Review Article

Safe and sound oxygen therapy for extremely preterm infants: a literature review

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Abstract: Liberal oxygen therapy increases the need for treatment of retinopathy of prematurity in extremely preterm infants, while restricted oxygen therapy increases the risks of severe necrotizing enterocolitis and death. Safe and sound oxygen therapy aims to achieve the best possible trade-off between these risks and benefits in a local neonatal intensive care unit. In this review, we pose common clinical questions, summarize the evidence-based responses, and flag uncertainties that require further research on oxygen use for extremely preterm infants. To monitor arterial oxygenation non-invasively, clinicians have used transcutaneous oxygen probes and pulse oximetry. Both devices were widely adopted many years before randomized trials had been performed to determine how these monitors should be used. Belated trials of different oxygen saturation target ranges and the meta-analysis of the individual participant data quantified the balance between the benefits and risks of higher pulse oximeter saturations. Neonatal intensive care units with high risks of death and severe necrotizing enterocolitis will benefit more from higher target saturations than units where the risks of these outcomes are low. Similarly, neonatal intensive care units with a high risk of severe retinopathy will experience more harm from higher target saturations than units where the risk of severe retinopathy is low. Manual titration of supplemental oxygen remains the current standard of care. Explicit titration protocols, training of bedside staff, sensible workloads and work hours, and regular use of pulse oximeter histograms for audit and feedback may improve compliance with the chosen oxygen saturation target range and pulse oximeter alarms.

Keywords: Oxygen; efficacy; safety; extremely preterm infant

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What is safe and sound oxygen therapy for extremely preterm infants?

Many extremely preterm babies need extra oxygen to breathe for several weeks or even months after birth. However, too liberal arterial oxygenation increases the risk of severe retinopathy of prematurity (ROP) (1,2) while too restricted arterial oxygenation increases the risks of death and necrotizing enterocolitis (NEC) (1). In addition, prolonged episodes of intermittent hypoxemia are associated with a late death after a postmenstrual age of 36 weeks or neurodevelopmental disability in survivors (3). The fine balance between the dangers of too much and too little supplemental oxygen requires especially careful and skillful adjustment of oxygen therapy in this population. Clinicians who practice "safe and sound" oxygen therapy strive to achieve this balance. Despite decades of research, however,

the evidence that guides oxygen therapy in extremely preterm infants is still evolving and remains incomplete. In this review, we pose common clinical questions, summarize the evidence-based responses, and flag uncertainties that require further research.

How do clinicians monitor arterial oxygenation?

It has been known since the mid-20th century that cyanosis is an unreliable clinical sign of hypoxemia (4,5). Arterial oxygenation should be measured reliably and accurately. In unstable and acutely ill patients, including preterm infants, arterial blood is submitted intermittently for blood gas analysis. The samples are preferably drawn from indwelling arterial catheters. Alternatively, samples can be obtained by arterial puncture. In addition, neonatal clinicians have used non-invasive monitoring of oxygenation for nearly 50 years. Non-invasive monitoring is feasible throughout the entire stay in the neonatal intensive care unit (NICU), avoids the pain and blood loss of arterial punctures, and the added risks of infection and thrombosis that are associated with indwelling arterial catheters (6,7).

Which non-invasive monitors are available for routine care?

Two types of non-invasive technologies are commercially available for the continuous monitoring of arterial oxygenation. Transcutaneous monitors measure the partial pressure of oxygen or oxygen tension while pulse oximeters estimate the arterial oxygen saturation (SaO_2) (5). Saturation values indicate what percentage of the hemoglobin in circulating red blood cells is bound to oxygen. The relationships between oxygen saturations and oxygen tensions are described by the shape and position of the oxygen dissociation curve of hemoglobin. In theory, pulse oximeters are less suitable than transcutaneous pO_2 ($tcpO_2$) monitors for detecting dangerous hyperoxemia in extremely preterm infants. This is because large changes in oxygen tension may lead to small or no changes in saturations because of the flattening of the upper part of the S-shaped oxygen dissociation curve (8).

