2019 American Heart Association Focused Update on Neonatal Resuscitation: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Marilyn B. Escobedo, MD, Chair; Khalid Aziz, MA, Med; Vishal S. Kapadia, MD; Henry C. Lee, MD; Susan Niermeyer, MD, MPH; Georg M. Schmölzer, MD, PhD; Edgardo Szyld, MD; Gary M. Weiner, MD; Myra H. Wyckoff, MD; Nicole K. Yamada, MD, MS; and Jeanette G. Zaichkin, RN, MN, NNP-BC

abstract

This 2019 focused update to the American Heart Association neonatal resuscitation guidelines is based on 2 evidence reviews recently completed under the direction of the International Liaison Committee on Resuscitation Neonatal Life Support Task Force. The International Liaison Committee on Resuscitation Expert Systematic Reviewer and content experts performed comprehensive reviews of the scientific literature on the appropriate initial oxygen concentration for use during neonatal resuscitation in 2 groups: term and late-preterm newborns (≥35 weeks of gestation) and preterm newborns (<35 weeks of gestation). This article summarizes those evidence reviews and presents recommendations. The recommendations for neonatal resuscitation are as follows: In term and late-preterm newborns (≥35 weeks of gestation) receiving respiratory support at birth, the initial use of 21% oxygen is reasonable. One hundred percent oxygen should not be used to initiate resuscitation because it is associated with excess mortality. In preterm newborns (<35 weeks of gestation) receiving respiratory support at birth, it may be reasonable to begin with 21% to 30% oxygen and to base subsequent oxygen titration on oxygen saturation targets. These guidelines require no change in the Neonatal Resuscitation Algorithm–2015 Update.

Key Words: infant, newborn ■ infant, premature ■ oxygen ■ resuscitation

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This 2019 focused update to the American Heart Association (AHA) neonatal resuscitation guidelines is based on the systematic review of initial oxygen concentration for term neonatal resuscitation[1] and initial oxygen concentration for preterm neonatal resuscitation[2] and the resulting "2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations" (CoSTR) from the International Liaison Committee on Resuscitation (ILCOR) Neonatal Life Support Task Force.[3–5]

The neonatal life support CoSTR drafts were posted online for public comment in January 2019.[3,4] In addition, the Neonatal Life Support Task Force has an expanded international committee of experts who collaborate to enrich these recommendations with a broader debate and vision. This committee meets in person twice a year. A summary containing the final wording of the 2 CoSTR documents has been published simultaneously with this focused update.[5]

AHA guidelines for cardiopulmonary resuscitation and emergency cardiovascular care are developed in concert with the ILCOR systematic review process. In 2015, the 5-year ILCOR evidence evaluation cycle transitioned to a continuous one, with systematic reviews performed as newly published evidence warrants or when the ILCOR Neonatal Life Support Task Force prioritizes a topic. The AHA writing group then reviews the evidence and updates the AHA guidelines as needed, typically on an annual basis. A description of the evidence review process is available in the 2017 CoSTR summary.[6] The ILCOR systematic review process uses the Grading of Recommendations Assessment, Development, and Evaluation methodology[7] and its associated nomenclature to determine the certainty of evidence and strength of recommendations for the CoSTR.

The AHA writing group for this 2019 focused update to the neonatal life support guidelines reviewed the studies and analyses of the 2018 ILCOR systematic reviews[1,2] and carefully considered the 2019 ILCOR Neonatal Task Force CoSTR[5] in the context of North American systems of care, levels of resource availability, and varied providers who follow AHA guidelines. In addition, the AHA writing group determined the Classes of Recommendation and Levels of Evidence according to the recommendations of the American College of Cardiology/AHA Task Force on Clinical Practice Guidelines[8] (Table) by using the process detailed in the "2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care."[9]

BACKGROUND

Although hypoxia and ischemia can injure multiple organs, adverse biochemical and physiologic outcomes also may result from even brief exposure to excessive oxygen during and after resuscitation.[10] In addition, preterm neonates are more susceptible than term neonates to clinical morbidities related to excessive oxygen exposure such as bronchopulmonary dysplasia, retinopathy of prematurity, and other important outcomes considered in the evidence review.[11,12] Consequently, separate CoSTRs were developed for term and late-preterm (≥35 weeks of gestation) newborns and for preterm (<35 weeks of gestation) newborns, reflecting differing indications for resuscitation, types of interventions, and outcomes of interest.[3,4]

