

Part 7: Neonatal Resuscitation

2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (Reprint)

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INTRODUCTION

Newborn Transition

The transition from intrauterine to extrauterine life that occurs at the time of birth requires timely anatomic and physiologic adjustments to achieve the conversion from placental gas exchange to pulmonary respiration. This transition is brought about by initiation of air breathing and cessation of the placental circulation. Air breathing initiates marked relaxation of pulmonary vascular resistance, with considerable increase in pulmonary blood flow and increased return of now-well-oxygenated blood to the left atrium and left ventricle, as well as increased left ventricular output. Removal of the low-resistance placental circuit will increase systemic vascular resistance and blood pressure and reduce right-to-left shunting across the ductus arteriosus. The systemic organs must equally and quickly adjust to the dramatic increase in blood pressure and oxygen exposure. Similarly, intrauterine thermostability must be replaced by neonatal thermoregulation with its inherent increase in oxygen consumption.

Approximately 85% of babies born at term will initiate spontaneous respirations within 10 to 30 seconds of birth, an additional 10% will respond during drying and stimulation, approximately 3% will initiate respirations after positive-pressure ventilation (PPV), 2% will be intubated to support respiratory function, and 0.1% will require chest compressions and/or epinephrine to achieve this transition.^{1–3} Although the vast majority of newborn infants do not require intervention to make these transitional changes, the large number of births worldwide means that many infants require some assistance to achieve cardiorespiratory stability each year.

AUTHORS: Jeffrey M. Perlman, Co-Chair*; Jonathan Wyllie, Co-Chair*; John Kattwinkel; Myra H. Wyckoff; Khalid Aziz; Ruth Guinsburg; Han-Suk Kim; Helen G. Liley; Lindsay Mildenhall; Wendy M. Simon; Edgardo Szyld; Masanori Tamura; Sithembiso Velaphi; on behalf of the Neonatal Resuscitation Chapter Collaborators

KEY WORDS

cardiopulmonary resuscitation ■ delivery room ■ newborns

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*Co-chairs and equal first co-authors.

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Newly born infants who are breathing or crying and have good tone immediately after birth must be dried and kept warm so as to avoid hypothermia. These actions can be provided with the baby lying on the mother's chest and should not require separation of mother and baby. This does not preclude the need for clinical assessment of the baby. For the approximately 5% of newly born infants who do not initiate respiratory effort after stimulation by drying, and providing warmth to avoid hypothermia, 1 or more of the following actions should be undertaken: providing effective ventilation with a face mask or endotracheal intubation, and administration of chest compressions with or without intravenous medications or volume expansion for those with a persistent heart rate less than 60/min or asystole, despite strategies to achieve effective ventilation (Figure 1).

The 2 vital signs that are used to identify the need for an intervention as well as to assess the response to interventions are heart rate and respirations. Progression down the algorithm should proceed only after successful completion of each step, the most critical being effective ventilation. A period of only approximately 60 seconds after birth is allotted to complete each of the first 2 steps, ie, determination of heart rate and institution of effective ventilation. Subsequent progression to the next step will depend on the heart rate and respiratory response.

Evidence Evaluation

GRADE

The task force performed a detailed systematic review based on the recommendations of the Institute of Medicine of the National Academies⁴ and using the methodological approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.⁵ After identification and prioritization of the questions

Neonatal Resuscitation Algorithm

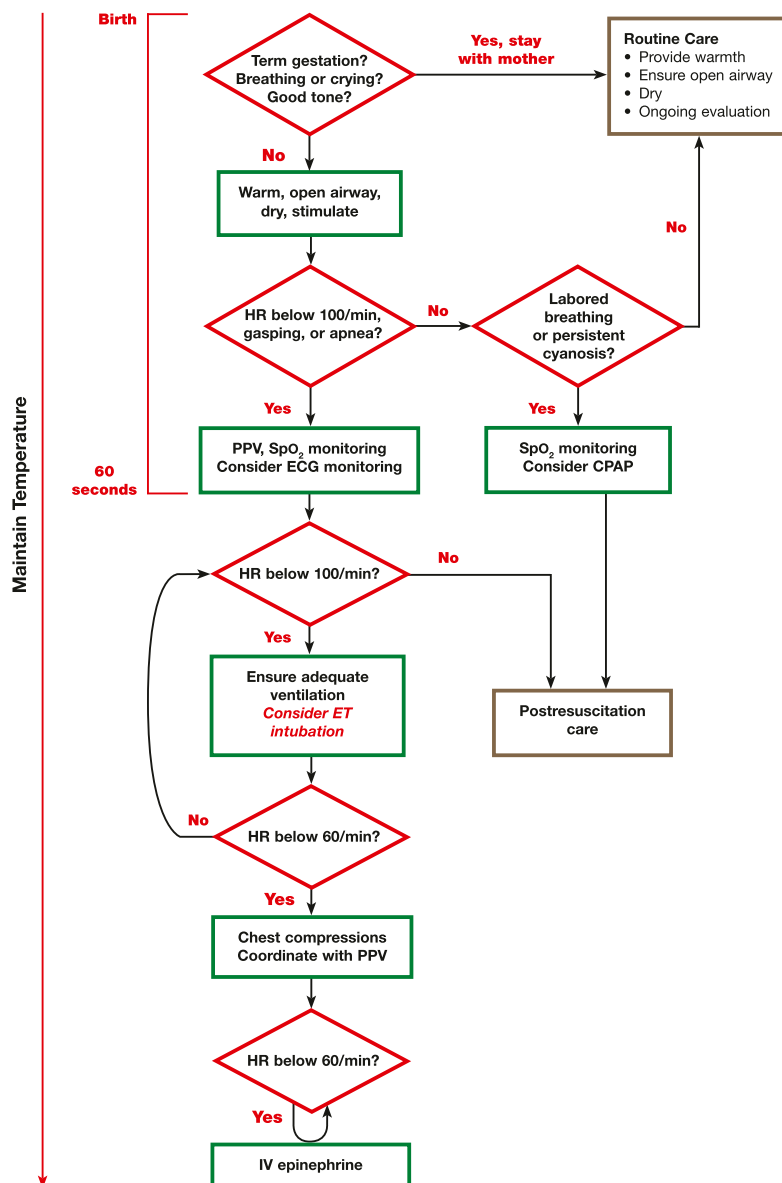


Figure 1
Neonatal Resuscitation Algorithm.

to be addressed (using the PICO [population, intervention, comparator, outcomes] format),⁶ with the assistance of information specialists, a detailed search for relevant articles was performed in each of 3 online databases (PubMed, Embase, and the Cochrane Library).

By using detailed inclusion and exclusion criteria, articles were screened for further evaluation. The reviewers for each question created a reconciled risk

of bias assessment for each of the included studies, using state-of-the-art tools: Cochrane for randomized controlled trials,⁷ Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 for studies of diagnostic accuracy,⁸ and GRADE for observational studies that inform both therapy and prognosis questions.⁹

GRADE is an emerging consensus process that rates quality of evidence and

strength of recommendations along with values and preferences. GRADE evidence profile tables¹⁰ were created to facilitate an evaluation of the evidence in support of each of the critical and important outcomes. The quality of the evidence (or confidence in the estimate of the effect) was categorized as high (where one has high confidence in the estimate of effect as reported in a synthesis of the literature), moderate (where one has moderate confidence, but there may be differences from a further elucidated truth), low (where one has low confidence in the estimate of the effect that may be substantially different from the true effect), or very low (where it is possible that the estimate of the effect is substantially different from the true effect).¹¹ These categorizations were based on the study methodologies and the 5 core GRADE domains of risk of bias, inconsistency, indirectness (ie, the population studied was not the same as that for which the guideline will be used), imprecision of effect estimates, and other considerations (including publication bias).¹² Randomized studies start as high quality but may be downgraded for methodological quality, whereas observational or cohort studies start off as low quality and can be further downgraded or upgraded depending on methodical quality or positive outcome effect.

Guideline users have to determine how much they can trust that a recommendation will produce more favorable rather than unfavorable consequences. The strength of a recommendation reflects a gradient in guidance, with a clearer expectation for adherence with strong recommendations (identified by the words *we recommend*) and lesser insistence in weak recommendations (identified by the words *we suggest*). In addition, the direction of effect may be in favor of or against the recommendation. GRADE points to several factors

that may influence the strength of a recommendation, including the risk-benefit balance, quality of evidence, patient values and preferences, and, finally, costs and resource utilization. If confidence in these values and preferences is high and variability is low, it is more likely that the recommendation will be strong (and vice versa). Recommendations, whether strong or weak, have different implications for patients, healthcare professionals, or healthcare management.

Generation of Topics

After publication of the *2010 International Consensus on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care Science With Treatment Recommendations* (CoSTR),^{13–15} it was apparent that several unclear and contentious delivery room resuscitation issues remained. In 2012, the Neonatal Task Force published an article titled “Neonatal Resuscitation: In Pursuit of Evidence Gaps in Knowledge,”¹⁶ in which the major gaps in knowledge were identified. The following critical randomized studies were proposed with the goal for completion before the ILCOR 2015 International Consensus Conference on CPR and Emergency Cardiovascular Care Science With Treatment Recommendations:

- Prophylactic postdelivery endotracheal suctioning versus no suctioning in a depressed baby with meconium
- Comparison of different saturation percentiles to use for targeting supplementary oxygen delivery in uncompromised and compromised premature infants
- Comparison of prolonged versus conventional inspiratory times to determine if the former is more effective in establishing functional residual capacity (FRC) and increasing the heart rate
- Studies to determine the optimum technique for maintaining the tem-

perature of very low birth weight (VLBW) infants from the time of delivery through admission to intensive care

One small randomized study has addressed the question of prophylactic endotracheal suctioning in the depressed baby with meconium¹⁷ (see NRP 865), and 1 randomized trial of sustained inflation (SI) has recently been published¹⁸ (see NRP 804). Additional studies addressing these critical questions are ongoing but were not available for the 2015 CoSTR review.

To achieve the goal of identifying a series of relevant questions, the Neonatal Task Force group comprising 38 members and representing 13 countries met for the first time in May 2012 in Washington, DC. At that meeting, a series of questions were identified, researched, culled, and eventually refined into 26 questions at subsequent meetings by using the GRADE approach. One additional question, related to the accurate and timely detection of heart rate immediately after birth, was identified in December 2014 as a major gap in knowledge and was introduced as a late-breaking PICO question. The meetings since May 2012 included 3 ILCOR group meetings (in Vienna, October 2012; Melbourne, April 2013; and Banff, April 2014) and neonatal-specific ILCOR meetings (in Denver, CO, May 2013; Washington, DC, December 2013; Vancouver, Canada, May 2014; and Washington, DC, December 2014).

The literature was researched and consensus was reached on the following issues:

- Optimal assessment of heart rate (NRP 898)
- Delayed cord clamping in preterm infants requiring resuscitation (NRP 787)
- Umbilical cord milking (NRP 849)
- Temperature maintenance in the delivery room (NRP 589)

- Maintaining infant temperature during delivery room resuscitation (NRP 599)
- Warming of hypothermic newborns (NRP 858)
- Babies born to mothers who are hypothermic or hyperthermic in labor (NRP 804)
- Maintaining infant temperature during delivery room resuscitation—intervention (NRP 793)
- Continuous positive airway pressure (CPAP) and intermittent positive-pressure ventilation (IPPV) (NRP 590)
- Sustained inflations (NRP 809)
- Outcomes for positive end-expiratory pressure (PEEP) versus no PEEP in the delivery room (NRP 897)
- T-piece resuscitator and self-inflating bag (NRP 870)
- Intubation and tracheal suctioning in nonvigorous infants born through meconium-stained amniotic fluid (MSAF) versus no intubation for tracheal suctioning (NRP 865)
- Oxygen concentration for resuscitating premature newborns (NRP 864)
- 2-Thumb versus 2-finger techniques for chest compression (NRP 605)
- Chest compression ratio (NRP 895)
- Oxygen delivery during CPR—neonatal (NRP 738)
- Laryngeal mask airway (NRP 618)
- Newborn infants who receive PPV for resuscitation, and use of a device to assess respiratory function (NRP 806)
- Use of feedback CPR devices for neonatal cardiac arrest (NRP 862)
- Limited resource—induced hypothermia (NRP 734)
- Delivery room assessment for less than 25 weeks and prognostic score (NRP 805)
- Apgar score of 0 for 10 minutes or greater (NRP 896)
- Predicting death or disability of newborns of greater than 34 weeks based on Apgar and/or absence of breathing (NRP 860)
- Resuscitation training frequency (NRP 859)
- Neonatal resuscitation instructors (NRP 867)

NEONATAL ALGORITHM

There was considerable debate with regard to modifying the algorithm. The first debate related to the necessity of a timeline. Many thought that a 30-second time rule was unreasonable and not evidenced based. On the other hand, because this is a global document, others advocated strongly that a reminder to assess and intervene if necessary, within 60 seconds after birth, should be retained to avoid critical delays in initiation of resuscitation. Thus, more than 95% of newly born infants will start breathing spontaneously or in response to stimulation within approximately 30 seconds.¹ If apnea persists PPV should be initiated within 60 seconds. As a compromise, the 30-second time point has been removed. Given the importance of hypothermia as a predictor of mortality and evidence from multiple studies that moderate hypothermia (temperature less than 36°C) can be avoided with simple intervention strategies, the new algorithm contains a running line reminding providers to maintain thermoregulation throughout the immediate newborn period.

INITIAL ASSESSMENT AND INTERVENTION

ECG/EKG in Comparison to Oximetry or Auscultation for the Detection of Heart Rate (NRP 898)

In babies requiring resuscitation (P), does electrocardiography (ECG/EKG) (I), compared with oximetry or auscultation (C), measure heart rate faster and more accurately (O)?

Introduction

Neonatal resuscitation success has classically been determined by detecting an increase in heart rate through auscultation. Heart rate also determines the need for changing interventions and escalating care. However, recent evidence demonstrates that auscultation of heart rate is inaccurate and pulse oximetry takes several minutes to achieve a signal and also may be inaccurate during the early minutes after birth. This PICO question is intended to review the evidence regarding how best to determine heart rate after birth.

Consensus on Science

For the important outcomes of **fast and accurate measurement of heart rate** in babies requiring resuscitation, we have identified

- Very-low-quality evidence from 5 nonrandomized studies enrolling 213 patients showing a benefit of ECG compared with oximetry^{19–23}
- Very-low-quality evidence from 1 nonrandomized study enrolling 26 patients showing a benefit of ECG compared with auscultation²⁴

The available evidence is from nonrandomized studies, downgraded for indirectness and imprecision.

Treatment Recommendation

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-quality evidence).

Values, Preferences, and Task Force Insights

There was much discussion and heated debate about the use of ECG to determine heart rate. Although the data suggest that the ECG provides a more accurate heart rate in the first 3 minutes, there were no available data to determine how outcomes would change

by acting (or not acting) on the information. Important issues were raised about inappropriate interventions being implemented based on a falsely low heart rate by pulse oximetry or auscultation that might be avoided if the heart rate could be determined by ECG. It was pointed out that pulse oximetry is still very important for the measurement of saturation values to define supplementary oxygen needs. Introducing ECG leads in the delivery room will take time, as will acquiring methods to rapidly apply electrodes. In view of these findings of false-positive readings by conventional means, we have no data on when to advise appropriate actions for bradycardia detected by the conventional measures such as pulse oximetry or auscultation. Some transient bradycardia may be normal and be reflective of timing of cord clamping. More studies are needed.

Knowledge Gaps

- Studies delineating differences in interventions and/or patient outcomes based on ECG versus pulse oximetry measurements
- Studies of heart rate in VLBW infants requiring resuscitation and in relationship to timing of cord clamping
- Improved technology for rapid application of ECG

Delayed Cord Clamping in Preterm Infants Requiring Resuscitation (Intervention) (NRP 787)

In preterm infants, including those who received resuscitation (P), does delayed cord clamping (greater than 30 seconds) (I), compared with immediate cord clamping (C), improve survival, long-term developmental outcome, cardiovascular stability, occurrence of intraventricular hemorrhage (IVH), necrotizing enterocolitis, temperature on admission to a newborn area, and hyperbilirubinemia (O)?

Introduction

In the past 50 years, the umbilical cords of babies born preterm have generally been cut soon after birth, so that the newborns can be transferred immediately to the neonatal team. However, there is recent evidence that a delay of clamping by 30 to 60 seconds after birth results in a smoother transition, particularly if the baby begins breathing before the cord is cut. In both animal and human models, the delay is associated with increased placental transfusion, increased cardiac output, and higher and more stable neonatal blood pressure. There is controversy about how long it is appropriate to delay clamping if the baby is perceived to require resuscitation.

Consensus on Science

For the critical outcome of **infant death**, we identified very-low-quality (downgraded for imprecision and very high risk of bias) evidence from 11 randomized clinical trials enrolling 591 patients showing no benefit to delayed cord clamping (odds ratio [OR], 0.6; 95% confidence interval [CI], 0.26–1.36).^{25–35}

For the critical outcome of **severe IVH**, we identified very-low-quality evidence (downgraded for imprecision and very high risk of bias) from 5 randomized clinical trials enrolling 265 patients showing no benefit to delayed cord clamping (OR, 0.85; 95% CI, 0.20–3.69).^{26,27,31,32}

For the critical outcome of **periventricular hemorrhage (PVH)/IVH**, we identified very-low-quality evidence (downgraded for imprecision and very high risk of bias) from 9 randomized clinical trials enrolling 499 patients showing benefit of delayed cord clamping (OR, 0.49; 95% CI, 0.29–0.82).^{26,27,29–35}

For the critical outcome of **neurodevelopment**, we did not identify any evidence.

