
- *It is not known to which extent this knowledge is transferred into clinical practice and if treatment strategies have changed.*

What is New:

- *Target values for oxygen saturation in ELBW infants decreased between 1997 and 2011 while target values for CO_2 and pH increased.*
- *Similar treatment strategies existed in different countries, hospitals of different size, or university versus nonuniversity hospitals in 2011.*

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Keywords Preterm · ELBW · Survey · Oxygen saturation · CO_2 · pH · Ventilation

Abbreviations

BIPAP	Biphasic positive airway pressure ventilation
BPD	Bronchopulmonary dysplasia
ELBW	Extremely low birth weight, less than 1000 g
FiO_2	Fraction of inspired oxygen
GA	Gestational age
GNPI	Gesellschaft für Neonatologie und pädiatrische Intensivmedizin, Society of Neonatology and Pediatric Intensive Care
IVH	Intraventricular hemorrhage
IMV	Intermittent mandatory ventilation
IPPV	Intermittent positive pressure ventilation
NICU	Neonatal intensive care unit
NIV	Non invasive ventilation
pCO_2	Partial pressure of carbon dioxide
PEEP	Positive end expiratory pressure
PiP	Peak inspiratory pressure
RDS	Respiratory distress syndrome
SaO_2	Arterial oxygen saturation
SIMV	Synchronized intermittent mandatory ventilation
SIPPV	Synchronized Intermittent positive pressure ventilation
VG	Volume guarantee ventilation
VLBW	Very low birth weight, less than 1500 g

Introduction

In Western Europe, 5–10 % of newborn infants are born prematurely defined as birth at a gestational age of less than 37 completed weeks. The majority of preterm infants are born between 34 and 37 weeks, and of these, around 5 % is born before 28 weeks [3]. The smallest preterm infants with a birth weight of less than 1000 g (extremely low-birth-weight (ELBW) infants) have the highest risk for long-term morbidity and mortality. One of the major long-term morbidities is the development of bronchopulmonary dysplasia (BPD) which is associated with prolonged hospitalization, increased use of medications, more frequent re-hospitalizations, and impaired neurodevelopmental outcome [8, 32, 24]. Since the development of BPD is increased with prolonged ventilation [13], changes of target values for oxygen saturation, pCO_2, and pH might have an impact on the duration of mechanical ventilation and thereby on the development of BPD.

Furthermore, increased oxygen saturation is associated with the development of retinopathy of prematurity [2]. Several publications have described this correlation and tried to establish optimal ranges for oxygen saturation.

During the last 15 years, guidelines and recommendations for neonatal care have changed substantially to account for results of many prospective trials published during this period [5, 25, 21]. However, it remains largely unknown if guidelines and recommendations have been implemented into local treatment algorithms. Therefore, we performed a representative, standardized survey in Germany in 1997 and a follow-up survey in all German-speaking countries (Germany, Austria, and Switzerland) in 2011 assessing changes in care of ELBW infants. This paper summarizes results on mechanical ventilation and target values for oxygen saturation, pCO_2, and pH.

Methods

Detailed description of methods has been published previously [9]. In brief, two surveys concerning routine management of preterm infants with a birth weight between 750 and 1000 g were performed in 1997 in Germany and in 2011 in all neonatal intensive care units (NICUs) in Germany, Austria, and Switzerland, including all Swiss centers with other languages. The questionnaire contained approximately 100 detailed questions about treatment of ELBW infants as well as questions characterizing the department approached. Both questionnaires were sent to the head of the individual NICUs, and it was expected to be answered by the head or a leading representative. The second questionnaire was a shortened version of the first questionnaire with identical wording of remaining questions. It was transferred to the online survey software Unipark (Globalpark AG, Cologne, Germany). It was sent via email to all German (n=171), Austrian (n=15), and Swiss (n=9) hospitals treating very-low-birth-weight (VLBW, birth weight less than 1500 g) infants. Non-responding institutions were reminded twice by mail and then once by telephone.