A comprehensive review of the engineering principles, and of the measurement properties of both types of non-invasive monitoring devices in infants has recently been published (8). In this article, we summarize the main practice points and highlight mistakes that were made in the past as the two technologies were introduced into routine neonatal care.

Transcutaneous pO_2 monitors

"*In 1971, during my first year at Medical School in Göttingen, Germany, I took driving lessons. One day, my instructor told me proudly that his daughter and son-in-law were measuring oxygen 'through the skin'. I smiled politely but did not believe him. However, I soon learnt that my instructor had been right: his daughter Renate and her husband Albert Huch had indeed developed a technology to measure the partial pressure of oxygen on the skin of adults and newborn babies (9).*"—Barbara Schmidt.

The development of transcutaneous oxygen sensors in the early 1970s was a major technological advance. A heated pO_2 electrode was applied to the skin and set initially to a temperature of 43 ℃. This localized and controlled hyperthermia "arterialized" the blood in the vasodilated skin capillaries (10,11). The temperature was subsequently increased to 44 ℃ for preterm and up to 45 ℃ for term infants (12). In expert hands and with adequate *in situ* calibration, the $tcpO_2$ values correlated reasonably well with concurrent arterial values under most clinical conditions (11,13).

Commercial development was swift. Soon, multiple manufacturers produced transcutaneous oxygen monitors which were rapidly adopted in European and North American NICUs (14). However, numerous problems were reported after this technology was introduced into routine care. The fragile skin of preterm infants could be damaged by both the adhesive ring of the probe and by the heating coil within the sensor. To prevent burns, the $tcpO_2$ electrode had to be moved frequently and carefully recalibrated each time. The placement and *in situ* calibration of the electrode may not have been performed correctly by some caregivers (14). Many clinicians assumed that transcutaneous and arterial oxygen tension were identical, and this assumption led to misinterpretations of the data and frustration with the device (14). At least one commercially available electrode was demonstrably far less accurate than the original electrode developed by Huch *et al.* (15).

In 1980, the Department of Health and Social Security in the UK issued a "hazard notice" about transcutaneous oxygen monitors, followed by Health and Welfare Canada's "medical device alert" in 1985 (14). The developers of the original transcutaneous oxygen electrode responded with an article entitled "Transcutaneous oxygen monitors are reliable indicators of arterial oxygen tension (if used correctly)" (12). In December 1986, an expert consensus meeting on transcutaneous oxygen monitors was convened by the American Academy of Pediatrics and co-sponsored

by the Food and Drug Administration (FDA). When finally published more than 2 years later, the task force report listed carefully the limitations of this technology and provided recommendations for manufacturers and users but concluded "*that this technique, when a quality electrode is used, and performed with care and understanding, is a valuable tool in newborn intensive care*" (16). However, by the late 1980s, $tcpO_2$ monitoring had been largely abandoned in favor of pulse oximetry. Presumably, this practice change occurred because oximeters were easier to use and because they had no immediately apparent side effects such as skin burns (14).

Do $tcpO_2$ devices reduce the risks of adverse consequences of hypoxemia and hyperoxemia such as death and severe ROP? As with many other new technologies, manufacturers and clinicians alike failed to ask this fundamental question about the clinical utility of the new technology before its widespread use (14). However, between 1982 and 1984, a team of investigators at the University of Miami performed the only randomized trial of $tcpO_2$ monitoring in a neonatal population. A total of 296 infants with birthweights of 500 to 1,300 g were randomly assigned to "standard care" ($tcpO_2$ monitoring during "the acute stage of their illness" only) or extended $tcpO_2$ monitoring for as long as the infants received supplemental oxygen. Extended monitoring did not reduce the risk of ROP, the main outcome of this single-center trial (17-19). A subsequent analysis explored the relationship between $tcpO_2$ and the incidence of severe ROP in the trial subgroup that had been randomly assigned to extended monitoring. This observational study showed an association between the duration of exposure to $tcpO_2$ values of 80 mmHg or higher and the risk of severe ROP (20).