For the critical outcome of **cardiovascular stability** as assessed by mean blood pressure at birth, we identified very-low-quality evidence (downgraded for imprecision and very high risk of bias) from 2 randomized clinical trials enrolling 97 patients showing higher blood pressure associated with delayed cord clamping (mean difference [MD], 3.52; 95% CI, 0.6–6.45).^{29,31}

For the critical outcome of **cardiovascular stability** as assessed by mean blood pressure at 4 hours after birth, we identified very-low-quality evidence (downgraded for imprecision and very high risk of bias) from 3 randomized clinical trials enrolling 143 patients showing increased mean blood pressure at 4 hours of age after delayed cord clamping (MD, 2.49; 95% CI, 0.74–4.24).^{25,31,32}

For the critical outcome of **cardiovascular stability** as assessed by blood volume, we identified very-low-quality evidence (downgraded for imprecision and very high risk of bias) from 2 randomized clinical trials enrolling 81 patients showing benefit of delayed cord clamping (MD, 8.25; 95% CI, 4.39–12.11).^{35,36}

For the critical outcome of **temperature**, on admission we identified very-low-quality evidence (downgraded for imprecision and very high risk of bias) from 4 randomized clinical trials enrolling 208 patients showing no statistically significant benefit from delayed cord clamping (MD, 0.1; 95% CI, –0.04 to 0.24).^{29,31,32,34}

For the important outcome of **need for transfusion**, we identified very-low-quality evidence from 7 randomized clinical trials enrolling 398 patients showing less need for transfusion after delayed cord clamping (OR, 0.44; 95% CI, 0.26–0.75).^{28–30,32,34–36}

For the important outcome of **necrotizing enterocolitis**, we identified

very-low-quality evidence (downgraded for imprecision and very high risk of bias) from 5 randomized clinical trials enrolling 241 patients showing lower incidence of necrotizing enterocolitis (OR, 0.3; 95% CI, 0.19–0.8).^{29,31–34}

For the important outcome of **hyperbilirubinemia** and peak bilirubin concentrations (mmol/L), we identified moderate-quality evidence from 6 randomized clinical trials enrolling 280 patients showing higher peak bilirubin value in those neonates with delayed cord clamping (MD, 16.15; 95% CI, 6.13–26.17).^{29–33,35}

For the important outcome of **treated hyperbilirubinemia** (need for phototherapy), we identified low-quality evidence from 1 randomized clinical trial enrolling 143 patients showing no statistically significant difference (relative risk [RR], 1.29; 95% CI, 1.00–1.67).³⁵

Treatment Recommendation

We **suggest** delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence).

There is insufficient evidence to recommend an approach to cord clamping for preterm infants who do receive resuscitation immediately after birth, because many babies who were at high risk of requiring resuscitation were excluded from or withdrawn from the studies.

Values, Preferences, and Task Force Insights

Overall, the quality of evidence for the question was very low. Despite drawing evidence from randomized controlled trials, the small sample size in most trials and the associated imprecision limited the quality of evidence for all outcomes of interest. Although 2 larger observational trials were considered, the quality and size of effect were not sufficient to influence the conclusions. The quality of evidence for necrotizing

enterocolitis and hyperbilirubinemia was limited by inconsistent definitions of the outcome, and inconsistent thresholds for treatment with phototherapy across studies.

- **Balance of consequences** favors delayed cord clamping, as desirable consequences *probably outweigh* undesirable consequences in most settings. The results of randomized controlled trials and nonrandomized observational studies with comparison groups were generally consistent. However, small and sick infants who received immediate resuscitation were generally excluded from the available randomized controlled trials, so data are very limited for this group at highest risk for physiologic instability, complications of prematurity, and mortality who may also realize highest benefit or harm from the intervention.

- **Preferences (parents')** favor delayed clamping, which has received strong popular support through social media and Internet sites. The advantages of delayed cord clamping assume heightened importance in resource-limited settings where specialty care for preterm neonates may be limited. Improving initial cardiovascular stability with maintenance of temperature and lower risk of morbidities such as necrotizing enterocolitis and severe intracranial hemorrhage may offer significant survival advantages, even where neonatal intensive care is not available. In areas where maternal anemia is prevalent, iron supplementation is limited, and a safe blood supply is often unavailable, the reduction in need for transfusion and improved blood volume at birth may have increased significance.

A major debate surrounded the issue as to whether the quality of the studies was

low or very low. Overall, the group thought that downgrading the evidence as suggested by the GRADE tool was not reasonable, given that this was one of the areas with the most randomized trial data. However, eventually based on the GRADE criteria, it was necessary to classify most of the outcomes as very-low-quality evidence. It was noted that the existing studies enrolled very few extremely premature infants and very few who received resuscitation. The group was unanimous in stressing the need for additional research, which parallels a Cochrane review reflecting similar sentiments of a need for more high-quality evidence. Some members questioned how to reconcile with obstetric guidelines, which has an out clause for babies requiring resuscitation.³⁷

Knowledge Gaps

- Results of ongoing large randomized controlled trials
- Comparison of delayed versus immediate cord clamping among preterm infants who receive resuscitation with PPV
- Comparison of delayed cord clamping with cord milking
- Outcome data of high importance, such as long-term neurodevelopment
- Need for resuscitative intervention at delivery
- Hyperbilirubinemia among high-risk populations

Umbilical Cord Milking—Intervention (NRP 849)

In very preterm infants (28 weeks or less) (P), does umbilical cord milking (I), in comparison with immediate umbilical cord clamping (C), affect death, neurodevelopmental outcome at 2 to 3 years, cardiovascular stability, ie, need for pressors, need for fluid bolus, initial mean blood pressure, IVH (any grade,

severe grade), temperature on admission, hematologic indices, (initial hemoglobin, need for transfusion), hyperbilirubinemia, need for phototherapy, or need for exchange transfusion (0)?

Introduction

There is some evidence that “milking” of the umbilical cord from the placental side toward the newborn may have a similar effect to delayed cord clamping (ie, increased placental transfusion, improved cardiac output, and increased neonatal blood pressure). If correct, this would offer a more rapid alternative to delayed clamping of the cord.

Consensus on Science

For the critical outcome of **death**, we found low-quality evidence (downgraded for very serious imprecision) from 3 randomized clinical trials^{38–40} showing that there is no difference in death (OR, 0.76; 95% CI, 0.25–2.29).

For the critical outcome of **cardiovascular stability**, we found low-quality evidence (downgraded for imprecision) from 2 randomized studies^{38,39} showing that the initial mean blood pressure was 5.43 mm Hg higher (range, 1.98–8.87 mm Hg) in the group receiving umbilical cord milking.

For the critical outcome of **IVH**, we found low-quality evidence (downgraded for very serious imprecision) from 2 randomized clinical trials^{38,40} showing a reduction of IVH (all grades: OR, 0.37; 95% CI, 0.18–0.77) but no difference (from 1 randomized clinical trial³⁸ in severe IVH; OR, 0.44; 95% CI, 0.07–2.76) (low-quality evidence, downgraded for very serious imprecision) when umbilical cord milking was performed.

For the critical outcome of **neurologic outcome at 2 to 3 years**, we did not identify any evidence to address this.

For the important outcome of **hematologic indices**, we found low-quality

evidence (downgraded for imprecision) from 2 randomized clinical trials^{38,39} showing that cord milking increased the initial hemoglobin level (MD, 2.27 g/dL; 95% CI, 1.57–2.98 g/dL) and low-quality evidence (downgraded for imprecision) from 3 randomized clinical trials^{38–40} showing that cord milking decreased transfusion (OR, 0.2; 95% CI, 0.09–0.44).

For the important outcome of **temperature**, we found low-quality evidence (downgraded for very serious imprecision) from 1 randomized clinical trial³⁹ showing that the temperature of the milking group was not different on admission.

For the important outcome of **bilirubin** indices, we found low-quality evidence (downgraded for very serious imprecision) showing that the maximum bilirubin measurement (3 randomized clinical trials^{38–40}) and use of phototherapy (1 study⁴⁰) was not different between groups.

Treatment Recommendation

We **suggest against** the routine use of cord milking for infants born at 28 weeks of gestation or less, because there is insufficient published human evidence of benefit. Cord milking may be considered on an individual basis or in a research setting, as it may improve initial mean blood pressure and hematologic indices and reduce intracranial hemorrhage. There is no evidence for improvement in long-term outcomes (weak recommendation, low-quality evidence).

All studies included in this evidence review milked 20 cm of umbilical cord toward the umbilicus 3 times while the infant was held at the level of the introitus or below the level of the placenta before cord clamping.

Values, Preferences, and Task Force Insights

In making this recommendation, we place a higher value on the unknown

safety profile and less value on the simplicity/economy of this intervention. Much of the deliberations focused on the wording of the treatment recommendation. The first recommendation proposed was, “We suggest that cord milking, as opposed to immediate cord clamping, be performed at delivery for VLBW infants.” A second recommendation was, “We suggest that cord milking, as opposed to immediate cord clamping, may be performed at delivery for VLBW but should not be regarded as a standard of care.” A third recommendation was, “We suggest that cord milking, as opposed to immediate cord clamping, may be performed at delivery for VLBW to improve initial mean blood pressure, hematologic indices, and IVH (Grades 1 and 2).” However, concerns were raised related to the absence of evidence pertinent to long-term outcomes and, in particular, neurologic outcome. Moreover, there was serious imprecision in the data. These factors led to the final treatment recommendation.

Knowledge Gaps

- Evidence regarding neurodevelopmental outcomes for cord milking compared with immediate cord clamping is necessary.
- Comparison of delayed cord clamping with cord milking
- Multiple studies of cord milking in this population are under way at this time, and additional data will be available in 2020.

TEMPERATURE

It has been known for more than a century that preterm babies who become hypothermic after birth have a higher mortality than those who remain normothermic.⁴¹ The association between hypothermia and neonatal mortality and morbidity, including

respiratory distress syndrome, metabolic derangements, IVH, and late-onset sepsis, has long been recognized, with premature infants being particularly vulnerable (see below). Specifically, moderate hypothermia (temperature less than 36°C) at birth has been recognized as an independent risk factor for death in premature infants.^{42,43}

These relationships reflect the fact that the premature infant is at very high risk of net heat loss because of a large surface area-to-volume ratio and increased evaporative fluid losses from the skin. Strategies introduced to minimize heat loss include use of occlusive wrapping, exothermic warming mattress, warmed humidified resuscitation gases, polyethylene caps, and increasing delivery room temperature, and have met with varying success. A by-product of these interventions to prevent hypothermia is more-frequent hyperthermia (temperature greater than 37.5°C). Hyperthermia (temperature greater than 37.5°C) also increases the risk for neonatal mortality and morbidity in both term and preterm infants. This section will review the importance of maintaining temperature in a goal range, interventions to minimize heat loss at delivery, how quickly a low temperature should be raised into a normal range, the impact of maternal hyperthermia and hypothermia on the newborn, and strategies to avoid hypothermia in the resource-limited setting.

Temperature Maintenance in the Delivery Room—Prognosis (NRP 589)

In nonasphyxiated babies at birth (P), does maintenance of normothermia (core temperature 36.5°C or greater and 37.5°C or less) from delivery to admission (I), compared with hypothermia (less than 36°C) or hyperthermia (greater than 37.5°C) (C), change survival to hospital discharge,

respiratory distress, survival to admission, hypoglycemia, intracranial hemorrhage, or infection rate (O)?

Consensus on Science

For the critical outcome of **mortality**, there is evidence from 36 observational studies of increased risk of mortality associated with hypothermia at admission^{42–77} (low-quality evidence but upgraded to moderate-quality evidence due to effect size, dose-effect relationship, and single direction of evidence). There is evidence of a dose effect on mortality, suggesting an increased risk of at least 28% for each 1° below 36.5°C body temperature at admission^{42,43} and dose-dependent effect size.^{42,43,48,66} One small randomized clinical trial⁷⁸ (very-low-quality evidence, downgraded for indirectness and serious imprecision) showed a reduction in adverse events, including death, intracranial hemorrhage, necrotizing enterocolitis, and oxygen dependence with improved temperature management, but 3 randomized controlled trials^{79–81} (low-quality evidence, downgraded for indirectness and imprecision) did not show any significant improvement in mortality with significantly improved temperature control. Four observational studies^{60,61,63,82} (very-low-quality evidence, downgraded for indirectness and imprecision) did not find any improvement in mortality with improved admission temperatures, but they were not sufficiently powered for this outcome.

For the critical outcome of **IVH**, 8 observational studies (very-low-quality evidence, downgraded for risk of bias and indirectness) show hypothermia (temperature less than 36°C) in preterm infants is associated with an increased likelihood of developing IVH.^{48,55,66,83–87} Eight observational studies (low-quality, downgraded for indirectness) found no association between hypothermia and IVH.^{43,60,61,88–92}

For the important outcome of **respiratory issues**, there is evidence from 9 observational studies^{44,48,50,67,83,93–96} (low-quality evidence) showing an association between hypothermia and respiratory disease. One large randomized controlled trial⁷⁹ (low-quality evidence, downgraded for imprecision and risk of bias) found a reduction in pulmonary hemorrhage associated with improved admission temperature (OR, 0.57; 95% CI, 0.35–0.94). Eight observational studies (very-low-quality evidence) have shown an improvement in respiratory outcomes after improved admission temperature maintenance.^{44,49,51,63,72,84,93,95} Two of these have shown a decrease in respiratory support with improved temperature maintenance.^{93,96} Two observational studies (very-low-quality evidence, downgraded for indirectness and imprecision) did not show any association.^{43,60}

For the serious outcome of **hypoglycemia**, there were seven observational studies (very-low-quality, downgraded for risk of bias and indirectness) showing a significant association between hypothermia (less than 36°C) and hypoglycemia.^{44,67,70,97–100} Two of these studies, using historical controls, showed improved glycemic control with improved normothermia.^{44,99}

For the serious outcome of **late sepsis**, 2 observational studies (very-low-quality evidence, downgraded for risk of bias and indirectness) indicated an association between hypothermia on admission and late sepsis.^{43,101} One observational study (low-quality, downgraded for risk of bias and indirectness) found no association after multivariate analysis.⁶⁶

For the serious outcome of **survival to admission**, there is no published evidence addressing any effect of delivery room hypothermia upon survival to admission.

For the serious outcome of **admission hyperthermia**, there is no published

evidence about newborn hyperthermia at admission.

Treatment Recommendations

Admission temperature of newly born nonasphyxiated infants is a strong predictor of mortality and morbidity at all gestations. It should be recorded as a predictor of outcomes as well as a quality indicator (strong recommendation, moderate-quality evidence).

We recommend that the temperature of newly born nonasphyxiated infants be maintained between 36.5°C and 37.5°C after birth through admission and stabilization (strong recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

In making these statements, we place a higher value on the strong association of inadvertent hypothermia with mortality, the apparent dose effect, the single direction of the evidence, the universal applicability, and the evidence for intervention improving respiratory outcomes over the lack of modern evidence for intervention changing mortality.

The group thought that this question should change to a prognostic one. A recurring question is whether some of the babies stay cold because of intrinsic factors. However, there are data that hypothermia upon admission impacts mortality through at least the first 6 months. It was suggested that a low temperature may also be related to the quality of care and environment. Most studies reviewed used an axillary temperature but some older studies utilized a rectal temperature. The relative benefits of one over the other were not assessed in this PICO. The task force felt that an axillary temperature should be used in the delivery room but that on admission it should be left to individual regional practice.

Knowledge Gaps

- Further studies are required to find if improved admission temperature improves mortality and other outcomes.

Maintaining Infant Temperature During Delivery Room Resuscitation—Intervention (NRP 599)

Among preterm neonates who are under radiant warmers in the hospital delivery room (P), does increased room temperature, thermal mattress, or another intervention (I), compared with plastic wraps alone (C), reduce hypothermia (less than 36°C) on admission to neonatal intensive care unit (NICU) (O)?

Introduction

A variety of strategies have been suggested to maintain a preterm infant's temperature; it is unknown which of these strategies is/are most effective. This PICO question was intended to identify the strategies and techniques that might be most effective.

Consensus on Science

Thermal Mattress Plus Plastic Wrap Plus Radiant Warmer (I) Versus Plastic Wrap Plus Radiant Warmer

For the critical outcome of **hypothermia** (temperature less than 36.0°C) at NICU admission, we identified low-quality evidence (downgraded for serious risk of bias) from 1 randomized controlled trial¹⁰² enrolling 72 preterm infants of less than 32 weeks of gestation showing no benefit to addition of a thermal mattress to the use of plastic wrap and radiant warmer (RR, 1.89; 95% CI, 0.18–19.95). Four observational studies (low-quality evidence, downgraded for serious risk of bias)^{82,103–105} including 612 patients of less than 32 weeks of gestation showed benefit to the addition of the thermal mattress (OR, 0.27; 95% CI, 0.18–0.42).

For the important outcome of **hyperthermia** (temperature greater than 38.0°C) at admission, we have identified low-quality evidence (downgraded for serious risk of bias) from the same randomized controlled trial¹⁰² and 4 observational studies^{82,103,105,106} including 426 patients showing no harm from the thermal mattress (RR, 3.78; 95% CI, 0.86–16.60 and OR, 6.53; 95% CI, 0.80–53.30).

Environmental Temperature 26°C or Greater Plus Plastic Wrap Plus Radiant Warmer (I) Versus Plastic Wrap Plus Radiant Warmer (C)

For the critical outcome of **hypothermia** (temperature less than 36.0°C) at NICU admission, we identified no studies addressing this intervention alone.

For the important outcome of **hyperthermia** (temperature greater than 38.0°C) at admission, we identified low-quality evidence (downgraded for serious risk of bias) from 1 observational study¹⁰⁷ including 40 patients of less than 29 weeks of gestation showing no harm from increasing the environmental temperature **26°C or greater** (OR, 8.45; 95% CI, 0.37–182.58).

Heated and Humidified Gases Plus Plastic Wrap Plus Radiant Warmer (I) Versus Plastic Wrap Plus Radiant Warmer (C)

For the critical outcome of **hypothermia** (temperature less than 36.0°C) at NICU admission, we identified very-low-quality evidence (downgraded for serious risk of bias) from 1 randomized controlled trial⁷⁸ enrolling 203 patients of less than 32 weeks of gestation showing no benefit (RR, 0.64; 95% CI, 0.31–1.35), and 1 observational study (low-quality evidence)¹⁰⁸ including 112 patients of less than 33 weeks of gestation showing benefit to the use of heated and humidified gases and to the use of plastic wrap and the radiant warmer (OR, 0.20; 95% CI, 0.08–0.47).

For the important outcome of **hyperthermia** (temperature greater than

38.0°C) at admission, we identified low-quality evidence (downgraded for serious risk of bias) from the same observational study¹⁰⁸ showing no harm (OR, not estimable).

Total Body and Head Plastic Wrap Plus Radiant Warmer (I) Versus Body Plastic Wrap Plus Radiant Warmer (C)

For the critical outcome of **hypothermia** (temperature less than 36.0°C) at NICU admission, we identified very-low-quality evidence (downgraded for serious risk of bias) from 1 randomized controlled trial¹⁰⁹ enrolling 100 patients of less than 29 weeks of gestation showing no benefit to the addition of wrapping (RR, 0.60; 95% CI, 0.24–1.53).

