Circulation

Neonatal Life Support

2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

ABSTRACT: This *2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations* (CoSTR) for neonatal life support includes evidence from 7 systematic reviews, 3 scoping reviews, and 12 evidence updates. The Neonatal Life Support Task Force generally determined by consensus the type of evidence evaluation to perform; the topics for the evidence updates followed consultation with International Liaison Committee on Resuscitation member resuscitation councils. The 2020 CoSTRs for neonatal life support are published either as new statements or, if appropriate, reiterations of existing statements when the task force found they remained valid.

Evidence review topics of particular interest include the use of suction in the presence of both clear and meconium-stained amniotic fluid, sustained inflations for initiation of positive-pressure ventilation, initial oxygen concentrations for initiation of resuscitation in both preterm and term infants, use of epinephrine (adrenaline) when ventilation and compressions fail to stabilize the newborn infant, appropriate routes of drug delivery during resuscitation, and consideration of when it is appropriate to redirect resuscitation efforts after significant efforts have failed.

All sections of the Neonatal Resuscitation Algorithm are addressed, from preparation through to postresuscitation care. This document now forms the basis for ongoing evidence evaluation and reevaluation, which will be triggered as further evidence is published.

Over 140 million babies are born annually worldwide (https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100). If up to 5% receive positive-pressure ventilation, this evidence evaluation is relevant to more than 7 million newborn infants every year. However, in terms of early care of the newborn infant, some of the topics addressed are relevant to every single baby born.

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Key Words: AHA Scientific Statements ■ cardiopulmonary resuscitation ■ neonatal resuscitation ■ neonate

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CONTENTS

Transition from intrauterine to extrauterine life at birth requires several critical interdependent physiological events to occur rapidly to allow successful conversion from placental to pulmonary gas exchange.[1] Air breathing leads to significant reductions in pulmonary vascular resistance, which increases pulmonary blood flow and thereby maintains left ventricular filling and output (vital for coronary and cerebral perfusion) when the umbilical cord is clamped.[2] When the low-resistance placental circulation is removed, systemic vascular resistance and blood pressure increase and right-to-left shunting across the ductus arteriosus decreases.

The majority (approximately 85%) of babies born at term will initiate breathing within 10 to 30 seconds of birth.[3] An additional 10% will do so in response to stimulation and drying.[4] Nevertheless, approximately 5% of term infants receive positive-pressure ventilation (PPV) to successfully transition, 2% are intubated, 0.1% receive cardiac compressions, and 0.05% receive compressions with epinephrine.[5–8] Although most infants successfully transition without assistance, the large number of births worldwide means that availability of appropriate, timely intervention can prevent morbidity and save millions of newborn lives each year.

Newborn infants who are breathing or crying and have good tone and an adequate heart rate may undergo delayed cord clamping and should be dried and placed skin to skin with their mothers to prevent hypothermia. This does not preclude the need for clinical assessment of the newborn as secondary apnea, persistent cyanosis, or breathing difficulties can still occur. For the approximately 5% of newborn infants who do not initiate adequate respiratory effort after stimulation by drying and warming, providers must deliver effective ventilation with a face mask. This is effective in most cases. If it is not effective, providers should take measures to eliminate mask leaks, check for airway patency, and ensure that adequate inflation pressures are used; if ventilation is still not effective, an alternative airway (endotracheal tube or supraglottic airway) must be considered. Providers must optimize ventilation because it is the most important step for successful transition. If, despite efforts to optimize ventilation, the newborn has a persistent heart rate less than 60/min or asystole, then chest compressions are needed. Epinephrine and administration of fluids for circulatory volume expansion may also be required. The neonatal resuscitation algorithm is shown in Figure 1 and is unchanged from 2015.[1,9,10]

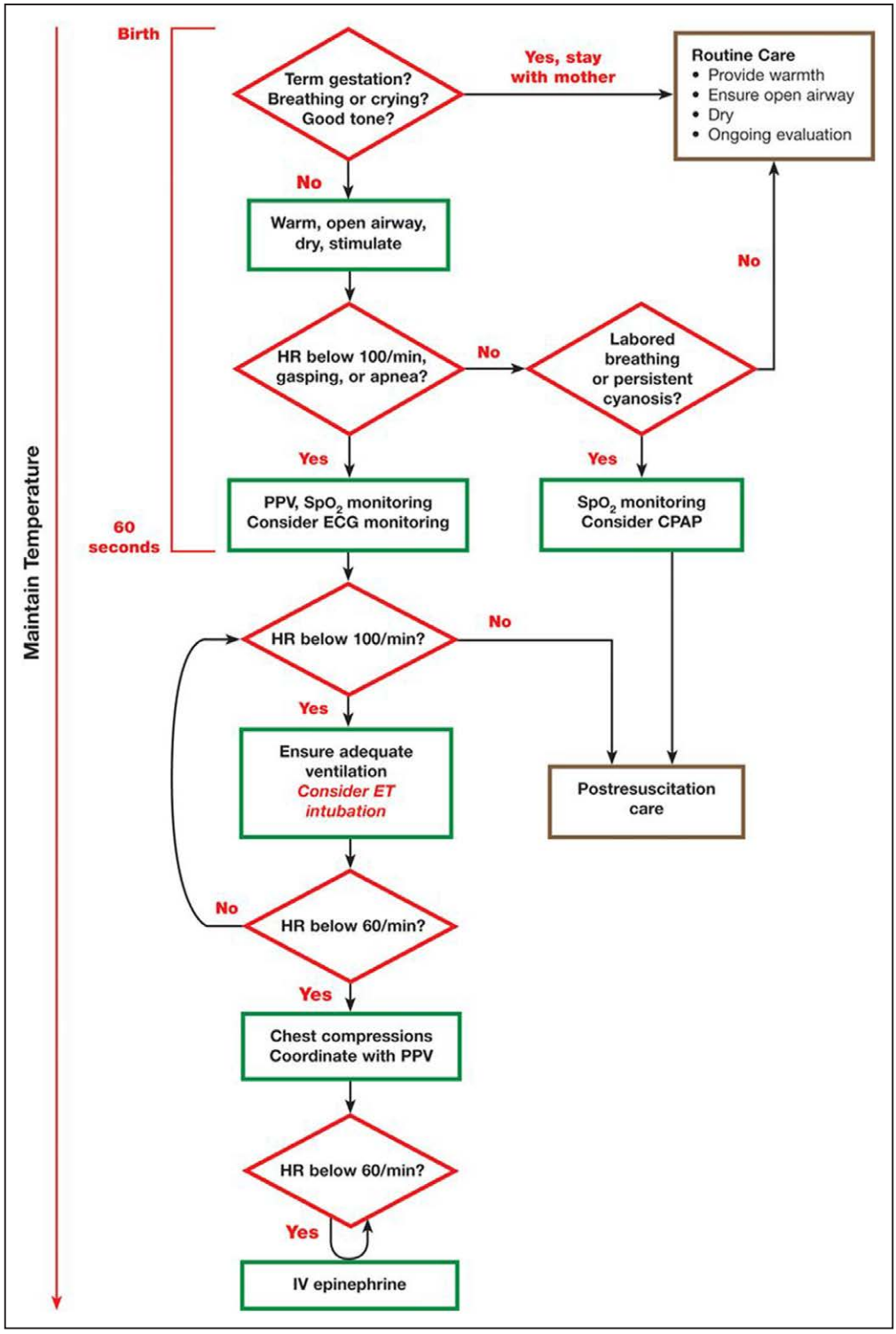

Figure 1. Neonatal Resuscitation Algorithm.
CPAP indicates continuous positive airway pressure; ECG, electrocardiographic; ET, endotracheal; HR, heart rate; IV, intravenous; and PPV, positive-pressure ventilation.

EVIDENCE EVALUATION PROCESS

The *2020 International Consensus on Cardiopulmonary Resuscitation* (CPR) *and Emergency Cardiovascular Care* (ECC) *Science With Treatment Recommendations* (CoSTR) is the fourth in a series of annual publications from the International Liaison Committee on Resuscitation (ILCOR) for neonatal life support (NLS). This 2020 CoSTR for NLS includes new topics addressed by systematic reviews performed within the past 12 months. It also includes updates of NLS treatment recommendations published from 2010 through 2019, based on additional evidence evaluations. The 3 types of evidence evaluation supporting this 2020 document

are the systematic review (SysRev), the scoping review (ScopRev) and the evidence update (EvUp). The choice of the type of evidence evaluation to perform was determined by consensus of the task force and, in the case of EvUps, recommendations of ILCOR member resuscitation councils.

The SysRev is a rigorous process following strict methodology to answer a specific question. The SysRevs informed NLS Task Force deliberations that are summarized in the NLS Task Force CoSTRs included in this document. The SysRevs were performed by a knowledge synthesis unit, an expert systematic reviewer, or by the NLS Task Force, and many resulted in separately published SysRevs.

To begin the SysRev, the question to be answered was developed using the PICOST (population, intervention, comparator, outcome, study design, time frame) format. The methodology used to identify the evidence was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA: http://www.prisma-statement.org). The approach used to evaluate the evidence was based on that proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (https://gdt.gradepro.org/app/handbook/handbook.html). By using this approach for each of the predefined outcomes, the task force rated as high, moderate, low, or very low the certainty/confidence in the estimates of effect of an intervention or assessment across a body of evidence. Randomized controlled trials (RCTs) generally began the analysis as high-certainty evidence, and observational studies generally began the analysis as low-certainty evidence; examination of the evidence using the GRADE approach could result in downgrading or upgrading the certainty of evidence. For additional information, refer to this supplement's "Evidence Evaluation Process and Management of Potential Conflicts of Interest" section.[11,11a] Disclosure information for writing group members is listed in Appendix 1. Disclosure information for peer reviewers is listed in Appendix 2.

Draft 2020 CoSTRs for NLS were posted on the ILCOR website (www.ilcor.org) for public comment between January 15, 2019, and February 20, 2020, with comments accepted through March 4 for the last NLS CoSTR posted. All of the NLS draft CoSTRs were viewed a total of 45 032 times, with 279 comments posted. When online viewing statistics were available for individual CoSTRs, these are included in the topic information.

This summary statement contains the final wording of the CoSTRs as approved by the ILCOR task forces and by the ILCOR member councils after review and consideration of comments posted online in response to the draft CoSTRs. Within this manuscript, each topic includes the PICOST as well as the CoSTR, an expanded "Justification and Evidence-to-Decision Framework Highlights" section, and a list of knowledge gaps requiring future research studies. In Appendix A in the Supplemental Materials, an evidence-to-decision table is included for each CoSTR and is based on a new SysRev.

The second type of evidence evaluation performed to support this 2020 CoSTR for NLS is the ScopRev. ScopRevs are designed to identify the extent, range, and nature of evidence on a topic or a question, and they were performed by topic experts in consultation with the NLS Task Force. The task force analyzed the identified evidence and determined its value and implications for resuscitation practice or research. The rationale for the ScopRev, the summary of evidence, and task force insights are all highlighted in the body of this manuscript. The most recent treatment recommendations are included. The NLS Task Force notes whether the ScopRev identified substantive evidence suggesting the need for a future SysRev to support the development of an updated CoSTR. Meanwhile, the current treatment recommendation is reiterated. All ScopRevs are included in their entirety in Appendix B in the Supplemental Materials.

The third type of evidence evaluation supporting this 2020 CoSTR for NLS is an EvUp. EvUps are generally performed to identify new studies published after the most recent NLS evidence evaluation, typically through use of similar search terms and methodologies used in previous reviews. These EvUps were performed by task force members, collaborating experts, or members of ILCOR member resuscitation council writing groups. The EvUps are cited in the body of this document with a note as to whether the evidence identified suggested the need to consider a SysRev; the existing ILCOR treatment recommendation is reiterated. In this document, no change in ILCOR treatment recommendations resulted from an EvUp. If substantial new evidence was identified, the task force recommended consideration of a SysRev. All draft EvUps are included in Appendix C in the Supplemental Materials.

GENERATION OF TOPICS

After publication of the *2015 International Consensus on CPR and ECC Science With Treatment Recommendations*,[1,9,10] the NLS Task Force, together with additional neonatal resuscitation content experts (approximately 50 neonatal medicine and nursing professionals, from 17 countries, with expertise in neonatal resuscitation research, education, and implementation), reviewed the list of prior neonatal resuscitation clinical questions to divide them into 3 categories: those that could be retired, those that remained relevant but required additional clinical studies to better address the PICOST question, and those with sufficient evidence to justify a SysRev in the near future. New questions were also proposed and categorized. The list was posted for public comment in June 2017, and as a result, some amendments were made. Using the new ILCOR process of continuous evidence evaluation (see "Evidence Evaluation Process and Management

of Potential Conflicts of Interest"[11] in this supplement), the active questions were prioritized for SysRevs as ILCOR resources became available. Other topics were slated for ScopRevs or EvUps as noted above. The task force met via webinar at least monthly and in person annually; in addition, the task force met with the larger content expert group semiannually to present the science and debate and discuss treatment recommendations. The task force and larger group of content experts identified and reviewed the published literature and reached consensus to review the topics included in this manuscript.

2020 TOPICS REVIEWED

Anticipation and Preparation
- Prediction of need of respiratory support in the delivery room (NLS 611: EvUp)
- Effect of briefing/debriefing following neonatal resuscitation (NLS 1562: ScopRev)

Initial Assessment and Intervention
- Warming adjuncts (NLS 599: EvUp)
- Suctioning of clear fluid (NLS 596: ScopRev)
- Tracheal intubation and suction of nonvigorous meconium-stained newborns (NLS 865: SysRev)

Physiological Monitoring and Feedback Devices
- Heart rate monitoring during neonatal resuscitation (NLS 898: EvUp)

Ventilation and Oxygenation
- Sustained inflation (NLS 809: SysRev)
- Positive end-expiratory pressure (PEEP) versus no PEEP (NLS 897: EvUp)
- Continuous positive airway pressure (CPAP) versus intermittent PPV (NLS 590: EvUp)
- T-piece resuscitator versus self-inflating bag for ventilation (NLS 870: ScopRev)
- Oxygen for preterm resuscitation (NLS 864: 2019 CoSTR publication)
- Oxygen for term resuscitation (NLS 1554: 2019 CoSTR publication)

Circulatory Support
- CPR ratios for neonatal resuscitation (NLS 895: EvUp)
- 2-thumb versus 2-finger compressions for neonatal resuscitation (NLS 605: EvUp)

Drug and Fluid Administration
- Epinephrine (adrenaline) for neonatal resuscitation (NLS 593: SysRev)
- Intraosseous versus umbilical vein for emergency access (NLS 616: SysRev)
- Volume infusion during neonatal resuscitation (NLS 598: EvUp)
- Sodium bicarbonate during neonatal resuscitation (NLS 606: EvUp)

Prognostication During CPR
- Impact of duration of intensive resuscitation (NLS 896: SysRev)

Postresuscitation Care
- Rewarming of hypothermic newborns (NLS 858: EvUp)
- Induced hypothermia in settings with limited resources (NLS 734: EvUp)
- Postresuscitation glucose management (NLS 607: EvUp)

ANTICIPATION AND PREPARATION

The keys to successful neonatal resuscitation include assessment of perinatal risk and a system to rapidly assemble team members with skills that are appropriate to the anticipated need for resuscitation on the basis of that risk. Other critical components of successful resuscitation include an organized resuscitation area that ensures immediate access to all needed supplies and equipment and the standardization of behavioral skills that foster optimal teamwork and communication.