Recently, a new optical method to measure transcutaneous oxygen tension has been tested in preterm infants (21,22). Preliminary studies have also been conducted to examine if the temperature of the electrode can be reduced without adversely affecting precision and accuracy of the measurements (23). If accurate and safe $tcpO_2$ probes can be developed for extremely preterm infants, this technology should be compared with pulse oximeters in randomized trials to determine which monitoring device is superior.

Pulse oximetry

Pulse oximeters do not measure SaO_2 directly. Instead, they use device-specific calibration software to generate the displayed saturation values (SpO_2). Manufacturers of conventional pulse oximeters derive their calibration curves from empirical measurements of SaO_2 in healthy subjects who volunteer to be made moderately hypoxemic (24). Oximetry data should only be interpreted with full awareness of the size of the likely measurement error at different saturation levels. The FDA in the United States recently reminded us of the following facts:

"*FDA-cleared prescription pulse oximeters are required to have a minimum average (mean) accuracy that is demonstrated by desaturation studies done on healthy patients. This testing compares the pulse oximeter saturation readings to arterial blood gas saturation readings for values between 70–100%. The typical accuracy … of recently FDA-cleared pulse oximeters is within 2% to 3% of arterial blood gas values. This generally means that during testing, about 66% of SpO_2 values were within 2% or 3% of blood gas values and about 95% of SpO_2 values were within 4% to 6% of blood gas values, respectively.*"

"*The SpO_2 reading should always be considered an estimate of oxygen saturation. For example, if an FDA-cleared pulse oximeter reads 90%, then the true oxygen saturation in the blood is generally between 86–94%. Pulse oximeter accuracy is highest at saturations of 90–100%, intermediate at 80–90%, and lowest below 80%. Due to accuracy limitations at the individual level, SpO_2 provides more utility for trends over time instead of absolute thresholds.*" (25).

Like $tcpO_2$ monitoring, pulse oximetry was introduced into routine neonatal care in the late 1980s without adequate evaluation of its accuracy and clinical utility (14). With a delay of approximately 20 years, the evidence gap for pulse oximetry was at least partially closed by 5 concurrent large randomized trials of SpO_2 target ranges and their synthesis in a prospective individual participant data meta-analysis (1). It is hoped that the mistakes of the past will not be repeated with new technology such as near-infra-red spectroscopy (NIRS) which remains a research tool (26). The efficacy of NIRS to reduce the risk of severe brain injury or death is currently under investigation in a large multi-center randomized trial (27). All monitoring devices including those that measure any parameter of blood or tissue oxygenation should perform like a robust diagnostic test. Before new devices are adopted for widespread use, responsible clinicians should know the answers to the following questions we adapted from the Users' Guides to the Medical Literature (28):

(I) Are the diagnostic device measurements valid?
- ❖ Was the device tested in the full range of patients in whom it will be applied?
- ❖ How accurate are the measurements when compared with an appropriate reference ("gold")

standard?

(II) Should I use the diagnostic device in my patients?
- ❖ Will the use of the device be safe and the interpretation of its measurements appropriate in my clinical setting?
- ❖ Will the device measurements change my management?
- ❖ Will my patients be better off using the device?

(III) What will be the economic impact of introducing the diagnostic device into my clinical setting?

What have we learnt from the Neonatal Oxygenation Prospective Meta-analysis (NeOProM)?

NeOProM is the individual participant data meta-analysis of 5 randomized trials of SpO_2 target ranges (1). Between 2005 and 2010, a total of 4,965 extremely preterm infants were randomly assigned in separate clinical trials to oxygen saturations of 85–89% or 91–95% and followed to a corrected age of 18 to 24 months (29-34). Before launching their own trials, the 5 study teams agreed to:

- ❖ Enroll similar populations of extremely preterm infants;
- ❖ Compare the same SpO_2 target ranges;
- ❖ Use the same modified pulse oximeters to mask the treatment allocation (Masimo Inc.).