For the important outcome of **hyperthermia** (temperature greater than 38.0°C) at admission, we identified low-quality evidence (downgraded for serious risk of bias) from the same randomized controlled trial¹⁰⁹ showing no harm (RR, 0.33; 95% CI, 0.01–7.99).

Combination of Interventions (Environmental Temperature 23°C to 25°C Plus Plastic Wrap Without Drying Plus Cap Plus Thermal Mattress Plus Radiant Warmer) Versus Plastic Wrap Plus Radiant Warmer (C)

For the critical outcome of **hypothermia** (temperature less than 36.0°C) at admission, we identified very-low-quality evidence (downgraded for serious risk of bias) from 4 observational studies^{93,95,96,110} enrolling 9334 patients of less than 35 weeks of gestation showing benefit from using a combination of interventions (ie, environmental temperature 23°C to 25°C plus plastic wrap without drying plus cap plus thermal mattress plus radiant warmer; OR, 0.40; 95% CI, 0.35–0.46).

For the important outcome of **hyperthermia** (temperature greater than 38.0°C) at admission, we have identified low-quality evidence (downgraded for serious risk of bias) from 3 observational studies^{93,95,110} enrolling 8985

patients showing no harm to the combination of interventions (OR, 1.12; 95% CI, 0.82–1.52).

Treatment Recommendations

Among newly born preterm infants of less than 32 weeks of gestation under radiant warmers in the hospital delivery room, we suggest using a combination of interventions, which 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-quality evidence).

We suggest that hyperthermia (greater than 38.0°C) be avoided due to the potential associated risks (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

We place value on the large numbers enrolled in the observational studies and consistent direction of effect.

Because many of the studies used multiple strategies, it was not possible to identify the different specific interventions that are effective in maintaining temperature. There was concern whether the recommendation should be so strong when the CIs for hyperthermia (0.80–53.30) comprising 3 studies are so wide, raising the potential chance for harm. A strong recommendation was made because of the large numbers in the studies and the consistent direction of effect. There was concern about 1 randomized thermal mattress trial, which was stopped for safety issues because of hyperthermia. However, this is the only study that has demonstrated an adverse effect with small numbers, suggesting some unclear negative (possible environmental) effect. In the treatment recommendation, it was suggested to add the words *may include* after the word *combination*.

Knowledge Gaps

- Although a combination of interventions (increasing environmental temperature, warm blankets, thermal mattress, and cap) linked to quality improvement initiatives are effective in reducing hypothermia (less than 36°C) on NICU admission among newly born preterm infants of less than 32 weeks of gestation who are under radiant warmers and plastic wrap, the contribution of each intervention (increasing environmental temperature, thermal mattress, heated and humidified gases, and cap) remains to be established.

Warming of Hypothermic Newborns—Intervention (NRP 858)

In newborns who are hypothermic (temperature less than 36.0°C) on admission (P), does rapid rewarming (I), compared with slow rewarming (C), change mortality rate, short and long-term neurologic outcome, hemorrhage, episodes of apnea and hypoglycemia, or need for respiratory support (O)?

Introduction

Neonates are at high risk for becoming hypothermic during resuscitation. Some early teaching for rewarming these neonates has suggested that slow rewarming is preferable over faster so as to avoid complications such as apnea and arrhythmias. This PICO question is intended to review the recent evidence on this issue.

Consensus on Science

We identified 2 randomized trials^{111,112} and 2 observational studies^{113,114} comparing rapid (greater than 0.5°C/hour) versus slow (less than 0.5°C/hour) rewarming strategies for hypothermic newborns (less than 36.0°C) on admission. All studies were dated (the most recent study

was published 28 years ago) and conducted in different settings (2 in low-resource countries and 2 in high-resource countries); enrolled patients had different baseline characteristics (postnatal age, gestational age, proportion of outborn/inborn, degree of hypothermia). The quality of the studies was very poor in terms of number of enrolled patients, inclusion criteria, randomization methods, study design, and outcome measures.

For the critical outcome of **mortality**, we identified low-quality evidence (downgraded for serious risk of bias) from 1 randomized clinical trial¹¹² including 30 patients showing no benefit (RR, 0.88; 95% CI, 0.36–2.10) and 2 observational studies^{113,114} including 99 patients showing benefit in favor of a rapid rewarming strategy (OR, 0.23; 95% CI, 0.06–0.83).

For the critical outcome of **convulsions/seizures**, we identified very-low-quality evidence (downgraded for serious risk of bias) from 1 randomized clinical trial¹¹² including 30 patients showing no benefit to rapid versus slow rewarming (RR, 0.88; 95% CI, 0.14–5.42).

For the critical outcome of **hemorrhage/pulmonary hemorrhage**, we identified very-low-quality evidence (downgraded for serious risk of bias) from 1 randomized clinical trial¹¹² including 30 patients and 1 observational study¹¹³ including 38 patients showing no benefit to rapid versus slow rewarming (RR, 1.31; 95% CI, 0.26–6.76 and OR, 0.16; 95% CI, 0.02–1.50, respectively).

For the important outcome of **need for respiratory support**, we identified very-low-quality evidence (downgraded for serious risk of bias) from 1 observational study¹¹⁴ including 56 patients showing benefit in a slower over a rapid rewarming strategy (OR, 7.50; 95% CI, 2.14–26.24).

For the important outcome of **episodes of hypoglycemia**, we identified very-

low-quality evidence (downgraded for serious risk of bias and very serious imprecision) from 1 randomized controlled trial¹¹¹ including 36 patients and 1 observational study¹¹⁴ including 56 patients showing no benefit to rapid versus slow rewarming (RR, 0.11; 95% CI, 0.01–1.81 and OR, 0.21; 95% CI, 0.01–4.06, respectively).

For the important outcome of **episodes of apnea**, we identified very-low-quality evidence (downgraded for serious risk of bias and very serious imprecision) from 2 randomized clinical trials^{111,112} including 66 patients showing no benefit to rapid versus slow rewarming (RR, 0.44; 95% CI, 0.04–4.32).

Treatment Recommendation

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

Values, Preferences, and Task Force Insights

It was considered important to distinguish the warming of infants where hypothermia is iatrogenic after birth, which in general is of a short duration, from hypothermia that is therapeutic and has been intentionally induced over 72 hours. The latter rewarming is generally recommended to be slow.

Knowledge Gaps

- Attempts should be made to study a more homogenous patient population with specific inclusion criteria stratified by gestational and postnatal age, severity of hypothermia on admission, and common outcome measures.
- Addressing these factors with attention to power of the study by using a multicenter study design will generate useful data on which

to base decisions on the rewarming strategy for hypothermic newborns.

Babies Born to Mothers Who Are Hypothermic or Hyperthermic in Labor—Prognosis (NRP 804)

In newborn babies (P), does maternal hypothermia or hyperthermia in labor (I), versus normal maternal temperature (C), result in adverse neonatal effects (O)? Outcomes include mortality, neonatal seizures, and adverse neurologic states.

Introduction

There is substantial literature from observational studies indicating an association between maternal hyperthermia and neonatal mortality and morbidity (see NRP 589). However, the mechanisms linking these associations remain unclear. In addition, the impact of maternal hypothermia on neonatal outcome remains unclear. This PICO question attempts to address this issue.

Consensus on Science

Maternal Hyperthermia

For the critical outcome of **mortality**, we identified low-quality evidence from 2 nonrandomized clinical trials (downgraded for risk of bias) showing an increased risk with maternal hyperthermia.^{115,116}

For the important outcome of **neonatal seizures**, we identified low-quality evidence from 7 nonrandomized clinical trials (downgraded for risk of bias) showing an increased risk with maternal hyperthermia.^{115–121}

For the important outcome of **adverse neurologic states** (encephalopathy), we identified low-quality evidence from 4 nonrandomized clinical trials (downgraded for risk of bias) showing an increased risk with maternal hyperthermia.^{122–125}

Maternal Hypothermia

For the critical outcome of **mortality** and the important outcomes of **seizures or adverse neurologic states (encephalopathy)**, we identified very-low-quality evidence from 5 randomized clinical trials (downgraded for very serious indirectness) that showed no significant risk of these outcomes with maternal hypothermia.^{126–130} However, the above studies did not specifically examine these outcomes.

There are no studies of neonatal outcomes after interventions to keep mothers normothermic.

Treatment Recommendations

Although maternal hyperthermia is associated with adverse neonatal outcomes, there is insufficient evidence to make a recommendation regarding the management of maternal hyperthermia. There is insufficient evidence to make a treatment recommendation about maternal hypothermia.

Values, Preferences, and Task Force Insights

There was discussion as to whether this is a prognostic versus a therapeutic question. The worksheet authors used observational studies, because the randomized clinical trials did not focus on the outcomes targeted. There was discussion as to whether it was possible to separate hypothermia from the cause of hypothermia.

Knowledge Gaps

- There are no randomized controlled trials of neonatal outcomes after interventions to keep mothers normothermic.
- Do interventions to achieve normothermia in mothers who are hyperthermic decrease risk of adverse outcomes for newborns? (Lack of randomized clinical trials)

- Do interventions to achieve normothermia in mothers who are hypothermic decrease risk of adverse outcomes for newborns? (Lack of critical/important outcomes)

Maintaining Infant Temperature During Delivery Room Resuscitation—Intervention (NRP 793)

In newborn infants (greater than 30 weeks of gestation) in *low-resource settings* during and/or after resuscitation/stabilization (P), does drying and skin-to-skin contact or covering with plastic (I), compared with drying and no skin-to-skin or use of radiant warmer or incubator (C), change body temperature (O)?

Introduction

The ability to maintain temperature in a resource-limited setting after birth is a significant problem (see NRP 589), with a dose-dependent increase in mortality for temperatures below 36.5°C. Moreover, premature infants demonstrated a 12-fold increase in mortality compared with term babies. Therefore, avoiding hypothermia at birth would seem to be a relatively simple intervention to reduce mortality.

Consensus on Science

Plastic Wraps With or Without Skin Drying and Swaddling Compared With Cot or Crib With or Without Initial Use of Radiant Warmer

For the important outcome of **normothermia or preventing hypothermia** during resuscitation, we could not find any studies reporting on use of plastic bags. During transition (from birth to 1–2 hours after delivery), we identified very-low-quality evidence (downgraded for risk of bias, inconsistency, and imprecision)^{131–133} from 3 randomized clinical trials enrolling 409 newborns of greater than 30 weeks of

gestation, showing either a reduction in incidence of hypothermia with plastic after drying^{131,132} (RR, 0.77; 95% CI, 0.65–0.90) or no difference in temperature¹³³ with plastic with or without drying compared with cot bed or open crib and swaddling with or without initial use of radiant warmer.

Skin-to-Skin Contact Versus Cot or Crib With or Without Use of Radiant Warmer

- During transition (birth to 1–2 hours after delivery), we identified very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 7 randomized clinical trials^{134–140} enrolling 600 newborns of greater than 30 weeks of gestation showing a reduction in the number of babies with hypothermia when nursed with skin-to-skin contact after delivery^{134,136,137,140} or similar body temperatures^{135,138,139} when compared with cot or crib and swaddling with or without initial use of radiant warmer.

Skin-to-Skin Contact Versus Incubator

For the important outcome of **normothermia or preventing hypothermia** during resuscitation, we could not find any studies reporting on skin-to-skin contact. During transition (birth to 1–2 hours after delivery), we identified very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 2 randomized clinical trials^{136,141} enrolling 66 newborns of greater than 30 weeks of gestation showing reduction in incidence of hypothermia by about 90%¹⁴¹ or a 50% reduction in drop in body temperature¹³⁶ with skin-to-skin contact compared with incubator.

Treatment Recommendations

There are no data examining the use of plastic wrap during resuscitation/

stabilization. To maintain body temperature or prevent hypothermia during transition (birth to 1–2 hours of life), we suggest that after a well newborn infant of greater than 30 weeks of gestation has been dried, his or her trunk and limbs may be put in a clean food-grade plastic bag and swaddled compared with open crib or cot and swaddling (weak recommendation, very-low-quality evidence).

There are no data on skin-to-skin contact during resuscitation/stabilization. To maintain normal body temperature or prevent hypothermia during transition (birth to 1–2 hours after delivery), we suggest well newborns of greater than 30 weeks of gestation be nursed with skin-to-skin contact or kangaroo mother care compared with a cot/open crib and swaddling or incubator (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

In making this suggestion on plastic wrap, we considered the decrease in hypothermia with plastic. However, clean plastic may not be available and could be costly, and use of unclean plastic may lead to infections.

In making this suggestion on skin-to-skin contact, we valued the prevention of hypothermia by using a free and effective intervention.

An issue was raised about the quality and the safety of occlusive wrap, and the suggestion was made to include food-grade quality. The question was raised with regard to the availability of thermometers.

Knowledge Gaps

- The feasibility of skin to skin during resuscitation
- Using plastic with or without drying during resuscitation

VENTILATION

The respiratory management of the newly born infant in part depends on whether the infant is making some respiratory effort or not. In the breathing term or preterm infant, application of CPAP may be sufficient to augment endogenous effort. In the absence of respiratory effort, establishment of FRC may be more difficult to establish in some cases. In the term infant, positive inflating pressure may be sufficient to establish FRC, whereas in other cases PEEP and/or an SI may be helpful. In this section, we will review the evidence for the use of CPAP in the spontaneously breathing infant, and the use of SI and/or PEEP in the non-breathing infant. This section will also examine the important question of whether a nonbreathing infant delivered in the presence of MSAF needs to be intubated for suctioning or not. Finally, the starting oxygen concentration in a premature newborn will be reviewed.

CPAP and IPPV—Intervention (NRP 590)

In spontaneously breathing preterm infants with respiratory distress requiring respiratory support in the delivery room (P), does the use of CPAP (I), compared with intubation and IPPV (C), improve outcome (O)?

Introduction

CPAP was introduced to neonatology in the 1970s for treatment of respiratory distress syndrome. However, because of equipment limitations, this treatment modality was not part of the early recommendations for neonatal resuscitation at birth. Over the past decade, the use of CPAP rather than the immediate intubation and ventilation for preterm babies who do not breathe well spontaneously after birth has been explored. Initially, this controversy was also complicated by the common

teaching that babies born very preterm (less than 32 weeks of gestation) should be intubated electively at birth for the purpose of administering surfactant. There was also a concern that the use of CPAP in the delivery room might lead to a higher incidence of pneumothorax. Several randomized controlled studies have tested these concerns, which prompted the following 2 PICO analyses.

Consensus on Science

For the critical outcome of **death or bronchopulmonary dysplasia**, we identified moderate-quality evidence (downgraded for risk of bias) from 3 randomized clinical trials^{142–144} enrolling 2358 preterm infants born at less than 30 weeks of gestation showing potential benefit to starting treatment with CPAP in the first 15 minutes after birth (RR, 0.91; 95% CI, 0.83–1.00).

For the critical outcome of **death**, we identified moderate-quality evidence (downgraded for risk of bias, imprecision) from the same 3 randomized clinical trials^{142–144} showing no benefit to starting treatment with CPAP (RR, 0.82; 95% CI, 0.66–1.03). However, we recognize that while the point estimate would suggest potential for benefit, the confidence intervals cross unity to 1.03, suggesting that the potential for harm is minimal.

For the critical outcome of **bronchopulmonary dysplasia**, we identified moderate-quality evidence (downgraded for indirectness) from the same 3 randomized clinical trials^{142–144} showing no benefit to starting treatment with CPAP (RR, 0.92; 95% CI, 0.82–1.03). However, we recognize that while the point estimate would suggest potential for benefit, the confidence intervals cross unity to 1.03, suggesting that the potential for harm is minimal.

For the critical outcome of **air leak**, we identified very-low-quality evidence (downgraded for inconsistency and very serious imprecision) from the

same 3 randomized clinical trials^{142–144} showing no benefit to starting treatment with CPAP (RR, 1.24; 95% CI, 0.91–1.69).

For the critical outcome of **severe IVH**, we identified very-low-quality evidence (downgraded for inconsistency and serious imprecision) from the same 3 randomized clinical trials^{142–144} showing no benefit to starting treatment with CPAP (RR, 1.09; 95% CI, 0.86–1.39).

For the important outcome of **necrotizing enterocolitis**, we identified moderate-quality evidence (downgraded for imprecision) from the same 3 randomized clinical trials^{142–144} showing no benefit to starting treatment with CPAP (RR, 1.19; 95% CI, 0.92–1.55).

For the important outcome of **severe retinopathy of prematurity**, we identified low-quality evidence (downgraded for very serious imprecision) from 2 randomized clinical trials^{143,144} enrolling 1359 infants showing no benefit to starting treatment with CPAP (RR, 1.03; 95% CI, 0.77–1.39).

Treatment Recommendation

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

Values, Preferences, and Task Force Insights

In making this suggestion, we recognize that the absolute reduction in risk of adverse outcome associated with starting with CPAP is small and that infants recruited to the trials had a high rate of treatment with antenatal steroids but we value the less invasive approach.

CPAP was introduced in the 2010 CoSTR13–15 as an option to be considered for babies who are breathing,

but breathing with difficulty. The previous recommendation had been to simply administer blow-by oxygen. The current PICO question did not address the option of using no support. There was a consensus that, in the absence of contrary evidence, administration of CPAP, with or without supplementary targeted oxygen, is preferable in this situation if resources permit.

Knowledge Gaps

- The balance of risks and benefits of this approach in infants who have not received antenatal steroids is unknown.
- A further trial of CPAP versus intubation and IPPV in high-risk preterm infants at lower gestations is required to determine the risks and benefits more clearly. It is not clear whether there is a significant effect on mortality. The CIs for the other morbidities of prematurity leave open the possibility that any benefit in relation to bronchopulmonary dysplasia might still be balanced by a small increase in risk of severe IVH or necrotizing enterocolitis.
- The utility of using an intubation-surfactant-extubation sequence (INSURE) approach¹⁴⁵ to facilitate early stabilization on CPAP soon after birth has been compared with CPAP alone in at least 2 trials. This should be the subject of a future worksheet.

Ventilation Strategies in the Delivery Room

The most effective method for establishing an FRC in the fluid-filled lung of a newborn who does not breathe spontaneously has been debated for many decades. In the 1980s, Vyas et al¹⁴⁶ suggested a technique of administering an SI of up to 5 seconds in duration. Both standard IPPV with or without

PEEP and inflation breaths up to 3 seconds in duration are currently initial strategies advocated to initiate ventilation (Neonatal Resuscitation Program, European Resuscitation Council). Several recent animal studies have suggested that a longer SI may be beneficial for short-term respiratory outcomes. The following 3 PICO analyses reflect an in-depth analysis of the different strategies that have been suggested for this initial establishment of FRC after birth.

