Improving manual oxygen titration in preterm infants by training and guideline implementation

Henriëtte A. van Zanten 1 · Steffen C. Pauws 1,2 · Evelien C. Beks 1 · Ben J. Stenson 3 · Enrico Lopriore 1 · Arjan B. te Pas 1

Communicated by Patrick Van Reempts

Abstract To study oxygen saturation (SpO2) targeting before and after training and guideline implementation of manual oxygen titration, two cohorts of preterm infants <30 weeks of gestation needing respiratory support and oxygen therapy were compared. The percentage of the time spent with SpO2 within the target range (85–95%) was calculated (%SpO2-wtr). SpO2 was collected every minute when oxygen is >21%. ABCs where oxygen therapy was given were identified and analyzed. After training and guideline implementation the %SpO2-wtr increased (median interquartile range (IQR)) 48.0 (19.6–63.9) % vs 61.9 (48.5–72.3) %; p < 0.005, with a decrease in the %SpO2 > 95% (44.0 (27.8–66.2) % vs 30.8 (22.6–44.5) %; p < 0.05). There was no effect on the %SpO2 < 85% (5.9 (2.8–7.9) % vs 6.2 (2.5–8) %; ns) and %SpO2 < 80% (1.9 (1.0–3.0) % vs 1.7 (0.8–2.6) %; ns). In total, 186 ABCs with oxygen therapy before and 168 ABCs after training and guideline implementation occurred. The duration of SpO2 < 80% reduced (2 (1–2) vs 1 (1–2) minutes; p < 0.05), the occurrence of SpO2 > 95% did not decrease (73% vs 64%; ns) but lasted shorter (2 (0–7) vs 1 (1–3) minute; p < 0.004).

Conclusion: Training and guideline implementation in manual oxygen titration improved SpO2 targeting in preterm infants with more time spent within the target range and less frequent hyperoxaemia. The durations of hypoxaemia and hyperoxaemia during ABCs were shorter.

What is Known:
- Oxygen saturation targeting in preterm infants can be challenging and the compliance is low when oxygen is titrated manually.
- Hyperoxaemia often occurs after oxygen therapy for oxygen desaturation during apnoeas.

What is New:
- Training and implementing guidelines improved oxygen saturation targeting and reduced hyperoxaemia.
- Training and implementing guidelines improved manual oxygen titration during ABC.

Keywords Preterm infant · Targeting oxygen · Apnoea · Hypoxaemia · Hyperoxaemia

Abbreviations
ABC Apnoea, bradycardia, cyanosis
BPD Bronchopulmonary dysplasia
FiO2 Fraction of inspired oxygen
GA Gestational age

1 Division of Neonatology, Department of Pediatrics, Leiden University Medical Center, J6-S, PO Box 9600, 2300, RC Leiden, The Netherlands
2 TiCC, Tilburg University, Tilburg, The Netherlands
3 Neonatal Unit, Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh, UK
Oxygen is the most commonly used therapy in neonatal intensive care units (NICUs) [34]. To assure adequate delivery of oxygen to the tissue without creating oxygen toxicity [29], infants admitted to the NICU are continuously monitored using pulse oximetry. Oxygen is titrated manually to maintain the pulse oxygen saturation (SpO₂) within target ranges, but this can be challenging. Several studies reported low compliance in oxygen saturation targeting and described a tendency of caregivers to accept higher SpO₂ [3, 9, 20–22, 26, 33]. It has been suggested that caregivers are more focused to prevent hypoxaemia rather than hyperoxaemia [4, 31]. However, improving the knowledge of caregivers in the hazards of hyperoxaemia could lead to more vigilance for alarm settings and oxygen titration and thus decrease the time outside target ranges in preterm infants considerably [4].

Oxygen is most frequently manually titrated when an apnoea occurs, defined as a respiratory pause >20 s and/or shorter accompanied by bradycardia or cyanosis, hypotonia, and pallor (usually termed ABC: apnoea, bradycardia, cyanosis) [12]. We recently demonstrated that manual titration of oxygen therapy in preterm infants during ABCs unintentionally led to the occurrence of hyperoxaemia (SpO₂ > 95%) [33]. To improve the compliance, especially during ABCs, all neonatal caregivers in our NICU received an additional training about the risk for hypoxaemia and hyperoxaemia, and a guideline for manual oxygen titration was introduced.

