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Targeting the Ideal Oxygen Saturation

In this Issue...

Use of supplemental oxygen to support preterm babies became commonplace in the 1940s when physicians noted that, compared to infants in room air, infants receiving concentrated oxygen had more regular breathing patterns and better color. Around the same time, physicians also noted a dramatic increase in the incidence of retrolental fibroplasia, now known as retinopathy of prematurity (ROP). In 1951, Dr. Mary Crosse of Birmingham, England, was the first to implicate concentrated oxygen as a cause of ROP. In the half century since that observation, we have yet to fully define an ideal level of supplemental oxygen for preterm infants—that is, one that prevents the ill effects of tissue hypoxia yet effectively minimizes the risk for ROP and other oxygen-related diseases—but progress is being made.

Among preterm infants, the use of supplemental oxygen can be divided into 3 time periods, based on the therapeutic goals: (1) the immediate transitional period, including delivery room care; (2) the acute neonatal period; and (3) the convalescent period of prematurity, during which the preterm infant recovers from acute lung injury and ROP. In this issue, we summarize recent literature and offer suggestions for oxygen saturation targeting in the acute neonatal period, when oxygen is most commonly used to treat respiratory distress syndrome and early chronic lung disease, and when normal retinal vascularization may be severely disrupted by excess oxygen exposure.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Explain the rationale for oxygen saturation targeting and the ranges of oxygen saturation that are safe and effective in minimizing retinopathy of prematurity (ROP) and other oxygen-related diseases of preterm infants.
- Describe a comprehensive supplemental oxygen management program, including recognition of barriers to achieving intended oxygen saturations and strategies that may be implemented to overcome these barriers.
- Discuss the evidence demonstrating that fluctuations in oxygen saturation, including intermittent episodes of hyperoxia, contribute substantially to the risk of ROP.

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- **Christoph U. Lehmann, MD**, has indicated a financial relationship of honoraria from Mead Johnson and Pediatrix. Dr. Lehmann is also the Editor-In-Chief of *Applied Clinical Informatics Journal*. He serves on the Board of Directors for the American Medical Informatics Association.
- **Anthony Bilenki, MA, RRT, Edward E. Lawson, MD, Lawrence M. Nogee, MD and Mary Terhaar, DNSc, RN** indicated they have no relevant financial relationships with any commercial supporters.

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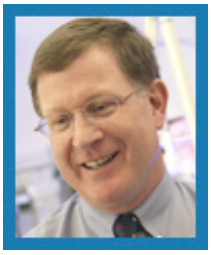

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Timothy P. Stevens, MD, MPH has disclosed no relevant financial relationships with any commercial supporters.

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COMMENTARY

In "A Cautionary Tale About Supplemental Oxygen: The Albatross of Neonatal Medicine," published in 2004, Dr. William Silverman reflected on the role of routine supplemental oxygen in the retinopathy of prematurity (ROP) epidemic of the 1940s and 1950s and recounted the first randomized clinical trial (RCT), in 1954, of routine vs. restrictive oxygen therapy. The investigators in that study concluded that restrictive use of oxygen (fraction of inspired oxygen [FiO_2] <0.4) was sufficient to completely eliminate ROP in preterm infants.[1] Though that bold statement has proved untrue, prospective and retrospective cohort studies have consistently shown that restrictive use of supplemental oxygen reduces the risk of ROP, decreases ROP severity, and decreases need for retinal surgery to treat ROP.[2-7] While confirming the benefit of restrictive oxygen therapy to prevent ROP, a recent RCT found that excessive oxygen restriction may be associated with harm. The commentary below will review these studies and offer suggestions for an oxygen management strategy that balances oxygen-related benefits and risks of harm for preterm infants at risk for ROP.

In 2003, Chow and colleagues (reviewed in this issue) reported an 80% reduction in the incidence of stages 3 to 4 ROP and a 30% reduction in retinal surgery for threshold ROP after introducing oxygen saturation targets of 85% to 93%, rather than to higher targets in infants with birth weights of 500 to 1500 gm. In the before-and-after study design, the

study intervention not only defined the target saturation, but also provided specific guidance on how and when to adjust the FiO_2 in response to oxygen saturations that were outside the target range. Using a similar oxygen intervention, Deulofeut and associates (reviewed herein) demonstrated that, compared with those managed with higher targets, patients managed with oxygen saturation targets of 85% to 93% experienced a 50% reduction in stage 2 ROP, along with a 30% reduction in the risk for bronchopulmonary dysplasia (BPD; defined as the need for oxygen at 36 weeks), higher mental developmental index, and similar rates of neurodevelopmental impairment. Similar results have been reported by Chen and coworkers (reviewed in this issue) in a systematic review of 5 cohort studies. A meta-analysis of these studies demonstrated a 52% reduction in the incidence of severe ROP (relative risk [RR], 0.48; 95% confidence interval [CI], 0.31 to 0.75) without increases in rates of mortality or cerebral palsy.[8]

