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Oxygenation of the Immature Infant: A Commentary and Recommendations for Oxygen Saturation Targets and Alarm Limits

Ola Didrik Saugstad

Department of Pediatric Research, Clinic of Child and Adolescent Medicine, Oslo University Hospital, University of Oslo, Oslo, Norway

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Immature infants · Oxygenation targets · Mortality · Retinopathy of prematurity · Necrotizing enterocolitis · Oxygen dilemma

Abstract
Background: For 70 years, there has been a search for the optimal oxygenation of premature infants. In spite of the lack of evidence, guidelines have successively reduced oxygenation targets during these years. ***Objectives:*** (1) To present a summary of previously published meta-analyses of 5 randomized studies (NeOProM) which tested a low (85–89%) versus a high (91–95%) oxygen saturation target the first weeks after birth on outcome of immature newborn infants. (2) To present international recommendations for oxygenation the first weeks after birth. ***Methods:*** Data were retrieved from meta-analyses and reviews of these studies. ***Results:*** Mortality and necrotizing enterocolitis (NEC) are significantly higher in patients with a low saturation target (relative risk, RR 1.16 and 1.24, respectively), while severe retinopathy of prematurity (ROP) is reduced (RR 0.74), fortunately without a change in the rate of blindness. Severe intraventricular hemorrhage, patent ductus arteriosus, and bronchopulmonary dysplasia (defined physiologically) were not significantly affected by the oxygen targets in the range of these studies. Based on these data, it is recommended that SpO_2 targets from birth to 36 weeks postconceptional age for infants <28 weeks gestational age (GA) should be between 90 and 94% (with alarm limits of 89 and 95%), respectively. It is recommended to keep infants small for GA well oxygenated within the suggested targets avoiding fluctuations. ***Conclusions:*** The ideal oxygen saturation targets for infants <28 weeks GA are not known. Mortality, ROP, and NEC seem to be particularly oxygen-sensitive outcome variables. The optimal oxygen saturation for premature infants >28 weeks GA has not been carefully studied.

Introduction

Optimal oxygenation of the preterm infant has been an issue ever since the association between hyperoxia and retrolental fibroplasia was understood almost 70 years ago. The goal of oxygenation has since then been to prevent this devastating disease, which today is named retinopathy of prematurity (ROP), without increasing mortality and other complications [1].

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E-Mail karger@karger.com
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Ola Didrik Saugstad, MD, PhD, FRCPE
Department of Pediatric Research, Clinic of Child and Adolescent Medicine
Oslo University Hospital, University of Oslo
PO Box 4950 Nydalen, NO–0424 Oslo (Norway)
E-Mail odsaugstad@rr-research.no

Table 1. Characteristics of the individual trials in NeOProM (Neonatal Oxygen Prospective Meta-Analysis)

	SUPPORT		COT		BOOST II UK		BOOST II NZ		BOOST II AU	
	low	high	low	high	low	high	low	high	low	high
GA, weeks	26.0 (1)	26.0 (1)	25.6 (1.2)	25.6 (1.2)	26.0 (1.3)	26.0 (1.3)	26.1 (1.2)	26.1 (1.2)	26.0 (1.2)	26.0 (1.2)
BW, g	836 (193)	825 (193)	827 (190)	844 (199)	821(182)	818 (189)	873 (202)	884 (188)	817 (177)	833 (190)
AS, %	96.8	95.6	88.2	90.0	93.7	91.6	88.2	89.4	88.7	92.5
Number	654	662	578	569	486	487	170	170	568	567

SUPPORT, Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial [14] (trial registry NCT 002333242); COT, Canadian Oxygen Trial [16] (trial registry NCT 006371693); BOOST, Benefits of Oxygen Saturation Targeting Trial (UK, AU, NZ) [17] (trial registry ISRCTN00842661); GA, mean (SD) gestational age; BW, mean (SD) birth weight; AS, antenatal steroids; UK, United Kingdom; AU, Australia; NZ, New Zealand.

