Current Recommendations and Practice of Oxygen Therapy in Preterm Infants

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KEYWORDS

• Oxygen • Oxygenation • Oximetry • Infant mortality • Necrotizing enterocolitis
• Retinopathy of prematurity • Extremely premature infant

KEY POINTS

- Because low-oxygen saturation targets increased mortality in extremely preterm infants, all guidelines since 2011, except one, have recommended targeting oxygen saturation ranges of 91% to 95% or 90% to 95%, or avoiding 85% to 89%.
- The quality of the evidence that the low target increased mortality has been rated as "high," "moderate," or "low" despite the low heterogeneity between randomized trials of oxygen saturation targeting, suggesting key differences in interpreting the GRADE guidelines.
- International surveys in 2015 and 2016 showed that the oxygen saturation target range had increased to levels that are more consistent with the evidence.
- Randomized controlled trials on oxygen saturation targeting have been limited to extremely preterm infants.
- Systematic reviews, guidelines, and consensus statements could be improved by including coauthors with advanced expertise in biostatistics and epidemiology.

INTRODUCTION

Authors of systematic reviews, editorial commentaries, opinions, consensus statements, and guidelines render a valuable service in summarizing the best available evidence for clinical practice. Similarly, those who undertake periodic questionnaire surveys reveal whether this appraisal of the evidence subsequently impacts clinical practice. After 2 systematic reviews, which were published in 2017 and 2018,[1,2] had

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assessed the 5 Neonatal Oxygen Prospective Meta-analysis (NeOProM) trials of low- (85%–89%) versus high- (91%–95%) oxygen saturation target ranges in infants of less than 28 weeks' gestation,[3–7] the authors evaluated published (i) recommendations for oxygen-saturation target ranges in these infants during oxygen therapy after admission to the neonatal unit and (ii) surveys of practice. Q10

The GRADE Working Group Guidelines Q11

Several systematic reviews, commentaries, and consensus statements have cited the GRADE guidelines[8–10] in assessing (a) the quality of evidence and (b) the strength of recommendations made. The 4 grades of evidence in the GRADE guidelines are high quality (indicating that further research is very unlikely to change the confidence in the estimate of effect), moderate quality (further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate), and very low quality (very uncertain about the estimate). Evidence from observational studies is initially rated as of low quality, but ratings can be modified upward, while evidence from randomized studies is initially rated as of high quality, but ratings can be modified downward. After assessing the quality of evidence, GRADE gives criteria to rate recommendations for practice as "strong" or "weak."[11]

The GRADE process begins with a Health Care Question (Patient Intervention, Comparator, Outcome), progresses through systematic reviews of all evidence addressing that question, rates the quality of evidence of each outcome across studies and overall, and then rates the strength of the resulting recommendations, as summarized in **Fig. 1**.

OXYGEN SATURATION TARGETS IN INFANTS LESS THAN 28 WEEKS' GESTATION

Methods

Search strategy

The authors searched PubMed for systematic reviews, editorial commentaries, opinions, consensus statements, and guidelines on oxygen therapy in infants less than 28 weeks' gestation, excluding (i) reports of individual randomized controlled trials (RCTs) of low- versus high-oxygen saturation targets, (ii) guidelines focusing on a single measure of outcome, for example, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and (iii) systematic reviews or commentaries on oxygen targeting during resuscitation or delivery room care. Further relevant articles were obtained from the reference lists of publications identified as above. The search was limited to the period since the publication in 2010 of SUPPORT,[3] the first of the NeOProM trials.[12] The search terms were "((clinical practice guidelines) AND preterm AND oxygen) NOT resuscitation," which yielded 18 hits and "systematic review AND preterm AND oxygen NOT resuscitation," which yielded 90 hits. Guidelines, systematic reviews, narrative reviews, commentaries, opinions, and consensus statements were selected from among these 108 hits. This search strategy yielded 21 publications (**Table 1**).[1,2,13–31] The authors also searched CINAHL using the terms (MM "Infant, Premature") AND (MM "Practice Guidelines"), which yielded 28 hits, none of which were relevant. Q12