In addition, all investigators promised to contribute their respective individual participant trial data to a prospective meta-analysis after the full publication of all 5 studies. Schmidt and Whyte recently published a comprehensive examination of the lessons learnt from NeOProM (35). Here, we highlight some insights that are most relevant to clinicians.

New evidence and remaining uncertainties

In the NeOProM study protocol, the primary outcome was a composite of death or disability at a corrected age of 18 to 24 months (36). This primary outcome did not differ significantly between the higher and lower SpO_2 target groups (1). Among the secondary outcomes, the rates of disability were also similar in the two comparison groups. However, targeting the higher SpO_2 range reduced the risks of death and severe NEC but increased the risk of treated ROP. The 5 trials of oxygen saturation target ranges and NeOProM provided belated and much needed evidence to guide oxygen therapy for very immature infants. Yet uncertainties remain, including the following:

- ❖ The NeOProM trials offer little guidance on where to set the oximeter alarm limits;
- ❖ The NeOProM trials provide no insights on how bedside staff should respond to alarms;
- ❖ Commercially available Masimo SET pulse oximeters today contain a calibration curve that has evolved slightly since the study oximeters were leased from this company for the NeOProM trials. It follows that the SpO_2 target ranges as studied in the NeOProM trials do not agree precisely with the same numerical saturation values on current pulse oximeters.

This also applies to other brands of pulse oximeters. Calibration curves are proprietary. Different manufacturers use calibration curves that are similar to each other but not identical (8).

Post-NeOProM guidelines have recommended SpO_2 target ranges of 90–94% (37) or 91–95% (38) for all very preterm infants. Adherence to these guidelines will have different consequences in different NICUs because the risks of death, severe NEC and treated ROP vary considerable between regions, between hospitals within a region, and over time (39-42). Reasons for this variation include differences in patient populations, organization of perinatal services, and care practices (39-42).

Impact of local rates of death and treated ROP on the absolute benefit and risk of higher SpO_2 targets

In NeOProM, the risk difference for death by 18–24 months corrected age was 2.8% [95% confidence interval (CI): 0.6% to 5.0%] in favor of the higher saturation target range (1). The reciprocal of the risk difference is the Number Needed to Treat (NNT) (43), in this case 1:0.028=36. Similarly, the reciprocals of the confidence limits for the risk difference are the confidence limits for the NNT, in this case 20 and 167, respectively. These data suggest that, on average, 36 infants must be exposed to the higher target range to prevent one death. Clinicians can be 95% confident that the true NNT will lie somewhere between 20 and 167 infants. For treated ROP, the risk difference in NeOProM was –4.0% (95% CI: –6.1% to –2.0%) in favor of the lower saturation target range (1). The Number Needed to Harm (NNH) with higher saturations and the corresponding 95% confidence limits are the reciprocals of these values. Using the higher target range will cause, on average, one additional case of severe ROP requiring treatment for every

Table 1 Estimated local NNT (95% CI) for death with higher SpO_2 target range

Local NICU risk of death with lower SpO_2 target range	"f" factor: local risk divided by NeOProM risk in the lower SpO_2 target range	Number Needed to Treat (NNT) with higher SpO_2 target range to prevent one death (95% CI)
25%	1.25	29 (16 to 134)
20%*	1	36 (20 to 167)
15%	0.75	48 (27 to 223)
10%	0.50	72 (40 to 334)

*, risk in NeOProM. CI, confidence interval; NICU, neonatal intensive care unit; NeOProM, Neonatal Oxygenation Prospective Meta-analysis.

25 infants exposed, and it is 95% probable for the true NNH to lie between 16 and 50 infants.