Answers from the first survey were transferred to and analyzed with Microsoft Excel (2007) and SPSS 19.0 (SPSS Inc., Chicago, USA). Unconditional confidence interval on difference of proportions [1] was used to compare results of the two surveys. To compare categorical subgroups of the 2011 survey, Fisher's exact test was used for comparison of two subgroups and Freeman-Halton test was applied to compare three subgroups. Missing values were excluded from analysis. Results with an alpha error of $p<0.05$ were considered significant.

Frequencies of therapy were categorized as "never," "rare," "frequent," or "always." Unless otherwise specified, the combined responses of never and rare were compared to the combined frequencies of frequent and always. For comparison, intensive care units were categorized into university and non-university hospitals. Small, medium, and large NICUs were arbitrarily defined as units with annual admissions of ≤12, 13–30, and >30 ELBW infants, respectively.

To improve response rates, a financial incentive was paid by hospital funds (Ludwig-Maximilians-University Munich, Germany, in 2007 and Inselspital Berne, Switzerland, in 2011).

Results

Response rate In 1997, 332 hospitals were approached and 211 (63.6 %) responded. Of these, 46 did not treat ELBW infants, 36 were excluded because they treated less than ten VLBW per year, and three responded but declined participation. This resulted in 126 units in the first survey of whom a complete questionnaire was available for analysis.

In 2011, 195 neonatal departments were approached and 129 answered (66.2 %). Response rates for Germany, Switzerland, and Austria were 110/171 (64.3 %), 9/9 (100 %), and 10/15 (66.7 %), respectively. The response rate was higher in Switzerland than in Germany ($p=0.029$), whereas no significant difference existed between Germany versus Austria ($p=1.000$) and Austria versus Switzerland ($p=0.118$).

Changes over time Target values for SaO_2, pCO_2, and pH changed significantly during the observation period as shown in Figs. 1, 2, and 3. In 2011, target values for CO_2 of 50–80 mmHg (6.7–10.7 kPa) (all $p<0.001$) were more frequently in the target range of the responding NICUs compared to 1997. In contrast, 35 mmHg (4.7 kPa) and 40 mmHg (5.3 kPa) were less frequently within the target range (both $p<0.001$), showing a general trend to higher CO_2. In line with these results is a lower pH target: a pH of 7.35, 7.40, and 7.45 was less frequently in the target range (both $p=0.003$, $p=0.003$, and $p<0.001$, respectively), while more NICUs aimed for 7.20 and 7.25 (both $p<0.001$) in 2011. Target values for SaO_2 also changed significantly from 1997 to 2011 with more units targeting 80, 85, and 90 % ($p<0.001$, $p<0.001$, and $p=0.001$, respectively) and fewer units aiming for 94 and 96 % (both $p<0.001$) in 2011.

Changes of invasive and non-invasive ventilation between 1997 and 2011 are shown in Table 1. Of the invasive modes of ventilatory support, synchronized intermittent mandatory ventilation (SIMV), intermittent positive pressure ventilation (IPPV), and synchronized intermittent positive pressure ventilation (SIPPV) were the most frequently used ventilation modes in 1997 with 67.5, 59.7, and 33.3 %, of the NICUs applying these modes always or frequently. In 2011, units reporting frequent or always use of IPPV decreased to 11.0 % ($p<0.001$), while SIMV (77.2 %) and SIPPV (26.8 %) did not change significantly in comparison to 1997. NICUs reporting frequent or always application of non-synchronized ventilation and high-frequency oscillation (HFO) changed significantly between 1997 and 2011: IPPV declined from 59.7 to 11.0 % ($p<0.001$) whereas HFO increased from 9.1 to 19.7 % ($p=0.018$). More advanced modes like volume guarantee, proportional assist ventilation, and biphasic positive airway pressure (BIPAP) were not assessed in 1997. In 2011, these techniques were applied frequently or always in 20.9, 7.9 and 4.7 % of the units, respectively.