Monitoring of oxygenation has changed dramatically during these years. In the 1940s and 1950s, the oxygen status was assessed by fraction of inspired oxygen (FiO_2). Blood gas analyses were introduced in the late 1950s and 1960s, and intermittent PaO_2 measurements together with metabolic components as base deficits and lactate became important indicators of oxygenation. In the 1970s and 1980s, immature babies developed ROP in spite of a tighter blood gas control. It was, therefore, hoped that the continuous transcutaneous PO_2 ($TcPO_2$) monitoring introduced in the 1970s would better prevent ROP. In the 1980 and 1990s, pulse oximetry became the preferred monitoring of oxygenation.

How did the change in techniques affect oxygenation of the preterm? In the 1950 and 1960s, an FiO_2 in the incubator <0.4 was recommended, and it was strongly believed that this eliminated the problem of ROP [1]. There is, however, reason to believe many infants were still exposed to PaO_2 >75 mm Hg (10 kPa) for a substantial time those days. In the 1960 and 1970s, a PaO_2 of 50–80 mm Hg (6.7–10.7 kPa) was recommended [2, 3].

A study concluded that increased risk of severe ROP was related to increased length of time that the $TcPO_2$ exceeded 80 mm Hg [4]. After introduction of pulse oximetry, a target SpO_2 of 85–95% was suggested [5], which corresponds to a PaO_2 range of 29–67 mm Hg (3.8–8.9 kPa) in oxygen-dependent preterm babies in the first 2 weeks of life [6]. Introduction of these new techniques to monitor oxygenation, FiO_2, PaO_2, $TcPO_2$, and SpO_2, has, therefore, resulted in successively lower oxygenation targets, however, without appropriate studies supporting the changes in practice.

Today, the goal of oxygen control is not only to prevent ROP. Mortality has to be balanced versus morbidities such as necrotizing enterocolitis (NEC) and perhaps bronchopulmonary dysplasia (BPD), in addition to secure an optimal neurocognitive outcome. The described downward trend in oxygenation was recently changed with recommendations of SpO_2 targets of 90–95% corresponding to PaO_2 of 35–67 mm Hg (4.6–8.9 kPa) [6].

Previous clinical guidelines were mainly based on observational studies, and data around the turn of the century indicated strongly that a low oxygen saturation or PO_2 protects premature infants against ROP without increasing mortality [7–10]. In 2 randomized trials, it was tested whether higher saturation targets could prevent progression of ROP. The STOP-ROP (Supplemental Therapeutic Oxygen for Pretreshold Retinopathy of Prematurity) trial randomized preterm infants with prethreshold ROP at 35 weeks of postmenstrual age to either 89–94% or 96–99% SpO_2. No difference in ROP was found; however, the highest target was associated with more adverse pulmonary events [11]. The BOOST (Benefits of Oxygen Saturation Targeting) trial randomized infants born before 30 weeks gestational age (GA) in need of oxygen supplementation at 32 weeks GA to either lower (91–94%) or higher (95–98%) SpO_2 targets. No important differences between the groups regarding ROP, growth, or development were found, but the higher target was associated with requirement for more home oxygen [12]. Both the low and high SpO_2 arms in these 2 studies aimed at quite high values, and today none of these studies would be acknowledged to study low saturation targets.