Prediction of Need of Respiratory Support in the Delivery Room (NLS 611: EvUp)

One important aspect of anticipating risk (determining if operative delivery conferred increased risk of need for intubation) was reviewed by the NLS Task Force most recently in 2010.[12–14] In 2020, The NLS Task Force undertook an EvUp to identify additional evidence published after 2010 that warranted consideration of a new SysRev.

An EvUp (see Supplement Appendix C-1) did not identify any evidence that would suggest the need for a new SysRev or a change in the 2010 treatment recommendation.[12–14] Most of the new studies confirmed previously identified risk factors for the need for PPV in the delivery room.

Population, Prognostic Factors, Outcome

Population: Newborn infants who are to be delivered

Prognostic factors: Maternal, perinatal, or delivery risk factors beyond age of gestation

Outcome: Prediction of need for PPV in the delivery room/operating suite

Treatment Recommendation

These treatment recommendations (below) are unchanged from 2010.[12–14]

When an infant without antenatally identified risk factors is delivered at term by cesarean delivery under regional anesthesia, a provider capable of performing assisted ventilation should be present at the delivery. It is not necessary for a provider skilled in neonatal intubation to be present at that delivery.

Effect of Briefing/Debriefing Following Neonatal Resuscitation (NLS 1562: ScopRev)

Rationale for Review

Although a prior review examined the utility of debriefing after simulation training, the NLS Task Force chose this topic for ScopRev because there is emerging evidence in many fields that briefing before and debriefing after clinical events may lead to improvement in practice and outcomes. There was no previous NLS Task Force treatment recommendation on this application of briefing and debriefing.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Among healthcare professionals involved in the resuscitation or simulated resuscitation of a neonate
- Intervention: Does briefing/debriefing
- Comparator: In comparison with no briefing/debriefing
- Outcome: Improve outcomes for infants, families, or clinicians
- Study design: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Manikin studies were eligible for inclusion; animal studies were excluded. Conference abstracts were included; unpublished studies (eg, trial protocols) were excluded.
- Time frame: All years and all languages were included if there was an English abstract.

Summary of Evidence

The ScopRev[14a] identified 1 RCT[15] and 3 observational studies of preintervention and postintervention design.[16–18] One study considered video debriefing,[16] 1 considered the use of a checklist combined with video debriefing,[18] and 1 considered the use of a checklist with a team prebrief/debrief as the key element in a quality improvement bundle.[17] The RCT determined whether there was benefit to rapid cycle deliberate practice compared with standard simulation debriefing.[15] This entire ScopRev[14a] can be found in Supplement Appendix B-1.

Task Force Insights

Because this is a new PICOST question for the NLS Task Force, the task force elected to perform a ScopRev to assess the extent and type of available studies. Although briefing and debriefing in resuscitation has been previously reviewed by the NLS Task Force[12–14] and the Education, Implementation, and Teams Task Force,[19,20] clinical outcomes specific to neonates or neonatal resuscitation were not included in those recommendations.

The evidence identified in this ScopRev is primarily from quality-improvement studies with preintervention and postintervention comparisons. There were no RCTs comparing briefing or debriefing with no briefing or no debriefing. In addition, many investigators studied briefing or debriefing in the context of bundles of interventions; these studies were not included in this evidence review because it was not possible to isolate the effects of briefing or debriefing alone on outcomes.

A small number of studies were identified that included adjuncts to briefing and debriefing (eg, the review of video recordings to assist debriefing, the use of checklists); these studies compared the use of adjuncts with no briefing or no debriefing. There is limited evidence that use of video-assisted debriefing may improve the process of care and adherence to resuscitation guidelines, but none of the included studies evaluated the effect on clinical outcomes. The use of checklists during briefings and debriefings may help improve team communication and process, but the evidence did not report changes in clinical outcomes, and the reported effects on the delivery of care were inconsistent.

We identified limited evidence that rapid-cycle deliberate practice may improve short term performance in a resuscitation simulation but not provider confidence in or retention of skills. These findings were similar to a recent SysRev completed by the ILCOR Education, Implementation, and Teams Task Force (see "Education, Implementation, and Teams: Spaced Versus Massed Learning," in this supplement [EIT 601: SysRev]), which included neonatal studies and also identified limited evidence that rapid-cycle deliberate practice may improve short-term performance in a resuscitation simulation but not provider confidence in or retention of skills.

We conclude that briefing or debriefing may improve short-term clinical and performance outcomes for infants and staff. The effects of briefing or debriefing on long-term clinical and performance outcomes are uncertain.

This scoping review did not identify sufficient evidence to prompt a SysRev.

Treatment Recommendation

There was no previous treatment recommendation on the topic.

INITIAL ASSESSMENT AND INTERVENTION

Warming Adjuncts (NLS 599: EvUp)

Maintenance of normal temperature is a key initial step in stabilization of the newborn at birth. There are multiple strategies to prevent hypothermia of the

newborn. The NLS Task Force published the most recent CoSTR summarizing the evidence supporting warming adjuncts in 2015.[1,9,10] In 2020, the NLS Task Force undertook an EvUp to identify any additional studies that would warrant consideration of a new SysRev.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Preterm neonates less than 32 weeks' gestational age who are under radiant warmers in the hospital delivery room
- Intervention: Increased room temperature, thermal mattress, or another warming adjunct
- Comparator: Compared with plastic wraps alone
- Outcome[21]:
  - Primary: Hypothermia (less than 36.0°C) on admission to neonatal intensive care unit (NICU)
  - Secondary:
    - Survival (critical)
    - Morbidities associated with hypothermia (important)
    - Hyperthermia and associated morbidities (important)

The EvUp (see Supplement Appendix C-2) identified 13 studies (5 SysRevs and 8 RCTs) supporting the 2015 CoSTR.[1,9,10] Although the 2015 treatment recommendations were limited to very preterm babies born at less than 33 weeks' gestational age, the recommendations remain relevant. The task force agreed to suggest the need for a SysRev on the topic of warming adjuncts in the near future. The task force also suggests division of the target populations to separately analyze effects and pertinent outcomes for term versus preterm infants.

Treatment Recommendation

These treatment recommendations (below) are unchanged from 2015.[1,9,10]

Among newborn preterm infants of less than 32 weeks' gestation under radiant warmers in the hospital delivery room, we suggest using a combination of interventions that may include environmental temperature 23°C to 25°C, warm blankets, plastic wrapping without drying, cap, and thermal mattress to reduce hypothermia (temperature less than 36.0°C) on admission to NICU (weak recommendation, very low-certainty evidence).

We suggest that hyperthermia (greater than 38.0°C) be avoided because it introduces potential associated risks (weak recommendation, very low-certainty evidence).

Suctioning of Clear Fluid (NLS 596: ScopRev)

Rationale for Review

Transition from an intrauterine (fetal) to an extrauterine (newborn) physiology involves the replacement of lung liquid in the airways with air. To support liquid clearance, oropharyngeal/nasopharyngeal suctioning at birth was traditionally used to remove oral and nasal secretions in vigorous infants at birth. The 2010 CoSTR for NLS suggested against this routine practice for the first time.[12–14] Similarly, the *2015 American Heart Association Guidelines Update for CPR and ECC* for neonatal resuscitation emphasized that "suctioning immediately after birth, whether with a bulb syringe or suction catheter, may be considered only if the airway appears obstructed or if PPV is required."[22] The balance of risks and benefits associated with routine suctioning remain controversial. Because this literature has not been systematically reviewed in over a decade, the task force agreed that a ScopRev would determine if there is sufficient evidence published after 2010 to warrant a new SysRev in the near future.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborns delivered through clear amniotic fluid
- Intervention: Immediate routine suctioning (oropharyngeal or nasopharyngeal)
- Comparator: No suctioning or wiping
- Outcome[21]:
  - Survival (critical)
  - Need for delivery room resuscitation and stabilization interventions (important)
  - Oxygen supplementation, use of PPV, intubation, CPR/medications, Apgar scores, time to reach heart rate greater than 100/min (important)
  - Complications following procedure (desaturation, delay in initiation of PPV, tissue injury, infection)
  - Respiratory complications (respiratory distress, tachypnea) (important)
  - Other inpatient morbidities (important)
- Study design: RCTs and nonrandomized studies (non-RCTs, interrupted times series, controlled before-and-after studies, cohort studies) were eligible for inclusion
- Time frame: All years and languages were included if there was an English abstract; unpublished studies (eg, conference abstracts, trial protocols) were excluded. Literature search was updated to November 30, 2019.

Summary of Evidence

Evidence supporting potential benefits of oropharyngeal/nasopharyngeal suctioning is limited and the practice remains controversial. Oropharyngeal suctioning does not impact liquid removal from the lung. The procedure can have serious side effects.

- It is possible that nasopharyngeal suctioning may result in vagal-induced bradycardia as well as increased risk of infection.[23]
- The procedure may take significant time to complete.[24]

- Suctioning may delay initiation of ventilation in nonbreathing infants.[3]
- Newborns who received suctioning compared with a control group had significantly lower oxygen saturation through the first 6 minutes of life and took longer to reach a normal saturation range.[24,25]
- There is a concern that suctioning may have serious additional consequences, such as irritation to mucous membranes and increased risk of iatrogenic infection,[26,27] bradycardia,[26,28] apnea,[28] hypoxemia and arterial oxygen desaturation,[25,27,29] hypercapnia,[30] impaired cerebral blood flow regulation,[31,32] increased intracranial pressure,[33] and development of subsequent neonatal brain injury.[34]

The entire ScopRev can be found in Supplement Appendix B-2.

Task Force Insights

The NLS Task Force noted several strengths and limitations of the evidence identified by the ScopRev:

- The identified studies were from diverse geographical areas, but the results were similar.
- The literature identified by this ScopRev allowed comparisons in 2 types of subgroups (vaginal versus cesarean delivery and preterm versus term infants).
- Most new studies appear to be consistent with the current recommendation of "no routine suctioning" of the newborns in the delivery room.
- Because of the large number of patients (greater than 1500) reported in studies published since 2015, a new SysRev including these patients is likely to increase the certainty of the evidence through GRADE evaluation.

The NLS Task Force suggests consideration of an updated SysRev for this PICO question: "Among vigorous infants delivered through clear amniotic fluid (P), does immediate routine suctioning (oropharyngeal or nasopharyngeal) (I) compared with no suctioning or wiping C) change outcome (O)?" Until such a SysRev is completed and analyzed, the current 2010 treatment recommendation remains.[12–14]

Treatment Recommendation

This treatment recommendation (below) is unchanged from 2010.[12–14]

Routine intrapartum oropharyngeal and nasopharyngeal suctioning for newborn infants with clear or meconium-stained amniotic fluid is no longer recommended.

Tracheal Intubation and Suction of Nonvigorous Meconium-Stained Newborns (NLS 865: SysRev)

Meconium-stained amniotic fluid is present in 5% to 15% of all deliveries and is more common in neonates who are nonvigorous at birth.[35,36] Approximately 3% to 5% of neonates born through meconium-stained amniotic fluid develop meconium aspiration syndrome (MAS), which remains a significant cause of neonatal morbidity and mortality, particularly in developing countries.[37] Optimal management of neonates born through meconium-stained amniotic fluid remains a topic of debate. For decades, routine intubation and endotracheal suctioning for nonvigorous, meconium-exposed neonates was suggested on the basis of extremely low-certainty evidence. In 2015, after publication and analysis of new (although limited) randomized trial data, the NLS Task Force changed the treatment recommendation to eliminate routine tracheal intubation and suctioning for nonvigorous meconium-stained infants.[1,9,10]

Additional studies have been published since 2015, prompting the NLS Task Force to complete a new SysRev with meta-analysis.[37]

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Nonvigorous infants born at 34 weeks' or greater gestation delivered through meconium-stained amniotic fluid (of any consistency) at the start of resuscitation (nonvigorous defined as heart rate less than 100/min, decreased muscle tone, and/or depressed breathing at delivery)
- Intervention: Immediate laryngoscopy with or without intubation and suctioning
- Comparator: Immediate resuscitation without direct laryngoscopy at the start of resuscitation
- Outcome[21]:
  - Primary
    - Survival to hospital discharge (critical)
  - Secondary
    - Neurodevelopmental impairment (critical)
    - MAS (critical)
    - Other respiratory outcomes (continuous positive airway pressure or mechanical ventilation, treatment of pulmonary hypertension with inhaled nitric oxide, oral medications or extracorporeal membrane oxygenation) (important)
    - Delivery room interventions (CPR/medications, intubation for PPV) (important)
    - Length of hospitalization (important)
- Study design: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, and cohort studies) were included in the review.
- Time frame: All years and languages were included if there was an English abstract; unpublished studies (eg, conference abstracts, trial protocols) and animal studies were excluded. The literature search was updated to May 2019.

A Priori Subgroups to Be Examined

Consistency of meconium (thin versus thick), gestational age categories (late preterm [34 weeks to 36 weeks and 6 days], term [37 weeks to 41 weeks and 6 days], postterm [42 weeks or greater]), presence or absence

of fetal bradycardia, route of delivery (spontaneous vaginal, instrumented vaginal, cesarean delivery), direct laryngoscopy with versus without suctioning.

International Prospective Register of Systematic Reviews (PROSPERO) Registration: CRD42019122778

Consensus on Science

The SysRev identified 4 eligible studies that included 680 newborn infants.[37] Data from 3 RCTs involving 449 newborns[38–40] and 1 observational study involving 231 newborn infants[41] were included.

A draft CoSTR document based on the SysRev was posted on the ilcor.org website for a 2-week public commenting period. During this period, the draft CoSTR was viewed over 5600 times and 65 comments were provided; most comments were very positive. However, there were concerns about clarity, which the task force subsequently addressed. Suggestions made were used to modify the wording of the treatment recommendations, justification and evidence-to-decision framework highlights, and the knowledge gaps to improve clarity. Although these treatment recommendations do not preclude the use of carefully considered clinical judgment for individual cases, the NLS Task Force cannot use unpublished, personal observations to inform an international consensus on science or to guide treatment recommendations.