This year, Ellsbury and collaborators (reviewed herein) reported the results of a quality improvement (QI) initiative in 80 neonatal intensive care units (NICUs) in which implementation of a comprehensive supplemental oxygen management program, including saturation targets of 85% to 93% rather than higher targets, was associated with a 50% reduction in the risk for severe ROP and fewer days on supplemental oxygen. In addition to confirming that mortality, necrotizing enterocolitis (NEC), and patent ductus arteriosus (PDA) rates were not altered by the QI initiative, this report provides an extensive discussion of personnel and system-based barriers to achieving intended oxygen saturations and offers suggestions for overcoming those obstacles.

Based on these and other studies,[7,9,10] an upper oxygen saturation limit not exceeding 95% is effective in reducing the incidence and severity of ROP and the duration of oxygen therapy without increasing mortality or neurodevelopmental impairment. Avoiding oxygen saturations >95% can now be considered a best practice for most preterm infants during the acute neonatal period.

Targeting lower oxygen saturations may be effective in reducing ROP, in part by reducing the frequency of hyperoxic events.[11,12] In a report comparing partial pressure of oxygen in arterial blood (PaO2) values obtained from indwelling arterial catheters with simultaneous pulse oxygen saturation values, patients with higher (>93%) vs. lower (85-93%) oxygen saturation targets experienced more hyperoxic episodes (PaO2 >80 mm Hg; 59.5% vs. 4.6%; P<.001), and those with lower targets experienced more hypoxic episodes (PaO2 <40 mm Hg; 8.6% vs. 1.0%; P<.001).[13] Although it is not yet known whether these hypoxic episodes are clinically important, the National Institute of Child Health and Human Development (NICHD) SUrfactant Positive Pressure Oxygenation Randomized Trial (SUPPORT; reviewed herein) recently raised safety concerns about supplemental oxygen therapy with saturation targets in the lower segments compared with the higher segments of the 85% to 95% saturation range.

In SUPPORT, enrolled patients were randomized to receive oxygen therapy to achieve saturation targets of either 85% to 89% or 91% to 95%. The target saturation assignment was masked using study oximeters with an electronic software offset, which by consensus of the study investigators, displayed 88% to 92% for all enrolled patients. The primary outcome of the combined risk for death or severe ROP did not differ between the treatment groups, with a reduction in the risk for severe ROP being offset by a greater risk for mortality. These results suggest that oxygen therapy to maintain saturation targets of 85% to 89% vs. 91% to 95% might be expected to result in 1 death for every 2 to 3 cases of severe ROP prevented. Although the duration of oxygen therapy was shorter in the low-saturation group, the incidence of BPD defined using the physiologic definition (i.e., need for oxygen after an attempt at oxygen withdrawal) did not differ between the groups. Assessments of neurodevelopmental and pulmonary outcomes at 18 to 22 months of corrected age are ongoing and will be reported in the future.

How are we to interpret the available data? With such a difficult trade-off between higher incidence of severe ROP or greater risk for mortality, the safest approach at this time, pending additional data, is likely to target oxygen saturations of 88% to 92%—the middle ground of a saturation range between a lower saturation alarm limit of 85% and an upper limit of 93% to 95%, and the consensus position used in SUPPORT. We may have greater clarity in the near future. There are 4 ongoing studies, enrolling nearly 5000 patients that compare saturation targets of 85% to 89% vs. 91% to 95%. The investigators of these studies are to be commended for agreeing in advance to share individual level data with each other for use in meta-analyses. This will add a great deal to our understanding.