NeOProM Studies

After publication of these studies, it became evident that large randomized studies were needed in order to penetrate in more depth the issue of optimal oxygenation of immature infants. Five clinical studies were initiated with rather similar protocols in order to undertake a prospective individual patient meta-analysis, The NeOProM

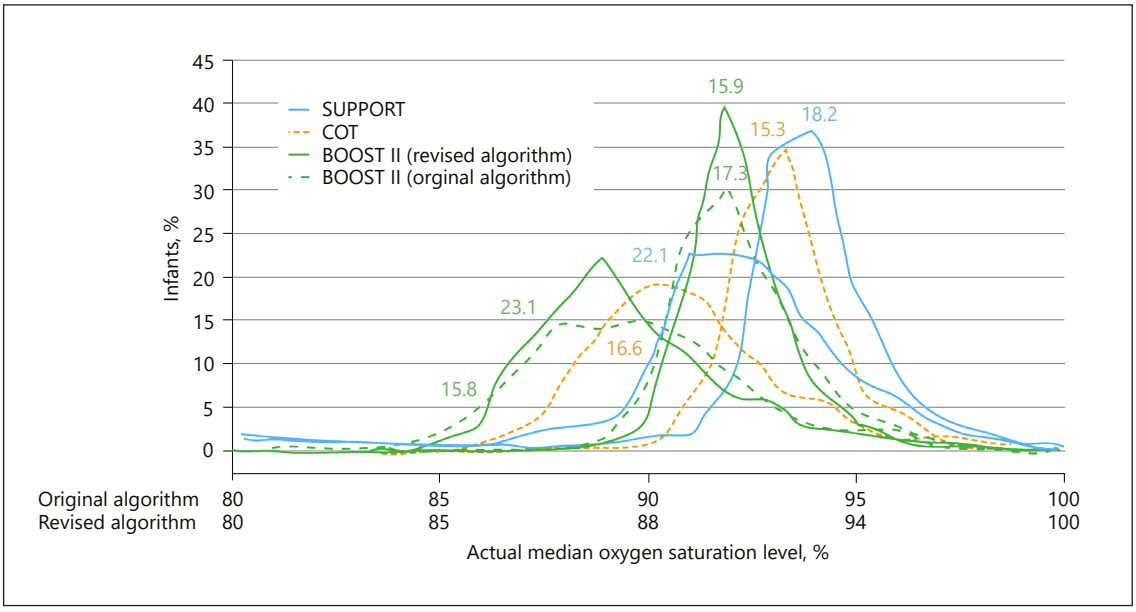

Fig. 1. Median SpO_2 in the trials in high and low oxygen saturation target groups. These data show that both the SUPPORT and COT study reached higher median SpO_2 than targeted for both the low and high group. BOOST II seems to hit the target better when assessed by median SpO_2 (from Manja et al. [22] with permission).

(Neonatal Oxygen Prospective Meta-Analysis) study randomized babies <28 weeks GA to a low or a high oxygen saturation target before the age of 24 h [13].

Table 1 gives an overview of the participating studies and some basic characteristics of the enrolled infants in the 2 groups of each of the studies [14–18].

Totally, 4,965 infants were enrolled, 2,480 to the low saturation target (85–89%) and 2,485 to the high oxygen saturation target (91–95%). The trial masked the caregivers to the SpO_2 target range allocation of the infants by using offset pulse oximeters that were adjusted to read 3% higher or lower than the underlying value measured [19].

In spite of almost identical protocols with similar masking of the pulse oximetry for groups, significant differences in targets were reached (Fig. 1). Median distribution of SpO_2 was higher than the target both for the SUPPORT and the COT (Canadian Oxygen Trial) trial. The 3 BOOST II trials were most successful in reaching the targets for both groups assessed by median values [20]. It must, however, be underlined that median values do not accurately reflect the real time each baby spent within the defined target range.

Centers in 3 trials (BOOST II Australia, BOOST II UK, and COT) changed all the study oximeters to a new calibration software (algorithm) partway through the recruitment making interpretation of results more complicated. In the present review, data are lumped together regardless of the algorithm used in the pulse oximeters. Four meta-analyses and systematic reviews of these data have been published [19, 21–23]; data from these are summarized in Table 2.