Efforts have been taken to increase the nurses’ compliance in SpO₂ targeting by creating awareness by training and implementing guidelines, with variable success [2, 11, 13, 14, 18, 19]. We aimed to investigate the effect of training combined with an oxygen titration guideline on the proportion of time SpO₂ was within target range (%SpO₂-wtr) and the occurrence and duration of hypoxaemia and hyperoxaemia during and after ABCs.

### Methods

A prospective observational study was performed in the NICU of the Leiden University Medical Center (LUMC), which is a tertiary level perinatal center in the Netherlands with an average of 650 intensive care admissions per year. This study was an audit and part of a quality improvement project and did not need to comply with the Dutch law on Medical Research in Humans; the Research Ethics Committee issued a statement of no objection. All infants <30 weeks of gestation admitted to the NICU in LUMC between March 2013 and December 2013 (before training and guideline) and between February 2014 and November 2014 (after training and guideline) were retrospectively compared.

To increase awareness in SpO₂ targeting and oxygen titration, all caregivers were trained in a months’ period (January 2014). Before the afternoon shift started, nurses were asked to attend a lesson that lasted 30–45 min. Each session was attended by 6–8 nurses. An attendance list was updated to make sure every nurse attended the lesson. The medical staff was trained separately during a grand round session. The training was given by the nurse (first author) or the neonatal consultant (last author) responsible for the quality improvement project. During this training the results of our previous study was discussed, which demonstrated frequent occurrence of hyperoxaemia after ABCs where oxygen therapy was given [33]. Caregivers were also educated about the risks for preterm infants exposed to frequent hypoxaemia and hyperoxaemia. To pursue a uniform approach for oxygen titration, a guideline for oxygen titration was introduced and discussed (Fig. 1). After the training, the nurse and the consultant responsible for the project were available during the daytime and frequently actively approached the staff whether there were questions or issues related to the oxygen titration and/or the guideline. Also, the medical staff was asked to standardly check the oxygen saturation distribution during the daily rounds.

The guideline was specially developed for a randomized trial comparing manual versus automated oxygen titration [32]. During the trial, the nurses used the guideline during the manual periods. The guideline was then discussed by members of the project and the nurses who received special training in ventilation. Based on their feedback, small amendments were made to make it more practicable for the nurses.

All preterm infants receiving respiratory support (endotracheal and noninvasive ventilation) in the NICU were included in the study. Infants with major congenital heart disease with different oxygen saturation target ranges were excluded. All infants received routinely a loading dose of 10 mg/kg caffeine directly after birth followed by 5 mg/kg/day. Dopram (2 mg/kg/h) was given in case of refractory apnoeas. Respiratory support was given by a mechanical ventilator (AVEA, Carefusion, Houten, The Netherlands), which is connected to the patient data management system (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). SpO₂ was measured using Masimo SET.
Radical pulse oximeter (software version 46.02) (Masimo Radical, Masimo Corporation, Irvine CA, USA), integrated into the bedside monitor (Philips Healthcare Nederland, Eindhoven, The Netherlands). The pulse oximeter probe was placed around the hand or foot of the infant (right hand in case of a patent ductus arteriosus). Basic characteristics were collected from the patients' files in PDMS. All clinical parameters were collected every minute from PDMS. In both periods, the SpO2 target range (TR) was 85–95% when FiO2 > 0.21, and the alarm limits were set at 84 and 96%. Before the start of each shift, the TR and alarm setting were checked by the nurse.

%SpO2-wtr, SpO2 < 85%, and SpO2 > 95%, when FiO2 > 0.21 was calculated for each patient during the time period, infants were respiratory supported. Additionally, all ABC events were documented and evaluated in all preterm infants on noninvasive ventilation (nasal CPAP and noninvasive intermittent mandatory ventilation). ABC was defined as apnoea (>20 s or shorter), accompanied with bradycardia (<80 beats per minute (bpm)) and cyanosis (SpO2 < 80%). Every ABC was evaluated in detail by documenting the following characteristics: depth and duration of bradycardia, depth and duration of SpO2 < 80%, baseline FiO2, additional FiO2, the duration of the additional FiO2, and incidence and duration of SpO2 > 95%. Hypoxaemia was defined as SpO2 < 80% and hyperoxaemia as SpO2 > 95%.