Identifying the ideal oxygen saturation, while not yet achieved, is only part of the challenge in managing oxygen therapy to prevent ROP. Barriers to achieving desired oxygen saturation targets have been well described.[14,15] A study of intended vs. actual oxygen saturations found that actual oxygen saturations were outside the intended range >50% of the time, and during two-thirds of that time, the saturations were high.[14] In addition to challenges associated with manually adjusting FiO_2, fluctuations in oxygen saturation, including periods of hyperoxia and hypoxia, increase the risk for severe ROP. Di Fiore and coworkers (study reviewed in this issue) found that infants experience progressively more frequent hypoxemic episodes over the first 8 weeks of age, and the number of such episodes is related directly to the risk for requiring retinal laser surgery to treat ROP. In addition to individual physiologic variability, a patient's care environment has long been recognized to influence oxygen saturation variability. In 1980, Long and coworkers reported that greater ambient noise and frequent handling increased the number of transient hypoxemic episodes among infants in an intensive care nursery.[16,17] Although not proved to reduce the rates of ROP, it seems reasonable to complement careful oxygen saturation targeting with care practices that limit preventable transient hypoxemic events.

The ability of clinical QI efforts to overcome barriers to effective oxygen saturation targeting is encouraging.[5,18] Identification of other care practices or technologies, such as automated inspired oxygen controllers that respond to changes in oxygen saturation and thus aid in tighter control of oxygen saturations, warrants ongoing, future investigation.[19,20] Until that happens, there is no substitute for exquisite nursing and medical attention to appropriate oxygen saturation targets and thoughtful response to their fluctuations.

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CLINICAL PRACTICE CHANGES ASSOCIATED WITH DECREASES IN RATES OF SEVERE ROP AMONG VERY LOW BIRTH WEIGHT INFANTS

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(2):339-345.

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In a prospective cohort study, Chow and coworkers reported a reduction in the incidence of ROP among infants with birth weights between 500 and 1500 gm after introduction of a rigorous, comprehensive oxygen therapy program. The primary objectives of the program were to avoid alternating periods of hypoxia and hyperoxia by minimizing fluctuations in saturations, and to minimize periods of hyperoxia by targeting oxygen saturations between 85% and 93% for infants <32 weeks' gestational age and 85% to 95% for those >32 weeks' gestation. The program was comprehensive, including careful oxygen management in the delivery room and during in-house transport. Increases in FiO_2 by NICU staff in response to low oxygen saturations prompted close direct observation until a saturation in the target range was achieved, whereas FiO_2 weans were gradual, limited to 2% to 5% per adjustment.

Compared with the 16-month period before the program, introduction of the new care practices was associated with reductions in the incidence of severe ROP (stage 3-4) from 12.5% to 2.5% and use of laser retinal surgery from 4.4% to 1.3%. Of note, survival among the very low birth weight cohort increased throughout the 5-year study period.

Assessments of neurodevelopmental and growth outcomes were not reported. As with any study using a before-and-after design, it is possible that unmeasured clinical factors changed, thus altering or confounding the primary outcome over the 5-year study period.

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AVOIDANCE OF HYPEROXIA IN VERY LOW BIRTH WEIGHT INFANTS ASSOCIATED WITH IMPROVED NEONATAL MORBIDITY AND MORTALITY

Deulofeut R, Critz A, Adams-Chapman I, Sola A. Avoiding hyperoxia in infants ≤1250 g is associated with improved short- and long-term outcomes. *J Perinatol*. 2006;26(11):700-705.

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Using an oxygen therapy program similar to that reported by Chow and colleagues, Deulofeut and associates compared survival, along with ophthalmologic, pulmonary, and neurodevelopmental outcomes, in a prospective cohort of infants <1250 gm managed with oxygen saturation targets of 85% to 93% with a historical cohort managed with targets of 92% to 100%.

Oxygen therapy with lower vs. higher saturation targets was associated with reductions in any ROP (45% vs. 59%, respectively; P<.01), stage 2 ROP (17% vs. 36%, respectively; P=.01), BPD (35% vs. 51%, respectively; P<.01), use of steroids to treat BPD (9% vs. 16%, respectively; P=.03), and length of hospital stay (76.5 days vs. 85.9 days, respectively; P=.01).

This study provided more detailed neurodevelopmental outcome data than did previous studies. Although the follow-up rates were not ideal, ranging from 56% to 63%, the mental developmental index (MDI) score was higher and the physical developmental index (PDI) score trended higher in the lower-saturation group (MDI 89.2 vs. 80.2; P=.02 and PDI 89.4 vs. 83.9; P=.08 in the lower- vs. higher-saturation groups, respectively).