In 2011, non-invasive ventilatory (NIV) support was used in 80.2 % of NICUs. Pharyngeal tube, mask, and prongs were used for NIV in 50.4, 76.8, and 97.6 %, respectively. Comparing the combined rare, frequent, and always application of NIV modes shows that noninvasive IPPV (NIPPV) (37.6 %) and noninvasive SIMV (NSIMV) (26.3 %) were the most frequently used ventilatory modes in 1997. In 2011, these were noninvasive BIPAP (NBIPAP) (34.9 %), NSIMV (34.9 %), and NIPPV (27.0 %).

Size of the unit Analyses revealed only two differences between NICUs of different size: IPPV was used less frequently in small units ($p=0.005$), and the frequency of NICUs never using prongs for non-invasive ventilation was also lower in small units ($p=0.031$).

Level of care Differences between university hospitals and non-university hospitals were minimal: university hospitals used intermittent positive pressure ventilation (IPPV) (21.9 % vs. 7.4 %; $p=0.044$) and considered an oxygen saturation of 80 % in the target range more frequently than non-university hospitals (29.0 vs. 11.7 %; $p=0.044$).

Countries In 2011, an oxygen saturation of 90 and 92 % was less frequently within the target range in Switzerland, while a saturation of 96 % was more frequently targeted in Austria ($p=0.034$, $p=0.034$, and 0.027, respectively). Of the invasive modes of ventilatory support, SIPPV and volume guaranty (VG) were used more often in Austria compared to Germany and Switzerland ($p=0.005$ and $p=0.010$, respectively). NIV was used more frequently ($p=0.015$) and was more frequently applied by pharyngeal tube ($p<0.001$) in Germany compared to Austria and Switzerland. For NIV, NISIMV was used in more NICUs in Germany ($p=0.035$), while fewer units never applied NBIPAP ($p=0.023$).

Discussion

The results of this representative survey show that modes of mechanical ventilation and target values for SaO_2, CO_2, and pH for ELBW infants changed significantly between 1997 and 2011.

The response rate of 63.6 % for all centers treating ELBW in 1997 in Germany and a combined response rate of 66.2 % in Germany, Austria, and Switzerland in 2011 make this survey representative for German-speaking countries. The response

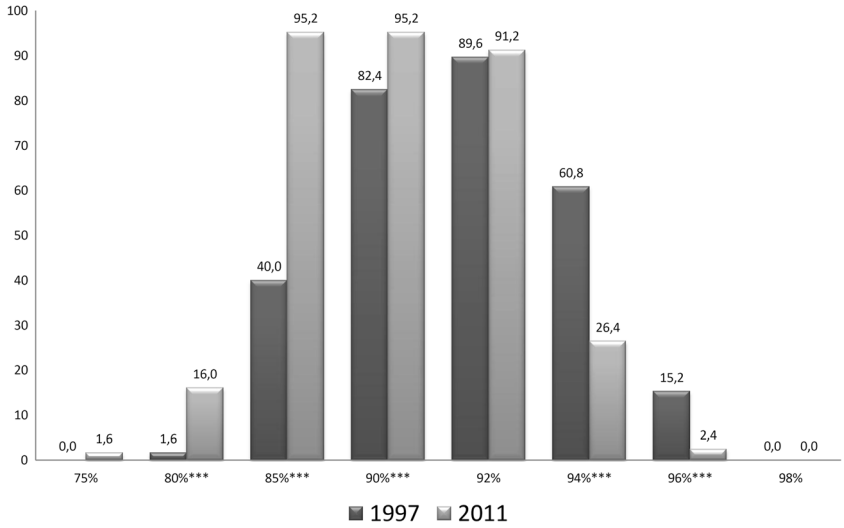

Fig. 1 Target values for SaO_2 during the observation period (1997–2011)

rate is comparable with other surveys in critical care medicine [7]. Differences between university and non-university hospitals and differences between countries were minimal. Therefore, the higher response rates of university hospitals and Switzerland are unlikely to lead to a relevant bias.