Death and/or Neurodevelopmental Impairment at 18–24 Months of Age

The primary outcome of NeOProM studies was the combined outcome of death and/or major disability/neurodevelopmental impairment (NDI: blindness, deafness, cognitive impairment, or cerebral palsy) at 18–24 months of age. Relative risk (RR) showed no difference between the low and high saturation target groups (RR 1.04, 95% CI 0.98–1.10). Askie et al. [19] also stratified into groups of infants <26 or ≥26 weeks GA and male versus female without finding significant differences between groups.

Mortality separately showed a significant increase in RR from 1.16 (95% CI 1.03–1.31) [19] to 1.18 (95% CI 1.03–1.36) [23] in the low saturation target group. For NDI alone, no differences were found between both groups (RR 1.01, 95% CI 0.93–1.09).

There was no significant difference between the groups regarding cerebral palsy (gross motor function classification system ≥2) at 18–24 months of age (RR 1.02, 95% CI 0.79–1.32).

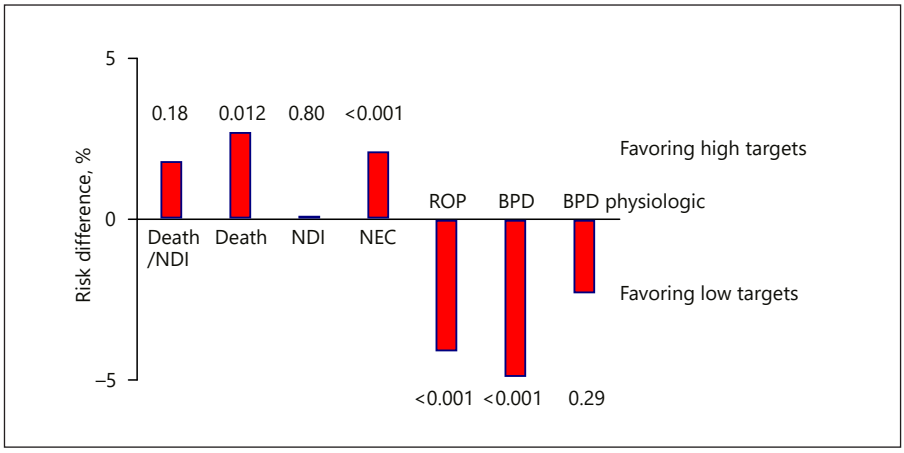

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Fig. 2. Risk difference for death and morbidities in the NeOProM studies. Low (85–89%) versus high (91–95%) SpO_2 targets. *p* values are given. Abbreviations: see text. Data from Askie et al. [19].

Table 2. Main results from 4 reviews of NeOProM studies

First author	Death and/or NDI	Death	NDI	ROP	NEC	BPD	PDA
Saugstad [21]		1.18 (1.04–1.34)		0.74 0.59–0.92)	1.25 (1.05–1.49)	0.95 (0.86–1.04)	1.01 (0.95–1.08)
Manja [22, 23]	1.05 (0.98–1.12)	1.18 (1.03–1.36)	1.00 (0.90–1,12)	0.72 (0.5–1.04)	1.24 (1.05–1.47)	0.95 (0.87–1.04)	
Askie [19]	1.04 (0.98–1.10)	1.16 (1.03–1.31)	1.01 (0.93–1.09)	0.72 (0.61–0.85)	1.24 (1.05–1.47)		1.00 (0.95–1.06)

NDI, neurodevelopmental impairment; ROP, severe retinopathy of prematurity; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; PDA, persistent ductus arteriosus. Data are given as relative risk with 95% confidence intervals. RR <1 favors low and >1 high oxygen saturation targets.

ROP, NEC, Patent Ductus Arteriosus, Intraventricular Hemorrhage, and Visual and Auditory Impairment

ROP requiring treatment showed an approximately 25% reduced risk in the low saturation group while severe NEC requiring treatment showed a 25% increased risk in this group. Patent ductus arteriosus needing treatment (RR 1.00, 95% CI 0.95–1.06), severe intraventricular hemorrhage grade 3–4 (RR 1.02, 95% CI 0.88–1.19), deafness (RR 1.01, 95% CI 0.72–1.42), and severe visual impairment (RR 1.14, 95% CI 0.65–2.00) did not show differences between the groups. BPD defined physiologically showed a nonsignificant tendency to a small reduction in the low saturation target group (RR 0.95, 95% CI 0.86–1.04). However, when BPD was defined as oxygen requirement at 36 weeks postconceptional age, there was a significant reduction in the low saturation target group (RR 0.87, 95% CI 0.81–0.94) (number needed to treat 20).