All ABCs were manually identified in PDMS and analyzed starting from the occurrence of an ABC until the additional oxygen given returned to the baseline oxygen that was given before the ABC occurred.
Statistical analyses

Quantitative data presented as median interquartile range (IQR), mean (SD), or number (percentage) were appropriate. Time with SpO2 within various ranges for FiO2 > 21% were collated for each infant individually before and after training and aggregated as proportions of the recorded time (median and IQR). Statistical analysis comprised nonparametric Kruskal-Wallis rank sum test. The Mann-Whitney U test for nonparametric comparisons for continuous variables is used to compare the patients’ characteristics and the ABC characteristics. P values < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Software, NY, USA, 2012) and R 3.2.0 (R Core Team (2015). R: A language and environment for statistical computing. R: A foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

We considered an increase of 10% SpO2-wtr clinically relevant. In previous studies, the standard deviation of the mean %SpO2-wtr was 16 [32]. To detect a change of 10% SpO2-wtr in each period by a Kruskal-Wallis test with an 80% power with a significant level of 0.05 (two-tailed test), at least 44 patients of each group were required. We calculated this by running a simulation taking samples from two normal distributions with means 0 and 10 and a standard deviation of 16 to model the clinically relevant increase in %SpO2-wtr.

Results

Patient characteristics

During two study periods of 10 months, in total 136 infants <30 weeks of gestation were admitted to our NICU, of which 79 infants before and 57 infants after education and guideline for oxygen titration. The median IQR gestational age was (28 + 2 (27 + 3–29) vs 28 + 3 (26 + 4–29) weeks; ns) and birthweight (1090 (857–1277) vs 1000 (855–1206); ns) were not different (Table 1).

Table 1. Patient characteristics

|                         | Before training | After training | p value |
|-------------------------|-----------------|----------------|---------|
| N = 79                  |                 | N = 57         |         |
| Gestational age at birth (weeks), median (IQR) | 28 + 2 (27 + 3–29) | 28 + 3 (26 + 4–29) | 0.36<sup>a</sup> |
| Birthweight (grams) median (IQR) | 1090 (857–1277) | 1000 (855–1206) | 0.56<sup>c</sup> |
| Male sex, no. (%) | 46 (58) | 32 (56) | 0.96<sup>b</sup> |
| Caesarean delivery, no. (%) | 39 (49) | 31 (54) | 0.56<sup>b</sup> |
| Singletons, no. (%) | 51 (65) | 39 (68) | 0.26<sup>b</sup> |
| Apgar at 5 min median, (IQR) | 7 (7–8) | 7 (6–9) | 0.66<sup>a</sup> |
| Days on respiratory support, median (IQR) | 9 (3–14) | 8 (4–24) | 0.89<sup>a</sup> |
| Length of stay on NICU, median (IQR) | 15 (8–25) | 19 (8–35) | 0.32<sup>a</sup> |

<sup>a</sup> Independent samples Mann-Whitney U test
<sup>b</sup> Chi-square test

Effect of training and guideline on the %SpO2-wtr

There was a small but significant decrease median SpO2, where IQR remained similar (before vs after training: 94 (91–96) % vs 93 (91–96)%; p = 0.02). After training and guideline implementation, the %SpO2-wtr significantly increased (before vs after training: 48.0 (19.6–63.9) % vs 61.9 (48.5–72.3)%; p < 0.005), with a concomitant decrease in SpO2 > 95% (44.0 (27.8–66.2) % vs 30.8 (22.6–44.5)%; p < 0.05) and a nonsignificant decrease in SpO2 > 98% (9.4 (4.2–26.8) % vs 6.1 (2.3–12.1)%; ns). %SpO2 < 85% remained similar (17.5 (8.5–27.9) % vs 17.2 (7.8–26.5)%; ns) as well as for SpO2 < 80% (1.9 (1.0–3.0) % vs 1.7 (0.8–2.6)%; ns) (Table 2) (Fig. 2).