These strategies also yielded 2 surveys of clinical practice, one conducted between November 2015 and February 2016 in 193 European neonatal intensive care units (NICUs),[32] and another among representatives of 329/390 NICUs of the International Network for Evaluating Outcomes in Neonates (iNeo), conducted in 2015.[33]

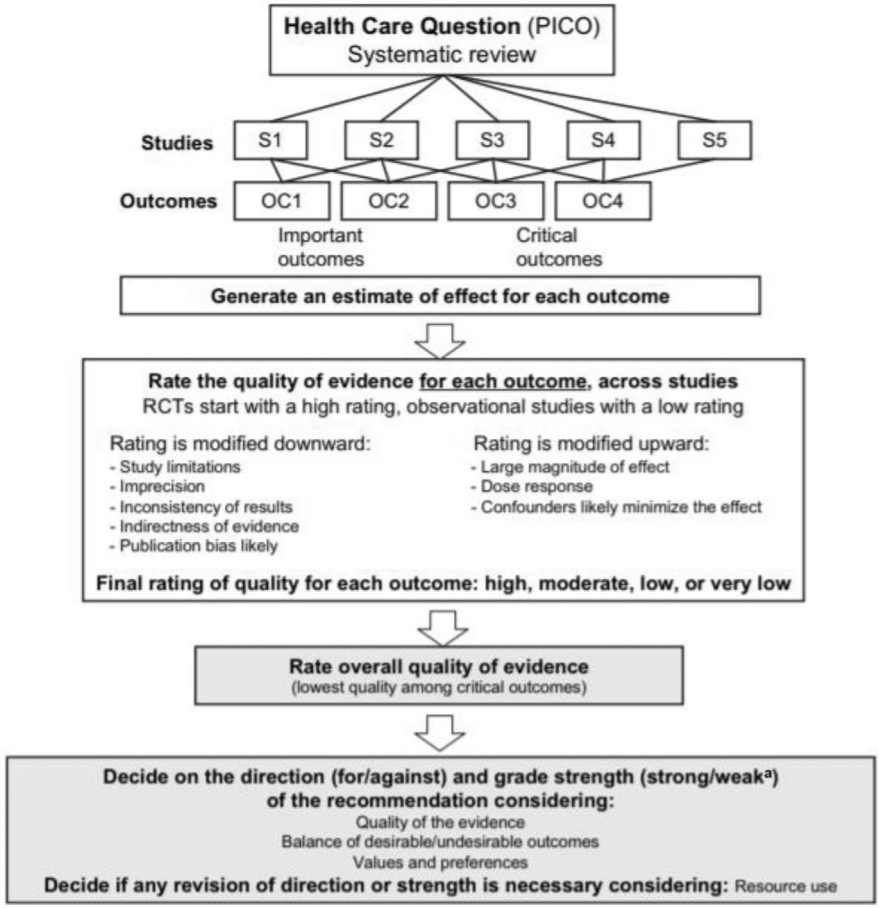

Fig. 1. Schematic view of GRADE's process for developing recommendations. [a] Also labeled "conditional" or "discretionary". (*Reproduced with permission*, from figure 1, Guyatt et al.[8]) Q24 Q25

Results

Recommendations for practice

The authors found 2 consensus guidelines,[19,29] a clinical report from the Committee on Fetus and Newborn of the American Academy of Pediatrics (AAP),[26] 5 systematic reviews,[1,2,20,22,28] and 13 commentaries or opinions (see **Table 1**).

European Consensus guidelines and American Academy of Pediatrics Clinical Report

In 2016, the European Consensus Guidelines on Management of Respiratory Distress Syndrome,[29] in an update of its earlier consensus statement,[19] suggested an oxygen saturation target of 90% to 94% for all preterm infants less than 28 weeks' gestation. Using the GRADE guidelines,[8] the European Consensus group assessed the overall quality of evidence for this recommendation overall, rather than for specific outcomes, as "moderate" and the strength of this recommendation as "weak."