Results of this survey show that target values for SaO_2 decreased significantly between 1997 and 2011 for ELBW infants. During the observation period, several studies showed the association between higher SaO_2 and the development of retinopathy of prematurity (ROP). Furthermore, a lower SaO_2 might seem more physiological for ELBW infants because intrauterine oxygenation has been shown to be much lower with preductal SaO_2 and postductal SaO_2 around 70 and 65 %, respectively. Therefore, it seemed reasonable to tolerate lower SaO_2 in spite of absence of guidelines that recommend precise target values.

Large and well-designed studies have been published within the last 4 years that show that higher SaO_2 leads to a higher incidence of ROP but show a higher mortality in patients with a lower SaO_2 [26, 4], while one other large trial did not show such results [23]. However, a recent meta-analysis confirmed that lower SaO_2 is associated with higher mortality [22]. It is important to notice that our survey was performed before these trials were published, and we expect that relevant changes of target values for SaO_2 occurred thereafter. Thus, target values assessed by our survey might already be outdated and have been replaced by higher values.

Hypercapnia leads to cerebral vasodilatation and increased cerebral blood flow and might cause intraventricular hemorrhage (IVH) by rupture of germinal matrix vessels [16]. Over the last 35 years, hypercapnia was repeatedly reported to be associated with IVH. However, the majority of studies were

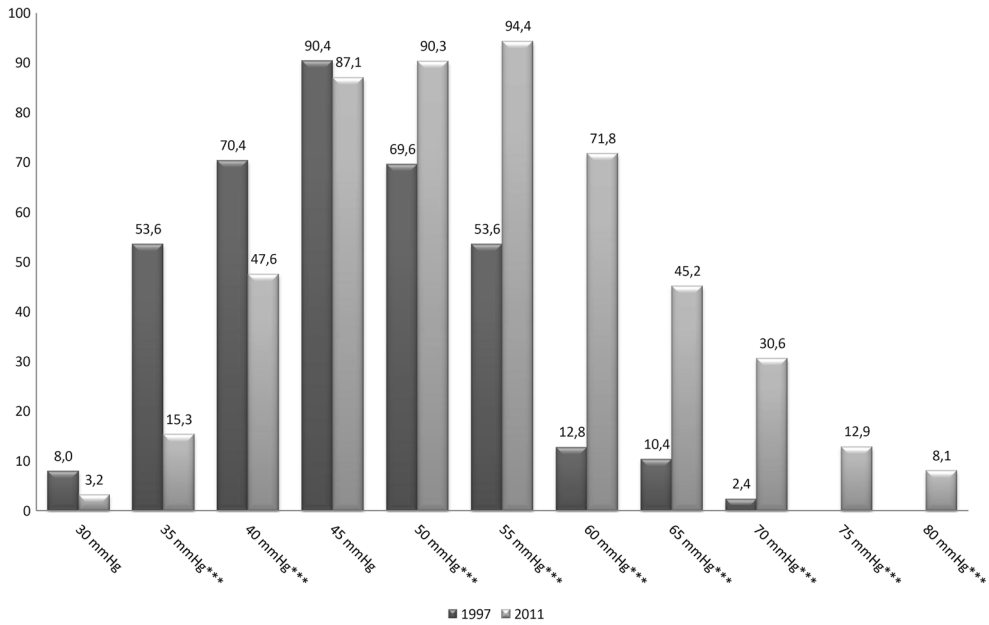

Fig. 2 Target values for pCO_2 during the observation period (1997–2011)