For the critical primary outcome of survival to discharge, we identified low-certainty evidence (downgraded for inconsistency and imprecision) from 3 RCTs[38–40] involving 449 nonvigorous newborns delivered through meconium-stained amniotic fluid which showed no benefit from the use of immediate laryngoscopy with or without tracheal suctioning when compared with immediate resuscitation without laryngoscopy (relative risk [RR], 0.99; 95% CI, 0.93–1.06; *P*=0.87); absolute risk reduction, –0.9%; (95% CI, –6.4% to 5.5%), or 9 fewer patients/1000 survived to discharge with the intervention (95% CI, 64 fewer to 55 more patients per 1000 survived to discharge with the intervention). For complete data, see Table 1.

For the remainder of the outcomes of interest (eg, neurodevelopmental impairment (NDI), hypoxic-ischemic encephalopathy (HIE), MAS, use of mechanical ventilation, use of respiratory support excluding mechanical ventilation, endotracheal intubation for PPV in the delivery room, chest compressions in the delivery room, use of epinephrine in the delivery room, treatment of pulmonary hypertension, and length of hospitalization), evidence of very low certainty (downgraded for risk of bias, indirectness, and imprecision) showed no benefit from the use of immediate laryngoscopy with or without tracheal suctioning compared with immediate resuscitation without laryngoscopy for nonvigorous newborns delivered through meconium-stained amniotic fluid (Table 1). The neurodevelopmental assessment from the single study that reported this outcome was performed at an early and nonstandard time, hence the results are poorly predictive of longer-term outcomes. Therefore, the task force concluded that the effect on NDI of immediate laryngoscopy with or without suctioning remains uncertain.

In 2015, the treatment recommendation indicated that there was insufficient human evidence to continue to suggest routine suctioning of meconium in nonvigorous babies born through meconium-stained amniotic fluid.[1,9,10] This new 2020 recommendation is more direct in its suggestion against this practice.

Treatment Recommendations

For nonvigorous newborn infants delivered through meconium-stained amniotic fluid, we suggest against routine immediate direct laryngoscopy with or without tracheal suctioning compared with immediate resuscitation without direct laryngoscopy (weak recommendation, low-certainty evidence).

Meconium-stained amniotic fluid remains a significant risk factor for receiving advanced resuscitation in the delivery room. Rarely, an infant may require intubation and tracheal suctioning to relieve airway obstruction.

Justification and Evidence-to-Decision Framework Highlights

The task force recognizes that, although the direction of the treatment recommendation has not changed, several studies published after 2015 provide additional evidence to support the recommendation. These studies contributed new evidence, but the certainty of the findings remains low or very low because it is difficult to perform unbiased studies of this clinical question. Finally, even combining the data from all studies does not provide sufficient power for certainty as the optimal information size is still not achieved.

The NLS Task Force considered that the procedure of laryngoscopy and suctioning with or without tracheal intubation is invasive and has potential to harm, particularly if initiation of ventilation is delayed. This, together with the evidence of no benefit of routine tracheal suctioning, led the task force to suggest against routine practice of these interventions. It is possible that the infant born through meconium-stained fluid will require intubation for resuscitation. Therefore, trained personnel and equipment for intubation should be readily available for births where meconium-stained amniotic fluid is present. If meconium is obstructing the trachea, suctioning by using an endotracheal tube with a meconium aspirator may be effective in relieving the obstruction.[42,43]

See Supplement Appendix A-1 for the evidence-to-decision table for this SysRev.

Table 1. Meta-analysis of RCTs of Immediate Laryngoscopy With or Without Tracheal Suctioning Versus Immediate Resuscitation Without Laryngoscopy for Nonvigorous Infants Born at 34 Weeks' or Greater Gestation and Delivered Through Meconium-Stained Amniotic Fluid

Outcome	Article With Outcome of Interest	Total, n	Certainty of Evidence	RR (95% CI); I^2	Absolute Difference (95% CI)
Survival at discharge	Chettri, 2015[38]; Nangia, 2016[39]; Singh, 2018[40]	449	Low	0.99 (0.93–1.06); 29%	9/1000 fewer survived to discharge when laryngoscopy ± suction was used (64 fewer to 55 more per 1000)
Cognitive NDI	Chettri, 2015[38]	86	Very low	0.75 (0.37–1.50); NA	80/1000 fewer with cognitive NDI when laryngoscopy ± suction was used (200 fewer to 159 more per 1000)
Motor NDI	Chettri, 2015[38]	86	Very low	0.91 (0.49–1.67); NA	31/1000 fewer with motor NDI when laryngoscopy ± suction was used (174 fewer to 228 more per 1000)
HIE	Nangia, 2016[39]; Singh, 2018[40]	327	Very low	0.85 (0.56–1.30); 0%	52/1000 fewer with HIE when laryngoscopy ± suction was used (152 fewer to 104 more per 1000)
MAS	Chettri, 2015[38]; Nangia, 2016[39]; Singh, 2018[40]	449	Very low	0.94 (0.67–1.33); 49%	23/1000 fewer with MAS when laryngoscopy ± suction was used (126 fewer to 126 more per 1000)
Use of mechanical ventilation	Chettri, 2015[38]; Nangia, 2016[39]; Singh, 2018[40]	449	Very low	1.00 (0.66–1.53); 0%	0/1000 fewer were mechanically ventilated when laryngoscopy ± suction was used (54 fewer to 84 more per 1000)
Use of respiratory support excluding mechanical ventilation	Nangia 2016[39]; Singh 2018[40]	327	Very low	0.99 (0.81–1.20); 0%	4/1000 fewer received respiratory support excluding mechanical ventilation when laryngoscopy ± suction was used (73 fewer to 76 more per 1000)
Endotracheal intubation for PPV in the DR	Chettri, 2015[38]; Nangia, 2016[39]	297	Very low	1.15 (0.83–1.59); 0%	41/1000 more were intubated for PPV in the DR when laryngoscopy ± suction was used (47 fewer to 162 more per 1000)
Chest compressions in the DR	Chettri, 2015[38]; Nangia, 2016[39]; Singh, 2018[40]	449	Very low	1.13 (0.40–3.20); 0%	4/1000 more received chest compressions in the DR when laryngoscopy ± suction was used (19 fewer to 68 more per 1000)
Epinephrine in the DR	Chettri, 2015[38]; Nangia, 2016[39]; Singh, 2018[40]	449	Very low	1.62 (0.37–7.05); 0%	8/1000 more received epinephrine in the DR when laryngoscopy ± suction was used (from 8 fewer to 80 more per 1000)
Treatment of pulmonary hypertension (iNO, medications, ECMO)	Chiruvolu, 2018[41]	231	Very low	0.52 (0.15–1.79); NA	29/1000 fewer received treatment of pulmonary hypertension when laryngoscopy ± suction was used (50 fewer to 47 more per 1000)
Length of hospitalization, days	Nangia, 2016[39]; Singh, 2018[40]	327	Very low	–0.5 days (–1.76 to 0.75); 80%	

DR indicates delivery room; ECMO, extracorporeal membrane oxygenation; HIE, hypoxic-ischemic encephalopathy; iNO, inhaled nitric oxide; MAS, meconium aspiration syndrome; NA, not applicable; NDI, neurodevelopmental impairment; PPV, positive-pressure ventilation; RCT, randomized controlled trial; and RR, relative risk.

Knowledge Gaps

Priorities for research include the following:

- Additional RCTs are needed that focus on nonvigorous infants in a variety of populations, such as where the incidence of MAS is low, and in settings with various levels of healthcare resources.
- Do risks or benefits of intubation with tracheal suctioning vary with any subgroup (gestational age, thickness of meconium, operator experience)?
- Long-term outcomes are needed in future studies. These include neurodevelopmental, behavioral, or educational assessment, which for future studies should be at or beyond 18 months of age and completed with a validated tool.

PHYSIOLOGICAL MONITORING AND FEEDBACK DEVICES

Heart Rate Monitoring During Neonatal Resuscitation (NLS 898: EvUp)

After birth, the newborn's heart rate is used to assess the effectiveness of spontaneous breathing and the need for interventions such as PPV, and it's used as the marker

of response to resuscitation interventions. Therefore, a rapid and reliable method of measuring the newborn's heart rate is a critical adjunct for neonatal resuscitation. The most recent review of this topic was included in the 2015 CoSTR for NLS.[1,9,10] The NLS Task Force undertook an EvUp to identify additional evidence published after 2015 that would warrant consideration of a new SysRev.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborns requiring resuscitation
- Intervention: ECG monitoring
- Comparator: Oximetry or auscultation
- Outcome: Measurement of heart rate (speed and reliability) (important)[21]

The EvUp (Supplement Appendix C-3) identified 7 additional studies published after the 2015 CoSTR SysRev,[1,9,10] including 2 SysRevs,[44,45]2 RCTs,[46,47] and 3 observational studies.[48–50] All 7 studies supported the 2015 treatment recommendation.[1,9,10] Thus, the NLS Task Force agreed that no new ILCOR SysRev is warranted at this time, and the current recommendation continues.

Of note, there is a need to develop an additional interventional PICOST to determine if routine use of ECG monitoring during neonatal resuscitation improves clinical outcomes. Also, improved tools and methods to enable detection and measurement of heart rate have been reported in the literature or are under development; as a result, the current PICOST question may be too limited in scope. Such methods include new heart rate monitors, digital stethoscopes, photoplethysmography methods in addition to pulse oximetry, and Doppler ultrasonography methods with auditory or visual displays. New interfaces for ECG monitoring include dry electrode technology. Future SysRevs will need to compare these technologies to the current "gold standard" of ECG monitoring with gel electrodes. Until such evidence is available, the NLS Task Force agreed that there is no justification to seek a new SysRev or alter the current (2015) treatment recommendations.

Treatment Recommendation

This recommendation (below) has not changed from 2015.[1,9,10]

In babies requiring resuscitation, we suggest the ECG can be used to provide a rapid and accurate estimation of heart rate (weak recommendation, very low-certainty evidence).

VENTILATION AND OXYGENATION

Sustained Inflation (NRP 809: SysRev)

When a newborn does not breathe spontaneously, establishing functional residual capacity requires clearing the lung fluid and replacing it with air. Debate continues about the most effective method to achieve this. Animal studies suggest that a longer sustained inflation may be beneficial for short term respiratory outcomes, but most such studies were performed in intubated animal models.[51] It is unknown whether the same is true in newborn infants.[52,53] In 2015, the NLS Task Force evaluated the evidence supporting use of sustained inflation for initiation of PPV in the delivery room and suggested against its routine use.[1,9,10] Multiple clinical trials of sustained inflation have been published after that 2015 recommendation, prompting the NLS Task Force to request a 2020 SysRev.[53a]

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants who receive PPV due to bradycardia or ineffective respirations at birth
- Intervention: Initiation of PPV with sustained inflation(s) more than 1 second
- Comparator: Initiation of PPV with intermittent inflations, lasting 1 second or less per breath
- Outcome[21]:
  - Primary: Death before discharge (critical)
  - Secondary:
    - Death in the delivery room (critical)
    - Death within first 48 hours (critical)
    - Need for mechanical ventilation during hospitalization (critical)
    - Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema) reported individually or as a composite outcome at any time during initial hospitalization and also within first 48 hours (critical)
    - Bronchopulmonary dysplasia, any grade,[54] defined as need for supplemental oxygen at 28 days of life; need for supplemental oxygen at 36 weeks' gestational age for infants born at or before 32 weeks of gestation (critical)
    - Intraventricular hemorrhage: Of any grade[55] and Grade 3 or above (critical)
    - Retinopathy of prematurity: Of any stage[56] and Stage 3 or above (critical)
    - Death by time of latest follow-up (critical)
    - Long-term neurodevelopmental or behavioral or education outcomes (greater than18 months of corrected age; test used to assess neurodevelopmental outcome should be of adequate quality and validated) (critical)
- Study design: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion.
- Time frame: All years and languages were included if there was an English abstract; unpublished studies (eg, conference abstracts, trial protocols) were excluded. Literature search was updated to October 25, 2019.

PROSPERO Registration: CRD 42020155639

A Priori Subgroup Analyses

Preterm infants at 28+0 weeks or less, 28 weeks and 1 day to 31 weeks and 6 days, 32 weeks to 36 weeks and 6 days, 37 weeks or more (term)

Duration of first sustained inflation: 1 to 5 seconds, 6 to 15 seconds, greater than 15 seconds

Inflation pressure used during first sustained inflation: 20 cm H_2O or less, greater than 20 cm H_2O

Interface or device used to generate sustained inflation: Nasopharyngeal tube, endotracheal tube, face mask, or T-piece device versus other device

A Priori Sensitivity Analyses

Effects of whether or not studies allowed multiple sustained inflations

Effects of the methodological quality of trials (to ascertain whether studies with high risk of bias overestimated treatment effects)

Consensus on Science

The SysRev identified 10 eligible RCTs including 1502 newborn infants. From analysis of this evidence, the NLS Task Force developed a draft CoSTR that was posted on the ILCOR website for a 2-week public commenting period beginning February 17, 2020. The Justification section was revised to address the public comments.

For the primary outcome of death before discharge, evidence of low certainty (downgraded for risk of bias and inconsistency) from 10 RCTs[57–66] enrolling 1502 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with sustained inflation greater than 1 second compared with initiating PPV with intermittent inflations lasting 1 second or less. See Table 2.

For the secondary critical long-term neurodevelopmental outcomes and death at latest follow-up, no studies were identified. The remainder of the secondary outcomes are reported in Table 2.

Subgroup Analysis for Primary Outcome

Subgroup Newborns Less Than 28+0 Weeks. For the critical outcome of death before discharge, low-certainty evidence (downgraded for risk of bias and imprecision) from 5 RCTs[57,58,61,62,65] enrolling 862 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed evidence of potential harm from initiating PPV with sustained inflation(s) greater than 1 second compared with initiating PPV with intermittent inflations lasting 1 second or less per breath (RR, 1.38; 95% CI, 1.00–1.91; I^2, 0%; 46 more patients/1000 died before hospital discharge with sustained inflation(s) [0 fewer to 110 more per 1000]). The number needed to harm is 22 (95% CI, 9–1000 or greater).

Subgroup Newborns 28+1 Weeks to 31+6 Weeks of Age. For the critical outcome of death before discharge, very low-certainty evidence (downgraded for risk of bias and very serious imprecision) from 4 RCTs[57,61,62,66] enrolling 175 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with sustained inflation(s) greater than 1 second when compared with initiating PPV with intermittent inflations lasting 1 second or less per breath (RR, 1.33; 95% CI, 0.22–8.20; I^2, 5%; 4 more patients/1000 died before hospital discharge with sustained inflation(s) [9 fewer to 86 more per 1000]).

Subgroup Newborns 32+0 to 36+6 Weeks. No published data for this gestational age group were available.

Subgroup Newborns 37+0 Weeks or More (Term). No published data for this gestational age group were available.