Table 1
Recommendations for oxygen saturation target ranges and alarm limits

First Author, y	Type of Publication	Recommended Target Range, %	Quality of Evidence (Strength of Recommendation)
Saugstad et al,[13] 2011	Commentary	>89	—
Bashambu et al,[14] 2012	Narrative review	>89	—
Askie,[15] 2013	Opinion	>90	—
Polin & Bateman[16] 2013	Commentary	90–95	—
Bancalari & Claure,[17] 2013	Commentary	90–95	
Stenson,[18] 2013	Opinion	90–95	
Sweet et al,[19] 2013	Consensus statement	90–95	Moderate
Saugstad & Aune,[20] 2014	**Systematic review**	**90–95**	**—**
Schmidt et al,[21] 2014	Commentary	85–88 to 93–94,[a] 89–90 to 95[b]	—
Manja et al,[22] 2015	**Systematic review**	**—**	**Low[c]**
Synnes & Miller,[23] 2015	Commentary	*85–95*	—
Isaacs,[24] 2016	Commentary	91–95	
Stenson,[25] 2016	Commentary	90–95	
Cummings et al,[26] 2016	Committee clinical report	90 to 95[d,e]	
Deschmann & Norman,[27] 2017	Commentary	91–95	—
Manja et al,[28] 2017	**Systematic review**	**91–95[e]**	**Moderate[c]**
Sweet et al,[29] 2017	Consensus statement	90–94[e]	Moderate (weak)
Askie et al,[1] 2017	**Systematic review**	**—**	**High[c]**
Askie et al,[2] 2018	*Systematic review*	—	—
Bizzarro,[30] 2018	Commentary	91–95	—
Stenson & Saugstad[31] 2018	Commentary	91–95[e]	

[a] For example, alarm limits in hospitals with low rates of mortality and NEC but high rates of severe ROP.
[b] For example, alarm limits in hospitals with low rates of severe ROP, but high rates of mortality and NEC.
[c] For effect on mortality.
[d] 90% to 95% may be safer than 85% to 89% in some infants.
[e] Lower alarm limit will generally need to extend somewhat below the lower target.

In 2016, the AAP Committee on Fetus and Newborn[26] concluded that an oxygen saturation target range greater than 89% may be safer, at least for some infants. Although the disproportionately high rate of mortality in small-for-gestational-age infants in the low-target group was discussed, the committee did not define those infants in whom it considered a higher saturation target safer. The AAP Committee on Fetus and Newborn did not apply the GRADE guidelines.

Systematic reviews

In 2014, Saugstad and Aune[20] published a systematic review and meta-analysis on infants less than 28 weeks' gestation reported in the 5 NeOProM trials. They reported no difference in death or disability up to 24 months corrected gestational age in 2463 infants in SUPPORT[3] and COT,[5] the 2 trials that had reported this outcome. However, all 5 trials reported an increased relative risk (RR) for mortality at discharge or follow-up (4884 infants; RR 1.41; 95% confidence interval [CI] 1.14–1.74) and for necrotizing enterocolitis (4929 infants; RR 1.25, 95% CI 1.05–1.49). Results were inconclusive for ROP, BPD, brain injury, and patent ductus arteriosus. They recommended adoption of an oxygen saturation target range of 90% to 95% until 36 weeks' gestation but did not use the GRADE guidelines to assess the quality of evidence or strength of this recommendation.

In 2015, Manja and colleagues[22] published a systematic review in 4929 infants reported in the 5 NeoProM trials, which was the first to use the GRADE guidelines[8] to assess the quality of evidence for each outcome. It reported (i) no effect for death or disability up to 24 months corrected gestational age in 3 trials (2716 infants; RR 1.02, 95% CI 0.94–1.14: quality of evidence downgraded to moderate[8]); (ii) increased hospital mortality in the low-target group across 4 trials (3757 infants; RR 1.18, 95% CI 1.03–1.36: quality of evidence downgraded to low[8] because, among other reasons, the separation in oxygen saturation achieved between low- and high-target groups was less than planned); (iii) that the low target increased NEC in 5 trials (4929 infants; Q14
RR 1.24%, 95% 1.05–1.47; quality of evidence downgraded to moderate); (iv) no effect for severe ROP in 5 trials (4066 infants; RR 0.72, 95% CI 0.5–1.04; quality of evidence downgraded to low[8] because of unexplained heterogeneity); and (v) no effect for BPD, neurodevelopmental outcomes at 18 to 24 months, and hearing loss (quality of evidence downgraded to moderate[8]).