The question of which initial oxygen concentration to use during resuscitation of term neonates was last reviewed by ILCOR in 2010.[13] The original AHA guidelines for oxygen use during neonatal resuscitation[14] were based on expert opinion and common practice and recommended the use of 100% oxygen for all newborns receiving respiratory support. Subsequent evidence from both animal and human studies has led to modifications of these recommendations. In 1998, the World Health Organization recommended 21% oxygen for basic newborn resuscitation when supplementary oxygen was not available.[15] Studies of normal transition after birth led to a recommendation that blended oxygen be titrated to achieve an oxygen saturation that is reflective of that observed in healthy babies born at term (ie, targeted saturation).[16,17] On the basis of studies that showed a lack of benefit of 100% oxygen for short-term respiratory outcomes and a decrease in mortality for term infants resuscitated with 21% oxygen, the ILCOR 2010 CoSTR[13] and AHA neonatal resuscitation guidelines[18] recommended the use of 21% oxygen to initiate positive-pressure ventilation for term infants.

The question of which initial oxygen concentration to use during the resuscitation of preterm neonates was last reviewed by ILCOR in 2015.[19] Most studies of preterm infants available at that time compared the use of high (60% to 100%) and low (21% to 30%) oxygen concentration and found no benefit from the use of high oxygen concentration for any of the outcomes of interest. This resulted in a recommendation for initiating resuscitation of preterm infants with a low oxygen concentration, as well as a specific recommendation against initiating resuscitation of preterm infants with high oxygen concentrations.[20] These recommendations reflected the value placed by the Neonatal Task Force on not exposing preterm infants to additional oxygen without proven benefit for critical or important outcomes.

The 2018 ILCOR systematic reviews addressed the use of lower initial oxygen concentrations compared with higher initial oxygen concentrations in both term[1] and preterm[2] neonatal resuscitation by using the Grading of Recommendations Assessment, Development, and Evaluation evidence evaluation methodology.[7]

INITIAL OXYGEN CONCENTRATION: TERM AND LATE-PRETERM NEWBORNS (≥35 WEEKS OF GESTATION)

Evidence Summary—Updated 2019

The 2018 ILCOR systematic review[1] compared the outcomes of term and

Table Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated August 2015)*

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

late-preterm newborns (≥35 weeks of gestation) who received respiratory support after birth that used either 21% or 100% oxygen because no identified studies evaluated intermediate concentrations (between 22% and 99%, inclusive). The complete review included 10 original studies and 2 follow-up studies involving 2164 newborns. Three of the original studies were included only in sensitivity analyses because they were determined to have a critical risk of bias. In total, 7 randomized controlled trials (RCTs) and quasi-RCTs enrolling 1469 term and late-preterm newborns were included in the primary meta-analysis.[12,21–26]

All 7 included trials evaluated the outcome of short-term mortality, defined as mortality either in the hospital or within 30 days. In the meta-analysis, the summary relative risk (RR) of short-term mortality was lower in the 21% oxygen group (RR, 0.73 [95% CI, 0.57–0.94]).[1] This estimate was of low-level certainty because of the risk of bias and imprecision.

Two studies examined the outcome of neurodevelopmental impairment in survivors at 1 to 3 years of age.[25,27] The pooled estimate showed no statistically significant difference in risk between the 21% and 100% oxygen groups (RR, 1.41 [95% CI, 0.77–2.60]).[1] Five studies examined the outcome of hypoxic-ischemic encephalopathy,[21,22,24–26] defined as Sarnat stage 2 or 3.[28] Again, there was no statistically significant difference between the 21% and 100% oxygen groups (RR, 0.90 [95% CI, 0.71–1.14]).[1] No identified studies evaluated all-cause long-term mortality. Collectively, the studies were downgraded for risk of bias and imprecision and assigned as evidence of low certainty with respect to hypoxic-ischemic encephalopathy and very low certainty for long-term neurodevelopmental impairment.

Recommendations—Updated 2019

1. **In term and late-preterm newborns (≥35 weeks of gestation) receiving respiratory support at birth, the initial use of 21% oxygen is reasonable (Class 2a; Level of Evidence B-R).**

2. **One hundred percent oxygen should not be used to initiate resuscitation because it is associated with excess mortality (Class 3: Harm; Level of Evidence B-R).**

The current recommendations affirm the 2010[18] and 2015 AHA guidelines[20] and extend the recommendation against starting ventilation with 100% oxygen to term and late-preterm newborns. This is based on the large undesirable effect on short-term mortality associated with high initial oxygen concentration and the value attached to this outcome by parents and clinicians. Ambient air (21% oxygen) is available in all low- and well-resourced settings. Despite the lack of published economic analyses, there is likely to be greater feasibility and lower cost when resuscitation is initiated without added oxygen. Although evidence is still lacking on titration to achieve oxygen saturation targets, the use of preductal oxygen saturation targeting approximating the interquartile range measured in healthy term infants after vaginal birth at sea level is consistent with the high value placed on avoiding excessive oxygen exposure.