Subgroup Analyses: by Duration of First Sustained Inflation or Inflation Pressure of the Sustained Inflation. For the critical outcome of death before discharge, subgroup analyses were conducted for the duration of the first sustained inflation (6–15 seconds versus greater than 15 seconds) and for the inspiratory pressure of the first sustained inflation with inspiratory pressure greater than 20 mm Hg versus 20 mm Hg or less). For each of these subgroup analyses, the evidence was of very low certainty (downgraded for risk of bias in all cases and variously for imprecision, very serious imprecision, and inconsistency). None of the subgroup analyses showed any significant benefit or harm of sustained inflation when compared with initiating PPV with intermittent inflations lasting 1 second or less per breath.

These conclusions were based on 9 RCTs[57–61,63–66] enrolling 1300 preterm newborns (sustained inflation 6–15 seconds), 2 RCTs[62,64] enrolling 222 preterm newborns (sustained inflation of greater than 15 seconds), 6 RCTs[58–62,66] enrolling 803 preterm newborns (inspiratory pressure greater than 20 mm Hg), and 4 RCTs[57,63–65] enrolling 699 preterm newborns (inspiratory pressure 20 mm Hg or less).

Sensitivity Analysis for Primary Outcome

Excluding Studies With High Risk of Bias. For the critical outcome of death before discharge, low-certainty evidence (downgraded for risk of bias and imprecision) from 9 RCTs[57–62,64–66] enrolling 1390 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with sustained inflation(s) greater than 1 second compared with initiating PPV with intermittent inflations lasting 1 second or less per breath. (RR, 1.24; 95% CI, 0.92–1.68; I^2, 24%; 21 more patients/1000 died before hospital discharge with sustained inflation(s) [95% CI, 7 fewer to 61 more per 1000]).

Table 2. Meta-analysis of RCTs Comparing Initiation of PPV With Sustained Inflation(s) Greater Than 1 Second Versus Initiation of PPV With Intermittent Inflations, Last 1 Second or Less per Breath

Outcome	Article With Outcome of Interest	Total, n	Certainty of Evidence	RR (95% CI); I^2	Absolute Difference (95% CI)
Death before discharge	Lindner, 2005[57]; Lista, 2015[58]; Schwaberger, 2015[59]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; Ngan, 2017[62]; El-Chimi, 2017[63]; El-Fattah, 2017[64]; Kirpalani, 2019[65]; La Verde, 2019[66]	1502	Low	1.09 (0.83–1.43); 42%	10/1000 more patients died before discharge when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (18 fewer to 47 more per 1000)
Death in the DR	Linder, 2005[57]; Lista, 2015[58]; Schwaberger, 2015[59]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; Ngan, 2017[62]; El-Chimi, 2017[63]; El-Fattah, 2017[64]; LaVerde, 2019[66]	1076	Very low	2.82 (0.45–17.66); 0%	4/1000 more patients died in the DR when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (1 fewer to 33 more per 1000)
Death within 48 h	Linder, 2005[57]; Lista, 2015[58]; Schwaberger, 2015[59]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; Ngan, 2017[62]; El-Chimi, 2017[63]; El-Fattah, 2017[64]; Kirpalani, 2019[65]; La Verde, 2019[66]	1502	Low	2.42 (1.15–5.09); 8%	18/1000 more patients died within 48 h after birth when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (2 more to 51 more per 1000). The number needed to harm is 55 (95% CI, 20–500).
Bronchopulmonary dysplasia	Linder, 2005[57]; Lista, 2015[58]; Schwaberger, 2015[59]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; Ngan, 2017[62]; El-Chimi, 2017[63]; El-Fattah, 2017[64]; Kirpalani, 2019[65]; La Verde, 2019[66]	1502	Low	0.93 (0.79–1.10); 8%	19/1000 fewer patients developed bronchopulmonary dysplasia when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (58 fewer to 27 more per 1000)
Intraventricular hemorrhage Grade 3 or 4	Linder, 2005[57]; Lista, 2015[58]; Schwaberger, 2015[59]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; Ngan, 2017[62]; El-Fattah, 2017[64]; Kirpalani, 2019[65]; La Verde, 2019[66]	1390	Low	0.88 (0.63–1.23); 0%	11/1000 fewer developed intraventricular hemorrhage Grade 3 or 4 when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (35 fewer to 22 more per 1000)
Retinopathy of prematurity Stage 3 or higher	Linder, 2005[57]; Lista, 2015[58]; Schwaberger, 2015[59]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; Ngan, 2017[62]; El-Fattah, 2017[64]; Kirpalani, 2019[65]; La Verde, 2019[66]	1342	Low	0.83 (0.62–1.11); 19%	22/1000 fewer patients developed retinopathy of prematurity Stage 3 or higher when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (49 fewer to 14 more per 1000)
Use of mechanical ventilation during hospitalization	Lista, 2015[58]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; El-Chimi, 2017[63]; El-Fattah, 2017[64]; La Verde, 2019[66]	813	Low	0.87 (0.74–1.02); 0%	51/1000 fewer patients received mechanical ventilation during their hospitalization when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (103 fewer to 8 more per 1000)

(*Continued*)

Table 2. Continued

Outcome	Article With Outcome of Interest	Total, n	Certainty of Evidence	RR (95% CI); I^2	Absolute Difference (95% CI)
Airleak during hospitalization	Linder, 2005[57]; Lista, 2015[58]; Schwaberger, 2015[59]; Mercadante, 2016[60]; Jiravisitkul, 2017[61]; Ngan, 2017[62]; El-Chimni, 2017[63]; El-Fattah, 2017[64]; La Verde, 2019[66]	1076	Low	1.26 (0.72–2.21); 17%	9/1000 more patients developed airleak during their hospitalization when PPV was initiated with sustained inflation(s) >1 s compared with initiating PPV with intermittent inflations lasting ≤1 s per breath (9 fewer to 41 more per 1000)

DR indicates delivery room; PPV, positive-pressure ventilation; RCT, randomized controlled trial; and RR, relative risk.

Excluding Studies That Allowed Only a Single Sustained Inflation During Resuscitation. For the critical outcome of death before discharge, low-certainty evidence (downgraded for risk of bias and imprecision) from 9 RCTs[57–63,65,66] enrolling 1402 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with sustained inflation greater than 1 second compared with initiating PPV with intermittent inflations lasting 1 second or less per breath (RR, 1.17; 95% CI, 0.88–1.55; I^2, 22%; 18 more patients/1000 died before hospital discharge with sustained inflation(s) [95% CI, 13 fewer to 58 more per 1000]).

Sustained Inflation With Mask Only. When considering only studies where a face mask was used to deliver initial sustained inflation, for the critical outcome of death before discharge, low-certainty evidence (downgraded for risk of bias and imprecision from 9 RCTs[58–66] enrolling 1441 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with sustained inflation(s) greater than 1 second compared with initiating PPV with intermittent inflations lasting 1 second or less per breath (RR, 1.06; 95% CI, 0.61–1.39; I^2, 42%; 7 more patients/1000 died before hospital discharge with sustained inflations [95% CI, 44 fewer to 44 more per 1000]).

Treatment Recommendations

For preterm newborn infants who receive PPV for bradycardia or ineffective respirations at birth, we suggest against the routine use of initial sustained inflation(s) greater than 5 seconds (weak recommendation, low-certainty evidence). A sustained inflation may be considered in research settings.

For term or late preterm infants who receive PPV for bradycardia or ineffective respirations at birth, it is not possible to recommend any specific duration for initial inflations due to the very low confidence in effect estimates.

Justification and Evidence-to-Decision Framework Highlights

This topic was prioritized by the NLS Task Force after completion of a large RCT[65] published after the 2015 CoSTR.[1,9,10] In making these recommendations, the NLS Task Force considered the potential for increased death within 48 hours in preterm infants and increased death before discharge in preterm infants less than 28+0 weeks, a predefined subgroup of the systematic review.[53a] The task force recognizes that the outcome of death within 48 hours was influenced primarily by 1 study for which death within 48 hours was one of multiple secondary outcomes.[65] The NLS Task Force also considered the absence of evidence for either benefit or harm after sustained inflation at birth for all other critical and important outcomes.

The study comparisons were compromised by methodological heterogeneity across studies, including indication, duration, the use of different inspiratory pressures during sustained inflation and different inflation durations. No study was identified comparing short duration sustained inflation (less than 5 seconds) with intermittent inflations by using inspiratory time of 1 second or less. There is no new evidence to support or refute the practice of inflations less than 5 seconds immediately after birth. Hunt et al[67] was excluded from this systematic review because the control group received short duration sustained inflations (5 inflations of 2–3 seconds each) and the intervention group received sustained inflations of 15 seconds duration (and thus did not meet predefined inflation duration criteria for the comparator group).

A patent airway is necessary for effective lung inflation or ventilation. A recent study demonstrated that preterm rabbit pups are prone to closure of the larynx (ie, it opens only briefly during a spontaneous breath); this impedes noninvasive PPV after birth.[53] Studies in preterm infants have shown that very little gas enters the lungs in the absence of spontaneous breathing, suggesting that the same phenomenon occurs in preterm infants.[68,69] This SysRev[53a] (and most studies it identified) focused on use of sustained inflation in newborns who are not breathing effectively, so inadequate

laryngeal patency could explain the absence of benefit from sustained inflation immediately after birth in preterm infants. In addition, the NLS Task Force noted that the trials included in the systematic review were pragmatic in design and did not include respiratory function monitors to assess actual pressure and volume delivered or the actual duration of the sustained inflation. It remains unknown if mask leak or airway obstruction influenced the effectiveness of the sustained inflations. This further decreases the confidence in the effect estimates, especially for the subgroup analyses.

See Supplement Appendix A-2 for the evidence-to-decision table for this SysRev.

Knowledge Gaps

- How much of a role does glottis closure play in determining the effectiveness of sustained inflation in newborn infants of different gestational ages?
- What is the optimal duration, optimal inspiratory pressure, and number of sustained inflation maneuvers that allow establishment of functional residual capacity without barotrauma?
- The NLS Task Force recognizes that the total number of infants studied thus far is insufficient to have confidence in the estimate of effect. Larger multicenter trials are needed in both term and preterm newborns to determine whether there are benefits or harms from sustained inflations.
- Studies comparing short duration sustained inflation (less than 5 seconds) with intermittent inflations (inspiratory time 1 second or less) are needed. This is an important knowledge gap as the European Resuscitation Council currently recommends using inflations of a 2- to 3-second duration for the first 5 breaths in infants who are gasping or not breathing.
- Is there a role for sustained inflation for other situations in resuscitation, such as during cardiac compressions? (For more detail, see EvUp for NLS 895 CPR Ratios)

PEEP Versus No PEEP (NLS 897: EvUp)

During resuscitation after birth, PPV is provided to inflate and ventilate the lungs. The lungs of sick or preterm newborns tend to collapse as they are not supported by a stiff chest wall and the infant's breathing efforts may be weak; the lungs may also be immature and surfactant-deficient.[70] PEEP provides low positive pressure to the airway, which helps prevent lung collapse at the end of expiration. PEEP maintains lung volume during PPV in animal studies and improves lung function and oxygenation.[71,72] PEEP may be beneficial during neonatal resuscitation, but the evidence from human studies is limited. The previously reported evidence for use of PEEP was evaluated as part of the 2015 CoSTR for NLS.[1,9,10] In 2020, The NLS Task Force undertook an EvUp to determine whether additional evidence published after 2015 warranted consideration of a new SysRev.

The evidence update (see Supplement Appendix C-4) identified no evidence that would suggest the need for a new SysRev or a change in the 2015 treatment recommendation.[1,9,10] Most of the new studies identified confirm the 2015 recommendation for use of PEEP during PPV in the delivery room.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Preterm/term newborn infants who do not establish spontaneous respiration at birth
- Intervention: Use of PEEP as part of the initial ventilation strategy
- Comparator: No PEEP
- Outcome[21]:
  - Survival to discharge (critical)
  - 5-minute Apgar scores (important)
  - Time for heart rate to rise above 100/min (important)
  - Intubation rate in the delivery room (important)
  - Chest compressions in the delivery room (important)
  - Incidence of air leaks (important)
  - Oxygen saturation/oxygenation (important)
  - F_{IO_2} exposure in the delivery room (important)
  - Mechanical ventilation in the first 72 hours (important)
  - Bronchopulmonary dysplasia (any) (important)

Treatment Recommendation

This treatment recommendation has not changed from 2015.[1,9,10]

We suggest using PEEP for the initial ventilation of premature newborn infants during delivery room resuscitation (weak recommendation, low-quality evidence).

We cannot make any recommendation for term infants because of insufficient data.

CPAP Versus Intermittent Positive Pressure Ventilation (NLS 590: EvUp)

Newborn infants who breathe spontaneously need to establish a functional residual capacity after birth.[73] Some newborn infants experience respiratory distress, which manifests as labored breathing or persistent cyanosis. Continuous positive airway pressure (CPAP), a form of respiratory support, helps prevent atelectasis in newborns. CPAP is especially helpful for preterm newborn infants with breathing difficulty after birth or after resuscitation.[74] CPAP may also reduce the risk of death or bronchopulmonary dysplasia in very preterm infants when compared with endotracheal intubation and PPV.[75–79] For the newborn infant, CPAP is a less-invasive form of respiratory support than intubation and PPV.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Spontaneously breathing preterm newborn infants with respiratory distress requiring respiratory support in the delivery room
- Intervention: CPAP
- Comparator: Intubation and intermittent PPV
- Outcome[21]:
  - Death or bronchopulmonary dysplasia (critical)
  - Death (critical)
  - Bronchopulmonary dysplasia[54] (important)
  - Air leak (important)
  - Necrotizing enterocolitis (important)
  - Severe intraventricular hemorrhage[55] (critical)
  - Severe retinopathy of prematurity[56] (critical)

This topic was last reviewed in the 2015 CoSTR.[1,9,10] The NLS Task Force sought an EvUp to identify any studies published after the 2015 CoSTR. The EvUp did not identify any new studies that would potentially change the current recommendation. The 2015 CoSTR treatment recommendation remains in effect.[1,9,10]

The entire EvUp can be reviewed in Supplement Appendix C-5.

Treatment Recommendations

This treatment recommendation (below) is unchanged from 2010.[1,9,10]

For spontaneously breathing preterm newborn infants with respiratory distress requiring respiratory support in the delivery room, we suggest initial use of CPAP rather than intubation and intermittent PPV (weak recommendation, moderate certainly of evidence).

T-Piece Resuscitator Versus Self-Inflating Bag for Ventilation (NLS 870: ScopRev)

Rationale for Review

In 2015, the ILCOR Neonatal Task Force published a CoSTR summarizing the evidence comparing the use of a T-piece resuscitator with the use of a self-inflating bag for newborns receiving ventilation during resuscitation.[1,9,10] The studies reviewed for the 2015 CoSTR noted that the use of T-piece resuscitators demonstrated marginal but not statistically significant benefits for the clinical outcome of achieving spontaneous breathing.