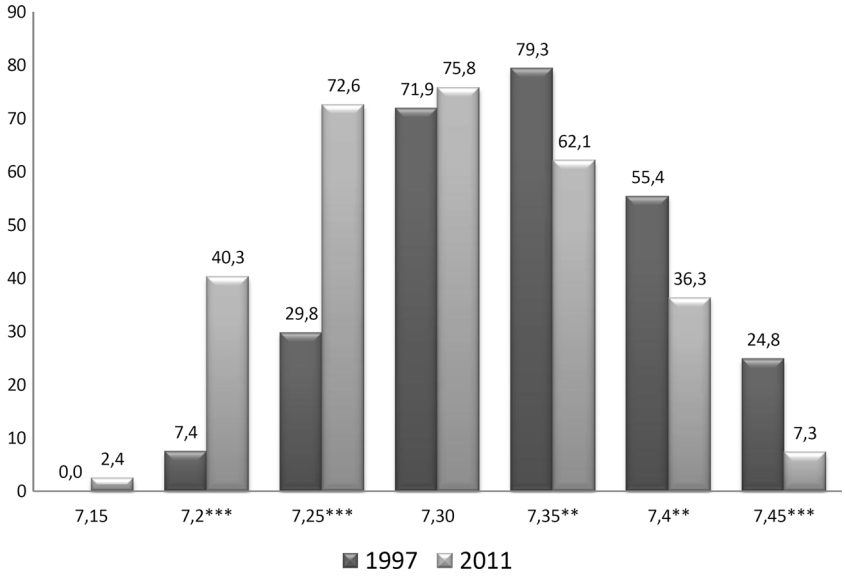

Fig. 3 Target values for pH during the observation period (1997–2011)

performed retrospectively and prospective randomized trials are lacking. Furthermore, the association was mostly described in univariate analyses [6, 27], while it disappeared in multivariate analyses [33, 15]. One larger and more recently published trial found that pCO_2 is a dose-dependent predictor of severe IVH, but the authors concluded that they could not determine causality and that "perhaps, hypercapnia during the surfactant and permissive hypercapnia eras still characterizes infants with the most severe acute lung disease" [11]. Therefore, while a trend to permissive hypercapnia can clearly be seen in our data, its safety concerning IVH needs to be proven.

Over the last years, a concept of "gentle ventilation" has increasingly been studied. This concept includes administration of limited plateau pressures, low tidal volumes, and permissive hypercapnia as well as tolerating a lower pH. It has been shown that mechanical ventilation with lower tidal

Table 1 Changes of ventilation strategies in extremely low-birth-weight infants between 1997 and 2011

	1997		2011		Estimated difference (%)	95 % CI	*p* value
Non-invasive ventilation (NIV)							
Use NIV			101/126	80.2 %			
CPAP	123/127	96.7 %	123/126	97.6 %	+0.9	−4.3 %; 6.0 %	0.793
IPPV	8/117	6.8 %	11/126	8.7 %	+1.9	−5.3 %; 9.2 %	0.601
HFO	0/111	0.0 %	2/126	1.6 %	+1.6	−2.1 %; 6.0 %	0.224
SIPPV	4/110	3.6 %	4/126	3.2 %	−0.4	−6.3 %; 4.9 %	0.884
SIMV	5/114	4.4 %	12/126	9.5 %	+5.1	−1.6 %; 12.4 %	0.125
BIPAP			20/126	15.9 %			
Device for CPAP/non-invasive ventilation							
Pharyngeal tube			63/125	50.4 %			
Mask			96/125	76.8 %			
Prongs			122/125	97.6 %			
Mechanical ventilation							
IPPV	72/119	59.7 %	14/127	11.0 %	**−48.7**	**−59.2**%; **−38.6**%	**<0.001**
HFO	11/121	9.1 %	25/127	19.7 %	**+10.6**	**1.9**%; **19.6**%	**0.018**
SIPPV	40/120	33.3 %	34/127	26.8 %	−6.5	−18.1 %; 5.0 %	0.274
SIMV	83/123	67.5 %	98/127	77.2 %	+9.7	−1.5 %; 20.8 %	0.089
BIPAP			6/127	4.7 %			
VG			26/127	20.5 %			
Prop assist			10/127	7.9 %			