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QUALITY IMPROVEMENT INITIATIVE INVOLVING COMPREHENSIVE OXYGEN MANAGEMENT FOR THE PREVENTION OF ROP

Ellsbury DL, Ursprung R. Comprehensive oxygen management for the prevention of retinopathy of prematurity: the Pediatrix experience. *Clin Perinatol*. 2010;37(1):203-215.

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In 2006, following Chow's report of a dramatically reduced incidence of severe ROP following introduction of a rigorous, comprehensive oxygen management program, the Pediatrix Network developed a QI program for implementation in 80 NICUs. Entitled Comprehensive Oxygen Management for the Prevention of Retinopathy of Prematurity (COMP-ROP), the basic principles of the program were (1) avoidance of hyperoxia and repeated episodes of hypoxia-hyperoxia; (2) system redesign to minimize or eliminate practices that result in periods of hyperoxia; (3) NICU staff education about the risks and benefits of supplemental oxygen administration in premature infants, including the limitations of pulse oximetry in detecting hyperoxia; and (4) frequent audits of compliance with oximeter alarm settings and the percentage of time patients spend below, within, and above the targeted oxygen saturation parameters, with the goal of providing short-term feedback to caregivers on the success of oxygen management practices.

Under the COMP-ROP program, oxygen therapy was managed by the participating center using either (1) a saturation alarm limit approach, which consisted of alarm limits set at the precise boundaries of the acceptable saturation range (85% to 93%), or (2) a saturation target approach, in which oxygen saturations of 88% to 92% were targeted within a broader range of alarm limits (e.g., 80% to 95%). The program sought to prevent periods of hyperoxia via the use of blended oxygen with routine oxygen saturation monitoring during delivery room care, transport, and nebulized medication delivery. In addition, the program was designed to avoid such therapeutic uses of hyperoxia as pre-oxygenation for procedures, treatment of apnea, "nitrogen washout" for the treatment of non–tension pneumothorax, and pulmonary vasodilatation for treating pulmonary hypertension in preterm infants 401 to 1500 gm at risk for ROP.

Between 2003 and 2008, severe ROP in the Pediatrix Network declined sharply from 11% in 2003 to 5.8% in 2008. The incidence of mortality, NEC, PDA, and PDA ligation fluctuated during the period, with no identifiable trend. Oxygen use at 28 days' and 36 weeks' postmenstrual age also decreased during the study interval.

The value of this report is that it provides a detailed description of barriers to implementing a comprehensive supplemental oxygen management program, as well as methods that may be used to help overcome these obstacles. Because of its size, involving 80 centers, the QI initiative described herein serves as a population-based estimate of the effect of oxygen saturation management on reducing the incidence of severe ROP.

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HIGH vs. LOW OXYGEN SATURATION TARGETS AMONG EXTREMELY PRETERM INFANTS

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959-1969.

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The NICHD SUPPORT trial is a randomized clinical study using a 2 x 2 factorial design to test the hypothesis that use of supplemental oxygen to maintain an oxygen saturation of 85% to 89% vs. 91% to 95% is associated with a reduction in the composite outcome of severe ROP, death before hospital discharge, or both. The investigators defined severe ROP as the presence of threshold ROP, the need for surgical ophthalmologic intervention, or the use of bevacizumab (humanized monoclonal antibody directed against vascular endothelial growth factor A) as treatment of ROP. Enrolled infants were also randomized to receive either continuous positive airway pressure or intubation and surfactant in the delivery room immediately after birth.

The study population comprised 1316 infants who were born between 24 weeks, 0 days and 27 weeks, 6 days of gestation, committed to full delivery room resuscitation if needed, and free of major anomalies. The participants were randomized before birth to supplemental oxygen management with either a saturation target of 85% to 89% (lower-oxygen-saturation group) or 91% to 95% (higher-oxygen-saturation group). Providers were blinded to the study intervention through use of electronically altered pulse oximeters that displayed 88% to 92% for both saturation target groups. Oxygen saturation data were stored electronically, downloaded, and analyzed to ensure that the study intervention created separation between the median oxygen saturation levels of the high-saturation and low-saturation groups.