Figure 2 shows the absolute risk differences (RD) between both oxygen saturation target groups for several outcome variables [19]. Infants randomized to the lower SpO_2 target range had significantly increased risk of death at 18–24 months corrected age (RD 2.8%) (number needed to produce 1 extra death with lower saturation targeting is 31). For NEC requiring surgery or causing death, RD was 2.2% (number needed to harm 37). Infants randomized to higher SpO_2 targets had a higher risk of ROP requiring treatment (RD 4.2%) (number needed to prevent 1 case with severe ROP is 34 with low saturation target). RD regarding BPD was 5.9% ($p < 0.01$) (number needed to prevent 1 case of BPD with low oxygen target is 20). This is not surprising because BPD definition was based on oxygen use at 36 weeks postconceptional age. When a physiologic definition was used in the SUPPORT and BOOST II UK trials, RD is reduced to 2.4% ($p = 0.29$).

Small for GA Infants

Data from the SUPPORT trial have been analyzed specifically for small for GA (SGA) infants defined as <10th percentile of weight. Appropriate for gestational GA infants had a mortality of 16.4% with no differences between both oxygen saturation target groups. By contrast, SGA children had a significantly higher risk of mortality (38.5%), which was more than 2-fold increased in the lower (56.1%) compared with the higher (25.5%) target

group [24, 25]. However, in the Cochrane review, a similar analysis was not performed [19].

SGA infants in the low saturation target group from the SUPPORT study had lower median oxygen saturation the first 3 days of life and more time with hypoxemia <80% and more long-standing intermittent hypoxemia around 2 weeks of age compared with the other 3 groups. SGA infants with saturations ≤92% the first 3 days of life had a substantially lower survival than the other 3 groups at the age of 13 weeks (54 vs. 83–91%) [25].

International Recommendations

Based on these data, international and national recommendations for oxygen targets for immature infants have recently been published.

The Committee on Fetus and Newborn of the American Academy of Pediatrics recommends SpO_2 targets between 90 and 95% [26] but underlines the ideal oxygen saturation range for infants with extremely low birth weights remains unknown and is likely patient specific and dynamic depending on various factors such as gestational and chronological age, underlying disease, and transfusion (hemoglobin F) status. Regardless of the chosen target, an upper alarm limit of approximately 95% while the infant remains on supplemental oxygen is reasonable. A lower alarm limit will generally need to extend somewhat below the lower target, as practical and clinical considerations, as well as the steepness of the oxygen saturation curve at lower saturation must be taken into account. Recently published European guidelines state that in preterm babies receiving oxygen, the saturation target should be between 90 and 94%. To achieve this, suggested alarm limits should be 89 and 95% [27] and alarming at 88 and 96%.

Discussion

During the last 70 years, oxygenation has been lowered in parallel with the new techniques for the assessment of oxygenation. Data from the NeOProM studies indicate that, in fact, an oxygen saturation target of 85–89% is too low in infants with extremely low birth weights.

A low saturation target increases mortality and NEC, but a high saturation target increases the risk of severe ROP. The Cochrane review of the NeOProM studies concludes that for every 31–40 premature infants <28 weeks GA targeted at a low oxygen range (85–89%), on average there would be 1 additional death and 1 additional case of severe NEC but with 1 infant with severe ROP less, and 8 less days of oxygen per patient [19]. This illustrates the so-called "oxygen dilemma," that both a high and low saturation target lead to excess complications although the complications differ between the 2 target groups. Data from these studies indicate that mortality, ROP, and NEC are oxygen sensitive in immature infants, whereas intraventricular hemorrhage, patent ductus arteriosus, and, surprisingly, physiologic BPD are independent on the oxygen level in the ranges applied in NeOProM.