Bold entries highlight significant results ($p<0.05$)

volumes leads to decreased inflammation and cytokine expression [19] and to decreased mortality in adults [30, 31]. While well-designed randomized trials in preterm infants are scarce [17], there is a large body of evidence from animal research, biochemical concepts, and trials in human adults indicating that this concept is safe and beneficial for preterm infants. A meta-analysis comparing volume-targeted ventilation to pressure-limited ventilation in preterm infants showed several advantages of volume-targeted ventilation, including reduced risks for death or BPD, pneumothorax, and intracranial hemorrhage [34]. These results suggest that gentle ventilation with limited tidal volumes is beneficial. Furthermore, recommendations for newborn infants with lung hypoplasia in form of congenital diaphragmatic hernia, who also have very fragile lungs, include these considerations and also seem to be associated with lower morbidity and mortality [20]. Several studies show an association between mechanical ventilation and the development of BPD in preterm infants. Therefore, reduced time of, or even avoidance of, mechanical ventilation is aimed for, which implies permissive hypercapnia and lower pH. Results of this survey mirror the given evidence showing significant changes of local treatment algorithms to target values of higher CO_2 and lower pH.

A different concept in avoidance of mechanical ventilation is the application of mechanical ventilation via pharyngeal tube, mask, or prongs without tracheal intubation (NIV). Several studies evaluated NIV concerning successful extubation and time on mechanical ventilation. Results showed a reduced risk for extubation failure and reintubation [14]. Fewer intubations in the delivery room have been reported [18]. A recent large study showing that NIV is not associated with decreased risk of BPD [12] was not yet published when the survey was performed. The survey did not assess the number of NICUs using NIV in 1997. However, 80.2 % of units stated that they were using NIV in 2011, showing that this concept is implemented in local treatment algorithms to a large extent.

Surveys on patient management are frequently performed in medicine. A crucial question is if they reflect what is actually done at the bedside. A survey such as ours cannot assess to what extent responses reflect actual practice, in contrast to general knowledge of the responding individual. This can probably be considered to be the most relevant weakness of our study. However, a recent European cross-sectional study showed that hypocapnia is a relatively uncommon finding in preterm infants whereas hypercapnia occurs comparably frequently [28]. Furthermore, a different study which was performed at the time of our survey showed that newer ventilation modes are used infrequently [29]. Results of these publications are in line with the results of our survey making it more likely that our survey reflects actual practice. On the other hand, significant differences between knowledge about preterm care and its application in practice have been described [10].

In summary, this survey provides valuable information about changes of respiratory target values between 1997 and 2011. Furthermore, it describes changes of used modes of mechanical ventilation and shows that current knowledge and concepts have been implemented into local treatment strategies.

Conclusion

The presented results of our surveys show that target values of SaO_2, CO_2, and pH for ELBW infants changed significantly between 1997 and 2011, aiming for lower SaO_2, higher CO_2, and lower pH. Furthermore, NIV is used in the majority of NICUs, showing that concepts of lung protective ventilation have been implemented into local treatment strategies. Treatment strategies are similar between German-speaking countries, NICUs of different size, and different level of care in 2011.