The NLS Task Force decided to reevaluate this topic through a ScopRev[79a] to determine whether sufficient new evidence had been published after the 2015 CoSTR[1,9,10] to justify a new SysRev.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants receiving ventilation (PPV) during resuscitation
- Intervention: T-piece resuscitator
- Comparator: Self-inflating bag
- Outcome[21]:
  - Survival to hospital discharge (critical)
  - Air leak (important)
  - Development of stable spontaneous breathing (no need for intubation in delivery room) (important)
  - Bronchopulmonary dysplasia (any) (important)
- Study design: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion.
- Time frame: All years and languages were included if there was an English abstract; unpublished studies (eg, conference abstracts, trial protocols) were excluded. Literature search was updated to January 3, 2020.

Summary of Evidence

Using the 2015 search strategy, this ScopRev[79a] identified 2 additional studies: 1 RCT[80] and 1 observational study[81] published after the review for the 2015 CoSTR was completed. When these 2 studies were added to the 2 studies identified in the 2015 CoSTR for NLS,[1,9,10] a total of 4 clinical studies could be included in the data analysis, representing a total of 2889 newborns (927 in 3 RCTs and 1962 in 1 observational study).[80–83]

The 4 studies investigated different populations; 2 studies included term and preterm infants,[80,83] and 2 studies enrolled preterm infants only.[81,82] The studies also differed in reported outcomes and were from diverse geographical areas. The large observational study found that use of a T-piece resuscitator increased survival and decreased bronchopulmonary dysplasia and intubation in the delivery room.[81] The latest RCT also found decreased intubation in the delivery room when T-piece resuscitators were used.[80]

The ScopRev can be reviewed in its entirety in Supplement Appendix B-3.

Task Force Insights

Data from a substantial number of additional patients reported in 1 RCT and 1 large observational study suggest improved survival, less need for intubation, and a lower incidence of bronchopulmonary dysplasia when a T-piece resuscitator is used (compared with a self-inflating resuscitator bag) during PPV at birth, particularly in preterm infants. The NLS Task Force concludes that these findings justify a new SysRev of the use of a T-piece resuscitator versus self-inflating bag for administering PPV at birth. The task force anticipates that not only the strength, but the direction of evidence may be changing toward support for using T-piece devices. Until a new SysRev is completed and results are analyzed by the NLS Task Force, the 2015 treatment recommendation remains in effect.[1,9,10]

Treatment Recommendation

This treatment recommendation (below) is unchanged from 2010.[1,9,10]

There is insufficient evidence regarding the use of T-piece resuscitator or self-inflating bag for initial PPV at birth, so the recommendation of one device over another would be purely speculative because the confidence in effect estimates is so low.

Oxygen for Preterm Resuscitation (NLS 864: 2019 CoSTR)

Preterm newborn infants are vulnerable to oxidative stress as a result of reduced antioxidant defenses and frequent exposure to oxygen during stabilization in the delivery room.[84] Many common preterm morbidities, such as bronchopulmonary dysplasia, retinopathy of prematurity and intraventricular hemorrhage are directly associated with oxygen toxicity. In the delivery room, it is imperative that clinicians prevent hypoxia while limiting hyperoxia. In 2019, the NLS Task Force published a SysRev with meta-analysis of the relevant available evidence on this topic,[85] and published an ILCOR CoSTR statement.[86,87]

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Preterm newborn infants (less than 35 weeks' estimated gestational age) who receive respiratory support at birth
- Intervention: Lower initial oxygen concentration (50% or less O_2)
- Comparator: Higher initial oxygen concentration (more than 50% O_2)
- Outcome[21]:
  - Primary: All-cause short-term mortality (in hospital or 30 days) (critical)
  - Secondary:
    - All-cause long-term mortality (1–3 years) (critical)
    - Long-term NDI (1–3 years) (critical)
    - Retinopathy of prematurity (Stages III–V)[56] (critical)
    - Necrotizing enterocolitis Stage II (pneumatosis) or III (surgical)[88] (important)
    - Bronchopulmonary dysplasia (moderate to severe)[54] (critical)
    - Major intraventricular hemorrhage (Grade III–IV)[55] (critical)
    - Time to heart rate more than 100/min (important)
- Study design: RCTs, quasi-RCTs and nonrandomized studies included; animal studies, unpublished studies, and published abstracts (eg, conference abstracts) excluded
- Time frame: Literature search was from 1980 to August 10, 2018.
- PROSPERO Registration: CRD42018084902

Treatment Recommendations

This treatment recommendation (below) is unchanged from 2019.[86,87]

For preterm newborn infants (less than 35 weeks' gestation) who receive respiratory support at birth, we suggest starting with a lower oxygen concentration (21% to 30%) rather than higher initial oxygen concentration (60% to 100%) (weak recommendation, very low-certainty evidence).

We suggest the range of 21% to 30% oxygen because all trials used this for the low oxygen concentration group. Subsequent titration of oxygen concentration using pulse oximetry is advised (weak recommendation, very low-certainty evidence).

Oxygen for Term Resuscitation (NLS 1554: 2019 CoSTR)

Administration of high oxygen concentrations leads to free radical formation and may be toxic to many tissues and organs of the newborn. Questions persist about the risks of hypoxia versus risks of exposure to excess oxygen for late preterm and term newborn infants who receive respiratory support in the delivery room. In 2019, the NLS Task Force published a SysRev with meta-analysis of the relevant available evidence on this topic[89] and also published an NLS CoSTR.[86,87] For complete review of the consensus on science for the secondary outcomes and subgroup analyses, please see the NLS Task Force section of the recently published 2019 CoSTR summary.[86,87]

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants (35 weeks' or greater gestation) who receive respiratory support at birth
- Intervention: Lower initial oxygen concentration (50% O_2 or less)
- Comparator: Higher initial oxygen concentration (greater than 50% O_2)
- Outcome[21]:
  - Primary: All-cause short-term mortality (in hospital or 30 days) (critical)
  - Secondary: All-cause long-term mortality (1–3 years) (critical)
  - Long-term NDI (1–3 years) (critical)
  - HIE (Sarnat Stage 2–3)[90] (critical)
- Study design: RCTs, quasi-RCTs, and nonrandomized studies included; animal studies, unpublished studies, and published abstracts (eg, conference abstracts) excluded
- Time frame: Literature search was from 1980 to August 10, 2018.
- PROSPERO Registration: CRD42018084902

Treatment Recommendations

This treatment recommendation (below) is unchanged from 2019.[86,87]

For newborn infants at 35 weeks' or greater gestation receiving respiratory support at birth, we suggest starting with 21% oxygen (air) (weak recommendation, low certainty of evidence). We recommend against starting with 100% oxygen (strong recommendation, low certainty of evidence).

CIRCULATORY SUPPORT

For each of the following topics, the EvUps were performed to identify any evidence relevant to the topic that was published after the most recent NLS CoSTR on the topic. The goal was to determine if there was sufficient evidence to suggest a need for a SysRev that might change recommendations about performance of cardiac compressions for the few neonates who require circulatory support at birth.

CPR Ratios for Neonatal Resuscitation (NLS 895: EvUp)

Chest compressions administered in a 3:1 compression-to-ventilation ratio are recommended for resuscitation of newborn infants.[1,9,10] At birth, the fluid filling the lungs of the newborn must be absorbed during the initial breaths. Lung aeration triggers an increase in pulmonary blood flow. If a newborn infant has sufficient compromise in gas exchange to cause severe bradycardia or cardiac arrest, successful resuscitation must first achieve adequate lung aeration and ventilation to avoid circulation of blood with progressively lower oxygen saturation.

Many newborn infants, even those who are asphyxiated, will respond to respiratory support alone. As a result, the focus of newborn resuscitation is aimed first at establishing effective ventilation, and support of circulation is provided only for those who have persistent bradycardia or asystole. When circulatory support is needed, it is important that it be as effective as possible. This EvUp was performed to identify the most effective compression-to-ventilation ratio for neonatal resuscitation.

Most studies identified by the EvUp (see Supplement Appendix C-6) either supported the 2015 treatment recommendations or did not refute it. As a result, the NLS Task Force agreed that no SysRev is needed and there is no change to the 2015 treatment recommendation.[1,9,10] The NLS Task Force is aware of an ongoing study of a new neonatal compression technique, with compressions delivered while maintaining a sustained inflation (NCT02858583 at Clinicaltrials.gov). The NLS Task Force agreed that a SysRev may be indicated after publication of the results of that study.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: In newborn infants receiving cardiac compressions
- Intervention: other ratios (5:1. 9:3, 15:2, synchronous, etc)
- Comparator: 3 compressions, 1 ventilation
- Outcome[21]:
  - Return of spontaneous circulation (ROSC) (critical)
  - Survival (critical)
  - Neurodevelopmental impairment (critical)
  - Time to ROSC (critical)
  - Perfusion (important)
  - Gas exchange (important)
  - Tissue injury (important)
  - Compressor fatigue (important)

Treatment Recommendation

This treatment recommendation (below) is unchanged from 2015.[1,9,10]

We suggest continued use of a 3:1 compression-to-ventilation ratio for neonatal CPR (weak recommendation, very low-quality evidence).

2-Thumb Versus 2-Finger Compressions for Neonatal Resuscitation (NLS 605: EvUp)

In the past, providers used a variety of techniques to perform chest compressions during resuscitation of newborn infants. The most common techniques used 2 thumbs with the remaining fingers surrounding the lateral and posterior chest, or 2 fingers placed vertically on the lower sternum. The most recent review of the topic of chest compressions was included in the 2015 CoSTR for NLS.[1,9,10] This EvUp was performed to identify any evidence published after the 2015 CoSTR that would suggest the need for a new SysRev and reevaluation of the treatment recommendation.

The only new evidence identified by the EvUp (see Supplement Appendix C-7) supports the 2015 treatment recommendations.[1,9,10] Thus, no new SysRev or change in the 2015 treatment recommendation is warranted.

The task force noted that initial reports of a few alternative compression techniques (vertical thumbs, thumb and index finger, 2 thumbs with fisted hands) have been studied in manikin models. Studies testing any of these in a comparative trial in human infants may prompt a future SysRev.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: In newborn infants receiving cardiac compressions
- Intervention: 2-thumb technique
- Comparator: 2-finger technique
- Outcome[21]:
  - ROSC (critical)
  - Survival (critical)
  - Neurodevelopmental impairment (critical)
  - Perfusion (important)

- Gas exchange (important)
- Compressor fatigue (important)

Treatment Recommendation

This treatment recommendation (below) is unchanged from 2015.[1,9,10]

We suggest that chest compressions in the newborn infant should be delivered by the 2-thumb, hands-encircling-the-chest method as the preferred option (weak recommendation, very low-certainty evidence).

DRUG AND FLUID ADMINISTRATION

Although seldom needed, the short list of medications and fluids used for delivery room resuscitation of the newborn includes epinephrine and volume expanders.

Epinephrine (Adrenaline) for Neonatal Resuscitation (NLS 593: SysRev)

When the heart is hypoxic and depleted of energy substrate to the point of cardiac arrest, providers must re-establish effective perfusion of the myocardium with oxygenated blood.[91] Epinephrine (adrenaline) causes vasoconstriction, which increases the amount of oxygenated blood entering the coronary arteries and improves myocardial blood flow. Perfusion of the myocardium with oxygenated blood facilitates the synthesis of ATP within myocardial mitochondria, thus enhancing cell viability, contractility, and ROSC.[91]

In 2010, the NLS CoSTR summarized the evidence comparing the endotracheal route with the intravenous (IV) route for delivery of epinephrine (adrenaline) and concluded that the IV route was preferable.[12–14] The NLS Task Force has never conducted a SysRev to evaluate the evidence for epinephrine dose, dose interval, or other routes of delivery. In 2019, the NLS Task Force initiated a new SysRev to identify the evidence addressing these gaps.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Among neonates (of any gestation) less than 28 days of age who have no detected cardiac output or who have asystole or heart rate less than 60/min despite ventilation and chest compressions
- Intervention: Any nonstandard dose, interval, or route of epinephrine (adrenaline)
- Comparator: Epinephrine (adrenaline) doses of 0.01 to 0.03 mg/kg via IV at intervals of every 3 to 5 minutes
- Outcome[21]:
  - Mortality before hospital discharge (critical)
  - Survival to neonatal unit admission (critical)
  - ROSC: incidence and time until (critical)
  - HIE stage moderate to severe (term infants only)[90] (critical)
  - Intraventricular hemorrhage Grades 3 to 4 (preterm infants only) (critical)[55]
  - Necrotizing enterocolitis[92] (important)
  - Retinopathy of prematurity[56] (important)
  - Bronchopulmonary dysplasia[54] (important)
  - Periventricular leukomalacia (critical)
  - Neurodevelopmental outcomes (critical)
- Study design: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Cohort studies may compare different interventions or include only 1 arm receiving 1 intervention. They were eligible for this review if they were considered representative of a defined population (eg, infants born at a hospital between specified dates). Otherwise, they were considered to be (ineligible) case series. All languages were eligible if there was an English abstract. Unpublished studies (eg, conference abstracts, trial protocols) were excluded.
- Time frame: Literature search was from inception of the searched databases to March 6, 2019.
- PROSPERO Registration: CRD42019132219

Consensus on Science

The SysRev identified 2 eligible studies including 97 newborn infants.[92a] A draft CoSTR document based on the SysRev was posted on the ilcor.org website for a 2-week public commenting period on February 18, 2020.

Only 2 observational studies were found that addressed any of the comparisons prespecified in the PICOST.[7,93] They included both preterm and term infants from the same neonatal unit, although the participants were from different epochs. The overall certainty of evidence was rated as very low for all outcomes, primarily for a very serious risk of bias and very serious imprecision. The individual studies were at a critical risk of bias due to confounding.

For the critical outcome of mortality before hospital discharge, we identified very low-certainty evidence (downgraded for very serious risk of bias and very serious imprecision) from 1 observational study[7] of 50 neonates treated with epinephrine (adrenaline). In this study, there was no benefit associated with initial endotracheal versus IV epinephrine (adrenaline) dose. This lack of benefit was observed despite the fact that larger initial doses of epinephrine (adrenaline) were given via the endotracheal route (0.03–0.05 mg endotracheal dose compared with 0.01 mg/kg per IV dose). See Table 3 for statistical data.

In a post hoc analysis, we identified very low-certainty evidence (downgraded for very serious risk of bias and very serious imprecision) from 2 observational studies[7,93] of 97 neonates treated with epinephrine (adrenaline). These studies showed no significant association between route of administration of first dose and receipt of a second dose (RR, 1.94; 95% CI, 0.18–20.96;

Table 3. Meta-Analysis of Outcomes After Initial Endotracheal Versus Intravenous Epinephrine

Outcome	Study With Outcome of Interest	Total, n	Certainty of Evidence	RR (95% CI); I^2	Absolute Difference (95% CI)
Neonatal Outcomes					
Mortality before hospital discharge	Halling, 2017[7]	50	Very low	1.03 (0.62–1.71); NA	17/1000 more neonates died when initial endotracheal (0.05–0.1 mg/kg) versus initial IV (0.01–0.03 mg/kg) epinephrine was used (209 fewer–391 more per 1000)
Failure to achieve ROSC	Halling, 2017[7] Barber, 2006[93]	97	Very low	0.97 (0.38–2.48); 0	7/1000 fewer failed to achieve ROSC when initial endotracheal (0.05–0.1 mg/kg) versus initial IV (0.01–0.03 mg/kg) epinephrine was used (135 fewer–322 more per 1000)
Time to ROSC (minutes)	Halling, 2017[7]	50	Very low		ROSC was 2 min later when initial endotracheal (0.05–0.1 mg/kg) versus initial IV (0.01–0.03 mg/kg) epinephrine was used (0.6 min earlier–4.6 min later)

IV indicates intravenous; NA, not applicable; ROSC, return of spontaneous circulation; and RR, relative risk.