The primary study outcome of death or severe ROP was similar in the low-saturation and high- saturation groups (28.3% vs. 32.1%, respectively; adjusted RR, 0.90; 95% CI, 0.76 to 1.06), with a 48% reduction in the incidence of severe ROP (8.6% vs. 17.9%, respectively; adjusted RR, 0.52; 95% CI, 0.37 to 0.73) offset by a 27% greater risk for death before hospital discharge (19.9% vs. 16.2%, respectively; adjusted RR, 1.27; 95% CI, 1.01 to 1.60). These results suggest that supplemental oxygen management with lower vs. higher saturation targets might be expected to result in 1 additional death for every 2 to 3 patients in whom severe ROP was prevented. There was no identifiable difference in the causes of death between the intervention groups. The authors observed that the absolute increase in mortality in their study (3.7%) between the restrictive and less restrictive oxygen groups was similar to that reported in the ROP studies from the 1950s (4.9%).

Among important secondary outcomes, although the need for supplemental oxygen was lower in the lower-saturation compared with the higher-saturation group (37.6 % vs. 46.7%, respectively; adjusted RR, 0.82; 95% CI, 0.72 to 0.93), the incidence of BPD defined using the physiologic definition (need for oxygen despite an attempt at oxygen withdrawal) did not differ between the groups (38.0% vs. 41.7%, respectively; adjusted RR, 0.92; 95% CI, 0.81 to 1.05). It is striking to note that the observed differences in the incidence of death, severe ROP, and duration of oxygen therapy occurred with only a 3% difference between groups in the median oxygen saturation among those requiring supplemental oxygen.

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ASSOCIATION BETWEEN HIGH INCIDENCE OF INTERMITTENT HYPOXEMIC EPISODES AND SEVERE ROP

Di Fiore JM, Bloom JN, Orge F, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr*. 2010;157(1):69-73.

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Fluctuations in oxygen saturation have been associated with a greater risk for severe ROP.[1,2] Di Fiore and collaborators evaluated the effect of intermittent hypoxemic episodes, defined as oxygen saturation <80% for >10 seconds and <3 minutes, on the development of ROP. The study enrolled 79 infants who were between 24 weeks, 0 days and 27 weeks, 6 days of gestation and were free of major anomalies. Infant oxygen saturation was measured using high-resolution pulse oximetry, with saturation data recorded continuously from day 1 to day 8 of age. The FiO_2 response to changes in oxygen saturation was carefully defined in the study protocol. The primary outcome was need for laser retinal therapy for the treatment of ROP.

In all infants studied, there was a direct relationship between the frequency of intermittent hypoxemic episodes and age over the first 8 weeks of age, with relatively few hypoxemic events occurring in the first week. Controlling for differences in gestational age, race, sex, multiple birth, and Score for Neonatal Acute Physiology and SNAP Perinatal Extension (SNAPPE)-II values, the investigators determined that the number of hypoxemic episodes was related directly to the risk for requiring laser retinal treatment for ROP.

The authors concluded that these findings are consistent with the concept that intermittent hypoxia may precipitate retinal neovascularization during the development of ROP.

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HIGH vs. LOW OXYGEN SATURATION AND SEVERE ROP: A META-ANALYSIS.

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(6):e1483-e1492.

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Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med*. 2003;349(10):959-967.

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Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics*. 2000;105(2):295-310.

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In a systematic literature review, Chen and associates reported on a meta-analysis of 9 studies that compared oxygen saturation targets among preterm neonates. The analysis was stratified by the age at which oxygen therapy was used. Stratum 1 included 5 cohort studies of high vs. low oxygen saturation targets in the acute neonatal period. Stratum 2 comprised 4 studies—2 RCTs and 2 cohort studies—that compared high vs. low oxygen saturations in the convalescent period (extremely preterm infants who were >32 weeks' postmenstrual age at the onset of the oxygen therapy intervention). Each of the 2 strata will be reviewed below.

Key Protocols

Acute neonatal period: meta-analysis of 5 cohort studies
Data from the low- and high-oxygen-saturation groups in each of the 5 studies were combined and analyzed using meta-analytic methods. In the analysis, saturation targets used in the 5 studies ranged from 70% to 96% in the low-saturation group and >94% to 99% in the high-saturation group.

Convalescent period: meta-analysis of 4 studies (2 RCTs and 2 cohort studies)
Data from the low- and high-oxygen-saturation groups were combined for this meta-analysis. Saturation targets ranged from 89% to 94% in the low-saturation group and >95% to 99% in the high-saturation group.