DISCUSSION

The 2010[18] and 2015 AHA guidelines for neonatal resuscitation[20] supported the initial use of 21% oxygen with subsequent supplementary oxygen use guided by target oxygen saturations measured by pulse oximetry in term and late-preterm newborns. At the time, these guidelines represented a departure from the decades-long use of 100% oxygen for all newborns receiving respiratory support. The guidelines were informed by 2 systematic reviews with meta-analyses.[29,30] The pooled estimates from these reviews reported lower mortality, fewer infants with time to first breath >3 minutes, and fewer infants with Apgar scores <7 at 5 minutes when 21% compared with 100% oxygen was used for initial mask ventilation. All studies included in these reviews were conducted >10 years ago, when pulse oximetry and oxygen titration were not routine. It remains unclear whether low versus high initial oxygen concentration will have the same result with oxygen titration as a cointervention.

The 2018 ILCOR systematic review and meta-analysis involved 1469 neonates ≥35 weeks of gestation enrolled in 7 randomized and quasi-randomized studies and reported a 27% relative survival benefit and a 4.6% absolute survival benefit (short-term) when 21% oxygen was compared with 100% oxygen for initial mask ventilation.[1] These benefits corresponded to 1 additional survivor (short-term) for 22 infants receiving 21% oxygen instead of 100% oxygen at birth. The Grading of Recommendations Assessment, Development, and Evaluation certainty of evidence was low for short-term mortality and hypoxic-ischemic encephalopathy and very low for long-term neurodevelopmental impairment. Furthermore, no studies were identified for the outcome of all-cause long-term mortality. All included studies compared 21% with 100% initial oxygen concentration. No studies were identified that compared intermediate oxygen concentrations, and no studies compared oxygen concentrations used during chest compressions.

The 2018 ILCOR systematic review and meta-analysis[1] confirmed a significant reduction in the critically important outcome of short-term mortality, without statistically significant differences in short- and long-term neurologic outcomes, with the use of initial 21% oxygen compared with 100% oxygen for term and late-preterm newborns (≥35 weeks of gestation) receiving respiratory support at birth. The authors estimated that 46 of 1000 fewer babies died when respiratory support at birth was started with 21% compared with 100% oxygen (95% CI, 73/1000 fewer–10/1000 fewer). As a result, the previous recommendations in the 2010 and 2015 AHA guidelines[18,20] are affirmed and extended to recommend against starting ventilation with 100% oxygen.

INITIAL OXYGEN CONCENTRATION: PRETERM NEWBORNS (<35 WEEKS OF GESTATION)

Evidence Summary—Updated 2019

The 2018 ILCOR systematic review compared several outcomes of preterm newborns (<35 weeks of gestation) who received respiratory support immediately after birth with

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Marilyn B. Escobedo	University of Oklahoma Medical School	None	None	None	None	None	None	None
Khalid Aziz	University of Alberta (Canada)	Canadian Institutes of Health Research (Parent-EPIQ quality improvement research)†, (family-integrated care 18-mo follow-up)†; Alberta Children's Hospital Research Institute (family-integrated care 6-mo follow-up)†	None	None	CMPA, national medical protective association opinions on national neonatal guidelines*	None	None	University of Alberta (professor)†
Vishal S. Kapadia	UT Southwestern	NIH (PI for a clinical trial)*	None	None	None	None	None	None
Henry C. Lee	Stanford University	NIH (PI on a grant to implement in situ simulation training for neonatal resuscitation)*	None	None	None	None	None	None
Susan Niermeyer	University of Colorado	None	None	None	None	None	None	None
Georg M. Schmölzer	NA	NIH (R01, co-PI for premature infants receiving milking or delayed cord clamping, RCT)*; CIHR (PI for the SURV1VE Trial RCT [2 different chest compression techniques in newborn infants])*; HFSC (PI for grant to examine chest compression in a piglet model)*; SickKids Foundation and CIHR (PI to examine chest compression in piglets)*; NHMRC grant for delivery room resuscitation in near-term lambs (co-PI)*	None	None	None	None	None	None
Edgardo Szyld	University of Oklahoma	None	None	None	None	None	None	None
Gary M. Weiner	University of Michigan	None	None	None	None	None	None	None
Myra H. Wyckoff	UT Southwestern	None	None	None	None	None	None	None
Nicole K. Yamada	Stanford University	AHRQ (PI on the effects of standardized communication on team performance during neonatal resuscitation)†; NICHD (collaborator on a grant investigating the implementation of in situ simulation to improve delivery room outcomes in the California Perinatal Quality Care Collaborative)*	None	None	None	None	None	None
Jeanette G. Zaichkin	Self-employed	None	None	None	HeplerBroom LLC*	None	American Academy of Pediatrics†	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-mo period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