Effect of training and guideline on the occurrence of ABCs

Before training and guideline implementation, 79 infants received noninvasive respiratory support, of which 29/79 infants had a total of 186 ABCs where extra FiO2 was given. After training and guideline implementation, 57 infants received noninvasive respiratory support, and 28/57 had a total of 168 ABCs (Table 3). After training and guideline implementation, the depth and duration of bradycardia did not change. Although no difference was observed in the depth of SpO2 < 80% during ABC, the duration of SpO2 < 80% decreased significantly (2 (1–2) minutes vs 1 (1–2) minute; p < 0.05) (Table 4).

Although the baseline and the maximum increase of FiO2 during the ABC did not change, the duration of titrating oxygen back to the baseline concentration had a smaller range (3 (2–16) minutes to 3 (2–7) minutes; p < 0.05). There was no significant change in the occurrence of hyperoxaemia after ABCs (73% (135/186) vs 64% (108/168); ns), but the duration significantly decreased from 2 (0–7) minutes to 1 (1–3) minute; p < 0.01 (Table 4).
Discussion

We observed in this retrospective study that extra training and implementing a guideline in oxygen titration improved the compliance of caregivers in our NICU in oxygen targeting and a more prompt handling of ABCs. Preterm infants receiving oxygen spent significantly more time within the SpO2 target range of 85–95%, with a significant decrease in time SpO2 above 95%. The occurrence of hypoxaemia and hyperoxaemia during ABCs did not decrease, but both episodes lasted significantly shorter. This initiative in quality improvement had a positive effect, and if the observed reduction in the risk for hypoxaemia and hyperoxaemia could be maintained through repetitive training, it would be likely to improve the outcome of preterm infants.

Previous studies have reported a quality improvement in oxygen titration and oxygen saturation targeting, using an approach comparable to ours [6, 14, 19]. The problems were initially assessed, followed by embedding education and implementing a protocol, where after effectiveness was evaluated. In line with our findings, Ford et al. reported a significant improvement in time spent within the target range (90–95%) and a reduction of SpO2 above TR [14]. Lau et al. did not report the time spent within TR (85–92%) but observed a significant reduction in SpO2 ≥ 93% [19]. Also, in the study of Chow et al., the time spent within TR was not reported; they observed a decrease in severe ROP after introduction of an educational program combined with a titration protocol [6, 14, 19]. The fact that the findings were similar in most studies performed, including ours, makes it likely that this approach (training and guideline implementation) can be successful in most neonatal units.

Which part of the quality improvement that has contributed the most to the effect on the compliance of caregivers in oxygen titration and oxygen saturation targeting is unclear. Previous studies reporting the effect of guideline or education only were less successful compared to our study [2, 7, 11]. Clarke et al. reported no improved time within TR using a titration guideline. Arawiran et al. observed no improved adherence to TR (85–92%) after an education intervention with oral and online presentations, discussions of adverse effects of excessive oxygen, and displaying oxygen saturation distributions [2]. Also, Deuber et al. studied the effect of training with the aim to reduce hyperoxaemia and to increase caregivers’ knowledge. The time spent within TR (88–92%) was not reported; the time above TR was increased after training [11].

| Table 2. Median (IQR) in different saturation ranges |
|---------------------------------|-------------|-------------|
| %SpO2 < 80%                     | 1.9 (1.0–3.0) | 1.7 (0.8–2.6) | ns |
| %SpO2 < 85%                     | 5.9 (2.8–7.9) | 6.2 (2.5–8.0) | ns |
| %SpO2 − wtr 85–95%              | 48.0 (19.6–63.9) | 61.9 (48.5–72.3) | <0.005 |
| %SpO2 > 95%                     | 44.0 (27.8–66.2) | 30.8 (22.6–44.5) | <0.05 |
| %SpO2 > 98%                     | 9.4 (4.2–26.8) | 6.1 (2.3–12.1) | 0.06 |

*p value for all statistical analysis comprised nonparametric Kruskal-Wallis rank sum test.

*Time with SpO2 within various ranges collated for each infant individually and aggregated as proportions of the recorded time median (IQR).