In 2017, Manja and colleagues[28] published a systematic review of RCTs evaluating the effect of lower (85%–89%) versus higher (91%–95%) pulse oxygen saturation (Spo_2) target on mortality and neurodevelopmental impairment at 18 to 24 months.[28] They concluded that the risks associated with restricting the upper Spo_2 target limit to 89% outweighed the benefits. The quality of evidence was moderate. They speculated that a wider target range (lower alarm limit, 89%, and upper alarm limit, 96%) might increase time spent within the 91% to 95% range.

In 2017, Askie and colleagues[1] published a Cochrane Review of the effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants, based on the 5 NeOProM trials, in a total of 4965 infants less than 28 weeks' gestation. They applied the GRADE guidelines to assess the quality of evidence for estimates of the effect of the low-target range on individual outcomes. Their assessments of the quality of evidence for these outcomes have been summarized alongside the assessments of Manja and colleagues[22] in **Table 2**.

In 2018, Askie and colleagues[2] published the results of the previously planned[12] prospective individual patient data meta-analysis of the effects of targeting 85% to 89% versus 91% to 95% oxygen saturation in all 4965 infants less than 28 weeks' gestation in the 5 NeOProM Collaboration trials. This publication[2] (which did not apply

Table 2
Observed effects of the low-target range 85% to 89% on individual outcomes in 2 systematic reviews of 5 trials, with quality of evidence assessed by GRADE

Outcome	Observed Effect of 85%–89% Target on This Outcome in Manja et al,[22] 2015	Quality of Evidence as Assessed in Manja et al,[22] 2015	Observed Effect of 85%–89% Target on This Outcome in Askie et al,[1] 2017	Quality of Evidence as Assessed in Askie et al,[1] 2017
Death or disability at 24 mo	No effect	Moderate	No effect	High
Hospital death	Increased	Low	Increased	High
Disability at 18–24 mo	No effect	Moderate	No effect	High
NEC	Increased	Moderate	Increased	High
Treated ROP	No effect	Low	No effect	Moderate
Hearing loss	No effect	Moderate	No effect	Not assessed
Blindness	No effect	Moderate	No effect	Not assessed

the GRADE guidelines[12]) and the Cochrane Review by Askie and colleagues[1] suggest that for every 1000 infants, targeting low- versus high-oxygen saturation made no difference in death or major disability up to 18 to 24 months, nor in major disability, including blindness, but led to 28 more deaths, 22 more cases of NEC, and 42 fewer infants being treated for ROP.[1,2,34]

Table 3 presents the authors' reasons for uprating the Quality of Evidence that the low target increases mortality in the NeOProM trials in 2 systematic reviews using GRADE from "low"[22] to "high."[1]

SURVEYS OF CLINICAL PRACTICE IN OXYGEN TARGETING AMONG INFANTS LESS THAN 28 WEEKS' GESTATION

In a Web-based survey among representatives of 390 NICUs of the iNeo conducted in 2015, responses were received from 329 (84%).[33] Of these, 60% had recently made changes to their upper and lower Spo_2 target limits, with the median value of the target range set higher than previously by 2% to 3% in 8 of 10 networks.

In a similar survey of 193 European NICUs conducted in 2015 and 2016,[32] there was considerable variation in practice. The most frequently targeted oxygen-saturation ranges were 90% to 95% (28%), 88% to 95% (12%), 90% to 94% (5%), and 91% to 95% (5%), reflecting the most commonly recommended target ranges shown in **Table 1**. A total of 156 NICUs (81%) had recently changed their oxygen saturation target limits. The median values for the oxygen-saturation ranges in clinical practice had increased by between 3% and 5% within the last 10 years.

Neither survey determined current practice in setting alarm limits nor in oxygen saturation targeting for preterm infants of 30 to 36 weeks' gestation.