Sustained Inflations—Intervention (NRP 809)

In term and preterm newborn infants who do not establish spontaneous respiration at birth (P), does administration of 1 or more pressure-limited sustained lung inflations (I), compared with intermittent PPV with short inspiratory times (C), change Apgar score at 5 minutes, establishment of FRC, requirement for mechanical ventilation in first 72 hours, time to heart rate greater than 100/min, rate of tracheal intubation, overall mortality (O)?

Consensus on Science

For the critical outcome of need for **mechanical ventilation** in the first 72 hours after birth, low-quality evidence (downgraded for inconsistency, indirectness, and imprecision) from 3 randomized clinical trials enrolling 404 newborns showed significant benefit of sustained lung inflations.^{18,147,148} In addition, very-low-quality evidence (downgraded for variability of interventions in SI and control populations) from 2 cohort studies with a total of 331 patients also showed benefit of sustained lung inflations as compared with intermittent PPV with short inspiratory times.^{18,149} One randomized clinical trial¹⁵¹ was excluded from analysis due to methodological concerns pertaining to differences in the various interventions between the study groups of which sustained lung inflation was merely one.

For the critical outcome of **mortality**, low-quality evidence (downgraded for indirectness and imprecision) from 3 randomized clinical trials enrolling 404 newborns^{18,147,149} and very-low-quality evidence (downgraded for variability of interventions in sustained lung inflation and control populations) from 2 cohort studies with a total of 331 patients showed no benefit as compared with IPPV with short inspiratory times.^{18,147,149}

For the critical outcome of **bronchopulmonary dysplasia**, low-quality evidence (downgraded for inconsistency, indirectness, and imprecision) from 3 randomized clinical trials enrolling 404 patients showed no benefit.^{18,147,149} Very-low-quality evidence (downgraded for variability of interventions in SI and control populations) from 2 cohort studies with a total of 331 patients showed significant benefit of sustained lung inflations as compared with IPPV with short inspiratory times.^{18,149}

For the critical outcome of **air leak**, low-quality evidence (downgraded for inconsistency, indirectness, and imprecision) from 3 randomized clinical trials enrolling 404 newborns^{18,147,148} and very-low-quality evidence (downgraded for variability of interventions in SI and control populations) from 2 cohort studies with a total of 331 patients showed no effect of sustained lung inflation as compared with IPPV with short inspiratory times.^{147,148}

For the important outcome of **Apgar score**, there was no difference between groups in any studies reviewed.^{18,147,148,149}

For the important outcome of **need for intubation**, very-low-quality evidence (downgraded for lack of controls) from 1 cohort study¹⁸ showed that the need in the delivery room was significantly lower in infants who received an SI compared with conventional management.

For the important outcome of **heart rate greater than 100/min**, no evidence was found.

For the important outcome of **establishment of FRC**, no evidence was found.

For the important outcome of **Fio₂ in the delivery room**, no evidence was found.

For the important outcome of **chest compressions in the delivery room**, no evidence was found.

Additional comments:

- No human studies evaluated time to heart rate greater than 100/min, establishment of FRC, Fio₂ in the delivery room, or need for chest compressions in the delivery room.
- In a small case series of 9 asphyxiated term infants (very-low-quality evidence), a prolonged initial inflation of 5 seconds produced a 2-fold increase in FRC compared with historic controls.¹⁴⁶
- Comparison of all studies (randomized clinical trials and cohort) was compromised due to the heterogeneity of methodology, ie, wide differences in duration of the initial SI (5–20 seconds) as well as the peak inspiratory pressure (20–30 cm H₂O) and use of a variety of interface devices to deliver the SI (endotracheal tube, face mask, or nasopharyngeal tube). Three studies repeated the initial sustained lung inflation once,^{18,149,150} 1 at a higher positive inflating pressure,¹⁸ whereas 1 study repeated the SI twice with increasing positive inflating pressure.¹⁴⁸
- No studies compared the efficacy of a single SI with multiple SIs.
- Animal studies of the effects of SI on alveolar recruitment have shown in lambs¹⁵¹ and preterm rabbits¹⁵² more uniform lung inflation and better lung compliance, if animals received an SI before initiation of mechanical ventilation.

However, a study by Klopping-Ketelaars¹⁵³ showed no benefit after an initial SI in preterm lambs, and another study showed that stepwise increases in PEEP resulted in better overall lung mechanics than treatment with an initial SI.¹⁵⁴

Treatment Recommendation

We **suggest against** the routine use of initial SI (greater than 5 seconds duration) for preterm infants without spontaneous respirations immediately after birth, but an SI may be considered in individual clinical circumstances or research settings (weak recommendation, low-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation, and in the absence of long-term benefits, we place a higher value on the negative aspect involving lack of clarity as to how to administer sustained lung inflations versus the positive findings of a reduced need for intubation at 72 hours.

Although the studies reviewed showed that administration of an SI reduced the need for mechanical ventilation in the first 72 hours of life, the use of SI did not change the incidence of important long-term outcomes related to lung function, including risk of bronchopulmonary dysplasia or overall mortality. Studies thus far are likely underpowered for these outcomes.

There was much debate about the use of SI. The methods used in delivering SI varied among studies. It was stressed that different devices varied in their ability to generate pharyngeal pressures. Moreover, a recent animal study suggests that there may be unintended glottis closure associated with SI. There was also concern that the current wording of the treatment recommendation may be viewed by some as limiting the potential for future clinical studies.

Evidence evaluators were asked to decide whether to include the te Pas article.¹⁵⁵ The decision was made to exclude it because of multiple confounding interventions. It was thought that more detail in the consensus on science was needed to reflect that studies used SI ranging from 5 to 25 seconds. There was debate about the use of the wording *suggest against*. Several members were in favor of using this term, because there is insufficient evidence regarding how to administer sustained lung inflation, how many such breaths should be applied, or whether it should be used with or without PEEP. It is difficult to extrapolate from animal data, because the animals in the studies were non-breathing and had tracheostomies, so that the anatomy, physics, and physiology are different. Although there was consensus agreement on the current wording, it was noted that individual councils may choose to interpret the recommendations differently.

Knowledge Gaps

- The duration of an SI, the appropriate peak initial inflation pressure, the number of SIs to be administered, and an early measure of response remain unclear.
- Further studies are essential to determine the optimal pressure and duration of SI that would allow the establishment of FRC while minimizing the risk of barotrauma in the newly born infant and long-term morbidity.

Outcomes for PEEP Versus No PEEP in the Delivery Room—Intervention (NRP 897)

In preterm/term newborn infants who do not establish respiration at birth (P), does the use of PEEP as part of the initial ventilation strategy (I), compared with no PEEP (C), improve Apgar score at

5 minutes, intubation in the delivery room, chest compressions in the delivery room, heart rate greater than 100/min by 2 minutes of life, time for heart rate to rise above 100/min, air leaks, oxygen saturation/oxygenation, Fio_2 in the delivery room, mechanical ventilation in the first 72 hours, bronchopulmonary dysplasia, survival to discharge (O)?

Introduction

In the 2010 CoSTR, new recommendations were introduced regarding the use of CPAP for babies exhibiting breathing difficulty and for using PEEP whenever IPPV was required. But problems have continued because of an inability of self-inflating bags to reliably deliver PEEP, and self-inflating bags are the most common devices used for neonatal resuscitation worldwide. This PICO question and the one immediately following (NRP 870) were constructed to examine the value of using one device over another and the need for PEEP when administering IPPV during resuscitation.

Consensus on Science

For the critical outcome of **mortality before discharge**, we identified low-quality evidence from 2 randomized trials of 596 preterm newborns showing no benefit (RR, 0.616; 95% CI, 0.274–1.382) to providing PEEP compared with no PEEP (downgraded for serious imprecision and risk of bias).^{156,157}

For the critical outcome of **chronic lung disease**, we identified moderate-quality evidence from 2 randomized trials of 596 preterm newborns showing no benefit (RR, 1.153; 95% CI, 0.711–1.871) to providing PEEP as compared with no PEEP (downgraded for imprecision and risk of bias).^{156,157}

For the critical outcome of **need for cardiac drugs or chest compressions in the delivery room**, we identified low-quality evidence from 2

randomized trials of 596 preterm newborns showing no benefit (RR, 1.468; 95% CI, 0.550–3.917) to providing PEEP as compared with no PEEP^{156,157} (downgraded for imprecision and risk of bias).

For the important outcome of **oxygen saturation at 5 minutes after birth**, we identified moderate-quality evidence from 1 randomized trial of 80 preterm newborns showing no benefit ($P=0.55$) to providing PEEP (median Spo_2 , 49%; interquartile range [IQR], 25%–90%) versus not providing PEEP (median Spo_2 , 59%; IQR, 33%–66%) (downgraded for imprecision and risk of bias).¹⁵⁶

For the important outcome of **maximum concentration of oxygen used during resuscitation**, we identified low-quality evidence from 1 randomized trial of 516 preterm newborns showing moderate benefit ($P=0.005$) to providing PEEP (mean, 48%; standard deviation [SD], 0.2) versus not providing PEEP (mean, 53%; SD, 0.2).¹⁵⁷

For the important outcome of **heart rate greater than 100/min at 2 minutes of age**, we identified low-quality evidence from 1 randomized trial of 516 preterm newborns showing no benefit to providing PEEP versus not providing PEEP (RR, 1.656; 95% CI, 0.938–2.923) (downgraded for imprecision and risk of bias).¹⁵⁷

For the important outcome of **time for heart rate to rise to greater than 100/min**, we identified moderate-quality evidence from 1 randomized trial of 516 preterm newborns showing no benefit to providing PEEP (median, 1 minute; IQR, 0.5–1.8) versus not providing PEEP (median, 1 minute; IQR, 0.5–1.9) (downgraded for imprecision and risk of bias).¹⁵⁷

For the important outcome of **need for intubation in the delivery room**, we identified moderate-quality evidence from 2 randomized trials of 596

preterm newborns showing no benefit (RR, 1.208; 95% CI, 0.907–1.609) to providing PEEP (downgraded for imprecision and risk of bias)^{156,157} versus not providing PEEP.

For the important outcome of **need for mechanical ventilation in the first 72 hours**, we identified low-quality evidence from 1 randomized trial of 80 preterm newborns showing no benefit (RR, 0.317; 95% CI, 0.093–1.086) to providing PEEP (downgraded for imprecision and risk of bias) versus not providing PEEP. We identified only 1 randomized clinical trial that included term infants,¹⁵⁷ which provided insufficient data to address this question as a secondary outcome measure in a subgroup analysis (very-low-quality evidence, downgraded for serious imprecision and risk of bias).

For the important outcome of **pulmonary air leaks**, we identified low-quality evidence from 2 randomized trials of 596 preterm newborns showing no benefit (RR, 1.401; 95% CI, 0.414–4.735) to providing PEEP (downgraded for imprecision and risk of bias)^{156,157} versus not providing PEEP.

For the important outcome of **Apgar score less than 6 at 5 minutes**, we identified moderate-quality evidence from 1 randomized trial of 516 preterm newborns showing no benefit to providing PEEP (RR, 0.813; 95% CI, 0.472–1.402) (downgraded for imprecision and risk of bias)¹⁵⁷ versus not providing PEEP.

For the less-important outcome of **Apgar score at 5 minutes**, we identified moderate-quality evidence from 1 randomized trial of 80 preterm newborns showing no benefit ($P=0.18$) to providing PEEP (median, 7; IQR, 6–8) versus no PEEP (median, 7; IQR, 6–9) (downgraded for imprecision and risk of bias).¹⁵⁶

Treatment Recommendations

We suggest using PEEP ventilation for premature newborns during delivery

room resuscitation (weak recommendation, low-quality evidence).

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

Values, Preferences, and Task Force Insights

In making this suggestion, we are considering the small reduction in maximum oxygen concentration needed during resuscitation with 5 cm H₂O PEEP compared with those not receiving PEEP shown in 1 human study, and considering the evidence from animal studies (see NRP 809). Interpretation of human studies is further complicated by varying interfaces (eg, face mask versus endotracheal tube) and methods of generating PEEP (eg, self-inflating bags with PEEP valve versus T-piece resuscitator).

Only 1 study was available to indirectly address the specific PICO question,¹⁵⁷ where a subgroup comparison was applied. Good animal studies are available but are classified as low levels of evidence from the point of applicability due to indirectness (see NRP 809). There was concern that the evidence based on the GRADE criteria was regarded as low quality. There was a major struggle to come up with a recommendation when the evidence was weak. The only positive effect found was a 5% change in Fio₂ (see comments after NRP 870).

Knowledge Gaps

- Properly powered, well-designed randomized trials specifically addressing important outcomes for the effects of PEEP in the delivery room are necessary.
- It remains unclear as to the optimal level of PEEP to use.
- The question of static PEEP versus dynamic PEEP needs to be delineated.

- Differential effects of PEEP at different gestational ages and for different pathologies remain to be determined.

T-Piece Resuscitator and Self-Inflating Bag—Intervention (NRP 870)

In newborns (preterm and term) receiving ventilation (PPV) during resuscitation (P), does using a T-piece resuscitator with PEEP (I), compared with using a self-inflating bag without PEEP (C), achieve spontaneous breathing sooner and/or reduce the incidence of pneumothorax, bronchopulmonary dysplasia, and mortality (O)?

Introduction

The T-piece resuscitator has replaced the self-inflating and flow-inflating bag in many institutions. One major reason for this change has been the inability of the self-inflating bag to deliver either CPAP or PEEP reliably. Advantages of the T-piece include ease of use and ability to deliver CPAP, PEEP, and/or IPPV. However, it also requires a pressurized-gas source to drive the device. This PICO question is intended to review the evidence of the utility of self-inflating bags versus T-piece resuscitators.

Consensus on Science

For the following consensus on science statements, the analysis is based on all patients ($n=80$) from 1 study¹⁵⁶ and from a subgroup analysis ($n=453$) in a second study.¹⁵⁷

For the critical outcome of **death before discharge**, we identified low-quality evidence (downgraded for risk of bias and imprecision) from 2 randomized clinical trials^{156,157} enrolling 532 patients showing no benefit to the use of a T-piece resuscitator as compared with a self-inflating bag (OR, 0.68; 95% CI, 0.31–1.56).

For the critical outcome of **bronchopulmonary dysplasia**, which was only

assessed for infants of less than 1500 g, we identified low-quality evidence (downgraded for risk of bias and imprecision) from 2 randomized clinical trials^{156,157} enrolling 151 patients showing no benefit to the use T-piece resuscitator as compared with self-inflating bag (OR, 0.92; 95% CI, 0.59–1.43).

For the critical outcome of **air leaks**, we identified low-quality evidence (downgraded for risk of bias and imprecision) from 2 randomized controlled trials^{156,157} enrolling 532 patients showing no benefit to the use of T-piece resuscitator as compared with self-inflating bag (OR, 1.72; 95% CI, 0.51–5.78).

For the important outcome of **achieving spontaneous breathing or reducing intubation in delivery room**, we identified very-low-quality evidence (downgraded for risk of bias, imprecision, and inconsistency) from 2 randomized clinical trials^{156,157} enrolling 532 patients showing no benefit to the use of T-piece resuscitator as compared with self-inflating bag (OR, 0.80; 95% CI, 0.59–1.07).

Treatment Recommendation

There is insufficient evidence, so the recommendation of one device over another would be purely speculative because the confidence in effect estimates is so low.

Values, Preferences, and Task Force Insights

The current studies suggest a benefit to using PEEP to assist establishment of an FRC during transition of the fluid-filled lung to an air-breathing organ. However, the evidence to date is not sufficiently compelling to recommend against using a self-inflating bag (in which reliable administration of PEEP is not achievable with current devices) during neonatal resuscitation, particularly in regions where pressurized

gases are not readily available. PEEP is recommended when the facilities and equipment permit it to be given reliably (approximately 5 cm H₂O).

Knowledge Gaps

- One cluster randomized controlled trial¹⁵⁷ showed benefit of using T-piece resuscitator for achieving spontaneous breathing in the late preterm (mean gestational age 36 weeks) population. Further research in this population would be important.
- There are no studies comparing the flow-inflating bag to either the self-inflating bag or the T-piece resuscitator (with or without PEEP) for neonatal resuscitation. Theoretically, the flow-inflating bag should be similar to the T-piece resuscitator, although ease of use may prove it to be less effective.
- Studies comparing the flow-inflating bag to the other 2 devices would be helpful.

Intubation and Tracheal Suctioning in Nonvigorous Infants Born Though MSAF Versus No Intubation for Tracheal Suctioning—Intervention (NRP 865)

In nonvigorous infants at birth born through MSAF (P), does tracheal intubation for suctioning (I), compared with no tracheal intubation (C), reduce meconium syndrome or prevent death (O)?

Introduction

For more than 30 years, it has been recommended that newborns with MSAF should receive endotracheal intubation, with tracheal suctioning using the endotracheal tube as a suction device. Approximately 15 years ago, as a result of a multicenter randomized clinical trial, the recommendation was

restricted to babies who appeared to have respiratory compromise at birth (ie, were nonvigorous). It remains controversial as to whether even nonvigorous babies benefit from this procedure. This PICO question is intended to address this issue.

Consensus on Science

For the critical outcome of **mortality and/or meconium aspiration syndrome (MAS)**, we identified 1 randomized study involving 122 infants (low-quality evidence, downgraded for risk of bias and imprecision)¹⁷ comparing tracheal intubation for suctioning versus no tracheal intubation for suctioning in nonvigorous infants showing no benefit to suctioning in either reduced mortality and/or MAS.

For the critical outcome of **mortality and/or MAS**, we identified very-low-quality evidence from 3 studies^{158–160} including 12 389 MSAF infants showing higher incidence of MAS in depressed infants (268/1022, 26%) who had tracheal intubation for suctioning compared with vigorous infants (34/11 367, 0.3%) who were not intubated (downgraded for indirectness).

For the critical outcome of **mortality and/or MAS**, we identified evidence from 7 very-low-quality observational studies^{161–167} demonstrating improved survival and lower incidence of MAS when infants (including depressed and/or vigorous infants) born through MSAF were intubated for tracheal suctioning (downgraded for indirectness and inconsistency).

For the critical outcome of **mortality and/or MAS**, we identified evidence from 9 very-low-quality observational studies^{158–160,168–173} demonstrating no improvement in survival and/or incidence of MAS (including depressed and/or vigorous infants) when infants born through MSAF were intubated for tracheal suctioning (downgraded for indirectness).