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Authors' contributions The authors contributed to the manuscript in the following way: Roland Gerull was involved in the design of the second questionnaire, center recruitment, and data analysis and wrote the manuscript. Helen Manser was responsible for the second questionnaire in terms of design, development of the database, and data management and center recruitment. Tina Arenz was responsible for development and realization of the first survey. Helmut Küster supervised the development and contributed to the realization of the first survey. Stephan Arenz was responsible for center recruitment, development of the database of the second questionnaire, and data analysis and wrote parts of the manuscript. Mathias Nelle supervised the development and realization of the second survey, acquired hospital funds for the incentive, and was involved in writing the manuscript. All authors have participated in the concept and design, analysis and interpretation of data, and drafting or revising of the manuscript and contributed in discussions, reviews, and corrections of the submitted manuscript. All listed authors on the manuscript have seen and approved the submitted version of the manuscript and take full responsibility for the manuscript.

References

1. Agresti A, Min Y (2001) On small-sample confidence intervals for parameters in discrete distributions. Biometrics 57(3):963–971
2. Askie LM, Henderson-Smart DJ, Ko H (2009) Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochrane Database Syst Rev 1, CD001077. doi:10.1002/14651858.CD001077.pub2
3. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE (2012) National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected

countries: a systematic analysis and implications. Lancet 379(9832):2162–2172. doi:10.1016/S0140-6736(12)60820-4
4. Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID 3rd, Piazza AJ, Sanchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD (2010) Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 362(21): 1959–1969. doi:10.1056/NEJMoa0911781
5. Cheong JL, Anderson P, Roberts G, Duff J, Doyle LW (2013) Postnatal corticosteroids and neurodevelopmental outcomes in extremely low birthweight or extremely preterm infants: 15-year experience in Victoria, Australia. Arch Dis Child Fetal Neonatal Ed 98(1):F32–F36. doi:10.1136/fetalneonatal-2011-301355
6. Cooke RW (1981) Factors associated with periventricular haemorrhage in very low birthweight infants. Arch Dis Child 56(6):425–431
7. Duffett M, Burns KE, Adhikari NK, Arnold DM, Lauzier F, Kho ME, Meade MO, Hayani O, Koo K, Choong K, Lamontagne F, Zhou Q, Cook DJ (2012) Quality of reporting of surveys in critical care journals: a methodologic review. Crit Care Med 40(2):441–449. doi:10.1097/CCM.0b013e318232d6c6
8. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA, Poole K (2005) Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 116(6):1353–1360. doi: 10.1542/peds. 2005-0249
9. Gerull R, Manser H, Kuster H, Arenz T, Nelle M, Arenz S (2013) Increase of caffeine and decrease of corticosteroids for extremely low birthweight infants with respiratory failure from 1997 to 2011. Acta Paediatr. doi:10.1111/apa.12419
10. Iriondo M, Thio M, Buron E, Salguero E, Aguayo J, Vento M (2009) A survey of neonatal resuscitation in Spain: gaps between guidelines and practice. Acta Paediatr 98(5):786–791. doi:10.1111/j.1651-2227.2009.01233.x
11. Kaiser JR, Gauss CH, Pont MM, Williams DK (2006) Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol 26(5): 279–285. doi:10.1038/sj.jp.7211492
12. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS (2013) A trial comparing noninvasive ventilation strategies in preterm infants. N Engl J Med 369(7):611–620. doi:10.1056/NEJMoa1214533
13. Laughon MM, Smith PB, Bose C (2009) Prevention of bronchopulmonary dysplasia. Semin Fetal Neonatal Med 14(6): 374–382. doi:10.1016/j.siny.2009.08.002
14. Lemyre B, Davis PG, De Paoli AG, Kirpalani H (2014) Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev 9, CD003212. doi: 10.1002/14651858.CD003212.pub2