Discussion

All 5 systematic reviews of trials of oxygen saturation targeting for infants of less than 28 weeks' gestation that were identified since 2010 concluded that the low target 85% to 89% increased mortality.[1,2,20,22,28] **Table 1** shows notable uniformity in

Table 3
Contrasting interpretations of the quality of evidence that the low target increased mortality in randomized controlled trials of oxygen saturation targets in infants less than 28 wk using GRADE[8]

Initial Reason for Downgrading Quality of Evidence[22]	Reinterpretation Using the GRADE Guidelines	Our Interpretation of the Effect on Quality of Evidence
1. Separation of achieved Spo_2 values was less than planned	Despite less than expected separation, mortality effects were still observed. This confounding is likely to have minimized the effect (see Fig. 1[8])	Rating should be modified upward
2. The oximeter algorithm was revised during enrollment to 3 trials[5,7]	The revised algorithm improved separation in oxygen saturation[34] and thus study power. The original algorithm reduced separation (see Fig. 1[8]), thus underestimating the average estimate of effect[34]	Rating should be modified upward
3. Mortality in infants on the revised algorithm was not a prespecified outcome; yet 2 BOOST II trials[7,35] were stopped early because of an increase in this outcome	The BOOST II protocols specified a difference in a major endpoint of >3 standard errors or >3 standard deviations (equivalent to $P<.0027$) to justify early stopping. After SUPPORT showed excess mortality,[3] the BOOST II trials[7,35] were stopped early because of a highly significant increase in pooled mortality in infants on revised oximeters (RR 1.65; $P = .0003$)[36]	Rating should be modified upward
4. Only 4[3,6,35] of 5 trials reported hospital death	The estimates of effect on hospital death in these 4 trials demonstrate low to moderate heterogeneity[37] (χ^2 4.76, $P = .19$; $I^2 = 37\%$)	No effect on rating
Other issues		
5. Effects on mortality using revised vs original oximeters; among infants on revised oximeters, low-target infants had consistently higher mortality than high-target infants, with (a) statistically significant interactions in 3 meta-analyses of mortality in low- vs high-target infants stratified by use of original vs revised oximeters ($P = .006$[36]; $P = .03$[1,20]; $P = .04$[22]) (but interactions were unreported in 2 meta-analyses[20,22]); (b) Infants using revised oximeters spent more time in their assigned target ranges than those on original oximeters[34]	The mortality risk for low- vs high-target infants was greater in those using revised vs original oximeters.[8] This, and the finding that targeting was more accurate in infants using revised oximeters,[34] is likely to have caused the average effect of the low target on mortality in infants on original oximeters to have been underestimated, as in 1 above (see Fig. 1[8])	Rating should be modified upward

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Table 3
(continued)

Initial Reason for Downgrading Quality of Evidence[22]	Reinterpretation Using the GRADE Guidelines	Our Interpretation of the Effect on Quality of Evidence
6. What was the potential for biased assessment of mortality?	None. Death was assessed without interobserver variation or bias	Shows high quality
7. Was there loss to follow-up in ascertainment of mortality?	No. 100% ascertainment of death at 36 wk and before hospital discharge	Shows high quality
8. Was the magnitude of the effect on mortality large?	Yes. The low target shows a 38% increase in RR of death in infants on revised oximeters (RR 1.38, 95% CI 1.13–1.68; $P = .014$)[1] (see Fig. 1[8])	Rating should be modified upward

recommendations for practice. Of 16 guidelines, commentaries, or opinions published since SUPPORT in 2010 (see **Table 1**), 15 recommended targeting a range greater than 90% or avoiding the low-target range of 85% to 89%. The exception was an editorial commentary,[23] which suggested that targeting an oxygen-saturation range between 85% and 95% remained acceptable. Two international surveys[32,33] in approximately 500 neonatal units reported considerable variation in clinical practice, but documented recent increases of 2% to 5% in the median values for target oxygen-saturation ranges.

CONTRASTING INTERPRETATIONS OF CURRENT RANDOMIZED EVIDENCE

The recommendation[23] that an oxygen-saturation target range of 85% to 89% remained acceptable[23] reflects a judgment in the systematic review of Manja and colleagues[22] that the GRADE quality of evidence that the low target increased mortality was low. This merits careful reconsideration. Reviewers may legitimately disagree when interpreting quality of evidence using GRADE, which provides a transparent framework guiding the assessment process (see **Fig. 1**).[8,9] **Table 2** shows judgments from 2 systematic reviews[1,22] about the quality of evidence for the effect of the low target on various outcomes. **Table 3** outlines the authors' reasons for reinterpreting the quality of evidence for the effect of the low target on mortality as "high" rather than "low," using GRADE. For example, a treatment effect for mortality was observed *despite* achieving the confounding effect of achieving less separation between study arms in actual oxygen saturation than planned. This supports an upward modification of the rating for quality (see **Fig. 1**).