Treatment Recommendation

There is insufficient published human evidence to suggest routine tracheal intubation for suctioning of meconium in nonvigorous infants born through MSAF as opposed to no tracheal intubation for suctioning.

Values, Preferences, and Task Force Insights

In making this suggestion, we place value on both harm avoidance (delays in providing bag-mask ventilation, potential harm of the procedure) and the unknown benefit of the intervention of routine tracheal intubation and suctioning.

Routine suctioning of nonvigorous infants is more likely to result in delays in initiating ventilation, especially where the provider is unable to promptly intubate the infant or suction attempts are repeated. In the absence of evidence of benefit for suctioning, the emphasis should be on initiating ventilation within the first minute of life in nonbreathing or ineffectively breathing infants.

Much of the deliberations focused on the wording of the treatment recommendation. There were 3 different treatment recommendation options. First “We suggest against the routine intubation of nonvigorous infants born through MSAF.” Second “We suggest that routine tracheal intubation for suctioning of meconium in nonvigorous infants should not be considered as a standard of care but may be considered a reasonable alternative to no tracheal intubation in some settings.” Third “We suggest that routine tracheal intubation for suctioning of meconium in nonvigorous infants should not be considered as a standard of care but may be considered a reasonable alternative to no tracheal intubation if a meconium plug is suspected.” There was concern that the legal profession could misinterpret the term *standard of care*.

Consensus was reached on the final treatment recommendation.

Knowledge Gaps

- Tracheal intubation or no tracheal intubation for suctioning in nonvigorous infants: Is there a benefit or harm?

Oxygen Concentration for Resuscitating Premature Newborns—Intervention (NRP 864)

Among preterm newborns (less than 37 weeks of gestation) who receive PPV in the delivery room (P), does the use of high O₂ (50%–100%) as the ventilation gas (I), compared with low concentrations of O₂ (21%–30%) (C), decrease mortality, decrease bronchopulmonary dysplasia, decrease retinopathy, decrease IVH (O)?

Introduction

The fact that high oxygen concentrations can be toxic to the newly born lungs has been recognized in all CoSTR statements since 2000. The original studies examined only 21% oxygen versus 100% and led to a recommendation that blended oxygen be used to titrate the concentration to achieve an oxygen saturation that is reflective of what healthy babies born at term experience (ie, targeted saturation). There has been an ongoing controversy as to what the initial oxygen concentration should be. Babies born at term should be started in air (21%), but there has been uncertainty as to whether the preterm baby should be started in a high concentration (50%–100%) versus low concentration (21%–30%) of oxygen while the pulse oximetry is being attached. This PICO question was intended to examine only the starting concentration of administered oxygen, not the targets.

Consensus on Science

For the critical outcome of **mortality before discharge**, we found moderate-

quality evidence from 7 randomized clinical trials enrolling 607 subjects showing no benefit to beginning resuscitation with high-oxygen as compared with low-oxygen concentration (RR, 1.48; 95% CI, 0.8–2.73). The quality of evidence was downgraded for imprecision.^{174–180} When limited to randomized clinical trials with concealed allocation and oxygen targeting as a coin-tervention, we found moderate-quality evidence from 5 trials enrolling 468 subjects showing no benefit to beginning resuscitation with a high-oxygen concentration as compared with low-oxygen concentration (RR, 1.33; 95% CI, 0.68–2.62). The quality of evidence was downgraded for imprecision.^{175,177–180} We found very-low-quality evidence from 1 cohort study including 125 subjects showing no benefit to beginning resuscitation with high-oxygen as compared with low-oxygen concentration (RR, 1.31; 95% CI, 0.41–4.24). The quality of evidence was downgraded for serious imprecision.¹⁸¹

For the critical outcome of **bronchopulmonary dysplasia**, we found low-quality evidence from 5 randomized trials enrolling 502 subjects showing no benefit to beginning resuscitation with a high-oxygen as compared with low-oxygen concentration (RR, 1.08; 95% CI, 0.59–1.98). The quality of evidence was downgraded for inconsistency and imprecision.^{175,177–180}

For the critical outcome of **intra-ventricular hemorrhage**, we found moderate-quality evidence from 4 randomized clinical trials enrolling 400 subjects showing no benefit to beginning resuscitation with a high-oxygen as compared with low-oxygen concentration (RR, 0.90; 95% CI, 0.47–1.72). The quality of evidence was downgraded for imprecision.^{175,178–180}

For the important outcome of **retinopathy of prematurity**, we found moderate-quality evidence from 3 randomized trials enrolling 359 subjects

showing no benefit to beginning resuscitation with a high- as compared with low-oxygen concentration (RR, 1.28; 95% CI, 0.59–2.77). The quality of evidence was downgraded for imprecision.^{175,178,179}

Treatment Recommendations

We **recommend against** initiating resuscitation of preterm newborns (less than 35 weeks of gestation) with high supplementary oxygen concentrations (65%–100%).

We **recommend initiating resuscitation** with a low-oxygen concentration (21%–30%) (strong recommendation, moderate-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation, we place value on not exposing preterm newborns to additional oxygen without proven benefit for critical or important outcomes. Our preference for each outcome, therefore, was to describe the risk of high-oxygen relative to low-oxygen concentration. In all studies, irrespective of whether air or high oxygen including 100% was used to initiate resuscitation, by the time of stabilization most infants were in approximately 30% oxygen. We recognize that all but 1 included study allowed adjustment of oxygen concentration based on pulse oximetry and/or heart rate response.

Concerns were expressed about the practical implications of recommending separate and simultaneous monitoring of both heart rate and oxygen saturation, although accurate measurements of both variables are important (see NRP 898). The chosen range for the low oxygen starting point (21%–30%) was also questioned, but the available articles defined it. Whether the high oxygen should be greater than 60% was also discussed.

Knowledge Gaps

- The most appropriate time-specific oxygen targets for premature newborns need to be defined.
- Neurodevelopmental outcomes for preterm newborns resuscitated with low- and high-oxygen concentrations need to be determined.

CIRCULATORY SUPPORT

Circulatory support focused on the most effective method of delivering chest compressions and included comparison of the 2-thumb versus the 2-finger techniques as well as comparing various compression-to-ventilation ratios. During the evidence evaluation in 2010, it was decided to continue recommending a chest compression-to-ventilation ratio of 3:1 as opposed to 15:2 or 30:2, predominantly because profound bradycardia or asystole in the newly born period is invariably secondary to an asphyxial rather than a primary cardiac event. Evidence in this review was sought to determine whether there was any recent evidence to change this recommendation. Moreover, factors important to the ergonomics of CPR for enhancing blood flow during chest compressions were identified. The evidence below summarizes these findings.

2-Thumb Versus 2-Finger Techniques for Chest Compression—Intervention (NRP 605)

In neonates receiving cardiac compressions (P), does the use of a 2-thumb technique (I), compared with a 2-finger technique (C), result in return of spontaneous circulation (ROSC), improved neurologic outcomes, improved survival, improved perfusion and gas exchange during CPR, and decreased compressor fatigue (O)?

Introduction

Two different techniques for administering chest compressions during re-

suscitation of neonates have been suggested: 2 thumbs, with fingers surrounding the lateral and posterior chest, versus 2 fingers placed vertically on the lower sternum. This PICO question is intended to evaluate which technique is preferable.

Consensus on Science

For the critical outcomes of **time to ROSC, survival rates, or neurologic injury**, we found no data.

For the critical outcome of **improved perfusion and gas exchange during CPR**, we identified low-quality evidence from 9 randomized controlled trials (downgraded for indirectness and imprecision)^{182–190} and 6 nonrandomized controlled trials (downgraded for indirectness, imprecision, and high risk of bias)^{191–196} identifying higher blood pressure generation with the 2-thumb versus the 2-finger method.

For the important outcome of **compressor fatigue**, we identified low-quality evidence from 4 randomized controlled trials (downgraded for indirectness and imprecision), with 2^{183,197} identifying less fatigue with the 2-thumb versus the 2-finger technique, and 2 studies finding no difference.^{189,198}

New compression methods:

- **Thumb and index finger (TIF)**¹⁹⁹ compared the new method versus the 2-thumb and 2-finger methods on manikins. Cardiac compressions lasted for only 5 minutes while recording rate, hand location, depth, incomplete recoil, excessive depth, and error rate during CPR. Two-thumb and TIF had less decay in “suitable chest compressions” over the 5 minutes compared with the 2-finger method.
- **Adhesive glove**²⁰⁰ compared using the adhesive glove with conventional CPR in 4 groups, including

an infant group in a manikin model. The 2-thumb method was used as standard in the infant group versus adhesive 2-thumb method. The theory is that the glove enables active compression-decompression. Rate, compression, and decompression depth were measured. No differences in fatigue variables were found amongst groups. Results showed more active decompression with the adhesive glove group.

Summary: No evidence was found supporting the new thumb and index finger technique as superior to the 2-thumb method. The adhesive glove enhanced active decompression but did not reduce fatigue.

Other issues:

- **Does the CPR technique cause fractures?** Franke²⁰¹ performed a 10-year retrospective survey to determine whether the 2-thumb technique causes rib fractures. All infants received CPR plus chest x-rays. Median age was 9 days.

Summary: There was no evidence of rib fractures in any case.

- **Best location on the sternum:** Using 4 assessment methods over a wide age range of infants,²⁰² it was confirmed that the heart lies under the lower third of the sternum. In addition, blood pressure readings were higher when cardiac compressions were applied to the lower versus the middle third of the sternum. Use of the infant computed tomography (CT) scan data (mean age, 4.4 months) and adult thumb side-by-side measurements on manikins²⁰³ confirmed that the left ventricle lies mostly under the lower quarter of the sternum. No functional data were collected to confirm better outcomes if compressions focused

on that area. An assumption was made that the lower third of the sternum was the best position for compressions.²⁰⁴

- **Term and preterm babies:** Correct positioning on the chest was determined to be much better with the 2-thumb method in both groups of babies, although incorrect placements were found for both techniques in infants less than 1500 g. Chest x-ray analysis of term and preterm babies²⁰⁵ found the heart to be under the lower third of the sternum. Chest CT scans of infants (mean age, 4.7 months), compared with adult thumb measurements on a manikin, comparing the 2-thumb method side by side or superimposed,²⁰⁶ demonstrated that the side-by-side method increases the likelihood of other organs (lungs and liver) being under the points of compressions application. A manikin study looked at fatigue levels with the 2-thumb technique, comparing side-by-side or superimposed thumb position²⁰⁷ demonstrated that the superimposed thumb technique generated higher simulated blood pressure and pulse pressure but had a higher fatigue-rating score. Physiologic indices of fatigue showed no difference between groups. CT scans of the chest to compare thumb (side-by-side)/fingers measurements placed on manikins were conducted to determine which method avoided compressing other structures when using the lower third of the sternum.²⁰⁸ Both methods compress other structures, but the 2-thumb method (side-by-side) performs better than the two finger method. The accuracy of using the nipple line to the xiphisternum landmarks for 2-finger chest compression was examined by Clem-

ents.²⁰⁹ They concluded that this method could result in abdomen and xiphisternum compression in all infants and suggested an alternate method of determining position.

Summary: The lower one third of the sternum remains the best location to press over the newborn heart. Superimposed thumbs may be the better technique.

Treatment Recommendations

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

We suggest that chest compressions should be delivered over the lower third of the sternum (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

None are noted.

Knowledge Gaps

- No studies of any kind regarding the most critical outcomes were available.
- No data from good transitional models were found.
- There are very limited human neonatal data.

Chest Compression Ratio—Intervention (NRP 895)

In neonates receiving cardiac compressions (P), do other ratios (5:1, 9:3, 15:2, synchronous, etc) (I), compared with 3:1 compressions to ventilations (C), increase survival rates, improve neurologic outcomes, improve perfusion and gas exchange during CPR, decrease time to ROSC, decrease tissue injury, or decrease compressor fatigue (O)?

Introduction

Chest compressions administered in a ratio of 3 compressions to 1 ventilation have been recommended for resuscitation of neonates at birth. The concept has been that newborns are born with lungs filled with fluid, much of which is absorbed directly across the alveolar membrane with the first few breaths. If a newborn is compromised sufficiently to prevent spontaneous breathing, resulting in bradycardia or cardiac arrest, successful resuscitation must achieve adequate lung aeration and ventilation to reverse an asphyxial pathophysiology. Thus, the focus of newborn resuscitation efforts must be primarily aimed at establishing ventilation first and cardiac support second. This PICO question is meant to identify which compression-to-ventilation ratio will be most effective at achieving this.

Consensus on Science

Animal studies demonstrate no advantage to higher compression-to-ventilation ratios (very-low-quality evidence, downgraded for potential bias, indirectness, and imprecision) regarding

- **Short-term survival** (2 randomized controlled trials including 54 pigs)^{210,211}
- **Gas exchange during CPR** (2 randomized controlled trials including 54 pigs)^{210,211}
- **Time to ROSC** (2 randomized controlled trials including 54 pigs)^{210,211}
- **Markers of tissue injury** (lung/brain) (2 randomized controlled trials including 54 pigs)^{212,213}

There was no evidence identified to address the critical issue of **neurologic outcome**.

Manikin studies demonstrated a disadvantage to higher compression-to-ventilation ratios (5:1, 9:3, 15:2) (very-low-quality evidence, downgraded for potential

bias, imprecision, and indirectness) with regard to

- **Compressor fatigue** (better depth of compression, less decay in depth over time; 1 randomized controlled trial including 32 resuscitation providers)²¹⁴
- **Minute ventilation** (1 randomized controlled trial including 32 resuscitation providers)²¹⁴
- A single manikin study demonstrated higher minute ventilation for asynchronous compressions (120 compressions: 40 ventilations) compared with 3:1 (90 compressions: 30 ventilations) (1 randomized controlled trial including 2 resuscitation providers with 5 different sessions per treatment arm)²¹⁵

Treatment Recommendation

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

Values, Preferences, and Task Force Insights

We prefer to retain our prior recommendation of 3:1 compression-to-ventilation ratio for neonatal CPR, because there is no compelling evidence suggesting a benefit to other ratios for the newborn. Since asphyxia is the predominant cause of cardiovascular collapse in the newborn, effective resuscitation requires significant focus on ventilation. In addition, we value consistency in the resuscitation algorithm and education programs unless new evidence drives the change.

All studies were done in young post-transitioned piglets (no human or animal data in a transitioning model). Since there is no evidence in either a human or animal with fluid-filled lungs, we need to be clear when communicating with other groups (pediat-

rics and basic life support providers) that neonates have unique cardiopulmonary physiology, prompting our unique 3:1 ratio.

Some may not agree, but the values and preferences statement expresses why we still favor a 3:1 ratio.

Knowledge Gaps

- Specific research is required, such as clinical and appropriate animal model studies.
- We need neonatal human data.
- How many compressions in a row are required to achieve forward blood flow and adequate coronary perfusion pressure during newborn asphyxial arrest?
- How many interposed ventilations are needed to achieve and maintain normocapnia during cardiac compressions due to newborn asphyxial arrest?
- Asynchronous technique deserves more investigation.
- Is ventilation adequate with SI cardiac compressions?
- How should we limit interruptions in compressions to assess efficacy?

Oxygen Delivery During CPR (Neonatal)—Intervention (NRP 738)

In neonates receiving cardiac compressions (P), does 100% O₂ as the ventilation gas (I), compared with lower concentrations of oxygen (C), increase survival rates, improve neurologic outcomes, decrease time to ROSC, or decrease oxidative injury (O)?

Introduction

Neonatal resuscitation has historically focused on achieving adequate oxygenation as quickly as possible. Recently, it has been recognized that excessive oxygen administration can be toxic. Current guidelines recommend

starting resuscitation with low inspired oxygen and then increasing inspired oxygen as necessary as guided by pulse oximetry. However, once the resuscitation has reached the need for chest compressions, it has been suggested to increase the FiO_2 . This PICO question is intended to consider evidence to determine if this is the correct or incorrect practice.

Consensus on Science

For the critical outcome of **ROSC**, we found 8 animal studies (lambs/pigs/rats)^{216–223} all demonstrating no advantage to 100% over 21% during CPR (very-low-quality evidence, downgraded for bias and indirectness).

For the critical outcome of **survival**, we found 8 of 9 animal studies (lambs/pigs/rats) reporting on survival demonstrated no advantage to 100% over 21% during CPR.^{216–223} However, 1 study (mouse) of 9 studies evaluating this outcome found an advantage to 100% O_2 ²²⁴ (very-low-quality evidence, downgraded for potential bias, inconsistency, and indirectness). All studies combined showed 80/100 (80%) versus 74/102 (73%) survival for 100% O_2 versus air (not different). Eight studies with no advantage showed 70/77 (91%) versus 71/79 (90%) survival. One study with advantage for 100% showed 10/23 (43%) versus 3/23 (13%) survival ($P=0.02$).

For the critical outcome of **neurologic outcome**, we found 4 animal studies (pigs/rats/mice)^{218,221,222,224} reporting on neurologic outcome with varying results (very-low-quality evidence, downgraded for potential bias, inconsistency, indirectness, and imprecision). One demonstrated no difference in neurologic deficits at 72 hours, and ischemic neurons in hippocampal were not different.²¹⁸ One demonstrated worse 4-hour neurologic examination in the 100% O_2 group.²²¹ One demonstrated more

hippocampal apoptosis in the 100% O_2 group.²²² One demonstrated more rapid restoration of cerebral blood flow but no difference in histologic brain injury scores.²²⁴

For the critical outcome of **oxidative injury**, we found 10 animal studies reported on oxidative injury with varying results^{212,213,216,219–223,225–227} (very-low-quality evidence, downgraded for potential bias, inconsistency, and indirectness). Six studies (pigs/mice) demonstrated no difference in various oxidative injury markers,^{212,213,219–221,224} 3 (lambs/rats) demonstrated more oxidative damage from using 100% O_2 including apoptosis,^{216,222,226} and a pig study reported less striatal and hippocampal apoptosis with 100% O_2 compared with 21% O_2 .²²⁷

Treatment Recommendation

There are no human data to inform this question.

Despite animal evidence showing no advantage to the use of 100% oxygen, by the time resuscitation of a newborn baby has reached the stage of chest compressions, the steps of trying to achieve ROSC using effective ventilation with low-concentration oxygen should have been attempted. Thus, it would seem prudent to try increasing the supplementary oxygen concentration (Good Practice Guidance).