However, these estimates of the benefits and risks of higher targeting apply only to NICUs where the rates of death and treated ROP in the lower target range are similar to the NeOProM rates. Those risks were 20% for death by 18 to 24 months corrected age, and 11% for treated ROP (1). Risk differences, NNT and NNH are *absolute* measures of a treatment effect that will change with changes in baseline risk (44). In NICUs where these baseline risks differ from those in NeOProM, the NNT for death and NNH for treated ROP and their CIs also differ and must be recalculated. The traditional starting point for such calculations is the published relative risk reduction in the original trial or meta-analysis. However, for clinicians without statistical training this calculation can be challenging, error-prone and time-consuming. Luckily, the following simple method developed by Cook and Sackett permits easy and accurate estimation of the local NNT based on the published trial results (44).

- Determine "factor f" according to the following formula: factor f = local baseline risk divided by control group risk in RCT or meta-analysis;
- Divide the study NNT by f;
- Divide the confidence limits for the study NNT by f.

Example: the local risk of death with lower SpO_2 targeting is 10% rather than 20% as observed in NeOProM.

- Factor f =10% divided by 20% =0.5;
- Local NNT is 36 divided by 0.5 =72 infants;
- Local 95% CIs for this NNT are 20 divided by 0.5 and 167 divided by 0.5, i.e., 40 to 334 infants.

Consequently, in NICUs with a low mortality rate of 10%, the staff can be 95% confident that they need to expose somewhere between 40 and 334 infants to the higher SpO_2 target range to prevent one death.

The same approach can be used to compute the local NNH for treated ROP. Using this method, we estimated the NNT and NNH values with their 95% CIs for different but plausible NICU baseline risks of death (*Table 1*) and treated ROP (*Table 2*).

A difficult trade-off

Blindness from severe ROP can largely be prevented by adequate screening and timely therapy. Most clinicians and parents will consider the death of a child to be worse than the development of severe ROP. However, treated ROP remains a marker for non-visual disability in childhood and adolescence even in high-income settings (45,46). Therefore, difficult questions about trade-offs still arise, as they do for every treatment with both beneficial and harmful effects (47). Clinicians and families of extremely preterm infants must understand the full implications of severe ROP and then ask themselves: "*How many cases of treated ROP can be tolerated for every death that is prevented?*" The answer will depend on their individual and subjective values and preferences. It follows that "*the trade-off between the potential benefits and risks of lower vs. higher saturations may not be the same in each nursery*" (48). As authors who interpret scientific evidence, we refrain from broadcasting our own values. Nonetheless we must ensure that decisions about difficult trade-offs are suitably informed.

Should clinicians target oxygen saturations of 85–89% exclusively after the publication of NeOProM? Our answer is "no". Depending on the local mortality and morbidity risks, we recommend slight adjustments to the alarm settings instead. In NICUs where rates of death and severe NEC are low while the rate of severe ROP is high, we suggest lower alarms between 85% and 88%, and upper alarms of 93% or 94% while the infants receive supplemental oxygen. In NICUs where rates of death and severe NEC are high while the rate of severe ROP is low,

Table 2 Estimated local NNH (95% CI) for treated ROP with higher SpO_2 target range

Local NICU risk of treated ROP with lower SpO_2 target range	"f" Factor: local risk divided by NeOProM risk in the lower SpO_2 target range	Number Needed to Harm (NNH) with higher SpO_2 target range to add one case of treated ROP (95% CI)
25%	2.27	11 (7 to 22)
20%	1.82	14 (9 to 28)
15%	1.36	18 (12 to 37)
11%*	1.00	25 (16 to 50)
10%	0.91	28 (18 to 55)

*, risk in NeOProM. ROP, retinopathy of prematurity; NICU, neonatal intensive care unit; CI, confidence interval; NeOProM, Neonatal Oxygenation Prospective Meta-analysis.

lower oximeter alarms of 89% or 90% and an upper alarm of 95% may be more appropriate (48). We acknowledge that the evidence base for these recommendations is weak because the NeOProM trials studied SpO_2 target ranges and not pulse oximeter alarm limits (35).

How can compliance with SpO_2 target ranges be improved?