P=0.59; absolute risk difference, 654 more newborn infants; 95% CI, 570 fewer to 1000 more per 1000 newborn infants would receive additional epinephrine (adrenaline) dose or doses after the first). This occurred despite infants receiving larger doses given via the endotracheal route in one of the studies.[7]

No studies specifically reported the critical outcome of survival to neonatal unit admission, but this was likely similar to the inverse of the reported outcome "failure to achieve ROSC." We found only 1 eligible study comparing different doses of IV epinephrine (adrenaline).[7] This study of 30 neonates who received initial endotracheal epinephrine (adrenaline) allowed a post hoc comparison of 30 newborn infants who received 2 different doses (0.03 versus 0.05 mg/kg per dose) of endotracheal epinephrine (adrenaline) in different epochs of the study. Although no statistically significant difference was found, there was such serious imprecision as to prevent any conclusion.

We did not find any eligible studies comparing different routes of administration other than the comparisons between IV versus endotracheal epinephrine (adrenaline).

We did not find any eligible studies comparing different intervals of epinephrine (adrenaline) administration.

We did not find any eligible studies that allowed comparison of any other prespecified important outcomes (HIE stage moderate-severe[90] [term infants only]; intraventricular hemorrhage Grades 3–4[55] [preterm infants only]; other morbidities in early infancy [eg, necrotizing enterocolitis,[92] retinopathy of prematurity,[56] bronchopulmonary dysplasia,[54] periventricular leukomalacia] or neurodevelopmental outcomes).

The NLS Task Force agreed that the key 2010 CoSTR recommendations about epinephrine (adrenaline) administration remain valid.[12–14] The 2020 treatment recommendations include some minor editorial revisions in the indications for epinephrine (adrenaline) administration and more specific dose information and guidance about repeat doses than were contained in the 2010 treatment recommendations.

Treatment Recommendations

If the heart rate has not increased to 60/min or greater after optimizing ventilation and chest compressions, we suggest the administration of intravascular epinephrine (adrenaline) (0.01–0.03 mg/kg) (weak recommendation, very low-certainty evidence).

If intravascular access is not yet available, we suggest administering endotracheal epinephrine (adrenaline) at a larger dose (0.05–0.1 mg/kg) than the dose used for IV administration (weak recommendation, very low-certainty evidence). The administration of endotracheal epinephrine (adrenaline) should not delay attempts to establish vascular access (weak recommendation, very low-certainty evidence).

We suggest the administration of further doses of epinephrine (adrenaline) every 3 to 5 minutes, preferably intravascularly, if the heart rate remains less than 60/min (weak recommendation, very low-certainty evidence).

If the response to endotracheal epinephrine (adrenaline) is inadequate, we suggest that an intravascular dose be given as soon as vascular access is obtained, regardless of the interval after any initial endotracheal dose (weak recommendation, very low-certainty evidence).

Justification and Evidence-to-Decision Framework Highlights

This topic was prioritized by the NLS Task Force because epinephrine (adrenaline) administration is considered to have a key role for newborns who have not responded to all previous steps in resuscitation. The last of NLS CoSTR addressing epinephrine (adrenaline) administration was conducted a decade ago,[12–14] at a time when the ILCOR evidence evaluation did

not use the GRADE assessment tools. Finally, the NLS Task force was aware of new cohort studies published after 2010.

In making these recommendations, the NLS Task Force considered the fact that the very limited human infant evidence does not demonstrate greater effect of endotracheal versus IV epinephrine (adrenaline). Although the population identified for this SysRev was human neonates, the task force reviewed 1 animal study. In a RCT of term lambs undergoing perinatal transition with asphyxia-induced cardiopulmonary arrest,[94] peak plasma epinephrine (adrenaline) concentrations were higher and were achieved sooner after central venous epinephrine (adrenaline) (right atrium 470±250 ng/mL or low umbilical venous cord 450±190 ng/mL at 1 minute) than after endotracheal epinephrine (adrenaline) (130±60 ng/mL at 5 minutes; *P*=0.03), despite lower administered central venous than endotracheal doses (0.03 mg/kg central venous IV dose versus 0.1 mg/kg endotracheal dose). In the same study, central venous compared with endotracheal epinephrine (adrenaline) administration resulted in a shorter median time (interquartile range) to achieve ROSC (2 [95% CI, 1.9–3] versus 4.5 [95% CI, 2.9–7.4] minutes; *P*=0.02), using a lower dose for central venous than for endotracheal administration. In addition, central venous compared with endotracheal epinephrine (adrenaline) administration resulted in higher rates of ROSC (86% [19/22] versus 54% [12/22]; *P*=0.02, respectively), using the same lower central venous compared with endotracheal doses.[94]

Subgroup Considerations

There was no evidence to suggest any variation in recommendations for subgroups of infants (eg, term versus preterm).

Implementation Considerations

This recommendation is similar to the 2010 treatment recommendation (ie, route and dose of epinephrine [adrenaline] NLS-008A, NLS-008B, NRP-009A, NRP-009B),[12–14] so the task force agreed that there are no new implications for implementation.

Monitoring and Implementation

We recommend that health services monitor the use of epinephrine (adrenaline) for newborn resuscitation, together with the outcomes of epinephrine (adrenaline) treatment reported in this review. Wherever possible, this monitoring should include the characteristics of the infants, the resuscitation measures they have received before epinephrine (adrenaline), the dose(s), route(s) and treatment intervals, and any adverse effects of treatment. It is unlikely there will be clinical trials to provide high-certainty evidence on which to base future treatment recommendations about epinephrine (adrenaline) doses, administration time intervals, and delivery routes. However, collection and publication of clinical observational studies can increase the volume of good-quality data to validate or improve treatment recommendations. Finally, the task force agreed that frequency of epinephrine (adrenaline) administration during resuscitation may reflect the quality of earlier steps in intrapartum management and resuscitation.

See Supplement Appendix A-3 for the evidence-to-decision table associated with this SysRev.

Knowledge Gaps

The NLS Task Force identified the following specific gaps in knowledge:

- Optimal (heart rate) thresholds for administration of epinephrine (adrenaline)
- Optimal dose and interval of epinephrine (adrenaline)
- Optimal epinephrine dose and intervals specific to gestational age
- Optimal route and method of epinephrine (adrenaline) administration
- Potential harms of epinephrine (adrenaline) (single or multiple doses)
- Effect of vasoactive drugs other than epinephrine (adrenaline)
- Human factors approach to achieve the timely administration of epinephrine (adrenaline)
- Neurodevelopmental outcomes after epinephrine (adrenaline) use

Providers must make the decision to administer epinephrine (adrenaline) rapidly during newborn resuscitation. In addition, epinephrine (adrenaline) use is uncommon and unpredictable. As a result, it may be difficult to perform adequate and ethical randomized trials of human newborn infants with prior parental informed consent. Prospective, multicenter cluster-randomized trials could be a good option.

Newborn animal studies are also needed to address pharmacokinetics and pharmacodynamics to determine the optimal dose and route of epinephrine (adrenaline) to inform the optimal design of human infant studies.

Intraosseous Versus Umbilical Vein for Emergency Access (NLS 616: SysRev)

In the rare circumstance where epinephrine (adrenaline) or volume is needed during neonatal resuscitation, vascular access is urgently required. There are questions as to the best route of vascular access to use. The last SysRev about this topic for neonates was in 2010 (NLS-020A intraosseous [IO] versus IV).[12–14] In 2020, the NLS Task Force joined the Advanced Life Support Task Force and the Pediatric Life Support Task Force to complete a joint SysRev with meta-analysis.[95]

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants in any setting (in-hospital or out-of-hospital) with cardiac arrest (includes severe bradycardia and inadequate perfusion requiring chest compressions)
- Intervention: Placement of an IO cannula with drug administration through this IO site during cardiac arrest
- Comparator: Placement of an IV cannula (umbilical vein in newborn infants) and drug administration through this IV during cardiac arrest
- Outcome[21]:
  - Death during event, within 24 hours and before hospital discharge (critical)
  - Long-term neurodevelopmental outcomes (critical)
  - ROSC: any signs of cardiac output with heart rate 60/min or greater, and time to ROSC (critical)
  - Brain injury (HIE Stage 2–3 Sarnat,[90] [term only], intraventricular hemorrhage Grades 3–4,[55] periventricular leukomalacia, preterm only) (critical)
  - Time to secure access (important)
  - Morbidity related to IO (osteomyelitis, fracture, epiphyseal plate injury, compartment syndrome) or to IV (extravasation, embolic phenomenon, phlebitis) (important)
- Study design:
  - Inclusion criteria: Randomized trials, non-RCTs, and observational studies (cohort studies and case-control studies) comparing IO with IV administration of drugs; randomized trials assessing the effect of specific drugs (eg, epinephrine [adrenaline]) in subgroups related to IO versus IV administration; studies assessing cost-effectiveness for a descriptive summary
  - Exclusion criteria: Ecological studies, case series, case reports, reviews, abstracts, editorials, comments, letters to the editor, or unpublished studies
  - Search: All years and languages were included if there was an English abstract. MEDLINE (Ovid interface), Embase (Ovid interface), and Cochrane Central Register of Controlled Trials literature search was conducted from 1946 to September 12, 2019, as well as ongoing trials on International Clinical Trials Registry Platform.

A Priori Subgroups to Be Examined

Cardiac and noncardiac causes of circulatory collapse; gestational age (preterm less than 37 weeks and term 37 weeks or greater); delivery room or other site; in-hospital or out-of-hospital; central or peripheral IV access; pediatric trained personnel versus non pediatric

PROSPERO Registration: CRD42020150877

Consensus on Science

Although small clinical series and case reports suggest that medications and fluids can be successfully delivered by the IO route during neonatal resuscitation,[96,97] case series also report complications with IO catheter insertion or use.[96,98–102] To determine if IO or intravascular access is more effective for neonatal resuscitation, evidence from neonatal literature was sought and considered by the NLS Task Force as part of a joint effort with the Adult Life Support and Pediatric Life Support Task Forces. No studies meeting the a priori inclusion criteria were found for newborn infants, precluding meta-analysis in this population. A draft CoSTR was developed that reflected the lack of data and was posted on the ILCOR website; the draft was viewed more than 2600 times, and more than 50 comments were posted. The majority were supportive of the conclusions.

No evidence was identified for newborn infants comparing use of IO and IV cannulas for drug administration in any setting (in-hospital or out-of-hospital) for any prespecified outcome of the review.

In 2010, the NLS Task Force said that temporary IO access to provide fluids and medications to resuscitate critically ill neonates may be indicated after unsuccessful attempts to establish IV vascular access or when caregivers are skilled at securing IO access.[12–14] The 2020 SysRev identified reports of serious complications after use of IO access in neonates.[96,98–102] As a result, the 2020 treatment recommendations are stronger in support of the umbilical venous route as the primary route for vascular access during delivery room resuscitation but continue to allow that in some circumstances the IO route is acceptable.

Treatment Recommendations

We suggest umbilical venous catheterization as the primary method of vascular access during newborn infant resuscitation in the delivery room. If umbilical venous access is not feasible, the intraosseous route is a reasonable alternative for vascular access during newborn resuscitation (weak recommendation, very low-certainty evidence).

Outside the delivery room setting, we suggest that either umbilical venous access or the IO route may be used to administer fluids and medications during newborn resuscitation (weak recommendation, very low-certainty evidence). The actual route used may depend on local availability of equipment, training, and experience.

Justification and Evidence-to-Decision Framework Highlights

In making this recommendation, we recognize the absence of data from human neonatal studies supporting any advantage of IO over umbilical venous access. There are a number of case reports of serious adverse effects of IO access in neonates, including tibial fractures and extravasation of fluid and medications resulting in compartment syndrome and amputation.[96,98–102]

The rate of adverse effects attributable to emergency umbilical venous catheterization is unknown. However, public feedback emphasized umbilical access as

the technique most commonly taught to and used by neonatal providers, recognizing that IO access may be helpful in out-of-hospital settings or later in the neonatal intensive care stay when the umbilical vein is no longer patent.

For further information, see the evidence-to-decision table in Supplement Appendix A-4.

Knowledge Gaps

The absence of clinical trials, cohort studies, and case-control studies leaves many gaps related to IO versus umbilical vein access during newborn resuscitation. We failed to identify even case series or case reports of IO use in neonatal resuscitation at delivery.

Specific research is required in preterm and term neonates:

- Determination of time from start of CPR to achieving successful IO placement
- Determination time from start of CPR to achieving successful IV placement in umbilical vein
- Optimal IO device suitable for newborn infants
- Optimal site (head of humerus, proximal tibia, other) for successful IO access and drug and fluid administration
- Short- and long-term safety of IO placement during newborn resuscitation
- Complications related to emergency umbilical venous catheterization
- Pharmacokinetics and plasma availability of drugs administered through IO compared with IV routes
- Optimal training for IO placement and IV umbilical vein placement during neonatal resuscitation
- How to best secure and maintain any emergency vascular access devices
- Optimal method to determine correct placement of any emergency vascular access device
- Whether results of studies in animal and simulation models apply to clinical practice
- IO access during neonatal resuscitation outside the delivery room

Volume Infusion During Neonatal Resuscitation (NLS 598: EvUp)

In the absence of a history of blood loss, there is limited evidence of benefit from administration of volume during resuscitation of newborns who have not responded to chest compressions and epinephrine (adrenaline). This topic was most recently reviewed by the NLS Task Force in 2010.[12–14] In 2020, the NLS Task Force undertook an EvUp to see if additional literature warranted consideration of a request for a new SysRev.