Fig. 2 Time with SpO2 within various ranges collated over all infants and aggregated as a total proportion of the recorded time. The smoothed bell-shaped line represents a fitted normal density function parameterized by the empirical mean and standard deviation estimated from the proportion data of the recorded time within various SpO2 ranges. The distribution of the proportional recorded time data is slightly negatively skewed with a long tail at the left and a higher mass at the right-hand side, when compared with a normal distribution.
However, there are many variables that could have influenced the effect of training. Differences in content, approach and duration of the training but also the general workload, and the nurse to patient ratio could have influenced the results [3]. As part of our education, we discussed the results of our previous study, showing that \( \text{SpO}_2 > 95\% \) occurred in 79\% of the ABCs where oxygen was increased [33]. During the training, we observed that caregivers felt personally addressed, resulting in behavioral change by better titration of oxygen during apnoeas.

It is clear that guidelines were not followed exactly, and compliance with the exact timing and step size was not measured. Nevertheless, when presented as part of the training, they provided a realistic framework on how to avoid hyperoxaemia, without increasing hypoxaemia. When the guideline was introduced and implemented in our unit, we took into account the factors that are important for adopting a guideline [1]. To get all caregivers involved, the guideline was openly discussed during the training sessions.

Recently, we reported how nurses responded to ABC and handled the oxygen titration [33]. In a retrospective study in preterm infants on nCPAP, we observed that when extra oxygen was given to treat ABCs, iatrogenic hyperoxaemia occurred and lasted significantly longer than the bradycardia or hypoxaemia. Although the duration of hypoxaemia was comparable, the duration of hyperoxaemia was significantly longer (13 (4-30) minutes) in our previous study than to what we currently observed in the cohort before the intervention. A possible explanation could be the use of the \( \text{B} \) increase \( \text{FiO}_2 \) key on the A VEA-ventilator. When this key is activated, the ventilator increases the oxygen concentration delivered to the infant for 2 min, where after the ventilator will return to prior settings. Nevertheless, training and guideline implementation

---

**Table 3. Patient characteristics with ABCs**

| Characteristics | Before training | After training | \( p \) value |
|-----------------|-----------------|---------------|--------------|
| Gestational age at birth (weeks), median (IQR) | 27 + 6 (26 + 5–29) | 27 + 2 (26–28 + 2) | 0.19\(^a\) |
| Birthweight (grams), median (IQR) | 1016 (812–1199) | 965 (692–1199) | 0.51\(^a\) |
| Male sex, no. (%) | 22 (76) | 16 (57) | 0.14\(^b\) |
| Cesarean delivery, no. (%) | 13 (45) | 15 (53) | 0.51\(^b\) |
| Singleton, no. (%) | 22 (76) | 22 (79) | 0.57\(^b\) |
| Apgar at 5 min, median (IQR) | 8 (7–8) | 7 (6–9) | 0.25\(^a\) |
| Days with respiratory support, no. median (IQR) | 14 (8–32) | 19 (9–31) | 0.5\(^a\) |

\( a \) Independent samples Mann-Whitney U test

\( b \) Chi-square test

---

**Table 4. ABC characteristics with FiO2-therapy**

| Characteristics | Before training | After training | \( p \) value |
|-----------------|-----------------|---------------|--------------|
| ABC with \( \text{SpO}_2 > 95\% \) | 73\% | 64\% | ns\(^b\) |
| Number of ABC, no. median (IQR) | 4 (1–9) | 4 (2–8) | 0.64\(^a\) |
| Depth of bradycardia, bpm median (IQR) | 70 (60–75) | 69 (61–75) | ns\(^a\) |
| Duration of bradycardia, min median (IQR) | 1 (1–1) | 1 (1–1) | ns\(^a\) |
| Depth of \( \text{SpO}_2 < 80\% \), % | 70 (62–76) | 72 (61–77) | ns\(^a\) |
| Duration \( \text{SpO}_2 < 80\% \), min median (IQR) | 2 (1–2) | 1 (1–2) | 0.03\(^a\) |
| Baseline oxygen concentration, % | 25 (21–31) | 25 (21–30) | ns\(^a\) |
| Max increase oxygen concentration, % | 44 (39–52) | 43 (37–51) | ns\(^a\) |
| Duration of titration to baseline oxygen concentration, min median (IQR) | 3 (2–16) | 3 (2–7) | 0.010\(^a\) |
| Duration \( \text{SpO}_2 > 95\% \), min median (IQR) | 2 (0–7) | 1 (1–3) | 0.004\(^a\) |

\( a \) Independent samples Mann-Whitney U test

\( b \) Chi-square test
significantly reduced the duration of hypoxaemia and hyperoxaemia even more. Apparently, nurses were more prompt in their handling when an ABC occurred, but also titrated more carefully. Poets et al. found an increased risk of adverse outcomes in preterm infants who experienced intermittent hypoxaemia, lasting for approximately 1 min or more [23]. This emphasizes the need for awareness and accurate handling of ABCs by the nurses.