If used, supplementary oxygen should be weaned as soon as the heart rate has recovered (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

Although most of the available animal evidence suggests that resuscitation using air during neonatal chest compressions is feasible and that 100% O_2 as the resuscitation gas may increase oxidative injury, we remain concerned that we have no human data to prove

feasibility and none of the animal studies have evaluated use of room-air CPR for more than brief asystole. We value balancing the desire to prevent ongoing hypoxic injury in these profoundly asphyxiated neonates with the desire to prevent subsequent hyperoxic injury.

This was a much-debated topic. In the case of hypotension and bradycardia, the experimental evidence is clear: You only need to use room air. Thus, in this case, we are making the recommendation independent of the evidence. Perhaps, we say, “Despite no evidence, for the following reasons, we recommend....” In training scenarios, once chest compressions are started, failing to turn up O_2 is a common error of the learner. But is it a serious error? The indirectness does not inform the recommendation. We are not even following low-level animal evidence. We are making a conscious decision to take no notice of the evidence. Can we say why this group values giving oxygen for asystole? The task force considered the option of making a neutral recommendation (with either 21% or 100% O_2) and allowing councils to decide what to do. Is this a place where we do not want to suggest air or oxygen? We have no data, but we need to say something.

Knowledge Gaps

- Specific research is required, ie, studies in good transitional animal model of asphyxia-induced severe bradycardia or asystole and any neonatal human data.

ASSIST VENTILATION DEVICES AND CPR FEEDBACK DEVICES

There are numerous techniques used and advocated to ventilate effectively. In addition there are devices used to assess respiratory function and to provide feedback during CPR. The following

reviews were undertaken to assess the role of alternative techniques to ventilate effectively when intubation is not feasible or unsuccessful and to ascertain the evidence of feedback devices on resuscitation skill performance and outcomes.

Laryngeal Mask Airway— Intervention (NRP 618)

In newborn infants at near term (greater than 34 weeks) or term who have indications for intermittent positive pressure for resuscitation (P), does use of a laryngeal mask as a primary or secondary device (I), compared with mask ventilation or endotracheal intubation (C), improve response to resuscitation or change outcome (O), including indicators of neonatal brain injury, achieving stable vital signs, increasing Apgar scores, long-term outcomes, reducing the need for subsequent intubation, or neonatal morbidity and mortality?

Introduction

Endotracheal intubation is the most difficult skill to learn and teach in neonatal resuscitation. The laryngeal mask has recently been suggested as an alternative, either as a primary device, replacing face-mask ventilation, or as a secondary device for failed or not-possible endotracheal intubation. This PICO question is intended to review the evidence for the utility and efficacy of the laryngeal mask for neonatal resuscitation.

Consensus on Science

For comparison of laryngeal mask airway to face mask as a **primary device** (ie, use of laryngeal mask ventilation rather than bag-mask ventilation for infants at term requiring PPV for resuscitation) we identified 3 randomized controlled trials enrolling a total of 469 patients:

- For the critical outcome of **achieving vital signs**, we identified low-

quality evidence (downgraded for very serious risk of bias) from 2 small randomized clinical trials and 1 large quasi-randomized clinical trial^{228–230} showing that the laryngeal mask was more effective than the face mask (OR, 11.43; 95% CI, 4.01–32.58).

- For the critical outcome of **need for subsequent endotracheal intubation after failed laryngeal mask or face mask**, we identified low-quality evidence (downgraded for very serious risk of bias) from the same randomized clinical trials^{228–230} showing that the laryngeal mask was more effective than the face mask (OR, 0.13; 95% CI, 0.05–0.34).
- For the critical outcome of **increasing Apgar Score**, we have identified low-quality evidence from the same randomized controlled trials (downgraded for very serious risk of bias); the method of reporting precluded analysis of this outcome.
- We did not identify any evidence to address the critical outcomes of **indicators of brain injury or long-term outcomes**.
- For the important outcome of **morbidity** (gastric distention or vomiting), we identified low-quality evidence (downgraded for imprecision and very serious risk of bias) from the same randomized clinical trials^{228–230} showing no difference for any variable between the laryngeal mask and the face mask (OR, 5.76; 95% CI, 0.7–47.32).

For comparison of laryngeal mask to endotracheal tube as a **secondary device** (ie, laryngeal mask or intubation when bag-mask ventilation has failed) for infants at term requiring PPV for resuscitation, we identified the following evidence (1 randomized clinical trial with 40 patients)²³¹:

- For the critical outcome of **achieving vital signs or successful resuscitation**, we identified very-low-quality evidence (downgraded for imprecision, risk of bias) from 1 randomized clinical trial²³¹ showing that laryngeal mask airway was as effective as the endotracheal tube.
- For the critical outcome of **need for subsequent endotracheal intubation after failed bag-mask ventilation**, we identified very-low-quality evidence (downgraded for imprecision, risk of bias) from the same randomized clinical trial²³¹ showing that the laryngeal mask was as effective as the endotracheal tube.
- For the critical outcome of **increasing Apgar score**, we identified very-low-quality evidence (downgraded for imprecision and risk of bias) from the same randomized clinical trial²³¹; the method of reporting precluded analysis of this outcome.
- For the critical outcome of **mortality**, we identified very-low-quality evidence (downgraded for imprecision and risk of bias) from the same randomized clinical trial²³¹ showing no difference between the laryngeal mask or the endotracheal tube.
- We did not identify any evidence to address the critical outcome of indicators of **brain injury or long-term neurologic outcomes** comparing laryngeal mask airway or endotracheal tube as a secondary device.
- For the important outcome of **morbidity**, we identified very-low-quality evidence (downgraded for imprecision and risk of bias) from the same randomized clinical trial²³¹ showing more trauma to tissue when comparing laryngeal mask versus endotracheal tube (OR, 2.43; 95% CI, 0.51–11.51).

Treatment Recommendations

We suggest the laryngeal mask may be used as an alternative to tracheal intubation during resuscitation of the late-preterm and term newborn (more than 34 weeks) if ventilation via the face mask is unsuccessful (weak recommendation, low-quality evidence).

In the unusual situation where intubation is not feasible after failed PPV, the laryngeal mask is recommended for resuscitation of the late-preterm and term newborn (more than 34 weeks) (strong recommendation, good clinical practice).

Values, Preferences, and Task Force Insights

In making these recommendations, we place a moderate value in the proven safety and feasibility for a laryngeal mask to provide ventilation in newborns while recognizing the necessity for more studies in other clinical settings (eg, premature infant). We also place high value on the idea that an alternative airway is a potentially life-saving intervention when face-mask ventilation has failed and/or endotracheal intubation is unsuccessful or not feasible. There is now reasonable evidence to add a recommendation for the late-preterm infant.

Knowledge Gaps

- The effectiveness and safety of laryngeal mask airway compared with mask ventilation as the primary interface in term and preterm infants; insertion technique, which model, and how to teach its use

Newborn Infants Who Receive PPV for Resuscitation, and Use of a Device to Assess Respiratory Function—Diagnostic (NRP 806)

In newborn infants who receive PPV for resuscitation (P), does use of a device to assess respiratory function with or

without pressure monitoring (I), compared with no device (C), change survival to hospital discharge with good neurologic outcome, IVH, time to heart rate greater than 100/min, bronchopulmonary dysplasia, pneumothorax (O)?

Introduction

Resuscitation of babies at birth often involves assisting ventilation with positive-pressure devices. Current guidelines for this technique have always involved recommending a specific pressure range to inflate the lungs. Recent research has indicated that excessive pressure can seriously injure the lungs, particularly in babies born preterm, and some have advocated that resuscitation guidelines should be based on volume rather than pressure. It has also been suggested that measuring exhaled CO₂ might indicate adequate ventilation. Devices for measuring both of these variables have been developed. This PICO question is meant to assess the advisability of recommending their use during resuscitation.

Consensus on Science

Flow and Volume Monitoring

For the critical outcome of **survival to hospital discharge** and **IVH**, we identified low-quality evidence (downgraded for risk of bias and imprecision) from 1 pilot randomized controlled trial enrolling 49 babies showing no benefit.²³²

For the critical outcome of **time to heart rate greater than 100/min** and **neurologically intact survival**, we found no evidence.

For the important outcome of **bronchopulmonary dysplasia** and **pneumothorax**, we found no evidence.

Capnography

For the critical outcome of **survival to hospital discharge and IVH**, we identified low-quality evidence (down-

graded for risk of bias and imprecision) from 1 pilot randomized clinical trial enrolling 48 babies showing no evidence.²³³

For the critical outcome of **time to heart rate greater than 100/min and neurologically intact survival**, we found no evidence.

For the important outcome of **bronchopulmonary dysplasia and pneumothorax**, we identified low-quality evidence (downgraded for risk of bias and imprecision) from 1 pilot randomized clinical trial enrolling 48 babies showing no evidence.²³³

Treatment Recommendations

Although a feasible technique, we **suggest against** the routine use of flow and volume monitoring for babies who receive PPV at birth, until more evidence becomes available (weak recommendation, low-quality evidence).

Although a feasible technique, we **suggest against** the routine use of capnography for babies who receive PPV at birth, until more evidence becomes available (weak recommendation, low-quality evidence).

Values, Preferences, and Task Force Insights

We should consider revising future PICO questions to embrace new technologies for more reasonable outcomes and benchmarks rather than death and disability. It was stressed that it is important to point out the human factors piece of the equation. The devices are only as useful as how well the human care provider can interface with and incorporate them appropriately into care. Another point raised is that we have process outcomes, but do they impact actual performance? Do we need this to be a more stepwise approach? What other process outcomes should be included? In the future, we need to look at device design, types of

alarms (visual or audio, color, font, etc). If this were a medication, we would suggest against something with such resource implications.

Knowledge Gaps

- There is a need for large studies powered for important clinical outcomes to determine the role of flow and volume monitoring and capnography in improving response to and outcomes of newborn resuscitation.
- There is a need for further research to determine whether routine use of flow and volume monitoring for task training in newborn resuscitation improves training or clinical outcomes.
- There is a need for specific research to determine whether continuous monitoring of flow and volume or exhaled CO₂ levels compete with other essential auditory and visual cues that need to be appreciated and responded to by resuscitation teams.

Use of Feedback CPR Devices for Neonatal Cardiac Arrest—Diagnostic (NRP 862)

In asystolic/bradycardic neonates receiving cardiac compressions (P), does the use of feedback devices such as end-tidal carbon dioxide (ETCO₂) monitors, pulse oximeters, or automated compression feedback devices (I), compared with clinical assessments of compression efficacy (C), decrease hands-off time, decrease time to ROSC, improve perfusion, increase survival rates, or improve neurologic outcomes (O)?

Introduction

The current measure for determining successful progress in neonatal resuscitation is to assess the heart rate response. Other devices such as CO₂ monitoring and pulse oximetry have

been suggested as more sensitive measures. This PICO question is designed to determine the current evidence regarding this issue.

Consensus on Science

For the critical outcomes of **improved perfusion, decreased time to ROSC, decreased hands-off time, increased survival rates, or improved neurologic outcomes**, we found no specific data.

Increased exhaled CO₂: Five small observational studies (2 piglet post-transitioned models,^{234,235} 2 dog post-transitioned models^{236,237} (these latter 2 articles were the identical sample of dogs and data but published in separate journals), and 1 human study²³⁸ of very low quality (downgraded for indirectness and risk of bias) assessed the ETCO₂ levels associated with the onset or presence/absence of ROSC.

- One piglet study²³⁴ and the dog studies^{236,237} associated the presence of decreased time to ROSC with an ETCO₂ of 27 to 28 mm Hg. CPR in these studies was started after 5 to 10 minutes of cardiac arrest.
- One piglet study²³⁵ associated the presence of a heart rate greater than 60/min with an ETCO₂ of 14 mm Hg (sensitivity, 93%; specificity, 81%). CPR was started at onset of asystole.
- One human study covered a wide age range of children, 1 week to 10 years.²³⁸ The majority were out-of-hospital arrests. ETCO₂ levels in all patients who did not attain ROSC never rose above 15 mm Hg.

Treatment Recommendation

In asystolic/bradycardic neonates, we **suggest against** the routine reliance on any single feedback device such as ETCO₂ monitors or pulse oximeters for detection of ROSC until

more evidence becomes available (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

Several questions were raised: Should detection of ROSC be the only real outcome for the question because identifying this is the first step to recovery? Thus, it is a critical tool for determining if your actions are effective or if you need to consider other interventions. Was there a need to rate the effectiveness of the equipment as the critical outcome, or is the effect on the patient what is important? Does the device measure what it is supposed to measure? What about human factors issues? Can providers effectively use the equipment? Does it impact outcome?

Knowledge Gaps

- There is a need for large studies powered for important clinical outcomes to determine the role of flow and volume monitoring and capnography in improving response to and outcomes of newborn resuscitation.
- There is a need for further research to determine whether routine use of flow and volume monitoring for task training in newborn resuscitation improves training or clinical outcomes.
- There is a need for specific research to determine whether continuous monitoring of flow and volume or exhaled CO₂ levels compete with other essential auditory and visual cues that need to be appreciated and responded to by resuscitation teams.

POSTRESUSCITATION MANAGEMENT

ILCOR previously reviewed postresuscitation strategies that focused on

glucose control and the implementation of therapeutic hypothermia to minimize or avoid reperfusion injury from intrapartum hypoxia-ischemia in well-resourced settings. For this cycle, we only reviewed the potential role of therapeutic hypothermia to minimize or avoid reperfusion injury from intrapartum hypoxia-ischemia where resources are limited.

Limited-Resource-Induced Hypothermia—Intervention (NRP 734)

In term infants with moderate/severe hypoxic-ischemic encephalopathy managed in resource-limited countries (P), does therapeutic hypothermia to core temperature of approximately 33.5°C for 72 hours delivered by passive hypothermia and/or ice packs (I), versus standard therapy (C), improve the rates of death, neurodevelopmental impairments at 18 months to 2 years (O)?

Introduction

Therapeutic hypothermia has been shown to reduce mortality and morbidity in term and near-term newborns who have had a hypoxic-ischemic insult and are at risk for evolving encephalopathy. This therapy has generally been restricted to developed countries where resources and regional systems permit the therapy to be administered under a strict protocol. This PICO question is intended to determine if therapeutic hypothermia can practically and effectively be practiced in countries with limited resources.

Consensus on Science

For the critical outcome of **death or disability**, we identified very-low-quality evidence (downgraded for risk of bias and indirectness) from 2 randomized controlled trials^{239,240} enrolling 338 infants showing benefit to the use of therapeutic hypothermia (OR, 0.43; 95% CI, 0.26–0.7).

For the critical outcome of **death to latest follow-up**, we identified very-low-quality evidence (downgraded for risk of bias, inconsistency, and indirectness) from 4 randomized controlled trials^{239–242} enrolling 416 infants showing no benefit to the use of therapeutic hypothermia (OR, 0.72; 95% CI, 0.44–1.16).

Treatment Recommendations

We suggest that newly born 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.

Values, Preferences, and Task Force Insights

In making this recommendation, we place a higher value on the demonstrated effectiveness of simple cooling methods and the lack of harm associated with these methods over the paucity of evidence specific to resource-limited settings.

It is difficult to define a low-resource setting. Even within a country (eg, India) resources may vary widely. Simple methods of cooling are successful in lowering body temperature. There was

a concern that passive cooling may not be so harmless (eg, extreme hypothermia, inappropriate hypothermia). Low-resource areas do not have nursing care to monitor the babies closely.

Knowledge Gaps

- Further adequately powered randomized controlled trials of simple methods of cooling in resource-limited settings are required to improve the quality of evidence relating to this question.
- Specific regional guidelines should take account of public health system priorities for allocation of available resources and the availability of sufficient nursing and ancillary resources to safely and effectively deliver cooling therapy in the facility.

DISCONTINUING RESUSCITATION

Deciding how long resuscitative efforts should continue in a newly born infant with no heart rate and/or absent respirations with a very low heart rate after sustained resuscitative efforts remains a critically important and difficult management decision. In recent years, long-term outcomes have shown some improvement.

Delivery Room Assessment for Less Than 25 Weeks and Prognostic Score (NRP 805)

In extremely preterm infants (less than 25 weeks) (P), does delivery room assessment with a prognostic score (I), compared with gestational age assessment alone (C), change survival to 18 to 22 months (O)?

Introduction

Antenatal assignment of prognosis for survival and/or disability of the neonate born extremely preterm has generally been made on the basis of gestational age alone. Recently, scoring systems for including additional variables

such as gender, use of maternal antenatal steroids, and multiplicity have been developed in an effort to improve prognostic accuracy. This PICO question was developed to examine the utility of these systems.

Consensus on Science

There is no evidence that addresses the clinical prospective use of prognostic scoring (the use of composite survival data using gestational age and other parameters) in infants of less than 25 weeks of estimated gestational age.

There is increasing retrospective evidence that prognostic accuracy is improved by using additional information such as birth weight, appropriateness of weight for gestational age, use of maternal antenatal steroids, multiplicity, and gender^{243–247} (low-quality evidence), but there are no prospective studies showing the postnatal effect of such improved accuracy in predicting outcome.

Treatment Recommendation

There is insufficient evidence to support the prospective use of any delivery room prognostic score presently described over estimated gestational age assessment alone in preterm infants of less than 25 weeks of gestation. No score has been shown to improve the ability to estimate the likelihood of survival through either 30 days or in the first 18 to 22 months after birth.

In individual cases, when constructing a prognosis for survival at gestations below 25 weeks, it is reasonable to consider variables including perceived accuracy of gestational age assignment, the presence or absence of chorioamnionitis, and the level of care available for location of delivery. It is also recognized that decisions about appropriateness of resuscitation below 25 weeks of gestation will be influenced by region-specific guidelines established by regional resuscitation councils.

Values, Preferences, and Task Force Insights

In making this statement, we put a higher value on the lack of evidence for a generalizable prospective approach changing important outcomes over improved retrospective accuracy and locally validated counseling policies. For antenatal counseling, the most useful data would give outcome figures for babies alive at the onset of labor, not just those born alive or admitted to the neonatal intensive care unit. In reality, many are already using such extended data in antenatal counseling to try to provide parents and healthcare professionals with the most accurate estimates for mortality (and morbidity).

It would obviously be preferable if there were studies to show that using such data can prospectively improve the outcome for these babies: Does using the most accurate information have a positive influence on the difficult decisions made about whether intensive care should be implemented?

There was agreement to amend the treatment recommendation to include consideration of possible inaccuracy of gestational age assessment, as well as to include evaluation for chorioamnionitis, and level of subsequent care that may be available. A question was raised with regard to the fact that we included weights in previous statements about prognosis; however, those were taken out to allow councils to make independent recommendations. Should antenatal steroids be mentioned in the treatment recommendation? The list may become exhaustive as more factors are added (eg, gender).