In spite of these 5 large studies, there are still a number of unanswered questions regarding how to oxygenate immature newborn infants beyond the delivery room until 36 weeks postconceptional age: we do not know the optimal SpO_2 for these infants, and we do not know if targets should differ between the most immature and the most mature infants of this group. We do not understand fully why there is a higher mortality in the low saturation group. We do not know whether SpO_2 targets should be fixed during the whole period or increase gradually as the child matures [28]. We do not know whether SGA infants should be treated differently than infants appropriate for GA? Data from SUPPORT indicate these infants should be kept well oxygenated; however, the increased mortality in the low saturation target SGA infants has so far not been confirmed by the Cochrane data [19]. The SUPPORT study differed from the other NeOProM studies by including the infants earlier, i.e., before 2 h of age, versus 24 h for the other studies. Therefore, infants with pulmonary hypertension, for instance, could have been included in SUPPORT but not in the other studies, contributing to a different and more unstable as well as more oxygen-dependent population in the SUPPORT trial.

Do the recent recommendations of a target of 90–94/95% SpO_2 lead to more blindness than treatment at lower saturation? Severe vision impairment was on average 1.2% in these studies. Fortunately, the meta-analyses did not show more blindness in spite of more severe ROP in the high saturation target group although some studies report increased blindness after new guidelines recommending higher target saturations were published. In a Swedish region, a significant 2.2-fold increase in treated ROP was found after changing recommendations to higher targets [29]. However, alarm limits were not tightly defined. It is probably important to focus on alarm limits, and the upper alarm limit is suggested to be 94 or 95%. In order to avoid overlap between alarm limits and targets, European guidelines now recommend targets between 90–94% with alarm limits of 89 and 95%, which means alarming at 88 or 96%.

With almost 5,000 enrolled infants <28 weeks GA, the 5 oxygen trials in NeOProM recently summarized [30] constitute one of the largest trials in newborn medicine. We still do not know the optimal oxygenation of these immature infants. We probably will not know this until new studies have been carried out, and a large sample size is needed to detect differences. It is, therefore, unlikely that all these questions will be solved in the nearest future. However, new techniques with closed loop control of FiO_2 based on SpO_2 might lead to tighter oxygen control and less fluctuations, hopefully, contributing to less mortality and morbidity due to nonoptimal oxygenation [31].

Conclusions and Recommendations

The "oxygen dilemma" of immature infants is not solved but it seems reasonable to prioritize survival and less NEC versus ROP which often is treatable. Therefore, saturation targets should aim at 90–94/95%. Alarm limits should be tight, for instance 89 and 95%, respectively. SGA infants should be kept high within this range trying to avoid fluctuations especially during the first 3 days of life.

Disclosure Statement

The author has no conflicts of interest to declare.