In the recent years, there is an increasing interest in an automatically titration of oxygen in preterm infants. Closed-loop devices designed for monitoring and controlling the oxygenation in (ventilated) preterm infants are clinically used in research related context [8, 15, 30, 35]. These studies have shown that using automated oxygen control significantly increased time of %SpO2-wtr of approximately 8–24%, however, the time outside TR varied between studies. Most studies, but not all, reduced hyperoxaemia, and some also reduced hypoxaemia [8, 15, 30, 35]. Our study within the manual control showed comparable results with automatic devices concerning the increased time %SpO2-wtr and decreased time %SpO2 above TR. To make sure that this effect remains, repetitive training should be implemented in our unit.

Recent randomized controlled trials demonstrated a lower mortality in preterm infants when SpO2 was targeted 91–95% as compared to 85–89% [5, 24, 25, 27, 28]. In the time period, this observational study was performed; our local guidelines recommended 85–95% but were changed to 90–95% after the study. It is possible that this change could lead to different results when measuring the effect of training and guideline implementation. Jones et al. recently demonstrated that preterm infants with BPD were much more stable and less difficult to target when higher SpO2 targets were used [17].

A limitation is the retrospective character of our study. The training and oxygen titration guidelines were initiated for the quality improvement in our unit, and for this reason, the effect was audited by comparing before and after the interventions instead of a randomized trial. The dip in the frequencies of SpO2 87–90% is associated with the generation of Masimo oximeters available in our unit at the time of this study, using an internal calibration algorithm that reduces the frequency of saturations of 87–90% and increases the frequency of higher values [16]. However, this would not have influenced the effect of training and guideline implementation as both groups were measured with the same oximeters.

Furthermore, we did not adjust for the contribution of the amount of ABCs of each patient, but we considered every ABC as an independent event because all ABCs are handled the same for each infant. An important factor that could have influenced the results is the workload of caregivers. However, the nurse to patient ratio, the number of patients, the severity of illness, and the NICU admission days were not different between the periods, which makes it unlikely that the workload differed between periods. In addition, based on the findings in recent large trials in oxygen saturation, in our unit, the TR was narrowed towards the higher end (90–95%). It is possible that not similar results will be reached as it will be more difficult to comply with a smaller TR.

Conclusion

Based on the observations of this study, training of caregivers combined with an oxygen titration guideline, improved the compliance to stay within SpO2 target range in preterm infants. Also, the amount of hyperoxaemia reduced, without an increase of hypoxaemia. Thereby, oxygen was better titrated and reduced the duration of hyperoxaemia after ABCs.

Authors’ contributions Ms. HAvZ was the executive researcher of the study. She performed literature search, data collection, data analysis, data interpretation, writing, and submitting of the manuscript. Mr. SCP was involved in the data analysis, critically reviewed the manuscript, and approved the final version. Mr. BJS was involved in the interpretation of the data, critically reviewed the manuscript, and approved the final version. Mr. EL critically reviewed the manuscript and approved the final version. Mr. ABtP was the project leader and performed literature search, designed the study, and coordinated the data analysis, data interpretation, writing, editing, and submitting of the manuscript.

Compliance with ethical standards The authors declare that they have no conflict of interest.

Ethical approval In the Netherlands, no ethical approval is required for anonymized studies with medical charts and patient data that were collected and noted for standard care. The LUMC Medical Ethics Committee provided a statement of no objection for obtaining and publishing the anonymized data.