Knowledge Gaps

- Insufficient or absent data concerning timing of death, ie, early versus later death
- Lack of information on factors other than gestational age known before birth

- Limited information on use of combined antenatal and postnatal information
- Inability to fully distinguish between outcomes driven by practice (eg, belief that mortality is universal below a certain gestational age), surrogate decision making by parents, and physiologic limitations

Apgar Score of 0 for 10 Minutes or Longer—Prognosis (NRP 896)

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 (P), what is the rate of survival to NICU admission and death or neurocognitive impairment at 18 to 22 months (O)?

Introduction

There has been an ongoing controversy as to how long after one has been attempting resuscitation after birth, and a heart rate cannot be detected, should one continue or discontinue resuscitation efforts. The balance must be between ceasing too early, when ROSC and long-term survival may still be achievable, and continuing too long, when ROSC may occur, but early death or an unacceptable degree of neurologic injury may have occurred. The Apgar score of 0 has classically been the criterion, because it indicates no detectable signs of life. The recommended duration of resuscitative efforts after birth has variously been 15, and more recently 10 minutes, after birth. The controversy has been generated from the following uncertainties: (1) It is often not clear whether resuscitation efforts have taken place throughout the 10-minute period, (2) There may be questions about whether the score has indeed been 0 throughout the 10 minutes and not just at 10 minutes, and (3) Have resuscitation efforts been optimal throughout the 10 minutes? Recently, the 10-minute guideline has been subjected to further controversy,

with published reports from therapeutic hypothermia trials of an increasing number of intact survivors after 10 minutes of an Apgar score of 0.

Consensus on Science

For the critical outcome of **death up to 22 months**, very-low-quality evidence (downgraded for risk of bias, inconsistency, and imprecision) from 6 studies encompassing 8 case series showed that 75 of 129 infants (58%) with an estimated gestational age of 36 weeks or greater and an Apgar score of 0 at 10 minutes of life died before 22 months of age.^{248–253} Results from 3 of these studies performed after 2009 that included nested observational series of cases from 3 randomized clinical trials of therapeutic hypothermia and a series of infants who received therapeutic hypothermia outside a randomized trial (low-quality evidence, downgraded for risk of bias) found that 46 of 90 infants (51%) with an Apgar score of 0 at 10 minutes died before 22 months of age.^{250,251,253}

For the critical outcome of **death or moderate/severe neurodevelopmental impairment** at 22 months of age or older, 6 studies (very-low-quality evidence, downgraded for risk of bias, inconsistency, indirectness, and imprecision) showed this outcome in 106 of 129 infants (85%) with a gestational age of 36 weeks or greater and an Apgar score of 0 at 10 minutes of life.^{248–253} Results from 3 of these studies performed after 2009 (very-low-quality evidence, downgraded for risk of bias, inconsistency, indirectness, and imprecision) that included nested observational series in randomized clinical trials of therapeutic hypothermia and series of infants who received therapeutic hypothermia showed that this adverse outcome occurred in 68 of 90 infants (76%) with an Apgar score of 0 at 10 minutes. Among the 44 survivors of these studies, 22 (50%) survived without major/moderate disabilities. Among the 56 cooled infants in these studies, 15 (27%)

survived without major/moderate disabilities^{250,251,253} (very-low-quality evidence, downgraded for risk of bias).

No studies differentiated between severe and moderate disability.

None of the studies described the resuscitation procedures that were provided.

Treatment Recommendation

An Apgar score of 0 at 10 minutes is a strong predictor of mortality and morbidity in late-preterm and term infants. We suggest that, in babies with an Apgar score of 0 after 10 minutes of resuscitation, if the heart rate remains undetectable, it may be reasonable to stop resuscitation; however, the decision to continue or discontinue resuscitative efforts should be individualized. Variables to be considered may include whether the resuscitation was considered to be optimal, availability of advanced neonatal care, such as therapeutic hypothermia, specific circumstances before delivery (eg, known timing of the insult), and wishes expressed by the family (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

In making this statement in infants of 35 weeks or greater with an Apgar score of 0 for 10 minutes or longer, the likelihood of dying or having severe or moderate developmental disabilities at 18 to 24 months is very high. Studies that included 69 infants with an Apgar score of 0 at 10 minutes after birth who were successfully resuscitated and randomly assigned to hypothermia or normothermia, and case series of 21 additional infants who were managed with therapeutic hypothermia, suggest improvement in outcome compared with previously reported cohorts. Among these 90 infants, 45 (50%) died and 22 (24%) survived without major or moderate disability at 18 to 24 months.

However, the number of infants with no heart rate at 10 minutes who died in the delivery room is unknown.

This topic resulted in a long and spirited debate. A question was raised as to how can we say that we should consider stopping with a 24% possibility of survival without major handicap? Is 10 minutes sufficient time to make this decision? It was suggested not to use the word *adequate*, because the resuscitation was not assessed. What would the adults do with 20% chance of survival? However, it was pointed out that it is not a 20% chance, because not all babies got to cooling. Someone advocated using the term *discontinue* instead of *withdraw*. The term *adequate* caused a lot of debate. What do we mean by it? Can it be clearer? Concern was expressed that providers will likely not use science to guide the decisions for this situation and will likely use their own judgment. Parents tend to choose continuation even when the data are presented to them. The decision to continue or discontinue should be based on consultation with the family. The optimal way to restore circulation can be in the qualifier. An Apgar score of 0 at 10 minutes is a strong predictor of disability at all gestations.

Knowledge Gaps

The major flaw in the available scientific evidence regarding outcome of term neonates with asystole after 10 minutes of adequate resuscitation is the absence of data regarding

- Number of infants born in the study centers or the transferring centers with asystole at 10 minutes who were not actively resuscitated (in the hypothermia studies many were transfers)
- Number of infants born in the study or the transferring centers with asystole at 10 minutes in whom delivery room resuscitation was attempted and unsuccessful

- Data regarding the quality and extension of resuscitation of these infants
- Only a prospective international registry with all needed information of infants with asystole/heart rate less than 60/min after 10 minutes of adequate resuscitation may provide evidence of sufficient scientific merit to answer this prognostic question

Predicting Death or Disability of Newborns of Greater Than 34 Weeks Based on Apgar and/or Absence of Breathing—Prognosis (NRP 860)

In newborn infants of greater than 34 weeks of gestation, receiving PPV at birth in settings where resources are limited (P), does presence of heart rate with no spontaneous breathing or Apgar scores of 1 to 3 at greater than 5 minutes predict mortality or morbidity or cerebral palsy (O)?

Introduction

The Apgar score is intended to be a retrospective predictor of outcome, particularly at 5 minutes of age. It has been suggested that an Apgar score of 0 at 10 minutes of age is an indication to consider discontinuing resuscitation efforts (see NRP 896), but there have been no other levels of Apgar assessment by which one might make discontinuation decisions, such as Apgar score of 3 or less at 20 minutes. This PICO question is intended to review the recent evidence regarding these additional predictors.

Consensus on Science

Apgar Score at 20 Minutes

For all the outcomes, we could not find studies that reported on individual Apgar scores (1, 2, or 3) beyond 10 minutes. One very-low-quality study (downgraded for indirectness) reported on Apgar scores at 20 minutes but included patients with an Apgar score of 0.²⁵⁴ This study reported

that in babies weighing greater than 2500 g with an Apgar score of 0 to 3 at 20 minutes, the mortality was 59%, and 57% of survivors developed cerebral palsy.

Apgar Score at 10 Minutes

For the critical outcome of **death**, we identified low-quality evidence (downgraded for imprecision) from 2 randomized studies involving babies who participated in induced-hypothermia studies.^{251,255} One study²⁵¹ reported mortality of 64%, 47%, and 39% for Apgar score of 1, 2, and 3, respectively, with an OR of 1.42 (95% CI, 1.19–1.69) at 18 to 22 months. The other study²⁵⁵ reported outcomes from the same study, but at 6 to 7 years. Babies with Apgar scores of 1, 2, and 3 had mortality rates of 67%, 43%, and 27%, respectively, if they were managed with induced hypothermia and 63%, 57%, and 62% if they were not cooled.

For the critical outcome of **moderate/severe disability**, we identified low-quality evidence (downgraded for imprecision) from 2 randomized studies involving babies who participated in induced hypothermia studies,^{251,255} one²⁵¹ reporting the outcome in 50%, 63%, and 38% for Apgar scores of 1, 2, and 3, respectively, with an OR of 1.30 (95% CI, 1.06–1.58) at 18 to 22 months. The other study²⁵⁵ reported at 6 to 7 years of life that 100%, 75%, and 9% of babies with Apgar score of 1, 2, and 3, respectively, had moderate/severe disability if managed with induced hypothermia and 67%, 67%, and 71% if not managed with hypothermia, although the sample size was small.

No Spontaneous Respiration

For the critical outcome of **death**, we identified very-low-quality evidence (downgraded for imprecision) from 2 observational studies^{256,257} that time to spontaneous respiration of more than 30 minutes was associated with 52% to 77% mortality.

For the critical outcome of **cerebral palsy** or **abnormal neurologic**

findings, we identified very-low-quality evidence (downgraded for imprecision)^{256–258} that time to respiration of more than 30 minutes was associated with 35% cerebral palsy and 67% to 100% abnormal neurologic findings.

For the critical outcome of **death and/or moderate-to-severe disability**, we identified very-low-quality evidence (downgraded for imprecision) from 2 observational studies^{259,260} that time to spontaneous respiration of 10 to 19 minutes and more than 20 minutes was associated with this outcome in 56% and 88% of patients, respectively,²⁵⁹ and time to spontaneous breathing of 30 minutes or more was a predictor of this outcome (OR, 2.33; 95% CI, 1.27–4.27).

Treatment Recommendation

Absence of spontaneous breathing or an Apgar score of 1 to 3 at 20 minutes of age in babies of greater than 34 weeks of gestation but with a detectable heart rate are strong predictors of mortality or significant morbidity. In settings where resources are limited, we suggest that it may be reasonable to stop assisted ventilation in babies with no spontaneous breathing despite presence of heart rate or Apgar score of 1 to 3 at 20 minutes or more (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

In making this statement, in infants of greater than 34 weeks with an Apgar score of 0, 1, 2, or 3 for 20 minutes or more, the likelihood of dying or having severe or moderate developmental disabilities at 18 to 24 months is very high. Importantly, each of the studies reviewed was conducted in a resource setting where therapeutic hypothermia was likely to be available (see NRP 734).

Perhaps there is a publication bias when those babies who did not respond at 20 minutes are not included in the numbers. The question was raised, if

the prognosis is the same, why would we recommend something different for resource-limited settings? A response was that in resource-limited regions, there will likely not be the regional systems and postresuscitation neonatal intensive care facilities and subspecialty personnel that were available in the recent studies reviewed in the Consensus on Science. If such facilities are available, this treatment recommendation may be less applicable.

Knowledge Gaps

- No studies identified from low-resource settings
- Outcome of babies with delayed onset of breathing who are managed with induced hypothermia in low-resource settings.
- Outcome of babies with gasping or irregular breathing and a heart activity at 20 minutes of life

EDUCATIONAL TECHNIQUES FOR TEACHING, ASSESSING, AND MAINTAINING RESUSCITATION KNOWLEDGE AND SKILLS

Resuscitation Training Frequency (NRP 859)

For course participants including (a) trainees and (b) practitioners (P), does frequent training (I), compared with less frequent training (annual or biennial) (C), change all levels of education or practice, prevention of adverse outcomes, overall mortality, scenario performance, medical knowledge, psychomotor performance, provider confidence, course satisfaction (O)?

Introduction

Training in the cognitive, technical, and behavioral skills necessary for successful neonatal resuscitation has historically been conducted at varying intervals of time, and there is little evidence to support the use of one interval over another. As an

example, the national steering committee of the US Neonatal Resuscitation Program has recommended that trainees complete the program once every 2 years, but in the United Kingdom, 4 years is the recommended interval; there is no objective evidence to validate these intervals. It is intuitive that individual trainees will require different training intervals to facilitate optimal acquisition and maintenance of different skills. This PICO question is intended to update the evidence as to what may be the most effective strategy.

Consensus on Science

Sixteen studies were identified that have investigated this PICO question. Ten randomized controlled studies^{261–270} and 6 nonrandomized controlled trials^{271–276} were identified for inclusion.

The evidence for frequency of resuscitation training is very low quality (downgraded for high risk of bias, inconsistency, and imprecision), with the exception of studies of psychomotor performance, which are of moderate quality (downgraded for risk of bias). Meta-analyses were greatly limited by the heterogeneity between studies of training frequency, educational interventions, and outcomes.

For the critical outcome of **patient outcomes**, 2 studies^{271,275} of very low quality (downgraded for high risk of bias, inconsistency, and imprecision) looked at endotracheal intubation success. Both studies included psychomotor skill training on an airway simulator, and Nishisaki²⁷⁵ included simulation-based training. There was no significant difference in first-time intubation success (RR, 0.879; 95% CI, 0.58–1.33) or any intubation success (RR, 0.87; 95% CI, 0.65–1.17) between the providers who were exposed to frequent training and controls.

For the important outcome of **prevention of adverse events**, the Nishisaki study also included the important outcome of prevention of adverse out-

comes and airway injury as a secondary outcome. No significant difference was seen between groups (RR, 1.097; 95% CI, 0.747–1.612).²⁷⁵

For the important outcome of **performance in simulation**, 3 studies^{264,267,273} of very low quality (downgraded for high risk of bias, inconsistency, and imprecision) investigated the important outcome of performance in simulated scenarios using both validated and nonvalidated evaluations. In all studies, subjects in the intervention groups trained more frequently than controls. The range of time between initial course completion and first additional training session was 1 to 4 months. The educational interventions were heterogeneous, including independent and facilitated practice on airway simulators,²⁶⁴ didactic lectures, skill station practice, mock codes,²⁷³ and periodic review of course material and case-based study.²⁶⁷ Kovacs²⁶⁴ and Stross²⁶⁷ found no significant difference between frequent and infrequent practice with respect to simulation-based performance. Only 1 of these studies (Nadel²⁷³) offered quantitative data: After averaging of multiple outcomes, there was a trend to improved performance in those exposed to increased frequency of training compared with controls (RR, 1.51; 95% CI, 0.971–2.35).

For the important outcome of **psychomotor performance**, there were 8 studies^{261,262,266,267,269,273,274,276} of moderate quality (downgraded for risk of bias) that evaluated the important outcome of impact of frequent training on psychomotor performance, demonstrated on a task trainer or simulator. With the exception of O'Donnell²⁷⁶ and Stross²⁶⁷ (which were neutral to the question), studies demonstrated improvements in psychomotor performance with no negative effect. The range of time between course completion and first additional training session was 1 week to 6 months. The educational interventions were

again heterogeneous. Psychomotor task trainers were used to achieve competency in a specific technical skill, including practice on a chest compression task trainer (Niles²⁷⁴), neonatal airway management task trainer (Ernst²⁶²), or a CPR task trainer where both chest compressions and ventilation were emphasized.^{261,266,276} The study by Stross²⁶⁷ included periodic review of course material and case-based study.²⁶⁷ The educational intervention in the Nadel²⁷³ study used didactic lectures, skill station practice, and mock codes. Although 8 studies were identified, only 1 randomized²⁷³ and 2 observational studies^{267,276} with dichotomous quantitative data were included in the analysis. The 1 randomized study²⁷³ demonstrated a significant improvement in psychomotor skills in subjects in the intervention group when compared with controls. One randomized study²⁶⁶ with multiple outcomes showed significantly improved performance of the important outcomes of manual ventilation volume and chest compression depth after practice every 3 months. However, an improvement in psychomotor skills in the intervention groups was not seen when 3 studies^{267,273,276} were included in a meta-analysis after averaging of scores (RR, 1.38; 95% CI, 0.87–2.2). For the important outcome of **knowledge**, 5 studies^{263,268,270,273,276} of very low quality (downgraded for high risk of bias, inconsistency, and imprecision) investigated the relationship between frequent training and the important outcome of acquisition of medical knowledge assessed by written tests or oral exams. Studies by Nadel,²⁷³ O'Donnell,²⁶⁰ and Turner²⁵⁴ demonstrated sustained knowledge with refreshers when compared with controls, whereas Kaczorowski²⁶³ and Su²⁵² were neutral to the question. The educational interventions for these studies have been described previously except for 2 studies: Su used a knowledge exam and mock resuscitation at 6 months, and the

Kaczorowski²⁶³ study included subjects in the intervention groups either watching a newborn resuscitation education video or hands-on practice. The range of time between course completion and first additional training session was 1 to 6 months. Although 5 studies were identified, only 2 had quantitative data.^{270,273} The analysis of the 2 observational studies was not possible because it was difficult to average the means \pm SDs and then pool the 2 studies for a meta-analysis. The Nadel²⁷³ study found a significant improvement in knowledge with more frequent training in a short answer test (mean scores 73 ± 11 versus 60 ± 10 ; $P=0.0003$). The Turner²⁵⁴ study showed significant improvement in 2 out of 3 test scores in the intervention group (mean scores 7.1 versus 6.2 and 29.0 versus 25.8, respectively; $P<0.05$ in both cases). O'Donnell²⁶⁰ demonstrated lower test scores in the control group than in the intervention group ($P<0.04$).

For the nonimportant outcome of **provider confidence**, Montgomery²⁶⁵ found that subjects who practiced CPR for 6 minutes every month were more likely than controls to report that they felt confident (RR, 1.60; 95% CI, 1.27–2.01), and Nadel²⁷³ found improved confidence in both leadership and technical skills.

No study demonstrated a negative or detrimental effect from more frequent training. Publication bias was difficult to assess.

Treatment Recommendation

We suggest that training should be recurrent and considered more frequently than once per year. This retraining may be composed of specific tasks and/or behavioral skills, depending on the needs of the trainees (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

In drawing our conclusions, we place value on improved psychomotor skills,

knowledge, and provider confidence during more-frequent training versus less-frequent training (and versus the established and unproven practice of training every 1 to 2 years).

The debate included the fact that the PICO question does not specify that it is resuscitation training, although the search did restrict itself to this. Should the costs of training be addressed? However, it was noted that it was hard to comment on cost based on studies, because the interventions themselves were so different. Could the follow-up programs be briefer and more focused on needs? What is best for the patient? What is the cost to the child and family when the patient does not receive adequate resuscitation? What is a technical proficiency program? How do we achieve it? There is no assessment of translation of increased training to improved outcomes. We need data to show that improved education is worth the stafftime. The PICO question specifically avoided looking at studies about decay of knowledge and skills.