The EvUp identified no human studies and a single animal RCT (see Supplement Appendix C-8); the results of this study supported the 2010 CoSTR for NLS treatment recommendations.[12–14] The NLS Task Force agreed that there is no reason at this time to suggest a new SysRev or a change in the 2010 treatment recommendations.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Term and preterm newborn infants who receive resuscitation immediately after birth and who have a heart rate less than 60/min after chest compressions and epinephrine (adrenaline) and/or suspected hypovolemia based on history and examination.
- Intervention: Blood volume expansion with blood (red cells or whole blood), colloid (eg, albumin, plasma), crystalloid (eg, 0.9% sodium chloride) or other solution
- Comparator: No blood volume expansion
- Outcome[21]:
  - Survival (to any stage) (critical)
  - Neurodevelopmental outcomes (with age-appropriate, validated tools) (critical)
  - Time to ROSC (or heart rate 60/min or greater) (important)
  - Subsequent use of vasopressor infusion(s) (important)
  - Blood pressure at specified time (important)
  - Pulmonary edema (important)
  - Serious neonatal morbidity (including intraventricular hemorrhage, necrotizing enterocolitis, persistent pulmonary hypertension of the newborn, HIE, pulmonary hemorrhage) (critical)

Treatment Recommendation

These treatment recommendations are unchanged from 2010.[12–14]

Early volume replacement with crystalloid or red cells is indicated for newborn infants with blood loss who are not responding to resuscitation.

There is insufficient evidence to support the routine use of volume administration in the newborn infant with no blood loss who is refractory to ventilation, chest compressions, and epinephrine. Because blood loss may be occult, a trial of volume administration may be considered in newborn infants who do not respond to resuscitation.

Sodium Bicarbonate During Neonatal Resuscitation (NLS 606: EvUp)

In 2019, a request was made by members of the European Resuscitation Council for the NLS Task Force to consider an EvUp concerning the use of sodium bicarbonate during neonatal resuscitation. Since 2005, inconsistency has developed internationally as to whether sodium bicarbonate is even mentioned in council guidelines. The 2010 CoSTR briefly mentioned that sodium bicarbonate may very rarely be useful after resuscitation.[12–14] In 2020, the NLS Task Force undertook

an EvUp to determine if additional evidence published after 2020 warranted consideration of a new SysRev.

The EvUp (see Supplement Appendix C-9) identified only evidence that supported the 2010 treatment recommendations.[12–14]

Thus, the task force agreed that no SysRev or change in the 2010 treatment recommendation is warranted.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants who are receiving resuscitation in the hospital
- Intervention: Sodium bicarbonate administration
- Comparator: No sodium bicarbonate
- Outcome[21]:
  - Survival (to hospital discharge or as defined by authors) (critical)
  - ROSC (critical)
  - HIE stage moderate to severe[90] (term infants only) (critical)
  - Intraventricular hemorrhage Grades 3 to 4[55] (preterm only) (critical)
  - Other morbidities in early infancy (eg, necrotizing enterocolitis,[92] retinopathy of prematurity,[56] bronchopulmonary dysplasia,[54] periventricular leukomalacia) (important)
  - Neurodevelopmental outcomes (critical)

Treatment Recommendation

This treatment recommendation (below) is unchanged from 2010.[12–14]

Sodium bicarbonate is discouraged during brief CPR but may be useful during prolonged arrests after adequate ventilation is established and there is no response to other therapies.

PROGNOSTICATION DURING CPR

Impact of Duration of Intensive Resuscitation (NLS 896: SysRev)

It can be difficult for clinicians to decide how long resuscitative efforts should continue in a newborn infant with no heart rate and/or absent respirations with a very low heart rate after sustained resuscitative efforts.[12–14] This critical decision involves knowing when to redirect the care of the newborn infant from resuscitation to the provision of comfort and contact with the parents. If such a decision is made too early, some infants with potential to survive with good neurodevelopmental outcome may die. If the decision is made too late, there is likely to be a diminishing potential for survival, especially without severe neurological injury.

In recent years, long-term outcomes for survivors requiring prolonged resuscitation have improved somewhat. In 2015, the CoSTR focused on the following question: "In infants with a gestational age of 36 weeks or greater and an Apgar score of 0 for 10 minutes or longer, despite ongoing resuscitation, what is the rate of survival to NICU admission and death or neurocognitive impairment at 18 to 22 months?" In 2019, the NLS Task Force revised the question slightly to better reflect the questions clinicians and families ask in such a crisis situation.

The current PICOST attempts to reduce the emphasis on the Apgar score at 10 minutes and puts more focus on the incremental time of resuscitation exposure from birth as related to outcome.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants presenting with at least 10 minutes of asystole, bradycardia (heart rate less than 60/min), or pulseless electric activity after birth for which CPR is indicated
- Intervention: Ongoing CPR for incremental time intervals beyond 10 minutes after birth
- Comparator: CPR discontinued at 10 minutes after birth
- Outcome[21]:
  - Survival (to any age) (critical)
  - Neurodevelopmental outcomes (critical)
  - Composite of survival to any age without moderate or severe neurodisability (critical)
- Study design: Cross-sectional or cohort studies were eligible for inclusion. Ancillary analyses of RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies, case series) were eligible for inclusion. All years and languages were included if there was an English abstract. Conference abstracts and trial protocols were excluded.
- Time frame: All years were included from inception of the searched databases to October 17, 2019.

A Priori Subgroups to Be Examined

Hypothermia postresuscitative care among newborn infants 36 weeks' or greater gestational age; 36 weeks' or greater gestational age versus less than 36 weeks'; birthweight 2500 g or greater; infants enrolled in population-level cohort studies

PROSPERO Registration: CRD42020157370

Consensus on Science

The SysRev[102a] identified 15 studies that included 470 infants (see Figure 2).

For the critical outcome of survival until last follow up, we identified very low-certainty evidence (downgraded for risk of bias and inconsistency) from 15 studies[103–117] reporting outcomes of 470 newborns to last known follow-up (range: 4 months–8 years of age). The number of enrolled newborns ranged from 3 to 177 per study. Across studies, reported survival rates to last follow up ranged from 1.7% to 100%. Among all 470 newborns reported in the literature, including studies that required survival

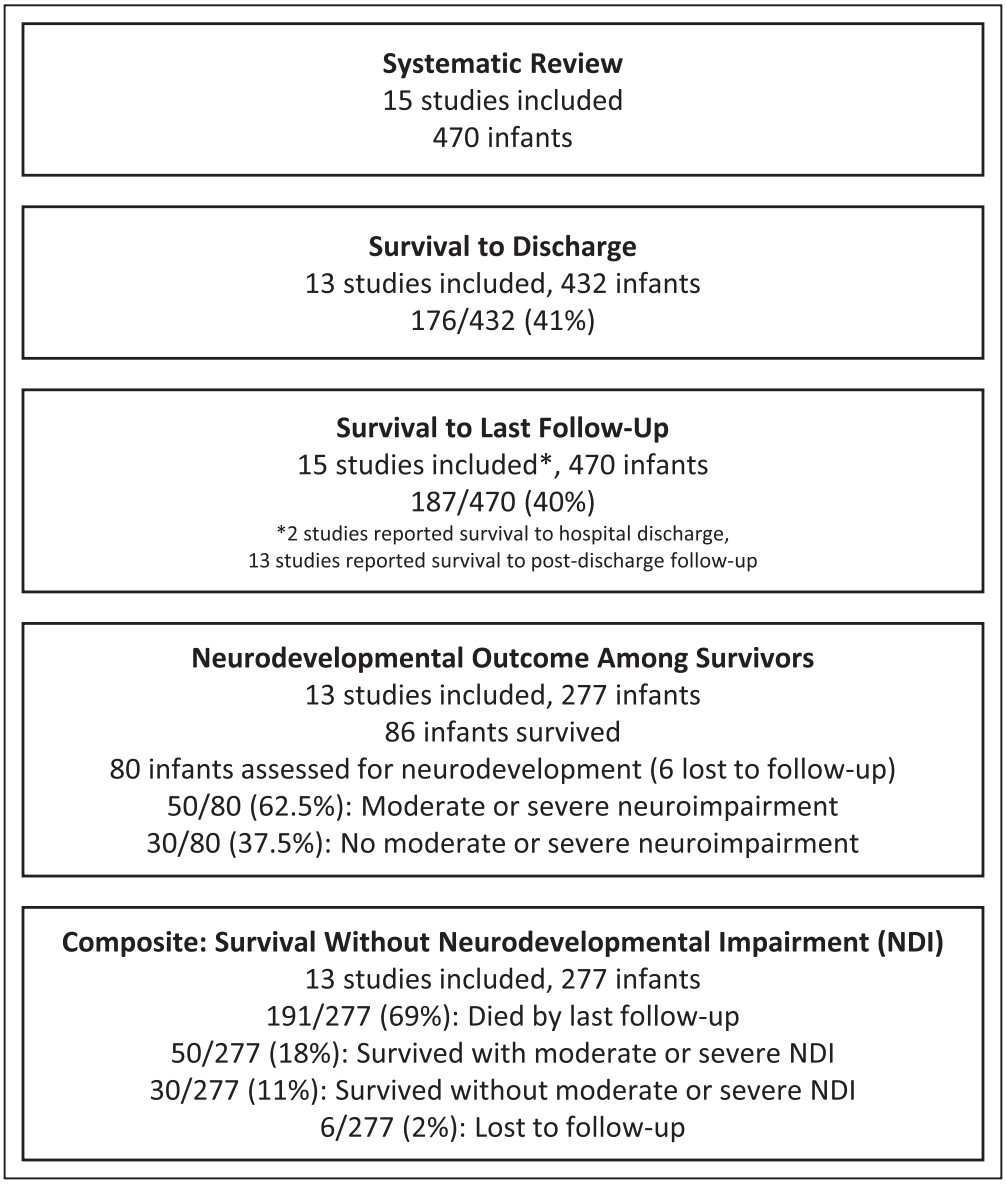

Figure 2. Modified flow diagram of number of studies and infants included for each specified outcome for infants experiencing resuscitation that exceeded 10 minutes.
Moderate to severe NDI was defined by each study.

to NICU admission or enrollment in a cooling protocol for inclusion, 187 (39.8%) survived to last follow-up. The decision was made not to calculate confidence intervals as a result of heterogeneity across included studies.

For the critical outcome of neurodevelopmental outcomes among survivors, we identified very low-certainty evidence (downgraded for risk of bias and inconsistency) from 13 studies including 277 infants.[103,104,106–112,114–117] Neurodevelopmental outcomes were assessed in 80 survivors. Thirty infants among 80 survivors (37.5%) did not have moderate or severe NDI (range: 0% to 100%). There was important heterogeneity across studies (and in some cases within studies) about the timing and tools used to assess neurodevelopmental outcomes that precluded calculation of confidence intervals.

For the composite critical outcome of survival without NDI, we identified very low-certainty evidence (downgraded for risk of bias and inconsistency) from 13 studies of 277 infants[103,104,106–112,114–117] reporting neurodevelopmental outcomes. Among all 277 infants reported in these studies, 69% died before last follow up, 18% survived with moderate to severe impairment, and 11% survived without moderate to severe impairment (2% lost to follow up). There was important heterogeneity across studies (and in some cases, within studies) about the timing and tools used to assess neurodevelopmental outcomes that precluded calculation of confidence intervals.

Note: Neurodevelopmental outcomes in postdischarge follow-up were reported in 13 studies using structured exams.[103,104,106–112,114–117] In 11 studies, these assessments used validated developmental assessment

tools.[106–112,114–117] These tools included developmental assessment tools such as the Bayley Scales of Infant and Toddler Development (any version) or a Japanese version of the Bayley Scales (Kyoto Scale of Psychological Development); motor assessment tools such as Gross Motor Function Classification System or Peabody Developmental Motor Scales; and cognitive evaluation tools such as Stanford-Binet Test, Griffiths Scales of Child Development (any version), or Wechsler Preschool and Primary Scale of Intelligence (any version). Two studies[103,104] reported only a formal neurological evaluation of the survivors. Auditory and visual assessment varied among studies. Of note, children assessed only by screening tools (such as Denver Developmental Screening Test) in any study were analyzed as lost to follow-up. Time of follow-up for the 80 survivors assessed for NDI was 12 months or greater in 83% (66/80) of the infants (range: 12 months–8 years) and less than 12 months in 6% (5/80) of the infants. Time of assessment was not reported in 1 study[114] with 11% (9/80) survivors. Moderate and severe NDI were defined by each study.

Subgroup Considerations

Prespecified subgroup analyses for the specified critical outcomes of survival to last follow-up, survival without NDI, and the composite of survival without moderate to severe NDI are depicted in Table 4. Insufficient details about birthweight precluded the planned subgroup analysis based on birthweight.

Given the small sample sizes and heterogeneity of study characteristics, there is no strong evidence on which to base recommendations for specific subgroups of infants.

Treatment Recommendations

Failure to achieve return of spontaneous circulation in newborn infants despite 10 to 20 minutes of intensive resuscitation is associated with a high risk of mortality and a high risk of moderate-to-severe neurodevelopmental impairment among survivors. However, there is no evidence that any specific duration of resuscitation consistently predicts mortality or moderate-to-severe neurodevelopmental impairment. If, despite provision of all the recommended steps of resuscitation and excluding reversible causes, a newborn infant requires ongoing cardiopulmonary resuscitation (CPR) after birth, we suggest discussion of discontinuing resuscitative efforts with the clinical team and family. A reasonable time frame to consider this change in goals of care is around 20 minutes after birth. (Weak recommendation, very low-certainty evidence).

Justification and Evidence-to-Decision Framework Highlights

In making this recommendation, we recognize the need to balance the risk of ceasing resuscitation too early, when ROSC and long-term survival may still be achievable, and continuing resuscitation for too long, when ROSC may occur but survival is associated with a high risk of severe neurological injury. The appreciable number of survivors without moderate or severe NDI after 10 minutes or greater of resuscitation suggests that early cessation of resuscitation may preclude survival of some infants who may have a good outcome.

While an Apgar score of 0 or 1 at 10 minutes is a strong predictor of mortality and morbidity, recent case reports and series have reported favorable outcomes among newborn infants with Apgar scores of 0 or 1 at 10 minutes after birth who achieved ROSC and received therapeutic hypothermia. In this subgroup of newborns with severe depression at birth, both survival and survival without moderate-to-severe impairment have been reported. Among 105 such infants reported in the literature with Apgar scores 0 or 1 who were successfully resuscitated, were treated with therapeutic hypothermia, and were assessed after discharge, 20% of all infants survived without moderate-to-severe NDI, and 37% of the survivors did not have moderate or severe NDI.[107,109–112,116,117]

The evidence supporting this recommendation is of very low certainty. However, we value the possibility of survival and intact survival after ongoing resuscitation. In a large multisite cohort of 659 newborn infants who survived to discharge after more than 1 minute of chest compressions in the delivery room, 25% of survivors received 10 minutes or more of resuscitation.[118] This study did not specifically report on infants with 10-minute Apgar scores of 0 or 1. While these data indicate that survival to discharge is possible after a lengthy duration of CPR, neurodevelopmental outcomes among survivors in this study were not reported.

Extremely limited data are available about outcomes of newborn infants who received 20 or more minutes of CPR after birth. Five studies included in this systematic review[110–112,116,117] reported results for 39 newborn infants in whom first detectable heart rate or heart rate 100/min or greater occurred at or beyond 20 minutes after birth. Of these, 38% (15/39) survived until last follow up and 40% (6/15) of survivors did not have moderate or severe neuroimpairment.

