Appendix B

Neonatal Task Force – 2025 Evidence Updates
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2025 Evidence Update
NLS 5002 – Effect of Briefing Before Neonatal Resuscitation

Worksheet Author(s): Yamada NK, Kawakami MD, Fawke J
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 29 October 2024
Conflicts of Interest: None

PICOST:
Population: Health care professionals involved in the resuscitation or simulated resuscitation of a neonate
Intervention: Briefing
Comparator: No briefing
Outcomes: Outcomes for infants, families or staff
Study designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Manikin studies were eligible for inclusion but animal studies were excluded. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded. All languages were included provided there was an English abstract
Timeframe: . All years were included from database inception. The literature search was updated to January 27, 2020

Note: The original PICOST also addressed debriefing, but the current Evidence Update focuses only on briefing as an intervention, since debriefing has been addressed in a Nodal review with the Education, Implementation and Teams Task Force.

Year of last full review: 2020 {Fawke 2021 100059}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST {Wyckoff 2020 S185}
Summary of Evidence:
The ScopRev identified 1 RCT {Magee 2018 192} and 3 observational studies of pre/post intervention design. {Katheria 2013 1552, Sauer 2016 37397, Skåre 2018 394} One study considered video debriefing {Skåre 2018 394}, one considered the use of a checklist combined with video debriefing {Katheria 2013 1552}, one considered the use of a checklist with a team pre-brief/debrief as the main part of a quality improvement bundle.{Sauer 2016 37397} The RCT determined whether rapid cycle deliberate practice compared to standard simulation debriefing was of benefit. {Magee 2018 192}The full ScopRev can be found in Supplement B-1 of the 2020 ILCOR Neonatal COSTR. {Wyckoff 2020 S185}

Narrative reporting of the Task Force discussions
Because this is a new PICOST question for the NLS Task Force, the task force elected to perform a ScopRev to assess the extent and type of available studies. Although briefing and debriefing in resuscitation has been previously reviewed by the NLS Task Force {Perlman 2010 S516} and the Education, Implementation, and Teams Task Force, {Bhanji 2015 S242, Finn 2015 e203} clinical outcomes specific to neonates or neonatal resuscitation were not included in those recommendations.

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

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

We identified limited evidence that rapid-cycle deliberate practice may improve short term performance in a resuscitation simulation but not provider confidence in or retention of skills. These findings were similar to a recent SysRev completed by the ILCOR Education, Implementation, and Teams Task Force which included neonatal studies and identified limited evidence that

rapid-cycle deliberate practice may improve short-term performance in a resuscitation simulation but not provider confidence in or retention of skills. {Yeung 2020 61}

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

Recommendation
When the scoping review was conducted, there did not appear to be enough new evidence to justify a new systematic review on the use of briefing/debriefing, and no treatment recommendations were formulated.

Search Strategy for the scoping review and evidence update: see appendix
Database searched: PubMed, Embase, Web of Science and Cochrane Library and clinical trial database (clinicaltrials.gov, Cochrane, WHO, Prospero
Time Frame: (2020 ScopRev): Literature search updated to 27 January 2020
Time Frame: (Evidence update): 30 December 2019 to 26 May 2024
Date Search Completed: 26 May 2024
Clinical trial database: to 6 October 2024- no new trials found

Search Results:
Identified: 174
Full-text screening: 6
Included: 4.

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews: None
RCT: None
Nonrandomized Trials, Observational Studies: 4

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Participants	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Brewer 2023 {Brewer 2023 110}	**Study Type:** Single center, prospective observational study using survey data; N=59 survey responses (Pre-intervention: N=33; Post-intervention: N=26) Surveys conducted before and after implementation of a 23-question tool to facilitate standardized communication between obstetric and neonatal teams prior to delivery	Three urban hospitals in the same healthcare organization with a total of 9718 births in 2019 and the neonatal resuscitation teams attending 1499 of those births Study was conducted in 2021 with an 8-week implementation period of the communication tool	**1° endpoint:** No named primary outcome Statistically significant improvements in 5-point Likert scale scores for the following behaviors when comparing pre- vs. post-intervention ($p<0.05$): *Hand-Off Communication* - easy to talk to L&D - communication open to the neonatal resuscitation team - information passed is accurate - nurses understand information given - report prepares me to care for newborn	Implementation of this communication tool improved communication to the neonatal resuscitation team during high-risk births and overall provider satisfaction. **Limitations:** Small sample size with few survey responses from physicians and respiratory therapists; most responses were from nurses and nurse practitioners. No data from labor and delivery room nurses about their perceptions on implementation of this standardized communication tool. No clinical outcome data, so unable to assess if improved communication prior to delivery is associated

			- not necessary to check accuracy of information *Risk Factor Communication* - gestational age is communicated - amniotic fluid color is communicated - antepartum risk factors are communicated - intrapartum risk factors are communicated Preparation and Satisfaction with *Communication* - receive information on fetal well-being - current communication makes you ready - satisfied with current communication	with improved clinical outcomes.
Jordache 2020 {Jordache 2020 e228}	**Study Type:** Single center, prospective observational study; N=40 teams (Pre-intervention: 20 teams; Post-intervention: 20 teams) Comparison pre/post of task execution in 20 deliveries before and after implementation of a briefing/debriefing tool adapted from team sports briefing/debriefing	Regional tertiary NICU with 550 admissions annually and delivery rate of 6200/year. Consultant physicians (n=10), Advanced Neonatal Nurse Practitioners (number not provided), Junior Doctors (n=20), and "various grades of nurses" (number not provided). All members of the staff actively participate in neonatal resuscitation with teams varying from shift to shift. Team members have Neonatal Life Support training	**1° endpoint:** No specified primary outcome Increases in the following behaviors when comparing pre- vs. post-intervention ($p<0.05$): - Prepare resus team for each shift - Identify roles within resus team for each shift - Discuss any potential changes to that team - Discuss potential deliveries that day - - Recap resus checklist - Discuss any maternal concerns that may indicate special attention when resus is called for - Discuss different outcomes of those concerns and how this will change the resus approach - Discuss any variable factors – GA, maternal	Developing a training program and then implementing a simple checklist or bundle facilitated improvement in perceived confidence levels and task execution by the NICU team. Survey data (albeit with limited response rate) about task execution before and after the intervention indicated an acceptance of the checklist and the tasks it contained, including those related to briefing and debriefing. **Limitations:** Short observation period (20 deliveries over 5 days) before and after implementation of the intervention, so unclear if intervention or benefits were sustained. No clinical outcome data, so unable to assess if greater task execution is associated with improved clinical outcomes.

			background, equipment, etc. - Announce where and when the debrief will occur - Go through the most likely scenario from the info you received when called - Motivate the team to communicate effectively Difference in mean number of tasks performed: pre-intervention 9.23 (46.2%) vs. post-intervention 18.0 (89.6%) [p<0.001]	
Ortiz-Movilla 2022 {Ortiz-Movilla 2022 405}	**Study Type:** Multicenter, prospective quasi-experimental interventional study; N=123 (Pre-intervention: 75 neonates; Post-intervention: 48 neonates)	**Inclusion Criteria:** Neonates 28-32 weeks' gestation born in pre-intervention phase (October 2018-September 2019) and post-intervention phase (June 2020-May 2021). During the intervention phase (October 2019-May 2020): implementation of structured procedure checklists and meetings of the resuscitation team (for checklists and briefings) to check equipment, supplies and medications, assign roles, and go over the resuscitation sequence. Real-time random safety audits (RTRSAs) were conducted to assess the setup of resuscitation bed	**1° endpoint:** **Infants:** *Improve axillary temperature (ºC) and proportion with normothermia at NICU admission* Median: 36.5 (IQR: 36.3-37) vs 36.4 (IQR: 36-36.8) <32: 0 vs 0 32−35.9: 8 (10.7%) vs 11 (22.9%) 36−36.4: 25 (33.3%) vs 14 (29.1%) 36.5-37.5: 41 (54.7%) vs 22 (45.8%) >37.5: 1 (1.3%) vs 1 (2%) *Increase SaO_2 measurement in the first 3 min after birth* Unknown: 16 (21.3%) vs 10 (20.8%) <60%: 13 (17.3%) vs 14 (29.1%) 60-80%: 35 (46.7%) vs 18 (37.5%) 80%: 11 (14.7%) >80: 6 (12.5%) *Delay in SaO_2 measurement:* median 300 vs 240 seconds; p=0.039 *Reduce need for intubation and surfactant*	**Authors conclusion:** Limited evidence of short-term improvement in resuscitation preparedness but no evidence on impact on patient outcomes. **Limitations:** Short time of the implementation of checklists, briefing and debriefing for clinical impact; higher complexity of the cases in post-intervention period (more intubation, use of surfactant and adrenaline, which reflects in delay to inform the family); decreased number of preterm births in post-intervention period due to COVID; risk of bias of documentation (done by a member of the care team). Data cannot be generalized to all neonatal intensive care units due to the profile of the ones included in the study (attendance of neonates with 28-32 weeks of GA). Intervention was a mixture of briefing only, briefing + checklists or briefing, checklists and debriefing; with the addition of real time

		and equipment, supplies, drugs. The audits were recorded as no errors (correct preparation), minor errors (easy to detect and fix and unlikely to cause adverse events in the newborn), or serious errors serious adverse events).	*administration in delivery room* Highest level of respiratory support None: 6 (8%) vs 4 (8.3%) p=0.612 CPAP: 27 (36%) vs 14 (29.1%) PPV: 34 (45.3%) vs 21 (43.7%) Intubation: 8 (10.7%) vs 9 (18.75%) Surfactant: 2 (2.7%) vs 2 (4.2%) p=0.647 Need for medication**:** 0 vs 4 (8.4%) p=0.011 *Delay in informing family (minutes post birth)* Median 17 vs 30; p=0.002 No statistical differences were found for other outcomes: prenatal information; adequate thermal support; FiO_2 at CPR initiation; time of maximum FiO_2; chest compressions; respiratory support at admission; SaO_2 at 5 min post birth**;** time of admission; Apgar score in 1 and 5 minutes; CRIB score (12hours post birth) *Problems emerged during stabilization:* technical problems: 14.7% vs 6.2%; p=0.151 performing the procedure: 10.7 vs 12.5%; p=0.754 (most frequent problem: intubation at the first attempt) *Tools used in post-intervention phase (n=48):* None: 5 (10.4% Only briefings: 3 (6.2%)/ Briefings + checklist: 4 (8.3%) Briefings + debriefings + checklists: 36 (75%)	random safety audits of resuscitation equipment.

			RTRSA detected no errors: 62.7% of 852 vs 81.1% of 877 audits; p<0.001	
Ortiz-Movilla 2024 {Ortiz-Movilla 2024 1645}	**Study Type:** Multicenter, prospective quasi-experimental interventional study; n=445 (Pre-intervention phase: 225 surveys; Post-intervention phase: 220 surveys)	**Inclusion Criteria:** Surveys of personnel involved in the resuscitation of newborns <32 weeks GA during the pre-intervention phase (Oct 2018-Sept 2019) and post-intervention phase (June 2020-May 2021). Surveys contained questions about the use of a "toolkit" consisting of random real-time safety audits (RTRSA), checklists, briefing or debriefing in their centers and assessed the perceived quality of the resuscitation (overall, coordination and role allocation) using the Likert scale (minimum value 0-strongly disagree to maximum of 10-strongly agree). Additional questions in the post-intervention regarding the usefulness of the tools, satisfaction with them and perceived quality in neonatal resuscitation. **Intervention period**: 8 months (October 2019-May 2020) with implementation of	**1° endpoint:** A. Scores obtained for questions asked in each study period (sample size-n; median score and IQR at pre-intervention vs post-intervention phase) *Proper role allocation in the resuscitation team:* n=196: 9 (8–10) vs n=153: 10 (9-10)* *Proper resuscitation team coordination:* n=195: 8 (7–9) vs n=153: 9 (8-10)* *RRSAs of resuscitation stations performed:* n=193: 3 (1–4) vs n=152: 9 (8-10)* *Structured checklist of equipment and materials prior to resuscitation performed:* n=193: 8 (6–10) vs n=152: 9 (8-10)* *Pre-resuscitation team briefings* n=193: 6 (3–8) vs n=151: 8 (5-9)* *Post-resuscitation team debriefings:* n=193: 4 (1–6) vs n=149: 6 (5-8)* *Personal comfort level with the resuscitation:* n=193: 8 (6–9) vs n=148: 9 (8-10)* *Perceived quality of resuscitation:* n=196: 8 (7–9) vs n=153: 9 (8-10)* **B. According to years of experience**, Scores were better among HCP with intermediate work	**Authors conclusion:** After the introduction of a comprehensive package of quality tools to improve preparation for neonatal resuscitation, personnel involved in neonatal stabilization perceived a better allocation of roles within the team and improved coordination, resulting in a greater personal comfort during resuscitation and a higher overall quality perception of stabilization**.** Implementation of checklists and pre-resuscitation meetings had been successfully adopted in the participating units, but post-resuscitation meetings were not fully established, as indicated by low scores for questions about their effective use in both phases of the research. The greater difficulty in conducting post-resuscitation meetings may be due to a lack of time to conduct meetings, the absence of qualified personnel to act as moderators, the lack of an appropriate location to hold them (ensuring the confidentiality of discussions), or fear of potential legal consequences. **Limitations:** Multicenter study limited to NICU level III A which may not be applicable to units with different levels of care.

		the toolkits with at weekly RRSA of at least 3 neonatal resuscitation stations, checklists with systematic use, briefing and debriefing. Debriefings were performed by the leader of the resuscitation team (experienced neonatologist) **Post-Intervention period (June 2020-May 2021)**: complete toolkits continued to be implemented for 12 months. In the last 2 months, the survey was again administered to healthcare personnel (HCP) **Team:** 3-4 resuscitation providers (neonatologists, pediatric or neonatal residents, neonatal nurses, midwives/assistant nurses)	experience (10-14 years), although other groups with different levels of experience had statistically significant differences, without following a clear pattern. **C. Professional category with significant increases in scores between the two periods:** Doctors and nurses for all 7 questions and only nurses for question 8 (Perceived quality of resuscitation) **D. Perception of the utility of introduced assistance tools in postintervention phase:** RTRSA of resuscitation stations/ structured checklists/ pre-resuscitation briefings and debriefings/ utility of all measures/ satisfaction with the set of measures introduced to improve <32 weeks GA resuscitation (n=152): median score (IQR): 10 (9-10) Improvement of the quality of resuscitation (n=149): median score (IQR): 9 (7-10) with higher and significant perception among doctors than nurses. *p<0.001	

Abbreviations: CPR; cardiopulmonary resuscitation, FiO_2; fraction of inspired oxygen, GA; gestational age. HCP; health care personnel, PPV; positive pressure ventilation, IQR; interquartile range, NB; newborn, NICU; neonatal intensive care, Real-time random safety audits; RTRSAs; SaO_2, oxygen saturation, CRIB score; clinical risk index for babies score

Reviewer Comments:

This evidence update found four new observational studies on the use of briefing before neonatal resuscitation. All studies compared outcomes before and after implementing briefing interventions. Two of the papers {Ortiz-Movilla 2024 1645, Ortiz-Movilla 2022 405} were from the same quality improvement study in which briefing was part of a bundle of interventions; one paper reported clinical outcome data and the other paper reported clinician survey data. A third study reported team performance data after implementation of a briefing/debriefing model that was adapted from sports, but not clinical outcome data. {Jordache 2020 e228} The fourth study reported various aspects of communication after implementation of a standardized communication tool for exchange of information between obstetric and neonatal teams. {Brewer 2023 110}

The single study reporting clinical outcomes found an increased rate of adrenaline administration, which the authors attributed to a higher complexity of the cases in post-intervention period rather than to the intervention. {Ortiz-Movilla 2022 405} All studies reported good acceptance of the interventions by the healthcare teams, with improvements in measures such as quality of communication, equipment preparation, and team readiness for the resuscitation.

Overall, the studies support that briefing may improve short-term clinician performance outcomes, e.g. communication, preparation and confidence. However, in the one study that reported short-term clinical outcomes, there were only slight differences in oxygen saturation monitoring, medication use and updating families.

There is no new evidence on the effect of briefing on long-term clinical and performance outcomes, and this remains uncertain.

The evidence from these new studies is not sufficient to elicit a new systematic or scoping review. However, the Task Force concluded that a good practice statement was justified, as follows:

Whenever the need for resuscitation of a newborn is anticipated, there should be a briefing of the neonatal team that includes communication with the obstetric and/or midwifery team to inform the neonatal management plan (good practice statement).

Reference list:

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Fawke J, Stave C, Yamada N. Use of briefing and debriefing in neonatal resuscitation, a scoping review. Resusc Plus. 2021;5100059.

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Jordache R, Doherty C, Kenny C, Bowie P. Preliminary Adaptation, Development, and Testing of a Team Sports Model to Improve Briefing and Debriefing in Neonatal Resuscitation. Pediatr Qual Saf. 2020;5(1)e228.

Katheria A, Rich W, Finer N. Development of a strategic process using checklists to facilitate team preparation and improve communication during neonatal resuscitation. Resuscitation. 2013;84(11)1552-7.

Magee MJ, Farkouh-Karoleski C, Rosen TS. Improvement of Immediate Performance in Neonatal Resuscitation Through Rapid Cycle Deliberate Practice Training. J Grad Med Educ. 2018;10(2)192-197.

Ortiz-Movilla R, Beato-Merino M, Funes Moñux RM, Martínez-Bernat L, Domingo-Comeche L, Royuela-Vicente A, et al. What Is the Opinion of the Health Care Personnel Regarding the Use of Different Assistive Tools to Improve the Quality of Neonatal Resuscitation? Am J Perinatol. 2024;41(12)1645-1651.

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Sauer CW, Boutin MA, Fatayerji AN, Proudfoot JA, Fatayerji NI, Golembeski DJ. Delivery Room Quality Improvement Project Improved Compliance with Best Practices for a Community NICU. Sci Rep. 2016;637397.

Skåre C, Calisch TE, Saeter E, Rajka T, Boldingh AM, Nakstad B, et al. Implementation and effectiveness of a video-based debriefing programme for neonatal resuscitation. Acta Anaesthesiol Scand. 2018;62(3)394-403.

Wyckoff MH, Wyllie J, Aziz K, de Almeida MF, Fabres J, Fawke J, et al. Neonatal Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2020;142(16_suppl_1)S185-s221.

Yeung J, Djarv T, Hsieh MJ, Sawyer T, Lockey A, Finn J, et al. Spaced learning versus massed learning in resuscitation - A systematic review. Resuscitation. 2020;15661-71.

Appendix: Search strategy

Sources searched	**Search strategy (as for previous ScopRev)**	**Search time frame**
PubMed	(“infant, newborn” [mesh] OR infant* [tw] OR preterm [tw] OR preemie* [tw] OR newborn* [tw] OR neonat* [tw]) AND (“resuscitation” [mesh] OR resuscitat* [tw] OR cpr [tw]) AND (“critical reflection” [tw] OR reflection [tw] OR “post simulation” [tw] OR “pre briefing” [tw] OR prebrief* [tw] OR debrie* [tw] OR brief [tw] OR briefing [tw] OR “after action review” [tw] OR feedback [tw] OR “communication” [mesh]) AND (English [lang] OR English Abstract[ptyp]).	30 Dec 2019 - 26 May 2024
Embase	('newborn'/exp OR 'newborn' OR infant*:ti,kw,ab OR preterm:ti,kw,ab OR preemie*:ti,kw,ab OR newborn*:ti,kw,ab OR neonat*:ti,kw,ab) AND ('resuscitation'/exp OR 'resuscitation' OR resuscitat*:ti,kw,ab OR cpr:ti,kw,ab) AND ('interpersonal communication'/exp OR 'interpersonal communication' OR 'debriefing'/exp OR 'debriefing' OR 'critical reflection':ti,kw,ab OR 'reflection'/exp OR 'reflection' OR reflection:ti,kw,ab OR 'post simulation':ti,kw,ab OR 'pre briefing':ti,kw,ab OR prebrief*:ti,kw,ab OR debrie*:ti,kw,ab OR brief:ti,kw,ab OR briefing:ti,kw,ab OR 'after action review':ti,kw,ab OR feedback:ti,kw,ab) AND ([embase]/lim OR [embase classic]/lim).	
Web of Science	(infant* OR preterm OR preemie* OR newborn* OR neonat*) AND (resuscitat* OR cpr) AND (“critical reflection” OR reflection OR “post simulation” OR “pre briefing” OR prebrief* OR debrie* OR brief OR briefing OR “after action review” OR feedback).	
Cochrane Library	(infant* OR preterm OR preemie* OR newborn* OR neonat*) AND (resuscitat* OR cpr) AND (communicat* OR “critical reflection” OR reflection OR “post simulation” OR “pre briefing” OR prebrief* OR debrie* OR brief OR briefing OR “after action review” OR feedback).	
clinicaltrials.gov		inception - 6 October 2024
Results identified	**Results screened full text**	**Results included**
174	6	4

2025 Evidence Update
NLS 5050 – Umbilical Cord Management at Birth for Term and Late Preterm Infants

Worksheet Author(s): Katheria A, Davis PG, Soraisham A, Lee H, Liley H.
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest: None

Note that this PICOST was intended to include both vigorous and non-vigorous infants, but the trials included in the previous systematic review largely excluded non-vigorous infants, or those at high risk of needing resuscitation. Recognizing that these latter infants are an important subgroup whose management may need to differ, we have now split NLS 5050 into:

- NLS 5050[a]: Umbilical cord management at birth for nonvigorous term and late preterm infants (addressed by a 2025 SysRev)
- NLS 5050[b]: Umbilical cord management at birth for vigorous term and late preterm infants (trials addressing this group were included in this evidence update)

PICOST
Population: Vigorous term and late preterm infants (≥34 weeks' gestation) or equivalent birth weight
Intervention:
- Later (delayed) cord clamping: Cord clamping after a delay of at least 30 seconds
- Intact-cord milking: Repeated compression of the cord from the placental side toward the baby with the connection to the placenta intact
- Cut-cord milking: Drainage of the cord by compression from the cut end toward the baby after clamping and cutting a long segment

Comparator:
- Early clamping of the cord (clamping at less than 30 seconds after birth) without cord milking or initiation of respiratory support compared with each of the above interventions
- Between-intervention comparisons
- Later (delayed) cord clamping at less than 60 seconds compared with 60 seconds or more
- Later (delayed) cord clamping based on time since birth compared with physiological approach to cord clamping (until cessation of pulsation of the cord or based on vital signs monitoring/initiation of breathing)

Outcome:
Neonatal:
- Mortality (critical)
- Moderate or severe hypoxic ischaemic encephalopathy {Sarnat 696} (critical)
- Resuscitation (PPV ± intubation ± chest compressions) (important)
- Respiratory distress (important)
- Admission to neonatal intensive or special care nursery (important)
- Hematologic outcomes; hemoglobin; hematocrit; hyperbilirubinemia treated with phototherapy; polycythaemia; (important) partial or full exchange transfusion (critical)

Infant:
- Moderate or severe neurodevelopmental impairment (critical)
- Ferritin concentration (important)

Maternal:
- Death or severe morbidity (critical)
- Severe postpartum hemorrhage (critical)
- Manual removal of the placenta (important)
- Post-partum infection (critical)

Study design:
RCTs, quasi-RCTs, and cluster RCTs were eligible for inclusion. For studies that reported on a broad population of infants (including preterm infants of <34 weeks' gestation, late preterm infants, and term infants), we considered studies that had a preponderance of late preterm and term infants (defined as study populations comprising >80% late preterm or term infants). Unpublished studies (e.g., conference abstracts, trial protocols) were excluded. All languages were included provided there was an English abstract
Time frame: . All years were included from database inception. The literature search was updated to July 26, 2019.
A priori subgroups

- Mode of birth: caesarean delivery vs vaginal delivery.
- Gestation at birth: 34^{+0} to 36^{+6} weeks vs ≥ 37^{+0} weeks vs mixed gestational ages vs not reported.
- Respiratory support: with the cord intact vs after the cord is cut vs unclear (whether with the cord intact, after the cord is cut or not recorded at all).
- Timing of administration of uterotonic agent: before clamping the cord vs after clamping the cord vs mixed vs not reported.
- Placement of the newborn relative to placenta: below placenta level vs at placenta level vs above placenta level vs unclear/not reported.
- Whether or not there was later (delayed) cord clamping before milking/stripping: cord clamping delayed before milking vs no delay before milking vs unclear/ not reported.
- Number of fetuses: multiples vs singletons vs multiples and singletons combined vs not reported.
- Newborn congenital anomalies or other conditions: anomalies or conditions noted at or prior to birth.
- Fetal anemia: anemia vs no anemia vs mixed vs not reported.
- Size for gestational age: small for gestational age vs appropriate for gestational age vs large for gestational age vs mixed vs not reported).
- Infant status at birth: vigorous or breathing vs non-vigorous or not breathing vs mixed vs not reported.
- Infants born in different-resourced countries: low-and middle-income countries vs high-income countries vs mixed vs not reported**.**

Year of last full review: 2021 {Gomersall 2021 e2020015404}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Wyckoff 2021 229}
Consensus on Science (summarized in table form – see the full on-line CoSTR for details of reasons for downgrading and additional details)

COMPARISON 1: LATER (DELAYED) CORD CLAMPING AT ≥30 SECONDS VS EARLY CORD CLAMPING AT <30 SECONDS AFTER BIRTH. Thirty-three studies (5263 mothers and their infants)

Outcome	**Studies**	**Results**	**Certainty of evidence**
Survival without moderate to severe neurodevelopmental impairment (critical)	No studies		
Neonatal mortality (critical)	4 RCTs, 537 infants {Backes 2015 826, Ceriani Cernadas 2006 e779, Chopra 2018 234, Datta 2017 418}	Could not exclude benefit or harm Risk ratio (RR) =2.54, 95% confidence interval (CI) 0.50 to 12.74, I^2 = 0%	Very low
Receiving resuscitation after birth (important)	3 RCTs, 329 infants {Datta 2017 418, Salari 2014 287, Withanathantrige 2017 }	Could not exclude benefit or harm RR=5.08, 95% CI 0.25 to 103.58, heterogeneity N/A as two studies reported no infants receiving resuscitation	Very low
Respiratory distress (important)	the poor definition, missing data, and inconsistency of the outcome in the available studies led to a decision not to pool the data for meta-analysis		
Admission to neonatal intensive care unit or special care nursery (important)	10 RCTs, 1968 infants {Andersson 2011 d7157, Ceriani Cernadas 2006 e779, Chen 2018 , De Paco 2011 1011, Mercer 2017 260, Mohammad 2021 231, Salari 2014 287, Vural 2019 555}	Could not exclude benefit or harm RR= 1.16, 95% CI 0.69 to 1.95, I^2 = 0%	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 24 hours after birth (important)	*Hb:* 9 RCTs**,** 1352 infants {Al-Tawil 2012 319, Chaparro 2006 1997, De Paco 2016 153, Emhamed 2004 218, Fawzy 2015 , Mohammad 2021 231, Salari 2014 287, Ultee 2008 F20, Yadav 2015 720}	*Higher Hb:* mean difference (MD)= 1.17 g/dL, 95% CI 0.48 to 1.86 I^2= 89% *Higher Hct:* MD= 3.38% 95% CI 2.08 to 4.67, I^2= 81%	Very low

	Hct: 12 RCTs, 2183 infants {Al-Tawil 2012 319, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chen 2018 , Chopra 2018 234, Emhamed 2004 218, Jahazi 2008 523, Philip 1973 334, Salari 2014 287, Ultee 2008 F20, Vural 2019 555, Yadav 2015 720}		
Polycythemia (hematocrit > 65%) (important)	13 RCTs, 1335 infants {Backes 2015 826, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chopra 2018 234, Emhamed 2004 218, Grajeda 1997 425, Krishnan 2015 183, Mercer 2017 260, Saigal 1972 406, Salae 2016 S159, Salari 2014 287, Ultee 2008 F20, van Rheenen 2007 603}	Higher rates of polycythemia: RR=2.26, 95% CI 1.56 to 3.28; number needed to treat to harm (NNTH) 20 (95% CI 13 to 33); I^2 = 0%, RD= 0.05 (95% CI 0.03 to 0.08); 50/1000 more infants had polycythemia after later cord clamping for ≥ 30 seconds compared to early cord clamping [95% CI: 30 more to 80 more per 1000]).	Low
Partial exchange transfusion (important)	2 RCTs, 164 infants {Chopra 2018 234, Vural 2019 555}	Could not exclude benefit or harm RR=2.11, 95% CI 0.55 to 8.02	Very low
Exchange transfusion (important)	1 RCT, 86 infants {Salae 2016 S159}	No events	N/A
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth (important)	*Hb:* 3 RCTs, 695 infants {Andersson 2011 d7157, Mercer 2017 260, Yadav 2015 720} *Hct:* 5 RCTs, 590 infants {Cavallin 2019 252, Mercer 2018 266, Philip 1973 334}	*Higher Hb:* MD= 1.11 g/dL, 95% CI 0.40 to 1.82, I^2= 82% *Higher Hct:* MD= 5.84%, 95% CI 2.74 to 8.95, I^2= 91%	Very low
Hyperbilirubinemia treated with phototherapy	15 RCTs, 2814 infants {Al-Tawil 2012 319, Andersson 2011 d7157, Backes 2015 826, Cavallin 2019 252, Chen 2018 , Emhamed 2004 218, Krishnan 2015 183, Mercer 2017 260, Oxford Midwives Research Group 1991 167, Salae 2016 S159, Ultee 2008 F20, van Rheenen 2007 603, Vural 2019 555, Withanathantrige 2017 , Yadav 2015 720}	Could not exclude benefit or harm RR= 1.28 95%, CI 0.90 to 1.82, I^2=19%	Very low
Neurodevelopmental impairment in early childhood	1 RCT, 245 children (Using Ages and Stages Questionnaire (ASQ)-3 total scores at four years of age, {Andersson 2015 631}	Could not exclude benefit or harm MD=3.40 points, 95% CI -2.86 to 9.66	Very low
Anemia at 4-6 months of age	4 RCCTs, 937 infants {Al-Tawil 2012 319, Andersson 2011 d7157, Chaparro 2006 1997, van Rheenen 2007 603}	Could not exclude benefit or harm RR=1.01, 95% CI 0.75 to 1.37, I^2 = 0%	Very low

Ferritin concentrations at 3-6 months of age	3 RCTs, 286 infants {Al-Tawil 2012 319, Chopra 2018 234, Mercer 2018 266}	Could not exclude benefit or harm High levels of ferritin in one study and the heterogeneity between the three studies made clinical interpretation difficult other than late cord clamping being associated with higher ferritin	Very low
Low ferritin concentrations (<9 µg/L, <20 µg/L and <50 µg/L) at 3-6 months of age	*Ferritin <9 µg/L*: 2 RCTs, 610 infants {Ceriani Cernadas 2010 201, Chaparro 2006 1997}, *Ferritin <20 µg/L:* 2 RCTs, 507 infants {Al-Tawil 2012 319, Andersson 2011 d7157} *Ferritin <50 µg/L:* 1 RCT, 82 infants {Chopra 2018 234},	Lower rates of low ferritin: *Ferritin <9 µg/L:* RR= 0.46, 95% CI 0.26 to 0.82, I^2 =47%, NNTB = 60/1000 fewer/1000 (95% CI 10 fewer to 100 fewer/1000) *Ferritin <20 µg/L:* RR= 0.10, 95% CI 0.03 to 0.35, I^2 = 0%, NNTB = 90 fewer/1000, 95% CI 50 fewer to 130 fewer/1000) *Ferritin <50 µg/L:* RR= 0.50, 95% CI 0.26 to 0.95, NNTB 240 fewer/1000, 95% CI 40 fewer to 440 fewer/1000)	Very low
Maternal mortality or severe morbidity (critical)	No studies		
Maternal postpartum hemorrhage (critical)	10 RCTS, 2675 women {Andersson 2013 567, Backes 2015 826, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chen 2018 , Krishnan 2015 183, Mohammad 2021 231, Oxford Midwives Research Group 1991 167, van Rheenen 2007 603, Withanathantrige 2017 }	Could not exclude benefit or harm RR= 0.89, 95% CI 0.70 to 1.13, I^2 =13%	Low
Maternal severe postpartum hemorrhage (critical	6 RCTs, 1828 women {Andersson 2015 631, Backes 2015 826, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chen 2018 , Withanathantrige 2017 }	Could not exclude benefit or harm RR= 0.75, 95% CI 0.42 to 1.35, I^2 =0%).	Very low
Manual removal of placenta (important)	2 RCTs, 247 women {van Rheenen 2007 603, Withanathantrige 2017 }	Could not exclude benefit or harm RR= 0.58, 95% CI 0.21 to 1.65	Low

COMPARISON 2: INTACT CORD MILKING VS EARLY CORD CLAMPING
One RCT, 24 infants.

Outcome	**Studies**	**Results**	**Certainty of evidence**
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth (important)	1RCT, 24 infants {Erickson-Owens 580}	*Higher Hb:* MD= 2.2 g/dL 95%, CI 0.48 to 3.92 *Higher Hct:* MD= 7.50%, 95% CI 2.30 to 12.70	Very low

COMPARISON 3: Cut cord milking vs early cord clamping

One RCT, 200 infants

Outcome	Studies	Results	Certainty of evidence
Neonatal mortality (critical)	1 RCT, 200 infants {Upadhyay 2013 120}	Could not exclude benefit or harm RR= 0.20, 95% CI 0.01 to 4.11	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 24 hours after birth (important)	1 RCT, 200 infants {Upadhyay 2013 120}	*Higher Hb:* MD= 1.60 g/dL, 95% CI 0.96 to 2.24 *Higher Hct:* MD= 4.30%, 95% CI 2.36 to 6.24	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth (important)	1 RCT, 200 infants {Upadhyay 2013 120}	*Higher Hb:* MD= 1.10 g/dL, 95% CI 0.74 to 1.46 *Higher Hct:* MD= 4.00%, 95% CI 2.29 to 5.71	Very low

COMPARISON 4: LATER (DELAYED) CORD CLAMPING VS INTACT CORD MILKING.
One RCT {Alzaree 2018 1399}. No reliable assessment of treatment effects could be drawn because of serious methodologic concerns with the study.

COMPARISON 5: LATER (DELAYED) CORD CLAMPING AT ≥ 30 SECONDS VS CUT CORD MILKING
Three RCTs, 740 infants.

Outcome	Studies	Results	Certainty of evidence
Neonatal mortality (critical)	1 RCT, 300 infants {Yadav 2015 720}	Could not exclude benefit or harm RR= 1.00, 95% CI 0.09 to 10.90	Very low
Admission to neonatal intensive care unit or special care nursery (important)	1 RCT, 200 infants {Jaiswal 2015 1159}	Could not exclude benefit or harm RR= 1.83, 95% CI 0.71 to 4.77	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 24 hours after birth (important)	2 RCTs, 500 infants {Jaiswal 2015 1159, Yadav 2015 720}	*Lower Hb:* MD = -0.56 g/dL, 95% CI -0.92 to -0.21, I^2 =9% *Lower Hct:* MD= -1.60%, 95% CI -3.11 to -0.09, I^2= 45	Very low
Hyperbilirubinemia treated with phototherapy (important)	2 RCTs, 500 infants {Jaiswal 2015 1159, Yadav 2015 720}	Could not exclude benefit or harm RR=1.36, 95% CI 0.66 to 2.81, I^2 = 0%	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth (important)	2 RCTs, 500 infants {Jaiswal 2015 1159, Yadav 2015 720}	*Lower Hb:* MD= -0.47 g/dL, 95% CI -0.81 to -0.13 *Lower Hct:* MD= -1.11%, 95% CI -2.12 to -0.09, I^2= 0%	Very low

COMPARISON 6: INTACT CORD MILKING VS CUT CORD MILKING
No trials were identified.

COMPARISON 7: LATER (DELAYED) CORD CLAMPING ≥ 60 SECONDS VS LATER (DELAYED) CORD CLAMPING <60 SECONDS.
Seven studies, 2745 mothers and their infants.

Outcome	Studies	Results	Certainty of evidence
Neonatal mortality (critical)	1 RCT, 231 infants {Andersson 2019 15}	Could not exclude benefit or harm RR= 0.10, 95% CI 0.01 to 1.98	Very low
Admission to neonatal intensive care unit or special care nursery (important)	1 RCT, 200 infants {Jaiswal 2015 1159}	Could not exclude benefit or harm RR=0.73, 95% CI 0.40 to 1.35, I^2 = 26%	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 24 hours after birth (important)	1 RCT, 60 infants {Katheria 2017 313}	*Higher Hb:* MD=1.30 g/dL, 95% CI 0.14 to 2.46	Very low
Hyperbilirubinemia treated with phototherapy (important)	2 RCTs, 906 infants {Kc 2017 264, Nouraie 2019 45}	Higher (or no difference) RR=1.93, 95% CI 1.00 to 3.72, I^2 = 60%	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth (important)	2 RCTs, 500 infants {Jaiswal 2015 1159, Yadav 2015 720}	*Lower Hb:* MD= -0.47 g/dL, 95% CI -0.81 to -0.13 *Lower Hct:* MD= -1.11%, 95% CI -2.12 to -0.09, I^2= 0%)	Very low
Receiving respiratory support (important)	1 RCT, 60 infants {Katheria 2017 313}	Could not exclude benefit or harm RR=0.53, 95% CI 0.27 to 1.07	Very low
Neurodevelopmental impairment in early childhood	1 RCT, 540 infants (Using Ages and Stages Questionnaire (ASQ)-3 total scores at 12 months of age {Rana 2019 }	Higher proportion had ASQ-3 scores >279: **higher** proportion of ASQ-3 scores >279 RR=2.33, 95% CI 1.44 to 3.78; NNTB; 103/1000 more infants had ASQ-3 scores >279 95% CI: 34/1000 more to 216/1000 more	Very low

COMPARISON 8: LATER (DELAYED) CORD CLAMPING AT ≥ 30 SECONDS VS PHYSIOLOGICAL APPROACH (E.G. CLAMPING DELAYED TO CESSATION OF PULSATION OF THE CORD OR BASED ON VITAL SIGNS MONITORING, OR INITIATION OF BREATHING).
Three studies, 1113 mothers and their infants.

Outcome	Studies	Results	Certainty of evidence
Neonatal mortality (critical)	1 RCT, 338 infants {Sun 2017 14}	Could not exclude benefit or harm RR=5.00, 95% CI 0.24 to 103.37	Very low
Receiving resuscitation after birth (important)	1 RCT, 338 infants {Sun 2017 14}	Could not exclude benefit or harm RR=1.67, 95% CI 0.84 to 3.30	Very low

Admission to neonatal intensive care unit or special care nursery (important)	2 RCTs, 878 infants {Chen 2018 , Sun 2017 14}	Could not exclude benefit or harm RR= 2.58, 95% CI 0.04 to 163.65, I^2 = 80%	Very low
Hematocrit values (%) within the first 24 hours after birth (important)	1 RCT, 540 infants {Chen 2018 }	*Lower Hb:* MD= -1.40%, 95% CI -2.79 to -0.01	Very low
Hyperbilirubinemia treated with phototherapy (important)	3 RCTs, 932 infants {Chen 2018 , Nelson 1980 655, Sun 2017 14}	Could not exclude benefit or harm RR=0.88, 95% CI 0.53 to 1.44, I^2 = 0%	Very low
Hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth (important)	1 RCT, 338 infants {Sun 2017 14}	*Lower Hb:* MD= -1.70 g/dL, 95% CI -1.97 to -1.43 *Lower Hct:* MD= -6.50%, 95% CI -7.64 to -5.16	Very low
Receiving respiratory support (important)	1 RCT, 60 infants {Katheria 2017 313}	Could not exclude benefit or harm RR=0.53, 95% CI 0.27 to 1.07	Very low
Neurodevelopmental impairment in early childhood	1 RCT, 540 infants (Using Ages and Stages Questionnaire (ASQ)-3 total scores at 12 months of age {Rana 2019 }	Higher proportion had ASQ-3 scores >279: RR=2.33, 95% CI 1.44 to 3.78; NNTB; 103/1000 more infants had ASQ-3 scores >279 95% CI: 34/1000 more to 216/1000 more	Very low
Maternal postpartum hemorrhage (critical)	2 RCTS, 594 women {Chen 2018 , Nelson 1980 655}	Could not exclude benefit or harm RR 0.92, 95% CI 0.40 to 2.07, I^2 = 0%	Very low
Maternal severe postpartum hemorrhage (critical	1 RCT, 540 women {Chen 2018 }	Could not exclude benefit or harm RR 1.82, 95% CI 0.10 to 33.4	Very low
Postpartum infection (important)	1 RCT, 54 women {Nelson 1980 655}	Could not exclude benefit or harm RR 0.15, 95% CI 0.01 to 2.83	Very low

SUBGROUP ANALYSES

The number of pre-specified subgroup analyses was large, was multiplied by the number of comparisons. The p-values were not adjusted for multiple comparisons. As a consequence, GRADE evaluations were not done for all subgroup analyses: instead, post hoc GRADE evaluations were requested for outcomes considered important for our justification, values and preferences statements. These subgroup analyses are exploratory and must be interpreted with caution, especially for interaction tests between studies and by strata that were not used in randomization.

COMPARISON 1: LATER (DELAYED) CORD CLAMPING AT ≥30 SECONDS VS EARLY CORD CLAMPING AT <30 SECONDS AFTER BIRTH.
A- Subgroups according to gestational age

*For the important outcome of **hyperbilirubinemia treated with phototherapy among term infants (≥ 37 weeks' gestation)***, the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **13 trials** involving 2691 infants {Al-Tawil 2012 319, Andersson 2011 d7157, Backes 2015 826, Cavallin 2019 252, Chen 2018 , Emhamed 2004 218, Krishnan 2015 183, Mercer 2017 260, Oxford Midwives Research Group 1991 167, van Rheenen 2007 603, Vural 2019 555, Withanathantrige 2017 , Yadav 2015 720} showed **more** term infants in the later cord clamping group received phototherapy for hyperbilirubinemia compared to

early cord clamping group (RR=1.54, 95% CI 1.01 to 2.34; RD= 0.01 [0.00, 0.03; NNTH= 100; I^2= 15%); 10/1000 more term infants had hyperbilirubinemia treated with phototherapy after later cord clamping compared to early cord clamping [95% CI: 0 to 30 more per 1000]).

Among **late preterm infants (34 – 36^{+6} weeks' gestation**), the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **2 trials** involving 123 infants {Salae 2016 S159, Ultee 2008 F20} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR= 0.72, 95% CI 0.37 to 1.40, I^2 = 0%). The p-value for interaction between subgroups was 0.06.

B- Subgroups according to different resource settings, based upon World Bank country classifications

*For the important outcomes of **hematocrit values (%) within the first 24 hours after birth***, the evidence from **8 trials** involving 1279 infants **in low- or middle- income countries** {Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chopra 2018 234, Emhamed 2004 218, Jahazi 2008 523, Salari 2014 287, Vural 2019 555, Yadav 2015 720} and from **4 trials** involving 904 infants in **high-income countries**; {Al-Tawil 2012 319, Chen 2018 , Philip 1973 334, Ultee 2008 F20} showed **higher** hematocrit values in the later cord clamping group compared to early cord clamping (MD= 2.42%, 95% CI 1.11 to 3.73, I^2=71% and MD= 5.75%, 95% CI 2.90 to 8.58, I^2= 88%) respectively. The effect was **greater** in studies performed in high-income countries than in studies performed in low- or middle-income countries (p-value for interaction between subgroups was 0.04).

C- Subgroup analyses according to the timing of uterotonic medication administration and according to size for gestational age did not reveal significant differences between subgroups.

TREATMENT RECOMMENDATIONS

For term and late preterm infants born at ≥34 weeks' gestation who are vigorous or deemed not to require immediate resuscitation at birth, we suggest later (delayed) clamping of the cord at ≥ 60 seconds (weak recommendation, very low certainty evidence).

Current Search Strategy: see appendix

New Search strategy
Database searched: Medline Embase Cochrane
Time Frame: updated from 26 July 2019 (last search) to 10 July 2024
Date Search Completed: 10 July 2024
Search Results:
Identified:
Full text screened:
Included: 43

Summary of Evidence Update: There were 43 new reports of randomized (or quasi-randomized trials) since the last review.

RCTs:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Purisch 2019 {Purisch 2019 1869}	**Study Aim:** Compare maternal blood loss with immediate cord clamping vs delayed cord clamping in scheduled cesarean deliveries at term (≥37 weeks). **Study Type:** RCT	**Inclusion Criteria:** Women with singleton gestations undergoing scheduled cesarean delivery at	**Intervention:** DCC 60 sec, (n=57) **Comparison:** ICC ≤ 15 sec (n=56)	**1° endpoint:** Maternal Hb at postoperative day 1 (compared to pre-operative level); mean decrease of −1.90 g/dL (95% CI, −2.14 to −1.66) in the DCC group and −1.78 g/dL (95% CI, −2.03	**Relevant 2° Endpoint:** At 24 to 72 hours of life, there was a 1.7 g/dL higher neonatal Hb level with DCC vs ICC (mean, 18.1 g/dL [95% CI, 17.4-18.8] vs 16.4 g/dL [95%

	N= 113	term (≥37+0 wks)		to −1.54) in the ICC group (MD, 0.12 g/dL [95% CI, −0.22 to 0.46]; *P* = .49).	CI, 15.9-17.0]; MD, 1.67 g/dL [95% CI, 0.75-2.59]; *P* < .001) **Study Limitations:** only scheduled term cesarean deliveries of singleton gestations.
Mangla 2020 {Mangla 2020 1119}	**Study Aim:** Compare the effect of intact UCM and DCC on venous hematocrit at 48 (±6) hours **Study Type:** RCT N=144	**Inclusion Criteria:** Women with singleton gestations undergoing scheduled cesarean delivery in late preterm and term neonates (35- 42 wk)	**Intervention:** UCM group (cord milked four times towards the baby while attached to the placenta) n=72 **Comparison:** DCC ≥60 sec n=72	**1° endpoint:** Venous hematocrit at 6 (±1) weeks was higher in UCM than in DCC group [mean (SD), 37.7 (4.3) vs. 36 (3.4); MD 1.75 (95% CI 0.53 to 2.9); P=0.005].	**Study Limitations:** only scheduled term cesarean deliveries of singleton gestations.
Ozbasli 2024 {Ozbasli 2024 1883}	**Study Aim:** Compare the effects of ECC, DCC and UCM on maternal and neonatal outcomes in elective cesarean births. **Study Type:** RCT (3 arms) N=204	**Inclusion:** Uncomplicated singleton pregnancies, written informed consent for C-section	**Intervention:** DCC 60 sec N=71 UCM: the cord was clamped after stripping the cord from the placenta toward the infant five times, with 2 s of milking and spontaneous blood flow. n=67 Control: ECC ≤15 sec n=66	**1° endpoint:** Intraoperative bleeding was significantly higher in the ECC group: ECC 500 mL DCC 300 mL UCM 225 mL p < 0.001.	**Relevant 2° Endpoint:** DCC and UCM did not negatively affect maternal and neonatal outcomes compared with ECC. **Study Limitations:** only scheduled term cesarean deliveries of singleton gestations.
Soliman 2024 {Soliman 2024 739}	**Study Aim:** Study the effect of DCC at 120 seconds compared with 30 seconds on multiple hemodynamic variables in full-term infants using an electrical cardiometry. **Study Type:** RCT N=68	**Inclusion Criteria:** Women with singleton gestations undergoing scheduled cesarean delivery in late preterm and term neonates (35- 42 wks)	**Intervention:** 120 sec n=34 **Comparison:** DCC 30 sec (or defined as ECC) n=34	**1° endpoint:** Cardiac Output was significantly increased in DCC 120 sec compared with DCC at 30 sec at 5, 10, 15 min, and 24 h after birth (p values of 0.004, 0.042, 0.021, and 0.035)	**Relevant 2° Endpoint:** Hb, Hct, and total bilirubin concentrations were higher in the DCC 120 sec group compared with DCC 30 sec at 24 h. **Study Limitations:** only scheduled term cesarean deliveries.
Rana 2020 {Rana 2020 71}	**Study Aim:** to investigate the effects of timing of cord clamping on the risk of hyperbilirubinemia.	**Inclusion Criteria:** Healthy newborns born by	**Intervention:** ECC <60 sec n=270 **Comparison:** DCC > 180 sec n=270	**1° endpoint:** mean transcutaneous bilirubin in the ECC group was 87.8 ± 41.1 µmol/L and 85.4	**Relevant Secondary endpoints** The combined number of newborn infants in

	Study Type: RCT N=540	vaginal delivery		± 36.1 µmol/L in the DCC group	the intermediate and high-risk groups were 85/261 (32.6%) for ECC group and 92/263 (35.0%) for DCC group (P = 0.58). Of those, 22/261 (8.4%) in the early group and 25/263 (9.5%) in the delayed group (P = 0.76) had a high risk of subsequent significant hyperbilirubinemia . **Study Limitations:** only healthy term vaginal delivery. Study not blinded
de Preud'homme d'Hailly de Nieuport 2024 {de Preud'homme d'Hailly de Nieuport 2024 101279}	**Study Aim:** To determine whether clamping the umbilical cord after 2 minutes is superior to cord milking during elective cesarean deliveries at term. hyperbilirubinemia. **Study Type:** RCT N=115	**Inclusion Criteria:** Planned elective caesarean delivery between 37 and 41 wks.	**Intervention:** DCC 120 sec. n=57 **Control:** CM was defined as milking the intact umbilical cord 4 times in the direction of the neonate. n=58	**1° endpoint:** Hb and Hct levels 48 hours after birth); no statistically significant difference was observed between the DCC and CM groups (Hb: 12.1 vs 12.2; 95% confidence interval [CI], 0.34 to 0.44; P=.80; Ht: 0.54 vs 0.54; 95% CI, 0.39 to 0.39; P=.99)	**Relevant 2° Endpoint:** There were no differences between groups in maternal blood loss, maternal infection, Hb at 4 months after birth, or ferritin levels 4 months after birth. **Study Limitations:** Only included elective CD. Also underpowered study to look at differences of superiority and safety.
Kilicdag 2022 {Kilicdag }	**Study Aim:** Evaluate the impact of cord clamping after the first spontaneous breath on placental transfusion in neonates born by CS. **Study Type:** RCT N=123	**Inclusion Criteria:** live singleton pregnancy at ≥ 37 weeks of gestation admitted for CS	**Intervention:** - Physiologic-based cord clamping (PBCC), n=31 - I-UCM, n=30 - DCC 30sec, n=32 **Control:** DCC 60 sec, n=30	**1° endpoint:** Mean Hb) and Hct significantly higher in the DCC 60 sec group than in the PBCC group p =0.028. but no difference was noted among the IUCM, 30s DCC, and PBCC groups at 36h of age.	**Relevant 2° Endpoint:** Peak total serum bilirubin (TSB) levels were higher in the DCC 60 sec group than in the IUCM and PBCC groups (p = 0.017), but there was no difference between the 60s DCC and 30s DCC groups during the first week of life.