Significant Findings
Acute neonatal period: meta-analysis of 5 cohort studies
The meta-analysis reported a 52% reduction in the incidence of severe ROP (RR, 0.48; 95% CI, 0.31 to 0.75) among infants treated with the low saturation targets in the first weeks of life. There were no differences between the groups in the incidence of mortality or cerebral palsy. Although overlap existed among the treatment groups in the combined analysis, the heterogeneity statistic for the combined studies was not significant, suggesting sufficient homogeneity among the studies to justify combining their results.

Convalescent period: meta-analysis of 4 studies (2 RCTs and 2 cohort studies)
A meta-analysis of the 4 studies found a reduction in the risk for severe or progressive ROP among patients treated with higher vs. lower oxygen saturation targets (RR, 0.54; 95% CI, 0.35 to 0.82). The heterogeneity statistic for the combined studies was p=0.001, suggesting significant variation in study outcomes. The 2 main randomized trials in the meta-analysis are reviewed briefly below.

The Benefits of Oxygen Saturation Targeting (BOOST) study was an RCT involving 258 infants born at <30 weeks' gestation who were randomized at >32 weeks to 1 of 2 oxygen saturation target ranges: (1) a low group at 91% to 94% and (2) a high group at 95% to 98%. The hypothesis of the trial was that supplemental oxygen to achieve higher saturation targets would improve growth and neurodevelopmental outcome. The study found no significant differences between the high- and low-saturation target groups in mortality, weight, length, head circumference, and neurodevelopmental outcome at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days in the low-saturation group; P<.001), and had a higher rate of dependence on supplemental oxygen at 36 weeks' postmenstrual age (64% vs. 46% RR 1.40 95% CI (1.15, 1.70)) and a higher frequency of use of home-based oxygen therapy (30% vs. 17%, RR 1.78 95% CI (1.20, 2.64).

The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP) trial was an RCT involving 649 infants born at <29 weeks' gestation who had a <94% saturation on room air. Enrolled infants were randomized at >36 weeks to 1 of 2 oxygen saturation target ranges: (1) a low group at 89% to 94% and (2) a high group at 96% to 99%. The study's hypothesis was that supplemental oxygen to achieve higher saturation targets would slow the progression of prethreshold to threshold ROP. No difference was reported in the primary outcome, with progression to threshold ROP in at least 1 eye of 48% in the low-saturation group vs. 41% in the high-saturation group. After adjustment for baseline ROP severity, race, and gestational age, the odds ratio (high- vs. low-saturation groups) for progression was 0.72 (95% CI, 0.52, 1.01). Among important secondary outcomes, all study eyes at 3 months of corrected age showed similar rates of severe sequelae (retinal detachments or folds and macular ectopia) in both treatment arms. In addition, rates of ROP progression, stratified by ROP severity, were lower in the high-saturation vs. low-saturation target group. Although ophthalmologic outcomes were not significantly better, infants in the high-saturation vs. low-saturation group were more likely to experience pneumonia or pulmonary exacerbation of BPD (13.2% vs. 8.5%, respectively; P=.066), remain hospitalized (12.7% vs. 6.8%, respectively; P<.012), be on

oxygen (46.8% vs. 37.0%, respectively; P<.02) or diuretics (35.8% vs. 24.4%, respectively; P<.002) at 50 weeks' postmenstrual age. Growth and developmental milestones did not differ between the 2 treatment arms.

Summarizing the Results

Acute neonatal period
A meta-analysis of 5 cohort studies of oxygen saturation in the acute neonatal period confirmed an approximate 50% reduction in the risk for ROP when lower rather than higher oxygen saturation targets are used. Safety data, including risk for mortality or cerebral palsy, were similar in the high- and low-saturation target groups.

Convalescent period
From BOOST and STOP-ROP, use oxygen of saturation targets >95% beginning at either >32 or >36 weeks' postmenstrual age was not associated with improved growth or neurodevelopmental outcomes. In the STOP-ROP trial, the high- vs. low-saturation group experienced higher rates of pulmonary morbidity, with only a nonsignificant reduction in the rate of progression of ROP. Final ophthalmologic outcomes were similar between the groups. In summary, routine use of oxygen saturation targets of >95% in infants >32 to 36 weeks' postmenstrual age is not associated with improvements in growth, neurodevelopmental, or final ophthalmologic outcomes but is associated with higher rates of pulmonary morbidity. Hence, routine oxygen saturation targets of >95% in all infants >32 to 36 weeks' postmenstrual age is not recommended.

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