References

1 Silverman WA: A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. Pediatrics 2004;113:394–396.
2 American Academy of Pediatrics. Committee on Fetus and Newborn, ACOG Committee on Obstetrics: Maternal and Fetal Medicine. Guidelines for Perinatal Care, ed 2. Elk Grove Village, American Academy of Pediatrics, 1988.
3 Darlow BA, Morley CJ: Oxygen saturation targeting and bronchopulmonary dysplasia. Clin Perinatol 2015;42:807–823.
4 Flynn JT, Bancalari E, Snyder ES, Goldberg RN, Feuer W, Cassady J, et al: A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med 1992;326:1050–1054.
5 American Academy of Pediatrics and the American College of Obstetricians and Gynecologists: Guidelines for Perinatal Care, ed 6. Elk Grove Village, American Academy of Pediatrics, 2007.
6 Quine D, Stenson BJ: Arterial oxygen tension (PaO_2) values in infants <29 weeks of gestation at currently targeted saturations. Arch Dis Child Fetal Neonatal Ed 2009;94:F51–F53.
7 Tin W, Milligan DW, Pennefather P, Hey E: Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106–F110.
8 Chow LC, Wright KW, Sola A; CSMC Oxygen Administration Study Group: Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003;111:339–345.
9 Anderson CG, Benitz WE, Madan A: Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. J Perinatol 2004;24:164–168.
10 Saugstad OD, Aune D: In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. Neonatology 2011;100:1–8.
11 Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics 2000;105:295–310.
12 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM: Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;349:959–967.
13 Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W; NeOProM Collaborative Group: NeOProM: Neonatal Oxygenation Prospective Meta-Analysis Collaboration study protocol. BMC Pediatr 2011;11:6.
14 SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al: Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959–1969.
15 Vaucher YE, Peralta-Carcelen M, Finer NN, et al; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network: Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. N Engl J Med 2012;367:2495–2504.
16 Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, et al: Canadian Oxygen Trial (COT) Group. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA 2013;309:2111–2120.
17 BOOST II United Kingdom Collaborative Group, BOOST II Australia Collaborative Group, BOOST II New Zealand Collaborative Group, Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, et al: Oxygen saturation and outcomes in preterm infants. N Engl J Med 2013;368:2094–2104.
18 Darlow BA, Marschner SL, Donoghoe M, et al: Randomized controlled trial of oxygen saturation targets in very preterm infants: two year outcomes. J Pediatr 2014;165:30–35.e2
19 Askie LM, Darlow BA, Davis PG, Finer N, Stenson B, Vento M, Whyte R: Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. Cochrane Database Syst Rev 2017;4:CD011190.
20 BOOST-II Australia and United Kingdom Collaborative Group, Tarnow-Mordi W, Stenson B, Kirby A, et al: Outcomes of two trials of oxygen-saturation targets in preterm infants. N Engl J Med 2016;374:749–760.
21 Saugstad OD, Aune D: Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology 2014;105:55–63.
22 Manja V, Lakshminrusimha S, Cook DJ: Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis. JAMA Pediatr 2015;169:332–340; erratum 507.
23 Manja V, Saugstad OD, Lakshminrusimha S: Oxygen saturation targets in preterm infants and outcomes at 18–24 months: a systematic review. Pediatrics 2017;139:e20161609.
24 Walsh MC, Di Fiore JM, Martin RJ, Gantz M, Carlo WA, Finer N: Association of oxygen target and growth status with increased mortality in small for gestational age infants: further analysis of the Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial. JAMA Pediatr 2016;170:292–294.

25 Di Fiore JM, Martin RJ, Li H, Morris N, Carlo WA, Finer N, Walsh M; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health, and Human Development Neonatal Research Network: Patterns of oxygenation, mortality, and growth status in the Surfactant Positive Pressure and Oxygen Trial Cohort. J Pediatr 2017;186:49–56.e1.
26 Cummings JJ, Polin RA; Committee on Fetus and Newborn: Oxygen targeting in extremely low birth weight infants. Pediatrics 2016;138:e20162904.
27 Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al: European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2016 update. Neonatology 2017;111:107–125.
28 Chen ML, Guo L, Smith LE, Dammann CE, Dammann O: High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. Pediatrics 2010;125:e1483–e1492.
29 Holmström G, Tornqvist K, Al-Hawasi A, Nilsson Å, Wallin A, Hellström A: Increased frequency of retinopathy of prematurity over the last decade and significant regional differences. Acta Ophthalmol 2017;96:142–148.
30 Stenson B, Saugstad OD: Oxygen treatment for immature infants beyond the delivery room. Lessons from randomized studies. J Pediatr, in press.
31 Claure N, Bancalari E: Closed-loop control of inspired oxygen in premature infants. Semin Fetal Neonatal Med 2015;20:198–204.