					The phototherapy requirement was higher in in IUCM and DCC 30 sec (p =0.001). **Study Limitations:** Only included CS and providers were not blinded so potential risk of bias for phototherapy rates
Ofojebe 2021 {Ofojebe 2021 99}	**Study Aim:** To compare the hemoglobin and serum bilirubin concentration of term newborn following delayed and immediate umbilical cord clamping **Study Type:** RCT N=204	**Inclusion Criteria:** Singleton pregnancy in labor at gestation 37 to 42 wks, vaginal delivery	**Interventions:** DCC 60 sec (n=102) **Control** ICC 0-15 sec (n=102)	**1° endpoint:** Neonatal Hb at 48 h after birth (mean ± SD): DCC; 15.51 ± 1.71 g/dl vs ICC 15.16 ± 2.27 g/dl; p < 0.001).	**Relevant 2° Endpoint:** Maternal blood loss of >500ml: DCC vs ECC (2 vs 2.9%, P=0.653) **Study Limitations:** Only included healthy vaginal deliveries
Seliga-Siwecka 2020 {Seliga-Siwecka 613}	**Study Aim:** To evaluate if placental transfusion (delayed cord clamping or cord milking) increases the risk hyperbilirubinemia requiring phototherapy in term infants **Study Type:** RCT N=359	**Inclusion Criteria:** Maternal-fetal dyads, in labour at 37–42 wks Non-smok ing mothers, willing to return for follow up visits, who planned to breastfeed for at least 6 months	**Interventions:** DCC 2 min n=118 UCM group milking the intact cord 4 times. n=117 **Control** ECC 30 sec, n=124	**1° endpoint:** Percentage of neonates requiring phototherapy did not differ significantly between the ECC, CM and DCC group (23%, 29% and 29%, respectively)	**Study Strengths:** Sufficient sample size for noninferiority Providers were blinded to allocation for determining the need for phototherapy
Kumawat 2022 {Kumawat 2022 258}	**Study Aim:** To investigate the effect of UCM on hematologic parameters at 10 to 14 weeks in term and late preterm neonates **Study Type:** RCT N=168	**Inclusion Criteria:** Gestation ≥ 34 weeks, (and mode of delivery)	**Interventions:** UCM group milking the intact cord 3 times. n=84 **Control** : ECC <30 sec n=84	**1° endpoint:** Hb (primary outcome) was slightly higher in the UCM group at 48 hours and at 10 to 14 weeks, than in the ECC group (P = .22)	**Relevant 2 endpoint** Serum Ferritin level was higher in the intervention group at 10 to 14 weeks of age (MD = 38.9 µg/L; P = .03) than that in the ECC group. Hb level and PCV (secondary outcomes) were

					higher at 48 hours of life than in the ECC group. **Study concerns:** Randomization was using odd numbers for UCM and even for ECC. High risk for bias.
Schwaberger 2022 {Schwaberger 1005947}	**Study Aim:** To evaluate cerebral tissue oxygenation index (cTOI) during neonatal transition in a group of healthy full-term neonates receiving either a physiological based approach of deferred cord clamping after the onset of stable regular breathing (PBCC group) or a standard approach of time-based CC **Study Type:** RCT N=71	**Inclusion Criteria:** Vaginally delivered healthy full-term neonates	**Interventions:** PBCC group The cord was clamped after onset of stable regular breathing n=35 **Control group** Time-based approach, in which the umbilical cord was clamped approximately 30–40 s after birth. n=36	**1° endpoint:** No significant differences between the two groups for cTOI (p=0.319), ΔCBV (p =0.814), SpO2 (p=0.322) and HR (p=0.878) during the first 15 min after birth.	**Study Limitations:** Only vaginal delivered infants were included
Orpak 2021 {Orpak 2019 1}	**Study aim:** To determine whether C-UCM is as effective as I-UCM. **Study Type:** RCT	**Inclusion Criteria:** Healthy infants, ≥ 37 wks gestation, regardless of delivery mode.	**Interventions:** Cut cord milking (C-UCM) n=31 intact cord milking (I-UCM) n=31 approximately 30-cm length of cord was milked towards the baby 2–4 times within 20 sec after birth with cord cut or intact respectively	**Main outcomes:** HRs of C-UCM group (§) were higher at 6th (*p* = .011), 7th (*p* = 0.004), 9th (*p* = .031), 10th (*p* = .031), 14th (*p* = .016), and 15th (*p* = .005) minutes compared to I-UCM group.	**Study Limitations:** Study was not designed as non-inferiority, rather looked for a 0.7 effect size. Also milking was done several times in the cut cord milking group which differs from other studies and may not be advantageous
Berg 2021 {Berg 2021 282}	**Study Aim:** To assess the effects of DCC (≥180 s) compared to ECC (≤60 s) on neurodevelopment using the Ages and Stages Questionnaire (ASQ) at age 3 years. **Study Type:** RCT N=350	**Inclusion Criteria:** Uncomplicated pregnancies, no complication at admission, healthy mothers (no clinical his tory of hypertension, infection,	**Interventions:** DCC ≥180 sec n=180 **Controls:** ECC ≤60 sec n=170	**Main outcomes:** No significant differences in ASQ scores in any domains between groups were found**.**	**Study Limitations:** Risk of bias; follow-up rates were low, 63% in the ECC group and 66% in the DCC group which make these results prone to bias

		diabetes, or any chronic medical condition), expected vaginal delivery, gestation age 34–41 wks, singleton pregnancy.			
Mercer 2022 {Mercer 2022 }	**Study aim:** To evaluate whether placental transfusion influences brain myelination at 12 months **Study Type:** RCT N=41	**Inclusion Criteria:** Healthy term infants, vaginal delivery	**Interventions:** DCC >5 min n=23 **Control:** ICC <20 sec n=21	**1° endpoint:** DCC group: increased white matter brain growth in right and left internal capsules, the right parietal, occipital, and prefrontal cortex. Developmental testing (Mullen Scales of Early Learning, nonverbal, and verbal composite scores) not significantly different between the two groups.	**Study Limitations:** Very small sample size and only included vaginal delivery. Long delay in DCC group - unclear impact of shorter durations.
Mukhtar 2023 {Mukhtar 2023 171}	**Study Aim:** Compare frequency of the anemia in neonates with ECC vs DCC. **Study design** RCT N=96	**Inclusion Criteria:** Gestation 37-41 wks	**Interventions:** DCC >3 min n=48 **Control:** ECC <15 sec n=48	**1° endpoint:** Neonatal anemia in early cord clamp versus delayed umbilical cord clamping) was 11 (22.92%) and 04 (8.33%) respectively p-value 0.049.	**Study Limitations:** Anemia not well defined. Randomization “by lottery method”
Cavallin 2019 {Cavallin 2019 252}	**Study Aim:** To compare DCC ECC with regard to postnatal adaptation **Study Type:** RCT N=80	**Patient Population** Neonates born through elective caesarean section >39 wks	**Study Intervention:** DCC > 60 sec n=40 **Comparator:** ECC < 10 sec n=40	**Endpoint Results** Mean Hct at day 2: 54% (SD 6) in DCC arm and 48% (SD 5) in ECC (MD 6%; 95% CI 3-8; p < 0.0001)	**Relevant 2° Endpoint** Transcutaneous bilirubin higher in DCC arm than ECC (MD = 1.2 mg/dL; 95% CI -0.02 to 2.5; p = 0.05). No infants needed phototherapy. Other secondary outcome measures not different. **Study limitations:** Only short term outcomes assessed.
Sahoo 2020 {Sahoo 2020 881}	**Study Aim:** To determine safety of DCC in Rh-	**Inclusion Criteria:**	**Intervention:** DCC n = 36	**1° endpoint:** The DCC group had a higher mean Hct at	**Relevant 2° Endpoint:**

	alloimmunized infants **Study Type:** RCT N=70	Rh-alloimmunised infants infants of 28- to 41-week gestation	**Comparison:** ECC n = 34	2 h (48.4 ± 9.2 vs. 43.5 ± 8.7, MD 4.9% (95% CI 0.6-9.1), *p* = 0.03).	incidence of exchange transfusion, phototherapy, echocardiography parameters, and blood were similar between the groups **Study Limitations:** N/A
Pan 2022 {Pan 2022 3111}	**Study Aim:** To investigate the effects of delayed cord clamping on bilirubin levels and phototherapy rates in neonates of diabetic mothers **Study Type:** RCT N=131	**Inclusion Criteria:** Enrolled pregnant women without pregnancy complications and those with and without diabetes	**Intervention:** Diabetic Pregnancies DCC n=42 **Comparison:** ECC n=38 Normal Pregnancies ICC n=50 DCC n=43	**1° endpoint:** Neonatal bilirubin levels on the 2–4 days postpartum and phototherapy rates were significantly higher in the DCC group than in the ICC group (7.65 ± 1.83 vs 8.25 ± 1.96, *P* = 0.039; 10.35 ± 2.23 vs 11.54 ± 2.56, *P* = 0.002; 11.54 ± 2.94 vs 12.83 ± 3.07 *P* = 0.024, 18.2% vs 6.3%, *P* = 0.042)	**Relevant 2° Endpoint:** **Study Limitations:** Study was not blinded so may have been biased regarding phototherapy rates.
Shao 2022 {Shao 2022 111}	**Study Aim:** To compare later cord clamping on umbilical arterial blood gas **Study Type:** RCT N=368	**Patient Population** Neonates born to diabetic mothers at term and non-diabetic mothers	**Study Intervention** DCC > 30 sec for diabetic n=73 non-diabetic n=107 **Comparator** ICC < 15 sec diabetic n=87 non-diabetic n=101	**Endpoint Results** In diabetic mothers, blood gas bicarbonate and base excess decreased and lactate increased for later clamping; no differences in Hb or Hct In non-diabetic mothers, blood base bicarbonate and base excess decreased and lactate and Hb increased in later clamping. No difference in Hct	**Relevant 2° Endpoint** Other blood gas variables not different. **Study limitations:** Only short term outcomes assessed.
Shinohara 2021 {Shinohara 2021 5}	**Study Aim:** To compare DCC and ECC on incidence of anemia in early infancy **Study Type:** RCT N=138	**Patient Population** Term singleton infants of low-risk pregnancies planning exclusive breastfeeding	**Study Intervention** DCC > 1 minor after cord pulsation stopped n=68 **Comparator** ICC ≤ 15 sec n=70	**Endpoint Results** At 4 months, no difference in estimated Hb, MD = 0.1 g/dL, 95% CI -0.14, 0.35, DCC 12.4 g/dL, ECC 12.3 g/dL.	**Relevant 2° Endpoint** Hct level days 3-5 higher in DCC 57.0% vs ECC 52.6%, MD = 4.4, 95% CI 2.61, 6.20 No difference in other outcomes related to jaundice.

					Study limitations: Reliability of measurements – estimate of Hb (SpHb not Hb level).
Rashwan 2022 {Rashwan 2022 515}	**Study Aim:** To assess delayed vs early cord clamping regarding maternal and neonatal outcomes **Study Type:** RCT N=62	**Patient Population** Elective CS for pre-eclampsia 36-38+6 wks	**Study Intervention** DCC 60 sec n=31 **Comparator** ECC <15 sec n=31	**Endpoint Results** Maternal estimated blood loss; no difference (p = 0.673) Mean Hct at day 2: 54% (SD 6) in DCC arm and 48% (SD 5) in ECC (MD 6%; 95% CI 3-8; p < 0.0001)	**Relevant 2° Endpoint** No difference in Apgar scores at 1 (p=1) and 5 minutes (p=0.114), bilirubin on day 1 (p=0.561), day 3 (p=0.676), and NICU admission (p=0.671) Hb and Hct higher in DCC day 1 and day 2 (p<0.001 for all 4) **Study limitations:** Only short term outcomes assessed.
Murali 2023 {Murali 2023 597}	**Study Aim:** To compare the neonatal outcomes of DCC and UCM at birth in vigorous neonates ≥35 weeks born via cesarean section. **Study Type:** RCT N=159	**Inclusion Criteria:** Vigorous neonates born ≥35 weeks of gestation by cesarean section	**Intervention:** DCC 60 sec n=79 **Comparison:** UCM: intact cord was milked at 25cm from the stump 3 times towards the neonate and then clamped. n=80	**1° endpoint:** Mean Hct at 72h higher in DCC group than UCM group; (55.60±4.50) vs (53.89±4.44), MD (95% CI)=1.71 (0.26, 3.16); p=0.021	**Relevant 2° Endpoint:** No significant difference in median serum ferritin between the groups; 102.88(84.67–173.24) vs 137.93(85.15–230.40); p=0.173 **Study Limitations:** Looked only at 3 times cord milking vs other trials of 4 or more at term delivery.
Singh 2024 {Singh 2024 e59046}	**Study Aim:** To compare later DCC and UCM at different intervals on 6 wk hematologic variable **Study Type:** RCT N=97	**Patient Population** Late preterm (>34 wks) and term neonates, BW > 2 kg	**Study Intervention** Group A – DCC with UCM at 60 sec n=48 Group B – DCC with UCM at 120 sec n=49 **Comparator** Group C – only DCC for 180 sec n=48	**Endpoint Results** Hb at 6 weeks – higher in Group B (14.41 +/- 1.135 g/dL) and Group c (14.21 +/- 1.010 g/dL) compared to Group A (13.31 +/- 0.829 g/dL	**Relevant 2° Endpoint** No neonatal complications noted in any groups **Study limitations:** Only short term follow-up. Technique is specific – milking technique was cut milking.

Chopra 2018 {Chopra 2018 234}	**Study Aim:** to compare effects of DCC and ECC on serum ferritin at 3 months in SGA infants born at ≥35 weeks **Study Type:** RCT N=142	**Inclusion Criteria:** Evidence of fetal growth restriction (weight for gestation less than 10th centile) on antenatal ultrasonography	**Intervention:** DCC ≥ 60 sec n=71 **Comparison:** ICC n=71	**1° endpoint:** 3 months of age, serum ferritin levels were higher in DCC group.	**Relevant 2° Endpoint:** Higher rates of polycythemia 41 vs 20%, p=0.01 **Study Limitations:** Due to attrition and unexpected hemolysis of samples, they could not reach the expected sample size. The study was stopped due to logistical issues.
Guner 2021 {Guner 2021 990}	**Study Aim:** determine the effect of delaying umbilical cord clamping time on anemia during the infancy **Study Type:** RCT N=65	**Inclusion Criteria:** gestation ≥37 wk, single live fetus, vertex presentation, no medical issues that could pose a risk for post partum bleeding, planned vaginal delivery, and the infants who did not need resuscitation	**Intervention:** DCC 60 sec n=27 **Comparison:** ICC 15 sec n=38	**1° endpoint:** 48h Hct and bilirubin levels of the intervention group were significantly higher than the control (P<0.001)	**Relevant 2° Endpoint:** Means of the intervention group Hct and Hb levels measured during anemia screening performed at four months were higher than those of the infants in the control group (P<0.001) **Study Limitations:** Not blinded, many infants were excluded post-delivery but after randomization. Values of DCC are much higher than other normal so high concern for bias.
Metha 2021 2020 & Songthamwat (same study in 2 journals) {Metha 2021 2930, Songthamwat 2020 481}	**Study Aim:** Compare effect of DCC at 30 sec and 1 min on neonatal Hct, anemia, maternal and neonatal complications in term cesarean delivered neonates. **Study Type:** RCT N=159	**Inclusion Criteria:** Singleton pregnancies, age ≥ 20 years, who delivered by elective cesarean section between 37 and 41 wks gestation.	**Intervention:** DCC 30 sec n=79 **Comparison:** DCC 60 sec n=80	**1° endpoint:** Mean neonatal Hct ± SD at 48–72 h was 49.9 ± 6.0% in DCC 30 sec group and 51.2 ± 5.9% in DCC 60 sec group MD −1.3 (−3.16 to 0.56) (p=0.169)	**Relevant 2° Endpoint:** Neonatal anemia (Hct < 45%) detected in 14/79 cases (17.7%) in DCC 30 sec group and 8/80 cases (10.0%) in DCC 60 sec group (p=0.159) **Study Limitations:** Not blinded, only caesarean deliveries.
Kc 2019 {Kc 2019 7}	**Study Aim:**	**Inclusion Criteria:**	**Intervention:** DCC ≥180 sec	**1° endpoint:**	**Relevant 2° Endpoint:**

	Evaluate the effect of DCC (≥180 s) vs ECC (≤60s) on peripheral blood oxygenation and heart rate up to 10min after birth **Study Type:** RCT N=1264	Normal vaginal delivery, women with no complication during delivery, fetal heart rate ≥100 and ≤160 bpm, gestation ≥33weeks	n=594 **Comparison:** ECC ≤60 sec n=670	Oxygen saturations 18% higher at 1 min, 13% higher at 5 min and 10% higher at 10 min in babies who had cord clamping in DCC group vs ECC group (p < 0.001). The heart rate was 9 bpm lower at 1 min and 3 bpm lower at 5 min in DCC vs ECC group (p <0.001)	**Study Limitations:** High protocol deviation rate in the DCC group. ITT analysis, so 25% of the infants reported in DCC group had cord clamped before 1 min
De Bernardo 2020 {De Bernardo 2020 71}	**Study Aim:** Determine whether there is a difference in pre-ductal saturation between DCC and ECC **Study Type:** RCT N=132	**Inclusion Criteria:** Term infants born by C-section in mothers were who had a BMI > 19 and were < 25 and ≤37 years of age	**Intervention:** DCC 1 min **Comparison:** ECC	**1° endpoint:** No significant differences between groups for SpO2 (88±7 vs 89±7.4, p=0.548)	**Relevant 2° Endpoint:** Higher Hct and (51±6 vs 56±2, p.001) bilirubin (7±3 vs 9±3, p=0.004) with ECC compared to ECC at 72 h. **Study Limitations:** Term healthy pregnancies only in mothers with normal BMI
Rana 2019 {Rana 2019 36}	**Study Aim:** Investigate the effects of DCC compared to early cord clamping (ECC) on Ages and Stages Questionnaire scores at 12 m. **Study Type:** RCT N=332	**Inclusion Criteria:** Healthy newborns born by vaginal delivery	**Intervention:** DCC >180 sec n=173 **Comparison:** ECC <60 sec n=159	**1° endpoint:** Fewer children in DCC group were "at risk" of neurodevelopmental impairment based on ASQ total score, 21 (7.8%) versus 49 (18.1%) in the ECC group	**Relevant 2° Endpoint:** **Study Limitations:** Retention to ASQ measurement 61%. ASQ is not validated in Nepal. Protocol deviations; 22.6% in the DCC arm underwent early cord clamping.
Tariq 2023 {Tariq 2023 14}	**Study Aim:** Detect the frequency of anemia in delayed and early umbilical cord clamping after birth in newborn babies. **Study Type:** RCT N=144	**Inclusion Criteria:** Healthy newborns (no other definition)	**Intervention:** DCC 90 sec n=72 **Comparison:** ECC <15 sec n=72	**1° endpoint:** Incidence of anemia wa slower with DCC compared to ECC 2(1.63%) vs 18(14.75%)	**Relevant 2° Endpoint:** **Study Limitations:** Very poorly reported. No defined inclusion criteria, no statistics done on any of the outcomes just presenting values.
Vural 2019 {Vural 2019 555}	**Study Aim:** To compare the post-natal effects of DCC vs ECC in term large-for-gestational age (LGA) infants	**Inclusion Criteria:** LGA babies over 4000 g with a gestational age	**Intervention:** DCC 60 sec n = 25 **Comparison:** ECC 15 s n = 26	**1° endpoint:** Hct at 2 hours ECC vs DCC 58±5 vs 59±5, p=0.79	**Relevant 2° Endpoint:** 24 h bilirubin ECC vs DCC (5.5±2.5 vs 5.5±3.1, p=0.86) **Study Limitations:**

	Study Type: RCT N=51	from >37 to <42 weeks delivered by either vaginal or cesarean delivery			Very small study and Hct drawn very early so may have missed changes.
Chaudhary 2023 {Chaudhary 2023 3701}	**Study Aim:** Compare the effects of three different timings of DCC at 30, 60, and 120 s on venous hematocrit **Study Type:** RCT N=135	**Inclusion Criteria:** Inborn late preterm and term neonates gestation 34–41 wks not requiring resuscitation were included	**Intervention:** DCC 60 sec n = 70 DCC 120 sec n = 69 **Comparison:** DCC 30 sec n = 65	**1° endpoint:** Venous Hct at 24 ± 2 h of life was significantly higher in neonates exposed to DCC for longer duration; 57.3 ± 5.4%, 57.4 ± 5.5% and 59.6 ± 5.3% in DCC 30, DCC 60, and DCC 120 group, respectively (p = 0.024)	**Relevant 2° Endpoint:** Polycythemia 4.6%, 2.9%, and 13.0% in DCC 30, DCC 60, and DCC 120 groups, respectively (p = 0.041). Only one neonate (1.4%) in DCC 120 group had symptomatic polycythemia and required a partial exchange transfusion. **Study Limitations:** Only short term Hct, no longer term measures of Iron stores.
Hosagasi 2024 {Hoşağası 2024 624}	**Study Aim:** investigate the impact of DCC on breast feeding behaviors, neonatal activity status, and maternal satisfaction during the first breastfeeding **Study Type:** RCT N=100	**Inclusion Criteria:** Term infants (gestation between 37 $^{0/7}$ and 42 $^{6/7}$ weeks) who were born by elective cesarean section with spinal anesthesia and did not require resuscitation at birth.	**Intervention:** DCC group 1 min and infant was observed to be breathing regularly. **Comparison:** ECC - cord clamping was performed as soon as possible after the infant was born, regardless of ventilation status.	**1° endpoint:** Scores on the IBFAT were significantly higher in the DCC group compared with the ECC group (p = 0.02).	**Relevant 2° Endpoint:** Maternal satisfaction with breastfeeding did not differ between the groups (p = 0.3). Infant alertness tended to be better in the DCC group, but the difference was not statistically significant (p = 0.08). **Study Limitations:** Study not blinded. Only initial breastfeeding was evaluated its influence on long term breastfeeding remains unknown.
Angadi 2023 {Angadi 2023 4185}	**Study Aim:** compared hemodynamic effects of UCM(UCM) with delayed cord	**Inclusion Criteria:** Antenatally detected IUGR > 28 wks gestation,	**Intervention:** UCM The umbilical cord was gently grasped, and 20 cm of the intact cord was	**1° endpoint:** Mean SVC flow (mL/kg/min) was significantly higher in	**Relevant 2° Endpoint:** CrSO2 in the UCM group 84.69 ± 5.23 vs DCC group 82.95 ± 5.85 MD (CI),

	clamping (DCC) in IUGR neonates > 28 weeks of gestation, not requiring resuscitation **Study Type:** RCT N=185	defined as estimated fetal weight < 10th centile for gestation by ultrasound	squeezed at the speed of 10 cm/s towards the infant four times with an interval of 2 s between two squeezing movements to allow cord refilling before clamping of the cord n=85 **Comparison:** DCC 60 sec n=85	UCM compared to DCC (111.95 ± 33.54 vs 99.49 ± 31.96 in UCM and DCC group, respectively; MD (CI), 12.50 (2.50, 22.4); p = 0.014).	1.74 (0.05, 3.42); p = 0.043). Hct UCM group 60.7 ± 5.0 vs DCC group 59.0 ± 5.0 MD (CI), 1.70 (0.18, 3.21); p = 0.028) **Study Limitations:** Included small number of babies < 32 wks. Some infants were excluded since they needed resuscitation.
Tekin 2023 {Tekin 2023 439}	**Study Aim:** evaluate the haemodynamic effects of UCM in term infants. **Study Type:** RCT N=149	**Inclusion Criteria:** Healthy singleton pregnancies from 37 to 41 weeks gestation	**Intervention:** UCM: milking the intact cord 5 times n=74 **Comparison:** ECC (timing not defined). n=75	**1° endpoint:** Superior vena cava flow (mL/kg/min) UCM 132.47±37.0 vs ICC 126.62±34.3 p=0.318	**Relevant 2° Endpoint:** N/A **Study Limitations:** Lack of reporting of clinical outcomes, lack of blinding could have altered echo results. Also no clear definition of early cord clamping.
George 2022 {George 2022 291}	**Study Aim:** Analyze the effects of UCM on the neonatal hematological parameters at 72 h and 6 weeks of age **Study Type:** RCT N=144	**Inclusion Criteria:** All healthy singleton pregnancies from 34 to 40 completed weeks	**Intervention:** UCM: milking the intact umbilical cord 3 times before clamping and cutting. n=73 **Comparison:** ICC: (time not defined). n=71	**1° endpoint:** The 95% confidence interval (CI) of gain in Hgb due to cord milking was 2.4–1.0 g/dl and HCT was 7–3% at 72 h and the gain had a CI of 1.9–1.1 g/dl for Hgb and 6–3% for HCT at 6 weeks.	**Relevant 2° Endpoint:** N/A **Study Limitations:** Not blinded. Strengths included longer term assessment of Hct at 6 weeks.
Korkut 2021 {Korkut 2021 242}	**Study Aim:** Investigate the effect of delayed cord clamping (DCC) in infants of diabetic mothers. **Study Type:** RCT N=80	**Inclusion Criteria:** Pregnant women who had diabetes (type 1, type 2, or GDM) and gave birth at 37 weeks of gestation or later were included in the study along with their babies.	**Intervention:** DCC 60 sec n=40 **Comparison:** ECC “as soon as possible after birth” n=40	**1° endpoint:** Venous Hct levels at postnatal 6 and 24 h were significantly higher in the DCC group (p = 0.0001).	**Relevant 2° Endpoint:** Polycythemia rates higher in the DCC group at both 6 and 24 h, but partial exchange transfusion not needed in either group. No differences between the groups in hypoglycemia or jaundice requiring phototherapy, or admission to the

					neonatal intensive care unit. **Study Limitations:** Unblinded so high risk of bias for phototherapy
Zanardo 2021 {Zanardo 2021 392}	**Study Aim:** whether intact Umbilical cord milking (UCM) is more effective than immediate cord clamping (ICC) in enhancing placental transfusion after elective cesarean delivery **Study Type:** RCT N=130	**Inclusion Criteria:** Singleton pregnancies 18 yo or older Elective C/S 39-40 weeks gestational age	**Intervention:** UCM: milking the intact cord 3 times n=65 **Comparison:** ICC n=65	**1° endpoint:** No significant differences in cord blood mean Hct values at birth (UCM, 44.5 ± 4.8 vs. ICC, 44.9 ± 4.2%, *p* = 0.74). At 48 h, the UCM group had higher capillary heel Hct values (UCM, 53.7 ± 5.9 vs. ICC, 49.8 ± 4.6%, *p* < 0.001), supporting a higher placental transfusion volume (Δ Hct, UCM 9.2 ± 5.2 vs. ICC 4.8 ± 4.7, *p* < 0.001), despite comparable neonatal body weight decrease (UCM, −7.3 vs. ICC,−6.8%, *p* = 0.77).	**Relevant 2° Endpoint:** TSB levels (scheduled at 48 hours of life together with mandatory metabolic test) were similar in intact UCM and ICC groups (7.40+2.12 vs. 7.17+1.87 mg% respectively p=0.57). **Study Limitations:** unblinded
Katariya 2021 {Katariya 2021 e17169}	**Study Aim:** Determine effects of different timings of DCC on maternal and neonatal outcomes **Study Type:** RCT – 3 arms	**Inclusion Criteria:** Vaginal birth at term.	**Intervention:** DCC 2 min n=44 DCC 3 min n=44 **Comparison:** DCC 1 min n=44	**1° endpoint:** Hb DCC 3 min 16.63 (+/-1.33) > DCC 2 min 16.26 (+/-2.03) > DCC 15.30 (+/-1.93) p=0.00	**Relevant 2° Endpoint:** Maternal blood loss, oxytocin use, birth weight not significantly different among groups. Bilirubin level higher in DCC 3 min group but no difference in phototherapy. **Study Limitations:** Not registered as clinical trial. 15 samples lost.
Manzoor 2020 {Manzoor 2020 561}	**Study Aim:** Effect on hemoglobin and hematocrit comparing early vs delayed cord clamping **Study Type:** RCT N=450	**Inclusion Criteria:** Low risk pregnancy	**Intervention:** DCC > 180 sec n=225 **Comparison:** ECC < 10 sec n=225	**1° endpoint:** Hct at 6 h ECC 51.0 +/-2.9 < DCC 55.0 +/-3.1. Hb ECC 16.8+/-1.0 < DCC 17.7+/-1.0, p < 0.01	**Relevant 2° Endpoint:** Hb and Hct at 24 h higher in DCC vs ECC. **Study Limitations:** Only short-term outcomes.

Patel 2021 {Patel 2021 15}	**Study Aim:** Compare ECC and DCC in term low birth weight **Study Type:** RCT N=200	**Inclusion Criteria:** Term low birth weight (< 2500 grams) with Apgar score of >7 and normal fetal heart rate pattern	**Intervention:** ECC 1 min n=100 **Comparison:** ECC 15 sec n=100	**1° endpoint:** Hct at 4 hours higher in DCC (57.38%) compared to ECC (48.14%). Also at day 3: 54.92% vs 46.11%	**Relevant 2° Endpoint:** Serum bilirubin at day 3 higher in DCC group. **Study Limitations:** Only short-term outcomes.
Panburana 2020 {Panburana 2020 301}	**Study Aim:** Study intact UCM vs DCC **Study Type:** RCT N=168	**Inclusion Criteria:** 37-42 wks GA	**Intervention:** DCC 60 secs n=84 **Comparison:** I-UCM (3 times milk) n=84	**1° endpoint:** No difference in Hb	**Relevant 2° Endpoint:** No difference in adverse maternal or neonatal outcomes. **Study Limitations:** Short-term follow-up.
Abbreviations: MD; mean difference, 95%CI; 95% confidence intervals, DCC; delayed cord clamping, ICC; immediate cord clamping, UCM; umbilical cord milking, ECC; early cord clamping, sec; seconds, min; minutes, wks; weeks, Hb; hemoglobin, Hct; hematocrit, TSB; total serum bilirubin, CrSO2; cerebral oxygen saturation, IBFAT; Infant Breastfeeding Assessment Tool, ASQ; Ages and Stages Questionnaire, cTOI; cerebral tissue oxygenation index, ΔCBV; change in cerebral blood volume, SpO2; oxygen saturation, HR; heart rate, CS; Cesarean Section					

Reviewer Comments:

There were **3 trials on post partum hemorrhage** looking at duration of 60 sec {Ofojebe 2021 99, Purisch 2019 1869} or 120-180 sec {Katariya 2021 e17169}

There have been **8 trials comparing effect on Hct or ferritin of intact cord milking (I-UCM) vs various durations of DCC**:

- I-UCM vs DCC 60 sec {Mangla 2020 1119}
- I-UCM vs DCC 120 sec vs ECC {Ozbasli 2024 1883}
- I-UCM after 2 min vs DCC 120 sec {de Preud'homme d'Hailly de Nieuport 2024 101279}
- I-UCM vs DCC 120 sec {Seliga-Siwecka 2020 613}
- I-UCM vs ECC <30 sec {Kumawat 2022 258}
- I-UCM vs DCC 60 sec DCC 60 sec {Murali 2023 597}
- I-UCM vs DCC 120 sec vs DCC 180 sec {Singh 2024 e59046}
- I-UCM vs DCC 60 sec {Panburana 2020 301}

There have been **7 studies comparing longer DCC (> 60 seconds) to shorter durations (≤60 sec)**

- 120 sec vs 30 sec {Soliman 2024 739}
- 180 sec vs 60 sec {Rana 2019 36}
- 180 sec vs <15 sec {Mukhtar 2023 171}
- 180 sec vs 60 sec {Kc 2019 7}
- 90 sec vs <15 sec {Tariq 2023 14}
- 30 vs 60 vs 120 sec {Chaudhary 2023 3701}
- 180 sec vs <10 sec {Manzoor 2020 561}

There have been **6 studies comparing short DCC (60 sec) to ICC**

- 60 sec vs <10 sec {Cavallin 2019 252}
- 60 sec or until pulsation stopped vs <15 sec) {Shinohara 2021 5}
- 60 sec vs <15 sec) {Guner 2021 990}
- 60 sec vs <10 sec {De Bernardo 2020 71}
- 60 sec vs 30 sec {Metha 2021 2930}

- 60 sec vs 15 sec {Patel 2021 15}

There have been **2 studies of physiologic based cord clamping compared to DCC or UCM**.

- I-UCM vs PBCC vs DCC {Kilicdag 2022 1308}
- PBCC vs DCC 30-40 sec {Schwaberger 2023 1005947}

There is one new trial comparing i**ntact (I-UCM) vs cut cord milking (C-UCM)** Orpak 2019 1} (I-UCM 2-4 times vs C-UCM 2-4 times)

There have been **4 studies measuring post discharge neurodevelopmental or brain outcome**s.

- Brain myelination at 12 months {Mercer 2022 } (5 min vs <20 sec)
- ASQ at 12 months {Rana 2019 36}, (180 sec vs <60 sec)
- ASQ at 3 years {Berg 2021 282} (180 sec vs ≤60 sec)

'There have been **8 trials on specific subgroups**.

- 1 new trial in infants of Rh alloimmunized mothers {Sahoo 2020 881} (DCC vs ECC)
- 4 new trials on infants of diabetic mothers or large for gestational age infants {Pan 2022 3111} (DCC vs ICC), {Shao 2022 111} (DCC 30 sec vs ICC <15 sec), {Korkut 2021 242} (DCC 60 sec vs ICC) and {Vural 2019 555} (DCC 60 sec vs ICC <15ec)
- 3 trials on mothers with pre-eclampsia, SGA or IUGR
    - Pre-eclampsia: {Rashwan 2022 515} (DCC 60 sec vs ICC <15 sec)
    - Small for gestational age infants: {Chopra 2018 234} (DCC 60 sec vs ICC <15 sec)
    - Infants with intrauterine growth restriction: {Angadi 2023 4185} (I-UCM vs DCC 60 sec).

1 new trial assessed effect of ICC vs DCC on breastfeeding scores: {Hoşağası 624} (ICC <10 sec vs 60 sec)

Conclusion

These studies report new information (including for extended durations of DCC, and about I-UCM), but it appears unlikely that they would yield the certainty of evidence to change current recommendations. Several studies appear to support findings of the previous review in relation to improvements in short-term hematologic outcomes and safety, and no new safety concerns were noted.

There are also new studies for subgroups (e.g. infants of diabetic mothers, fetal growth restriction, Rh hemolytic disease), but these studies are relatively small and few in number, and are unlikely to change current treatment recommendations, including their subgroup considerations.

To critically appraise this evidence and add it to that from the previous review, a new systematic review is justified within the next 1-3 years but is not urgently needed.

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Appendix: search strategy

Sources searched	Search strategy	Search time frame
Search 1 for RCTs		
Ovid MEDLINE	(exp Umbilical Cord/ OR (cord or cords or umbilicus or umbilical or navel-string).mp.) AND (exp Constriction/ OR exp Ligation/ OR (clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict*).mp. OR ((cord or cords) adj3 management).mp. OR (DCC or ICC or ECC or LCC).ti,ab. OR exp Placental Circulation/ OR ((placental or placenta or placentofetal or placentofoetal) adj2 (transfusion* or circulation)).mp.) AND (exp infant, newborn/ OR (newborn* or new born or new borns or newly born or baby* or babies or infant or infants or infantile or infancy or neonat*).ti,ab.) AND (randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.) NOT (exp animals/ not humans.sh.) AND (2019* or 2020* or 2021* or 2022* or 2023* or 2024*).dt.	26 July 2019 (previous search) - 10 July 2024 Results from previous SysRev were incorporated into this EvUp
PubMed	(“Umbilical Cord”[Mesh] OR cord[TW] OR cords[TW] OR umbilicus[TW] OR umbilical[TW] OR navelstring[TW]) AND (“Constriction”[Mesh] OR “Ligation”[Mesh] OR clamp[TW] OR clamping[TW] OR clamped[TW] OR milking[TW] OR milked[TW] OR stripping[TW] OR stripped[TW] OR ligation[TW] OR ligature[TW] OR constrict*[TW] OR ((cord[TW] OR cords[TW]) AND management[TW]) OR DCC[TIAB] OR ICC[TIAB] OR ECC[TIAB] OR LCC[TIAB] OR “Placental Circulation”[Mesh] OR ((placental[TW] OR placenta[TW] OR placentofetal[TW] OR placentofoetal[TW]) AND (transfusion*[TW] OR circulation[TW]))) AND (infant,newborn[MeSH] OR newborn*[TIAB] OR “new born”[TIAB] OR “new borns”[TIAB] OR “newly born”[TIAB] OR baby*[TIAB] OR babies[TIAB] OR infant[TIAB] OR infants[TIAB] OR infantile[TIAB] OR infancy[TIAB] OR neonat*[TIAB]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) AND 2019/01/01:2024/12/31 [crdt]	

CINAHL (via EBSCOHost)	(cord or cords or umbilicus or umbilical or navel-string) AND (clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict* OR ((cord or cords) AND management) OR ((placental or placenta or placentofetal or placentofoetal) AND (transfusion* or circulation))) AND (infant or infants or infantile or infancy or newborn* or “new born” or “new borns” or “newly born” or neonat* or baby* or babies) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial) AND EM 20190101-	
EMBASE	('umbilical cord'/exp OR (cord OR cords OR umbilicus OR umbilical OR navel-string)) AND (ligation/exp OR (clamp OR clamping OR clamped OR milking OR milked OR stripping OR stripped OR ligation OR ligature OR constrict*) OR 'umbilical cord clamp'/exp OR ((cord OR cords) NEAR/3 management) OR (DCC OR ICC OR ECC OR LCC):ti,ab OR 'placenta circulation'/exp OR ((placental OR placenta OR placentofetal OR placentofoetal) NEAR/2 (transfusion* OR circulation))) AND (infant/exp OR (newborn* OR 'new born' OR 'new borns' OR 'newly born' OR baby* OR babies OR infant OR infants OR infantile OR infancy OR neonat*):ti,ab) AND ('randomized controlled trial' OR 'controlled clinical trial' OR randomized OR placebo OR 'clinical trials as topic' OR randomly OR trial OR 'clinical trial') NOT (('animal experiment'/de OR animal/exp) NOT ('human experiment'/de OR 'human'/exp)) AND [01-01-2019]/sd	
Cochrane CENTRAL	([mh "Umbilical Cord"] OR cord:ti,ab,kw OR cords:ti,ab,kw OR umbilicus:ti,ab,kw OR umbilical:ti,ab,kw OR navelstring:ti,ab,kw) AND ([mh Constriction] OR [mh Ligation] OR clamp:ti,ab,kw OR clamping:ti,ab,kw OR clamped:ti,ab,kw OR milking:ti,ab,kw OR milked:ti,ab,kw OR stripping:ti,ab,kw OR stripped:ti,ab,kw OR ligation:ti,ab,kw OR ligature:ti,ab,kw OR constrict*:ti,ab,kw OR ((cord:ti,ab,kw OR cords:ti,ab,kw) NEAR/4 management:ti,ab,kw) OR DCC:ti,ab OR ICC:ti,ab OR ECC:ti,ab OR LCC:ti,ab OR [mh "Placental Circulation"] OR ((placental:ti,ab,kw OR placenta:ti,ab,kw OR placentofetal:ti,ab,kw OR placentofoetal:ti,ab,kw) NEAR/4 (transfusion*:ti,ab,kw OR circulation:ti,ab,kw))) AND ([mh "infant, newborn"] OR newborn*:ti,ab OR "new born":ti,ab OR "new borns":ti,ab OR "newly born":ti,ab OR baby*:ti,ab OR babies:ti,ab OR NICU:ti,ab OR infant:ti,ab OR infants:ti,ab OR infantile:ti,ab OR infancy:ti,ab OR neonat*:ti,ab)	

	Limited by 'Date added to CENTRAL trials database' to 01/01/2019 to 31/12/2024	
Search 2 for cohort studies and case series		
Ovid MEDLINE	(exp Umbilical Cord/ OR (cord or cords or umbilicus or umbilical or navel-string).mp.) AND (exp Constriction/ OR exp Ligation/ OR (clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict*).mp. OR ((cord or cords) adj3 management).mp. OR (DCC or ICC or ECC or LCC).ti,ab. OR exp Placental Circulation/ OR ((placental or placenta or placentofetal or placentofoetal) adj2 (transfusion* or circulation)).mp.) AND (exp infant, newborn/ OR (newborn* or new born or new borns or newly born or baby* or babies or infant or infants or infantile or infancy or neonat*).ti,ab.) AND ("Epidemiologic studies"/ OR "Case Reports".pt. OR exp "case control studies"/ OR exp "cohort studies"/ OR "Observational Study".pt. OR "case control".tw. OR cohort.tw. OR "follow up stud*".tw. OR "observational stud*".tw. OR longitudinal.tw. OR retrospective.tw. OR prospective.tw. OR "cross sectional".tw. OR "Cross-sectional studies"/ OR "case series".tw. OR "case report*".tw. OR "case stud*".tw. OR "case presentation*".tw.) AND (nonvigorous.mp. OR non-vigorous.mp. OR depressed.mp. OR "requiring resuscitation".mp. OR resuscitated.mp. OR inactive.mp. OR atonic.mp. OR unresponsive.mp. OR nonresponsive.mp. OR non-responsive.mp. OR floppy.mp. OR hypotonic.mp. OR hypotonia.mp. OR non-reactive.mp. OR nonreactive.mp. OR "at risk".mp. OR "not breathing".mp. OR non-breathing.mp. OR "not crying".mp. OR non-crying.mp. OR "meconium stain*".mp. OR "meconium aspiration".mp. OR apnea.mp. OR apnoea.mp. OR asphyxia.mp. OR bradycardia.mp. OR ((low.mp. OR lower.mp. OR poor*.mp. OR weak.mp. OR decreased.mp.) AND ("apgar score*".mp. OR "heart rate".mp. OR "muscle tone".mp. OR "respiratory effort".mp.))) NOT (exp animals/ NOT humans.sh.)	
PubMed	(“Umbilical Cord”[Mesh] OR cord[TW] OR cords[TW] OR umbilicus[TW] OR umbilical[TW] OR navelstring[TW]) AND (“Constriction”[Mesh] OR “Ligation”[Mesh] OR clamp[TW] OR clamping[TW] OR clamped[TW] OR milking[TW] OR milked[TW] OR stripping[TW] OR stripped[TW] OR ligation[TW] OR ligature[TW] OR constrict*[TW] OR ((cord[TW] OR cords[TW]) AND management[TW]) OR DCC[TIAB] OR ICC[TIAB] OR ECC[TIAB] OR LCC[TIAB] OR “Placental Circulation”[Mesh] OR ((placental[TW] OR placenta[TW] OR placentofetal[TW] OR placentofoetal[TW]) AND (transfusion*[TW] OR circulation[TW]))) AND (infant, newborn[MeSH] OR newborn*[TIAB] OR “new born”[TIAB] OR “new borns”[TIAB] OR “newly born”[TIAB] OR baby*[TIAB] OR babies[TIAB] OR infant[TIAB] OR infants[TIAB] OR infantile[TIAB] OR infancy[TIAB] OR neonat*[TIAB]) AND ("Epidemiologic studies"[Mesh:NoExp] OR "Case Reports" [Publication Type]	

	OR "case control studies"[Mesh] OR "cohort studies"[Mesh] OR "Observational Study" [Publication Type] OR "case control"[tiab] OR cohort[tiab] OR "follow up stud*"[tiab] OR "observational stud*"[tiab] OR longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab] OR "cross sectional"[tiab] OR "Cross-sectional studies"[Mesh:NoExp] OR "case series"[tiab] OR "case report*"[tiab] OR "case stud*"[tiab] OR "case presentation*"[tiab]) AND (nonvigorous[TW] OR non-vigorous[TW] OR depressed[TW] OR "requiring resuscitation" [TW] OR resuscitated[TW] OR inactive[TW] OR atonic[TW] OR unresponsive[TW] OR nonresponsive[TW] OR non-responsive[TW] OR floppy[TW] OR hypotonic[TW] OR hypotonia[TW] OR non-reactive[TW] OR nonreactive[TW] OR "at risk"[TW] OR "not breathing"[TW] OR "non-breathing"[TW] OR "not crying"[TW] OR "non-crying"[TW] OR "meconium stain*"[TW] OR "meconium aspiration"[TW] OR apnea[TW] OR apnoea[TW] OR asphyxia[TW] OR bradycardia[TW] OR ((low[TW] OR lower[TW] OR poor*[TW] OR weak[TW] OR decreased[TW]) AND ("apgar score*"[TW] OR "heart rate"[TW] OR "muscle tone"[TW] OR "respiratory effort"[TW]))) NOT (animals[mh] NOT humans[mh])	
CINAHL (via EBSCOhost)	**(**cord or cords or umbilicus or umbilical or navel-string**)** AND **(**clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict* OR ((cord or cords) AND management) OR ((placental or placenta or placentofetal or placentofoetal) AND (transfusion* or circulation))**)** AND **(**infant or infants or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies**)** AND (MH "Case Studies" OR MH "Epidemiological Research" OR MH "Case Control Studies+" OR MH "Prospective Studies+" OR PT "Case Study" OR MH "Correlational Studies" OR TI "case control" OR AB "case control" OR TI cohort OR AB cohort OR TI "follow up stud*" OR AB "follow up stud*" OR TI "observational stud*" OR AB "observational stud*" OR TI longitudinal OR AB longitudinal OR TI retrospective OR AB retrospective OR TI prospective OR AB prospective OR TI "cross sectional" OR AB "cross sectional" OR MH "Cross Sectional Studies" OR TI "case series" OR AB "case series" OR TI "case report*" OR AB "case report*" OR TI "case stud*" OR AB "case stud*" OR TI "case presentation*" OR AB "case presentation*") AND (nonvigorous OR non-vigorous OR depressed OR "requiring resuscitation" OR resuscitated OR inactive OR atonic OR unresponsive OR nonresponsive OR non-responsive OR floppy OR hypotonic OR hypotonia OR non-reactive OR nonreactive OR "at risk" OR "not breathing" OR non-breathing OR "not crying" OR non-crying OR "meconium stain*" OR "meconium aspiration" OR apnea OR apnoea OR asphyxia OR bradycardia OR ((low OR lower OR poor* OR weak OR decreased) AND ("apgar score*" OR "heart rate" OR "muscle tone" OR "respiratory effort")))	
EMBASE	('umbilical cord'/exp OR (cord OR cords OR umbilicus OR umbilical OR navel-string)) AND (ligation/exp OR (clamp OR clamping OR clamped OR milking OR milked OR stripping OR stripped OR ligation OR ligature OR constrict*) OR 'umbilical cord clamp'/exp OR	

	((cord OR cords) NEAR/3 management) OR (DCC OR ICC OR ECC OR LCC):ti,ab OR 'placenta circulation'/exp OR ((placental OR placenta OR placentofetal OR placentofoetal) NEAR/2 (transfusion* OR circulation))) AND (infant/exp OR (newborn* OR 'new born' OR 'new borns' OR 'newly born' OR baby* OR babies OR infant OR infants OR infantile OR infancy OR neonat*):ti,ab) AND ('case control study'/exp OR 'cohort analysis'/exp OR 'observational study'/exp OR 'panel study'/exp OR 'case report'/exp OR 'case study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'case control':ti,ab OR cohort:ti,ab OR 'follow up stud*':ti,ab OR 'observational stud*':ti,ab OR longitudinal:ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR 'cross sectional':ti,ab OR 'cross-sectional study'/exp OR 'case series':ti,ab OR 'case report*':ti,ab OR 'case stud*':ti,ab OR 'case presentation*':ti,ab) AND (nonvigorous OR non-vigorous OR depressed OR 'requiring resuscitation' OR resuscitated OR inactive OR atonic OR unresponsive OR nonresponsive OR non-responsive OR floppy OR hypotonic OR hypotonia OR non-reactive OR nonreactive OR 'at risk' OR 'not breathing' OR non-breathing OR 'not crying' OR non-crying OR 'meconium stain*' OR 'meconium aspiration' OR apnea OR apnoea OR asphyxia OR bradycardia OR ((low OR lower OR poor* OR weak OR decreased) AND ('apgar score*' OR 'heart rate' OR 'muscle tone' OR 'respiratory effort'))) NOT (('animal experiment'/de OR animal/exp) NOT ('human experiment'/de OR 'human'/exp))	
Results identified	**Results screened full text**	**Results included**
Missing	Missing	43

2025 Evidence Update
NLS 5051 – Umbilical Cord Management at Birth for Preterm Infants

Worksheet Author(s): El-Naggar W, Davis PG, Josephsen J, Seidler L, Soll R, Costa-Nobre D, Isayama T, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest:
*Walid El-Naggar***:** Member of the iCOMP collaborative group**,** received NICHD grant as a co-investigator of the Umbilical Cord Milking in Non-Vigorous Infants (MiNVI Trial)**,** received a grant from IWK Research as the principal investigator of the MoCC trial**,** received a grant from Nova Scotia Health Research Foundation (NSHRF) as a principal investigator of the study: The effect of umbilical cord milking on hemodynamic status of preterm infants: a randomized controlled trial**,** received a grant from National Health and Medical Research Council (NHMRC) as a co-investigator of the Australian Placental Transfusion study (APTS)
Peter Davis: Member of the iCOMP collaborative group, received Australian NHMRC funding for BabyDUCC trial
Justin Josephsen: Member of the iCOMP collaborative group*,* published an UCM trial that was considered for inclusion in iCOMP, received NICHD funding as co-investigator of the VentFirst trial.
Lene Seidler: Lead of iCOMP collaborative group, received a grant from the Australian National Health and Medical Research Council (NHMRC) to support iCOMP.
Helen Liley (Task Force Chair): Member of the iCOMP panel of expert advisors: Site investigator for the APTS study which was included in iCOMP analyses. Received a grant from the Australian National Blood Authority to study mediators of red cell transfusions in the APTS study.