Manual adjustments of the inspired fraction of oxygen by bedside staff remain the current standard of care. Studies of automated oxygen control systems are ongoing, but this technology is not yet ready for widespread adoption. It remains to be determined which of the commercially available oxygen control algorithms performs best in a head-to-head comparison (49). In addition, it should be demonstrated whether this technology improves infant outcomes. Alternatively, it should be shown that automatic oxygen control reduces the workload for bedside staff substantially while achieving sufficiently similar clinical outcomes as good manual FiO_2 adjustments.

Protocols and training for manual titration of supplemental oxygen

Various algorithms of automatic control systems have been developed. These algorithms explicitly dictate in different but objective and reproduceable ways when and by how much the FiO_2 is to be adjusted in an individual infant (49). In contrast, manual adjustments of oxygen therapy are usually not explicit. They are performed at the discretion of the bedside staff and hence subjective. Compliance with target ranges and alarm settings is often poor (50). There is evidence that bedside staff respond less diligently to hyperoxemia than to hypoxemia (50). This tolerance of high SpO_2 values was greater during the night than during the day in one study of 24 mechanically ventilated infants (51). Reports of explicit clinical titration protocols are rare (52). Interestingly, one recently published oxygen titration guideline was only developed when it was needed for the manual periods in a cross-over randomized trial of manual versus automated control (53). When combined with adequate training, explicit guidelines improve compliance with the desired SpO_2 target ranges (52,53).

Workload and fatigue of bedside staff

In one of the centers in the Canadian Oxygen Trial (COT) where compliance with the study SpO_2 target range was consistently excellent, the NICU nurses identified a favorable patient to staff ratio as one of the 5 most important reasons for their strong performance (54). In a quantitative study by Sink *et al.*, fewer patients per nurse were also associated with improved achievement of oxygen saturation goals (55). A recent prospective cohort study of video-recorded care in a large pediatric medical unit showed that "*each hour that elapsed during a nurse's shift was associated with a 15% longer response time*" to physiologic monitor alarms (56). Sensible workloads and workhours for bedside staff are an obvious strategy to improve neonatal intensive care (57), including compliance with SpO_2 target ranges.

SpO_2 histograms for audit and feedback

The Study Operations Manual for Investigators and Research Staff of the COT was released in February 2007. It contained a section entitled "*Auditing the Histogram*" that opened with the following recommendation:

"*Bedside auditing of the histogram should be done as frequently as possible on all COT study babies. Research personnel can use*

these histograms for teaching/feedback to bedside caregivers."

However, COT did not systematically study how well this guidance was implemented in each of the 25 participating clinical sites. Since then, the authors of a small number of single-center quality improvement initiatives have concluded that regular reviews of oxygen saturation histograms may improve compliance with SpO_2 target ranges (58-60).

Practice points

- ❖ In extremely preterm infants, liberal oxygen therapy increases the risk of severe ROP while restricted oxygen therapy increases the risks of severe NEC and death;
- ❖ Safe and sound oxygen therapy aims to achieve the best possible trade-off between these risks and benefits in a local NICU;
- ❖ Transcutaneous oxygen monitoring and pulse oximetry were both widely adopted by neonatal clinicians many years before randomized trials had been performed to determine how these devices should be used;
- ❖ In future, clinicians caring for extremely preterm infants should be more demanding and refrain from using technologies before they have undergone rigorous evaluation;
- ❖ Belated randomized trials of oxygen saturation targeting and their analysis of individual participant data in NeOProM showed reduced risks of death and severe NEC but an increased risk of treated ROP with a higher target range;
- ❖ NICUs with high risks of death and severe NEC will benefit more from higher target saturations than NICUs where the risks of these outcomes are low;
- ❖ NICUs with a high risk of severe ROP will experience more harm from higher target saturations than NICUs where the risk of severe ROP is low;
- ❖ Explicit protocols for the manual titration of supplemental oxygen, training of bedside staff, sensible workloads and work hours, and regular use of SpO_2 histograms for audit and feedback may improve compliance with the chosen oxygen saturation target range and pulse oximeter alarm settings.

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