* Modest.

† Significant.

the use of a low initial oxygen concentration (≤50%) compared with a high initial oxygen concentration (>50%).[2] The reviewers identified 16 eligible studies enrolling 5697 newborns, including 10 RCTs,[11,31–39] 2 follow-up studies,[40,41] and 4 observational cohort studies.[42–45] Low initial oxygen was defined as 21% in 5 RCTs,[31,33,34,36,39] 30% in 4 RCTs,[11,35,37,38] and 50% in 1 RCT.[32] Oxygen saturation targeting was a cointervention in 8 RCTs[11,33–39] and in all 4 cohort studies.[42–45] When oxygen saturation targeting was used, nearly all newborns randomized to initiate resuscitation with 21% oxygen required supplementary oxygen to achieve the specified target. Because oxygen saturation targeting resulted in rapid changes in inspired oxygen concentrations, the subjects enrolled in these trials were exposed to different oxygen concentrations for only the first 5 to 7 minutes of life.

The pooled estimate of 10 RCTs enrolling 968 preterm newborns showed no statistically significant difference in the outcome of all-cause short-term mortality (hospital discharge or 30 days) when respiratory support initiated with a lower oxygen concentration was compared with support initiated with a higher oxygen concentration (RR, 0.83 [95% CI, 0.50–1.37]).[2] In a subgroup analysis of 7 RCTs[11,33,34,36–39] enrolling 467 newborns ≤28 weeks of gestation, there was no significant difference in short-term mortality (RR, 0.92 [95% CI, 0.42–1.94]).[2]

Similarly, the ILCOR systematic review found no differences in any of the prespecified secondary outcomes, including long-term mortality, long-term neurodevelopmental impairment, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, or major (grade III or IV) intraventricular hemorrhage.[2] White matter injury of prematurity was not included as a secondary outcome. Additional subgroup analyses that assessed the effect of varying the definition of low and high oxygen concentration, the risk of bias, and the use of oxygen saturation targeting as a cointervention found no differences in primary or secondary outcomes. When data from 2 observational cohort studies were pooled,[44,45] initiating resuscitation with lower oxygen was associated with a statistically significant benefit in long-term mortality for all preterm newborns and the subgroup of newborns ≤28 weeks of gestation.[2]

Most of the studies included in the ILCOR systematic review were judged to have an unclear risk of bias because of imprecision, inconsistency, and lack of blinding of interventions and outcomes.[2] As a result of the unclear risk of bias and the small number of very preterm newborns enrolled in the randomized trials, there was very low certainty for all outcome estimates, and the benefit or harm from initiating positive-pressure ventilation with low compared with high oxygen concentrations remains inconclusive. Large randomized trials enrolling very preterm newborns are needed to achieve the optimal information size. Furthermore, scant evidence exists on the use of intermediate oxygen concentrations (30% to 60%).

Recommendation—Updated 2019

1. **In preterm newborns (<35 weeks of gestation) receiving respiratory support at birth, it may be reasonable to begin with 21% to 30% oxygen with subsequent oxygen titration based on pulse oximetry (Class 2b; Level of Evidence C-LD).**

The current recommendation remains consistent with the 2015 AHA guidelines update.[20] Given that nearly all trials included in the 2018 ILCOR review defined low initial oxygen as 21% to 30% oxygen,[2] the current recommendation suggests this as a reasonable initial oxygen concentration. In this recommendation, high value is placed on avoiding additional oxygen exposure without evidence of benefit for critical or important outcomes. The writing group acknowledges that