PICOST:
Population: Preterm infants born at <37^{+0} weeks' gestation and their mothers.
Interventions:
1- Deferred (delayed/later) cord clamping (DCC)
2- Umbilical cord milking (UCM)
Comparisons:
1- Immediate (early) cord clamping (ICC)- compared to each of the above interventions.
2- Between-intervention comparisons (i.e. DCC vs. UCM).
Outcomes:
9 (Critical) Infant's mortality before hospital discharge (primary)
7 (Critical) Infant's inpatient morbidities (e.g., intraventricular hemorrhage (IVH), necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia) for preterm infants <32 weeks' gestation
9 (Critical) Maternal mortality
7 (Critical) Maternal complications (post-partum hemorrhage and infection)
6 (Important):

- Resuscitation and stabilization interventions (e.g. receiving positive pressure ventilation ± intubation ± chest compressions ± medications)
- Blood transfusion
- Hematologic and cardiovascular status (in-hospital)
- Hyperbilirubinemia treated with phototherapy

Study design:
RCTs and cluster RCTs in preterm infants (<34 weeks' gestational age) or low birthweight infants (<2500 g) were included. For those studies that reported a broad population of infants (including both preterm infants of <34 weeks' gestation, late preterm infants, and term infants), studies recruiting a preponderance of preterm infants (defined as a mean gestational age <34 weeks or reported >80% of infants as preterm <34 weeks' gestational age) were included. Unpublished studies (e.g., conference abstracts, trial protocols) were excluded. All languages were included provided there was an English abstract.
Time frame:
The search was conducted from database inception to 6 June 2023

Year of last full review: 2023 {Seidler 2023 2209}

Current ILCOR Consensus on Science and Treatment Recommendations for this PICOST: {Berg 2023 e187}

COMPARISON 1: DEFERRED CORD CLAMPING (DCC) COMPARED TO IMMEDIATE CORD CLAMPING (ICC)
The pairwise IPD MA identified **21 eligible studies** including 3,292 infants. Median sample size was 65 (interquartile range [IQR] 40-101). Median (IQR) gestational age at birth was 29 (27-33) weeks. DCC ranged from 30 to ≥180 seconds (some trials encouraging deferrals up to 5 minutes where feasible). For ICC, most trials (n=14) specified clamping within 10 seconds. Of all infants, 61% were born by cesarean delivery, 25% were multiples, and 56% were male. Trials were conducted in high-income (9/21), upper-middle-income (5/21) and lower-middle-income (7/21) countries as defined by world bank country classification (https://blogs.worldbank.org/opendata/new-world-bank-group-country-classifications-income-level-fy24). {Backes 2016 35, Chu 2011 S201, Datta 2017 418, Duley 2018 F6, Finn 2019 , García 2023 2483, Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Liu 2018 , Oh 2011 , Okulu 2022 838444, Rana 2018 655, Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Salae 2016 S159, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the critical outcome of **death before discharge,*** there was **clinical benefit** for DCC compared to ICC (odds ratio (OR) 0.68, 95% confidence interval (CI) 0.51 to 0.91; number needed to treat for benefit (NNTB) 40, 95% CI 143 to 26; I^2 = 0%; 25 fewer infants per 1000 died before discharge [95% CI, 38 to 7 fewer per 1000]), **high certainty evidence** from 20 trials including 3,263 infants. {Backes 2016 35, Chu 2011 S201, Datta 2017 418, Duley 2018 F6, Finn 2019 , García 2023 2483, Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 , Liu 2018 , Oh 2011 , Okulu 2022 838444, Rana 2019 , Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Salae 2016 S159, Tarnow-Mordi 2017 2445, Yunis 2021 157}

Relevant outcomes for the subgroup of preterm infants <32 weeks' gestation
*For the important outcome of **any intraventricular hemorrhage,*** **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.98, 95% CI 0.79 to 1.22; I2 = 0%), low certainty evidence (downgraded for serious risk of bias and imprecision) from 13 trials involving 2124 infants. {Backes 2016 , Chu 2011 S201, Duley 2018 F6, Finn 2019 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Oh 2011 , Rana 2018 655, Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 , Yunis 2021 157}

*For the critical outcome of **severe intraventricular hemorrhage (grade III, IV),*** **clinical benefit or harm cannot be determined** for DCC compared to ICC, low certainty evidence (downgraded for serious risk of bias and imprecision) from 11 trials involving 2096 infants (OR 0·83, 95% CI 0·54 to 1·26; I2 = 0%). {Backes 2016 , Chu 2011 S201, Duley 2018 F6, Finn 2019 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Oh 2011 , Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 , Yunis 2021 157}

*For the critical outcome of **bronchopulmonary dysplasia** (supplemental oxygen at 36 weeks' postmenstrual age)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.06, 95% CI 0·87 to 1.30; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 10 trials including 1929 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 , Gregoraci 2023 203, Kugelman 2007 , Oh 2011 , Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the critical outcome of necrotizing enterocolitis (Bell staging greater than or equal to stage 2 or per author's definition), clinical
*For the critical outcome of **necrotizing enterocolitis** (Bell staging greater than or equal to stage 2 or per author's definition)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.82, 95% CI 0·59 to 1·13; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 11 trials including 2052 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 , García 2023 2483, Gregoraci 2023 203, Kugelman 2007 , Oh 2011 , Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the critical outcome of **patent ductus arteriosus receiving medical treatment***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.91, 95% CI 0.73-1.19; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 1928 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 , Gregoraci 2023 203, Kugelman 2007 , Oh 2011 , Ruangkit 2019 156, Tarnow-Mordi 2017 2445}

*For the critical outcome of **patent ductus arteriosus receiving surgical treatment***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.93, 95% CI 0.73-1.15; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 1678 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 , Gregoraci 2023 203, Kugelman 2007 , Oh 2011 , Tarnow-Mordi 2017 2445}

*For the critical outcome of **late onset sepsis** (sepsis that occurred at least 72 hours after birth or as per author's definition)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.93, 95% CI 0·74 to 1·17; I^2 = 0%), **low certainty evidence**

(downgraded for serious risk of bias and imprecision) from 9 trials including 2052 infants. {Chu 2011 S201, Duley 2018 F6, Finn 2019 , Gregoraci 2023 203, Oh 2011 , Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the important outcomes of ***hemoglobin concentrations (g/dL) and hematocrit values (%)*** *within the first 24 hours after birth*, hemoglobin concentrations and hematocrit values are **probably higher** after DCC compared to ICC (mean difference (MD)= 0.88 g/dL, 95% CI 0.52 to 1.24 (corresponds to MD of 8.8 mg/L, 95% CI 5.2 to 12.4), I^2= 0% and MD= 2.69%, 95% CI 1.43 to 3.95%; I^2 = 0% respectively), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 523 infants reporting ***hemoglobin concentrations*** {Chu 2011 S201, Finn 2019 , García 2023 2483, Gharehbaghi 2020 11095, Gregoraci 2023 203, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}and 8 trials including 260 infants reporting ***hematocrit values*** {Backes 2016 35, García 2023 2483, Gharehbaghi 2020 11095, Kugelman 2007 , Oh 2011 , Ranjit 2015 29, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*

For the important outcome of ***receiving transfusion of red blood cells***, there is **probable clinical benefit** (OR 0.59, 95% CI 0.47 to 0.73; I^2 = 0%; NNTB=7, 95% CI 5 to 12; 131 fewer infants per 1000 received blood transfusion after DCC than after ICC, [95% CI, 186 fewer to 78 fewer]), **Moderate certainty evidence** (downgraded for serious risk of bias) from 13 trials including 1929 infants. {Chu 2011 S201, Duley 2018 F6, Finn 2019 , García 2023 2483, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 , Oh 2011 , Rana 2018 655, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the important outcome of ***hypothermia on admission*** *(body temperature <36·5°C)*, there is **probable clinical harm** as more infants developed hypothermia after DCC compared to ICC (OR 1.28, 95% CI 1.06 to 1.56; I^2 = 0%; NNTH 16, 95% CI 9 to 71; 62 more infants per 1000 were hypothermic on admission, [95% CI, 14 more to 111 more]), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 1995 infants. {Duley 2018 F6, Finn 2019 , García 2023 2483, Kugelman 2007 , Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the important outcome of ***body temperature on admission,*** the temperature is **possibly lower** after DCC compared to ICC clamping (MD -0.13, 95% CI -0.20 to -0.06; I^2 =58.4), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 8 trials including 1995 infants.{Duley F6, Finn , García 2483, Kugelman , Rana 655, Ruangkit 156, Tarnow-Mordi 2445, Yunis 157}. *Note that the GRADE certainty of evidence was assessed post-hoc.*

For the important outcome of ***respiratory support after birth***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 2.01, 95% CI 0.58 to 7.03), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) from 11 trials including 1845 infants. {Duley 2018 F6, Finn 2019 , García 2023 2483, Kugelman 2007 , Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the important outcome of ***receiving inotropic support for hypotension*** *within the first 24 hours after birth*, **clinical benefit or harm cannot be determined** from DCC compared to ICC (OR 0.85, 95% CI 0.33 to 2.21), **very low certainty evidence** (downgraded for serious risk of bias and very serious of imprecision) from 5 trials including 172 infants. {Finn 2019 , Gregoraci 2023 203, Oh 2011 , Ruangkit 2019 156, Yunis 2021 157}

Relevant outcomes for the subgroup of preterm infants ≥32 weeks' gestation

Hemoglobin concentrations within the first 24 hours after birth *(important outcome),* are **probably higher** after DCC compared to ICC (MD 1.26 g/dL, 95% CI 0.72 to 1.80 (corresponds to MD of 12.6 mg/L, 95% CI 7.2 to 18.2), I^2= 0%, **low certainty evidence** (downgraded for risk of bias and inconsistency) from 7 trials including 302 infants. {García 2023 2483, Gharehbaghi 2020 11095, Gregoraci 2023 203, Liu 2018 , Okulu 2022 838444, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*

Hematocrit values within the first 24 hours after birth are **probably higher** after DCC compared to ICC (MD 3.69%, 95% CI 2.43 to 4.95%; I^2 = 0%), **moderate certainty evidence** (downgraded for risk of inconsistency) from 8 trials including 420 infants {García 2023 2483, Gharehbaghi 2020 11095, Kugelman 2007 , Liu 2018 , Okulu 2022 838444, Ranjit 2015 29, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*

For the important outcome of ***hypothermia on admission*** *(body temperature <36·5°C)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.95, 95% CI 0.51 to 1.79; I^2 = 0%), **very low certainty evidence** (downgraded for serious risk of imprecision and inconsistency) from 8 trials including 396 infants. {Duley 2018 F6, García 2023 2483, Kugelman 2007 , Liu 2018 , Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the important outcome of **body temperature on admission,*** **clinical benefit or harm cannot be determined** for DCC compared to ICC (MD -0.03, 95% CI -0.04 to 0.10; I^2= 0%), **moderate certainty evidence** (downgraded for risk of bias) from 8 trials including 396 infants. {Duley 2018 F6, García 2023 2483, Kugelman 2007 , Liu 2018 , Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc*

Relevant maternal outcomes:
*For the critical outcome **maternal mortality,*** an OR was **not estimable** (no reported death after deferred cord clamping or immediate cord clamping).

*For the critical maternal outcome of **postpartum hemorrhage** (blood loss >500 ml, or as estimated by the investigator)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.95, 95% CI 0.49 to 1.83; I^2 = 13%) **very low certainty evidence** (downgraded for serious risk bias and very serious risk of imprecision) from 9 trials including 853 mothers. {Duley 2018 F6, Finn 2019 , Gregoraci 2023 203, Kamal 2019 66, Liu 2018 , Ranjit 2015 29, Ruangkit 2019 156, Salae 2016 S159, Yunis 2021 157}

*For the critical maternal outcome of **post-partum blood transfusion,*** **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.74, 95% CI 0.41 to 1.85; I^2 = 9.7%), **very low certainty evidence** from 8 trials including 2017 mothers. {Duley 2018 F6, Finn 2019 , Gregoraci 2023 203, Liu 2018 , Sahoo 2020 881, Salae 2016 S159, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the critical maternal outcome of **manual removal of the placenta***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.99, 95% CI 0.55 to 1.80; I^2 = 0%), **very low certainty evidence** (downgraded for serious risk bias and very serious risk of imprecision) from 5 trials including 657 mothers. {Duley F6, Finn , Kamal 66, Liu 2018 , Salae S159}

*For the critical maternal outcome of **postpartum infection***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.00, 95% CI 0.59 to 1.70), **very low** certainty evidence (downgraded for serious risk of bias and very serious risk of imprecision) from **4 trials** including 448 mothers. {Duley 2018 F6, Finn 2019 , Liu 2018 , Salae 2016 S159} *Note that the GRADE certainty of evidence was assessed post-hoc.*

*For the important maternal outcome of **administration of uterotonic agents***, the effect was **not estimable**.

Post hoc analysis:
*For the important outcome of **hyperbilirubinemia treated with phototherapy*** for infants <32 weeks' gestation, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.7, 95% CI 1.00 to 2.90, I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk of bias, indirectness and imprecision) from 12 trials including 585 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 , García 2023 2483, Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 , Rana 2018 655, Ranjit 2015 29, Sahoo 2020 881, Yunis 2021 157}

*For the important outcome of **hyperbilirubinemia treated with phototherapy*** for infants ≥32 weeks' gestation, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.12, 95% CI 0.79 to 1.58, I^2 = 30.8%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 11 trials including 801 infants. {García 2023 2483, Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 , Liu 2018 , Okulu 2022 838444, Ranjit 2015 29, Ruangkit 2019 156, Salae 2016 S159, Yunis 2021 157}

COMPARISON 2: UMBILICAL CORD MILKING (UCM) COMPARED TO IMMEDIATE CORD CLAMPING (ICC)
The pairwise IPD MA identified 18 trials including 1565 infants. Median sample size was 60 [IQR] 45-122. Median (IQR) gestational age at birth was 29 (27-31) weeks. The cord was milked intact (2–4 times) in 12 trials (n=866 infants), whereas in four trials (n=340 infants) the cut-cord was milked once and in two trials (n=359) there was a delay before intact-cord milking. Of all infants, 64% were born by cesarean section, 13% were multiples, and 56% were male. Trials were conducted in high-income (n=10/18), upper-middle-income (n=4/18) and lower-middle-income (4/18) countries. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , George 2022 291, Gharehbaghi 2020 11095, Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

*For the critical outcome of **death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.73, 95% CI 0.44 to 1.20; I^2 = 7.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 18 trials including 1565 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , George 2022 291, Gharehbaghi

2020 11095, Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

Relevant outcomes for the subgroup of preterm infants <32 weeks' gestation:
*For the important outcome of **any intraventricular haemorrhage,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.02, 95% CI 0.76 to 1.38; I^2 = 8.6%), **moderate certainty evidence** (downgraded for serious imprecision) from 15 trials including 1069 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Gharehbaghi 2020 11095, Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Ram Mohan 2018 88, Tanthawat }

*For the critical outcome of **severe intraventricular haemorrhage,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.78, 95% CI 0.45 to 1.35; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 14 trials including 939 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Gharehbaghi 2020 11095, Hosono 2008 F14, Hosono 2015 , Lago Leal 2019 57, March 2013 , Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat }

*For the critical outcome of **bronchopulmonary dysplasia,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.96, 95% CI 0.63 to 1.47; I^2 = 0.0%), **low certainty evidence** (downgraded for very serious imprecision) from 12 trials including 836 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Hosono 2008 F14, Josephsen 2022 436, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

*For the critical outcome of **necrotizing enterocolitis,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.90, 95% CI 0.52 to 1.56; I^2 = 3.7%), **low certainty evidence** (downgraded for very serious imprecision) from 13 trials including 1047 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

*For the important outcome of **Patent ductus arteriosus receiving medical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.25, 95% CI 0.88 to 1.76; I^2 = 0.0%)***,*** **very low certainty evidence** (downgraded for serious risk of bias and very serious imprecision) from 12 trials including 893 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Tanthawat }

*For the critical outcome of **Patent ductus arteriosus receiving surgical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.84, 95% CI 0.46 to 1.52; I^2 = 0.0%), **low** certainty evidence (downgraded for serious risk of bias and imprecision) from **11 trials** including 888 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912}

*For the critical outcome of **late-onset sepsis*****, clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.07, 95% CI 0.76 to 1.51; I^2 = 39.2%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 12 trials including 977 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Hosono 2008 F14, Hosono 2015 , Katheria 2014 e94085, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Ram Mohan 2018 88, Xie 2022 31}

*For the important outcome of severe **retinopathy of prematurity*****, clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.05, 95% CI 0.73 to 1.51; I^2 = %), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) from 7 trials including 762 infants. {Alan e493, El-Naggar F145, Hosono F14, Hosono 2015 , Josephsen 436, Ram Mohan 88, Shen 912}

Hemoglobin concentrations (g/dL) within the first 24 hours after birth (*important outcome)* **were possibly higher** after UCM compared to ICC (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL; I^2 = 66.6%), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 12 trials including 944 infants. {Alan 2014 e493, El-Naggar 2019 F145, Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat } *Note that the GRADE certainty of evidence was assessed post-hoc.*

Hematocrit values (%) within the first 24 hours after birth **were possibly higher** after UCM compared to ICC (MD 1.71%, 95% CI 0.78 to 2.64%; I^2 = 36.9%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 12 trials including 900

infants. {Alan 2014 e493, Chellappan 2022 A178, Gharehbaghi 2020 11095, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Yadav 2015 720} *Note that the GRADE certainty of evidence was assessed post-hoc.*

For the important outcome of ***receiving red blood cell transfusions,*** there is **probable clinical benefit** for UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I^2 = 20%; NNTB 10, 95% CI 5 to 55; 92/1000 fewer infants received red cell transfusion after UCM compared to ICC, 95% CI 167 fewer to 18 fewer), **moderate certainty evidence** (downgraded for serious risk of bias) from 15 trials including 1163 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , George 2022 291, Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

For the important outcome of ***hypothermia on admission,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.95, 95% CI 0.69 to 1.31; I^2 = 52.4%), **very low certainty evidence** (downgraded for serious inconsistency and very serious imprecision) from 8 trials including 688 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Hosono 2008 F14, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Tanthawat }

For the important outcome of ***body temperature on admission,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (MD -0.03, 95% CI -0.12 to 0.06; I^2 = 41.3), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 688 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Katheria 2014 e94085, Mercer 2016 50, Ram Mohan 2018 88, Xie 2022 31} *Note that the GRADE certainty of evidence was assessed post-hoc.*

For the important outcome of ***receiving inotropic support for hypotension*** *within the first 24 hours after birth*, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.89, 95% CI 0.57 to 1.38), **very low certainty evidence** (downgraded for serious risk of bias and very serious of imprecision) from 10 trials including 827 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 , Hosono 2008 F14, Hosono 2015 , Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat } *Note that the GRADE certainty of evidence was assessed post-hoc.*

Relevant outcomes for the subgroup of preterm infants ≥32 weeks' gestation:

Hemoglobin concentrations (g/dL) within the first 24 hours after birth (*important outcome)* were **possibly higher after** UCM compared to ICC (MD 1.69 g/dL, 95% CI 0.90 to 2.48 g/dL); I^2 = 67.5%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 5 trials including 143 infants. {George 2022 291, Gharehbaghi 2020 11095, Lago Leal 2019 57, Okulu 2022 838444, Tanthawat } *Note that the GRADE certainty of evidence was assessed post-hoc.*

Hematocrit values (%) within the first 24 hours after birth were **possibly higher** after UCM compared to ICC (MD 4.47%, 95% CI 2.85 to 6.09%); I^2 = 55.9%), **low certainty evidence** (downgraded for serious risk of bias and indirectness) from 7 trials including 332 infants. {George 2022 291, Gharehbaghi 2020 11095, Lago Leal 2019 57, Okulu 2022 838444, Ram Mohan 2018 88, Tanthawat , Xie 2022 31} *Note that the GRADE certainty of evidence was assessed post-hoc.*

For the important outcome of ***receiving transfusion of red blood cells*****,** there is **possible clinical benefit** for UCM compared to ICC (OR 0.31, 95% CI 0.09 to 0.99); I^2 = 0.0%; NNTB 22, 95% CI 16 to 1000; 44/1000 fewer infants received blood transfusion with UCM compared to ICC, 95% CI 59 fewer to 1 fewer), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 6 trials including 330 infants. {George 2022 291, Lago Leal 2019 57, Okulu 2022 838444, Ram Mohan 2018 88, Tanthawat , Xie 2022 31}

For the important outcome of ***hypothermia on admission***, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.57 (0.84 to 2.93) I2 = 28.3%), **very low certainty evidence** (downgraded for very serious risk of bias and extremely serious imprecision) from 2 trials including 190 infants. {Ram Mohan 2018 88, Xie 2022 31}

Temperature on admission *(important outcome) was* **possibly lower** after UCM compared to ICC (MD -0.20, 95% CI -0.35 to -0.05; I^2 = 81.4%, **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 2 trials including 190 infants. {Ram Mohan 2018 88, Xie 2022 31} *Note that the GRADE certainty of evidence was assessed post-hoc.*

Relevant Maternal Outcomes

For the critical outcome ***maternal mortality,*** an OR was not estimable (only one death after ICC).

For the critical outcome of ***post-partum hemorrhage***, ***post-partum infection, post-partum blood transfusion***, and ***manual removal of the placenta***, the effect size was not estimable.

Post hoc analysis:
For the important outcome of ***hyperbilirubinemia treated with phototherapy*** *for infants <32 weeks' gestation*, **clinical benefit or harm cannot be determined** for UCM clamping compared to ICC (OR 1.09, 95% CI 0.73 to 1.63, I^2 = 3.2%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 12 trials including 1097 infants. {Alan 2014 e493, El-Naggar 2019 F145, Finn 2019 , Gharehbaghi 2020 11095, Hosono 2015 , Katheria 2014 e94085, Lago Leal 2019 57, March 2013 , Mercer 2016 50, Shen 2022 912, Tanthawat , Xie 2022 31}

For the important outcome of ***hyperbilirubinemia treated with phototherapy*** *for infants* ≥32 *weeks' gestation***, clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.19, 95% CI 0.71 to 1.98, I^2 = 0.0), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 5 trials including 350 infants. {George 2022 291, Gharehbaghi 2020 11095, Lago Leal 2019 57, Okulu 2022 838444, Xie 2022 31}

COMPARISON 3: UMBILICAL CORD MILKING (UCM) COMPARED TO DEFERRED CORD CLAMPING (DCC)
The pairwise IPD MA identified 15 trials (1655 infants). Median sample size was 44 (IQR 36-171). Median (IQR) gestational age at birth was 30 (28-33) weeks. One trial with six infants milked the cut cord once, whereas 14 studies with 1649 infants milked the intact cord (2-4 times). Deferral times in the DCC group ranged from 30 to 120 seconds. Off all infants, 64% were born by cesarean delivery, 15% were multiples, and 54% were male. Trials were conducted in high-income (8/15), upper-middle-income (3/15) and lower-middle-income (4/15) countries. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 , Okulu 2022 838444, Pratesi 2018 , Rabe 2011 , Schober 2018 NCT03748914, Trongkamonthum 2018 22}

For the critical outcome of ***death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.95, 95% CI 0.59 to 1.53; I^2 = 0.0%), **low certainty evidence** (downgraded for very serious imprecision) from **12 trials** including 1303 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 , Okulu 2022 838444, Pratesi 2018 , Rabe 2011 , Schober 2018 NCT03748914, Trongkamonthum 2018 22}

Relevant outcomes for the subgroup of preterm infants <32 weeks' gestation:
For the important outcome of ***any intraventricular hemorrhage,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.04, 95% CI 0.75 to 1.44; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 9 trials including 1022 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 , Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Pratesi 2018 , Rabe 2011 , Schober 2018 NCT03748914, Sura 2020 S612, Trongkamonthum 2018 22}

For the critical outcome of ***severe intraventricular hemorrhage,*** there is **possible clinical harm** after UCM compared to DCC (OR 2.20, 95% CI 1.13 to 4.31; I^2 = 0.0%) NNTH 24 (95% CI 9 to 200 infants more have severe IVH after UCM compared to DCC), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 860 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 , Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Pratesi 2018 , Rabe 2011 , Schober 2018 NCT03748914, Trongkamonthum 2018 22}

For the critical outcome of ***bronchopulmonary dysplasia,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.02, 95% CI 0.56 to 1.87; I^2 = 0.0%,), **very low certainty evidence** (downgraded for very serious risk of bias and serious imprecision) from 4 trials including 293 infants. {Finn 2019 , Katheria 2015 , Rabe 2011 , Trongkamonthum 2018 22}

For the critical outcome of ***necrotizing enterocolitis,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.95, 95% CI 0.55 to 1.66; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 976 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Katheria 2019 1877, Katheria 2015 , Rabe 2011 , Trongkamonthum 2018 22}

For the important outcome of ***patent ductus arteriosus receiving medical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.88, 95% CI 0.56 to 1.37; I^2 = 0.0%), **low certainty evidence** (downgraded for serious

risk of bias and imprecision) from 5 trials including 631 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Katheria 2015 , Trongkamonthum 2018 22}

*For the critical outcome of **patent ductus arteriosus receiving surgical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.43, 95% CI 0.63 to 3.25; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 5 trials including 631 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Katheria 2019 1877, Trongkamonthum 2018 22}

*For the critical outcome of **late-onset sepsis,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.91, 95% CI 0.57 to 1.48; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 6 trials including 787 infants. {Al-Wassia 2015 18, Finn 2019 , Katheria 2019 1877, Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **retinopathy of prematurity***, **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.73, 95% CI 0.43 to 1.24; I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) from 6 trials including 753 infants. {Al-Wassia 2015 18, Atia 2022 714, Katheria 2019 1877, Katheria 2015 , Rabe 2011 }

*For the important outcome of **hemoglobin concentrations (g/dL)*** within 24 hours after birth**, clinical benefit or harm cannot be determined** for UCM compared to DCC (MD 0.28g/dL mg/dL, 95% CI -0.04 to 0.60 g/dL); I^2 = 3.3%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 9 trials including 867 infants. {Atia 2022 714, Finn 2019 , Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 , Ling 2021 332, Rabe 2011 , Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **hematocrit (%)** within 24 hours after birth**,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (MD 0.67%, 95% CI -0.39 to 1.73%; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 637 infants. {Atia 2022 714, Gharehbaghi 2020 11095, Katheria 2019 1877, Ling 2021 332, Rabe 2011 , Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **receiving transfusions of red cells,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.07, 95% CI 0.77 to 1.50; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 985 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Katheria 2019 1877, Katheria 2015 , Ling 2021 332, Rabe 2011 , Trongkamonthum 2018 22}

*For the important outcome of **hypothermia on admission,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.90, 95% CI 0.64 to 1.26; I^2 = 34.1%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 875 infants. {Atia 2022 714, Finn 2019 , Katheria 2019 1877, Katheria 2015 , Pratesi 2018 , Rabe 2011 , Trongkamonthum 2018 22}

<u>Relevant outcomes for the subgroup of preterm infants ≥32 weeks' gestation:</u>
*For the important outcome of **hemoglobin concentrations (g/dL)*** within 24 hours after birth, **clinical benefit or harm cannot be determined** for UCM compared to DCC (MD -0.12g/dL mg/dL, 95% CI -0.50 to 0.26 g/dL); I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 456 infants. {Atia 2022 714, Gharehbaghi 2020 11095, Ling 2021 332, Okulu 2022 838444, Rabe 2011 , Schober 2018 NCT03748914, Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **hematocrit values (%)*** within 24 hours**, clinical benefit or harm cannot be determined** for UCM compared to DCC (MD -0.53%, 95% CI -1.66 to 0.60%); I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk of bias and imprecision) from 9 trials including 469 infants. {Atia 2022 714, Gharehbaghi 2020 11095, Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Rabe 2011 , Schober 2018 NCT03748914, Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **receiving red cell transfusion***, **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.67, 95% CI 0.60 to 4.60); I^2 = 0.0%), **very low certainty evidence** (downgraded for very serious risk of bias and imprecision) from 8 trials including 251 infants. {Al-Wassia 2015 18, Atia 2022 714, Ling 2021 332, Okulu 2022 838444, Rabe 2011 , Schober 2018 NCT03748914, Trongkamonthum 2018 22}

For the important outcome of ***hypothermia on admission,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.40 (0.54 to 3.69) I2 = 0.0%), **very low certainty evidence** (downgraded for very serious risk of bias and imprecision) from 5 trials including 209 infants. {Atia 2022 714, Katheria 2015 , Rabe 2011 , Schober 2018 NCT03748914, Trongkamonthum 2018 22}

Maternal outcomes:
For the critical outcome ***maternal mortality,*** an OR could not be estimable (only one death after UCM and after DCC).

For the critical outcome of ***post-partum hemorrhage,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.29, 95% CI 0.48 to 3.67), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) imprecision from 5 trials including 632 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Sura 2020 S612, Trongkamonthum 2018 22}

For the critical maternal outcome of ***post-partum receipt of blood transfusion***, there is **possible clinical harm** after UCM compared to DCC (OR 2.72, 95% CI 1.11 to 6.65; I^2 = 0.0%; NNTH 26 (95% CI 8 to 333) 39 more/1000 (95% CI from 3 more to 118 more), **low certainty evidence** from 4 trials including 653 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Katheria 2015 }

For the critical maternal outcome of ***manual removal of the placenta,*** **clinical benefit or harm cannot be determined** from UCM compared to DCC (OR 0.21, 95% CI 0.04 to 0.99; I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk bias and very serious risk of imprecision) from **3 trials** including 341 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 }

For the important maternal outcome of ***administration of uterotonic agents***, the effect was not estimable.

Post hoc analysis:
For the important outcome of ***hyperbilirubinemia treated with phototherapy*** *for infants* <32 *weeks' gestation***, clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.73, 95% CI 0.48 to 1.11, I^2 = 16.5%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 8 trials including 1080 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 , Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 , Rabe 2011 , Sura 2020 S612}

For the important outcome of ***hyperbilirubinemia treated with phototherapy*** for *infants ≥32 weeks' gestation,* **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 101, 95% CI 0.62 to 1.66, I^2 = 36.1%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from **8 trials** including 448 infants. {Al-Wassia 2015 18, Atia 2022 714, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Okulu 2022 838444, Pratesi 2018 , Schober 2018 NCT03748914, Sura 2020 S612}

Subgroup analyses
Several participant-level and hospital/trial-level subgroups were pre-specified using a test of interaction to assess differential treatment effects ***for the primary outcome of death*** before discharge. There was no evidence of differential treatment effects for any of the pre-specified subgroups, but **certainty was low or very low** due to insufficient sample size. Pre-specified participant-level subgroups included:

A- ***Gestational age at birth****:* Gestational age at birth did not influence the effect of DCC on mortality before discharge when:
   a. DCC was received compared to ICC (interaction OR (iOR) 0.93 95% CI 0.78 to 1.11), **high certainty evidence** from 13 trials.
   b. UCM was received compared to ICC (iOR 1.01 95% CI 0·97 to1·05), **low certainty evidence** from 11 trials.
   c. UCM was received compared to DCC (iOR 1.08 95% CI 0.80 to1.47), **low certainty evidence** from 7 trials.

B- ***Multiple birth (singleton/multiple pregnancy)****:* Multiple births did not influence the effect of DCC on mortality before discharge when:
   a. DCC was received compared to ICC (OR 1.11 95% CI 0.49 to 2.50), **low certainty evidence** from 4 trials.
   b. UCM was received vs ICC (iOR 1.52 95% CI 0.37 to 6.32), **very low certainty evidence** from 7 trials.
   c. UCM was received vs DCC (iOR 1.26 95% CI 0.34 to 4.67), **very low certainty evidence** from 4 trials.

C- ***Mode of birth (cesarean/ vaginal):*** Mode of delivery did not influence the effect of DCC on mortality before discharge when:
   a. DCC was received compared to ICC (iOR 0.69 95% CI 0.39-1.22), **low certainty evidence** from 4 trials
   b. UCM was received compared to ICC (iOR 0.59 95% CI 0.20 to 1.75), **very low certainty evidence** from 13 trials
   c. UCM was received compared to DCC (iOR 0.83 95% CI 0.33 to 2.12), **low certainty evidence** from 8 trials.

D- ***Study start (year):*** Study year did not influence the effect of DCC on mortality before discharge when**:**
   a. DCC was received compared to ICC (iOR 1.00 95% CI 0.92 to 1.08), **very low certainty evidence** from 13 trials.
   b. UCM was received vs ICC (iOR 1.02 95% CI 0.99 to 1.04). Evidence of **low** certainty from 8 trials.
   c. UCM was received vs DCC (iOR 0.89 95% CI 0.74 to 1.08).

E- ***Country's perinatal mortality rate (per 1,000***): Country's perinatal mortality rate did not influence the effect of DCC on mortality before discharge when:
   a. DCC was received compared to ICC (iOR 1.00 95% CI 0.97 to 1.02), **low certainty evidence** from 13 trials.
   b. UCM was received vs ICC (iOR 0.98 95%CI 0.85 to 1.12), **very low certainty evidence** from 13 trials.
   c. UCM was received vs DCC (iOR 0.98 95% CI 0.88 to 1.09), **low** certainty evidence from 8 trials.

F- ***Sex (male/female)***: (note that this subgroup analysis was conducted post-hoc). Infant's sex did not influence the effect of DCC on mortality before discharge when:
   a. DCC was received compared to ICC (iOR 1.00 95% CI 0.64 to 1.86), evidence from 11 trials,
   b. UCM was received vs ICC (iOR 1.22 95% CI 0.44 to 3.37), evidence from 11 trials,
   c. UCM was received vs DCC (iOR 0.54 95% CI 0.20 to 1.48), evidence from 7 trials.

Pre-specified subgroup analyses of **whether initial resuscitation was provided at bedside with cord intact, planned position of the infant relative to the placenta, and non-linear interactions of gestational age** could not be performed due to insufficient data or convergence issues.

The IPD network meta-analysis identified **47 eligible studies** (6,094 infants). Median sample size was 60 infants (IQR 40-127). The median gestational age at birth was 29.6 weeks (IQR 27.6 to 33.3). Of all infants, 54% were male, 61% were born by cesarean delivery, and 17% were multiples. The primary outcome was missing for 4 (<0.1%) infants. {Seidler 2023 2223}

The following five comparisons are included in the NMA (Figure 1).

1. Immediate (early) cord clamping (ICC).
2. Short deferral of cord clamping.
3. Medium deferral of cord clamping.
4. Long deferral of cord clamping for.
5. Intact cord milking immediately after birth.

*For the critical outcome of **death before discharge***, **30 trials** (4,712 infants) reported at least one event and were available in the network. Direct comparisons were available for all but one intervention pair (long versus medium deferral).

- Compared to immediate clamping, **long deferral (≥120 s) reduced death** before discharge (OR 0.31; 95%CrI 0.11-0.80, number needed to treat to benefit (NNTB) = 18, 95% CrI 4-143). **moderate certainty evidence**
- Compared to immediate clamping, credibility intervals for **medium** and **short** deferral crossed the line of **no effect**: medium deferral (OR 0.76; 95% CrI 0.48-1.39, **low certainty evidence**) and short deferral (OR 0.82; 95%CrI 0.41-1.73, **very low certainty evidence**).
- Compared to immediate clamping, **Intact cord milking** crossed the line of no effect (OR 0·75; 95%CrI 0·41-1·43, **very low certainty evidence**).

Ranking probabilities of different interventions:

- Long deferral had a 91% probability of being the highest ranked treatment to prevent *death before discharge*.
- Immediate clamping had <1% probability of being the best treatment to prevent *death before discharge*, and a 53% probability of being the worst treatment.
- Medium length deferral and intact cord milking had a high probability of being second or third best (Figure 2).

*For the important outcome of **any intraventricular haemorrhage,*** 27 trials including 4,283 infants) reported at least one event and were available in the network. Direct comparisons were available for all but one intervention pair (long versus medium deferral).

- Compared to immediate clamping, long deferral (≥120 sec) crossed the line of no effect (OR 0·77; 95%CrI 0·34-1.64, **very low certainty evidence**).
- Compared to immediate clamping, medium and short deferral crossed the line of no effect: medium deferral (OR 0.98; 95%CrI 0.69-1.51, **very low certainty evidence**).
- Compared to immediate clamping, intact cord milking crossed the line of no effect (OR 0.99; 95%CrI 0.67-1.50, **very low certainty evidence**).

*For the important outcome of **receiving red cell transfusions***, 29 trials including 4,746 infants were available. Direct comparisons were available for all but one intervention pair (long versus medium deferral).

- Compared to immediate clamping, all **short and medium deferral and intact-cord milking reduced the receipt of red cell transfusions** by about 50%. For **short** deferral the OR was 0·44 (95%CrI 0·17-0·90, **moderate certainty evidence**), for medium deferral OR was 0·45 (95%CrI 0·23-0·75, **moderate certainty evidence**) and for intact-cord milking OR was 0·56 (95%CrI 0·31-0·97, **low certainty evidence**).
- For **long deferral**, evidence was inconclusive due to insufficient evidence (OR 0.55; 95%CrI 0.12-2.43, **very low certainty evidence**).

Treatment Recommendations:

In preterm infants born at less than 37 weeks' gestational age who are deemed not to require immediate resuscitation at birth, we recommend deferring clamping of the umbilical cord for at least 60 seconds (strong recommendation, moderate-certainty evidence.

In preterm infants born at 28^{+0} to 36^{+6} weeks' gestational age who do not receive deferred cord clamping, we suggest umbilical cord milking as a reasonable alternative to immediate cord clamping to improve infant hematologic outcomes. Individual maternal and infant circumstances should be taken into account (conditional recommendation, low-certainty evidence).

We suggest against intact cord milking for infants born at less than 28 weeks' gestation (weak recommendation, low-certainty evidence). There is insufficient evidence to make a recommendation regarding cut-cord milking in this gestational age group.

In preterm infants born at less than 37 weeks' gestational age who are deemed to require immediate resuscitation at birth, there is insufficient evidence to make a recommendation with respect to cord management (weak recommendation, low-certainty evidence).

There is insufficient evidence to make recommendations on cord management for maternal, fetal, or placental conditions that were considered exclusion criteria in many studies (monochorionic multiple fetuses, congenital anomalies, placental abnormalities, alloimmunization and/or fetal anemia, fetal compromise, and maternal illness). In these situations, we suggest individualized decisions based on severity of the condition and assessment of maternal and neonatal risk (weak recommendation, very low–certainty evidence).

Whenever circumstances allow, the plan for umbilical cord management should be discussed between maternity and neonatal providers and parents before delivery and should take into account individual maternal and infant circumstances (good practice statement).

Evidence Update Search strategy: - See appendix
For the evidence update, we followed the same search strategy used by the iCOMP group. {Seidler 2023 2209}.

Database searched:
Ovid MEDLINE(R) from 1946, Embase Classic and Embase from 1947, Clinical trials registries.

Time Frame: (2024 SysRev): from database inception to 6 June 2023. {Seidler 2023 2209}.
New Search (current EvUp): 7 June 2023 to 6 June 2024.
Search Strategy: see appendix
Search Results:
Full text screened:
Included: 11 RCT publications and 2 systematic reviews.
Three RCTs were excluded from the update; two because the majority of included infants were full-term with no subgroup analysis of preterm infants. {Chaudhary 2023 3701, Murali 2023 597} The third trial was excluded based on the study quality and the undefined gestational age of its population. {Tariq 2023 14} One excluded systematic review included 8 RCTs that had also been included in iCOMP and two additional observational studies. {Zaman 2023 99}

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Watson 2024 {Watson 2024 248}	**Study Aim** to assess the effectiveness of umbilical cord milking (UCM) and delayed cord clamping (DCC) for the prevention of neonatal hypoglycemia. **Study Type** Systematic review and meta-analysis **Study Size** N=14,268 infants.	**P:** Full-term and Preterm infants **I:** DCC or UCM **C:** Control **O:** Neonatal hypoglycemia (study defined).	71 studies (14,268 infants) were included; 50 studies (11,731 infants) compared DCC with ECC and 22 studies (2,537 infants) compared UCM with control.	- There was no evidence that DCC reduced the incidence of hypoglycemia (6 studies, 444 infants, RR (CI)=0.87 (0.58 to 1.30), p=0.49, I^2=0%. - DCC was associated with a 27% reduction in neonatal mortality (15 studies, 3 041 infants, RR (CI)=0.73 (0.55 to 0.98), p=0.03, I^2=0%. - No evidence for an effect of DCC on any of the other outcomes. - The certainty of evidence was low for all outcomes. - For UCM, there were no data on neonatal hypoglycemia, and no differences between groups for any of the secondary outcomes. - In subgroup analysis for gestational age (term vs preterm infants), there were no significant interactions for available outcomes	- No evidence that DCC reduces the incidence of hypoglycemia. - No data for the effectiveness of UCM on neonatal hypoglycemia.
Abbreviations: UCM-umbilical cord milking; DCC-delayed cord clamping					

RCTs:

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
VentFirst; Fairchild 2024 {Fairchild 2024 e2411140}	**Study Aim** To compare any grade IVH on head ultrasonography or death before day 7 in extremely preterm infants. **Study Type**	**Inclusion Criteria:** Women expected to deliver extremely preterm infants at 23 $^{0/7}$- 28 $^{6/7}$	**Intervention:** Respiratory support with cord clamping at 120 seconds (n-CPAP if breathing well or positive-pressure ventilation if not). N= 278 **Comparison:**	**1° endpoint:** - Overall, IVH or death occurred in 34.9% in the intervention group and 32.5% in the control group (adjusted RR, 1.02; 95% CI, 0.81-1.27).	**Study Limitations:** - Generalizability: Antenatal consent was required but often not feasible; thus, excluding infants born under emergency conditions reduces

	Phase 3, 1:1, parallel-stratified unblinded multicenter RCT (12 centers). **Study Size** N=570 infants.	weeks' gestation (and their children).	30-60 sec of delayed cord clamping (DCC) followed by standard resuscitation. N= 292	- In the pre-specified not-breathing-well cohort (47.5%, 271 of 570); IVH or death occurred in 38.7% (58 of 150) of infants in the intervention group and 43.0% (52 of 121) in the control group (RR, 0.91; 95%CI, 0.68-1.21). **Secondary outcomes:** No significant differences in death, severe brain injury, or major morbidities	representativeness of study population. - Blinding was not possible because of the nature of the intervention. - Delivery room clinicians were aware of study arm, potentially introducing bias for breathing assessment - Lung aeration couldn't be assessed prior to cord clamping (respiratory and vital sign monitoring were not done before cutting the cord) - Small sample size especially for the non-breathing infants.
EXPLAIN Kuehne 2023 {Kuehne 2023 e2340597}	**Aim of the Study** To test whether extrauterine placental perfusion (EPP) for physiological-based cord clamping (PBCC) in resuscitation of infants with very low birth weight results in higher hematocrit levels, better oxygenation, or improved infant outcomes compared with DCC. **Study Type** Unblinded single center randomized clinical trial. **Study size** N=59 infants	**Inclusion criteria** Preterm infants >23^{+6} weeks' gestation and estimated fetal weight <1500 grams, born by cesarean section.	**Intervention** EPP: During C-deliveries, infant and placenta, connected by an intact umbilical cord, were detached from the uterus and transferred to the resuscitation unit. Respiratory support was initiated while holding the placenta 40-50 cm above the infant. Umbilical cord was clamped when infants showed regular spontaneous breathing, stable heart rates >100 bpm, and adequate oxygen saturations. N=29 **Comparison** DCC for 30-60 sec (at least 30 sec) before infants were transferred to the	**1˚ endpoint** - Mean hematocrit value during the first 24 hours (3 tests) was not significantly different. (mean difference [MD], 2.1%; 95% CI, −2.2 to 6.4%). **Secondary outcomes** - During transition, infants in the EPP group had significantly higher peripheral oxygen saturation (by pulse oximetry (adjusted MD at 5 min, 15.3% [95% CI, 2.0 to 28.6%]) and regional cerebral oxygen saturation (adjusted MD at 5 min, 11.3% [95% CI, 2.0 to 20.6%]). - Neonatal outcomes were similar in the 2 groups.	**Study Limitations** - Blinding was not possible because of the nature of the intervention. - Concerns about performance bias; infants in the DCC group received DCC for a mean of only 39 sec, infants in the EPP group received higher mean airway pressure and FIO2 initially (could explain the better oxygenation found). - Small sample size, not powered for safety outcomes (especially for severe IVH and maternal blood loss) and clinical outcomes. - Questions about the external validity and reproducibility (restrictive inclusion criteria, experience with EPP and use of escalating CPAP pressures rather than PPV in resuscitation).

			resuscitation unit for respiratory support. N=30 - In both groups, nasal CPAP was started at 8-10 cm H_2O with stepwise increase up to a maximum of 30cm H_2O using the Benveniste valve as CPAP generator.		- Questions about the use of the EPP in twins (if attached placentae) - Long term neuro-developmental outcomes were not assessed (will be reported later).
Garcia 2024 {García 2024 2483}	**Aim of the Study** To investigate hematological and cardiac changes after DCC vs. ECC in preterm infants. **Study Type** Unblinded single center randomized clinical trial. **Study Size** N=96 infants	**Inclusion criteria** Preterm infants born at 24-34 weeks of gestation.	**Intervention:** DCC for 40-60 sec. (N=47) **Comparison** ECC after <10 sec (N=49)	**1° endpoint:** - DCC group had higher hemoglobin levels on admission (18.7± 3.0 vs. 16.8± 2.4, $p < 0.01$) **Secondary outcomes:** - DCC group had higher hematocrit on admission (53.9 ± 8.0 vs. 48.8 ± 6.4, $p < 0.01$), higher hemoglobin on day 7 (16.4 ± 3.8 vs 13.9 ± 2.5, $p < 0.005$), and higher hematocrit on day 7 (49.3 ± 12.7 vs 41.2 ± 8.4, $p < 0.008$). - Less blood transfusion after DCC (8.5% vs 24.5%; OR: 0.29, 95% CI: 0.09-0.97, $p < 0.036$). - Higher receipt of phototherapy after DCC (80.9% vs 63.3%; OR: 0.23, 95% CI: 0.06-0.84, $p <0.03$). - No differences in cardiac echo parameters, clinical outcomes, or maternal blood tests.	**Study Limitations:** - Blinding was not possible because of the nature of the intervention. - No stratification by gestational age - Underpowered for important clinical outcomes
Rao 2024 {Rao 2024 2791}	**Study Aim:** To determine if intact umbilical cord milking (I-UCM) is non-inferior to DCC and can be used as a safer alternative to DCC.	**Inclusion criteria** Stable preterm neonates (28-36 weeks) born via C-section	**Intervention:** I-UCM 4 times, each for 2 seconds, N= 36 **Comparison:** DCC for at least 45 seconds N= 54	**1° endpoint:** Infants who underwent I-UCM had significantly higher hemoglobin at 72 hours of life than those receiving DCC, 19.97 g/dL ± 1.44 vs. g/dL	**Limitations:** - Small sample size - There was substantial imbalance between the numbers allocated to each intervention.

	Study Type: Non-inferiority RCT **Study Size:** N=99 infants			18.62 g/dL ± 0.98 p<0.0001. **Secondary Outcomes:** No differences in mortality (p=0.3) or IVH > grade II (p=0.56) between the groups.	
Angadi 2023 {Angadi 2023 4185}	**Study Aim:** To compare the effects of I-UCM with DCC on the hemodynamic parameters measured by echocardiography and color Doppler and regional cerebral oxygenation saturation ($CrSO_2$) measured by near-infrared spectroscopy (NIRS) in IUGR infants. **Study Type:** RCT **Study Size:** N=170 infants	**Inclusion criteria** IUGR neonates >28 weeks of gestation, not requiring resuscitation. Randomization occurred after determination of need for resuscitation.	**Intervention:** I-UCM: 20 cm of the intact cord was squeezed 4 times N: 85 **Comparison:** DCC for at least 60 seconds N: 85	**Primary Endpoint:** Mean superior vena cava (SVC) blood flow (mL/kg/min) at 24 ± 2 hrs of life was significantly higher in I-UCM (111.9 ± 33.5 vs 99.5 ± 32 MD (CI), 12.5 (2.5,22.4); p= .01 **Secondary Outcomes:** - $CrSO_2$ was significantly higher in the I-UCM (84.69 ± 5.23 vs 82.95 ± 5.85; MD (CI), 1.74 (0.05, 3.42); p= 0.04 - Venous hematocrit was significantly higher in the I-UCM (60.7 ± 5.0 vs 59.0 ± 5.0; MD (CI), 1.7 (0.2, 3.2); *p*= 0.03 - Peak serum bilirubin was higher in I-UCM MD (CI), 1.70 (0.46, 2.94) p=0.007 - Non-invasive ventilation was higher in I-UCM RR(CI) 1.80 (1.03, 3.14) p=0.037 - No significant difference in other hemodynamic outcomes, severe IVH, NEC or mortality	**Study limitations:** -The inclusion of a fewer neonates <32 weeks of gestation (most of these neonates required some resuscitation at birth and were excluded). Number unspecified. - No mention about the inter/intra-operator reliability in hemodynamic measurements/ assessment. - Study is underpowered for important clinical outcomes.
Zhang 2024 {Zhang 2023 e36121}	**Study Aim:** To explore the effectiveness and safety of different I-UCM lengths versus DCC. **Study Type:** Triple blinded RCT **Study Size (N):** N=182 randomized (143 analyzed)	**Inclusion Criteria:** Preterm infants of a single birth; born between 28^{+0} and 36^{+6} weeks of gestation	**Intervention 1:** I-UCM 10cm group: 10cm segment from the root of the umbilical cord was squeezed 3 times toward the infant. N= 45 (35 analyzed) **Intervention 2:** I-UCM 20cm group: 20cm segment	**Primary Endpoint:** Order: 10cm, 20cm, 30cm and DCC (comparator) Capillary hemoglobin level at birth was significantly lower after I-UCM 10 cm than the rest of the groups: (18.229 ± 2.215, 20.283 ± 2.146,	**Study Limitations:** - Sizable attrition from those randomized to those analyzed - Analysis was per protocol. - Small sample size

			from the root of the umbilical cord was squeezed 3 times toward the infant. N=45 (35 analyzed) **Intervention 3:** I-UCM 30cm group: 30cm segment from the root of the umbilical cord was squeezed 3 times toward the infant. N= 46 (38 analyzed) **Comparison:** DCC: The umbilical cord was cut when pulsation ceased. N=46 (35 analyzed)	20.882 ± 2.072, and 19.846 ± 2.492, P<.001 **Secondary Outcomes:** - Blood transfusion was significantly higher after I-UCM 10 cm than the rest of the groups: (34.3% vs 11.4% vs 5.3% vs 8.6%, p= .002) - No significant differences in IVH (not defined), other morbidity, mortality or phototherapy	
Bora 2023 {Bora 2023 3883}	**Aim of the study** To examine the effect of cut umbilical cord milking (C-UCM) as compared to early cord clamping (ECC) on hematological, hemodynamic and clinical outcomes in non-vigorous preterm neonates of 30-35 weeks' gestation. **Study Type** Unblinded single center randomized clinical trial. **Study Size** N=134 infants.	**Inclusion criteria:** Inborn non-vigorous preterm neonates ($30^{0/7}$- $34^{6/7}$ weeks) requiring resuscitation at birth	**Intervention:** - The cord was clamped and cut within 30 sec of delivery at a length of about 30 cm. followed by 3x C-UCM while resuscitation (C-UCM group). N=67 **Comparison:** - The cord was clamped and cut within 30 sec of delivery followed by resuscitation of the infant without cord milking (ECC group). N= 67	**1° endpoint:** - Mean Hct at 48h was higher in the C-UCM compared to the ECC group, 50.24% (4.20) vs 46.16 % (2.96), p< 0.01. **Secondary outcomes:** **-** Mean Hct at 12 h and 6 wks, serum ferritin at 6 wks of age were significantly higher in the C-UCM group (P < 0.01). - Mean blood pressure at 1 and 6 hrs was higher in the C-UCM group (p < 0.05) - Clinical outcomes were not different.	**Study Limitations:** - Blinding was not possible because of the nature of the intervention. - Preterm infants <30 weeks' gestation were excluded - Not powered to detect efficacy and safety of C-UCM on clinical outcomes - No RR/OR (95% CI) provided.
Raja 2023 {Raja 2023 257}	**Study Aim:** To assess the efficacy of a novel method of placental transfusion at birth: gravity aided cord blood transfusion (GCT) compared to standard care (DCC for vigorous infants and ICC for non-vigorous infants)	**Inclusion Criteria:** Infants <30 weeks of gestation irrespective of the mode of delivery and need for resuscitation at birth.	**Intervention:** After birth, the umbilical cord was clamped as far away from baby. Baby was shifted to the warmer. GCT was performed by holding the infant's umbilical cord vertically after untwisting it and allowing gravity-	**Primary Endpoint:** The median (IQR) hemoglobin at 24 hours of life was 16.9 (16.3-18.9) in the GCT group and 16.4 (14.8-17.8) in standard care, the difference was not statistically significant, p=0.46 **Secondary Outcomes:**	**Limitations:** - Very small sample size.