The task force agreed that in addition to considering duration of resuscitation, it was important to consider whether all recommended resuscitation interventions were provided. Studies suggest that the time taken to accomplish steps of a resuscitation up to the point of administration of 1 or more doses of epinephrine varies widely across studies but may take as long as 20 minutes.[7,93,111,119] The variation in the interval from birth to completion of these steps may depend on the characteristics and time to attendance of the resuscitation team. Thus, using a single time interval after birth to discontinue intensive resuscitation for all newborns might mean in some cases that the full repertoire of

Table 4. Subgroup Analyses for Specified Outcomes for Infants Who Had Resuscitation That Exceeded 10 Minutes

Subgroup	Studies Contributing	Infants, n	Survival to Last Follow-up	Assessed for NDI	Survivors Assessed Without Moderate or Severe NDI	Composite: Survival Without Moderate or Severe NDI
Population level studies	Casalaz, 1998[104] Harrington, 2007[103] Jain, 1991[106] Sproat, 2017[111] Zhang, 2019[117]	131	13% (17/131)	88% (15/17)	60% (9/15)	7% (9/131)
Therapeutic hypothermia	Ayerapetyan, 2019[116] Kasdorf, 2015[107] Natarajan, 2013[108] Sarkar, 2010[109] Shah, 2015[110] Shibasaki, 2020[112] Sproat, 2017[111] Zhang, 2019[117] Zhong, 2019[113]	206	60% (122/206)	47% (57/122)	37% (21/57)	20% (21/105)*
Gestational age ≥36 wk	Ayerapetyan, 2019[116] Casalaz, 1998[104] Harrington, 2007[103] Kasdorf, 2015[107] Natarajan, 2013[108] Patel, 2004[114] Sarkar, 2010[109] Shah, 2015[110] Shibasaki, 2020[112] Sproat, 2017[111] Zhang, 2019[117] Zhong, 2019[113]	286	51% (146/286)	50% (73/146)	32% (23/73)	14% (23/166)†
Gestational age <36 wk	Casalaz, 1998[104] Harrington, 2007[103] Shah, 2015[110] Sproat, 2017[111] Zhang, 2019[117] Zhong, 2019[113]	99	34% (34/99)	24% (8/34)	63% (5/8)	12% (5/42)‡

*Eight studies with 105 infants reported postdischarge outcomes.
†Eleven studies with 166 infants reported postdischarge outcomes.
‡Five studies with 42 infants reported postdischarge outcomes.
NDI indicates neurodevelopmental impairment.

recommended resuscitation interventions were not provided before cessation of resuscitation.

Another issue considered by the task force was the potential impact on infants and their families. Among the included studies, most deaths occurred either in the delivery room/birth suite or during the initial hospitalization. In this systematic review, rates of survival to discharge were similar to rates of survival to last follow up (see Figure 2). For those infants who ultimately die in early infancy, achieving even this short-term survival may provide the family the time and opportunity to participate in decision-making and care of their infant. Moreover, intact survival is possible among surviving infants. In this systematic review, 38% of surviving infants did not have moderate or severe impairment.

Given these considerations, we do not recommend a specific duration of resuscitation after which point resuscitative efforts should cease. Instead, we suggest that providers consider changing the goals of care if a newborn infant has not responded to all recommended steps of resuscitation that are appropriate to the given setting. We acknowledge that cultural and religious differences, including different perceptions of the value of extending life, the quality of life, and the acceptance of comfort care as an option, may influence the decision.[120–122]

Ultimately, the decision to initiate and continue resuscitative efforts should be individualized and informed by factors such as gestational age, the presence of congenital anomalies, the timing of perinatal insult (if known), the perceived adequacy of resuscitative interventions, the family's stated preferences and values, and the availability of postresuscitative resources, such as neonatal intensive care, and neuroprotective strategies, such as therapeutic hypothermia. Finally, in low-resource settings, where emphasis is given to face-mask ventilation with 21% oxygen for nonbreathing neonates,[123] advanced resuscitation procedures and prolonging resuscitation may not be an option. Therefore, caution must be taken in the global adoption of this treatment recommendation as local/regional discussion and customization are necessary.

Implementation Considerations

Acceptability of the intervention should be thoroughly discussed in the different settings according to cultural, ethical, and moral standards that prevail in each country or region. High-quality resuscitation should be available for infants in need, and training of skills and team performance are critical to achieve it. Communication with families should be optimized, and whenever possible, parents' wishes and values must be considered, even in urgent and stressful situations. Availability of neonatal intensive care and neuroprotective strategies for postresuscitation care is another aspect that may be considered in the decision-making process.

Monitoring and Implementation

It is important to monitor both short- and long-term outcomes for infants who had a prolonged interval between birth and ROSC. In addition, although health equity was not objectively reported for prolonged neonatal resuscitation, it is possible that prolonged resuscitation may be offered to a higher proportion of infants in higher-resource settings; outcomes may also be better in settings with full availability of intensive care and neuroprotective strategies.

Prolonged CPR after birth is relatively rare, so an international registry of events, with detailed description of procedures and their timing in the delivery room, postresuscitation care, and neurological outcomes assessed in follow-up, would provide essential evidence to inform the discussion of how long is too long. Such a registry would also provide valuable information about variability in practice regarding duration of resuscitation in different settings.

For more information, refer to the evidence-to-decision table in Supplement Appendix A-5.

Knowledge Gaps

Many studies reported only outcomes of infants who survived resuscitation and met a specific study eligibility criterion, such as NICU admission or initiation of therapeutic hypothermia. Therefore, estimates of mortality after prolonged resuscitation are likely to underestimate the true rate of death after prolonged resuscitation because this would need to also include infants for whom resuscitation had failed. Studies that account for the full population of newborn infants who receive CPR after birth by using consistent definitions of stillbirths and resuscitation failures are needed to identify the incidence of death and NDI after prolonged resuscitation of term and preterm infants.

In addition, the extent and timing of resuscitation interventions were not reported in most studies; therefore, prognosis of newborn infants after prolonged resuscitation at birth is inferred from the available data. Further, most available studies characterized the infant's response to resuscitation using the Apgar score at 10 minutes, which is prone to subjective assessment and does not provide information about ongoing assessments or responses to resuscitation beyond 10 minutes. More granular information about the interval from birth to detectable heart rate that uses objective measures such as ECG and time to ROSC is needed to inform more precise recommendations about the duration of intensive resuscitation after birth. Additionally, as the ECG is used more frequently in the delivery room environment, additional information about the presenting rhythm (bradycardia, asystole, pulseless electric activity) preceding chest compressions will be helpful to identify outcomes after these varied presentations.

Therefore, studies that report outcomes on the full population of infants who present without signs of life and receive intensive resuscitation are needed with the following:

- A priori definitions of stillbirths and completeness of resuscitation attempts
- Complete description of cointerventions (resuscitation procedures), timing of procedures at birth, and interventions in postresuscitative care
- Description of methods to assess the heart rate during resuscitation by using objective measures, such as ECG, and report of timing for detection of heart rate and heart rate 60/min or greater and 100/min or greater
- Complete follow-up of survivors with accurate and consistent methods of assessment of neurodevelopment, comparable across studies and population

POSTRESUSCITATION CARE

Rewarming of Hypothermic Newborns (NLS 858: EvUp)

The most recent review of this topic was published in the 2015 CoSTR for NLS.[1,9,10] In 2020, the NLS Task Force undertook an EvUp to determine if any additional evidence was published after 2015 that would necessitate consideration of a new SysRev.

An EvUp (see Supplement Appendix C-10) identified 133 studies; of these, 2 were considered eligible for inclusion. Although the EvUp identified no new prospective trials of rates of rewarming, the 2 new retrospective studies[124,125] increased the number of infants in observational trials nearly 4-fold to 379 infants. Both studies found that the rate of rewarming (after adjustment for confounders) was not associated with the critical outcomes identified in each study. However, 1 study[125] suggested that rapid rewarming reduces the risk for respiratory distress syndrome.

The NLS Task Force agreed that a SysRev that includes the new studies analyzed by using GRADE criteria will likely allow the development of a weak recommendation in relation to the rate of rewarming of hypothermic infants, as opposed to the "no recommendation" that was made in 2015. As a result, the task force will consider prioritization of a SysRev in the near future. Until

the completion of a new SysRev, the 2015 recommendation remains in effect.[1,9,10]

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants who are hypothermic (less than 36.0°C) on admission
- Intervention: Rapid rewarming
- Comparator: Slow rewarming
- Outcome[21]:
  - Survival (to hospital discharge or as defined by authors) (critical)
  - Convulsions/seizures (critical)
  - Hemorrhage/pulmonary hemorrhage (critical)
  - Need for respiratory support (important)
  - Hypoglycemia (important)
  - Episodes of apnea (important)

Treatment Recommendation

This treatment recommendation (below) is unchanged from 2015.[1,9,10]

The confidence in effect estimates is so low that a recommendation for either rapid rewarming (0.5°C/h or greater) or slow rewarming (0.5°C/h or less) of unintentionally hypothermic newborn infants (temperature less than 36°C) at hospital admission would be speculative.

Induced Hypothermia in Settings With Limited Resources (NLS 734: EvUp)

This topic was most recently reviewed in 2015.[1,9,10] In 2020, the NLS Task Force undertook an EvUp to identify any studies published after 2015.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants with HIE managed in limited-resource settings
- Intervention: Therapeutic hypothermia delivered by passive hypothermia and/or ice packs
- Comparator: Standard care
- Outcome[21]:
  - Survival (critical)
  - Neurodevelopmental impairment (any) (important)

The EvUp (see Supplement Appendix C-11) identified 142 studies; 13 of these were thought worthy of inclusion.[126–138] The NLS Task Force agreed that these 13 studies did not identify sufficient new evidence to consider a new SysRev and, even if added to previous studies, would not likely add to the level of certainty of the evidence summarized in 2015.[1,9,10]

It is becoming increasingly difficult (as a result of clinician and parent preferences) to perform large, multicenter randomized trials with a "no-therapeutic hypothermia" control group. However, a protocol was published for 1 such study in hospitals in India, Bangladesh, or Sri Lanka; a multicenter RCT of therapeutic hypothermia using a servo-controlled cooling device compared with standard care without therapeutic hypothermia has a planned enrollment of 418 infants.[139] When completed, such a study (NCT02387385) could provide valuable additional information. Accumulation of data from such a study or from a group of smaller studies might warrant an updated SysRev.

Future studies of this subject should ideally try to examine the contributions of population characteristics, cooling method, and availability of concomitant intensive care to outcomes. Interestingly, a survey of hospitals in California identified a range of practices and opinions about the additional services (specialized nurses, video electroencephalogram monitoring, pediatric neurology and neuroradiology services, developmental follow-up services, etc) that should be required of centers providing neonatal therapeutic hypothermia.[140] In addition to wide variation in opinions about necessary resources such as electroencephalogram monitoring, only 92% of centers reported using an evidence-based protocol, and there was a lack of universal agreement that therapeutic hypothermia centers should treat a minimum volume of patients annually. Considering this variation across high-resource locations, it is not surprising that there is lack of certainty supporting recommendations for when and how to provide therapeutic hypothermia for low- and middle-income countries.

Treatment Recommendation

This recommendation (below) is unchanged from 2015.[1,9,10]

We suggest that newborn infants at term or near-term with evolving moderate-to-severe hypoxic-ischemic encephalopathy in low-income countries and/or other settings with limited resources may be treated with therapeutic hypothermia (weak recommendation, low-quality evidence).

Cooling should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care and availability of adequate resources to offer intravenous therapy, respiratory support, pulse oximetry, antibiotics, anticonvulsants, and pathology testing. Treatment should be consistent with the protocols used in the randomized clinical trials in developed countries, ie, cooling to commence within 6 hours, strict temperature control at 33°C to 34°C for 72 hours and rewarming over at least 4 hours.

Postresuscitation Glucose Management (NLS 607: EvUp)

The most recent review of this topic was published in the 2010 CoSTR.[12–14] In 2020, the NLS Task Force undertook an EvUp to determine if any additional studies were published after 2015 that would necessitate an update to the prior SysRev.

The EvUp (see Supplement Appendix C-12) identified 648 studies; 52 were reviewed and, of those, 13

were worthy of inclusion. Overall, this EvUp suggests the need to maintain vigilance for neonatal hypoglycemia and hyperglycemia in the aftermath of resuscitation, that the use of protocols for blood glucose management may avoid both hypoglycemia and hyperglycemia, and that these protocols may also avoid large swings in blood glucose concentration that have also been associated with harm. The NLS Task Force agreed that the EvUp highlights the fact that research is needed to determine the optimal protocols for glycemic management for preterm and term infants in the aftermath of resuscitation, and identifying the optimal target glucose range should be a high priority. Because the most recent review of the topic was published in 2010, the NLS Task Force agreed that there has been sufficient new evidence published about glucose management after newborn resuscitation to consider prioritizing a SysRev on the topic of blood glucose management.

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

- Population: Newborn infants who have received drugs for resuscitation
- Intervention: Glucose infusion
- Comparator: No glucose infusion
- Outcome[21]:
  - Survival (to hospital discharge or as defined by authors) (critical)
  - Convulsions/seizures (critical)
  - Hemorrhage/pulmonary hemorrhage (critical)
  - Need for respiratory support (important)
  - Hypoglycemia (important)
  - Episodes of apnea (important)

Treatment Recommendation

This treatment recommendation (below) is unchanged from 2010.[12–14]

Intravenous glucose infusion should be considered as soon as practical after resuscitation, with the goal of avoiding hypoglycemia.

TOPICS NOT REVIEWED IN 2020

- Term umbilical cord management (NLS 1551-SysRev in process)
- Preterm umbilical cord management (NLS 787-Sys Rev in process)
- Babies born to mothers who are hypothermic or hyperthermic (NLS 804)
- Stimulation for apneic newborns (NLS 1558)
- Respiratory function monitoring in the delivery room (NLS 806)
- Laryngeal mask for neonatal resuscitation (NLS 618)
- Less-invasive surfactant administration (New)
- CPAP versus increased oxygen for term infants in the delivery room (NLS 1579)
- Optimal peak inspiratory pressure (NLS New)
- Oxygen saturation target percentiles (NLS 1580)
- Use of feedback CPR devices for neonatal cardiac arrest (NLS 862)
- Oxygen use post-ROSC for newborns (NLS 1569)
- Oxygen delivery during CPR (Neonatal) (NLS 738)
- Hypovolemia (risk factors for newborns) (NLS 1555)
- Effect of monitoring technology on team function (NLS 1559)

ARTICLE INFORMATION

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Disclosures

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(*Continued*)

Appendix 1. Continued

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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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-month 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.

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Taylor Sawyer	Seattle Children's Hospital/University of Washington	None	None	None	None	None	None	None
Birju A. Shah	University of Oklahoma	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-month 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.

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