15. Levene MI, Fawer CL, Lamont RF (1982) Risk factors in the development of intraventricular haemorrhage in the preterm neonate. Arch Dis Child 57(6):410–417
16. Levene MI, Shortland D, Gibson N, Evans DH (1988) Carbon dioxide reactivity of the cerebral circulation in extremely premature infants: effects of postnatal age and indomethacin. Pediatr Res 24(2):175–179. doi:10.1203/00006450-198808000-00007
17. Mariani G, Cifuentes J, Carlo WA (1999) Randomized trial of permissive hypercapnia in preterm infants. Pediatrics 104(5 Pt 1): 1082–1088
18. Meneses J, Bhandari V, Alves JG (2013) Questions concerning nasal intermittent positive-pressure ventilation vs nasal continuous positive airway pressure—reply. JAMA Pediatr 167(9):873. doi:10.1001/jamapediatrics.2013.2212
19. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, Wheeler AP (2005) Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 33(1):1–6, discussion 230-232
20. Reiss I, Schaible T, van den Hout L, Capolupo I, Allegaert K, van Heijst A, Gorett Silva M, Greenough A, Tibboel D (2010) Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. Neonatology 98(4):354–364. doi:10.1159/000320622
21. Ruegger C, Hegglin M, Adams M, Bucher HU (2012) Population based trends in mortality, morbidity and treatment for very preterm- and very low birth weight infants over 12 years. BMC Pediatr 12: 17. doi:10.1186/1471-2431-12-17
22. Saugstad OD, Aune D (2014) Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology 105(1):55–63. doi:10.1159/000356561
23. Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, Solimano A, Roberts RS (2013) Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA 309(20):2111–2120. doi:10.1001/jama.2013.5555
24. Short EJ, Kirchner HL, Asaad GR, Fulton SE, Lewis BA, Klein N, Eisengart S, Baley J, Kercsmar C, Min MO, Singer LT (2007) Developmental sequelae in preterm infants having a diagnosis of bronchopulmonary dysplasia: analysis using a severity-based classification system. Arch Pediatr Adolesc Med 161(11):1082–1087. doi:10.1001/archpedi.161.11.1082
25. Soll RF, Edwards EM, Badger GJ, Kenny MJ, Morrow KA, Buzas JS, Horbar JD (2013) Obstetric and neonatal care practices for infants 501 to 1500 g from 2000 to 2009. Pediatrics 132(2):222–228. doi:10.1542/peds. 2013-0501
26. Stenson B, Brocklehurst P, Tarnow-Mordi W (2011) Increased 36-week survival with high oxygen saturation target in extremely preterm infants. N Engl J Med 364(17):1680–1682. doi:10.1056/NEJMc1101319
27. Van de Bor M, Van Bel F, Lineman R, Ruys JH (1986) Perinatal factors and periventricular-intraventricular hemorrhage in preterm infants. Am J Dis Child 140(11):1125–1130
28. van Kaam AH, De Jaegere AP, Rimensberger PC (2013) Incidence of hypo- and hyper-capnia in a cross-sectional European cohort of ventilated newborn infants. Arch Dis Child Fetal Neonatal Ed 98(4):F323–F326. doi:10.1136/archdischild-2012-302649
29. van Kaam AH, Rimensberger PC, Borensztajn D, De Jaegere AP (2010) Ventilation practices in the neonatal intensive care unit: a cross-sectional study. J Pediatr 157(5):767–771 e761–763. doi:10.1016/j.jpeds.2010.05.043
30. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network (2000). N Engl J Med 342(18):1301–1308. doi:10.1056/NEJM200005043421801
31. Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A (2006) A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med 34(5): 1311–1318. doi:10.1097/01.CCM.0000215598.84885.01
32. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, Simon NP, Wilson DC, Broyles S, Bauer CR, Delaney-Black V, Yolton KA, Fleisher BE, Papile LA, Kaplan MD (2000) Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. Pediatrics 105(6):1216–1226

33. Wallin LA, Rosenfeld CR, Laptook AR, Maravilla AM, Strand C, Campbell N, Dowling S, Lasky RE (1990) Neonatal intracranial hemorrhage: II. Risk factor analysis in an inborn population. Early Hum Dev 23(2):129–137

34. Wheeler KI, Klingenberg C, Morley CJ, Davis PG (2011) Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Neonatology 100(3):219–227. doi:10.1159/000326080