	Study Type: Non-inferiority RCT **Study Size:** N=22 infants		dependent blood flow, until completion of cord blood drainage (shrinkage of cord size and decreased umbilical vessel prominence). N: 9 **Comparison:** Standard practice (DCC for 60 sec in vigorous neonates or ICC in non-vigorous neonates) N: 13	Mortality was 25% in both groups, p=1.0.	
Abbreviations: IVH- intraventricular hemorrhage; DCC-delayed cord clamping; ECC- early cord clamping; I-UCM-intact umbilical cord milking; C-UCM- cut umbilical cord milking; ICC- immediate cord clamping.					

Reviewer Comments:
This evidence update review included one systematic review assessing the effect of DCC and UCM on neonatal hypoglycemia {Watson 2024 248} and 8 RCTs:

- Two trials compared respiratory support during DCC with standard DCC for 30-60 sec {Fairchild 2024 e2411140, Kuehne 2023 e2340597} with one of these trials using a new placental transfusion/DCC strategy (EPP) in infants born by C-delivery. {Kuehne 2023 e2340597}
- One trial compared DCC to ECC. {García 2024 2483}
- Two trials compared I-UCM to DCC. {Angadi 2023 4185, Rao 2024 2791}
- One trial compared different lengths of I-UCM (10cm, 20cm and 30 cm) to each other and to DCC. {Zhang 2023 e36121}
- One trial {Bora 2023 3883} compared C-UCM to ECC in non-vigorous preterm infants. {Bora 2023 3883}
- Finally, one trial compared a new approach of gravity-aided transfusion from the long-cut cord to the standard of care (DCC for vigorous infants and ECC for non-vigorous infants). {Raja 2023 257}

The included trials were mostly underpowered to detect important differences in clinical outcomes. Trial methodology and quality were variable. In general, the review of these trials supports the benefits of placental transfusion whether by DCC or UCM over ECC/ICC with no major adverse effects reported. The optimal approach for preterm infants who are deemed to require resuscitation at birth remains uncertain.

Overall, we found no important new evidence related to the current PICOST that would drive the need to conduct a new systematic review or warrant a change in the current treatment recommendations.

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Appendix: search strategy

Sources searched	Search strategy as per {Seidler 2023 2209}	Search time frame
MEDLINE (Ovid)	1. umbilical-cord.mp. or exp umbilical cord/ 2. (Clamp$ OR Milk$).af. 3. (Placenta$ adj2 transfus$).af 4. 2 or 3 5. exp Infant, Premature/ or preterm*.mp. 6. prematur*.mp.	7 June 2023 (previous search) - 6 June 2024

	7. exp Infant, Low Birth Weight/ or exp Infant, Very Low Birth Weight 8. exp Infant, Extremely Low Birth Weight 9. 5 or 6 or 7 or 8 10. 1 and 4 and 9 11. limit 10 to (humans and clinical trial, all) 12. limit 11 to ed=20181001-20190213	
Embase (and Embase Classic?)	2. (Clamp$ OR Milk$).af. 3. (Placenta$ adj2 transfus$).af 4. 2 or 3 5. exp Infant, Premature/ or preterm*.mp. 6. prematur*.mp. 7. exp Infant, Low Birth Weight/ or exp Infant, Very Low Birth Weight 8. exp Infant, Extremely Low Birth Weight 9. 5 or 6 or 7 or 8 10. 1 and 4 and 9 11. limit 10 to (human and randomized controlled trial) 12. limit 11 to yr="2018 -Current"	
Clinical trials registries	*ICTRP:* 1. placental transfusion 2. cord clamp* 3. umbilical cord clamp* 4. cord milking 5. milking 6. umbilical cord 7. preterm 8. pre-term 9. prematur* *ClinicalTrials.gov:* Interventional studies | cord clamping Interventional studies | cord milking Interventional studies | cord stripping *Cochrane Register of Controlled trials:* 2. (Clamp$ OR Milk$).af. 3. (Placenta$ adj2 transfus$).af 142 4. 2 or 3 5. exp Infant, Premature/ or preterm*.mp. 6. prematur*.mp. 7. exp Infant, Low Birth Weight/ or exp Infant, Very Low Birth Weight 8. exp Infant, Extremely Low Birth Weight 9. 5 or 6 or 7 or 8 10. 1 and 4 and 9 11. limit 10 to yr="2018 -Current"	
Results identified	**Results screened full text**	**Results included**
Missing	Missing	1 RCTs and 2 systematic reviews

2025 Evidence Update
NLS 5100 – Maintaining Normal Temperature Immediately After Birth in Late Preterm and Term Infants

Worksheet Author(s): Dawson JA**,** de Almeida MF, Ramaswamy VV, Trevisanuto D, Nakwa FL, Kamlin COF, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 29 October 2024
Conflicts of Interest: Several authors with conflicts of interest in the original SR, none for this evidence update**.**

PICOST:
Population: In late preterm and term infants (≥34 weeks' gestation, or equivalent birth weight), immediately after birth
Intervention: Increased room temperature ≥23.0°C, thermal mattress, plastic bag or wrap, hat, heating and humidification of gases used for resuscitation, radiant warmer (with or without servocontrol), early monitoring of temperature, warm bags of fluid, warmed swaddling/clothing, skin to skin care with a parent, or any combination of these interventions
Comparators: Drying, without any of the above interventions.
Outcomes:
Primary outcomes:
- Survival (critical)
- Rate of normothermia on admission to neonatal unit or postnatal ward (important)

Secondary outcomes:
- Rate of either hypothermia or hyperthermia on admission to neonatal unit or postnatal ward (important)
- Response to resuscitation- e.g., need for assisted ventilation, highest FiO_2 (important)
- Important morbidity e.g., rates of admission to neonatal special or intensive care nursery, need for respiratory support (important)

Outcomes ratings using the GRADE classifications of critical or important were decided according to a consensus for international neonatal resuscitation guidelines. {Strand 2020 328} Outcomes were converted into main outcomes and additional outcomes for submission to PROSPERO CRD42021270739
Potential subgroups were defined a priori: by gestation groups, early vs later umbilical cord clamping, by low- vs high-resourced setting or by inborn vs outborn status) for any comparison.
Study Design: Randomized controlled trials (RCTs), quasi-RCTs, observational studies including retrospective and prospective cohort studies, controlled before-after studies, interrupted time series studies and quality improvement (QI) initiatives were included. Conference abstracts, unpublished studies and study protocols were excluded. A languages were included provided there was an English abstract.
Time Frame: The literature was searched from database inception, first on 2 August 2021 and updated on 20 July 2022.

Year of last full review: 2022 {Ramaswamy 2022 81, Wyckoff 2022 e645}

2022 ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Ramaswamy 2022 81, Wyckoff 2022 e645}
Consensus on Science
COMPARISON 1: INCREASED ROOM TEMPERATURE COMPARED TO NO INCREASED ROOM TEMPERATURE
The systematic review found one study enrolling 825 infants born by caesarean section at a single hospital. {Duryea 2016 505.e1}
For an operating room temperature 23°C vs. an operating room temperature of 20°C, for late preterm and term neonates ≥34 weeks' gestation (or equivalent birth weight) born by caesarean section:
- For the critical primary outcome **survival to hospital discharge,** there were no data.
- For the primary outcome of **normothermia on admission**, there was possible benefit (very low certainty evidence, downgraded for very serious risk of bias and serious indirectness from 1 RCT enrolling 825 participants).

Secondary outcomes:
- For **mean temperature on admission** there was possible benefit (mean temperature 0.3°C higher, 95% CI 0.23 to 0.37 higher) (very low certainty evidence, downgraded for very serious risk of bias and serious indirectness from 1 RCT enrolling 825 participants).
- For **hypoglycemia**, there was no benefit or harm (RR 0.69, 95% CI 0.20 to 2.42) (very low certainty evidence, downgraded for very serious risk of bias and serious indirectness and imprecision from 1 RCT enrolling 825 participants).
- For **moderate hypothermia**, there was probable benefit (RR 0.26, 95% CI 0.16 to 0.42) (very low certainty evidence, downgraded for very serious risk of bias, and serious indirectness and imprecision from 1 RCT enrolling 825 participants).

- For **receipt of respiratory support** benefit or harm cannot be excluded (RR 2.06, 95% CI 0.63 to 6.80) (very low certainty evidence, downgraded for very serious risk of bias, and serious indirectness and imprecision from 1 RCT enrolling 825 participants).

The rationale for considering the overall effect moderate was that **mean temperatures on** admission were higher by 0.3°C, a difference that was considered clinically significant. Furthermore, for every 100 infants exposed to an operating room temperature of 23ºC compared to a temperature of 20°C

- from 6 more to 21 more were normothermic
- 7 fewer to 17 fewer were hypothermic <36.5°C
- 11 fewer to 16 fewer were moderately hypothermic.

For **hyperthermia** clinical benefit or harm cannot be excluded (RR 4.13 95% CI 0.88 to 19.32) (very low certainty evidence, downgraded for very serious risk of bias, and serious indirectness and imprecision from 1 RCT enrolling 825 participants).

COMPARISON 2. THERMAL MATTRESS VS. NO THERMAL MATTRESS

The systematic review found one RCT enrolling 199 infants who were admitted to neonatal unit at a single hospital in a three arm study, comparing the addition of either a plastic bag or a thermal nest (comprised of a phase changing material) to standard hospital care (which included room temperature ≥25°C, drying, swaddling, a cotton cap and a radiant warmer) vs standard hospital care. {Shabeer 2018 1324} For the comparison between the thermal nest and standard hospital care, the only significant outcome difference (among 7 relevant to the review that were reported) was an increase in body temperature (MD 0.2°C, 95% CI 0.07 to 0.33°C higher, which was not considered sufficient to make a recommendation about practice because the change did not cross a line of treatment effect. Evidence for all outcomes was very low certainty, downgraded for serious indirectness and imprecision.

COMPARISON 3. PLASTIC BAG OR WRAP COMPARED TO STANDARD HOSPITAL CARE.

The systematic review found that **for use of a plastic bag or wrap, (with or without prior drying) compared to no plastic bag or wrap:**

- For the critical primary outcome of **survival to hospital discharge, clinically significant benefit or harm cannot be excluded** (**very low certainty of evidence**, downgraded for very serious risk of bias and inconsistency and serious indirectness and imprecision from 2 RCTs enrolling 305 participants). {Leadford 2013 e128, Shabeer 2018 1324}
- For the important primary outcome of **normothermia on admission**, there was **possible benefit** RR; 1.50, 95% CI 1.20 to 1.89, ARD; 203 more per 1,000, 95% CI 81 more to 362 more) (**very low certainty evidence**, downgraded for very serious risk of bias and serious indirectness and imprecision from 2 RCTs enrolling 305 participants). {Leadford 2013 e128, Shabeer 2018 1324}

Secondary outcomes:

- **For body temperature on admission**, there was **possible benefit** (MD; 0.2°C 95% CI 0.2 to 0.38, I^2=22%) (**very low certainty evidence**, downgraded for very serious risk of bias and serious indirectness from 3 RCTs enrolling 425 participants). {Cardona-Torres 2012 129, Leadford 2013 e128, Shabeer 2018 1324}
- For **hypoglycemia, clinical benefit or harm cannot be excluded** (**very low certainty evidence** downgraded for very serious risk of bias and serious indirectness and imprecision from 1 RCT enrolling 201 participants). {Shabeer 2018 1324}
- For any **hypothermia <36.5°C**, there was **possible benefit** (RR; 0.57 95% CI 0.45 to 0.73, ARD; 204 fewer per 1,000 95% CI 261 fewer to 128 fewer) (**very low certainty evidence**, downgraded for very serious risk of bias and serious indirectness and imprecision from 3 RCTs enrolling 425 participants). {Cardona-Torres 2012 129, Leadford 2013 e128, Shabeer 2018 1324}
- For **hypothermia <35°C**, there was **possible benefit** (RR; 0.21 95% CI 0.05 to 0.91, ARD; 40 fewer per 1,000, 95% CI 48 fewer to 4 fewer) (very low certainty evidence, downgraded for serious risk of bias and serious indirectness and imprecision from 2 RCTs enrolling 400 participants). {Cardona-Torres 2012 129, Shabeer 2018 1324}
- For **moderate hypothermia (temperature 32.0-35.9°C)**, **clinical benefit or harm cannot be excluded** (**very low certainty evidence**, downgraded for very serious risk of bias, serious indirectness and serious imprecision from 1 RCT enrolling 199 participants for this comparison). {Shabeer 2018 1324}
- For **admissions** to a neonatal special or intensive care nursery, there was no data.

The rationale for considering the overall effect moderate was that although no difference was demonstrated for either primary or several secondary outcomes (or there were no data), mean temperatures on admission were higher by 0.29°C, a difference that

was considered clinically significant. Furthermore, for every 1000 infants exposed to a plastic bag or wrap (with our without prior drying) compared to no plastic bag or wrap;

- from 81 more to 362 more were normothermic
- from 128 fewer to 261 fewer had hypothermia <36.5°C
- from 4 fewer to 48 fewer had hypothermia <35°C

For the important secondary outcome of **hyperthermia**, **benefit or harm could not be excluded** (**very low certainty evidence** from 3 RCTs enrolling 425 participants, downgraded for serious indirectness and very serious imprecision). {Cardona-Torres 2012 129, Leadford 2013 e128, Shabeer 2018 1324}

COMPARISON 4. PLASTIC BAG OR WRAP COMBINED WITH SKIN-TO-SKIN CARE WITH A PARENT, VS SKIN TO SKIN CARE ALONE.

- The systematic review found two RCTs for this comparison. {Belsches 2013 e656, Travers 2021 55} Findings were:
- For the critical primary outcome **survival to hospital discharge,** the effect of the intervention could not be evaluated because there was no mortality in either group in the 1 RCT enrolling 271 participants that reported this outcome. {Belsches 2013 e656}
- For the important primary outcome of **normothermia** on admission, there was **possible benefit** (relative risk (RR) 1.39 95% confidence intervals (CI) 1.08 to 1.79 I^2=0%, ARD; 86 more per 1,000 95% CI 18 more to 174 more) (**low certainty evidence**, downgraded for serious indirectness and imprecision from 2 RCTs enrolling 692 participants). {Belsches 2013 e656, Travers 2021 55}

Secondary outcomes:

- For **mean temperature** on admission there was **possible benefit** (mean temperature 0.2°C higher, 95% CI 0.1 to 0.3°C higher I^2=0%) (**low certainty evidence**, downgraded for serious indirectness and imprecision from 2 RCTs enrolling 692 participants). {Belsches 2013 e656, Travers 2021 55}
- For **hypoglycemia**, the only study reporting this outcome did not provide a breakdown by study group, so no analysis was possible.
- For **admission to a neonatal intensive or special care unit, benefit or harm could not be excluded** (**low certainty evidence**, downgraded for serious indirectness and imprecision, from 1 RCT enrolling 275 participants). {Belsches 2013 e656}
- For **hypothermia <36.5°C** there was **possible benefit** (RR 0.89 95% CIS 0.81 to 0.97, I^2 30% ARD 85 fewer per 1,000 95% CI 148 fewer to 23 fewer) (**low certainty evidence**, downgraded for serious indirectness and imprecision from 2 RCTs enrolling 692 participants). {Belsches 2013 e656, Travers 2021 55}

    - For **mild hypothermia**, **benefit or harm could not be excluded** (RR 1.19 95% CI 0.98 to 1.44) (**low certainty evidence**, downgraded for serious indirectness and imprecision from 2 RCTs enrolling 692 participants). {Belsches 2013 e656, Travers 2021 55}
    - For **moderate hypothermia**, there was **possible benefit** (RR 0.66 95% CI 0.54 to 0.81,I^2=5%, ARD 148 fewer per 1,000 95% CI 200 fewer to 83 fewer) (**low certainty evidence**, downgraded for serious indirectness and imprecision from 2 RCTs enrolling 692 participants). {Belsches 2013 e656, Travers 2021 55}

The rationale for considering the effect moderate was that for every 1000 infants exposed to a plastic bag or wrap with skin to skin care, compared to skin to skin care alone

- From 18 more to 174 more were normothermic
- 23 fewer to 148 fewer were hypothermic <36.5°C
- 83 fewer to 200 fewer were moderately hypothermic.

Mean temperatures on admission were higher by 0.2°C , however, this difference that was considered to be of only marginal clinical significance because the mean temperatures remained in the cold-stressed range.

COMPARISON 5. THERMAL MATTRESS VS. NO THERMAL MATTRESS

The systematic review found one RCT enrolling infants who were admitted to neonatal unit at a single hospital in a three arm study, comparing the addition of either a plastic bag or a thermal nest (comprised of a phase changing material) to routine hospital care

(which included room temperature ≥25°C, drying, swaddling, a cotton cap and a radiant warmer). {Shabeer 2018 1324}. Among the 199 infants in the study for whom the comparison between the thermal nest and standard hospital care applied, the only significant outcome difference (among 7 outcomes relevant to the review that were reported) was an increase in body temperature in the thermal mattress group (MD 0.2°C, 95% CI 0.07 to 0.33°C). Various relative risks for other outcomes fell on both sides of the line of no effect. Thus this study was not considered sufficient to make a recommendation for practice, so an evidence to decision table was not constructed and further results are not presented. Evidence for all outcomes was very low certainty, downgraded for serious indirectness and imprecision.

COMPARISON 6. PLASTIC BAG OR WRAP WITH DRYING COMPARED TO PLASTIC BAG OR WRAP WITHOUT DRYING
The review found one RCT enrolling 60 participants that examined two secondary outcomes relevant to the review and found no significant differences. {Cardona-Torres 2012 129}

COMPARISON 7. PLASTIC BAG OR WRAP WITHOUT DRYING COMPARED TO A THERMAL MATTRESS
The review found one RCT enrolling 200 participants that examined seven outcomes relevant to the review and found no significant differences. {Shabeer 2018 1324}

COMPARISON 8. EARLY SKIN TO SKIN CARE COMPARED TO LATER SKIN-TO-SKIN CARE.
The review found two RCTs enrolling 87 participants that together, examined 4 outcomes relevant to the review. {Crenshaw 2019 731, Walsh 2021 95} There were no significant differences for 3 of these outcomes. One study enrolling 47 participants found a difference of in the rate of normothermia favouring early skin to skin group, but the very small sample size and the serious risk of bias, indirectness and imprecision led to a decision to not develop an Evidence to Decision table. {Walsh 2021 95}

COMPARISON 9. CONTINUOUSLY ACTIVE WARMING BLANKETS WITH SKIN-TO-SKIN CARE COMPARED TO STANDARD HOSPITAL CARE.
The review found one RCT enrolling 139 participants that examined 1 outcome relevant to the review and found no significant difference. {Stirparo 2013 186}

COMPARISON 10. SKIN- TO-SKIN CARE COMPARED TO A PLASTIC BAG OR WRAP.
The review found one RCT enrolling 197 participants that examined 2 outcomes relevant to the review and found no significant differences. {Johanson 1992 859}

COMPARISON 11. WOOLLEN VS COTTON CAP
The review found one RCT enrolling 126 participants that examined 2 outcomes relevant to the review and found small differences in mean temperature and the rate of moderate hypothermia favouring the woollen cap group. {Lang 2004 843}

Subgroup analyses
There were insufficient data to conduct any of the prespecified subgroup analyses (by gestation groups, early vs later umbilical cord clamping, by low- vs high-resourced setting or by inborn vs outborn status) for any comparison.

For the following comparisons*, or for any combination of these interventions, the systematic review found no RCTs*:

- *Heating and humidification of gases used for resuscitation, vs. any other intervention or standard hospital care*
- *The use of a radiant warmer, vs any other intervention or standard hospital care*
- *Early monitoring of temperature vs no early monitoring of temperature*
- *Warm bags of fluid compared to any other intervention or standard hospital care*
- *Warmed swaddling/clothing vs any other intervention or standard hospital care*

Observational studies and quality improvement studies
In addition to the RCTs or quasi-RCTs described above, the systematic review found 10 observational studies. {Agudelo 2020 105020, Albuquerque 2016 e2741, Aley-Raz 2020 476, Andrews 2018 e20171214, Datta 2017 e000183, Hill 1979 287, Nissen 2019 1, Patodia 2021 277, Shaw 2018 126, Sprecher 2021 270} Six of these studies used quality improvement (QI) methodology and examined multifaceted interventions. {Aley-Raz 2020 476, Andrews 2018 e20171214, Datta 2017 e000183, Patodia 2021 277, Shaw 2018 126, Sprecher 2021 270} These studies did not allow any definite conclusions to be drawn about the effectiveness of any component intervention. The overall risk of bias for all 10 studies was rated as serious or critical for all outcomes. Because of this

and a high degree of heterogeneity in the interventions used, no meta-analyses could be performed, and individual studies are difficult to interpret.

Of the (QI) studies that used methods such as “plan-do-study-act” cycles to reduce risk of hypothermia in newborn infants, all demonstrated improvements. {Aley-Raz 2020 476, Andrews 2018 e20171214, Datta 2017 e000183, Patodia 2021 277, Shaw 2018 126, Sprecher 2021 270} However, only one of the included studies described a sufficient ‘post-intervention’ phase to confirm sustainability of the interventions. {Patodia 2021 277}

Nevertheless, taken together, these studies suggest that hypothermia can be a common problem among late preterm and term infants in both low-income and high-income settings. They also suggest that multidisciplinary teams, working together to recognize local place, people, policy and procedure contributors to risk, and to test the effect of locally devised solutions, may be an effective way to reduce rates of hypothermia.

Treatment Recommendations (2022)

Ambient temperature of birthing environment
In late preterm and term infants (≥34 weeks' gestation), we suggest the use of room temperatures of 23°C compared to 20°C at birth in order to maintain normothermia (weak recommendation, very low certainty evidence).

Skin to Skin (SSC) versus no SSC
In late preterm and term infants (≥34 weeks' gestation) at low risk of needing resuscitation, we suggest the use of skin to skin care immediately after birth rather than no skin to skin care to maintain normal temperature (weak recommendation, very low certainty evidence).

Plastic Bag or Wrap (PBW) vs no PBW
In some situations where skin-to-skin care is not possible, it is reasonable to consider the use of a plastic bag or wrap, among other measures, to maintain normal temperature (weak recommendation, very low–certainty evidence).

PBW with SSC versus SSC alone
The Task Force considered that in late preterm and term infants ≥34 weeks' gestation, for routine use of a plastic bag or wrap in addition to skin to skin care immediately after birth compared to skin to skin care alone, the balance of desirable and undesirable effects was uncertain. Furthermore, the cultural values and maternal preferences in relation to the use of plastic bags or wraps and the cost implications are not known, and therefore no treatment recommendation can be formulated**.**

Current Search Strategy: see appendix

Database searched: PubMed
Time Frame: (existing PICOST) – updated from end of last search 20 July 2022
Date Search Completed: 20 July 2024
Search Results:
Identified: 313
Full-text screening: 66
Included: 3

Summary of Evidence Update:
Two randomized control trials addressing the PICOST were found. One non-randomized study was identified.

Relevant Guidelines or Systematic Reviews: none

RCT addressing the PICOST:

Study Acronym; Author; Year Published	Aim of Study; Study Design; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator	Endpoint Results	Relevant 2° Endpoints (if any); Study Limitations; Adverse Events

			(# patients)		
Ambia 2023 {Ambia 2024 S 01} Relevant subgroup data have been obtained from the study authors	**Study Aim** To measure the effect of Operating Room (OR) temperature on neonatal morbidity (note that infants received resuscitation, if needed, in the same OR) **Study Design** Cluster RCT (weekly allocation) (N=5221, of whom 4948 were ≥34 weeks' gestation)	**Inclusion Criteria** Caesarean delivery, newborns without congenital anomalies	**Intervention** OR 24°C ≥34 wks (n=2268) **Comparator** OR 20°C ≥34 wks (n= 2680)	**1° endpoint** Proportion of newborns with temperature < 36.5°C on arrival to the nursery **Intervention** n= 406 (18.2%) **Comparator** n=1142 (43.4%)	**2° Endpoints** Proportion of newborns with hyperthermia (temperature >37.5°C) on admission to NICU/PNW **Intervention** n= 201 (9.0%) **Comparator** n=81 (3.1%), No statistically significant difference between groups in the composite outcome of neonatal morbidities namely, the type of respiratory support, sepsis, hypoglycemia, and neonatal mortality (p=0.11) **Study Limitations** Single center Resistance from obstetricians and OR personnel to work in the higher ambient temperature

Chanvorachote 2022 {Chanvorachote 2022 1966}	**Study Aim** To compare the efficacy of Aluminum Coated Fabric (ACF), cotton swaddle, and combined method to prevent neonatal hypothermia. **Study Design** Randomized controlled trial (N=175)	**Inclusion Criteria:** BW >2500 g, Apgar at 5 min >7 DR temperature of 27°C Transport to the nursery by crib	**Intervention** Ia. ACF (n=55) Ib. ACF+Cotton swaddle (n=60) **Comparator** Cotton swaddle (n=60)	**1° endpoint** Mean rectal temperature (SD) before swaddling in DR and at nursery admission. **Before swaddling in the DR** **Intervention** 1a: 36.7 (0.3)°C 1b: 36.7 (0.3)°C **Comparator** 36.6 (0.2)°C **Nursery admission** **Intervention**	**2° Endpoints** No difference between groups at any timepoint in the proportion of infants with hypothermia <36.5°C; or hyperthermia >37.5°C None of the reported outcomes showed any statistically significant or clinically relevant differences between the groups **Study Limitations**

	Not stated when swaddling commenced after birth			1a: 36.6 (0.3)°C 1b: 36.7 (0.2)°C **Comparator** 36.7 (0.2)°C	Small sample size (underpowered) Single center

Nonrandomized Trials, Observational Studies addressing the PICOST

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results**	**Summary/Conclusion Comment(s)**
Gopalakrishnan 2022 {Gopalakrishnan 2022 S49}	Retrospective observational study (N=256) **Intervention** Use of a thermal mattress (comprised of phase-changing material) on a radiant warmer during resuscitation or stabilization immediately after birth **Control** No thermal mattress	**Inclusion Criteria** BW 1500 to 2499 g without malformations or asphyxia **GA** **Intervention** 33.2 (1.6) wks (n=154) **Comparator** 33.6 (1.8) wks (n=102)	**Primary Outcome:** Mean axillary temperature mean (SD) in DR before transport and at arrival in the PNW/NICU. **Temperatures in DR** **Intervention** 36.3 (0.8) °C **Comparator** 36.2 (0.6) °C (p=0.28) **Admission temperature at PNW/NICU** **Intervention** 36.6 (0.6)°C **Comparator** 36.4 (0.5)°C (p<0.01	Use of a conductive thermal mattress in the DR was feasible and an effective method of preventing hypothermia. No hyperthermia (temperature > 37.5°C) was reported in either of the groups.
Abbreviations: ACF: aluminum coated fabric; GA: gestational age; BW: birth weight; DR: delivery room; SD: standard deviation; NICU: neonatal intensive care unit; PNW: postnatal ward; HRC: hospital routine care; OR: operating room; wks weeks; temp temperature; g: grams				

Reviewer Comments:

This update of the evidence found two RCTs {Ambia 2024 S 01, Chanvorachote 2022 1966} and one observational study addressing the PICOST. {Gopalakrishnan 2022 S49} In addition, we found one systematic review, two RCTS and one QI study providing indirect evidence regarding management of thermoregulation soon after birth.

The systematic review with clinical guidelines by Tourneux {Tourneux 2022 1490} focused on warming methods that could be used during, or as an alternative to skin to skin care, either in the delivery area or soon after admission to a NICU or postnatal ward. The review and recommendations included both preterm and term neonates. Search strategies were similar and were conducted with similar date limits (Tourneux search completed on 31 December 2021 and the ILCOR SR on 2 Aug 2021). Recommendations from the Tourneux review resemble those in our previous Systematic Review (SR).

We found two RCTS that measured the effect of SSC during transfer from the DR to the NICU or post-natal ward. Singh {Singh 2023 109840} enrolled 100 neonates comparing SSC with use of a radiant warmer soon after birth. The authors found a statistically significant increase in the incidence of cold stress (36-36.4°C) at 60 min after birth in neonates nursed skin to skin compared to those under a radiant warmer. In addition to the above RCT we found one observational study {Toprak 2022 103489} and one QI study {M'Rini 2024 1379763} examining the effect of SSC. Toprak compared neonates held SSC by their father with standard care and found that the SSC group had a significantly lower temperature at 30 min after birth. However, the mean temperatures of both groups were within the normal range {Toprak 103489}. The single-arm QI study by M'Rini showed that among neonates requiring

NICU admission, in the sub-group of term neonates, almost half were hypothermic on admission to NICU following transfer to the NICU with SSC combined with a customized transfer device.

The skin-to-skin intervention in these studies was started after initial resuscitation when infants were ready for transfer to the NICU or postnatal ward. They provide evidence for management of thermoregulation during transfer and not immediately after birth and provide at best, indirect evidence for the PICOST addressed in this evidence update. However, the question regarding the best method of transfer after initial resuscitation could be explored in a scoping review.

Ambient temperature of birthing environment

We found one RCT that compared operating room (OR) ambient temperature of 24°C with an OR temperature of 20°C. {Ambia 2024 S 01}

There was evidence of **benefit** for the important secondary outcome of **hypothermia < 36.5°C** on admission among neonates born at ≥ 34 weeks' gestation (RR: 0.42 (95%CI: 0.38 – 0.46), P <0.00, NNTB: 4 (95%CI: 3 – 5)), the absolute risk difference (ARD) being 291 fewer per 1000 (from 311 fewer to 270 fewer). {Ambia 2024 S 01}

For the outcome **hyperthermia > 37.5°C** on admission there was evidence of **harm**; (RR: 2.93 (95%CI: 2.28 – 3.77), P <0.00, NNTH: 17 (95%CI: 14 – 22), ARD being 69 more per 1000 (from 45 more to 98 more) {Ambia 2024 S 01}

The new evidence supports the current recommendation to use a higher ambient temperature in operating rooms. Since the trial evaluated in the previous systematic review included only 825 participants, this new trial which included overall 5221 neonates may increase the certainty of evidence and therefore justify updating the SR for this sub-question. The direction of effect was similar to that found in our previous review, but there was additional information about an ambient temperature higher than that examined in detail in the previous review.

Skin to Skin (SSC) versus no SSC

No new studies were found

Plastic Bag or Wrap (PBW) vs no PBW

We found one three-arm RCT including 175 participants that compared use of an aluminum coated fabric with or without cotton swaddling compared with cotton swaddling alone which reported little effect on temperature outcomes at any time including admission. {Chanvorachote 1966}

The evidence from this new trial is not sufficient to change the current recommendation or to elicit a new systematic or scoping review.

Thermal mattress versus standard care

We found one retrospective observational study enrolling 256 neonates comparing exothermic mattress versus standard care during transport from the birth area to the NICU or postnatal ward. {Gopalakrishnan S49}. On admission to the NICU, there was a significant reduction in hypothermia among neonates transported on the exothermic mattress. Importantly, there was no hyperthermia in either of the two groups.

This study does not provide sufficient new direct evidence about use of thermal mattresses for care immediately after birth to warrant a new SR or to formulate a new good practice statement.

Other comparisons

No new studies were found addressing any of the other comparisons evaluated in the previous SR (PBW vs no PBW, PBW along with SSC vs SSC alone, PBW with and without drying, PBW compared to a thermal mattress, early vs late SSC, continuously active warming blankets with SSC vs standard care, SSC vs PBW, or woolen vs cotton cap) , or among the comparisons between interventions that could not be addressed in the review because no studies were found at the time.

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Appendix: search strategy

Sources searched	Search strategy	Search time frame
PubMed	newborn*[tiab] OR "new born*"[tiab] OR "Infant, Newborn"[Mesh] OR neonat*[tiab] OR neo-nat*[tiab] OR "newly born"[tiab] OR premature[tiab] OR prematurity[tiab] OR preterm[tiab] OR "pre term"[tiab] OR "Premature Birth"[Mesh] OR "low birth weight"[tiab] OR "low birthweight"[tiab] OR VLBW[tiab] OR LBW[tiab] OR postnatal[tiab] OR post-natal[tiab] OR "golden hour"[tiab] OR "Perinatal Care"[Mesh]) AND ("room temperature"[tiab] OR "ambient temperature"[tiab] OR "admission temperature"[tiab] OR "radiant warm*"[tiab] OR mattress*[tiab] OR "radiant heat*"[tiab] OR skin-to-skin[tiab] OR kangaroo*[tiab] OR swaddling[tiab] OR covering*[tiab] OR "plastic bag*"[tiab] OR wrap*[tiab] OR hat[tiab] OR hats[tiab] OR cap[tiab] OR caps[tiab] OR "warm bag*"[tiab] OR "warm fluid*"[tiab] OR	July 20, 2022 to July 20, 2024

	polyethylene[tiab] OR polythene[tiab] OR polyurethane[tiab] OR woolen[tiab] OR transwarmer*[tiab] OR trans-warmer*[tiab] OR humidifi*[tiab] OR servo-control*[tiab] OR protocol*[tiab] OR checklist*[tiab] OR project*[tiab] OR "care bundle*"[tiab] OR "quality improvement"[tiab] OR "Heating"[Mesh]) AND (temperature[tiab] OR "Body Temperature"[Mesh] OR normothermi*[tiab] OR normo- thermi*[tiab] OR euthermi*[tiab] OR hypothermi*[tiab] OR hypo-thermi*[tiab] OR "Hypothermia"[Mesh] OR hyperthermi*[tiab] OR hyper-thermi*[tiab] OR "Hyperthermia"[Mesh] OR thermoregulat*[tiab] OR thermo-regulat*[tiab] OR thermoprotect*[tiab] OR thermo-protect*[tiab] OR "heat loss*"[tiab] OR "cold stress*"[tiab]) NOT (animals[mh] NOT humans[mh])	
Results identified	**Results screened full text**	**Results included**
313	66	3

2025 Evidence Update
NLS 5101 – Maintaining Normal Temperature Immediately After Birth in Preterm Infants

Worksheet Author(s): Dawson JA, de Almeida MF, Ramaswamy VV, Trevisanuto D, Nakwa FL, Kamlin COF, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 29 October 2024
Conflicts of Interest: Several authors with conflicts of interest in the original SR (declared and managed), none in this evidence update.

PICOST:
Population: Preterm infants (less than 34 weeks' gestation at birth) immediately after birth
Intervention: Increased room temperature ≥23.0°C or thermal mattress or plastic bag or wrap or hat or heating and humidification of gases used for resuscitation or radiant warmer (with or without servo control) or early monitoring of temperature or warm bags of fluid or swaddling or skin to skin care with mother or combinations of these interventions
Comparators: Drying alone or with use of a plastic bag or wrap
Note that comparisons between interventions or combinations of interventions will also be meta-analysed if there are sufficient trials and participants to draw meaningful conclusions.
Since we expect that most studies will compare bundles of interventions rather than single interventions, we will also focus on the following likely clustered interventions and comparators:

Intervention: Thermal mattress and wrap or bag with or without a cap or hat and radiant warmer
Comparator: Wrap or bag with or without a cap or hat and radiant warmer
Intervention: Wrap/bag and cap/hat and increased room temperature and radiant heater
Comparator: Wrap or bag with radiant heater
Intervention: Thermal mattress and wrap or bag with or without a cap or hat and radiant warmer and heated and humidified gases
Comparator: Wrap or bag with or without a cap or hat and radiant warmer

Outcomes:
Primary outcomes:
- Survival to hospital discharge (Critical)
- Rate of normothermia on admission to neonatal unit or postnatal ward (important)

Secondary outcomes:
- Body temperature (and rates of moderate hypothermia, cold stress and hyperthermia) on admission to neonatal unit or before transfer to neonatal unit or postnatal ward, or at times ≤ 1 hour of age (as defined by authors).
- Response to resuscitation, e.g., need for assisted ventilation, highest FiO_2
- Major morbidity; bronchopulmonary dysplasia (important), intraventricular hemorrhage all grades (important) and severe (critical), necrotising enterocolitis (important), respiratory distress syndrome (surfactant treatment for), late onset sepsis.

Study designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies were excluded. All languages were included provided there was an English abstract.
Time frame: No date restrictions were placed on the search. The literature search was updated to July 20, 2022.

Year of last full review: 2023 {Berg 2023 e187, Ramaswamy 2023 109934}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Berg 2023 e187, Ramaswamy 2023 109934}

Seventy-four studies were identified (29 RCTs, 16 observational studies and 29 quality improvement studies) which addressed the PICOST question. Of these, 18 of the RCTs and 7 of the observational studies provided data that could be extracted to evidence tables (for various comparisons between interventions) for the review. {Ahmed 2013 169, Bhavsar 2015 23, Chantaroj 2011 S32, Chawla 2011 780, de Almeida 2014 271, Farhadi 2012 19, Ibrahim 2010 795, Knobel 2005 304, Lewis 2011 160, Mathew 2013 317, McCarthy 2013 e135, McCarthy 2011 1534, McGrory 2018 47, Meyer 2015 245, Pinheiro 2011 357, Reilly 2015 262, Reilly 2019 37, Simon 2011 33, Singh 2010 45, Smith 2013 235, te Pas 2010 e1427, Trevisanuto 2010 914, Vohra 1999 547, Vohra 2004 750} Among the 13 pairs of interventions from RCTs and 10 pairs of interventions from observational studies for which evidence tables were

developed, 5 comparisons (designated comparisons 2 to 6 below) were considered to provide sufficient data to allow the development of Evidence to Decision (EtD) tables that would inform the development of treatment recommendations. For 3 of these EtD tables (comparisons 2, 4 and 5), evidence from both RCTs and an observational studies was available and was included. For the other EtD tables only RCT evidence was used because either there were no observational studies, or the evidence from them was assessed as of such low certainty that they would not change the conclusions. The results for other comparisons for which evidence was found are summarized in a narrative.

COMPARISON 1. INCREASED ROOM TEMPERATURE ≥23.0°C VS LOWER ROOM TEMPERATURE.

Two RCTs {Duryea 2016 505.e1, Jia 2013 264} and 2 observational studies {de Almeida 2014 271, Kent 2008 325} addressed whether higher ambient temperature vs. lower ambient temperature contributed to maintaining normal temperature in preterm infants. The data could not be combined in meta-analysis because the boundaries of higher and lower temperatures in each study differed (and overlapped) and because of differences in study design. Therefore, the results are summarized in narrative form, and no Evidence to Decision table was developed.

One RCT enrolling infants of all gestations compared operating room temperatures of 23°C (I) to 20°C (C). {Duryea 2016 505.e1} From enquiry to the authors, subgroup data were available for infants <28 weeks (n=8), 28-31 weeks' (n=14) and 32-36 weeks' gestation (n=124). The data for the first two subgroups (n=22) was evaluated for the current review and **could not exclude benefit or harm** for any outcome relevant to this review, **very low certainty evidence** downgraded for very serious risk of bias and very serious imprecision. Reported outcomes included death, mean body temperature, hypothermia <36.5 and <36, hyperthermia >37.5, IVH any grade and >grade 2 and delivery room intubation. Nevertheless, the study as a whole (all gestations, including late preterm and term infants) found improved body temperatures and reduced rates of hypothermia when a temperature of 23°C was used. Of interest, rates of hypothermia were strikingly lower in the two groups of lower gestation than in the study as a whole. The authors suggested that this was likely to be because of more use of other measures to prevent hypothermia in infants of lower gestation, thereby masking an effect of ambient temperature.

One study infants of ≤32 weeks' gestation randomly assigned births to a room with an ambient temperature of 24 to 26°C vs another with an ambient temperature of 20 to 23°C. {Jia 2013 264}. Among outcomes relevant to the review, the study reported only secondary outcomes. **Use of the higher temperature range increased body temperature on admission** (mean difference 0.5°C higher with higher room temperature 95% CI 0.15 to 0.85°C higher) and **reduced rates of moderate hypothermia <36°C** (RR 0.51 95% CI 0.32 to 0.80, 337 fewer per 1,000 were hypothermic 95% CI from 467 fewer to 137 fewer), **very low certainty evidence** downgraded for very serious risk of bias and serious imprecision from 1 study including 91 infants. {Jia 2013 264}. This study did not report rates of hyperthermia.

A cohort study compared outcomes for infants ≤31 weeks' gestation during an epoch when ambient operating room temperatures were 20°C (n=73) with those during an epoch when operating room temperatures were 25 to 28°C (n=35), and reported mean body temperature, hypothermia <36.5, NEC, IVH>grade 2 and late onset neonatal sepsis. The study found that **rates of hypothermia <36.5°C were lower with use of higher room temperatures** (RR 0.69, 95% CI 0.51-0.94), **very low certainty evidence** downgraded for risk of bias and very serious imprecision. {Kent 2008 325} None of the other findings were statistically significant.

A retrospective observational study used logistic regression to examine risk factors for admission hypothermia <36.0°C in inborn infants of 23 to 33 weeks' gestation. {de Almeida 2014 271} The study reported that **DR temperature <25°C** was among the variables that were **independently associated with risk of hypothermia** (odds ratio 1.44, 95% CI 1.10-1.88) ungraded observation from 1 retrospective study including 1764 infants. {de Almeida 2014 271}

One observational study compared ambient temperatures of **34°C to 28°C** and found **higher admission temperatures** (MD 0.4°C higher, 95% CI 0.24 to 0.5°C higher in infants exposed to the 34°C ambient temperatures) and **increased risk of hyperthermia** (RR 11.48 95% CI 1.54 to 85.54, ARD 115 more infants were hyperthermic per 1000 95% CI 6 more to 92 more), **very low certainty evidence** from 1 observational study including 202 infants. {Johannsen 2017 235}

COMPARISON 2. THERMAL MATTRESS VS NO THERMAL MATTRESS

The systematic review found four RCTs that examined use of a thermal mattress; because of critical differences in the comparator they were meta-analysed as:

Two RCTs enrolling 174 participants that compared use of a thermal mattress with no thermal mattress. {Chawla 2011 780, McCarthy 2013 e135} In these studies, a plastic bag or wrap was used (by hospital protocol) for all infants {McCarthy 2013 e135} or for those <28 weeks' gestation. {Chawla 2011 780} and all other measures to maintain normal temperature were also similar in both study arms.

Two RCTs enrolling 77 infants that compared use of a thermal mattress with use of a plastic bag or wrap. {Mathew 2013 317, Simon 2011 33} The difference in exposure of the infants in each arm of these studies to plastic bags or wraps will have confounded the assessment of the effect of the thermal mattress itself. Therefore, for the purposes of this comparison, the evidence from these trials was downgraded for very serious indirectness and they were meta-analysed separately.

For the critical primary outcome **survival to hospital discharge**:
From the studies that assessed thermal mattress vs no thermal mattress, **clinical benefit or harm cannot be excluded** (RR 1.02, 95% CI 0.98 to 1.06), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from two RCTs enrolling 174 participants. {Chawla 2011 780, McCarthy 2013 e135}

From the studies that assessed thermal mattress vs plastic bag or wrap, **clinical benefit or harm cannot be excluded** (RR 0.96, 95% CI 0.87 to 1.05), **very low certainty evidence** downgraded for very serious indirectness and serious imprecision from two RCTs enrolling 77 participants. {Mathew 2013 317, Simon 2011 33}

The important primary outcome **normothermia on admission** was reported by only one study which reported **possible clinical harm** (RR 0.53, 95% CI 0.34 to 0.81, ARD 363 fewer infants per 1000 were normothermic on admission 95% CI 147 fewer to 509 fewer infants per 1000, number needed to treat to harm (NNTH) 3 infants), **moderate certainty evidence** downgraded for serious imprecision from one RCT including 72 participants. {McCarthy 2013 e135}

Secondary outcomes:
For **mean body temperature on admission**, from the studies that assessed thermal mattress vs no thermal mattress, there was **possible clinical benefit** (mean body temperature was 0.46°C higher with use of a thermal mattress than with no thermal mattress, 95% CI 0.22°C higher to 0.6°C higher), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from two RCTs enrolling 174 participants. {Chawla 2011 780, McCarthy 2013 e135}

For **mean body temperature on admission**, from the studies that assessed thermal mattress vs plastic bag or wrap, **clinical benefit or harm could not be excluded** (mean body temperature was 0.1°C higher with use of a thermal mattress than with a plastic bag or wrap, 95% CI 0.6°C lower to 0.8°C higher), **very low certainty evidence** downgraded for serious risk of bias and serious imprecision from two RCTs enrolling 174 participants. {Mathew 2013 317, Simon 2011 33}

For the important adverse outcome **hyperthermia** (temperature on admission > 37.5) there was **possible harm** (RR 2.77 95% CI 1.24 to 6.17, ARD 126 more infants were hyperthermic per 1000, 95% CI 17 more to 369 more, NNTH 8 infants) **low certainty evidence**, downgraded for risk of bias and imprecision from two RCTs enrolling 174 participants that compared thermal mattress to no thermal mattress {Chawla 2011 780, McCarthy 2013 e135}. In the RCTs comparing a thermal mattress without a plastic bag or wrap to a plastic bag or wrap without a thermal mattress, only one reported this outcome but the confidence intervals were so wide as to preclude any conclusion; (RR 12.29 95% CI 0.02 to 77700.79), **very low certainty evidence** downgraded for indirectness and imprecision from one RCT enrolling 36 participants. {Simon 2011 33}

For other secondary outcomes, only the evidence from the studies that compared thermal mattress to no thermal mattress is described here, {Chawla 2011 780, McCarthy 2013 e135} For these other secondary outcomes the results reported in either of the studies comparing thermal mattress with plastic bag or wrap, the very low certainty evidence from these studies {Mathew 2013 317, Simon 2011 33} would not have changed the conclusions of the review. Additional data for these studies is shown in the Evidence to Decision table.

For hypothermia on admission, BPD, IVH>grade 2, and NEC, confidence intervals crossed the line of no effect and were so wide that no conclusions can be drawn about clinical benefit or harm, **moderate or low certainty evidence** downgraded for serious risk of bias and imprecision). {Chawla 2011 780, McCarthy 2013 e135}

The systematic review also found **5 observational studies** that examined use of a thermal mattress combined with use of a plastic bag or wrap compared to use of a plastic bag or wrap alone in a total of 1027 infants, which contributed evidence for some of the systematic review outcomes. {Ibrahim 2010 795, Lewis 2011 160, McCarthy 2011 1534, Pinheiro 2011 357, Singh 2010 45}

For beneficial outcomes, the observational studies did not change the outcomes of the review, so they are not described further. Of note, for the **important adverse outcome** of **hyperthermia on admission** there was **evidence of possible harm** (RR 3.44 95% CI 1.91 to 6.20, ARD 113 more per 1,000 infants 95% CI from 42 more to 241 more infants, NNTH 9 infants), **moderate certainty evidence** from 4 studies including 703 infants, downgraded for very serious risk of bias. {Ibrahim 2009 256, McCarthy 2011 1534, Pinheiro 2011 357, Singh 2010 45}

COMPARISON 3. PLASTIC BAG OR WRAP VS NO PLASTIC BAG OR WRAP

For the critical primary outcome of **survival to hospital discharge,** there was **probable clinical benefit** from use of a plastic bag or wrap (RR 1.05 95% CI 1.00 to 1.10, ARD 41 more infants per 1,000 95% CI 0 fewer to 82 more infants per 1000, survived, number needed to treat to benefit (NNTB) 24 infants), **high certainty evidence** from 11 RCTs enrolling 1419 infants. {Ahmed 2013 169, Bhavsar 2015 23, Chantaroj 2011 S32, Farhadi 2012 19, Knobel 2005 304, Reilly 2015 262, Reilly 2019 37, Smith 2013 235, Trevisanuto 2010 914, Vohra 1999 547, Vohra 2004 750}

For the important primary outcome of **normothermia on admission** to a neonatal unit, there was **possible clinical benefit** from use of a plastic bag or wrap (RR 2.86 95% CI 1.66 to 4.91, ARD 238 more infants per 1,000 were normothermic, 95% CI 85 more to 501 more infants per 1000, NNTB 4 infants), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from 5 RCTs enrolling 449 infants. {Chantaroj 2011 S32, Knobel 2005 304, Nimbalkar 2019 122, Rohana 2011 468, Trevisanuto 2010 914}

Secondary outcomes:

For **mean body temperature on admission** to a neonatal unit, **there was possible clinical benefit** from use of a plastic bag or wrap. Mean temperature measured by axilla was 0.65°C higher (95% CI 0.44 to 0.86°C), and measured by rectum was 0.77°C (95% CI 0.44 to 0.86°C), **low certainty evidence** downgraded for serious risk of bias and suspected publication bias from 12 RCTs enrolling 821 infants {Ahmed 2013 169, Bhavsar 2015 23, Chantaroj 2011 S32, Farhadi 2012 19, Gathwala 2010 24, Knobel 2005 304, Nimbalkar 2019 122, Reilly 2019 37, Rohana 2011 468, Smith 2013 235, Talakoub 2015 322, Trevisanuto 2010 914, Vohra 1999 547, Vohra 2004 750}

For **hypothermia < 36.5°C on admission** to a neonatal unit **there was probable clinical benefit** from use of a plastic bag or wrap (RR 0.64, 95% CI 0.50 to 0.82, ARD 313 fewer infants were hypothermic per 1000 95% CI 435 fewer to 157 fewer infants per 1000, NNTB 3 infants), **moderate certainty evidence** downgraded for serious risk of bias from 6 RCTs enrolling 489 infants. {Chantaroj 2011 S32, Farhadi 2012 19, Knobel 2005 304, Nimbalkar 2019 122, Rohana 2011 468, Trevisanuto 2010 914}

For **moderate hypothermia on admission** to a neonatal unit there was **possible clinical benefit** from use of a plastic bag or wrap (RR 0.40 ,95% CI 0.19 to 0.81, ARD 142 fewer infants had moderate hypothermia per 1000, 95% CI 192 fewer to 45 fewer infants per 1000, NNTB 5 infants), **very low certainty evidence** downgraded for serious risk of bias, serious indirectness and serious imprecision from 4 RCTs enrolling 1055 infants. {Bhavsar 2015 23, Reilly 2015 262, Rohana 2011 468, Smith 2013 235}

For **IVH >grade 2** it was **improbable that there was clinical benefit** (RR 0.76 95% CI 0.37 to 1.55), **moderate certainty evidence** downgraded for serious imprecision from 4 RCTs enrolling 972 infants. {Knobel 2005 304, Reilly 2015 262, Reilly 2019 37, Rohana 2011 468}

For **NEC, clinical benefit or harm could not be excluded** (RR 0.95, 95% CI 0.61 to 1.50), **low certainty evidence** downgraded for serious indirectness and imprecision from 3 RCTs enrolling 935 infants. {Reilly 2015 262, Reilly 2019 37, Rohana 2011 468}

For **late onset sepsis**, **clinical benefit or harm could not be excluded** (RR 0.92, 95% CI 0.76 to 1.11), **low certainty evidence** downgraded for serious inconsistency and serious imprecision from 3 RCTs enrolling 853 infants. {Reilly 2015 262, Reilly 2019 37, Smith 2013 235}

For **intubation in the delivery room, clinical benefit or harm could not be excluded** (RR 1.02, 95% CI 0.82 to 1.26), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from 2 RCTs enrolling 174 infants. {Rohana 2011 468, Trevisanuto 2010 914}

For the **important adverse outcome hyperthermia (> 38.0°C**) there was **probable harm** (RR 3.73 95% CI 1.81 to 7.69 ARD 29 more infants were hyperthermic per 1000, 95% CI 9 to 72 infants, NNTH 34), **moderate certainty evidence**, downgraded for serious risk of bias from 12 RCTs enrolling 1652 infants. {Bhavsar 2015 23, Farhadi 2012 19, Gathwala 2010 24, Knobel 2005 304, Lyu 2015 e150277, Nimbalkar 2019 122, Reilly 2015 262, Rohana 2011 468, Smith 2013 235, Trevisanuto 2010 914, Vohra 2004 750}

COMPARISON 4. CAP VS NO CAP

Plastic cap (no bag) compared to no bag or cap:

The systematic review found a single small three-arm RCT (with no serious risk of bias) that compared use of a plastic cap (similar to a shower cap) with use of a plastic bag (no cap, only head dried) or with no plastic cap or bag. {Trevisanuto 2010 914} For both the plastic cap and the no bag or cap groups, the infants' bodies were dried and they were placed on prewarmed towels. All other interventions, including use of a prewarmed radiant warmer, were similar in both groups.