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Jennifer Armstrong	University of Colorado Denver	None	None	None	None	None	None	None
Stephen A. Back	Oregon Health Sciences University	None	None	None	None	None	None	None
Roberta L. Keller	University of California, San Francisco	None	None	None	None	None	None	None
Helen G. Liley	Mater Mothers' Hospital (Australia)	None	None	None	None	None	None	None
Janet Soul	Boston Children's Hospital	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-mo period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

although the evidence identified in the 2018 ILCOR review was weak and uncertain, it also showed no statistically significant difference in outcomes when low versus high initial oxygen concentration was chosen for preterm resuscitation at birth. In the absence of a new evidence review for subsequent oxygen titration, it remains prudent to continue to titrate oxygen concentrations to achieve preductal oxygen saturation approximating the interquartile range measured in healthy term infants after vaginal birth at sea level, as recommended in the 2015 AHA guidelines update.[20]

Discussion

The 2015 AHA guidelines update for neonatal resuscitation recommended that resuscitation of preterm newborns <35 weeks of gestation should be initiated with low oxygen (21% to 30%) and that the oxygen concentration should be titrated to achieve a preductal oxygen saturation approximating the interquartile range measured in healthy term infants after vaginal birth at sea level.[20]

Since the release of the 2015 guidelines, new data have been published on the initial oxygen concentration used in the delivery room for preterm infants (<35 weeks of gestation), prompting the ILCOR Neonatal Life Support Task Force to complete a new systematic review of the available evidence.[2] Of particular concern was the recent publication of the To2rpido RCT (Targeted Oxygen in the Resuscitation of Preterm Infants and Their Developmental Outcomes).[39] In a subgroup analysis of preterm infants <28 weeks of gestation, the To2rpido investigators reported that the use of 21% oxygen for initial positive-pressure ventilation, compared with 100% oxygen, increased the risk of death before hospital discharge (RR, 3.9 [95% CI, 1.1–13.4]).[39] However, the ILCOR systematic review identified significant concerns about the risk of bias in this study, including very limited enrollment, early study termination, lack of investigator equipoise, use of an unblinded intervention, and increased risk seen only in a post hoc subgroup analysis.[2] Because the review and meta-analysis found no difference in any primary or secondary outcomes with the To2rpido trial included, the recommendation that resuscitation of preterm newborns should begin with low oxygen with subsequent titration to meet goal saturations remains unchanged. This reflects a continued preference to avoid exposing preterm newborns to additional oxygen without evidence demonstrating a benefit for critical or important outcomes. Important knowledge gaps remain in the understanding of oxygen use for positive-pressure ventilation among term, late-preterm, and preterm newborns after birth. Additional research is needed to evaluate the role of intermediate oxygen concentrations for the initiation of positive-pressure ventilation and to define the most appropriate oxygen saturation targets. Many subpopulations of newborns (eg, newborns with congenital heart disease and other malformations) have not been adequately studied, and many outcomes (eg, white matter injury of prematurity) have not been fully assessed. These newborns and their outcomes may be affected by either hypoxemia or hyperoxemia. Until reliable data on a specific population or outcome are available, the consistent and practical educational approach will be to manage them according to the guidelines for the wider population of preterm and term newborns requiring resuscitation.

SUMMARY

This review of the initial use of oxygen in newborns receiving respiratory support at birth remains consistent with the 2015 AHA neonatal resuscitation guidelines.[20] In term and late-preterm newborns (≥35 weeks of gestation), the initial use of 21% oxygen is reasonable (*Class 2a; Level of Evidence B-R*). In term and late-preterm newborns, the initial use of 100% oxygen is not recommended (*Class 3: Harm; Level of Evidence B-R*).

In preterm newborns (<35 weeks of gestation), starting with 21% to 30% oxygen with subsequent targeted titration of supplementary oxygen may be reasonable (*Class 2b; Level of Evidence C-LD*). These guidelines do not alter the Neonatal Resuscitation Algorithm–2015 Update.[19,20]

Knowledge gaps for term, late-preterm, and preterm newborn resuscitation include the following: (1) uncertainty about the impact of changes in umbilical cord management; (2) uncertainty about the impact of changes in oxygen saturation monitoring and targeted titration of inspired oxygen; (3) uncertainty about the effects of intermediate initial inspired oxygen concentrations; (4) uncertainty about whether a single initial oxygen concentration is optimal for newborns with varying pathology or conditions such as antenatal fetal distress at any given gestational age; and (5) uncertainty about the impact of lower initial oxygen use on neurodevelopmental outcomes in preterm newborns. With so many unanswered questions, it is expected that future scientific evidence will provide new insights, and guideline updates will be required.

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