Informed consent No informed consent was obtained and no informed consent is required for anonymized studies with medical charts and patient data that were collected and noted for standard care.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Alanen S, Valimaki M, Kaila M (2009) Nurses’ experiences of guideline implementation: a focus group study. J Clin Nurs 18(18):2613–2621. doi:10.1111/j.1365-2702.2008.02754.x
2. Arawiran J, Curry J, Welde L, Alpan G (2014) Sojourn in excessively high oxygen saturation ranges in individual, very low-

Springer
birthweight neonates. Acta Paediatrica (Oslo, Norway : 1992). doi:10.1111/apa.12827

3. Armbruster J, Schmidt B, Poets CF, Bassler D (2010) Nurses’ compliance with alarm limits for pulse oximetry: qualitative study. J Perinatol 30(8):531–534. doi:10.1097/jjp.0b013e3181d03e4d

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, Piazzia AJ, Sanchez PJ, Morris BH, Lario 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. Chow LC, Wright KW, Sola A (2003) Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 111(2):339–345

6. Clarke A, Yeomans E, Elsayed K, Medhurst A, Berger P, Skuza E, Tan K (2014) A randomised crossover trial of clinical algorithm for oxygen saturation targeting in preterm infants with different desaturation episodes. Neonatology 107(2):130–136. doi:10.1159/000368295

7. Deuber C, Abbasi S, Schwoebel A, Terhaar M (2011) Hyperoxia in very preterm infants: a systematic review of the literature. The Journal of Perinatal & Neonatal Nursing 25(3):268–274. doi:10.1097/JPN.0b013e318226ece2c

8. Deuber C, Abbasi S, Schwoebel A, Terhaar M (2013) The toxigen initiative: targeting oxygen saturation to avoid sequelae in very preterm infants. Advances in neonatal Care 13(2):139–145. doi:10.1111/anc.12013

9. Eichenwald EC (2016) Apnea of prematurity. Pediatrics 137(1). doi:10.1542/peds.2015-3757

10. Ellsberry DL, Ursprung R (2010) Comprehensive Oxygen Management for the Prevention of Retinopathy of Prematurity: the pediatric experience. Clin Perinatol 37(1):203–215. doi:10.1016/j.clp.2010.01.012

11. Ford SP, Leckie-Rude MK, Meinert KA, Anderson B, Sheehan MB, Haney BM, Leeks SR, Simon SD, Jackson JK (2006) Overcoming barriers to oxygen saturation targeting. Pediatrics 118(Suppl 2):S177–S186. doi:10.1542/peds.2006-0913P

12. Hallenberger A, Poets CF, Horn W, Seyfang A, Urschitz MS (2014) Closed-loop automatic oxygen control (CLAC) in preterm infants: a randomized controlled trial. Pediatrics 133(2):e379–e385. doi:10.1542/peds.2013-1834

13. Johnston ED, Boyle B, Juszczak E, King A, Brocklehurst P, Stenson BJ (2011) Oxygen targeting in preterm infants using the Masimo SET Radical pulse oximeter. Arch Dis Child Fetal Neonatal Ed 96(6):F429–F433. doi:10.1136/adc.2010.206011

14. Jones JG, Lockwood GG, Fung N, Lasenby J, Ross-Russell RL, Quine D, Stenson BJ (2016) Influence of pulmonary factors on pulse oximeter saturation in preterm infants. Arch Dis Child Fetal Neonatal Ed 101(4):F319–F322. doi:10.1136/archdischild-2015-308675

15. Laptook AR, Salhab W, Allen J, Saha S, Walsh M (2006) Pulse oximetry in very low birth weight infants: can oxygen saturation be maintained in the desired range? J Perinatol 26(6):337–341. doi:10.1038/ sj.jp.7211500

16. Lau YY, Tay YY, Shah VA, Chang P, Loh KT (2011) Maintaining optimal oxygen saturation in premature infants. The Perinatal Journal 15(1):e108–e113

17. Lim K, Wheeler KL, Gale TJ, Jackson HD, Kählstrand JF, Sand C, Dawson JA, Dargaville PA (2014) Oxygen saturation targeting in preterm infants receiving continuous positive airway pressure. J Pediatr 164(4):730–736.e731. doi:10.1016/j.jpeds.2013.11.072

18. Mills BA, Davis PG, Donath SM, Lucus LM, Doyle LW (2010) Improving compliance with pulse oximetry alarm limits for very preterm infants? J Paediatric Child Health 46(5):255–258. doi:10.1111/j.1440-1754.2009.01680.x