For the critical primary outcome of **survival**, **clinical benefit or harm could not be excluded** for the use of a plastic cap compared to no plastic cap. (RR 0.97 95% CI 0.84 to 1.12), **moderate certainty evidence** from 1 RCT enrolling 64 participants. {Trevisanuto 2010 914}

For the important primary outcome of **normothermia on admission** to a neonatal unit, there was **possible clinical benefit** with the use of a plastic cap compared to no plastic cap (RR 6.00 95% CI 1.96 to 18.38, ARD 469 more infants per 1000 were normothermic, 95% CI 90 more to 1000 infants more, NNTB 2 infants), **moderate certainty evidence** from 1 RCT enrolling 64 participants. {Trevisanuto 2010 914}

Secondary outcomes:

For **mean body temperature** there was **probable clinical benefit** (MD 0.8°C higher (0.41 to 1.19°C higher with the use of a plastic cap compared to no plastic cap), **moderate certainty evidence** downgraded for imprecision from 1 RCT with 64 participants {Trevisanuto 2010 914}

For **hypothermia < 36.5 C** there was **probable clinical benefit** (RR 0.48 95%CI 0.32 to 0.73, ARD 471 fewer infants were hypothermic per 1,000 95% CI 616 fewer to 245 fewer per 1000 infants) **moderate certainty evidence** downgraded for imprecision from 1 RCT with 64 participants (RR 0.48 95%CI 0.32 to 0.73) {Trevisanuto 2010 914}

For the **outcome of delivery room intubation clinical benefit or harm cannot be excluded, (**RR 0.82 95% CI 0.49 to 1.37, ARD 96 fewer infants were intubated per 1000, 95% CI 271 fewer to 197 more per 1000), **moderate certainty evidence** downgraded for imprecision from 1 RCT with 64 participants. {Trevisanuto 2010 914}

For the important adverse outcome **hyperthermia (> 37.5),** there were no events in either arm of the study, so the effect is not estimable. {Trevisanuto 2010 914}

Cloth cap compared to no cap:

An observational study compared the use of various interventions that included use of a plastic bag or wrap, a linen or woollen cap and a transport incubator. All infants were cared for under radiant heaters in the DR, and thermal mattresses were not used. After adjustment maternal and neonatal characteristics at birth, variables related to care in the DR and variables related to transport from the DR to the NICU, **not using a cloth cap was an independent risk factor for hypothermia <36.0 at NICU admission** (adjusted odds ratio 0.55, 95% CI 0.39-0.78), ungraded observation from 1 retrospective study including 1764 infants. {de Almeida 2014 271}

COMPARISON 5. HEATING AND HUMIDIFICATION OF GASES USED FOR RESUSCITATION, VS NO HEATING AND HUMIDIFICATION

For the critical primary outcome of **survival to hospital discharge**, **clinical benefit or harm cannot be excluded** (RR 1.00 95% CI 0.94 to 1.0 ARD 0 fewer per 1,000 infants 95% CI 95% CI 55 fewer to 46 more per 1000 infants), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} This result was supported by an observational study enrolling 112 participants, which also produced evidence of very low certainty, downgraded for serious risk of bias and very serious imprecision. {te Pas 2010 e1427}

For the important primary outcome of **normothermia on admission** to a neonatal unit **clinical benefit or harm cannot be excluded** (RR 1.23 95% CI 0.93 to 1.62, ARD 305 more per 1,000 infants 95% CI 78 more to 791 more per 1000 infants), **very low certainty**

evidence downgraded for serious risk of bias and inconsistency, and very serious imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} An observational study enrolling 112 participants found **possible clinical benefit** from use of heated and humidified gases (RR 3.53, 95% CI 1.65 to 7.55), **low certainty evidence** downgraded for serious risk of bias and serious imprecision. {te Pas 2010 e1427}

Secondary outcomes:
For **mean body temperature on admission**, **there was possible benefit although the clinical significance is uncertain** (mean body temperature was 0.15°C higher 95% CI 0.03 to 0.26°C higher), **moderate certainty evidence** downgraded for serious risk of bias from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **any hypothermia <36.5°C** there was **possible clinical benefit** (RR 0.67 95% CI 0.51 to 0.87, ARD 128 fewer infants were hypothermic per 1,000, 95% CI 191 fewer to 51 fewer, NNTB 8 infants), **low certainty evidence** downgraded for serious risk of bias and imprecision from 2 RCTs enrolling 476 participants). {McGrory 2018 47, Meyer 2015 245}

For **mild hypothermia clinical benefit or harm cannot be excluded** (RR 0.61 95% CI 0.35 to 1.05), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **moderate hypothermia <36°C** there was **possible clinical benefit** (RR 0.58 95% CI 0.36 to 0.94 ARD 72 fewer infants were moderately hypothermic per 1,000, 95% CI 110 fewer to 10 fewer, NNTB 14 infants), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **RDS requiring surfactant clinical benefit or harm cannot be excluded** (RR 0.91 95% CI 0.76 to 1.09), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **delivery room intubation, clinical benefit or harm cannot be excluded** (RR 1.10 95% CI 0.88 to 1.39), **low certainty evidence** downgraded for risk of bias, indirectness and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **BPD, clinical benefit or harm cannot be excluded** (RR 0.89 95% CI 0.70 to 1.13), **very low certainty evidence** downgraded for risk of bias, indirectness and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **IVH >Grade 2,** there was **probable clinical benefit** (RR 0.39 95% CI 0.17 to 0.91, ARD 24 fewer infants had IVH >grade 2 per 1000 95% CI 68 fewer to 7 fewer infants per 1000, NNTB 42 infants), **moderate certainty evidence** downgraded for imprecision from 2 RCTs enrolling 476 participants). {McGrory 2018 47, Meyer 2015 245}

For **NEC clinical benefit or harm cannot be excluded** (RR1.55 CI 95% 0.45 to 5.31), **very low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For the important adverse outcome of **hyperthermia (> 37.5°C**), **clinical benefit or harm could not be excluded** (RR 1.46 95% CI 0.60 to 3.52, ARD 41 more infants per 1000 were hypothermic with use of heated and humidified gases, 95% CI 36 fewer to 227 more), **very low certainty evidence** downgraded for risk of bias, inconsistency, and imprecision from 2 RCTs enrolling 476 infants). {McGrory 2018 47, Meyer 2015 245} The observational study provided low certainty evidence also supporting that clinical benefit or harm cannot be excluded. {te Pas 2010 e1427}

For other secondary outcomes, (receipt of positive pressure ventilation in the delivery room, late onset neonatal sepsis) outcome data were not reported.

COMPARISON 6. RADIANT WARMER (WITH OR WITHOUT SERVO CONTROL)

For this comparison, no studies were found that compared the use of a radiant warmer to no radiant warmer. The only study found for inclusion compared a servo-controlled radiant warmer to manual control. Evidence from the study showed that **when a servo-controlled radiant warmer was used compared to using a radiant warmer in manual mode** for preterm infants in the delivery room:

For the critical primary outcome of **survival to hospital discharge**, **clinical benefit or harm could not be excluded** (RR 1.05, 95% CI 0.99 to 1.11, ARD 44 more infants per 1000 survived with the use of servo control 95% CI 9 fewer to 97 more per 1000 infants), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 participants. {Cavallin 572}

For the important primary outcome of **normothermia on admission to a neonatal unit**, **clinical benefit or harm could not be excluded** (RR 0.94, 95% CI 0.75 to 1.17, ARD 25 fewer infants per 1000 were normothermic on admission with use of servo control, 95% CI 106 fewer to 72 more per 1000 infants), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 participants. {Cavallin 572}

Secondary outcomes:
For **mean body temperature on admission, there was probable clinical harm** (mean difference (MD) 0.2°C lower 95% CI 0.33 to 0.07 lower with use of servo control), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 participants. {Cavallin 572}

For **any hypothermia < 36.5°C there was probable clinical harm** (RR 1.20 95% CI 1.01 to1.42, ARD 100 more per 1,000 had hypothermia <36.5°C with use of servo control, 95% CI 5 more to 209 more infants per 1000, NNTH 10 infants), **moderate certainty evidence** downgraded for imprecision from 1 trial enrolling 450 infants. {Cavallin 572} As shown by the next two outcomes, the main contribution to this outcome was from infants who had mild hypothermia/cold stress (36.0 to 36.4°C).

For **mild hypothermia (36.0 to 36.4°C)** there was **probable clinical harm** (RR 1.48 (95% CI 1.09 to 2.01, ARD 107 more per 1,000 had mild hypothermia with use of servo control 95% CI 20 more to 224 more per 1000, NNTH 9 infants), **moderate certainty evidence**, downgraded for serious imprecision from 1 RCT enrolling 450 infants. {Cavallin 572}

For **moderate hypothermia < 36.0°C, clinical benefit or harm cannot be excluded** (RR 0.97 (95% CI 0.71 to 1.31, ARD 8 fewer infants per 1000 were hypothermic with use of servo control, 95% CI 80 fewer to 85 more per 1000), **moderate certainty evidence,** downgraded for serious imprecision from 1 RCT enrolling 450 infants) {Cavallin 572}

For **IVH > grade 2, clinical benefit or harm cannot be excluded** (RR 0.87 95% CI 0.42 to 1.78, ARD 9 fewer infants per 1000 had IVH with use of servo control 95% CI 39 fewer to 52 more per 1000 infants), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants). {Cavallin 572}

For **late onset neonatal sepsis, clinical benefit or harm cannot be excluded** (RR 1.39 95% CI 0.89 to 2.18, ARD 49 more infants per 1000 had sepsis with use of servo control 95% CI 14 fewer to 147 more per 1000), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants). {Cavallin 572}

For **bronchopulmonary dysplasia, clinical benefit or harm cannot be excluded** (RR 0.98 95%CI 0.68 to 1.41, ARD 4 fewer per 1000 had BPD with use of servo control 95% CI 67 fewer to 86 more per 1000), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants. {Cavallin 572}

For **delivery room intubation, there was possible clinical benefit** (RR 0.67 95%CI 0.46 to 0.93, ARD 79 fewer infants per 1000 were intubated 95% CI 130 fewer to 7 fewer per 1000, NNTB 13 infants), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants. {Cavallin 572} However, there was no difference in the use of delivery room nasal positive pressure ventilation or in the combined outcome of intubation plus nasal positive pressure ventilation.

For the following comparisons, or for any combination of these interventions, the systematic review found no RCTs or observational studies that allowed assessment of the effectiveness of the intervention.

COMPARISON 7: EARLY MONITORING OF TEMPERATURE

This comparison aimed to determine whether early or frequent checking of temperature during or immediately after initial resuscitation improved temperatures on admission to a NICU (e.g., by allowing prompt initiation of other interventions to improve temperature. No RCTs or observational studies that addressed this comparison were found. Early measuring of temperature was a component of several QI studies, but the design and reporting of the studies precluded assessment of the magnitude of effect of this specific intervention.

COMPARISON 8. WARM BAGS OF FLUID VS NO WARM BAGS OF FLUID

No RCTs or observational trials provided data for this comparison.

COMPARISON 9. SWADDLING VS NO SWADDLING

No RCTs or observational trials provided data for this comparison.

COMPARISON 10. SKIN TO SKIN CARE VS NO SKIN TO SKIN CARE

Only two small RCTs were identified, and they reported only secondary outcomes. {Bergman 2004 779, Linnér 2020 697} Therefore an evidence to decision table and treatment recommendations were not developed.

For the **outcome of mean body temperature clinical benefit or harm cannot be excluded** (MD 0.59°C higher with use of skin to skin care 95% CI 1.17°C lower to 2.36°C higher) **very low certainty evidence** downgraded for very serious risk of bias and inconsistency, and serious imprecision from 2 RCTs enrolling 62 infants. {Bergman 2004 779, Linnér 2020 697}

One of these trials including 55 infants found no difference in rates of RDS treated with surfactant. {Linnér 2020 697}

Subgroup analyses

The only comparison for which there were sufficient data for formal subgroup analysis was use of a **plastic bag or wrap vs no plastic bag or wrap;**

For subgroup analysis by gestational age groups: (<28 weeks vs 28-33^{+6} weeks) a plastic bag or wrap was more efficacious in preventing moderate hypothermia in the lower gestation subgroup (test for subgroup differences (random effects): $\chi 2 = 5.27$, df = 1 (p = 0.02)). For all other outcomes results of tests for subgroup differences were not statistically significant.

For subgroup analysis high income vs middle income country setting a plastic bag or wrap was more efficacious in preventing moderate hypothermia in high income countries, (test for subgroup differences (random effects): $\chi 2 = 5.20$, df =1 (p =0.02)). For all other outcomes results of tests for subgroup differences were not statistically significant.

For subgroup analysis by setting high resource vs low resource setting there were no data.

For subgroup analysis by site (inborn vs outborn) the tests for subgroup differences were not statistically significant.

Observational studies and quality improvement studies

In addition to the RCTs or observational studies described above, the systematic review found 29 studies that used quality improvement (QI) methodology. {Aley-Raz 2020 476, Ashmeade 2016 73, Billimoria 2013 455, Caldas 2018 368, Castrodale 2014 9, Choi 2018 239, Cleator 2022 75, Croop 2020 530, DeMauro 2013 e1018, Ferretti 2021 e240, Frazer 2018 520, Frazer 2021 , Godfrey 2013 311, Harer 2017 1242, Harriman 2018 462, Keir 2022 375, Lee 2008 754, Manani 2013 8, Peleg 2019 387, Pinheiro 2014 e218, Reuter 2014 , Russo 2014 31055, Sharma 2020 1851, Sivanaridan 2016 , Sprecher 2021 270, Vinci 2018 e125, Wlodaver 2016 182, Yip 2017 922, Young 2021 } Most of the (QI) studies demonstrated improvements.

Some examined multifaceted interventions either as a bundle of care or sequentially introduced using 'plan-do-study-act' cycles. These studies did not allow any definite conclusions to be drawn about the effectiveness of any component intervention. Any assessment of component interventions would have been at critical risk of bias because of confounding from other co-interventions. Because of this and a high degree of heterogeneity in the interventions used, no meta-analyses could be performed, and individual studies are difficult to interpret.

Nevertheless, taken together, these QI studies suggest that hypothermia can be a common problem among preterm infants in both low-income and high-income settings. They also suggest that multidisciplinary teams, working together to recognize local place, people, policy and procedure contributors to risk, and to test the effect of locally devised solutions, may be an effective way to reduce rates of hypothermia.

Treatment recommendations

Comparison 1. Increased room temperature ≥23.0°C vs lower room temperature:

In preterm infants (<34 weeks' gestation), as for late preterm and term infants (≥34 weeks' gestation), we suggest the use of room temperatures of 23°C compared to 20°C at birth in order to maintain normal temperature. (Weak recommendation, very low certainty evidence).

Comparison 2. Thermal mattress vs no thermal mattress:

In preterm infants (< 34 weeks' gestation) immediately after birth, where hypothermia on admission is identified as a problem, it is reasonable to consider addition of a thermal mattress, but there is a potential risk of hyperthermia. (Conditional recommendation, low certainty evidence).

Comparison 3. Plastic bag or wrap vs no plastic bag or wrap

In preterm infants (<34 weeks' gestation) immediately after birth we recommend the use of plastic bag or wrap to maintain normal temperature. (Strong recommendation, moderate certainty of evidence).

The risk of hyperthermia should be carefully monitored and managed. (Good practice statement).

Comparison 4. Cap vs no cap

In preterm infants (<34 weeks' gestation) immediately after birth we suggest the use of a head covering to maintain normal temperature. (Strong recommendation, moderate certainty evidence).

It is reasonable to consider the use of a plastic cap unless another form of head covering is used. (Conditional recommendation, moderate certainty evidence).

There is currently little published evidence that head coverings of other materials are effective in preterm infants (< 34 weeks' gestation), but they may also help maintain normothermia based on an observational study and studies in infants ≥ 34 weeks' gestation.

Comparison 5. Heated and humidified gases compared to no heating and humidification:

In preterm infants (<34 weeks' gestation) immediately after birth, we suggest heated and humidified gases for respiratory support in the delivery room can be used where audit shows that admission hypothermia is a problem and resources allow. (Conditional recommendation, very low certainty evidence)

Comparison 6. Radiant warmer - servo control vs manual mode

In preterm infants (<34 weeks' gestation) immediately after birth there is insufficient published human evidence to suggest for or against the use of a radiant warmer in servo-controlled mode compared to manual mode for maintaining normal temperature. (Weak recommendation, moderate certainty evidence).

Comparison 7. Skin to skin care vs no skin to skin care:

In preterm infants (<34 weeks' gestation), use of skin to skin care immediately after birth may be helpful for maintaining normal temperature where few other effective measures are available. (Good practice statement).

Current Search Strategy
New Search strategy: See appendix

Database searched: eg Pub Med
Time Frame: (existing PICOST) – updated from end of last search July 20, 2022 to July 20, 2024

Date Search Completed: 28 April 2024
Search Results: The literature search yielded 313 records, from which 66 full text articles were reviewed 3 RCTs and one systematic review were identified that addressed the PICOST.

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Tourneux 2022 {Tourneux 2022 1490}	Systematic review and guidelines	Prevention of hypothermia	7 meta-analyses and 64 clinical studies were included in the review	Little data on DR management to support normothermia. Findings and recommendations were generally on NICU Care	Routine use of a stockinette skullcap is recommended whenever the newborn infant is not in a temperature-and humidity-controlled environment (Evidence Grade B). A polyurethane skullcap can be used for the preterm infant in the DR, in order to prevent a decrease in post-stabilization temperature (Grade B). The use of a polyethylene bag in the delivery room (without drying) is recommended for newborn infants <32 wks GA and/or < 1000 g (Grade A). No assessment of gestational age or birthweight subgroups Certainty of evidence was assessed using a method supported by the French Neonatal Society.

RCT:

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Ambia 2023 {Ambia 2024 S 01} These subgroup data have been obtained from the study authors	**Study aim** To measure the effect of OR temperature on. neonatal morbidity. **Study type** Cluster RCT (weekly allocation) (N=5221, of which 273 were <34 weeks)	**Inclusion criteria** Caesarean birth without congenital anomalies **Intervention** < 34 wks n=136 **Comparator** <34 wks n=137	**Intervention** OR temp 24°C < 34 wks n=136 **Comparator** OR temp 20°C <34 wks n=137	**1° endpoint:** Proportion of infants with temperature less than 36.5°C on arrival to the nursery **Intervention** n=8 (6.1%) **Comparator** n=53 (41.7%), (p < 0.001)	**2° Endpoint** Proportion of infants with temperature > 37.5°C **Intervention** n=40 (30.5%) **Comparator** n=15 (11.8%), No difference between groups in a composite outcome measuring

	Intervention OR 24°C (n=136) **Control** OR 20°C (n=137)				neonatal morbidity that included type of respiratory support, sepsis, hypoglycemia, and neonatal death. **Study Limitations** Single center, Resistance from obstetricians and OR personnel to working in the higher ambient temperature
Dunne 2024 {Dunne 2024 317}	**Study aim** To determine if infants in a plastic bag before umbilical cord clamping (UCC), compared with after UCC, increased proportion of infants with a temp in the normal range on NICU admission **Study type** RCT (N=198)	**Inclusion criteria** GA <32 wks	**Intervention** Plastic bag before UCC (n=99) GA wks median (IQR) 29 (27 - 31) **Comparator** Plastic bag after UCC (n=99) GA wks median (IQR) 29 (27 - 31)	**1° endpoint** Rectal temp on admission to NICU. Proportion of infants in the normal range 36.5°C–37.5°C **Intervention** 54 (55%) **Comparator** 55 (56%) (p=0.82)	**2° Endpoint** No significant difference between groups for NICU admission temp <36.0°C or >37.5°C Almost half the infants in each group were outside the normal range on admission to the NICU. Placement of the PB before UCC did not improve normothermia. **Study Limitations** Single center
Possidente 2023 {Possidente 2023 514}	**Study aim** To compare the effect of two types of PBs on NICU admission temp **Study type** Quasi-RCT (n=171)	**Inclusion criteria** GA $24^{0/7}$ - 33 $^{6/7}$wks	**Intervention** PB designed for purpose (NeoHelp™) (n=76) **Comparator** Commercial grade PB (n=95)	**1° endpoint** Proportion of infants with admission temp <36°C **Intervention** 2.6% **Comparator** 14.7% (p<0.01)	**2° Endpoint** Proportion of infants with hyperthermia >37.5°C **Intervention** 9.2 % **Comparator** 1% (p=0.02) **Study Limitations** Single center Underpowered for thermoregulation outcomes

Abbreviations: GA: gestational age; BW: birth weight; DR: delivery room; IQR: interquartile range; NICU: neonatal intensive care unit; NB: newborn; NR: not reported; HRC: hospital routine care; OR: operating room; PT; preterm; SSC: skin-to-skin contact; wks weeks; temp temperature; UCC: umbilical cord clamping; g grams

Nonrandomized Trials, Observational Studies: none identified

Reviewer's comments
This evidence update found one systematic review, and 3 RCTs addressing the PICOST.

The systematic review by Tourneaux et al. focuses on warming methods that could be used during or as an alternative to SSC not just in the NICU but during subsequent neonatal unit care. {Tourneux 2022 1490} Searches were similar and covered a similar time frame; the Tourneux et al. search was completed on 31 Dec 2021 and the ILCOR SR on 2 Aug 2021. We reviewed the reference list from the Tourneux review and did not find any additional studies to include in this evidence update. Recommendations from this review resemble those in our previous SR.

Increased room temperature ≥23.0°C vs lower room temperature:
We found one RCT that compared operating room (OR) ambient temperature 24°C with that hospital's standard OR temperature of 20°C. {Ambia 2024 S 01} Additional data were obtained from the authors for the subgroup of infants <34 weeks' gestation. In these 273 infants < 34 weeks gestation for the primary **outcome survival** there was no difference between groups 97.05 % compared with 96.35% in OR temperature 24°C and OR temperature of 20°C respectively.

For OR temperature of 24°C compared to 20°C:

- For the important secondary outcome of **hypothermia < 36.5°C** on admission, there was evidence of benefit (RR: 0.15 (95% CI: 0.07 to 0.30), P < 0.00, NNTB: 3 (95%CI: 2 to 4)), the absolute risk difference (ARD) being 329 per 1000 (from 360 fewer to 271 fewer). {Ambia S 01}
- For the important secondary outcome of **hyperthermia > 37.5°C** on admission, there was evidence of harm (RR:2.69 (95% CI: 1.56 – 4.63), P =0.00, NNTH: 5 (95%CI: 4 – 11)), ARD being 185 more per 1000 (from 61 more to 397 more) {Ambia S 01}.

These new results are generally consistent with our previous recommendation for preterm infants (<34 weeks' gestation), that suggested the use of room temperatures of 23°C compared to 20°C at birth in order to maintain normal temperature but continue to raise concerns that interventions to prevent hypothermia can carry risk of hyperthermia, particularly when multiple interventions are combined.

Plastic bag or wrap vs no plastic bag or wrap:

We found 2 RCTs measuring the effect of a plastic bag on admission temperature. {Dunne 2024 317, Possidente 2023 514} Dunne found that placing infants in a PB before cord clamping compared with after cord clamping did not improve the rate of normothermia at admission to the NICU. {Dunne 2024 317} Possidente compared a purpose designed double wall plastic bag with a single wall plastic bag. {Possidente 2023 514} The double wall plastic bag significantly reduced hypothermia but significantly increased hyperthermia after admission to the NICU.

These studies support out previous treatment recommendation to of a plastic bag or wrap to maintain normothermia and they reinforce our previous good practice statement; *The risk of hyperthermia should be carefully monitored and managed*.

***Skin to skin care vs no skin to skin care*:** No new studies addressing the PICOST were found

We found no studies that directly addressed the PICOST but some studies that provided indirect evidence. These included studies addressing prevention of hypothermia after DR resuscitation and stabilization during transfer to the neonatal unit. Two RCTs {Kristoffersen 2023 e001831, Lode-Kolz 2023 934} and two observational studies {Carneiro 2024 e1037, M'Rini 2024 1379763} measured the effect of skin to skin care (SSC) vs. standard care during transfer. Findings from these two studies showed little difference between groups in admission temperature, but did show an increased rate of hyperthermia in the standard care groups. A small observational study also showed an increased rate of hypothermia in the SSC group. {M'Rini 2024 1379763}

Because of insufficient direct evidence of use of SSC immediately after birth, the previous SR did not make any recommendations regarding SSC to promote normothermia. However, we did make a good practice statement; *In preterm infants (<34 weeks' gestation), use of skin to skin care immediately after birth may be helpful for maintaining normal temperature where few other effective measures are available.*

The World Health Organization (WHO) recommends skin-to-skin contact (SSC) to reduce mother-infant separation. {Arya 2021 2028} This practice is important for promoting attachment and breastfeeding between mothers and babies. In light of the indirect evidence to prevent hypothermia we suggest that a scoping review might be useful to assess the effects of SSC compared to non-SSC including to assess physiological variables such as heart rate and SpO2 in addition to thermoregulation. It should consider the role of SSC during transfer from delivery room setting to neonatal unit (which was considered beyond scope of the current review). and should also examine the occurrence of adverse events, including hypothermia, hyperthermia, unplanned extubation, and increased respiratory support

Other comparisons

No new studies were found addressing any of the other comparisons addressed in the previous systematic review (plastic bag or wrap vs no plastic bag or wrap, plastic bag or wrap plus skin to skin care, vs skin to skin care alone, plastic bag or wrap with and without drying, plastic bag or wrap compared to a thermal mattress, early vs late skin to skin care, continuously active warming blankets with skin to skin care vs standard care, skin to skin care vs plastic bag or wrap, or woolen vs cotton cap) , or among the comparisons between interventions that were not addressed in the review because no studies were found at the time.

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Appendix: search strategy

Sources searched	Search strategy	Search time frame
PubMed	(newborn*[tiab] OR "new born*"[tiab] OR "Infant, Newborn"[Mesh] OR neonat*[tiab] OR neo-nat*[tiab] OR "newly born"[tiab] OR premature[tiab] OR prematurity[tiab] OR preterm[tiab] OR "pre term"[tiab] OR "Premature Birth"[Mesh] OR "low birth weight"[tiab] OR "low birthweight"[tiab] OR VLBW[tiab] OR LBW[tiab] OR postnatal[tiab] OR post-natal[tiab] OR "golden hour"[tiab] OR "Perinatal Care"[Mesh]) AND ("room temperature"[tiab] OR "ambient temperature"[tiab] OR "admission temperature"[tiab] OR "radiant warm*"[tiab] OR mattress*[tiab] OR "radiant heat*"[tiab] OR skin-to-skin[tiab] OR kangaroo*[tiab] OR swaddling[tiab] OR covering*[tiab] OR "plastic bag*"[tiab] OR wrap*[tiab] OR hat[tiab] OR hats[tiab] OR cap[tiab] OR caps[tiab] OR "warm bag*"[tiab] OR "warm fluid*"[tiab] OR polyethylene[tiab] OR polythene[tiab] OR polyurethane[tiab] OR woolen[tiab] OR transwarmer*[tiab] OR trans-warmer*[tiab] OR humidifi*[tiab] OR servo-control*[tiab] OR protocol*[tiab] OR checklist*[tiab] OR project*[tiab] OR "care bundle*"[tiab] OR "quality improvement"[tiab] OR "Heating"[Mesh]) AND (temperature[tiab] OR "Body Temperature"[Mesh] OR normothermi*[tiab] OR normo- thermi*[tiab] OR euthermi*[tiab] OR hypothermi*[tiab] OR hypo-thermi*[tiab] OR "Hypothermia"[Mesh] OR hyperthermi*[tiab] OR hyper-	July 20, 2022 to July 20, 2024

	thermi*[tiab] OR "Hyperthermia"[Mesh] OR thermoregulat*[tiab] OR thermo-regulat*[tiab] OR thermoprotect*[tiab] OR thermo-protect*[tiab] OR "heat loss*"[tiab] OR "cold stress*"[tiab]) NOT (animals[mh] NOT humans[mh])	
Results identified	**Results screened full text**	**Results included**
174	6	4

2025 Evidence Update
NLS 5120 – Suctioning of Clear Amniotic Fluid at Birth

Worksheet Author(s): Fawke J, Udaeta E
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 6 November 2024
Conflicts of Interest: None

PICOST:
Population: Neonates born through clear amniotic fluid in the delivery room
Intervention: Initial suctioning of the mouth and nose
Comparator: No initial suctioning
Outcomes:
Primary outcome:

- Receipt of assisted ventilation (important).

Secondary outcomes:

- Advanced resuscitation (critical)
- Receipt and duration of oxygen supplementation (important)
  Adverse effects of intervention (important)
- Unanticipated admission to the neonatal Intensive Care Unit (NICU) (important).

Study designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Manikin studies were eligible for inclusion, but animal studies were excluded. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded. All languages were included provided there was an English abstract.

Timeframe: Databases were searched from inception to September 11, 2021, then an updated search was conducted to 16 June 2022. Database searches: Embase 1974 to 2022 June 16, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to June 16, 2022

Year of last full review: Systematic review 2022 {Fawke 2022 100298, Wyckoff 2022 208}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST {Wyckoff 2022 208}
This systematic review found 9 randomized controlled trials and 2 observational studies which met inclusion criteria for the review.

The results of 2 RCTs, (one including infants born by caesarean section and the other vaginal births) for oxygen saturation and heart rate levels are almost identical and have much smaller standard deviations than other studies. {Gungor 2006 9, Gungor 2005 453} The task force has sought clarification from the authors about the data. While awaiting a response, outcome data with and without these 2 RCTS are presented.

For the important primary outcome of receiving **assisted ventilation,** 5 RCTS, including 1022 participants found that for suctioning compared to no suctioning, **clinical benefit or harm could not be excluded** (RR 0.72; 95% CI, 0.40, 1.31; absolute risk (AR) 13 fewer per 1000 95% CI, 28 fewer to 15 more per 1000). Inclusion criteria for 4 of the RCTS included no maternal or fetal pathological changes during gestation or delivery, single fetus, term gestation. **Evidence was of very low certainty** (downgraded for very serious risk of bias, serious inconsistency, very serious indirectness and very serious imprecision). {Bancalari 2019 271, Gungor 2006 9, Gungor 2005 453, Kelleher 2013 326, Modarres Nejad 2014 400} Analysis without the Gungor 2005 and Gungor 2006 studies did not change the RR and adjusted the absolute risk to 18 fewer (95% CI, 39 fewer to 20 more).

For the important primary outcome of receiving ***advanced resuscitation and stabilization interventions (intubation, chest compressions / epinephrine (adrenaline) in DR),*** 5 RCTS, including 1022 participants found that for suctioning vs no suctioning, **clinical benefit or harm could not be excluded (**RR 0.72; 95% CI, 0.40, 1.31; AR 13 fewer per 1000 95% CI, 28 fewer to 15 more patients per 1000). Inclusion criteria for 4 of the RCTS included no maternal or fetal pathological changes during gestation or delivery, single fetus, term gestation. **Evidence was of very low certainty** (downgraded for very serious risk of bias, serious inconsistency, very serious indirectness and very serious imprecision). {Bancalari 2019 271, Gungor 2006 9, Gungor 2005 453,

Kelleher 2013 326, Modarres Nejad 2014 400} Analysis without the Gungor 2005 and Gungor 2006 studies did not change the RR and adjusted the absolute risk to 18 fewer (95% CI, 39 fewer to 20 more).

For the important secondary outcome of ***receipt and duration of oxygen supplementation*** 4 RCTs included 534 healthy term infants and reported that all newborns were born in good clinical condition and did not need any supplemental oxygen. **Clinical benefit or harm could not be excluded** as the event rate was zero in both groups so a relative risk could not be calculated**.** Evidence was of **very low certainty (**downgraded for very serious risk of bias, serious inconsistency, very serious indirectness and very serious imprecision). {Bancalari 2019 271, Gungor 2006 9, Gungor 2005 453, Modarres Nejad 2014 400} Analysis without the Gungor studies did not alter this finding.

For the important secondary outcome of ***Adverse effects of intervention (e.g., apnoea, bradycardia, injury, infection, low Apgar scores, dysrhythmia)*** we identified:

Outcomes related to oxygen saturations:

For the important secondary outcome of of **oxygen saturations at 5 minutes** 5 RCTs including a total of 560 participants found for suctioning vs no suctioning **possible harm** (mean difference (MD] -9.08% (95%CI, -9.51 to -8.66%) Evidence was of **very low certainty** (downgraded for serious risk of bias, serious inconsistency, very serious indirectness). {Bancalari 2019 271, Gungor 2006 9, Gungor 2005 453, Modarres Nejad 2014 400, Takahashi 2009 261}

Analysis without the two Gungor studies found for suctioning vs no suctioning, **clinical benefit or harm could not be excluded** (MD -0.26% (95%CI, -1.77 to 1.26%). {Bancalari 2019 271, Modarres Nejad 2014 400, Takahashi 2009 261}

For the important secondary outcome of of **oxygen saturations at 9 minutes** 3 RCTs including 280 participants, for suctioning vs no suctioning found **possible harm (**MD -1.52% 95% CI, -2.69 to -0.35%). Evidence was of **very low certainty** (downgraded for serious risk of bias, serious inconsistency, very serious indirectness) {Bancalari 2019 271, Modarres Nejad 2014 400, Takahashi 2009 261}

For the important secondary outcome of of **oxygen saturations at 10 minutes** 2 RCTs including 110 participants found **clinical benefit or harm could not be excluded**. Average oxygen saturations at 10 minutes in the no suction group were 94.0% and there was no significant difference in saturations in the infants receiving suction [MD -0.14 (95%CI, -1.17, 0.89)]. Evidence was of **very low certainty** (downgraded for serious risk of bias, serious inconsistency, very serious indirectness) {Bancalari 2019 271, Modarres Nejad 2014 400, Takahashi 2009 261}

For the important secondary outcome of **oxygen saturations** the data were presented in different ways in different studies, precluding a comprehensive meta-analysis of all studies that reported data on this outcome.

For the important secondary outcome of **oxygen saturations over the first 10 minutes from birth** 3 RCTs {Bancalari 2019 271, Carrasco 1997 832, Gungor 2006 9} including 254 participants provided evidence of **very low certainty** (downgraded for serious risk of bias, serious imprecision and very serious indirectness) and 1 prospective observational study {Konstantelos 2015 777} including 346 participants gave graphical representations of saturations over time from birth. All show slightly lower oxygen saturations over the first 10 minutes of life in infants who received suctioning of clear amniotic fluid at birth. By 10 minutes of age saturations were very similar in infants who did and did not receive suctioning at birth.

One RCT including 20 healthy term participants reported slightly lower saturations in those receiving suctioning at 5 minutes but slightly higher saturation readings at 10- and 15-minutes Evidence was of **very low certainty** (downgraded for very serious risk of bias, very serious indirectness and very serious imprecision). {Waltman 2004 32}

Time to reach target saturations of 86% or 92% or 96%

Some studies reported the proportion of infants that received suctioning or no suctioning who achieved target saturations at certain time points whilst another reported mean (SD) time to achieve target saturations. The target saturations reported are those selected by studies included in this systematic review.

For the important secondary outcome of time to reach target oxygen saturations of 86% or 92%

Two RCTs provided data in a form that could not be meta-analyzed. In one RCT including 170 participants all infants with suctioning achieved 92% saturations by 11 minutes vs. 9 minutes in the group receiving no suction. {Modarres Nejad 2014 400} The authors

also noted that no babies in the suctioned group achieved 92% saturations before 8 minutes. In one RCT including 30 participants, mean (SD) time to achieve saturations of 86% was 8.2 +/-3.3 minutes in those receiving suction and 5.0 minutes +/- 1.2 in those not receiving suction. For 92% saturations the times (suctioning vs. no suctioning) were 10.2 +/-3.3 minutes and 6.8 +/- 1.8 minutes respectively {Carrasco 1997 832}

Two RCTs including 280 participants (all healthy, term infants) found 140 infants with no suctioning all achieved oxygen saturations of 86% by 5 minutes and 92% by 6 minutes. In contrast only 2.9% of the 140 infants with suctioning achieved saturations of 86% by 5 minutes and none achieved saturations of 92% by 6 minutes. In the suctioning group the maximum time to achieve saturations of 86% and 92% were 8 and 11 minutes. Evidence was of **very low certainty** (downgraded for serious imprecision and very serious indirectness) {Gungor 2006 9, Gungor 2005 453}

One prospective observational study {Konstantelos 777} including 346 participants reported 1 episode of severe desaturation to <75% following suctioning.

One prospective observational study enrolled 138 infants born at term by elective caesarean section into a study of cerebral and peripheral muscle tissue oxygenation. {Pocivalnik 2015 153} They reported on 36 infants who received oropharyngeal suctioning and 36 controls and found no significant difference in heart rate, oxygen saturations, cerebral and peripheral muscle tissue oxygenation between infants receiving and not receiving suctioning.

For the important secondary outcome of **respiratory rate >60 in the first 24 hours** evidence from one RCT with 488 participants (not restricted to healthy infants and including those ≥35 weeks gestation), showed **clinical benefit or harm could not be excluded** (relative risk [RR], 0.99; 95% CI, 0.82, 1.20) absolute risk reduction 5 fewer per 1000 with those receiving suctioning vs. no suctioning (95% CI, 83 fewer per 1000 to 92 more patients per 1000 patient receiving suctioning). Evidence was of **moderate certainty**. {Kelleher 2013 326}

For the important outcome of **heart rate at 5 minutes,** 3 RCTs including 364 participants found **clinical benefit or harm cannot be excluded** (MD 5 95% CI 3.8,6.2) however both groups had a heart rate in the normal range and no bradycardias were reported in either group. Evidence was of **very low certainty** (downgraded for serious inconsistency and very serious indirectness) {Bancalari 2019 271, Gungor 2006 9, Gungor 2005 453, Modarres Nejad 2014 400, Takahashi 2009 261}Analysis without the Gungor 2005 and Gungor 2006 studies did not change this finding but altered the MD [MD -1.00 (95%CI, -7.96, 5.96)].

For the important secondary outcome of low Apgar scores (<7) insufficient data were available for analysis.

For the secondary outcome of **Apgar scores** (score of 10 at 5 minutes) 3 RCTs including 450 participants showed **possible harm** (relative risk [RR], 0.63; 95% CI, 0.57, 0.70) absolute risk reduction 370 fewer per 1000 with those receiving suctioning vs. no suctioning (95% CI, 430 fewer per 1000 to 300 fewer patients per 1000 patient receiving suctioning). Evidence was of **very low certainty** (downgraded for serious indirectness. {Gungor 2006 9, Gungor 2005 453, Modarres Nejad 2014 400}

Analysis without the Gungor 2005 and Gungor 2006 studies showed no significant difference in Apgar scores (score of 10 at 5 minutes) [MD 1.00 (0.98, 1.02)] so in this analysis **clinical benefit or harm could not be excluded**.

For the important secondary outcome of **unanticipated admission to the NICU** one RCT included 448 infants of ≥35 weeks' gestation, **clinical benefit or harm cannot be excluded** (Relative risk [RR], 1.50; 95% CI, 0.96, 2.30) absolute risk increase 91 more per 1000 with no suctioning vs. suctioning (95% CI, 8 fewer per 1000 to 238 more patients per 1000 patient receiving no suctioning). Evidence was of very low certainty (downgraded for serious risk of bias and indirectness and very serious imprecision). {Kelleher 2013 326}

Insufficient data were available to be able to report on the important secondary outcomes of **soft tissue injury or infection or bradycardia.**

Subgroup Analyses:
A priori subgroup analyses:

- Gestational age categories (gestational age is used define categories and birthweight is only used in studies that only used birthweight)

  - ≥34 +0 weeks or >2000g
  - 28 +0 - 33 +6 weeks or 1000-2000g
  - <28 +0 weeks or <1000g
- Route and method of delivery
  - Vaginal vs Caesarean section
- Suction device used (Bulb vs Catheter Suction)

Gestational age: Insufficient data were available for this subgroup analysis as the studies included in this systematic review were predominantly in term babies. Only one prospective observational study {Konstantelos 777} and one RCT {Kelleher 326} included both preterm and term infants.
The Kelleher study included infants ≥35 weeks although the median (IQR) gestation was 39 (38–40) weeks for the no suction (wipe) group and 39 (38–40) for suction group. {Kelleher 326} The majority of the infants in the Konstantelos study were born at term. {Konstantelos 777}

Vaginal vs Caesarean section: insufficient data were available for a subgroup analysis of the following outcomes: receipt of assisted ventilation, advanced resuscitation, receipt of supplemental oxygen, unanticipated NICU admission.

For the outcome of oxygen saturations at 5 minutes there is a difference favoring no suction in both vaginal delivery and caesarean section subgroups with high heterogeneity within subgroups (I^2 =97%) and evidence of an interaction by delivery type (test for subgroup differences 0.03) also with high heterogeneity between subgroups (I^2=78.6%). Given the very high heterogeneity, despite almost identical results in two studies, {Gungor 2006 9, Gungor 2005 453} a sensitivity analysis was carried out. With the two Gungor studies removed from both subgroups there was no difference in saturations in either subgroup with no interaction (p=0.86) and heterogeneity reduced (I^2=0%).

Among the two methodologically identical RCTs, one studied vaginally born infants and the other those born by caesarean section, each included 140 participants and found identical time to achieve saturations of 86% or 92%. {Gungor 2006 9, Gungor 2005 453}

Suction device used (Bulb vs Catheter Suction)
Two RCTs studied babies receiving bulb suction vs no suction or wiping. {Kelleher 2013 326, Waltman 2004 32} No studies compared bulb suction to catheter suction. Outcomes in the Kelleher study (respiratory rates) were not comparable to outcomes in studies that used catheter suction, precluding subgroup analysis. The Waltman study was a pilot RCT that compared bulb suctioning to no suctioning but the low numbers (n=20), high risk of bias and inaccuracies in saturation measurements meant that data were unsuitable for subgroup analysis.

Treatment Recommendations

We suggest that suctioning of clear amniotic fluid from the nose and mouth should not be used as a routine step for newborn infants at birth (weak recommendation, very low certainty of evidence). Airway positioning and suctioning should be considered if airway obstruction is suspected (good practice statement).

New Search strategy: see appendix

Database searched: Embase
Time Frame: 1st January 2020 to 23rd June 2024
Date Search Completed: 23rd June 2024

Search Results:
Identified: 175
Full-text screening: 3
Included: 1

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews: None
RCT: None
Nonrandomized Trials, Observational Studies: 1

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Nesterenko 2023 {Nesterenko 2023 387}	**Study Type:** Single center, quality improvement project Objective: To test the hypothesis that newborn resuscitation is feasible with the following two guidelines: 1) avoiding any suctioning until the infant establishes spontaneous respiration, and 2) avoiding the use of deep suction with catheters. Infants' mouth was cleaned with a dry cloth. No suction was started until infants establish spontaneous breathing. Then, bulb suction was used to clear secretions from the sides of the mouth and the nose without reaching the back of the pharynx. Deep suction using catheters was not used. Neonatal staff and physicians received biweekly training to support these changes. Resuscitation data before and after the practice change were compared. N=999 infants	This study included all mother-infant dyads delivered at a single women's center with pediatricians attending deliveries. Pediatric team was called by obstetric providers before delivery in conditions when resuscitation was anticipated such as preterm delivery, meconium stained fluids, and non-reassuring fetal heart tones. The team was also called emergently during or after delivery if an infant did not have spontaneous breathing. The obstetric providers were not involved in this quality improvement project and the pediatric team did not have any influence on obstetric decision when to be called. Since this project included a comparison of two groups before and after the implementation of the new guidelines, an institutional review board approval was obtained. Informed consent was not indicated for this quality improvement initiative.	A total of 999 sequential cases were compared; 501 infants were resuscitated before the implementation of the quality improvement project, and 498 infants were resuscitated after starting the new practice. The two cohorts did not differ in maternal and neonatal characteristics except for less maternal hypertension and more maternal diabetes ($P < 0.05$) in the post implementation cohort. The pediatric team attended more cesarean sections in the second cohort (68% vs 60%, $P = 0.004$). Suction before spontaneous breathing occurred in 61 (12.2%) infants in the first cohort. In the second cohort 26 (4.8%) infants received suction before breathing ($P < 0.001$). All infants suctioned in the second cohort ($n = 26$) were after the failure to establish adequate bag-and-mask ventilation. There were no differences between groups, except for less supplemental oxygen use in the delivery room with the new	The study concluded that avoidance of any suction prior to spontaneous breathing (including bulb suction and deep suction with catheters) is feasible during newborn resuscitation. This practice is associated with a decreased exposure to oxygen in the delivery room. We recommend clearing the airway during the first minute of life by wiping the face and swabbing the mouth with a warm, dry cloth to allow uninterrupted physiologic establishment of spontaneous breathing.

			guidelines (12.4% vs. 4.2%, $P < 0.001$).	

Reviewer Comments:
This evidence update found one new quality improvement study on suctioning clear amniotic fluid in the delivery room. {Nesterenko 2023 387} This study included 999 infants, of whom 12% received oropharyngeal suctioning in the first epoch of the study and 4% in the second. The study found no disadvantages of the more selective suctioning approach. The authors conclude that avoiding suctioning of clear amniotic fluid, including deep pharyngeal suction, prior to the onset of breathing is feasible and that suctioning clear amniotic fluid at birth may be associated with an increased need for supplemental oxygen in the delivery room. This study did include wiping the mouth with a dry cloth in both the pre and post implementation arms and following the onset of spontaneous breathing bulb suction was used to clear secretions from the sides of the mouth and the nose without reaching the back of the pharynx in the post implantation arm. Whilst the authors recommend wiping the face with a dry cloth in the first minute of life as this occurred in both arms of the study it is not possible for the paper to assess the efficacy of this manoeuvre.

The previous systematic review resulted in a good practice statement; *We suggest that suctioning of clear amniotic fluid from the nose and mouth should not be a routine step for newborn infants at birth (weak recommendation, very low–certainty evidence). Airway positioning and suctioning should be considered if airway obstruction is suspected (good practice statement).*

The conclusions from the included study support the conclusions of the 2020 ILCOR systematic review on suctioning of clear amniotic fluid at birth but would not change the certainty of evidence. The evidence from this study does not support a change to the current good practice statement or necessitate a new systematic or scoping review.

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Appendix: search strategy

Sources searched	**Search strategy**	**Search time frame**
EmBase	No. Query Results #16. #14 AND (2022:py OR 2023:py OR 2024:py) AND [medline]/lim #15. #14 AND (2022:py OR 2023:py OR 2024:py) #14. #11 NOT #12 #13. #11 NOT #12 #12. 'trachea'/exp #11. #8 NOT #9 AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [data papers]/lim OR [preprint]/lim) #10. #8 NOT #9 #9. ('animal model' OR 'animal' OR 'animal experiment' OR 'disease model') AND ([animal experiment]/lim OR [animal model]/lim) #8. #4 AND #7 #7. #5 OR #6 #6. suction*:ab,kw,ti OR onps:ab,kw,ti OR (mechanical*:ab,kw,ti AND adj4:ab,kw,ti AND aspirat*:ab,kw,ti) OR (airway*:ab,kw,ti AND adj4:ab,kw,ti AND (clear*:ab,kw,ti OR aspirat*:ab,kw,ti)) OR 'nasopharyngeal stimulation':ab,kw,ti OR 'oronasopharyngeal suction':ab,kw,ti OR 'oro-nasopharyngeal suction':ab,kw,ti #5.'suction' #4. #1 OR #2 #3. ((newborn* OR 'new born*' OR infant* OR neonat* OR 'neo nat*' OR newly) AND born* OR delivery) AND room* OR preterm OR postmatur* OR prematur* OR 'pre term' OR 'post matur*' OR prematuritas OR postnatal OR 'post natal.':ab,kw,ti #2. ((newborn* OR 'new born*' OR infant* OR neonat* OR 'neo nat*' OR newly) AND born* OR delivery) AND room* OR preterm OR postmatur* OR prematur* OR 'pre term' OR 'post matur*' OR prematuritas OR postnatal OR 'post natal.':ab,kw,ti #1. 'newborn'/exp OR 'newborn' OR 'infant' OR 'prematurity'	1st January 2020 to 23rd June 2024
Results identified	**Results screened full text**	**Results included**

175	3	1

2025 Evidence Update
NLS 5130 – Tracheal Suctioning for Meconium-stained Amniotic Fluid

Worksheet Author(s): Trevisanuto D, Fabres J, Kawakami MD, Lee H, Weiner G, Liley H, Strand M.
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest: None

PICOST:
Population: Non-vigorous infants born at ≥ 34 weeks' gestation delivered through meconium-stained amniotic fluid of any consistency (non-vigorous defined as heart rate <100 bpm, decreased muscle tone and/or depressed breathing at delivery).
Intervention: Performing immediate laryngoscopy with or without intubation and suctioning at the start of resuscitation.
Comparison: Performing immediate resuscitation without direct laryngoscopy at the start of resuscitation.
Outcomes:

- Survival to hospital discharge (Primary)
- Neurodevelopmental impairment (Secondary)
- Meconium aspiration syndrome (Secondary)
- Other respiratory outcomes - continuous positive airway pressure or mechanical ventilation, treatment of pulmonary hypertension with inhaled nitric oxide, oral medications or extracorporeal membrane oxygenation (Secondary)
- Delivery room interventions - cardiopulmonary resuscitation/medications, intubation for positive pressure ventilation (Secondary)
- Length of hospitalization (Secondary)

Study Designs: Randomized controlled trials (RCT) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, and cohort studies) were included in the review. Unpublished studies (e.g., conference abstracts, trial protocols) and animal studies were excluded. All languages were included provided there was an English abstract;
Timeframe: All years were included and the literature search updated to November 7, 2019.