Knowledge Gaps

- Although some outcomes are of critical importance, the quality of evidence is very low. Serious methodological flaws occur, such as lack of randomization, multiple primary outcomes with inadequate sample size and power analysis, lack of blinding, controls that consist of no educational intervention resulting in a comparison of training to no training, insufficiently validated evaluation tools, and significant heterogeneity of outcomes and interventions.
- There is a need for well-designed and well-powered clinical trials, possibly cluster randomized, that answer key questions with critical outcomes: How frequently should learning occur? What type of intervention is most effective? What

validated tools are available to measure educational outcomes?

- How do high-opportunity versus low-opportunity environments differ in their need for frequent training?
 - Did we take experience into account?
 - What about knowledge, skills, and behaviors?
 - Are patient outcomes lacking?
 - Is cost impact lacking?
 - Is high-frequency, low-dose training effective?
 - Decay and boosting rates?
 - Should we add “within the constraints of local resources”?
 - Reinforcement from other domains, for example

Neonatal Resuscitation Instructors (NRP 867)

In neonatal resuscitation instructors (P), does formal training on specific aspects of how to facilitate learning (I), compared with generic or nonspecific training (C), change clinical outcome, improve all levels of education or practice (O)?

Introduction

Around the world, millions of healthcare professionals bear the responsibility for resuscitating neonates in the delivery room, and they must not only acquire the necessary cognitive, technical, and behavioral skills but also maintain them over time, often for decades. The precise roles and mandatory skills of the instructors charged with training healthcare professionals have yet to be defined, and thus how to best prepare instructors to fulfill these roles and acquire these skills is not yet objectively described. It is intuitive that training of instructors should be based on specific learning objectives targeting the specific instructor skills that are necessary to facilitate the acquisition of specific skills in specific populations of learners.

Comprehensive assessment of resuscitation instructor training requires identification and development of (1) objective markers of performance for instructors, (2) appropriate objective markers of performance for the trainees who are trained by the instructors, and (3) objective markers of patient outcome that are directly related to how well they were resuscitated. This PICO question is intended to identify literature that is pertinent to these and other issues involving the preparation of instructor of neonatal resuscitation.

Consensus on Science

For the critical outcome of **improvement in patient outcome**, we identified no evidence.

For the critical outcome of **improvement in learner performance** in the real clinical environment, we identified very-low-quality evidence from 1 randomized clinical trial²⁷⁷ (downgraded for indirectness, risk of bias, and imprecision) that providing structured self-reflection and peer group feedback to psychiatry registrars improved their students' performance of standardized psychiatric interviews.

For the critical outcome of **improvement in learner performance in educational settings**, we identified very-low-quality evidence (downgraded for indirectness, imprecision, and risk of bias) from 1 randomized clinical trial²⁷⁸ in which 18 emergency medicine instructors were randomly assigned to 2 intervention groups and trained 193 medical students. The study found that learners trained by instructors who underwent a 2-day teacher training course focused on education principles performed at an equal or lower level of proficiency in technical skills when compared with those trained by instructors who did not attend the 2-day course.

For the critical outcome of **improvement in all levels of education or**

practice, we identified low-quality evidence (downgraded for indirectness and bias) from 5 randomized clinical trials^{278–282} enrolling 271 participants (not estimable). Several studies did note at least temporary deterioration in instructor performance after commencement of new instructor training intervention.

For the critical outcome of **improvement in clinical outcome**, we identified no evidence.

For the important outcome of **improvement in instructor performance**, we identified very-low-quality evidence (downgraded for indirectness and bias) from 5 randomized clinical trials^{278–282} and 2 nonrandomized trials.^{283,284} No meaningful numerical summary of the results of these studies could be performed. These studies indicate that preparation of instructors produces inconsistent results in terms of instructor performance. While it does seem that written and verbal feedback, delivered in a constructive and timely manner, often produces improvement in instructor performance, in other instances posttraining deterioration in aspects of instructor performance was seen, at least initially.

Treatment Recommendation

We suggest that training of resuscitation instructors incorporate timely, objective, structured, individually targeted verbal and/or written feedback (weak recommendation, low-quality evidence).

Values, Preferences, and Task Force Insights

While common sense dictates that instructors be properly prepared before engaging learners, it is clear that such instruction must be based on specific learning objectives targeting the specific skills that are necessary to facilitate learning. Definitions of these skills will require collaboration with

colleagues in fields such as human factors and ergonomics who have experience in examining human performance in high-risk domains (similar to the delivery room) rather than relying solely on those with expertise in traditional education settings such as the classroom.

Deliberations of the Task Force and Writing Group

The PICO question may be too global/broad. Perhaps we need to be more specific in the future. We may need to move away from dependence on traditional methodologies and look to those industries where adults are trained to be proficient in specific tasks. Instructors need to know how to do specific tasks and give feedback to improve performance. Perhaps we have made instructors poor trainers. People who develop curricula need to address this critical deficit. How do we teach task proficiency? That is what is most needed.

Knowledge Gaps

- How is optimal instructor performance defined?
- What are the skills necessary to achieve this?
- What are the optimal methods for selection of candidate instructors, initial skill acquisition by instructors, ongoing maintenance of instructor skill, and (objective and subjective) assessment of instructor skill?

2010 PICO QUESTIONS NOT REVIEWED IN 2015

- Suctioning (other than meconium)
- Inflation pressures
- Face mask characteristics
- CO₂ detectors to confirm endotracheal tube placement
- Epinephrine dose and route
- Volume expansion
- Sodium bicarbonate

- Glucose
- Therapeutic hypothermia
- Personnel needs at elective cesarean delivery
- Briefing and debriefings during learning activities

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DISCLOSURES

2015 CoSTR Part 7: Neonatal Resuscitation: Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Jeffrey M. Perlman	Weill Cornell Medical College	None	None	None	None	None	None	None
Jonathan Wyllie	James Cook University Hospital	None	None	None	None	None	None	None
Khalid Aziz	University of Alberta Pediatrics	None	None	None	None	None	None	None
Ruth Guinsburg	Federal University of Sao Paulo	None	None	None	None	None	None	None
John Kattwinkel	University of Virginia Health System	None	None	None	None	None	None	None
Han-Suk Kim	Seoul National University College of Medicine	None	None	None	None	None	None	None
Helen G. Liley	Mater Mother's Hospital	NHMRC (Australia)*	None	None	None	None	None	Mater Foundation†
Lindsay Mildenhall	Middlemore Hospital	None	None	None	None	None	None	None
Wendy M. Simon	American Academy of Pediatrics	None	None	None	None	None	None	AAP staff†
Edgardo Szyld	University of Oklahoma	None	None	None	None	None	None	None
Masanori Tamura	Saitama Medical Center	None	None	None	None	None	None	None
Sithembiso Velaphi	Resuscitation Council of Southern Africa	None	None	None	None	None	None	None
Myra H. Wyckoff	UT Southwestern	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10,000 or more during any 12-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.

APPENDIX

CoSTR Part 7: PICO Appendix

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 7	NRP	NRP 589	Temperature Maintenance in the Delivery Room—Prognosis	In nonasphyxiated babies at birth (P), does maintenance of normothermia (core temperature 36.5°C or greater and 37.5°C or less) from delivery to admission (I), compared with hypothermia (less than 36°C) or hyperthermia (greater than 37.5°C) (C), change survival to hospital discharge, respiratory distress, survival to admission, hypoglycemia, intracranial hemorrhage, or infection rate (O)?	Jonathan Wyllie, Jeffrey Perlman
Part 7	NRP	NRP 590	CPAP and IPPV—Intervention	In spontaneously breathing preterm infants with respiratory distress requiring respiratory support in the delivery room (P), does the use of CPAP (I), compared with intubation and IPPV (C), improve outcome (O)?	Tetsuya Isayama, Ben Stenson
Part 7	NRP	NRP 599	Maintaining Infant Temperature During Delivery Room Resuscitation—Intervention	Among preterm neonates who are under radiant warmers in the hospital delivery room (P), does increased room temperature, thermal mattress, or another intervention (I), compared with plastic wraps alone (C), reduce hypothermia (less than 36°C) on admission to neonatal intensive care unit (NICU) (O)?	Daniele Trevisanuto, Maria Fernanda de Almeida
Part 7	NRP	NRP 605	Thumb Versus 2-Finger Techniques for Chest Compression—Intervention	In neonates receiving cardiac compressions (P), does the use of a 2-thumb technique (I), compared with a 2-finger technique (C), result in return of spontaneous circulation (ROSC), improved neurologic outcomes, improved survival, improved perfusion and gas exchange during CPR, and decreased compressor fatigue (O)?	Myra Wyckoff, Lindsay Mildenhall
Part 7	NRP	NRP 618	Laryngeal Mask Airway—Intervention	In newborn infants at near term (greater than 34 weeks) or term who have indications for intermittent positive pressure for resuscitation (P), does use of a laryngeal mask as a primary or secondary device (I), compared with mask ventilation or endotracheal intubation (C), improve response to resuscitation or change outcome (O), including indicators of neonatal brain injury, achieving stable vital signs, increasing Apgar scores, long-term outcomes, reducing the need for subsequent intubation, or neonatal morbidity and mortality?	Edgardo Szyld, Enrique Udaeta
Part 7	NRP	NRP 734	Limited-Resource-Induced Hypothermia—Intervention	In term infants with moderate/severe hypoxic-ischemic encephalopathy managed in resource-limited countries (P), does therapeutic hypothermia to core temperature of approximately 33.5°C for 72 hours delivered by passive hypothermia and/or ice packs (I), versus standard therapy (C), improve the rates of death, neurodevelopmental impairments at 18 months to 2 years (O)?	Peter Davis, Jeffrey Perlman
Part 7	NRP	NRP 738	Oxygen Delivery During CPR (Neonatal)—Intervention	In neonates receiving cardiac compressions (P), does 100% O ₂ as the ventilation gas (I), compared with lower concentrations of oxygen (C), increase survival rates, improve neurologic outcomes, decrease time to ROSC, or decrease oxidative injury (O)?	Myra Wyckoff, Lindsay Mildenhall
Part 7	NRP	NRP 787	Delayed Cord Clamping in Preterm Infants Requiring Resuscitation (Intervention)	In preterm infants, including those who received resuscitation (P), does delayed cord clamping (greater than 30 seconds) (I), compared with immediate cord clamping (C), improve survival, long-term developmental outcome, cardiovascular stability, occurrence of intraventricular hemorrhage (IVH), necrotizing enterocolitis, temperature on admission to a newborn area, and hyperbilirubinemia (O)?	Masanori Tamura, Susan Niermeyer
Part 7	NRP	NRP 793	Maintaining Infant Temperature During Delivery Room Resuscitation—Intervention	In newborn infants (greater than 30 weeks of gestation) in low-resource settings during and/or after resuscitation/stabilization (P), does drying and skin-to-skin contact or covering with plastic (I), compared with drying and no skin-to-skin or use of radiant warmer or incubator (C), change body temperature (O)?	Sithembiso Velaphi, Hege Ersdal, Nalini Singhal

Continued

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 7	NRP	NRP 804	Babies Born to Mothers Who Are Hypothermic or Hyperthermic in Labor—Prognosis	In newborn babies (P), does maternal hypothermia or hyperthermia in labor (I), versus normal maternal temperature (C), result in adverse neonatal effects (O)? Outcomes include mortality, neonatal seizures, and adverse neurologic states.	Henry Lee, Marilyn Escobedo
Part 7	NRP	NRP 805	Delivery Room Assessment for Less Than 25 Weeks and Prognostic Score	In extremely preterm infants (less than 25 weeks) (P), does delivery room assessment with a prognostic score (I), compared with gestational age assessment alone (C), change survival to 18 to 22 months (O)?	Steven Ringer, Steve Byrne
Part 7	NRP	NRP 806	Newborn Infants Who Receive PPV for Resuscitation, and Use of a Device to Assess Respiratory Function—Diagnostic	In newborn infants who receive PPV for resuscitation (P), does use of a device to assess respiratory function with or without pressure monitoring (I), compared with no device (C), change survival to hospital discharge with good neurologic outcome, IVH, time to heart rate greater than 100/min, bronchopulmonary dysplasia, pneumothorax (O)?	Helen Liley, Vishal Kapadia
Part 7	NRP	NRP 809	Sustained Inflations—Intervention	In term and preterm newborn infants who do not establish spontaneous respiration at birth (P), does administration of 1 or more pressure-limited sustained lung inflations (I), compared with intermittent PPV with short inspiratory times (C), change Apgar score at 5 minutes, establishment of FRC, requirement for mechanical ventilation in first 72 hours, time to heart rate greater than 100/min, rate of tracheal intubation, overall mortality (O)?	Jane McGowan, David Boyle
Part 7	NRP	NRP 849	Umbilical Cord Milking—Intervention	In very preterm infants (28 weeks or less) (P), does umbilical cord milking (I), in comparison with immediate umbilical cord clamping (C), affect death, neurodevelopmental outcome at 2 to 3 years, cardiovascular stability, ie, need for pressors, need for fluid bolus, initial mean blood pressure, IVH (any grade, severe grade), temperature on admission, hematologic indices (initial hemoglobin, need for transfusion), hyperbilirubinemia, need for phototherapy, or need for exchange transfusion (O)?	Marya Strand, Takahiro Sugiura
Part 7	NRP	NRP 858	Warming of Hypothermic Newborns—Intervention	In newborns who are hypothermic (temperature less than 36.0°C) on admission (P), does rapid rewarming (I), compared with slow rewarming (C), change mortality rate, short and long-term neurologic outcome, hemorrhage, episodes of apnea and hypoglycemia, or need for respiratory support (O)?	Cheo Yeo, Daniele Trevisanuto
Part 7	NRP	NRP 859	Resuscitation Training Frequency	For course participants including (a) trainees and (b) practitioners (P), does frequent training (I), compared with less frequent training (annual or biennial) (C), change all levels of education or practice, prevention of adverse outcomes, overall mortality, scenario performance, medical knowledge, psychomotor performance, provider confidence, course satisfaction (O)?	Chris Colby, Khalid Aziz
Part 7	NRP	NRP 860	Predicting Death or Disability of Newborns of Greater Than 34 Weeks Based on Apgar and/or Absence of Breathing—Prognosis	In newborn infants of greater than 34 weeks of gestation, receiving PPV at birth in settings where resources are limited (P), does presence of heart rate with no spontaneous breathing or Apgar scores of 1 to 3 at greater than 5 minutes predict mortality or morbidity or cerebral palsy (O)?	Sithembiso Velaphi, Nalini Singhal, Hege Ersdal
Part 7	NRP	NRP 862	Use of Feedback CPR Devices for Neonatal Cardiac Arrest—Diagnostic	In asystolic/bradycardic neonates receiving cardiac compressions (P), does the use of feedback devices such as end-tidal carbon dioxide (ETCO ₂) monitors, pulse oximeters, or automated compression feedback devices (I), compared with clinical assessments of compression efficacy (C), decrease hands-off time, decrease time to ROSC, improve perfusion, increase survival rates, or improve neurologic outcomes (O)?	Lindsay Mildenhall, Takahiro Sugiura

Continued

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 7	NRP	NRP 864	Oxygen Concentration for Resuscitating Premature Newborns—Intervention	Among preterm newborns (less than 37 weeks of gestation) who receive PPV in the delivery room (P), does the use of high O ₂ (50%–100%) as the ventilation gas (I), compared with low concentrations of O ₂ (21%–30%) (C), decrease mortality, decrease bronchopulmonary dysplasia, decrease retinopathy, decrease IVH (O)?	Gary Weiner, Douglas McMillan
Part 7	NRP	NRP 865	Intubation and Tracheal Suctioning in Nonvigorous Infants Born Through MSAF Versus No Intubation for Tracheal Suctioning—Intervention	In nonvigorous infants at birth born through MSAF (P), does tracheal intubation for suctioning (I), compared with no tracheal intubation (C), reduce meconium syndrome or prevent death (O)?	Sithembiso Velaphi, Jeffrey Perlmán
Part 7	NRP	NRP 867	Neonatal Resuscitation Instructors	In neonatal resuscitation instructors (P), does formal training on specific aspects of how to facilitate learning (I), compared with generic or nonspecific training (C), change clinical outcome, improve all levels of education or practice (O)?	Helen Liley, Louis Halamek
Part 7	NRP	NRP 870	T-Piece Resuscitator and Self-Inflating Bag—Intervention	In newborns (preterm and term) receiving ventilation (PPV) during resuscitation (P), does using a T-piece resuscitator with PEEP (I), compared with using a self-inflating bag without PEEP (C), achieve spontaneous breathing sooner and/or reduce the incidence of pneumothorax, bronchopulmonary dysplasia, and mortality (O)?	Yacov Rabi, Han Suk Kim
Part 7	NRP	NRP 895	Chest Compression Ratio—Intervention	In neonates receiving cardiac compressions (P), do other ratios (5:1, 9:3, 15:2, synchronous, etc) (I), compared with 3:1 compressions to ventilations (C), increase survival rates, improve neurologic outcomes, improve perfusion and gas exchange during CPR, decrease time to ROSC, decrease tissue injury, or decrease compressor fatigue (O)?	Qi Feng, Myra Wyckoff
Part 7	NRP	NRP 896	Apgar Score of 0 for 10 Minutes or Longer—Prognosis	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 (P), what is the rate of survival to NICU admission and death or neurocognitive impairment at 18 to 22 months (O)?	Ruth Guinsburg, Jane McGowan
Part 7	NRP	NRP 897	Outcomes for PEEP Versus No PEEP in the Delivery Room—Intervention	In preterm/term newborn infants who do not establish respiration at birth (P), does the use of PEEP as part of the initial ventilation strategy (I), compared with no PEEP (C), improve Apgar score at 5 minutes, intubation in the delivery room, chest compressions in the delivery room, heart rate greater than 100/min by 2 minutes of life, time for heart rate to rise above 100/min, air leaks, oxygen saturation/oxygenation, FiO ₂ in the delivery room, mechanical ventilation in the first 72 hours, bronchopulmonary dysplasia, survival to discharge (O)?	Yacov Rabi, Colm O'Donnell
Part 7	NRP	NRP 898	ECG/EKG (I) in Comparison to Oximetry or Auscultation for the Detection of Heart Rate	In babies requiring resuscitation (P), does electrocardiography (ECG/EKG) (I), compared with oximetry or auscultation (C), measure heart rate faster and more accurately (O)?	Marya Strand, Hege Ersdal

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