Neither the European Consensus Guidelines nor the AAP Guidance has been updated since these most recent data were published.[1,2] Future recommendations may benefit from inviting coauthorship by colleagues with advanced biostatistic and epidemiologic expertise.

Future international clinical surveys[32,33] are warranted, to assess the impact on practice of the final results of the NeOPrOM trials.[1,2] Future practice may also be influenced by increasing attention to 4 issues:

i. The pulse oximeters in the NeOProM trials underestimate hypoxemia with progressively wider limits of accuracy as true oxygen-saturation values decrease from

93% to 80% (Fig. 2),[38] exposing substantially more infants in the lower-target group to values of oxygen tension less than 50 mm Hg (6.7 kPa).[39] The study authors[38] wrote, *"The large sample size of each of these (NeOProM) trials and the planned meta-analysis should address the question of whether infants assigned to the lower range are at higher risk of low Pa_{O_2}-induced pulmonary vasoconstriction, patent ductus arteriosus, abnormal neuro-developmental outcome, and potentially death. Our data may provide partial explanations if differences in short- or long-term outcomes are observed."*[38]

ii. Targeting an intermediate oxygen-saturation range, such as 87% to 93%, is an untested practice that may increase mortality, because current oximeters permit increasingly disproportionate exposure to hypoxemia as oxygen saturation decreases less than 93%.[7,38]

iii. At present, the most rigorously evaluated evidence for policy is that targeting an oxygen saturation of 91% to 95% is safer overall than targeting an oxygen saturation of 85% to 89%.[1,2,7]

iv. Future practice may also be influenced by recent analyses of the impact of original versus revised oximeters in the Australian and UK Benefits of Oxygen Saturation Targeting-II (BOOST II) trials.[34,40] Although there was no difference in separation of median oxygen values between infants managed with original or revised oximeters,[40] infants using revised oximeters spent more time within their planned pulse oximeter saturation target ranges than infants using the original oximeters ($P<.001$).[34] This latter finding could explain the larger mortality difference seen between low- and high-target infants managed with revised oximeters. Importantly, it suggests that average treatment effects in the BOOST II trials are underestimates, because they include data from infants managed with the original oximeters.[34]

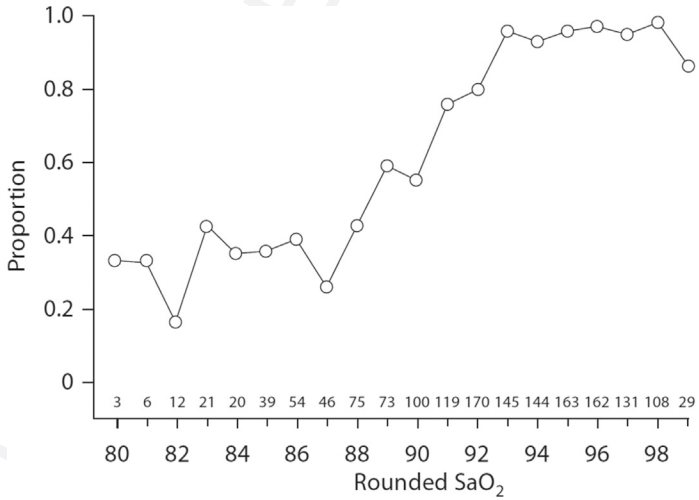

Fig. 2. Proportions of Spo_2 values that are ±3% of the corresponding Sao_2 value are plotted. The numbers above the x-axis on the graph denote the number of measurements at each value of Sao_2. (*From* Rosychuk RJ, Hudson-Mason A, Eklund D, Lacaze-Masmonteil T. Discrepancies between arterial oxygen saturation and functional oxygen saturation measured with pulse oximetry in very preterm infants. Neonatology 2012;101:14–9; with permission.)