A priori subgroups to be examined: Consistency of meconium (thin vs thick), gestational age categories (late preterm (34-36+6/7 weeks), term (37-40+6/7 weeks), post-term (≥42 weeks)), presence or absence of fetal bradycardia, route of delivery (spontaneous vaginal, instrumented vaginal, caesarean section), direct laryngoscopy with vs without suctioning.

Year of last full review: November 7, 2019. {Trevisanuto 2020 117}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Trevisanuto 2020 117}
For the critical outcome of **survival to discharge**, we have identified **low certainty evidence** (downgraded for inconsistency and imprecision) from **3 RCTs** {Chettri 2015 1208, Nangia 2016 79, Singh 2019 165} enrolling 449 non-vigorous newborns delivered through meconium-stained amniotic fluid (MSAF) which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 0.99; 95% CI, 0.93-1.06; p=0.87; absolute risk reduction [ARR], -0.9%; 95% CI -6.4% to 5.5%, or 9 fewer patients/1000 survived to discharge with the intervention [95% CI, 64 fewer patients/1000 to 55 more patients/1000 survived to discharge with the intervention]).

For the critical outcome of **cognitive neurodevelopmental impairment**, we have identified **very low certainty evidence** (downgraded for risk of bias, indirectness and imprecision) from **1 RCT** {Chettri 2015 1208} enrolling 86 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 0.75; 95% CI, 0.37-1.50; p=0.41; absolute risk reduction [ARR], -8%; 95% CI -20% to 15.9%, or 80 fewer patients/1000 with mental neurodevelopmental impairment with the intervention [95% CI, 200 fewer patients/1000 to 159 more patients/1000 with mental neurodevelopmental impairment with the intervention]). The neurodevelopmental assessment from this one study was done at an early and non-standard time, hence the results are poorly predictive of longer-term outcomes. The effect of the intervention on neurodevelopmental impairment remains uncertain.

For the critical outcome of **motor neurodevelopmental impairment**, we have identified **very low certainty evidence** (downgraded for risk of bias, indirectness and imprecision) from **1 RCT** {Chettri 2015 1208} enrolling 86 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to

immediate resuscitation without laryngoscopy (RR, 0.91; 95% CI, 0.49-1.67; p=0.76; absolute risk reduction [ARR], -3.1%; 95% CI -17.4% to 22.8%, or 31 fewer patients/1000 with motor neurodevelopmental impairment with the intervention [95% CI, 174 fewer patients/1000 to 228 more patients/1000 with motor neurodevelopmental impairment with the intervention]). The neurodevelopmental assessment from this one study was done at an early and non-standard time, hence the results are poorly predictive of longer-term outcomes. The effect of the intervention on neurodevelopmental impairment remains uncertain.

For the critical outcome of **hypoxic ischemic encephalopathy**, we have identified **very low certainty evidence** (downgraded for risk of bias, inconsistency and imprecision) from **2 RCTs** {Nangia 2016 79, Singh 2019 165} enrolling 327 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 0.86; 95% CI, 0.62-1.18; p=0.34; absolute risk reduction [ARR], -4.8%; 95% CI -13.1% to 6.2%, or 48 fewer patients/1000 with hypoxic ischemic encephalopathy with the intervention [95% CI, 131 fewer patients/1000 to 62 more patients/1000 with hypoxic ischemic encephalopathy with the intervention]).

For the critical outcome of **meconium aspiration syndrome (MAS),** we have identified **very low certainty evidence** (downgraded for risk of bias, inconsistency and imprecision) from **3 RCTs** {Chettri 2015 1208, Nangia 2016 79, Singh 2019 165} enrolling 449 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 0.93; 95% CI, 0.73-1.19; p=0.57; absolute risk reduction [ARR], -2.7%; 95% CI -10.3% to 4.5%, or 27 fewer patients/1000 with MAS with the intervention [95% CI, 103 fewer patients/1000 to 45 more patients/1000 with MAS with the intervention]).

For the important outcome of **use of mechanical ventilation,** we have identified **low certainty evidence** (downgraded for risk of bias and imprecision) from **3 RCTs** {Chettri 2015 1208, Nangia 2016 79, Singh 2019 165} enrolling 449 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 1.00; 95% CI, 0.66-1.53; p=0.99; absolute risk reduction [ARR], 0%; 95% CI -5.4% to 8.4%, or 0 fewer patients/1000 received mechanical ventilation with the intervention [95% CI, 54 fewer patients/1000 to 84 more patients/1000 received mechanical ventilation with the intervention]).

For the important outcome of **use of respiratory support** excluding mechanical ventilation, we have identified low certainty evidence (downgraded for risk of bias and imprecision) from **2 RCTs** {Nangia 2016 79, Singh 2019 165} enrolling 327 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 0.99; 95% CI, 0.81-1.20; p=0.88); absolute risk reduction [ARR], -0.4%; 95% CI -7.3% to 7.6%, or 4 fewer patients/1000 received respiratory support excluding mechanical ventilation with the intervention [95% CI, 73 fewer patients/1000 to 76 more patients/1000 received respiratory support excluding mechanical ventilation with the intervention]).

For the important outcome of **endotracheal intubation for PPV** in the delivery room, we have identified **low certainty evidence** (downgraded for risk of bias and imprecision) from **2 RCTs** {Chettri 2015 1208, Nangia 2016 79} enrolling 297 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 1.15; 95% CI, 0.83-1.59; p=0.40; absolute risk reduction [ARR], 4.1%; 95% CI -4.7% to 16.2%, or 41 more patients/1000 received endotracheal intubation in the delivery room with the intervention [95% CI, 47 fewer patients/1000 to 162 more patients/1000 received endotracheal intubation in the delivery room with the intervention]).

For the important outcome of **chest compressions in the delivery room**, we have identified **very low certainty evidence** (downgraded for risk of bias and imprecision) from **3 RCTs** {Chettri 2015 1208, Nangia 2016 79, Singh 2019 165} enrolling 449 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 1.13; 95% CI, 0.40-3.20; p=0.82; absolute risk reduction [ARR], 0.4%; 95% CI -1.9% to 6.8%, or 4 more patients/1000 received chest compressions in delivery room with the intervention [95% CI, 19 fewer patients/1000 to 68 more patients/1000 received chest compressions in the delivery room with the intervention]).

For the important outcome of **use of epinephrine in the delivery room**, we have identified **very low certainty evidence** (downgraded for risk of bias and imprecision) from **3 RCTs** {Chettri 2015 1208, Nangia 2016 79, Singh 2019 165} enrolling 449 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without

tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR,1.62; 95% CI, 0.37-7.05; p=0.52; absolute risk reduction [ARR], 0.8%; 95% CI -0.8% to 8%, or 8 more patients/1000 received epinephrine in delivery room with the intervention [95% CI, 8 fewer patients/1000 to 80 more patients/1000 received epinephrine in the delivery room with the intervention]).

For the important outcome of treatment of **pulmonary hypertension** (iNO, medications, ECMO), we have identified **very low certainty evidence** (downgraded for risk of bias, indirectness and imprecision) from **1 observational study** {Chiruvolu 2018 } 231 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (RR, 0.52; 95% CI 0.15-1.79; p=0.30; absolute risk reduction [ARR], -2.9%; 95% CI -5% to 4.7%, or 29 fewer patients/1000 received treatment of pulmonary hypertension (iNO, medications, ECMO) with the intervention [95% CI, 50 fewer patients/1000 to 47 more patients/1000 received treatment of pulmonary hypertension (iNO, medications, ECMO) with the intervention]).

For the important outcome of **length of hospitalization**, we have identified **very low certainty evidence** (downgraded for risk of bias, inconsistency and imprecision) from **2 RCTs** {Nangia 2016 79, Singh 2019 165} enrolling 327 non-vigorous newborns delivered through MSAF which showed **no benefit** for the use of immediate laryngoscopy with or without tracheal suctioning when compared to immediate resuscitation without laryngoscopy (mean difference, 0.5 days lower; 95% CI, 1.76 days lower to 0.75 days higher; p=0.43).

Treatment Recommendations
For non-vigorous newborns delivered through meconium-stained amniotic fluid, we suggest against routine immediate direct laryngoscopy after delivery with or without tracheal suctioning when compared to immediate resuscitation without direct laryngoscopy. Meconium-stained amniotic fluid remains a significant risk factor for receiving advanced resuscitation in the delivery room. A provider may perform intubation and tracheal suctioning to relieve airway obstruction.

Current Search Strategy: see appendix
Database searched: Medline
Time Frame – Systematic review: 1966 to Nov 7, 2019.
Time Frame – Evidence update: Nov 2018-June 2024
Date Search Completed: June 23, 2024
Search Results:
Identified: 70
Full-text screening: 12
Included: 10

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Phattraprayoon 2021 {Phattraprayoon 2021 31}	Systematic review and metanalysis of RCTs	To review and analyze the outcomes of no tracheal suctioning versus tracheal suctioning in non-vigorous neonates delivered through meconium-stained amniotic fluid.	4 studies	**Primary outcome:** *MAS:* 100/289 (35%) vs. 101/292 (35%); RR, 95% CI: 0.98, 0.71-1.35. **Secondary outcomes:** *Mortality:* RR, 95% CI: 0.83, 0.46-1.49. *Hypoxic ischemic encephalopathy (HIE):* RR, 95% CI: 1.10, 0.85-1.43.	The results confirm that there is no difference in clinical outcomes, including MAS, between ETS versus non- ETS in non- vigorous neonates delivered through

				Pneumothorax: RR, 95% CI: 0.82, 0.25-2.66. *Persistent pulmonary hypertension of the newborn (PPHN):* RR, 95% CI: 0.79, 0.36-1.73. *Secondary pneumonia:* RR, 95% CI: 1.14, 0.70-1.88. *Positive pressure ventilation via tracheal tube:* RR, 95% CI: 0.89 (0.71-1.12) *Chest compression in the delivery room (DR):* RR, 95% CI: 1.11 (0.48-2.55) *Use of epinephrine in the DR:* RR, 95% CI: 0.85 (0.24-2.97) *Need for respiratory support (including mechanical ventilation):* RR, 95% CI: 1.02, 0.92-1.13. *Need for mechanical ventilation:* RR, 95% CI: 0.98, 0.67-1.43. Length of hospital stay (days): RR, 95% CI: 0,19, -0.59 to 0.97.	meconium-stained amniotic fluid. This review and meta-analysis included the same 4 RCTs that were included in the previous ILCOR TF meta-analysis {Wyckoff 2020 S185} and confirms the same results.
Ramaswamy 2023 {Ramaswamy 2023 161}	Pragmatic Systematic Review and Meta-Analysis of Evidence outside Randomized Trials.	Observational studies comparing the effect of implementing immediate resuscitation without routine tracheal suctioning versus routine suctioning in neonates born through MSAF.	13 studies.	**Primary outcome:** *Mortality or requirement of ECMO:* relative risk (RR), 95% CI: 0.74, 0.47–1.17. **Secondary outcomes:** *Mortality:* RR, 95% CI: 0.68, 0.42–1.11. *MAS:* RR, 95% CI: 0.60, 0.38–0.94. *Invasive positive pressure ventilation in DR:* RR, 95% CI: 3.28, 0.77-13.83 *Chest compression and drugs:* RR, 95% CI: 0.77, 0.39-1.49 *Risk of hospital admission for respiratory symptoms:* RR, 95% CI: 0.54, 0.34-0.88./ 0.69, 0.53-0.90 *Invasive mechanical ventilation:* RR, 95% CI: 0.62, 0.40-0.95	This is a review and meta-analysis of observational studies assessing pre-post implementation of the AHA guidelines. Most of the studies predominantly had a serious risk of bias for the domains of confounding and classification of interventions. Due to the very low CoE for the outcomes evaluated, no definitive

				Surfactant treatment: RR, 95% CI: 0.28, 0.10-0.75 *Air leak:* RR, 95% CI: 0.41, 0.20-0.84 *Low-flow oxygen therapy:* RR, 95% CI: 0.63, 0.43-0.93. *PPHN:* RR, 95% CI: 0.73, 0.44-1.19 *HIE:* RR, 95% CI: 1.22, 0.92-1.61	conclusions can be drawn.
Abbreviations: RCT; randomized controlled trial, MAS; meconium aspiration syndrome, HIE; hypoxic ischemic encephalopathy, RR; relative risk, CI; confidence intervals, ECMO; extracorporeal membrane oxygenation, CoE; certainty of evidence, NRP; Neonatal Resuscitation Program, MSAF; meconium-stained amniotic fluid, NICU; neonatal intensive care unit, NS; not significant, CPAP; continuous positive airway pressure, PPHN; persistent pulmonary hypertension of the newborn, HIE; hypoxic ischemic encephalopathy					

RCT:
No eligible RCTs were found for inclusion.

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results**	**Summary/Conclusion Comment(s)**
Aldhafeeri 2019 {Aldhafeeri 2019 87}	**Study Type:** Single center retrospective cohort study; n. 420.	**Inclusion Criteria:** Term (≥37 weeks) infants born through MSAF before (n. 261; Jan-Dec 2016) and after (n. 159; Jan-Dec 2017) the implementation of the new NRP guidelines	**1° endpoint:** *NICU admission:* 10 (3.8%) vs. 5 (3.1%); p=0.79. *MAS:* 4 (1.5%) vs 1 (0.6%); p=0.65. *In-hospital mortality:* 1 (0.4%) vs 0 (0%); p=1.00. *Non-invasive ventilation:* 8 (3.0%) vs 4 (2.5%); p=0.64. **HIE:** 3 (1.1%) vs. 2 (1.3%); p=1.00.	No differences in primary and secondary outcomes. Only 22/420 infants (17 pre and 5 post NRP guideline implementation) were non-vigorous at birth. Only 6/261 (2.3%) and 1/159 (0.6%) infants were intubated at birth in the pre and post NRP guidelines implementation periods. Single center study in high income country (Saudi-Arabia). Concerns for selection bias, and information bias due to the retrospective nature of the study.
Kalra 2022 {Kalra 2022 769}	**Study Type:** Single-center retrospective study. n.	**Inclusion Criteria:** All ≥36-week gestation neonates born through MSAF before (tracheal	**1° endpoint:** *MAS:* 6/39 (15.4%) vs. 16/30 (53.3%); p<0.05.	Non-vigorous infants born through MSAF without routine-tracheal suctioning had

	562 (of these, 69 were non-vigorous at birth).	suctioning group, n=280 (39 non-vigorous); Sept 2013 to Dec 2014) and after NRP guidelines implementation (no tracheal suctioning group, n=282 (30 non-vigorous); Jan 2017 to Dec 2018).	**Secondary outcomes:** *DR intubation:* 30/39 (76.9%) vs. 1/30 (3.3%); p<0.05. *NICU admission:* 19/39 (48.7%) vs. 21/30 (70.0%); p=NS. *NICU admission due to respiratory distress or requiring respiratory support:* 7/39 (17.9%) vs. 18/30 (60.0%); p<0.05. *Need for respiratory support:* 6/39 (15.4%) vs. 18/30 (60.0%); p<0.05. *Intubated ventilation:* 3/39 (7.7%) vs. 1/30 (3.33%); p=NS *PPHN: 0* (0.0%) vs. 0 (0.0%). *Pneumothorax: 1*/39 (2.5%) vs. 2/30 (6.7%); p=NS *HIE:* 3/39 (7.7%) vs. 3/30 (10.0%); p=NS *Duration of hospital stay:* 9±9.4 vs. 6.2±6.1 days; p=NS. *Mortality:* 0 (0.0%) vs. 0 (0.0%).	a higher incidence of NICU admission for MAS and respiratory distress compared to the routine-suction era. Single center study in high income country (USA). Concerns for selection bias, and information bias due to the retrospective nature of the study.
Kumar 2024 {Kumar 2024 1163}	**Study Type:** Single center prospective cohort study with historical controls; n. 547.	**Inclusion Criteria:** Non vigorous term neonates (> 37 weeks' gestation) born through MSAF born before (tracheal suctioning group, n=271; July 2015 to June 2016) and after NRP guidelines implementation (no tracheal suctioning group, n=276; July 2018 to June 2019).	**1° endpoint:** *MAS:* 68/271 (25.1%) vs. 75/276 (27.2%); p=0.58. *Secondary outcomes:* *NICU admission:* 180/271 (66.4%) vs. 201/276 (72.8%); p=0.11. *HIE:* 74/271 (27.3%) vs. 53/276 (19.2%) p=0.02. *PPHN:* 17/271 (6.3%) vs. 19/276 (6.9%); p=0.78. *Air leak syndromes:* 7/271 (2.6%) vs. 17/276 (6.2%); p=0.04. *Need for invasive ventilation:* 27/271 (10%) vs. 39/276 (14.1%) p=0.14.	Not performing tracheal suction in NV MSAF infants is not associated with increase in the incidence of MAS. Initiating immediate resuscitation without tracheal suctioning was associated with decreased risk of HIE but increased receipt of any respiratory support and air leak. Study conducted in a low-middle income country (India). Single center study. Concerns for selection bias, and information

			Need for any respiratory support: 123/271 (45.4%) vs. 161/276 (58.3%); p<0.01. *Mortality before discharge:* 23/271 (8.5%) vs. 34/276 (12.3%); p=0.15.	bias due to the retrospective nature of the study.
Li 2022 {Li 2022 65}	**Study Type:** Single center retrospective cohort study; n. 151.	**Inclusion Criteria:** Non vigorous neonates born through MSAF. tracheal suctioning group (intervention), n=71; (July 1, 2018 to June 30, 2019) No tracheal suctioning group (control), n=80; Jul 1, 2017 to Jun 30, 2018).	**1° endpoint:** *Mortality:* 1% vs. 0%; p=0.37. *MAS: 7%* vs. 11%; p=0.28. **Secondary outcomes:** *PPHN:* 4% vs. 5%; p=NS. *Pneumothorax:* 1% vs. 3%; p=NS. *Need for oxygen therapy:* 33% vs. 16%; p<0.05. *Need for noninvasive respiratory support:* 25% vs 41%, P<0.05. *Need for MV:* 10% vs. 23% p<0.05. *Duration of noninvasive ventilation:* 58±24 hours vs. 83±41 hours; p<0.05. *Length of hospital stay:* 6 (4-8) days vs 7 (5- 10) days; p<0.05.	Only abstract available in English. Study conducted in a high-middle income country (China). No differences in MAS, mortality rate, or the incidence rate of serious complications. Tracheal intubation for meconium suction immediately after birth may shorten the duration of respiratory support for mild respiratory problems. No tracheal suctioning group refers at Epoch 1, while tracheal suctioning group refers to Epoch 2. Single center study. Concerns for selection bias, and information bias due to the retrospective nature of the study.
Myers 2020 {Myers 2020 295}	**Study Type:** Large, single-center retrospective study with data prospectively registered. n. 572 including depressed and non-depressed infants with MSAF.	**Inclusion Criteria:** All >37-week gestation neonates born through MSAF before (tracheal suctioning group, n=364; Jan 1, 2014 to Dec 31, 2015) and after NRP guidelines implementation (no tracheal suctioning group, n=208; Jan 1, 2016 to Jun 30, 2017).	**1° endpoint:** *Mortality:* 0.2% vs. 0.2%; p= 0.79). **Secondary outcomes***:* *Intubation in DR:* 69/364 **(**19%) vs. 6/208 (3%); p<0.001. *NICU admission:* 47/364 (13%) vs. 27/208 (13%); p=0.98**.** *Respiratory support on NICU admission:* 20/47	NRP guidelines implementation was associated with an improvement in 1-minute Apgar scores and decreased the need for respiratory support after the first day of life. There was also a significant decrease in total intubations performed in the DR.

			(43%) vs. 11/27 (41%); p=0.88. *Respiratory support >24 h: 17*/47 (36%) vs. 3/27 (11%); p=0.02. *Duration of hospital stay:* 66.7 (+56) vs. 56.1 (+37) hours; p=0.16.	As data were retrospectively collected, it was not possible to ascertain if infants were vigorous or nonvigorous at time of delivery. For this reason, we cannot differentiate between depressed and non-depressed patient subgroups. No data on MAS patients and/or MAS incidence was reported. Single center study in a high-income country with large white population. Concerns for selection bias, and information bias due to the retrospective nature of the study.
Oommem 2021 {Oommen 2021 324}	**Study Type:** Single- center cohort study (prospective study with historical controls). n. 1138 (of these, 229 were non-vigorous at birth: 72 (16.1%) and 157 (22.7%) in historical cohort and prospective cohort, respectively).	**Inclusion Criteria:** Neonates of ≥34 weeks' gestational age who were born through MSAF born before ((tracheal suctioning group, n=446) Aug 1, 2015 and July 31, 2016) and after NRP guidelines implementation (no tracheal suctioning group, n=692; Oct 1, 2016 and Sept 30, 2017).	**1° endpoint:** *MAS:* 25/446 (5.6%) vs. 30/692 (4.3%); p=0.33. **Secondary outcomes:** *NICU admissions of non- vigorous neonates born through MSAF:* 40/72 (55.6%) vs. 30/157 (19.1%); p<0.0001. *Mechanical ventilation among infants with MAS:* 6/25 (24%) vs. 5/30 (16.7%); p=0.50. *Requirement of high-frequency oscillation ventilation among infants with MAS:* 2/25 (8%) vs. 0/30 (0.0%); p=0.11. *Surfactant treatment among infants with MAS:* 1/25 (4%) vs. 2/30 (6.7%); p=0.67.	This study shows fewer NICU admissions of non- vigorous neonates born through MSAF since policy change. No differences in primary (MAS) and secondary outcomes. Single center study in a high income country. Concerns for selection bias, and information bias due to the retrospective nature of the study.

			Requirement of inhaled nitric oxide among infants with MAS: 5/25 (20%) vs. 5/30 (16.7%); p=0.75. *Severe respiratory morbidity among infants with MAS:* 14/25 (56%) vs. 12/30 (40%); p=0.24.	
Saint-Fleur 2023 {Saint-Fleur 2023 e0289945}	**Study Type:** Single-center retrospective cohort study, n. 223.	**Inclusion Criteria:** Non vigorous neonates (gestational age 35-42 weeks) born through MSAF born before (tracheal suctioning group, n=117; Jan 1, 2014 to Dec 30, 2015) and after NRP guidelines implementation (no tracheal suctioning group, n=106; Jan 1, 2017 to Dec 30, 2018).	**Outcomes:** *MAS:* 27/117 (23.1%) vs. 18/106 (17.0%); OR, 95%CI: 0.63, 0.31–1.28. *NICU respiratory admission:* 75/117 (64.1%) vs. 63/106 (59.4%); OR, 95%CI: 1.33, 0.69-2.57. *Need for supplemental oxygen:* 70/117 (59.8%) vs. 70/106 (66%); OR, 95%CI: 0.88, 0.51-1.54. *Need for ventilatory support:* 22/117 (18.8%) vs 19/106 (17.9%); OR, 95%CI: 1.21, 0.54-2.75. *Surfactant therapy:* 1/117 (0.9%) vs 5/106 (4.7%). *Length of stay (days):* 7.6±7.4 vs 7.7±7.6; OR, 95%CI: -0.01, -1.74-1.72). *Tracheal suctioning at birth:* 72/117 (61.5%) vs. 15/106 (14.2%); p<0.001. *Pneumothorax:* 15/117 (12.8%) vs. 15/106 (14.2%); OR, 95%CI: 0.56, 0.25-1.26.	Despite a marked reduction in rates of intubation and endotracheal suctioning *[Endotracheal suctioning at birth: Pre: 72/117 (61.5%) vs. Post: 15/106 (14.2%); p<0.001],* this study did not find difference in outcomes between pre-guideline implementation vs post-guideline implementation in non-vigorous MSAF infants, supporting the NRP guideline change. Single center study in a high income country. Concerns for selection bias, and information bias due to the retrospective nature of the study.
Sheikh 2024 {Sheikh 2024 1366}	**Study Type:** Single-center retrospective, prospective cohort study; n. 186.	**Inclusion Criteria:** Non vigorous term neonates (> 37 weeks' gestation) born through MSAF born before (tracheal suctioning group, n=95; Jan 1, 2013 to Dec 31, 2015) and after NRP guidelines	**1° endpoint:** *:* *Death:* 1/95 (1%) vs. 3/91 (3%); p=0.57. *MAS:* 10/95 (11%) vs. 16/91 (17%); p=0.41. **Secondary outcomes:** *Intubation for resuscitation in the DR:*	No difference in the incidence of MAS or death between the two periods since the 2015 guidelines. However, the incidence of NICU respiratory admissions increased with the need for intubation in the DR for resuscitation in the no ET-group.

		implementation (no tracheal suctioning group, n=91; Jan 1, 2017 to Dec 31, 2020).	11/95 (12%) vs. 26/91 (28%); p=0.04 *Chest compression for resuscitation in the DR:* 6/95 (6%) vs. 4/91 (3%); p=0.34 *Epinephrine use for resuscitation in the DR:* 3/95 (3%) vs. 1/91 (0%); p=0.10 *Respiratory NICU admission:* 35/95 (37%) vs. 56/91 (61%); p=0.02. *Respiratory support of NCPAP or more at NICU admission:* 19/95 (20%) vs. 37/91 (41%); p=0.08. **PPHN:** 5/95 (5%) vs. 11/91 (12%); p=0.15. *Hypoxic ischemic encephalopathy:* 5/95 (5%) vs. 9/91 (10%); p= 0.10 *Pneumothorax:* 0/95 (0%) vs. 1/91 (1%); p=0.99 *Surfactant therapy:* 0/95 (0%) vs. 5/91 (5%); p=0.69 *NICU stay >7 days:* 14 (15%) vs. 25 (27%); p=0.10. *Feeding problems:* 9 (9%) vs. 3 (3%); p=0.10.	Single center study in a high-income country. Concerns for selection bias, and information bias due to the retrospective nature of the study.
Abbreviations: RCT; randomized controlled trial, MAS; meconium aspiration syndrome, HIE; hypoxic ischemic encephalopathy, RR; relative risk, CI; confidence intervals, ECMO; extracorporeal membrane oxygenation, CoE; certainty of evidence, NRP; Neonatal Resuscitation Program, MSAF; meconium-stained amniotic fluid, NICU; neonatal intensive care unit, NS; not significant, CPAP; continuous positive airway pressure, NPCAP; nasal prong CPAP				

Reviewer Comments:

This update of the evidence found 1 meta-analysis of previously reviewed RCTs, 1 meta-analysis of observational studies and 8 newer observational studies. All these studies are single-center, and retrospective or prospective with historical controls. The meta-analysis {Phattraprayoon 2021 31} (published more recently but which included the same RCTs that we had assessed previously) supports the recommendations previously made for this subject, that for non-vigorous newborns delivered through meconium-stained amniotic fluid, we suggest against routine immediate direct laryngoscopy after delivery with or without tracheal suctioning when compared to immediate resuscitation without direct laryngoscopy. The risk of bias in the newer observational studies suggests that together, they are unlikely to reach a level of certainty of evidence to influence the recommendation, or to warrant a new systematic or scoping review at this time.

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Appendix: search strategy

Sources searched	Search strategy	Search time frame

Medline (EmBase platform)	((Meconium OR Meconium Aspiration Syndrome OR meconium*.tw,kf.) AND (Laryngoscopy OR Laryngoscopes OR Laryndgoscop*.tw,kf. OR exp Intubation OR Intubation*.tw,kf. OR Suction OR Suction*.tw,kf. OR Trachea OR Trachea.tw,kf. OR Tracheal.tw,kf. OR Intratracheal.tw,kf. OR endotracheal.tw,kf.)) limit to not (animals/ not humans/ comment/ editorial/ letter).	Nov 2018-June 2024
Results identified	**Results screened full text**	**Results included**
70	12	10

2025 Evidence Update
NLS 5140 – Tactile Stimulation for Resuscitation Immediately After Birth

Worksheet Author(s): Finan E, Guinsburg R, de Almeida, MF, Isayama T, Nimbalkar S, Wyckoff MH, Weiner G, Liley HG.
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 24 October 2024
Conflicts of Interest: None

PICOST:
Population: Term or preterm newborn infants immediately after birth with absent, intermittent, or shallow respirations
Intervention: Any tactile stimulation performed within 60 seconds after birth and defined as 1 or more of the following: rubbing the chest/sternum, rubbing the back, rubbing the soles of the feet, flicking the soles of the feet, or a combination of these methods. This intervention should be done in addition to routine handling with measures to maintain temperature.
Comparison: Routine handling with measures to maintain temperature, defined as care taken soon after birth, including positioning, drying, and additional thermal care
Outcomes:

- Critical: Survival as reported by authors; neurodevelopmental outcomes
- Important: Establishment of spontaneous breathing without PPV (yes or no); time to the first spontaneous breath or crying from birth; time to a heart rate of ≥100 bpm from birth; intraventricular hemorrhage (only in preterm infants with <34 weeks' gestation); oxygen or respiratory support at admission to a neonatal special care unit or NICU; admission to a neonatal special care unit or NICU for those not admitted by protocol on the basis of gestational age or birth weight

Potential subgroups were defined a priori: gestational age (<34, 34–36 6/7, and ≥37 weeks' gestation), cord management (early cord clamping, delayed cord clamping, and cord milking), clinical settings (high and low resource), and method of stimulation (type, number, duration of stimuli).
Outcomes ratings using the GRADE classifications of critical or important were decided according to a consensus for international neonatal resuscitation guidelines. {Strand 2020 328} Outcomes were converted into main outcomes and additional outcomes for submission to PROSPERO (CRD 42021227768)

Study design:
RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, and cohort studies) were *eligible for inclusion. Unpublished studies (conference abstracts, trial protocols) and animal studies were excluded.*
Time frame:
All years and all languages were included if there was an English abstract. The literature search was first done on 6 December 2020, with the final update on 17 September 2021.

Year of last full review: 2022 {Guinsburg 2022 e2021055067, Wyckoff 2022 208}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Guinsburg 2022 e2021055067, Wyckoff 2022 208}

The previous systematic review identified two observational studies. {Baik-Schneditz 2018 952, Dekker 2017 61} The study by Baik-Schneditz was not eligible for data analysis due to critical risk of bias (mainly by confounding by indication). Therefore, only the study by Dekker et al with 245 preterm newborn infants was analyzed.

For the important outcome of tracheal intubation in delivery room, evidence of very low certainty (downgraded for risk of bias, indirectness, and imprecision, and upgraded by the strong association) from 1 observational trial {Dekker 2017 61} involving 245 preterm newborns showed possible benefit from receiving tactile stimulation in addition to routine handling compared to routine handling only (including measures to maintain temperature) (RR 0.41, 95%CI 0.20-0.85; ARD 105/1000 fewer newborns with tracheal intubation when receiving tactile stimulation, 95%CI 142/1000 fewer to 27/1000 fewer).

For the important primary outcomes of establishment of spontaneous breathing without PPV, time to the first spontaneous breath or crying, and time to heart rate ≥100 bpm, no data were reported in the included study.

For the critical secondary outcomes of survival, neurodevelopmental outcomes, and intraventricular hemorrhage in preterm infants <34 weeks, no data were reported in the included study.

For the important secondary outcomes of admission to a neonatal special unit or intensive care unit and oxygen and/or respiratory support at admission, no data were reported in the included study.

Subgroup Analyses:

No data were reported to perform subgroup analyses by gestational age (<34 weeks, 34-36 6/7 weeks, and ≥37 weeks), cord management (early and delayed/cord milking), settings (high and low resourced), and method of stimulation (type, number and/or duration of stimuli)

2022 Treatment Recommendation
We suggest it is reasonable to apply tactile stimulation in addition to routine handling with measures to maintain temperature in newborn infants with absent, intermittent, or shallow respirations during resuscitation immediately after birth (weak recommendation, with very low certainty due to risk of bias, indirectness, and imprecision). Tactile stimulation should not delay the initiation of positive pressure ventilation for newborns who continue to have absent, intermittent, or shallow respirations after birth.

Search Strategy for the original systematic review – See Appendix (same search strategy for 2024 evidence update)

Database searched: Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). The International Clinical Trials Registry Platform and the US Clinical Trials Registry were also searched.
Time Frame – systematic review: 1946 to 17 September 2021.
Time Frame – Evidence Update: 2021 to 30 June 2024
Date Search Completed: June 30, 2024
Search Results:
Identified: 361 references screened (2021-2024)
Full text articles assessed:9
Included: 4 observational studies included in the evidence update. {Gaertner 2022 508, Kaufmann 2022 1041898, Kc 2021 e001207, Mayer 2022 864431} Searching NLS monthly updated literature, we found 1 systematic review. {Kaufmann 616}

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Author; Year	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Kaufmann 2024 {Kaufmann 2024 616}	Narrative review of physiological mechanisms of respiratory drive after birth and a SR to evaluate the available evidence on TS in the delivery room	Patients: PT and term NB Intervention: TS in the delivery room. Outcome: effects of TS on spontaneous breathing, HR and SpO_2 Types of study: RCTs and observational, retrospective studies	6	TS done in 43-90% NB Median time to start TS: 1-134s Median duration of TS: 15 to 86s Number of episodes of TS/NB: 0-8 4 studies reported on HR and showed no effect of TS on HR 3 studies reported on SpO_2:	The authors conclude that "TS varies widely between, as well as within different centers and no consensus exists which stimulation method is most effective. Some evidence shows that repetitive stimulation within the first minutes of resuscitation improves oxygenation.

				- {Gaertner 2022 508} did not detect effects of TS on SpO_2 - {Baik-Schneditz 2018 952} showed a median SpO_2 increase of 9% 30s after TS in PT but not in term NB - {Dekker 2017 61} showed SpO2 higher in NB who got repetitive TS in the first 4 minutes than in those who received standard TS	Further studies are warranted." All studies included in this SR were also evaluated and included in the SR done by the ILCOR group {Guinsburg 2022 e2021055067} Therefore, this SR does not add information to the current treatment recommendation.
Abbreviations: HR: heart rate; NB: newborn infants; PT: preterm infants; RCT: randomized controlled trial; SpO2: oxygen saturations; s: seconds; SR: systematic review; TS: tactile stimulation.					

Nonrandomized Trials, Observational Studies

Author; Year; Country	**Study Type/Design; Study Size (N)**	**Patient Population <u>Inclusion Criteria:</u>**	**Primary Endpoint and Results <u>1° endpoint:</u>**	**Summary/Conclusion Comment(s)**
Gaertner 2022 Australia {Gaertner 2022 508}	Single center observational study 40 NB and 57 stimulations	NB receiving TS during PPV GA ≥34 weeks	Median paired change in spontaneous breaths from before to during stimulation: 1 (IQR 0-3; p_{adj} <0.001) Paired VTe showed a median increase of 0.5 mL/kg (IQR −0.5 to 1.7; p_{adj}=0.028) Mask leak and percentage of obstructed inflations did not change with TS. Increased duration of stimulation (p<0.001) and surface area of applied stimulus (p=0.026) were associated with a larger increase in spontaneous breaths in response to TS	The authors conclude that "TS during PPV was associated with an increase in the number of spontaneous breaths compared with immediately before stimulation without a change in mask leak and obstruction." Note: The study did not compare NB that received or did not receive TS.

Kaufmann 2022 Germany {Kaufmann 2022 1041898}	Single center observational study 47 NB	GA <32 weeks or BW <1500g All NB received TS at least once during resuscitation. NB on non-invasive respiratory support divided in 3 groups: - late respiratory stability >320s - early respiratory stability) ≤320s - immediate respiratory stability without PPV.	51% of infants received TS within the 1st minute Rubbing the feet = main form of stimulation (75%) TS lasted for a median of 278s (IQR: 193; 447) The overall duration of TS was: - late respiratory stability: 445s (IQR 253; 643) - early respiratory stability: 260s (IQR 183; 357) - immediate respiratory stability: 184s (IQR 52; 277) Those with late respiratory stability received TS to multiple areas more frequently but it was started later than those with early respiratory stability.	The authors conclude that: "TS is routinely used in preterm NB at need of respiratory support independent of GA and an easy-to use method to stimulate spontaneous breathing. Concomitant stimulation at different body parts might be beneficial." Note: The study did not compare NB that received or did not receive TS.
Kc 2021 Nepal {Kc 2021 e001207}	Multicenter observational study 2563 NB	≥34 weeks non-crying NB. All NB received TS and were divided into two groups: - 671 (26%) with cord intact (median time to cord clamping 58s; IQR 34-71) - 1892 (74%) with cord clamped (median time to cord clamping 25s; IQR 18-31).	Breathing started after TS in: - Intact cord group: 81% of 671 NB - Clamped cord group: 69% of 1892 NB (p<0.0001) Use of bag-and-mask ventilation: - Intact cord group: 18% of 671 NB - Clamped cord group: 32% of 1892 NB (p<0.0001)	The authors conclude that: "Stimulation of non-crying neonates with intact cord was associated with more spontaneous breathing than among infants who were stimulated with cord clamped. Intact cord stimulation may help establish spontaneous breathing in apneic neonates" Note: The study did not compare NB that received or did not receive TS.
Mayer 2022 South Africa {Mayer 2022 864431}	2 center observational study 496 NB	≥37 weeks (n=256) < 37 weeks (n=240) Observed interventions and time of implementation amongst infants at birth.	410 (82.7%) NB established spontaneous breathing shortly after delivery (median time 17s) Of the 86 babies who did not breathe, 25 (29%) responded to stimulation.	Most infants established breathing shortly after birth and of those who did not, 29% responded to TS. Note: The study did not compare NB that received or did not receive TS.

Abbreviations: BW: birthweight; GA: gestational age; IQR: interquartile range; NB: newborn infants; p_{adj}: adjusted p-value; PPV: positive pressure ventilation; s: seconds; TS: Tactile stimulation; VTe: expiratory tidal volume

Reviewer Comments:
None of the 4 observational studies that reported on outcomes of tactile stimulation in newly born infants addressed the PICOST, as outlined in table below. {Gaertner 2022 508, Kaufmann 2022 1041898, Kc 2021 e001207, Mayer 2022 864431} In addition, the review article published in 2022 {Kaufmann 2022 1041898} did not add new information to the systematic review published by ILCOR NLS Task Force. {Guinsburg 2022 e2021055067}

Table Characteristics of the four studies that reported any outcome of tactile stimulation in newly born infants, according to patients, intervention, control, and outcomes

	Patients	**Intervention**	**Control**	**Primary Outcome**			**Secondary Outcome**
	Newborn at birth with inadequate respiratory effort	TS in addition to routine handling with measures to maintain temperature	Routine handling with measures to maintain temperature	Spontaneous breaths without PPV	Time to 1st breath or crying	Time HR >100 bpm	O_2 and/or respiratory support at admission
{Gaertner 2022 508}	Yes	Newborns on PPV	No	No	No	No	Tracheal intubation
{Kaufmann 2022 1041898}	Yes (mixed)	Yes (before & at PPV)	No	No	No	No	No
{Kc 2021 e001207}	Yes (not crying)	Yes (before/after CC)	No	Yes	No	No	No
{Mayer 2022 864431}	Yes	Yes	No	Yes	No	No	No

Abbreviations: bpm: beats per minute; CC: cord clamping; HR: heart rate; PPV: positive pressure ventilation; TS: tactile stimulation

Therefore, the evidence retrieved from the new studies and the systematic review is not sufficient to change the current recommendation: "*We suggest it is reasonable to apply tactile stimulation in addition to routine handling with measures to maintain temperature in newborn infants with absent, intermittent, or shallow respirations during resuscitation immediately after birth (weak recommendation, with very low certainty due to risk of bias, indirectness, and imprecision). Tactile stimulation should not delay the initiation of positive pressure ventilation for newborns who continue to have absent, intermittent, or shallow respirations after birth."* {Wyckoff 2022 208}

The evidence retrieved from the new studies and the systematic review is not sufficient to elicit a new systematic or scoping review.

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Appendix – Search strategy

Sources searched	Search strategy	Search time frame
EmBase	#1 'newborn'/exp OR 'infant'/exp OR 'baby'/de OR 'delivery room'/de OR neonat*:ti,ab,kw OR newborn$:ti,ab,kw OR infant*:ti,ab,kw OR baby:ti,ab,kw OR babies:ti,ab,kw OR birth:ti,ab,kw OR 'new* born':ti,ab,kw OR 'delivery room':ti,ab,kw #2 'resuscitation'/exp OR 'assisted ventilation'/exp OR 'respiratory effort'/de OR 'oxygenation'/de OR 'blood oxygenation'/de OR 'oxygen saturation'/de OR 'heart rate'/exp OR resuscitation:ti,ab,kw OR ventilation:ti,ab,kw OR 'respiratory effort':ti,ab,kw OR oxygenation:ti,ab,kw OR 'oxygen saturation':ti,ab,kw OR 'heart rate':ti,ab,kw OR asphyxia:ti,ab,kw OR apnea:ti,ab,kw OR 'asphyxia'/de OR 'apnea'/de #3 #1 AND #2 #4 'newborn apnea'/de OR 'perinatal asphyxia'/de OR 'newborn apnea attack'/de OR (((newborn$ OR born OR birth OR perinatal OR neonatal) NEAR/3 (apnea OR asphyxia)):ti,ab) #5 #3 OR #4 #6 'tactile stimulation'/de OR 'sensory stimulation'/de OR 'touch'/de OR tactile:ti,ab,kw OR stimulat*:ti,ab,kw OR rub:ti,ab,kw OR rubbing:ti,ab,kw OR flick*:ti,ab,kw OR touch:ti,ab,kw #7 #5 AND #6 #8 'tactile stimulation':ti,ab OR rub:ti OR rubbing:ti OR flick*:ti OR touch:ti OR 'tactile stimulation'/de OR 'sensory stimulation'/de OR 'touch'/de #9 #1 AND #8 #10 #7 OR #9 #11 #10 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de) #12 #11 NOT ([animals]/lim NOT [humans]/lim) #13 'randomized controlled trial'/exp OR 'controlled study'/exp OR 'clinical study'/de OR 'case control study'/exp OR 'clinical trial'/exp OR 'intervention study'/de OR 'major clinical study'/de OR 'open study'/de OR 'prospective study'/de OR 'retrospective study'/de OR random*:ti,kw OR trial:ti,kw OR control*:ti,kw OR compar*:ti,kw OR observational:ti,kw OR prospective:ti,kw OR retrospective:ti,kw OR study:ti,kw OR clinical:ti,kw	2021 to 30 June 2024

	#14 #12 AND #13 AND [2020-2021]/py #15 'systematic review'/de OR 'systematic review':ti #16 #12 AND #15 NOT #14 AND [2020-2021]/py	
clinicaltrials.gov, Cochrane, ICTR, ANZCTR		
Results identified	**Results screened full text**	**Results included**
361	9	4

2025 Evidence Update
NLS 5200 – Heart Rate Monitoring in the Delivery Room –Diagnostic Characteristics

Worksheet Author(s): Kawakami MD, Kapadia V, Strand M
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of interest: Vishal Kapadia authored one of the manuscripts included in the SR. {Abbey 2022 1445} Mandira D Kawakami and Marya Strand: no conflicts of interest to declare

PICOST:
Population: Newborn infants in the delivery room
Intervention: Use of auscultation, palpation, pulse oximetry, Doppler device, digital stethoscope, photoplethysmography, video plethysmography, dry electrode technology or any other newer modalities
Comparison
1. Electrocardiography (ECG)
2. In between intervention comparison

Outcomes:
Accuracy of heart rate (HR) assessment (primary), time to first heart rate assessment from the device placement, time to first heart rate assessment from birth (secondary)
Study Design:
Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) were excluded. All languages were included provided there was an English abstract
Timeframe:. The search was updated to 16 Aug, 2023

For the purposes of this SysRev, electrocardiographic heart rate was considered the gold standard. Accuracy of heart rate assessment by other methods was examined with the following:
- Pooled Bland-Altman analysis {Bland 1995 1085, Bland 1999 135, Bland 1986 307, Giavarina 2015 141, Montenij 2016 750} to estimate bias, a measure of accuracy, and the limits of agreement, a measure of precision. For the purposes of the review, agreement within ±10 bpm (beats per minute) was considered acceptable.
- Pooled sensitivity and specificity analysis to identify electrocardiographic heart rate <100 and < 60 bpm

Year of last full review: 2023 {Berg 2023 e187, Kapadia 2024 100668}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST {Berg 2023 e187, Kapadia 2024 100668}
Rationale for Review: Heart rate is considered one of the most important indicators of an infant's condition at birth. Limitations of assessing heart rate by palpation of pulses or by pulse oximetry were identified in a 2015 ILCOR SysRev, which found that electrocardiography was faster and more accurate. {Perlman 2015 S204} A 2020 EvUp found studies using newer devices and methods. {Wyckoff 2020 S185} A 2022 ILCOR SysRev found little evidence to suggest improvement in critical and important clinical outcomes with the use of electrocardiography compared with pulse oximetry. {Kapadia 2024 100665, Wyckoff 2022 208} However, heart rate influences critical decisions about resuscitation at birth, so a SysRev was conducted to assess the diagnostic characteristics of various devices and methods for measuring heart rate in the first minutes after birth.

Consensus on Science

The systematic review identified 3 RCTs {Abbey 2022 1445, Murphy 2019 F547, Murphy 2021 438} including 187 infants and 11 cohort studies {Bjorland 2020 175, Bobillo-Perez 2021 783, Bush 2021 550, Dawson 2013 955, Henry 2021 72, Iglesias 2018 F233, Iglesias 2016 271, Kamlin 2008 756, Katheria 2012 e1177, Mizumoto 2012 205, van Vonderen 2015 49} including 490 infants.

A. Time from first heart rate assessment from the device placement:

A1: For the important outcome of **time for first heart rate assessment from the device placement**, **PO was slower in presenting a HR signal than ECG** (pooled difference HR from PO was 57 seconds (s) slower, 95% CI 13 s slower to 101 s slower, p<0.05), **low**

certainty evidence downgraded for risk of bias and imprecision from **6 observational studies** including 323 infants. {Bjorland 2020 175, Bush 2021 550, Iglesias 2018 F233, Iglesias 2016 271, Katheria 2012 e1177, van Vonderen 2015 49}

A2: For the important outcome of **time for first heart rate assessment from the device placement**, there was **no significant difference between PO and ECG** (pooled difference HR from PO 12 seconds slower, 95% CI 13s faster to 38s slower, p>0.05), **very low certainty evidence** downgraded for risk of bias, inconsistency and imprecision from 2 **RCTs** including 136 infants. {Murphy 2019 F547, Murphy 2021 438}

B. Time for first heart rate assessment from birth

B1: For the important outcome of **time for first heart rate assessment from birth, PO was slower than ECG** (pooled difference HR from PO 52 seconds slower, 95% CI 9 s slower to 94 s slower, p<0.05), **low certainty evidence** downgraded for risk of bias and imprecision from **6 observational studies** including 334 infants. {Bjorland 2020 175, Bobillo-Perez 2021 783, Dawson 2013 955, Kamlin 2006 319, Mizumoto 2012 205, van Vonderen 2015 49}

B2: For the important outcome of **time for first heart rate assessment from birth**, there was **no significant difference between PO and ECG** (pooled difference HR from PO 6 seconds slower, 95% CI 10 s faster to 23 s slower, p>0.05), **low certainty evidence** downgraded for risk of bias and imprecision from **2 RCTs** including 87 infants. {Abbey 2022 1445, Murphy 2021 438}

C. Accuracy of heart rate assessment: For this comparison, the index test was PO and the reference standard was ECG.

C1: One RCT {Abbey 2022 1445} and 4 cohort studies {Dawson 2013 955, Henry 2021 72, Kamlin 2008 756, van Vonderen 2015 49} assessed whether HR measured by PO (HR_{PO}) agreed with HR measured by ECG (HR_{ECG}) by reporting average difference (mean bias) and level of agreement (LoA). This was graphically depicted by Bland-Altman (B-A) plots in these studies. We meta-analyzed these data and calculated pooled average difference (summary mean bias), LoA and the 95% confidence limit around LoA. This analysis showed that PO may be accurate but imprecise for HR estimation at birth (summary mean bias ($HR_{PO} – HR_{ECG}$) -1.2 bpm; LoA: -17.9 to 15.5, 95% CI -32.8, 30.4), **very low certainty evidence** downgraded for risk of bias, inconsistency and imprecision from 218 infants and 28,211 observations. Thus, the average difference in the HR measured by PO (index test) and ECG (reference standard) in this population was small but 95% CI of limits of agreement was very wide, indicating that at times, PO may underestimate or overestimate the HR substantially.

C2: For the identification of neonatal bradycardia (HR_{ECG} < 100 bpm) at birth, the pooled sensitivity of PO was 0.83 (95 % CI 0.76,0.88) and a pooled specificity was 0.97 (95 % CI 0.93,0.94), **very low certainty evidence** downgraded for risk of bias, inconsistency and imprecision from one RCT {Abbey 2022 1445} and 2 cohort studies {Iglesias 2018 F233, Kamlin 2008 756} enrolling 145 infants.

C3: For the identification of severe neonatal bradycardia (HR_{ECG} < 60 BPM) at birth, we could not calculate sensitivity and specificity as no studies reported these data.

Subgroup Analyses:

Receipt of Resuscitation: No studies reported data sufficient to perform this subgroup analysis. One study noted that there were slightly larger differences between HR obtained from the PO and those from ECG when HR_{ECG} <100 bpm. {Dawson 2013 955}

Time epoch for heart rate assessment (≤60 seconds, 61 seconds – 120 seconds, ≥ 121 seconds): No studies reported data sufficient to perform this subgroup analysis.

- One study noted that for the first 2 minutes after birth, measured HR_{PO} values were significantly lower than HR_{ECG}. {van Vonderen 2015 49}
- Another study noted that PO displayed lower HR values during the first 6 minutes after birth. {Iglesias 2016 271}

Gestational age subgroups: No study provided sufficient data to perform this subgroup analysis. One study compared subgroups of infants of 29-32 and 32-35 weeks' gestational age and found no difference between them in the time to HR display from the start of monitoring for either ECG or PO. {Murphy 2021 438}

Summary of evidence: PO is slower and imprecise for newborn HR assessment in the delivery room compared to ECG. PO may display lower heart rate values compared to ECG for the first 2 to 6 minutes after birth. There is limited evidence for HR assessment using PO vs ECG in extremely preterm newborns, newborns requiring resuscitation and newborns who have ECG HR< 100 bpm and < 60 BPM.