19. Ngiem TH, Hagadom JI, Terrin N, Syke S, MacKinnon B, Cole CH (2008) Nurse opinions and pulse oximeter saturation target limits for preterm infants. Pediatrics 121(5):e1039–e1046. doi:10.1542/peds.2007-2257

20. Poets CF, Roberts RS, Schmidt B, Whyte RK, Azstalos EV, Bader D, Bairam A, Moddemann D, Pielowski A, Rabi Y, Solimano A, Nelson H (2015) Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. JAMA 314(6):595–603. doi:10.1001/jama.2015.8841

21. Saugstad OD, Aune D (2011) In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. Neonatology 100(1):1–8. doi:10.1159/000322001

22. Schmidt B, Whyte RK, Azstalos 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 310(20):2111–2120

23. Sink DW, Hope SA, Hagadom JI (2011) Nurse-patient ratio and achievement of oxygen saturation goals in premature infants. Arch Dis Child Fetal Neonatal Ed 96(2):F93–F98. doi:10.1136/archdischild-2011.278616

24. Stenson BJ (2016) Oxygen saturation targets for extremely preterm infants after the NeOProM trials. Neonatology 109(4):352–358. doi:10.1007/s00109-016-04493

25. Tarnew-Mordi W, Stenson B, Kirby A, Juszczak E, Donoghoe M, Deshpande S, Morley C, King A, Doyle LW, Fleck BW, Davis PG, Halliday HL, Hague W, Cairns P, Darlow BA, Fielder AR, Gebski V, Marlow N, Simmer K, Tin W, Ghadge A, Williams C, Keech A, Wardle SP, Keeskes Z, Kluckow M, Gole G, Evans N, Malcolm G, Luig M, Wright I, Stack J, Tan K, Pritchard M, Gray PH, Morris S, Headley B, Dargaville P, Simes RJ, Brocklehurst P (2016) Outcomes of two trials of oxygen-saturation targets in preterm infants. N Engl J Med 374(8):749–760. doi:10.1056/NEJMoa1514212

26. Tin W, Gupta S (2007) Optimum oxygen therapy in preterm babies. Arch Dis Child Fetal Neonatal Ed 92(2):F143–F147. doi:10.1136/adc.2005.092726

27. Urschitz MS, Horn W, Seyfang A, Hallenberger A, Herberts T, Miksch S, Popow C, Muller-Hansen I, Poets CF (2004) Automatic control of the inspired oxygen fraction in preterm infants: a randomized crossover trial. Am J Respir Crit Care Med 170(10):1095–1100. doi:10.1164/rccm.200407-929OC

28. van der Eijk AC, Dankelman J, Schutte S, Simonzh HJ, Smit BJ (2012) An observational study to quantify manual adjustments of the inspired oxygen fraction in extremely low birth weight infants. Acta Paediatrica (Oslo, Norway : 1992) 101(3):e97–e104. doi:10.1111/j.1651-2227.2011.02506.x

29. van Kaam AH, Hummeler HD, Wiltens M, Swietlinski J, Lal MK, te Pas AB, Lista G, Waitz M, Warakomska M, Cavugoli F, Bancalari E, Claire N, Bachman TE (2015) Automated versus manual oxygen control with different saturation targets and modes of respiratory support in preterm infants. J Pediatr 167(5):545–550.e541–542. doi:10.1016/j.jpeds.2015.06.012

30. van Zanten HA, Tan RN, Thio M, de Man-van Ginkel JM, van Zware LM, Lopriore E, Te Pas AB (2014) The risk for hyperoxemia after apnoea, bradycardia and hypoxaemia in preterm infants. Arch Dis Child Fetal Neonatal Ed. doi:10.1136/archdischild-2013-305745
34. Vento M (2014) Oxygen supplementation in the neonatal period: changing the paradigm. Neonatology 105(4):323–331. doi:10.1159/000360646

35. Zapata J, Gomez JJ, Araque Campo R, Matiz Rubio A, Sola A (2014) A randomised controlled trial of an automated oxygen delivery algorithm for preterm neonates receiving supplemental oxygen without mechanical ventilation. Acta Paediatrica (Oslo, Norway: 1992) 103(9):928–933. doi:10.1111/apa.12684