Table 4
Sample sizes to show 10% or 20% reductions in relative risk of mortality or disability

Event Rate in Control Group (C), %	Event Rate in Treatment Group (T), %	Risk Difference (C − T = Δ), %	Relative Risk or Risk Ratio (RR = T/C)	Relative Risk Reduction (1 − RR)	Number Needed to Benefit or Harm (100/Δ)	Total Sample to Show Effect in a 2-Arm Comparison with 90% Power, 2*P* = .05 and Nonadherence to Protocol Due to:		
						0% Crossover in Each Group (Perfect Adherence to Protocol)	5% Crossover in Each Group (Total 10% Crossover)	10% Crossover in Each Group (Total 20% Crossover)
20	16	4	0.8	0.2	25	3868	4776	6044
20	18	2	0.9	0.1	50	16,166	19,960	25,260
10	8	2	0.8	0.2	50	8598	10,616	13,436
10	9	1	0.9	0.1	100	36,136	44,164	56,464

Data from Sealed envelope. Trial sample size calculator. Available at: https://www.sealedenvelope.com/power/. Accessed 24 Jan 2018.

LACK OF EVIDENCE FROM TRIALS IN MODERATELY PRETERM OR LATE PRETERM INFANTS

No trials or systematic reviews have evaluated the effects of different oxygen saturation targets or saturation alarm limits on short- or long-term outcomes in preterm infants of 28 to 36 weeks' gestation, who may outnumber extremely preterm infants of less than 28 weeks' gestation by 10-fold or 20-fold.[41] This represents a major evidence gap. Q19

OBTAINING EVIDENCE FOR FUTURE RECOMMENDATIONS ON OXYGEN TARGETS IN PRETERM INFANTS

In 1998, Peto and Baigent wrote,[42] "*…medical research needs to find practicable ways of greatly increasing the size of randomized studies; otherwise moderate but worthwhile benefits will continue to be missed …*" As event rates fall, if mortality and disability are to improve further, large, well-designed perinatal trials with increasingly large sample sizes will be needed.[43] **Table 4** illustrates the sample sizes needed to detect moderate, worthwhile reductions of 10% and 20% in key outcomes, such as mortality or disability, with adequate power and realistic rates of nonadherence to protocol.[44] This might mean about 1 additional survivor without major disability for every 50 to 100 patients treated, which many would consider worthwhile for a widely available, affordable treatment like oxygen. All this underlines the need for increasing international collaboration, a major goal of the newly conceived ALPHA Collaboration for *A*dvancing *L*arge, collectively *P*rioritized perinatal trials of *H*ealth outcomes *A*ssessment.[45–47] Q20

Best Practices

What is the current practice for oxygen saturation targeting in infants of less than 28 weeks' gestation?

Surveys conducted in 2015 and 2016 in more than 500 NICUs showed wide variation in practice, with between 60% and 81% of NICUs having increased their median oxygen saturation target ranges by 2% to 5%.[32,33] The most up-to-date guidance for practice, published since the NeOProM Collaboration results in 2017 and 2018,[1,2] recommends a target range of 91 to 95.[30,31]

What changes in current practice are likely to improve outcomes?

Targeting an oxygen saturation of 91% to 95% will reduce mortality and necrotizing enterocolitis and increase retinopathy without increasing blindness or disability, compared with targeting an oxygen saturation of 85% to 89%.[1,2,7] Targeting an intermediate oxygen-saturation range, such as 87% to 93%, is an untested practice that may increase mortality compared with targeting 91% to 95%, because current oximeters permit increasingly disproportionate exposure to hypoxemia as oxygen saturation decreases to less than 93%.[7,38]

Is there a Clinical Algorithm? No.

New trials are needed in infants of 28.0 to 35.6 weeks' gestation to determine which targets minimize mortality and NEC and ROP. However, the incidence of ROP is likely to be proportionately much lower than the incidence of the first 2 outcomes in these infants. Q21

Major Recommendations:

Adopt a target range of 91% to 95% for oxygen saturation in infants less than 28 weeks' gestation.

Rating for the Strength of the Evidence: High.[1]

Bibliographic Source(s): Refs.[1,2,34,38]

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