Comparison 2: Auscultation compared to ECG

The systematic review identified 5 observational studies including 171 infants. {Bobillo-Perez 2021 783, Cavallin 2020 88, Kamlin 2006 319, Murphy 2018 F490, Treston 2019 F227}

For the important outcome of **time for first heart rate assessment from the device placement**, there was **no significant difference** between auscultation and ECG (pooled difference HR by auscultation 4 s faster, 95% CI 10 s faster to 2 s slower, $p > 0.05$), **moderate certainty evidence** downgraded for risk of bias from 3 cohort cross sectional studies enrolling 105 infants. {Bobillo-Perez 2021 783, Murphy 2018 F490, Treston 2019 F227}

For the important outcome of **time for first heart rate assessment from birth**, **auscultation detected heart rate faster than ECG at birth** (pooled difference HR by auscultation 24 s faster, 95% CI 45 s faster to 2 s faster), **low certainty evidence** downgraded for risk of bias and imprecision from 3 observational studies enrolling 105 infants. {Bobillo-Perez 2021 783, Murphy 2018 F490, Treston 2019 F227} This was considered likely to be due to the time required for the placement of ECG leads and turning on the ECG monitor.

For the important outcome of **accuracy of heart rate assessment**, **auscultation was accurate but imprecise** (summary mean bias ($HR_{AUSC} – HR_{ECG}$) was -9.9 bpm; LoA -32 to 12, 95% CI-217, 198), **very low certainty evidence** downgraded for risk of bias and imprecision from 3 observational studies including 91 infants. {Kamlin 2006 319, Murphy 2018 F490, Treston 2019 F227}

Subgroup Analyses:

For the pre-defined subgroup analyses by receipt of resuscitation and gestation, no data were available.

Time epoch for heart rate assessment (≤60 seconds, 61 seconds – 120 seconds, ≥ 121 seconds): No studies reported data sufficient to fully perform this subgroup analysis. Some data were available to compare accuracy at 90 s vs 120 s after birth. These analyses showed very wide confidence intervals for the comparison of methods at both times, so the only conclusion that can be drawn is that auscultation was accurate but imprecise at both times.

For **accuracy of heart rate assessment at 90 seconds**, **auscultation was accurate but imprecise (**summary mean bias ($HR_{AUSC} – HR_{ECG}$) -9.6 bpm; LoA -52 to 33 bpm, 95% CI -307, 203), **very low certainty evidence** downgraded for risk of bias and imprecision from 2 observational studies including 80 infants. {Bobillo-Perez 2021 783, Cavallin 2020 88}

For **accuracy of heart rate assessment at 120 seconds**, **auscultation was accurate but imprecise** (summary mean bias ($HR_{AUSC} – HR_{ECG}$) – 0.4 bpm; LoA: -34 to 35 bpm, 95% CI -594, 189 bpm), **very low certainty evidence** downgraded for risk of bias and imprecision from 2 observational studies including 80 infants. {Bobillo-Perez 2021 783, Cavallin 2020 88}

Comparison 3: Palpation compared to ECG

The systematic review identified 2 observational studies including 86 infants. {Cavallin 2020 88, Kamlin 2006 319}

For the important outcome of **time for first heart rate assessment from the device placement** neither study reported this outcome.

For the important outcome of **time for first heart rate assessment from birth** neither study reported this outcome.

For the important outcome of **accuracy of heart rate assessment, palpation was inaccurate and imprecise** (mean bias of -21bpm with SD of 21 bpm), **very low certainty evidence** downgraded for risk of bias and applicability concerns from one observational study including 26 infants. {Kamlin 2006 319}

Subgroup analysis:

For the pre-defined subgroup analyses by receipt of resuscitation and gestation, no data were available.

For **accuracy of heart rate assessment** by time epochs, **palpation was similarly inaccurate and imprecise when assessed at 60s, 90s, 120s and 300s** (mean difference between HR palpation and HR ECG of -20 bpm (95% agreement limits -80 to 40 bpm) at 60 seconds, -25 bpm (95% agreement limits -73 to 22 bpm) at 90 seconds, -23 bpm (95% agreement limits -67 to 20 bpm) at 120 seconds, and -31 bpm (95% agreement limits -96 to 34 bpm) at 300 seconds), **very low certainty evidence** downgraded for risk of bias and applicability concerns from one observational study including 60 infants. {Cavallin 2020 88}

Comparison 4: Palpation compared to auscultation

The systematic review identified 1 RCT including 60 infants {Owen 2004 213} and 1 observational study including 60 infants. {Cavallin 2020 88}

For the important outcome of **time for first heart rate assessment from the device placement** neither study reported this outcome.

For the important outcome of **time for first heart rate assessment from birth** neither study reported this outcome.

For the important outcome of **accuracy of heart rate assessment,** data were not available in a format that allowed calculation of a pooled summary estimate. {Owen 2004 213} The study authors noted that all palpation methods (femoral pulse, brachial pulse and umbilical cord pulse) showed very poor agreement with auscultated HR. {Owen 2004 213}

Comparison 5: Digital stethoscope compared to ECG

The systematic review identified 2 observational studies including 77 infants, {Gaertner 2017 F370, Treston 2019 F227} only one of which provided data assessing prespecified outcomes of the review. {Gaertner 2017 F370}

For the important outcome of **time for first heart rate assessment from the device placement** neither study reported this outcome.

For the important outcome of **time for first heart rate assessment from birth** neither study reported this outcome.

For the important outcome of **accuracy of heart rate assessment, the digital stethoscope was accurate but imprecise** (mean difference (HR_{DS}-HR_{ECG}) of 0.2 bpm 95% CI −17.6 to 18 including crying periods and 1 bpm 95% CI −10.5 to 12.6 if excluding crying periods), **very low certainty evidence** downgraded for risk of bias and applicability concerns from 1 observational study including 37 infants. {Gaertner 2017 F370} The study authors found the digital stethoscope unreliable in detecting a signal during crying but suggested that since crying may be a sign of a successful transition, measurement of HR may not be necessary during crying.

Comparison 6: Doppler ultrasound (DU) compared to ECG

The systematic review identified 2 observational studies including 164 infants. {Agrawal 2021 2053, Shimabukuro 2017 1069}

For the important outcome of **time for first heart rate assessment from the device placement** neither study reported this outcome.

For the important outcome of **time for first heart rate assessment from birth**, **DU was faster for presenting a HR signal than ECG** (time to HR_{DU} 76 s interquartile range (IQR) 51 s to 91 s vs HR_{ECG} 96.5 s, IQR 74.2 s to 118 s, $p<0.05$), **very low certainty evidence** downgraded for severe risk of bias and applicability concerns from 1 observational study including 131 infants. {Agrawal 2021 2053}

For the important outcome of **accuracy of heart rate assessment, DU was accurate and precise** (summary mean bias (HR_{DU} – HR_{ECG}) was – 0.2 bpm; LoA -5 to 6, 95%CI -222, 223), **very low certainty evidence** downgraded for risk of bias, imprecision and applicability concerns from 2 observational studies including 164 infants. {Agrawal 2021 2053, Shimabukuro 2017 1069}

Comparison 7: Dry electrodes incorporated in a belt (DEB) compared to (conventional 3 lead) ECG

The systematic review identified 3 observational studies including 94 infants. {Bush 2021 550, Rettedal 2021 1092, van Twist 2022 1137}

For the important outcome of **time for first heart rate assessment from the device placement**, **DEB was faster for presenting a HR signal than ECG** (HR_{DEB} at 22 s, IQR CI 13s to 45s, HR_{ECG} at 171 s, IQR 129s to 239s), **very low certainty evidence** downgraded for risk of bias and imprecision from 1 observational study including 48 infants. {Rettedal 2021 1092}

For the important outcome of **time for first heart rate assessment from birth**, **DEB was faster for presenting a HR signal than ECG** (HR_{DEB} at 13 s IQR 10s to 18s, HR_{ECG} at 42 s IQR 31 s to 63 s), **very low certainty** evidence downgraded for severe risk of bias and imprecision from 1 observational study including 28 infants. {Bush 2021 550}

For the important outcome of **accuracy of heart rate assessment, DEB was accurate and precise for HR estimation** (summary mean bias (HR_{DEB} – HR_{ECG}) – 1.4 bpm; LoA -2.5 to 5.2, 95% CI -30, 33), **very low certainty evidence** downgraded for risk of bias and applicability concerns from 2 observational studies including 66 infants. {Rettedal 2021 1092, van Twist 2022 1137}

Treatment Recommendations

When accurate heart rate estimation is needed for a newborn infant immediately after birth and resources permit, we suggest that the use of electrocardiography is reasonable (conditional recommendation, low-certainty evidence).

Pulse oximetry and auscultation may be reasonable alternatives to electrocardiography for heart rate assessment, but the limitations of these modalities should be kept in mind (conditional recommendation, low-certainty evidence).

There is insufficient evidence to make a treatment recommendation for the use of any other device for heart rate assessment of a newborn infant immediately after birth.

Auscultation with or without pulse oximetry should be used to confirm the heart rate when electrocardiography is unavailable or is not functioning or when pulseless electrical activity is suspected (good practice statement).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
See Appendix 1
New Search strategy for the evidence update review:
The new search strategy was the same as original strategy for 2023 systematic review.

Database searched: Medline and clinical trial database (clinicaltrials.gov, Cochrane, ICTR, ANZCTR)
Time Frame: (existing PICOST) – All years until 16 Aug, 2023
Time Frame: From 2022 to 30 June, 2024
Date Search Completed: 30 June 2024
Clinical trial database: 5th Oct 2024 (no new trials found)

Search Results:
Identified: 505 studies screened
Full text articles assessed: 0
Included: 0

Summary of Evidence Update: No new articles relevant to this question were identified.
Relevant Guidelines or Systematic Reviews: None
RCT: None
Nonrandomized Trials, Observational Studies: None

Reviewer Comments:
A systematic review on this question was completed in 2023.{Kapadia 2024 100668} Since that review there are no additional relevant articles found in the literature. As this was a recent review, the current recommendation stands, and we do not recommend either a systematic or scoping review on this topic.

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Abbreviations: B-A plots: Bland Altman plots; bpm: beats per minute; DEB: dry electrodes incorporated in a belt; DU: Doppler ultrasound; ECG: electrocardiogram; HR: heart rate; HRAUSC: heart rate determined by auscultation through stethoscope; HRDEB: heart rate obtained by using ECG device with dry electrodes incorporated in a belt; HRECG: heart rate determined by ECG; HRDU: heart rate obtained by doppler ultrasound device; HRDU: heart rate obtained by doppler ultrasound device; HRPO: heart rate obtained by pulse oximetry; IQR: interquartile range; LoA: limit of agreement; PO: pulse oximetry; RCT: randomized controlled trial; s: seconds; SysRev: systematic review

Appendix 1 —Search strategy

Sources searched	Search strategy	Search time frame
Medline	1 Delivery Rooms/ 1781 2 Resuscitation/ 28494 3 Cardiopulmonary Resuscitation/ 21635 4 "delivery room*".ti,ab. 2958	From 2022 to 30 June, 2024

	5 resuscitat*.ti,ab. 74642 6 birth.ti,ab. 349597 7 childbirth.ti,ab. 22374 8 transition*.ti,ab. 515976 9 stabilization.ti,ab. 115570 10 cpr.ti,ab. 15365 11 "heart massage".ti,ab. 279 12 "cardiac massage".ti,ab. 1143 13 "chest massage".ti,ab. 76 14 "chest compression*".ti,ab. 4627 15 "cardiac compression*".ti,ab. 628 16 "thoracic compression*".ti,ab. 250 17 intubation.ti,ab. 55896 18 "positive pressure respiration".ti,ab. 234 19 "positive pressure ventilation".ti,ab. 6541 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 1130660 21 Infant/ 867503 22 Infant, Newborn/ 670616 23 Infant, Premature/ 61656 24 Infant, Extremely Premature/ 3919 25 Infant, Extremely Low Birth Weight/ 2234 26 Infant, Very Low Birth Weight/ 9917 27 Infant, Small for Gestational Age/ 8633 28 Infant, Postmature/ 396 29 Premature Birth/ 21354 30 infant.ti,ab. 191730 31 infants.ti,ab. 300790 32 newborn.ti,ab. 137692 33 neonate.ti,ab. 31209 34 neotates.ti,ab. 1 35 neonatal.ti,ab. 240497 36 "low birth weight".ti,ab. 31793 37 "small for gestational age".ti,ab. 13015 38 postmature.ti,ab. 239 39 preterm.ti,ab. 92019 40 "post term birth".ti,ab. 110 41 "live birth".ti,ab. 13440 42 baby.ti,ab. 44304 43 babies.ti,ab. 42122 44 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 1565164 45 Heart Rate, Fetal/ 5450 46 Heart Rate/ 175760 47 Heart Rate Determination/ 202 48 "heart beat".ti,ab. 1941 49 Heart Auscultation/ 5237 50 heartbeat.ti,ab. 5155 51 "cardiac beat".ti,ab. 153 52 pulse.ti,ab. 188318 53 HR.ti,ab. 303599 54 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 648714 55 Echocardiography/ 98619 56 Oximetry/ 14470 57 Electrocardiography/ 202096 58 Monitoring, Physiologic/ 58781	

	59 ultrasonography/ 200496 60 electrocardiogram.ti,ab. 46188 61 auscultat*.ti,ab. 6678 62 oximetry.ti,ab. 12143 63 ekg.ti,ab. 3523 64 ecg.ti,ab. 72517 65 vectorcardiography.ti,ab. 912 66 echocardiography.ti,ab. 126277 67 "body surface potential mapping".ti,ab. 242 68 doppler.ti,ab. 113057 69 "video plethysmography".ti,ab. 9 70 Photoplethysmography.ti,ab. 2905 71 stethoscope*.ti,ab. 2289 72 "oxygen saturation".ti,ab. 32906 73 electrode*.ti,ab. 199058 74 ultrasonography.ti,ab. 102161 75 neobeat.ti,ab. 16 76 echocardiogram.ti,ab. 16841 77 assessment.ti,ab. 1233698 78 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 2175558 79 20 and 44 and 54 and 78 1874 80 limit 79 to yr="2022 -Current" 151	
clinicaltrials.gov, Cochrane, ICTR, ANZCTR		
Results identified	**Results screened full text**	**Results included**
505	0	0

2025 Evidence Update
NLS 5201 – Heart Rate Assessment in the Delivery Room – Clinical Outcomes

Worksheet Author(s): Kawakami MD, Kapadia V, Strand M
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest: Vishal Kapadia authored one of the manuscripts included in the previous SR. {Abbey 2022 1445} Mandira D Kawakami and Marya Strand: no conflicts of interest to declare

PICOST:
Population: Newborn infants in the delivery room
Intervention: Use of electrocardiography (ECG), Doppler device, digital stethoscope, photoplethysmography, video plethysmography, dry electrode technology or any other newer modalities
Comparison:
1. Pulse oximeter with or without auscultation
2. Auscultation alone
3. In between intervention comparison

Outcomes:
Duration of positive pressure ventilation (PPV) in delivery room from the start of PPV; tracheal intubation in delivery room; chest compressions or epinephrine (adrenaline) administration in delivery room; time from birth to heart rate ≥100 bpm as measured by ECG; resuscitation team performance in the delivery room; unanticipated admission to neonatal intensive care unit (as defined by authors); death before hospital discharge;
Study Design:
Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies and case series were excluded.
Timeframe: All years and all languages were included provided there was an English abstract. The search was updated to 16 Aug, 2023

Year of last full review: 2022 {Kapadia 2024 100665, Wyckoff 2022 208}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST {Wyckoff 2022 e645}
Rationale for Review: Monitoring heart rate in the first minutes after birth was last reviewed by the NLS Task Force in 2015, at which time the focus was on which methods resulted in the most accurate measurement at the earliest time. This Systematic Review focused on critical and important patient outcomes and was initiated from a priority list from the ILCOR NLS Task Force.
Consensus on Science
<u>COMPARISON: ECG versus auscultation plus pulse oximeter during resuscitation of newborn infants</u>
The systematic review identified 2 randomized controlled trials {Abbey 2022 1445, Katheria 2017 e0187730} involving 91 neonates and 1 cohort study {Shah 2019 10} involving 632 neonates.

For the important outcome of duration of PPV from the start of PPV, the evidence of very low certainty (downgraded for risk of bias and serious imprecision) from 1 RCT involving 51 infants {Abbey 2022 1445} could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room (mean difference 91 s, 95% CI -18 s to 200 s; p 0.1).

For the important outcome of time from birth to heart rate ≥100 bpm as measured by ECG, the evidence of very low certainty (downgraded for risk of bias and serious imprecision) from 1 RCT involving 51 infants {Abbey 2022 1445} could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room (mean difference -21 s, 95% CI -78 s to 36 s; p 1.0).

For the important outcome of tracheal intubation in the delivery room, the evidence of low certainty (downgraded for risk of bias and imprecision) from 2 RCTs involving 91 infants {Abbey 2022 1445, Katheria 2017 e0187730} could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room [RR 1.34,

95%CI 0.69-2.59; ARD 81 more DR intubations/1000 when using ECG in the DR (95% CI 74 fewer/1000 to 384 more/1000 delivery room tracheal intubation when using ECG in the DR)].

For the important outcome of tracheal intubation in the delivery room, the evidence of low certainty (downgraded for risk of bias and imprecision) from 1 observational study involving 632 infants {Shah 2019 10} suggests that use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room may reduce tracheal intubations in the delivery room [RR 0.75,95%CI 0.62-0.90; ARD 119 fewer delivery room intubations/1000 when using ECG in the delivery room (95% CI 181 fewer/1000 to 48 fewer/1000 delivery room tracheal intubation when using ECG in the delivery room)].

For the important outcome of chest compressions, evidence of very low certainty (downgraded for risk of bias and serious imprecision) from 2 randomized control trials {Abbey 2022 1445, Katheria 2017 e0187730} involving 91 newborns could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room. As the event rate was zero, relative risk cannot be calculated.

For the important outcome of chest compressions, evidence of low certainty (downgraded for risk of bias and imprecision) from 1 observational study {Shah 2019 10} involving 632 newborns suggests that the use of ECG compared to auscultation plus pulse oximeter for heart rate assessment in the delivery room may increase or have little to no effect on number of infants receiving chest compressions in the delivery room [RR 2.14, 95%CI 0.98-4.70; ARD 35 more newborns receiving chest compressions per 1000 (1 fewer per 1000 to 113 more per 1000)].

For the important outcome of use of epinephrine (adrenaline) administration in the delivery room, evidence of very low certainty (downgraded for risk of bias and serious imprecision) from 2 randomized control trials {Abbey 2022 1445, Katheria 2017 e0187730} involving 91 newborns could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room. As the event rate was zero, relative risk cannot be calculated.

For the important outcome of use of epinephrine (adrenaline) administration in the delivery room, evidence of low certainty (downgraded for risk of bias and imprecision) from 1 observational study {Shah 2019 10} involving 632 newborns could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room [RR 3.56, 95%CI 0.42-30.3; ARD 10 more newborns receiving epinephrine (adrenaline) per 1000 (2 fewer per 1000 to 111 more per 1000)].

For the critical outcome of death before discharge, evidence of very low certainty (downgraded for risk of bias and serious imprecision) from 1 randomized control trial {Abbey 2022 1445} involving 51 newborns could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room [RR 0.96, 95%CI 0.15-6.31; ARD 3 fewer newborn deaths before discharge per 1000 (74 fewer per 1000 to 462 more per 1000)].

For the critical outcome of death before discharge, evidence of low certainty (downgraded for risk of bias and imprecision) from 1 observational study {Shah 2019 10} involving 632 newborns could not exclude benefit or harm from use of ECG compared to use of auscultation plus pulse oximeter for heart rate assessment in the delivery room [RR 0.96, 95%CI 0.57-1.61; ARD 3 fewer newborn deaths before discharge per 1000 (38 fewer per 1000 to 53 more per 1000)].

For the important outcomes of unanticipated admission to the neonatal intensive care unit and resuscitation team performance in the delivery room no data were reported in the included studies.

Subgroup Analyses:

No data were reported to perform subgroup analyses by receipt of resuscitation (yes or no), gestational age ($<28^{+0}$ weeks, 28^{+0}-33^{+6} weeks, $\geq 34^{+0}$ weeks) and cord management (early and delayed clamping or intact or cut cord milking).

Other Comparisons: We did not find any studies for Doppler device, digital stethoscope, photoplethysmography, video plethysmography, dry electrode technology or any other newer modalities versus pulse oximetry and/or auscultation. No studies were identified for in between intervention comparisons.

Treatment Recommendations

Where resources permit, we suggest that the use of ECG for heart rate assessment of a newly born infant requiring resuscitation in the delivery room is reasonable (weak recommendation, low certainty of evidence).
Where ECG is not available, auscultation with pulse oximetry is a reasonable alternative for heart rate assessment, but the limitations of these modalities should be kept in mind (weak recommendation, low certainty of evidence)
There is insufficient evidence to make a treatment recommendation regarding use of digital stethoscope, audible or visible Doppler ultrasound, dry electrode technology, reflectance-mode green light photoplethysmography or transcutaneous electromyography of the diaphragm for heart rate assessment of a newborn in the delivery room.
Auscultation with or without pulse oximetry should be used to confirm the heart rate when ECG is unavailable, not functioning or when pulseless electrical activity is suspected. (Good practice statement)

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
See Appendix 1
New Search strategy for the evidence update review:
The new search strategy was the same as original strategy for 2023 systematic review.

Database searched: Medline and clinical trial database (clinicaltrials.gov, Cochrane, ICTR, ANZCTR)
Time Frame: (existing PICOST) – All years until 16 Aug, 2023
Time Frame: (new PICOST) – From 2022 to 30 June, 2024
Date Search Completed: 30 June, 2024
Clinical trial database: 5th Oct 2024 (no new trials found)

Search Results:
Identified: 505
Full text articles assessed: 3 (2 studies excluded for wrong outcomes and wrong study design)
Included: 1

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews: None
RCT: None

Nonrandomized Trials, Observational Studies: 1

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Mende 2024 {Mende 2024 685}	Longitudinal cohort including data from 2015 (pre-implementation of ECG use), 2017 (upon implementation) and 2021 (4 years post-implementation); N=1011	Inborn infants who received positive pressure ventilation (PPV) or higher support in the delivery room	*In-hospital Mortality*: no change between study epochs: • 2015 (n=263): 23 (8.7%) • 2017 (n=369): 30 (8.1%) • 2021 (n=379): 32 (8.4%) *Respiratory interventions (PPV, Continuous positive airway pressure (CPAP) and supplemental oxygen):* *PPV:* • 2015 (n=263): 239 (91.9%) • 2017 (n=369): 360 (97.6%) • 2021 (n=379): 365 (96.3%); p<0.05 *Tracheal intubation:* • 2015 (n=263): 125 (47.5%) • 2017 (n=369): 131 (35.5%)	Use of ECG along with ongoing education on the importance of ventilation, tailors ventilation strategies more specifically to individual infant needs. Limitations: retrospective nature of data collection as well as limited data on long-term neonatal outcomes

			• 2021 (n=379): 166 (43.8%) Intubation increased in infants <34 weeks and decreased in infants ≥34 weeks (p<0.05) <u><34 weeks</u>: • 2015 (n=263): 71/133 (53.4%) • 2017 (n=369): 88/194 (45.4%) • 2021 (n=379): 108/185 (58.4%); p<0.05 from 2017 to 2021 ≥34 weeks: • 2015 (n=263): 54/130 (41.5) • 2017 (n=369): 43/175 (24.6%) • 2021 (n=379): 58/194 (29.9%) p<0.05 *Chest compression:* initially increased but returned to pre-implementation rates with education on importance of ventilation • 2015 (n=263): 8(3.0%) • 2017 (n=369): 24 (6.5%) • 2021 (n=379): 8 (2.1%) *Epinephrine use:* • 2015 (n=263): 1 (0.4%) vs 2017 (n=369): 5 (1.4%) vs 2021 (n=379): 7 (1.9%) *Supplemental oxygen:* • 2015 (n=263): 224 (85.2%) • 2017 (n=369): 330 (89.4%) • 2021 (n=379): 378 (99.7%) p<0.05 *CPAP:* • 2015 (n=263): 186 (70.7%) • 2017 (n=369): 323 (87.5%) • 2021 (n=379): 329 (86.8%) p<0.05	
Abbreviations: ECG: electrocardiogram; PPV: positive pressure ventilation; CPAP: Continuous positive airway pressure				

Reviewer Comments:
A systematic review on this question was completed in 2023. {Kapadia 2024 100665} Since that review one observational study was found in the literature. {Mende 2024 685} This observational retrospective cohort study compared the frequency of resuscitation methods used before and after implementation of electrocardiogram in the delivery room. It reported an initial increase in chest compressions at birth and decrease frequency of intubation which was mitigated by a focused educational intervention on the importance of achieving effective ventilation. This new data does not impact the recommendation as it is written. As this was a recent review, the current recommendation stands, and we do not recommend either a systematic or scoping review on this topic.

References:

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Shah BA, Wlodaver AG, Escobedo MB, Ahmed ST, Blunt MH, Anderson MP, et al. Impact of electronic cardiac (ECG) monitoring on delivery room resuscitation and neonatal outcomes. Resuscitation. 2019;14310-16.

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Wyckoff MH, Singletary EM, Soar J, Olasveengen TM, Greif R, Liley HG, et al. 2021 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Neonatal Life Support; Education, Implementation, and Teams; First Aid Task Forces; and the COVID-19 Working Group. Circulation. 2022;145(9)e645-e721.

Appendix 1—Search strategy

Sources searched	Search strategy		Search time frame
Medline	1	Delivery Rooms/ 1781	2021 to 30 June 2024
	2	Resuscitation/ 28494	
	3	Cardiopulmonary Resuscitation/ 21635	
	4	"delivery room*".ti,ab. 2958	
	5	resuscitat*.ti,ab. 74642	
	6	birth.ti,ab. 349597	
	7	childbirth.ti,ab. 22374	
	8	transition*.ti,ab. 515976	
	9	stabilization.ti,ab. 115570	
	10	cpr.ti,ab. 15365	
	11	"heart massage".ti,ab. 279	
	12	"cardiac massage".ti,ab. 1143	
	13	"chest massage".ti,ab. 76	
	14	"chest compression*".ti,ab. 4627	
	15	"cardiac compression*".ti,ab. 628	
	16	"thoracic compression*".ti,ab. 250	
	17	intubation.ti,ab. 55896	
	18	"positive pressure respiration".ti,ab. 234	
	19	"positive pressure ventilation".ti,ab. 6541	
	20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 1130660	

	21 Infant/ 867503 22 Infant, Newborn/ 670616 23 Infant, Premature/ 61656 24 Infant, Extremely Premature/ 3919 25 Infant, Extremely Low Birth Weight/ 2234 26 Infant, Very Low Birth Weight/ 9917 27 Infant, Small for Gestational Age/ 8633 28 Infant, Postmature/ 396 29 Premature Birth/ 21354 30 infant.ti,ab. 191730 31 infants.ti,ab. 300790 32 newborn.ti,ab. 137692 33 neonate.ti,ab. 31209 34 neotates.ti,ab. 1 35 neonatal.ti,ab. 240497 36 "low birth weight".ti,ab. 31793 37 "small for gestational age".ti,ab. 13015 38 postmature.ti,ab. 239 39 preterm.ti,ab. 92019 40 "post term birth".ti,ab. 110 41 "live birth".ti,ab. 13440 42 baby.ti,ab. 44304 43 babies.ti,ab. 42122 44 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 1565164 45 Heart Rate, Fetal/ 5450 46 Heart Rate/ 175760 47 Heart Rate Determination/ 202 48 "heart beat".ti,ab. 1941 49 Heart Auscultation/ 5237 50 heartbeat.ti,ab. 5155 51 "cardiac beat".ti,ab. 153 52 pulse.ti,ab. 188318 53 HR.ti,ab. 303599 54 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53648714 55 Echocardiography/ 98619 56 Oximetry/ 14470 57 Electrocardiography/ 202096 58 Monitoring, Physiologic/ 58781 59 ultrasonography/ 200496 60 electrocardiogram.ti,ab. 46188 61 auscultat*.ti,ab. 6678 62 oximetry.ti,ab. 12143 63 ekg.ti,ab. 3523 64 ecg.ti,ab. 72517 65 vectorcardiography.ti,ab. 912 66 echocardiography.ti,ab. 126277 67 "body surface potential mapping".ti,ab. 242 68 doppler.ti,ab. 113057 69 "video plethysmography".ti,ab. 9 70 Photoplethysmography.ti,ab. 2905 71 stethoscope*.ti,ab. 2289 72 "oxygen saturation".ti,ab. 32906 73 electrode*.ti,ab. 199058 74 ultrasonography.ti,ab. 102161 75 neobeat.ti,ab. 16	

	76 echocardiogram.ti,ab. 16841 77 assessment.ti,ab. 1233698 78 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 2175558 79 20 and 44 and 54 and 78 1874 80 limit 79 to yr="2022 -Current" 151	
Results identified	**Results screened full text**	**Results included**
505	3	1

2025 Evidence Update
NLS 5300 – Devices for Administering Positive Pressure Ventilation (PPV) at Birth

Worksheet Author(s): Trevisanuto D, Roehr CC, Davis PG, Madar J, Liley HG, Rabi Y, Weiner GM
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest: None

PICOST:
Population: Newborns receiving ventilation (PPV) during resuscitation
Comparisons **Interventions vs Comparators:**

1. T-piece resuscitator vs Self-inflating bag
2. T-piece resuscitator vs Flow-inflating bag
3. Flow-inflating bag vs Self-inflating bag
4. Self-inflating bag with PEEP valve vs Self-inflating bag without PEEP valve

Outcomes:
Primary outcome

- In-hospital mortality (critical)

Secondary outcomes

- Severe intraventricular hemorrhage, Papile grade III-IV (critical)
- Intraventricular hemorrhage (any) (important)
- Bronchopulmonary dysplasia (critical)
- CPR or medications in delivery room (critical)
- Air leak (important)
- Intubation in delivery room (important)
- Duration of PPV in delivery room (important)
- Length of stay (important)
- Admission to NICU (important)

Study types: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) were excluded.
Timeframe: All years and all languages were included as long as there was an English abstract; Literature search was updated to 30th December 2020.

Year of last full review: 2020. {Trevisanuto 2021 e2021050174}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Wyckoff 2020 S185}

CONSENSUS ON SCIENCE:
COMPARISON 1: T-PIECE RESUSCITATOR COMPARED TO SELF-INFLATING BAG (with or without PEEP valve).

The systematic review identified 4 RCTs {Dawson 2011 , Kookna 2019 66, Szyld 2014 234, Thakur 2015 } involving 1247 neonates and 1 prospective cohort study {Guinsburg 2018 } involving 1962 neonates.

*For the critical outcome of **in-hospital mortality**,* the evidence of **very low** certainty (downgraded for serious risk of bias, indirectness and imprecision) from **4 trials** involving 1247 infants {Dawson 2011 , Kookna 2019 66, Szyld 2014 234, Thakur 2015 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (risk ratio (RR) 0.74; 95% confidence interval (CI) 0.40 to 1.34; P = 0.31; Absolute Risk Difference [ARD], 10 fewer patients/1000 die when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 23 fewer patients/1000 to 13 more patients/1000 die when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the critical outcome of **in-hospital mortality**,* the evidence of **very low certainty** from **1 prospective cohort study** involving 1962 preterm infants {Guinsburg 2018 } showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.71; 95% CI 0.63 to 0.80; P <0.001; ARD -12.8%; 95% CI -16.4% to -8.9%; NNT = 8).

*For the critical outcome of **bronchopulmonary dysplasia**,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency and indirectness) from **4 trials** involving 1247 infants {Dawson 2011 , Kookna 2019 66, Szyld 2014 234, Thakur 2015 } showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.64, 95% CI 0.43 to 0.95; P = 0.03; ARD -3.2%; 95% CI -5.1% to -0.4; NNT = 32.

*For the critical outcome of **bronchopulmonary dysplasia,*** the evidence of **very low certainty** from 1 **prospective cohort study** involving 1327 preterm infants {Guinsburg 2018 } showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR, 0.79, 95% CI, 0.65 to 0.96; P = 0.02; ARD -6.6%; 95% CI -11.0% to -1.3%; NNT = 15).

*For the critical outcome of **severe intraventricular hemorrhage (grade III-IV)***, the evidence of **very low certainty** from **1 prospective cohort study** involving 1594 preterm infants {Guinsburg 2018 } showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.75, 95% CI 0.57 to 0.98; P = 0.04; ARD -4.0%; 95% CI -6.9% to -0.3%; NNT = 24).

*For the critical outcome of **cardio-pulmonary resuscitation or medications in the delivery room**,* the evidence of **very low** certainty (downgraded for serious risk of bias, indirectness and imprecision) from **4 trials** involving 1247 infants {Dawson 2011 , Kookna 2019 66, Szyld 2014 234, Thakur 2015 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.58, 95% CI 0.28 to 1.23; P = 0.16; ARD, 12 fewer patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 21 fewer patients/1000 to 7 more patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the critical outcome of **cardio-pulmonary resuscitation or medications in delivery room**,* the evidence of **very low certainty** from **1 prospective cohort study** involving 1962 preterm infants {Guinsburg 2018 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.82, 95% CI 0.60 to 1.12; P = 0.22; ARD, 18 fewer patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 40 fewer patients/1000 to 12 more patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **intraventricular hemorrhage (all grades) and** the critical outcome of **severe intraventricular hemorrhage (grade III-IV),*** unpublished data obtained from the author of one small RCT {Thakur 2015 } and from the author of a cluster RCT {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag. However, the lack of adjustment for center and risk of ascertainment bias culminated in such extremely low certainty in these results that the data are not presented.

*For the important outcome of **intraventricular hemorrhage (all grades)**,* the evidence of **very low certainty** from **1 prospective cohort study** involving 1594 preterm infants {Guinsburg 2018 } **s**howed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.72, 95% CI 0.63 to 0.83; P < 0.001; ARD -12.9%; 95% CI -17% to -7.8%, NNT = 8).

*For the important outcome of **air leak**,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **4 trials** involving 1247 infants {Dawson 2011 , Kookna 2019 66, Szyld 2014 234, Thakur 2015 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 1.29, 95% CI 0.60 to 2.77; P = 0.52; ARD 5 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 7 fewer patients/1000 to 31 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **air leak,*** the evidence of **very low certainty** from **1 prospective cohort study** involving 1962 preterm infants {Guinsburg 2018 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 1.23, 95% CI 0.82 to 1.85; P = 0.32; ARD 13 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 10 fewer patients/1000 to 47 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **duration of positive pressure ventilation in the delivery room,*** the evidence of **moderate** certainty (downgraded for serious risk of bias) from **3 trials** involving 1098 infants {Kookna 2019 66, Szyld 2014 234, Thakur 2015 } showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (Mean Difference (MD) -19.8 seconds; 95% CI -27.7 to -12.0 seconds; P < 0.001).

*For the important outcome of **intubation in the delivery room,*** the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency and indirectness) from **4 trials** involving 1266 infants {Dawson 2011 , Kookna 2019 66, Szyld 2014 234, Thakur 2015 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.89, 95% CI 0.76 to 1.05; P = 0.15; ARD, 37 fewer intubated patients/1000 when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 80 fewer patients/1000 to 17 more intubated patients/1000 when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **intubation in the delivery room,*** the evidence of **very low** certainty from **1 prospective cohort study** involving 1962 preterm infants {Guinsburg 2018 } showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.57, 95% CI 0.46 to 0.70*;* P < 0.01; ARD -28.9%; 95% CI -36.3% to -20.2%; NNT = 8).

*For the important outcome of **admission to a neonatal intensive care unit,*** the evidence of **low** certainty (downgraded for serious risk of bias and indirectness) from **3 trials** involving 1184 infants {Dawson 2011 , Szyld 2014 234, Thakur 2015 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (RR 0.98, 95% CI 0.89 to 1.07; P = 0.60; ARD, 12 fewer patients/1000 admitted to a neonatal intensive care unit when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 65 fewer patients/1000 to 42 more patients/1000 admitted to a neonatal intensive care unit when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **length of hospitalization,*** the evidence of **moderate** certainty (downgraded for serious risk of bias) from **2 trials** involving 1090 infants {Szyld 2014 234, Thakur 2015 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (MD -0.25 days, 95% CI 3.39 days shorter to 2.89 days longer duration of hospitalization; P = 0.88).

*For the important outcome of **length of hospitalization,*** the evidence of **very low certainty** from **1 prospective cohort study** involving 1962 preterm infants {Guinsburg 2018 } **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag (MD -0.00 days, 95% CI -4.15 days shorter to 4.15 days longer duration of hospitalization; P = 1.00).

COMPARISON 2: T-PIECE RESUSCITATOR COMPARED TO FLOW-INFLATING BAG
We did not identify any eligible studies comparing a T-piece resuscitator with a flow-inflating bag.

COMPARISON 3: FLOW-INFLATING BAG COMPARED TO SELF-INFLATING BAG
We did not identify any eligible studies comparing a flow-inflating bag with a self-inflating bag.

COMPARISON 4: SELF-INFLATING BAG WITH PEEP VALVE COMPARED TO SELF-INFLATING BAG WITHOUT PEEP VALVE
The systematic review identified two studies, {Holte 2020 e20200494, Szyld 2014 234} (933 infants).

*For the critical outcome of **in-hospital mortality,*** the evidence of **very low** certainty (downgraded for serious risk of bias, indirectness and imprecision) from **2 trials** involving 933 infants {Holte 2020 e20200494, Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (RR 0.99, 95% CI 0.59 to 1.67; P = 0.97; ARD 1 fewer patients/1000 died when receiving positive pressure

ventilation with a T-piece resuscitator [95% CI 24 fewer patients/1000 to 39 more patients/1000 died when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the critical outcome of **bronchopulmonary dysplasia**,* the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 516 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (RR 1.03, 95% CI 0.58 to 1.81; P = 0.93; ARD 3 more patients/1000 with bronchopulmonary dysplasia when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 35 fewer patients/1000 to 68 more patients/1000 with bronchopulmonary dysplasia when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the critical outcome of **cardiopulmonary resuscitation or medications in the delivery room**,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 516 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (RR 1.43, 95% CI 0.54 to 3.80; P = 0.48; ARD 11 fewer patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 12 fewer patients/1000 to 74 more patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **intraventricular hemorrhage (all grades) and** the critical outcome of **severe intraventricular hemorrhage (grades III-IV),*** unpublished data obtained from the author of a cluster RCT {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve. However, the lack of adjustment for center and risk of ascertainment bias results in such extremely low certainty in these results that the data are not presented.

*For the important outcome of **air leak**,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 516 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (RR 2.34, 95% CI 0.48 to 11.47; P = 0.30; ARD 12 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 5 fewer patients/1000 to 93 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **duration of positive pressure ventilation in the delivery room**,* the evidence of **very low** certainty (downgraded for serious risk of bias, indirectness and imprecision) from **2 trials** involving 886 infants {Holte 2020 e20200494, Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (MD -3.8 seconds, 95% CI 29.4 seconds shorter to 21.7 seconds longer duration of positive pressure ventilation; P = 0.77).

*For the important outcome of **intubation in the delivery room**,* the evidence of **moderate** certainty (downgraded for serious risk of bias) from **1 trial** involving 516 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (RR, 1.19; 95% CI; 0.88 to 1.61; P = 0.25; ARD 15.1 more patients/1000 intubated in delivery room when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 30 fewer patients/1000 to 151 more patients/1000 intubated in delivery room when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **admission to neonatal intensive care unit**,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency, indirectness and imprecision) from **2 trials** involving 933 infants {Holte 2020 e20200494, Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (RR 1.12; 95% CI 0.96 to 1.30; P = 0.14; ARD 47 more patients/1000 admitted to a neonatal intensive care unit when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 16 fewer patients/1000 to 117 more patients/1000 admitted to a neonatal intensive care unit when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **length of hospitalization**,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency, indirectness and imprecision) from **2 trials** involving 914 infants {Holte 2020 e20200494, Szyld 2014 234} **could not**

exclude benefit or harm from receiving positive pressure ventilation with a self-inflating bag with PEEP valve compared to a self-inflating bag without PEEP valve (MD 0.15 days, 95% CI -0.25 to 0.55 days; P = 0.46).

SUBGROUP COMPARISONS:

A – SUBGROUP ANALYSIS ACCORDING TO GESTATIONAL AGE: A) FULL TERM INFANTS; B) PRETERM INFANTS 28-36 WEEKS' GESTATION; C) PRETERM INFANTS < 28 WEEKS' GESTATION

The planned analyses by gestational age subgroups were not feasible due to limited data from the available studies. All 4 RCTs {Dawson 2011 , Kookna 2019 66, Szyld 2014 234, Thakur 2015 } (1247 infants) identified for this review included preterm infants but with different gestational age cut-offs, so the planned comparisons were not feasible. One study included only preterm infants (n=80) with gestational age <29 weeks {Dawson 2011 }; one study included infants with gestational age >26 weeks, but reported results of a sub-group of low birthweight infants (n=195) {Szyld 2014 234} ; one study reported data from a subgroup of infants with gestational age < 34 weeks (n=37) {Thakur 2015 }; and one study included only 7 preterm infants. {Kookna 2019 66}

One prospective cohort study {Guinsburg 2018 } (1962 infants) included only preterm infants with gestational age 23-33 weeks.

B – SUBGROUP ANALYSIS COMPARING T-PIECE RESUSCITATOR WITH SELF-INFLATING BAG WITH OR WITHOUT PEEP VALVE
The systematic review identified 1 RCT {Szyld 2014 234} involving 1027 infants.

T-PIECE RESUSCITATOR vs SELF-INFLATING BAG WITH PEEP VALVE

*For the critical outcome of **in-hospital mortality**,* the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 575 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag with PEEP valve (RR 0.51, 95% CI 0.15 to 1.67, P = 0.27; ARD 14 fewer patients/1000 died when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 23 fewer patients/1000 to 18 more patients/1000 died when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the critical outcome of **bronchopulmonary dysplasia**,* the evidence of **moderate** certainty (downgraded for serious risk of bias) from **1 trial** involving 575 infants {Szyld 2014 234} showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag with PEEP valve (RR 0.49, 95% CI 0.25 to 0.95; P = 0.04; ARD -4.4%; 95% CI -6.5% to -0.4%; NNT = 23).

*For the critical outcome of **cardio-pulmonary resuscitation or medications in the delivery room**,* the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 575 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag with PEEP (RR 0.56, 95% CI 0.21 to 1.48; P = 0.24; ARD,17 fewer patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 30 fewer patients/1000 to 18 more patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **air leak**,* the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 575 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag with PEEP valve (RR 1.19, 95% CI 0.40 to 3.49; P = 0.76; ARD 4 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 12 fewer patients/1000 to 52 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **intubation in delivery room**,* the evidence of **moderate** certainty (downgraded for serious risk of bias) from **1 trial** involving 575 infants {Szyld 2014 234} showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared a self-inflating bag with PEEP valve (RR 0.69, 95% CI 0.51 to 0.93; P = 0.02; ARD -8.7%; 95% CI -13.7% to -2.0%; NNT 12).

T-PIECE RESUSCITATOR vs SELF-INFLATING BAG WITHOUT PEEP VALVE

*For the critical outcome of **in-hospital mortality**,* the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 452 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag without PEEP valve (RR 1.00, 95% CI 0.36 to 2.80; P = 1.0; ARD 0 fewer patients/1000 died when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 20 fewer patients/1000 to 55 more patients/1000 died when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the critical outcome of **bronchopulmonary dysplasia**,* the evidence of **moderate** certainty (downgraded for serious risk of bias) from **1 trial** involving 452 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag without PEEP valve (RR 0.47, 95% CI 0.22 to 1.02; P = 0.06; ARD 45 fewer patients/1000 with BPD when receiving positive pressure ventilation with a T-piece resuscitator, 95% CI 66 fewer to 2 more infants with bronchopulmonary dysplasia per 1000 infants).

*For the critical outcome of **cardio-pulmonary resuscitation or medications in the delivery room**,* the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 452 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag without PEEP valve (RR 0.33, 95% CI 0.07 to 1.63; P = 0.18; ARD 18 fewer patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 25 fewer patients/1000 to 17 more patients/1000 receive cardio-pulmonary resuscitation or medications in the delivery room when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **air leak**,* the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **1 trial** involving 452 infants {Szyld 2014 234} **could not exclude benefit or harm** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag without PEEP valve (RR 3.00, 95% CI 0.61 to 14.71; P = 0.18; ARD 18 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator [95% CI 3 fewer patients/1000 to 121 more patients/1000 with air leak when receiving positive pressure ventilation with a T-piece resuscitator]).

*For the important outcome of **intubation in the delivery room**,* the evidence of **moderate** certainty (downgraded for serious risk of bias) from **1 trial** involving 452 infants {Szyld 2014 234} showed **benefit** from receiving positive pressure ventilation with a T-piece resuscitator compared to a self-inflating bag without PEEP valve (RR 0.58, 95% CI 0.39 to 0.88; P = 0.009; ARD -9.8%; 95% CI -14.3% to -2.8%; NNT = 10).

Treatment recommendations:

COMPARISON 1: T-PIECE RESUSCITATOR vs SELF-INFLATING BAG
Where resources permit, we suggest the use of a T-Piece resuscitator over the use of a self-inflating bag in infants receiving positive pressure ventilation at birth. (Weak recommendation, very low certainty of evidence). A self-inflating bag should be available as a back-up device for the T-piece resuscitator in case of gas supply failure (technical remark).

COMPARISON 2: T-PIECE RESUSCITATOR COMPARED TO FLOW-INFLATING BAG
There are no data to make a treatment recommendation.

COMPARISON 3: FLOW-INFLATING BAG COMPARED TO SELF-INFLATING BAG
There are no data to make a treatment recommendation.

COMPARISON 4: SELF-INFLATING BAG WITH PEEP VALVE COMPARED TO SELF-INFLATING BAG WITHOUT PEEP VALVE
The confidence in effect estimates is so low that the panel feels any recommendation for the use of a PEEP valve with a self-inflating bag versus a self-inflating bag without a PEEP valve is too speculative.

<u>Subgroup considerations:</u>

Gestational age
There is insufficient data on which to base a recommendation based on gestational age, since the planned sub-group analyses according to gestational age were not feasible.

T-Piece resuscitator compared with self-inflating bag with or without PEEP valve:

Where resources permit, we suggest the use of a T-piece resuscitator over the use of a self-inflating bag either with or without a PEEP valve (Weak recommendation, very low certainty of evidence). However, a self-inflating bag should be available as a backup for the T-piece resuscitator in the event of a gas supply failure (technical remark). For use of self-inflating bag with PEEP valve vs use of self-inflating bag without PEEP valve, the data are too uncertain, so no recommendation can be made.

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
See Appendix
Database searched: Medline Embase Cochrane
Medline using the Embase platform.
Time Frame: (existing PICOST) – updated from end of last search (please specify)
Inception – 31 December 2020.
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
1 January 2020 to 1 July 2024.
Date Search Completed:
1 July 2024.
Search Results (Number of articles identified and number identified as relevant):
Articles identified: Total 227
Full-text screening: 11
Included: 4

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Bellos 2024 {Bellos 2024 690}	Systematic review and meta-analysis	Compare T-piece resuscitator or a self-inflating bag with a PEEP valve versus resuscitation with a self-inflating bag without a PEEP valve.	10 studies; 4268 neonates, (5 RCTs, 1 quasi-randomized trial, 2 prospective, and 2 retrospective cohort studies).	**1° Outcome:** **Mortality**: (6 RCTs, 2 cohort studies; 3433 infants) Total: OR 0.60, 95%CI 0.49–0.74. - preterm infants: OR 0.57, 95%CI 0.46–0.69. - term infants: OR 1.03, 95% CI 0.52–2.02. When the largest obs study (Guinsburg, 2018) was removed: OR 0.72, 95%CI 0.44–1.16. **Secondary outcomes:** *Intubation in DR:* (5 RCTs, 4 cohort studies; 3558 infants) OR 0.66, 9%CI 0.44–0.98. *Surfactant administration:* (2 RCTs, 3 cohort studies; 2383 infants) OR 0.72, 95%CI 0.58–0.88. *Mechanical ventilation:*	This review evaluated the effects of administering PEEP during neonatal resuscitation at birth. This is different from our specific PICOST question which compared different devices. However, in their subgroup analysis, the T-piece resuscitator was compared with SIB for the primary outcome. In this case, mortality was significantly reduced (OR 0.57, 95%CI 0.47-0.70). It is important to remember that when the largest cohort study (Guinsburg, 2018) was removed, the difference was not significant. Certainty of evidence: low to moderate.

				(2 RCTs, 1 cohort studies; 3079 infants) OR 1.4, 95%CI 0.45–2.00. *Compressions/drugs:* (3 RCTs, 2 cohort studies; 1670 infants) OR 1.40, 95%CI 0.81–2.44. *Air leaks:* (2 RCTs, 3 cohort studies; 2582 infants) OR 1.17, 95%CI 0.82–1.68. *BPD:* (4 RCTs, 1 cohort study; 3167 infants) OR 0.90, 95%CI 0.71–1.13.	
Tribolet 2023 {Tribolet 2023 109681}	Systematic review and meta-analysis	Compare fixed pressure devices (FPD; T-pieces or ventilators) and hand driven pressure devices (HDPD; self- or flow-inflating bags) during resuscitation at birth.	9 studies; 3621 neonates, (5 RCTs, 2 RCTs with interventions bundles and 2 prospective cohorts).	**<u>1° Outcome:</u>** *Mortality:* (5 RCTs or qRCT) OR 0.68, 95% CI 0.38–1.20. *Hypoxic-ischemic encephalopathy (HIE):* ND *BPD in preterm infants:* RR 0,68, 95%CI 0.48–0.96, NNT 31. **<u>Secondary outcomes:</u>** *Intubation in DR:* (4 RCTs or qRCT) OR 0.72, 9%CI 0.58–0.88. *Surfactant administration:* (3 RCTs or qRCT) OR 0.79, 95%CI 0.64–0.96. *Mechanical ventilation:* (3 RCTs or qRCT) OR 0.81, 95%CI 0.67–0.96. *Air leaks:* (4 RCTs or qRCT) OR 0.98, 95%CI 0.50–1.95. The global analysis (including RCTs, qRCTs and cohort studies) focused on **preterm**	This systematic review and meta-analysis of 9 studies, including 3621 infants, demonstrated improved outcomes following support of neonatal transition with “fixed pressure devices” (mostly T-piece resuscitators) compared to “hand-driven pressure devices” (e.g. self-inflating bags). Certainty of evidence: very low or moderate for overall analysis. This review is consistent with our previous ILCOR review and meta-analysis (Trevisanuto, 2021 e2021050174). It confirms that using “fixed pressure devices” at birth is associated with a reduction of BPD, but not mortality, HIE and air leaks. This systematic review reports a reduction of other important (not critical!) outcomes such

				infants found statistically significant benefits with FPD: decreases in mortality (OR 0,57[0,46–0,69]- NNT 8,7); DR intubation (OR 0,51[0,31–0,82]- NNT 6,4); and MV requirements (OR 0,60[0,46–0,78]- NNT 9,3).	as DR intubation, need for mechanical ventilation and surfactant.
PEEP: positive end-expiratory pressure; qRCT: quasi-randomized controlled trial; RCT: randomized controlled trial					

RCTs:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Khan 2023 {Khan 2023 265}	**Study Aim:** To compare proportions of target range tidal volumes achieved with the self-inflating bag vs. the T-piece in resuscitation of preterm newborns at delivery. **Study Type:** Single center, RCT; n 20.	**Inclusion Criteria:** Preterm infants ≤ 32 weeks' gestational age needing PPV for at least 30 seconds during the first 10 minutes of life.	**Intervention:** PPV with TPR (n. 9). **Comparison:** PPV with SIB (n. 9).	**1° endpoint:** **Proportion of inflations with end-tidal volumes (TV) between 4–8 ml/kg:** TPR 51% vs. SIB 29%; OR 1.8, 95%CI 1.1–3.1, p= 0.02. **Secondary outcomes:** **Proportion of inflations with TV <4 ml/kg**: TPR 35% vs. SIB 60%; OR 0.47, 95%CI 0.23–0.97, p= 0.04. **Proportion of inflations with TV >8 ml/kg:** TPR 15% vs. SIB 11%; OR 1.5, 95%CI 0.42–5.6, p= 0.5	**Study Limitations:** Small sample size; lack of relevant clinical outcomes related to the use of the two devices.
Pallapothu 2023 {Pallapothu 2023 5565}	**Study Aim:** To compare changes in peripheral SpO2, heart rate (HR), and cerebral regional oxygen saturation (crSO2)	**Inclusion Criteria:** Preterm neonates <37 weeks' gestation requiring PPV in DR.	**Intervention:** PPV with TPR (n. 36). **Comparison:** PPV with SIB (n. 36).	**1° endpoint:** **SpO2 (%) at 5 min:** 74.5 ± 17.8% and 69.4 ± 22.4%, mean difference, 95%CI 5.08 (-4.41, 14.58); p = 0.289]	**Study Limitations:** Small sample size with a very limited number of ELBWIs (8/72).

	with the use of a T-piece resuscitator (TPR) versus self-inflating bag (SIB) during DR resuscitation in preterm neonates. **Study Type:** Single center, parallel-group, RCT; n 72.			**Secondary outcomes:** SpO2≥ 80% and >85%, HR > 100/min, FiO2 requirement, minute-specific SpO2, HR and FiO2 trends for the first 5 min of life, need for DR-intubation, need and duration of respiratory support, and other in-hospital morbidities (HIE, BPD, Air leak, Death before discharge): ND. crSO2 (%) at 1 hour: 78.3 ± 10.5 vs. 83.6 ± 9.8; p=0.030.	
DR: delivery room; ELBWI: extremely low birth weight infants; HR: heart rate; PPV: positive pressure ventilation; RCT: randomized controlled trial; SpO2: oxygen saturation; TPR: T-piece resuscitator; TV: tidal volume;					

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Siripattanapipong 2017 {Siripattanapipong 2017 7}	**Study Type:** Retrospective cohort study; n. 128 (TPR n. 67; SIB n. 61).	**Inclusion Criteria:** Infants with gestational age <33 weeks and/or birth weight <1,500 grams and who received PPV at birth.	**1° endpoint:** *Intubation in DR:* TPR 58.2% vs. SIB 54.1%; OR 0.83, 95%CI 0.38–1.80; p=0.64. *Mortality and/or BPD:* TPR 44.8% vs SIB 25.4%; p=0.02. *Air leaks:* TPR 11.9% vs SIB 9.8%; p=0.73. *Surfactant administration:* TPR 19.4% vs SIB 18%; p=0.84.	TPR for PPV in preterm infants less than 33 weeks gestation or VLBWI did not change intubation rate in a real-life clinical setting when compared to SIB. The risk of the combined outcome of 'mortality or BPD' was significantly higher in TPR group. This study has a critical bias: according to hospital policy, PPV was initiated in infants less than 30 weeks' gestation using a TPR. For this reason, baseline characteristics of the 2 groups are different: Gestational age (weeks), 28.6±2.3 vs. 30.2±2.7 <0.001; Birth weight (grams), 1,061.1± 312.5 vs. 1,288.3±321.4 <0.001. Single center study. Concerns for selection bias, and information bias due to the retrospective nature of the study.

DR: delivery room; PPV: positive pressure ventilation; SIB: self-inflating bag; TPR: T-piece resuscitator; VLBWI: very low birth weight infants

Reviewer Comments:
This update of the evidence found two new reviews and meta-analyses, which included RCTs and cohort studies that were mostly already included in the 2020 ILCOR review and meta-analysis {Bellos 2024 690, Tribolet 2023 109681}. It is noteworthy that the two new systematic reviews addressed different questions (Bellos - PEEP vs no PEEP, Tribolet - any "fixed" pressure device vs any hand-driven pressure device"), and therefore additional studies and comparisons were included (e.g. a study ventilator vs flow inflating bag (Menakaya 2004 in Tribolet et al)), as well as studies that had other, potentially confounding interventions.

Additionally, our review identified two newer small RCTs, one of which did not report relevant clinical outcomes {Khan 2023 265}, and one of which was so small {Pallapothu 2023 5565} that it would have made little difference to the size or direction of effect and no difference to the certainty of evidence in our previous review {Trevisanuto 2021 e2021050174}. The one new observational study had such significant selection bias that it would also not have altered previous conclusions {Siripattanapipong 2017 7}.

Consistent with the 2020 ILCOR review and meta-analysis {Trevisanuto 2021 e2021050174}, these new reviews and meta-analyses of RCTs confirm that using “fixed pressure devices” at birth is associated with a reduction of BPD, but does not change mortality, HIE or air leaks. These reviews report a significant reduction in other important (though not critical) outcomes such as DR intubation, need for mechanical ventilation, and surfactant administration.

The evidence from the newer studies is not sufficient to change the current recommendation or to elicit a new systematic or scoping review.

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Trevisanuto D, Roehr CC, Davis PG, Schmolzer GM, Wyckoff MH, Liley HG, et al. Devices for Administering Ventilation at Birth: A Systematic Review. Pediatrics. 2021;148(1)e2021050174.

Tribolet S, Hennuy N, Rigo V. Ventilation devices for neonatal resuscitation at birth: A systematic review and meta-analysis. Resuscitation. 2023;183109681.

Wyckoff MH, Wyllie J, Aziz K, de Almeida MF, Fabres J, Fawke J, et al. Neonatal Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2020;142(16_suppl_1)S185-s221.

Appendix: Search Strategies

Sources searched	Search strategy	Search time frame
Medline	((((((((((("Masks"[Mesh:NoExp]) OR Insufflation[MeSH Terms]) OR self-inflating bag[Title/Abstract]) OR flow-inflating bag[Title/Abstract]) OR anesthesia bag[Title/Abstract]) OR bag valve mask[Title/Abstract]) OR Ambu bag [Title/Abstract]) OR manual resuscitator*[Title/Abstract]) OR t-piece resuscitator*[Title/Abstract]) OR "Ventilators, Mechanical"[Mesh:NoExp])) AND (((((Positive- Pressure Respiration[MeSH Terms]) OR positive end expiratory pressure*[Title/Abstract]) OR PEEP[Title/Abstract]) OR positive pressure respiration [Title/Abstract]) OR positive pressure ventilation[Title/Abstract]))) AND ((("Respiratory Distress Syndrome, Newborn"[Mesh] OR "Bronchopulmonary Dysplasia"[Mesh] OR "Infant, Newborn"[Mesh] OR "Delivery Rooms"[Mesh] OR "Gestational Age"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Premature, Diseases"[Mesh:NoExp] OR "Term Birth"[Mesh] OR "Live Birth"[Mesh] OR "Birth Injuries"[Mesh] OR "Birthing Centers"[Mesh] OR "Neonatal Nursing"[Mesh] OR "Neonatal Screening"[Mesh] OR "Intensive Care, Neonatal"[Mesh] OR "Intensive Care Units, Neonatal"[Mesh] OR "Animals, Newborn"[Mesh] OR "Transient Tachypnea of the Newborn"[Mesh] OR "Persistent Fetal Circulation Syndrome"[Mesh] or newborn[TIAB] or neonatal[TIAB] or neonate[TIAB] or neonates[TIAB] OR "Low Birth Weight "[TIAB] or "Small for Gestational Age"[TIAB] or prematur*[TIAB] or preterm[TIAB] OR infant[TIAB] OR infants[TIAB] OR birth[TIAB] OR "delivery room"[TIAB])))))) NOT ((animals[mh] NOT humans[mh]))	1 January 2020 to 1 July 2024
Embase	#39 (('masks'/exp OR 'insufflation' OR 'self inflating bag':ab,ti OR 'flow-inflating bag':ab,ti OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ti,ab) OR 'bag valve mask*':ti,ab OR 'ambu bag*':ti,ab OR 'manual resuscitator*':ti,ab OR (('t piece':ab,ti AND resuscitator*:ab,ti OR tpiece:ab,ti) AND resuscitator*:ab,ti) OR 'mechanical ventilator') AND ('positive pressure ventilation' OR 'positive end expiratory pressure*.':ab,ti OR 'peep':ab,ti OR 'positive pressure respiration':ab,ti OR 'positive pressure ventilation':ab,ti) AND ('neonatal respiratory distress syndrome' OR (bronchopulmonary AND dysplasia) OR 'newborn' OR 'delivery rooms' OR 'gestational age' OR 'prematurity' OR 'term birth' OR 'live birth' OR 'birth injury' OR ('birthing centers'/exp OR 'birthing centers') OR 'newborn nursing' OR 'newborn screening' OR 'newborn intensive care' OR 'neonatal intensive care unit' OR (('animals,'/exp OR animals,) AND ('newborn'/exp OR newborn)) OR 'transient tachypnea of the newborn' OR 'persistent pulmonary hypertension' OR ((((newborn:ab,ti OR neonatal:ab,ti OR neonate:ab,ti OR neonates:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm*:ab,ti OR infant:ab,ti OR infants:ab,ti OR birth:ab,ti OR delivery:ab,ti) AND room*:ab,ti))) NOT animal* AND [2020-2024]/py 228 #38 animal* 7470164	

	#37 ('masks'/exp OR 'insufflation' OR 'self inflating bag':ab,ti OR 'flow-inflating bag':ab,ti OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ti,ab) OR 'bag valve mask*':ti,ab OR 'ambu bag*':ti,ab OR 'manual resuscitator*':ti,ab OR (('t piece':ab,ti AND resuscitator*:ab,ti OR tpiece:ab,ti) AND resuscitator*:ab,ti) OR 'mechanical ventilator') AND ('positive pressure ventilation' OR 'positive end expiratory pressure*.':ab,ti OR 'peep':ab,ti OR 'positive pressure respiration':ab,ti OR 'positive pressure ventilation':ab,ti) AND ('neonatal respiratory distress syndrome' OR (bronchopulmonary AND dysplasia) OR 'newborn' OR 'delivery rooms' OR 'gestational age' OR 'prematurity' OR 'term birth' OR 'live birth' OR 'birth injury' OR ('birthing centers'/exp OR 'birthing centers') OR 'newborn nursing' OR 'newborn screening' OR 'newborn intensive care' OR 'neonatal intensive care unit' OR (('animals,'/exp OR animals,) AND ('newborn'/exp OR newborn)) OR 'transient tachypnea of the newborn' OR 'persistent pulmonary hypertension' OR ((((newborn:ab,ti OR neonatal:ab,ti OR neonate:ab,ti OR neonates:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm*:ab,ti OR infant:ab,ti OR infants:ab,ti OR birth:ab,ti OR delivery:ab,ti) AND room*:ab,ti)) 570 #36 'neonatal respiratory distress syndrome' OR (bronchopulmonary AND dysplasia) OR 'newborn' OR 'delivery rooms' OR 'gestational age' OR 'prematurity' OR 'term birth' OR 'live birth' OR 'birth injury' OR ('birthing centers'/exp OR 'birthing centers') OR 'newborn nursing' OR 'newborn screening' OR 'newborn intensive care' OR 'neonatal intensive care unit' OR (('animals,'/exp OR animals,) AND ('newborn'/exp OR newborn)) OR 'transient tachypnea of the newborn' OR 'persistent pulmonary hypertension' OR ((((newborn:ab,ti OR neonatal:ab,ti OR neonate:ab,ti OR neonates:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm*:ab,ti OR infant:ab,ti OR infants:ab,ti OR birth:ab,ti OR delivery:ab,ti) AND room*:ab,ti) 1104068 #35 (((newborn:ab,ti OR neonatal:ab,ti OR neonate:ab,ti OR neonates:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm*:ab,ti OR infant:ab,ti OR infants:ab,ti OR birth:ab,ti OR delivery:ab,ti) AND room*:ab,ti 23557 #34 'persistent pulmonary hypertension' 4049 #33 'transient tachypnea of the newborn' 1310 #32 ('animals,'/exp OR animals,) AND ('newborn'/exp OR newborn) 775194 #31 'neonatal intensive care unit' 49784 #30 'newborn intensive care' 29838 #29 'newborn screening' 27092 #28 'newborn nursing' 4094 #27 'birthing centers'/exp OR 'birthing centers' 4929 #26 'birth injury' 8205 #25 'live birth' 43589 #24 'term birth' 6732 #23 'prematurity' 159911 #22 'gestational age' 236249 #21 'delivery rooms' 423 #20 'newborn' 842644 #19 bronchopulmonary AND dysplasia 14006 #18 'neonatal respiratory distress syndrome' 11565	

	#17 'positive pressure ventilation' OR 'positive end expiratory pressure*.':ab,ti OR 'peep':ab,ti OR 'positive pressure respiration':ab,ti OR 'positive pressure ventilation':ab,ti 30313 #16 'positive pressure ventilation':ab,ti 9905 #15 'positive pressure respiration':ab,ti 248 #14 'peep':ab,ti 11709 #13 'positive end expiratory pressure*.':ab,ti 9182 #12 'positive pressure ventilation' 16113 #11 'masks'/exp OR 'insufflation' OR 'self inflating bag':ab,ti OR 'flow-inflating bag':ab,ti OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ti,ab) OR 'bag valve mask*':ti,ab OR 'ambu bag*':ti,ab OR 'manual resuscitator*':ti,ab OR (('t piece':ab,ti AND resuscitator*:ab,ti OR tpiece:ab,ti) AND resuscitator*:ab,ti) OR 'mechanical ventilator' 79721 #10 'mechanical ventilator' 9036 #9 ('t piece':ab,ti AND resuscitator*:ab,ti OR tpiece:ab,ti) AND resuscitator*:ab,ti 173 #8 'manual resuscitator*':ti,ab 85 #7 'ambu bag*':ti,ab 175 #6 'bag valve mask*':ti,ab 904 #5 'anesthesia bag*':ab,ti OR 'anaesthesia bag*':ti,ab 50 #4 'flow-inflating bag':ab,ti 34 #3 'self inflating bag':ab,ti 237 #2 'insufflation' 10820 #1 'masks'/exp 59599	
Results identified	**Results screened full text**	**Results included**
227	11	4

2025 Evidence Update
NLS 5310 – CPAP vs. Positive Pressure Ventilation for Preterm Infants

Worksheet Author(s): Shah BA, Strand M, Fabres J, Leone T, Szyld E
Task Force: Neonatal Life Support
Conflicts of Interest: None

PICOST:
Population: Spontaneously breathing preterm infants with respiratory distress requiring respiratory support in the delivery room
Intervention:CPAP
Comparison: Intubation and IPPV
Outcomes:

- Death or bronchopulmonary dysplasia (critical)
- death (critical), bronchopulmonary dysplasia (critical)
- air leak (critical)
- necrotizing enterocolitis (important
- severe IVH (critical)
- severe retinopathy of prematurity (important)

Study Design: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) are excluded.

Timeframe: New Scoping or Systematic Review search strategy: All years and all languages are included provided there was an English abstract

Year of last full review: 2015 {Perlman 2015 S204}, Evidence Update 2019 {Wyckoff 2020 S185}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Perlman 2015 S204}
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 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). {Dunn 2011 e1069, Finer 2010 1970, Morley 2008 700}

For the critical outcome of **death**, we identified moderate quality evidence (downgraded for risk of bias, imprecision) from the same 3 randomized clinical trials 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. {Dunn 2011 e1069, Finer 2010 1970, Morley 2008 700}

For the critical outcome of **bronchopulmonary dysplasia**, we identified moderate-quality evidence (downgraded for indirectness) from the same 3 randomized clinical trials142–144 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 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 certainty of evidence)

For the critical outcome of a**ir leak**, we identified very low- quality evidence (downgraded for inconsistency and very serious imprecision) from the same 3 randomized clinical trials showing no benefit to starting treatment with CPAP (RR, 1.24; 95% CI, 0.91–1.69). {Dunn 2011 e1069, Finer 2010 1970, Morley 2008 700}

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 showing no benefit to starting treatment with CPAP (RR, 1.09; 95% CI, 0.86–1.39). {Dunn 2011 e1069, Finer 2010 1970, Morley 2008 700}

For the important outcome of **necrotizing enterocolitis**, we identified moderate-quality evidence (downgraded for imprecision) from the same 3 randomized clinical trials showing no benefit to starting treatment with CPAP (RR, 1.19; 95% CI, 0.92–1.55). {Dunn 2011 e1069, Finer 2010 1970, Morley 2008 700}

For the important outcome of severe retinopathy of prematurity, we identified low-quality evidence (downgraded for very serious imprecision) from 2 randomized clinical trials enrolling 1359 infants showing no benefit to starting treatment with CPAP (RR, 1.03; 95% CI, 0.77–1.39). {Dunn 2011 e1069, Finer 2010 1970}

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).

Current and past search strategies: See appendix

Database searched: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to September 13, 2024>
Time Frame: 1 Nov 2019—30 Sep 2024
Date Search Completed: 30 Sep 2024
Search Results:
Identified: 221 articles
Included: 1 systematic review

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Subramanian 2021 {Subramaniam 2021 Cd001243}	Systematic review		3 {Dunn 2011 e1069, Finer 2010 1970, Morley 2008 700}	• CPAP probably reduces BPD at 36 weeks and combined outcome of death and BPD. • CPAP reduces the need for MV and reduces use of surfactant. • Little/no difference in air leak, NEC, severe IVH and ROP.	"There is moderate certainty evidence that CPAP applied prophylactically within the first 15 minutes of life or very early within the first hour of life reduces the incidence of bronchopulmonary dysplasia (BPD), the combined outcome of death and BPD, as well as the need for mechanical ventilation".
Abbreviations: CPAP; continuous positive airway pressure, BPD; bronchopulmonary dysplasia, NEC; necrotizing enterocolitis, IVH; intraventricular hemorrhage, ROP; retinopathy of prematurity					

RCTS: None
Observational studies: None

Reviewer Comments:
This question was last fully reviewed in 2015 {Perlman 2015 S204} Based on moderate certainty of evidence, the initial use of CPAP in the delivery room, rather than intubation and mechanical ventilation, was a weak recommendation for spontaneously breathing

preterm infants. This recommendation was based on 3 randomized trials (including 2,574 infants) {Dunn 2011 e1069, Finer 2010 1970, Morley 2008 700} and a 2013 meta-analysis {Schmölzer 2013 f5980} of those studies. Since that time a Cochrane review was undertaken{Subramaniam 2021 Cd001243} No additional studies were found for inclusion in that systematic review and the recommendations were unchanged from previous conclusions.

An evidence update for this PICOST was completed in 1019 for the 2020 statement of the Consensus on Science of Resuscitation with Treatment Recommendations. {Wyckoff 2020 S185} The evidence update found one additional RCT including 208 infants which compared prophylactic surfactant followed by nasal CPAP with early nasal CPAP. {Sandri 2010 e1402} That study concluded that early prophylactic surfactant followed by CPAP was not superior to early CPAP followed by selective surfactant in decreasing mortality, need for mechanical ventilation in the first 5 days, major morbidities or adverse events. The conclusion of the 2020 evidence update was therefore that there were no new studies that would change the existing treatment recommendation, and that no update of the previous systematic review was required at that time. The authors suggested that future studies with high-risk infants preterm infants at lower gestation would be helpful. Of note, inclusion criteria for the three trials in the previous systematic review were; 26+0 to 29+6 weeks {Dunn 2011 e1069}, 24+0 to 27+6 weeks {Finer 2010 1970} and 25 to 28 weeks {Morley 2008 700}, and this suggestion may still be applicable.

Given the lack of new studies to inform this question there is no change to the current recommendation. An update to the systematic review is not indicated at this time. A decision about timing of a future update may be based on surveillance of the literature.

References:

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Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362(21)1970-9.

Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358(7)700-8.

Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal Resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2015;132(suppl 1)(16)S204–S241.

Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics. 2010;125(6)e1402-9.

Schmölzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ. 2013;347f5980.

Subramaniam P, Ho JJ, Davis PG. Prophylactic or very early initiation of continuous positive airway pressure (CPAP) for preterm infants. Cochrane Database Syst Rev. 2021;10(10)Cd001243.

Wyckoff MH, Wyllie J, Aziz K, de Almeida MF, Fabres J, Fawke J, et al. Neonatal Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2020;142(16_suppl_1)S185-s221.

Appendix – Search strategies

2010/2015 Systematic Review Search Strategy:

Pubmed: (positive end expiratory pressure OR peep OR Intermittent Positive-Pressure Breathing OR Intermittent Positive-Pressure Ventilation) AND (resuscitate* OR (delivery room))

Filters activated: Case Reports, Clinical Trial, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial, Systematic Reviews, Meta-Analysis, Infant: birth-23 months, Newborn: birth-1 month

Embase: (positive end expiratory pressure OR peep OR Intermittent Positive-Pressure Breathing OR Intermittent Positive-Pressure Ventilation) AND (resuscitate* OR (delivery room))
Filters activated: up to one year of age

Cochrane: (PEEP OR “Positive pressure” (phrase) AND (respiration OR ventilation OR breathing (all with word variations)) AND Infant, Newborn (includes premature)

2019 Evidence Update Search Strategy:
Pubmed: (positive end expiratory pressure OR peep OR Intermittent Positive-Pressure Breathing OR Intermittent Positive-Pressure Ventilation) AND (resuscitate* OR (delivery room))
Filters activated: Case Reports, Clinical Trial, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial, Systematic Reviews, Meta-Analysis, Infant: birth-23 months, Newborn: birth-1 month

Embase: (positive end expiratory pressure OR peep OR Intermittent Positive-Pressure Breathing OR Intermittent Positive-Pressure Ventilation) AND (resuscitate* OR (delivery room))
Filters activated: up to one year of age

Cochrane: (PEEP OR “Positive pressure” (phrase) AND Delivery Room AND Infant, Newborn (includes premature)

2024 Evidence Update Search Strategy:

Sources searched	**Search strategy**	**Search time frame**
Medline	(("2019/11/01"[Date - Publication] : "3000"[Date - Publication])) AND (((((continuous positive airway pressure[MeSH Terms]) OR ((((continuous) AND (positive)) AND (airway)) AND (pressure))) OR (continuous positive airway pressure)) AND (((infant, newborn[MeSH Terms]) OR ((infant) AND (newborn))) OR (newborn infant))) AND ((((((((((clinical trial[Publication Type]) OR (comparative study[Publication Type])) OR (controlled clinical trial[Publication Type])) OR (evaluation studies[Publication Type])) OR (multicenter study[Publication Type])) OR (randomized controlled trial[Publication Type])) OR (systematic review[Publication Type])) OR (twin study[Publication Type])) OR (validation study[Publication Type])) OR (meta-analysis[Publication Type]))))	1 Nov 2019—30 Sep 2024
Results identified	**Results screened full text**	**Results included**
221	MISSING	1

2025 Evidence Update
NLS 5312 – CPAP vs. No CPAP for Term and Late Preterm Respiratory Distress in the Delivery Room

Worksheet Authors: Shah BA, Strand M, Fabres J, Leone T, Szyld E, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest: Birju Shah, Jorge Fabres, Tina Leone, Edgardo Szyld and Georg Schmölzer are now participating in PLaNT study (A Pragmatic Randomized Controlled Pilot Trial to Evaluate the Impact of Early Prophylactic Continuous Positive Airway Pressure with or without Supplemental Oxygen in Spontaneously Breathing Late Preterm Newborn Infants Born by Cesarean Delivery, Compared to No Early Prophylactic Continuous Positive Airway Pressure with or without Supplemental Oxygen, on the Need for Further Respiratory Support Leading to NICU Admissions.) (NCT05204719)

PICOST:
Population: Spontaneously breathing ≥34+0 weeks gestation infants having or at risk of having respiratory distress during transition after birth
Intervention: Continuous positive airway pressure (CPAP) at different levels with or without supplemental oxygen
Comparison: No CPAP with or without supplemental oxygen
Outcomes: Admission to neonatal intensive care unit (NICU) or higher level of care (important), provision of tracheal intubation or chest compressions in the delivery room (important), use and duration of respiratory support in NICU (important), air-leak syndromes (important), death prior to hospital discharge (critical), length of hospital stay (important)
Study Design: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) are excluded.
Timeframe: All years and all languages were included if an English abstract was available. The literature search was first performed on November 30, 2020 and updated on October 11, 2021.

Year of last full review: 2021 {Shah 2022 100320}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Shah , Wyckoff 2022 208} The systematic review identified two RCTs {Celebi 2016 99, Osman 2019 597} and two observational studies, one of which was reported in two publications. {Hishikawa 2016 1, Hishikawa 2015 F382, Smithhart 2019 e20190756} Relevant data from the author via electronic communications have been collated into one study for purpose of this meta-analysis {Hishikawa 2016 1, Hishikawa 2015 F382}

*For the important outcome of **NICU admissions*** we have identified **very low-certainty** evidence (downgraded for imprecision and risk of bias) from two RCTs {Celebi 2016 99, Osman 2019 597} enrolling 323 infants born by caesarean section with or without respiratory distress showing benefit with the use of early CPAP (absolute effect 94 fewer per 1,000; 95% CI 115 fewer to 44 fewer per 1,000, number needed to treat 11; 95% CI 9 to 23).

*For the important outcome of **air leak syndromes*** we have identified **very low-certainty** evidence (downgraded for risk of bias) from two observational studies {Hishikawa 2016 1, Hishikawa 2015 F382, Smithhart 2019 e20190756} enrolling 8476 infants showing positive association with CPAP use and air leak syndromes (absolute effect 133 more per 1,000; 95% CI 106 more to 166 more per 1,000). The two RCTs available for this review comparing 168 subjects with CPAP of 5 cm H2O versus 155 subjects with no CPAP reported no cases of pulmonary air leak.

*For the important outcome of **NICU respiratory support*** we identified **very low-certainty** evidence (downgraded for risk of bias and imprecision) from two RCTs {Celebi 2016 99, Osman 2019 597} enrolling 323 infants showing

benefit with the use of early CPAP (absolute effect 79 fewer per 1,000; 95% CI 91 fewer to 39 fewer per 1,000, number needed to treat 13; 95% CI 11 to 26).

*For the critical outcome of **death at discharge*** we identified **very low-certainty** evidence (downgraded for risk of bias and imprecision) from two RCTs {Celebi 2016 99, Osman 2019 597} enrolling 323 infants showing we could not exclude benefit or harm (absolute effect 5 fewer per 1,000; 95% CI 6 fewer to 39 more per 1,000).

*For the important outcome of **tracheal intubation or chest compressions in the delivery room*** we did not identify any evidence in the included studies.

*For the critical outcome of **neurodevelopmental impairment*** we did not identify any evidence in the included studies.

Subgroup Analyses:

Not enough data were reported to perform prespecified subgroup analyses on late preterm (34^{+0}-36^{+6} weeks), term (37^{+0}-41^{+6} weeks), post term (greater than or equal to 42 weeks); mode of delivery: caesarean section versus vaginal delivery; any previous positive pressure support (positive pressure ventilation or sustained inflation); supplemental oxygen for targeting oxygen saturation goals; mode of support: interface (facemask vs. nasal prongs/cannula); device (T-piece vs. flow-Inflating bag) and level of continuous positive airway pressure support: high continuous positive airway pressure (>6 cm H_2O) versus low continuous positive airway pressure (4-6 cm H_2O).

Treatment Recommendation:
For spontaneously breathing term and ≥34+0 weeks' gestation newborn infants having or at risk of having respiratory distress in the delivery room, there is insufficient published evidence to suggest for or against routine use of CPAP compared with no CPAP.

Current Search Strategy: See appendix
Database searched: (via Ovid interface) Cochrane Central Register of Controlled Trials (CENTRAL), Medline and Embase
Time Frame: The search was updated from 2021- June 2024
Date Search Completed: June 2024
Search Results:
Identified: 43
Included: 1

Summary of Evidence Update:
Systematic reviews or Guidelines: none relevant
RCTs: none
Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Stocks 2022 {Stocks 2022 761}	**Study Type:** Observational (retrospective cohort study) before (epoch 1) and after (epoch 2)	**Inclusion Criteria:** *Full birth cohort* 2012-2020 (94,469 neonates) • Epoch 1 n= 51,818 • Epoch 2 n=42,651	**Pneumothorax on day 1** *Full birth cohort* • Epoch 1; 201/58,818 (0.4%) • Epoch 2; 113/42,651 (0.3%)	In both the study as a whole and among infants admitted to the NICU, pneumothoraces after DR-CPAP were reduced among infants

	change in guidelines "to avoid delivery room CPAP (DR-CPAP) in infants ≥35 wks exhibiting grunting, tachypnea or retractions without preductal saturation lower than the NRP guidelines" N=94,469	*NICU subgroup* (8087 neonates) who "had a resuscitation team call and were subsequently admitted to the NICU" • Epoch 1; n=2951 • Epoch 2; n=2852 *Received DR-CPAP:* • Epoch 1; 1014 (2.0%) • Epoch 2; 916 (2.1%)	p<0.001 *After DR-CPAP*: • Epoch 1; 112/1014 (11%) • Epoch 2; 55/916 (6%) p=0.003 *After no DR-CPAP* • Epoch 1; 89/50,804 (0.2%) • Epoch 2 58/41735 (0.1%) p=0.17 Adjusted RR of pneumothorax after DR-CPAP exposure was 66.44, (95% CI 53.06–83.20) p<0.001 Estimated RD was 0.10 (95% CI 0.09–0.12) and adjusted NNH 10, CI 8–11	who did not require PPV or supplemental oxygen There was an unexpected increase in spontaneous pneumothoraces among infants exposed only to oxygen in the DR (9.4 vs 6.2%, P=0.009) No ultrasound surveillance for pneumothoraces, so they were more likely to have been diagnosed in symptomatic infants who had a chest radiograph.
Abbreviations: DR-CPAP – received CPAP in the delivery room as a sole intervention, wks; weeks, NICU; neonatal intensive care unit, 95% CI; 95% confidence intervals, RR; risk ratio, RD; risk difference, NNH; number needed to treat (to harm).				

Reviewer Comments:
From the previous systematic review, there was insufficient published evidence to suggest for or against routine use of CPAP compared with no CPAP in spontaneously breathing term and ≥34+0 weeks' gestation newborn infants having or at risk of having respiratory distress in the delivery room. {Shah 2022 100320, Wyckoff 2022 208} This conclusion was based on 2 randomized trials {Celebi 2016 99, Osman 2019 597} and 2 observational studies. {Hishikawa 2016 1, Smithhart 2019 e20190756} The two RCTs, both from from lower-middle-income countries included only 323 newborn infants born from caesarean deliveries showed a potential benefit of early CPAP for reduced likelihood of NICU admissions with a number needed to treat of 10.8 (95% CI: 8.7, 22.7). {Celebi 2016 99, Osman 2019 597} The larger of the RCTs (n=259) used prophylactic CPAP. {Celebi 2016 99} No incidences of air-leak or other complications were reported in either the RCTs. The evidence was considered indirect with respect to the PICOST question due to the narrow eligibility criteria and the use of prophylactic CPAP in one study, and imprecise due to the small total sample size.

The two large observational studies included in the previous review (pre- and post-changes in guidelines or CPAP availability) found an association between delivery room CPAP use and the presence of air-leak syndromes. {Hishikawa 2016 1, Smithhart 2019 e20190756} One cohort included only term infants {Hishikawa 2016 1} and the other reported pneumothorax rates only for those admitted to the NICU. {Smithhart 2019 e20190756}

Therefore, in making decision from the limited available evidence, we integrated the values placed on avoidance of potential harm as noted by the positive association between CPAP use and air leak syndromes, and potential benefit as noted by the risk reduction in NICU admission among infants born by Caesarean section. {Wyckoff 2022 208}

The new study included in this evidence update suggested no harm and possible benefit from *reducing* the use of CPAP for term and late preterm infants immediately after birth who have signs of respiratory distress (e.g. grunting, retractions or tachypnea) but whose saturations are reaching target ranges. {Stocks 2022 761} However,

despite adjustment for possible confounders, the observational nature of the study means that there is still the potential for residual confounding.

Given the lack of new RCTs to inform this question there is no change to the current recommendation. An updated systematic review is not currently recommended. The timing of a future update may be informed by ongoing surveillance of literature.

References:

Celebi MY, Alan S, Kahvecioglu D, Cakir U, Yildiz D, Erdeve O, et al. Impact of Prophylactic Continuous Positive Airway Pressure on Transient Tachypnea of the Newborn and Neonatal Intensive Care Admission in Newborns Delivered by Elective Cesarean Section. Am J Perinatol. 2016;33(1)99-106.

Hishikawa K, Fujinaga H, Fujiwara T, Goishi K, Kaneshige M, Sago H, et al. Respiratory Stabilization after Delivery in Term Infants after the Update of the Japan Resuscitation Council Guidelines in 2010. Neonatology. 2016;110(1)1-7.

Hishikawa K, Goishi K, Fujiwara T, Kaneshige M, Ito Y, Sago H. Pulmonary air leak associated with CPAP at term birth resuscitation. Arch Dis Child Fetal Neonatal Ed. 2015;100(5)F382-7.

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Shah BA, Fabres JG, Szyld EG, Leone TA, Schmölzer GM, de Almeida MF, et al. Continuous positive airway pressure versus no continuous positive airway pressure for term and late preterm respiratory distress in the delivery room (NLS#5312 [Internet] Brussels, Belgium. Available from: https://costr.ilcor.org/document/continuous-positive-airway-pressure-cpap-versus-no-cpap-for-term-respiratory-distress-in-delivery-room-nls-5312.

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Wyckoff MH, Greif R, Morley PT, Ng KC, Olasveengen TM, Singletary EM, et al. 2022 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. Resuscitation. 2022;181208-288.

Appendix – Search Strategy

Sources searched	**Search strategy**	**Search time frame**
Ovid MEDLINE	1 Continuous Positive Airway Pressure/ 2 (cpap or ncpap).mp. 3 (contin$ positiv$ air$ pressur$ or contin$ positiv$ pressur$ or contin$ disten$ air$ pressur$ or contin$ positiv$ trans$ pressur$ or contin$ inflat$ pressur$ or contin$ negat$ disten$ pressur$ or contin$	2021- June 2024

	negat$ pressur$ or contin$ air$ pressur$ or contin$ disten$ pressur$).mp. 4 or/1-3 5 (infan$ or neonat$ or neo-nat$ or newborn$ or new$ born$ or baby$ or babies).mp. 6 4 and 5 7 limit 6 to animals 8 6 not 7 9 remove duplicates from 8 10 limit 9 to (case reports or comment or editorial or letter or news) 11 9 not 10 12 Term Birth/ 13 ((term or fullterm$ or full$ term$ or late$ preterm$ or near$ term$) adj (birth$ or childbirth$ or infant$ or neonat$ or neo-nat$ or newborn$ or new$ born$ or baby$ or babies)).mp. 14 ((34$ or 35$ or 36$ or 37$ or 38$ or 39$ or 40$ or 41$ or 42$) adj2 (gestat$ or week$ or ag$)).mp. 15 or/12-14 16 11 and 15 17 ((term or fullterm$ or full$ term$ or late$ preterm$ or near$ term$) adj (birth$ or childbirth$ or infant$ or neonat$ or neo-nat$ or newborn$ or new$ born$ or baby$ or babies)).ti. 18 ((34$ or 35$ or 36$ or 37$ or 38$ or 39$ or 40$ or 41$ or 42$) adj2 (gestat$ or week$ or ag$)).ti,kf. 19 delivery rooms/ 20 ((deliver$ or childbirth$ or birth$) adj2 room$).ti,kf. 21 or/12,17-20 22 16 and 21 32 16 not 22 33 11 not 16	
EMBASE	1 positive end expiratory pressure/ 2 (cpap or ncpap).mp. 3 (contin$ positiv$ air$ pressur$ or contin$ positiv$ pressur$ or contin$ disten$ air$ pressur$ or contin$ positiv$ trans$ pressur$ or contin$ inflat$ pressur$ or contin$ negat$ disten$ pressur$ or contin$ negat$ pressur$ or contin$ air$ pressur$ or contin$ disten$ pressur$).mp. (4 or/1-3 5 (infan$ or neonat$ or neo-nat$ or newborn$ or new$ born$ or baby$ or babies).mp 6 4 and 5 7 limit 6 to animals 8 6 not 7 9 limit 8 to conference abstracts 10 8 not 9 11 limit 10 to (conference paper or editorial or letter or note) (930) 12 10 not 11 13 case report/ 14 12 not 13 15 term birth/	

	16 ((term or fullterm$ or full$ term$ or late$ preterm$ or near$ term$) adj (birth$ or childbirth$ or infant$ or neonat$ or neo-nat$ or newborn$ or new$ born$ or baby$ or babies)).mp. (36303) 17 ((34$ or 35$ or 36$ or 37$ or 38$ or 39$ or 40$ or 41$ or 42$) adj2 (gestat$ or week$ or ag$)).mp. 18 delivery room/ 19 ((deliver$ or childbirth$ or birth$) adj2 room$).mp. 20 or/15-19 21 14 and 20 22 *positive end expiratory pressure/ 23 (cpap or ncpap).ti,kw. 24 (contin$ positiv$ air$ pressur$ or contin$ positiv$ pressur$ or contin$ disten$ air$ pressur$ or contin$ positiv$ trans$ pressur$ or contin$ inflat$ pressur$ or contin$ negat$ disten$ pressur$ or contin$ negat$ pressur$ or contin$ air$ pressur$ or contin$ disten$ pressur$).ti,kw. 25 or/22-24 26 14 and 25 27 21 or 26	
EBM Reviews - Cochrane Central Register of Controlled Trials	1 Continuous Positive Airway Pressure/ 2 (cpap or ncpap).mp. 3 (contin$ positiv$ air$ pressur$ or contin$ positiv$ pressur$ or contin$ disten$ air$ pressur$ or contin$ positiv$ trans$ pressur$ or contin$ inflat$ pressur$ or contin$ negat$ disten$ pressur$ or contin$ negat$ pressur$ or contin$ air$ pressur$ or contin$ disten$ pressur$).mp. 4 or/1-3 5 (infan$ or neonat$ or neo-nat$ or newborn$ or new$ born$ or baby$ or babies).mp. 6 4 and 5	
Results identified	**Results screened full text**	**Results included**
43	MISSING	1

2025 Evidence Update
NLS 5320 – Sustained Inflation at Birth

Worksheet Author(s): Soraisham A, Urlesberger B, Kapadia V, Rüdiger, M
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 29 October 2024
Conflicts of Interest: None

PICOST:
Population: For newborn infants who receive positive pressure ventilation for bradycardia or ineffective respirations at birth
Intervention: Initiating positive pressure ventilation (PPV) with sustained inflation(s) >1 second (s) (SI)
Comparator: Initiating PPV with intermittent inflations, lasting ≤1 s per breath
Outcome: (Note: Additional details on outcomes and prioritization are provided in the full online CoSTR.{El-Naggar W 2021 })
Primary outcomes: Death before hospital discharge (critical)
Secondary outcomes:

- Death in the delivery room (critical); death within first 48 hours (critical); death at the latest follow-up (critical)
- Long term neurodevelopmental (ND) or behavioral or education outcomes at >18 months corrected age, using validated assessment tool(s) (critical)
- Use of mechanical ventilation during hospitalization (important)
- Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema) reported individually or as a composite outcome, at any time during initial hospitalization (important)
- Bronchopulmonary dysplasia, defined as use of supplemental oxygen at 28 days of age; need for supplemental oxygen at 36 weeks of gestational age for infants born at or before 32 weeks of gestation (latest reported outcome) (critical)
- Intraventricular hemorrhage, grade 3 or 4 (critical)
- Retinopathy of prematurity, stage 3 or above (critical)

Study Design: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) were excluded.
Timeframe: from inception of the databases to 20 July 2020 .

Year of last full review: 2019 {Kapadia 2021 e2020021204}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Wyckoff 2020 S185}
Consensus on Science

For the critical outcome of **death before discharge**, evidence of low certainty (downgraded for risk of bias and inconsistency) from 10 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1502 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with sustained inflation(SI) >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.09; 95% CI 0.83-1.43; I^2 = 42%; 10 more patients/1000 died before discharge when SI was used [18 fewer to 47 more per 1000]).

For the critical outcome of **death in the delivery room**, evidence of very low certainty (downgraded for risk of bias and very serious imprecision) from 9 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1076 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 2.82; 95% CI 0.45-17.66; I^2 = 0%; 4 more patients/1000 died in the delivery room with SI [95% CI, 1 fewer to 33 more per 1000]).

For the critical outcome of **death within 48 hours**, low certainty evidence (downgraded for risk of bias and imprecision) from 10 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1502 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed evidence of harm when initiating PPV with SI >1 s

compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 2.42; 95% CI 1.15-5.09; I^2 = 10%; 18 more patients/1000 died within 48 hours with SI [95% CI, 2 more to 51 more per 1000]) The number needed to harm is 55 [95% CI, 20 - 500].

For the critical outcome of long term neurodevelopmental or behavioural or educational outcomes, no studies were identified.

For the critical outcome of **death at latest follow up**, no studies were identified.

For the critical outcome of **bronchopulmonary dysplasia**, low certainty evidence (downgraded for risk of bias and imprecision) from 10 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1502 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 0.93; 95% CI 0.79-1.10; I^2 = 8%; 19 fewer patients/1000 developed bronchopulmonary dysplasia with SI [95% CI, 58 fewer to 27 more per 1000]).

For the critical outcome of **intraventricular hemorrhage grade 3 or 4**, low certainty evidence (downgraded for risk of bias and imprecision) from 9 RCTs {Abd El-Fattah 2017 409, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1390 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 0.88; 95% CI 0.63-1.23; I^2 = 0%; 11 fewer patients/1000 developed intraventricular haemorrhage grade 3 or 4 with SI[95% CI, 35 fewer to 22 more per 1000]).

For the critical outcome of **retinopathy of prematurity stage 3 or higher**, low certainty evidence (downgraded for risk of bias and imprecision) from 9 RCTs {Abd El-Fattah 2017 409, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} reporting this outcome for 1342 of 1390 enrolled preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no benefit or harm when initiating PPV with SI >1 s when compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 0.83; 95% CI 0.62-1.11; I^2 =19% ; 22 fewer patients/1000 developed retinopathy of prematurity stage 3 or higher with SI [95% CI, 49 fewer to 14 more per 1000]). In one of the studies {Kirpalani 2019 1165}, this outcome was not available for 48 of the enrolled infants.

For the important outcome of **use of mechanical ventilation during hospitalization**, low certainty evidence (downgraded for risk of bias and imprecision from 6 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, La Verde 2019 S110, Lista 2015 e457, Mercadante 2016 443} enrolling 813 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no benefit or harm when initiating PPV with SI >1 s when compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 0.87; 95% CI 0.74-1.02; I^2 = 0%; 51 fewer patients/1000 used mechanical ventilation during the hospitalization with SI [95% CI, 103 fewer to 8 more per 1000]).

For the important outcome of **air leak during hospitalization**, low certainty evidence (downgraded for risk of bias and imprecision) from 9 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1076 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s when compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.26; 95% CI 0.72-2.21; I^2 = 17%; 9 more patients/1000 developed air leak during hospitalization with the SI [95% CI, 9 fewer to 41 more per 1000]).

<u>Subgroup analysis for primary outcome:</u>
Subgroup newborns <28+0 weeks
For the critical outcome of **death before discharge**, low certainty evidence (downgraded for risk of bias and imprecision) from 5 RCTs {Jiravisitkul 2017 68, Kirpalani 2019 1165, Lindner 2005 303, Lista 2015 e457, Ngan 2017 F525} enrolling 862 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed evidence of potential harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.38; 95% CI 1.00-1.91; I^2 = 0%; 46 more patients/1000 died before discharge with the SI [95% CI, 0 fewer to 110 more per 1000]) The number needed to harm is 22[95% CI, 9 - >1000].

Subgroup newborns 28+1 weeks to 31+6 weeks
For the critical outcome of **death before discharge**, very low certainty evidence (downgraded for risk of bias and very serious imprecision) from 4 RCTs {La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Ngan 2017 F525} enrolling 175 preterm

newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s when compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.33; 95% CI 0.22-8.20; I^2 = 5%; 4 more patients/1000 died before hospital discharge with SI [95% CI, 9 fewer to 86 more per 1000]).

Subgroup 1st sustained inflation of 6-15 s duration
For the critical outcome of **death before discharge**, very low certainty evidence (downgraded for risk of bias, inconsistency and imprecision) from 9 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Schwaberger 2015 e0138964} enrolling 1300 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV using SI >1 s when compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.10; 95% CI 0.83-1.46; I^2 = 45%; 12 more patients/1000 died before hospital discharge with SI [95% CI, 20 fewer to 53 more per 1000]).

Subgroup 1st sustained inflation of >15 s duration
For the critical outcome of **death before discharge**, very low certainty evidence (downgraded for risk of bias and very serious imprecision) from 2 RCTs {Abd El-Fattah 2017 409, Ngan 2017 F525} enrolling 222 preterm newborns who received PPV for bradycardia for ineffective respirations at birth showed no significant benefit or harm from

initiating PPV using SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 0.70; 95% CI 0.31-1.60; I2 = 31%; 28 fewer patients/1000 died before hospital discharge with SI [95% CI, 65 fewer to 57 more per 1000]).

Subgroup 1st sustained inflation with inspiratory pressure >20 mmHg
For the critical outcome of **death before discharge**, low certainty evidence (downgraded for risk of bias and imprecision) from 6 RCTs {Jiravisitkul 2017 68, La Verde 2019 S110, Lindner 2005 303, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 803 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.26; 95% CI 0.71-2.24; I^2 = 0%; 12 more patients/1000 died before hospital discharge with SI [95% CI, 14 fewer to 59 more per 1000]).

Subgroup 1st sustained inflation with inspiratory pressure ≤20 mmHg
For the critical outcome of **death before discharge**, very low certainty evidence (downgraded for risk of bias, inconsistency and imprecision from 4 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Kirpalani 2019 1165, Lindner 2005 303} enrolling 699 preterm newborns who received PPV for bradycardia or ineffective respirations at birth could not exclude benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.04; 95% CI 0.77-1.42; I^2 = 69%; more patients/1000 died before hospital discharge with SI [95% CI, 43 fewer to 73 more per 1000]).

<u>Sensitivity analysis for primary outcome:</u>
Excluding studies with very high risk of bias
For the critical outcome of **death before discharge**, low certainty evidence (downgraded for risk of bias and imprecision) from 9 RCTs {Abd El-Fattah 2017 409, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964}enrolling 1390 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.24; 95% CI 0.92-1.68; I^2 = 24%; 21 more patients/1000 died before hospital discharge with SI [95% CI, 7 fewer to 61 more per 1000]).

Excluding studies that allowed only a single sustained inflation during resuscitation
For the critical outcome of **death before discharge**, low certainty evidence (downgraded for risk of bias and imprecision) from 9 RCTs {El-Chimi 2017 1273, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lindner 2005 303, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1402 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.17; 95% CI 0.88-1.55; I^2 = 22%; 18 more patients/1000 died before hospital discharge with SI [95% CI, 13 fewer to 58 more per 1000]).

Sustained inflation with mask only
For the critical outcome of **death before discharge**, low certainty evidence (downgraded for risk of bias and imprecision from 9 RCTs {Abd El-Fattah 2017 409, El-Chimi 2017 1273, Jiravisitkul 2017 68, Kirpalani 2019 1165, La Verde 2019 S110, Lista 2015 e457, Mercadante 2016 443, Ngan 2017 F525, Schwaberger 2015 e0138964} enrolling 1441 preterm newborns who received PPV for

bradycardia or ineffective respirations at birth showed no significant benefit or harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.06; 95% CI 0.61-1.39; I^2 = 42%; 7 more patients/1000 died before hospital discharge with SI [95% CI, 44 fewer to 44 more per 1000])

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

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

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
New Search strategy: See appendix.
Database searched: Embase, Medline.
Time Frame: updated from 1 January 2020 to 2 July 2024 (6 months overlap with previous search)
Date Search Completed: 2 July 2024
Search Results:
Identified: 126
Included: 1

Summary of Evidence Update:

RCT:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Abuel Hamd 2021 {Abuel Hamd 2021 1}	**Study Aim:** To investigate the effect of application of SLI at birth on the respiratory outcome of preterm infants with respiratory distress syndrome. **Study Type:** RCT N=160	**Inclusion Criteria:** GA ≥ 27 weeks and ≤ 32 weeks Appropriate for GA Weight >800 grams **Exclusion criteria:** Major anomalies, Fetal hydrops	**Intervention:** SLI was given using a peak pressure of 20 cm H_2O sustained for 15 seconds, using a T-piece resuscitator, (Neopuff ® device) followed by CPAP N=80 **Comparison:** No SLI Resuscitation according to the American NRP guidelines. Then CPAP alone N=80	**1° endpoint:** No difference in the need for IMV in the first 72 h of life between SLI and control (OR: 0.62, 95% CI: 0.33–1.18; p = 0.15).	**Relevant 2° Endpoint:** There was no difference in the incidence of pneumothorax (13% vs 14%, p=0.82), BPD among Survivors (14% vs 18%, p =0.63) or mortality (45% vs 58%, p=0.11) between SLI and control groups. Mortality in the first 72 hours of age was not different (19% vs 11%, p =0.18) **Subgroup analysis:** SLI significantly reduced the primary outcome in the sicker infants, who had clinical eligibility criteria

					(defined as presence of HR<100, gasping, apnea or labored breathing or persistent cyanosis) (CEC; OR: 0.224, 95% CI: 0.076–0.663; p= 0.005) and in the smaller babies: whose GA was <30 weeks (OR: 0.183, 95% CI: 0.053–0.635; p= 0.005). **Study Limitations:** Non-blinded nature of the study.
Abbreviations: SLI; sustained lung inflation, RCT; randomized controlled trial, CPAP; continuous positive airway pressure, NRP; Neonatal Resuscitation Program, BPD; bronchopulmonary dysplasia, OR; odds ratio, CI; confidence intervals; GA; gestational age					

Reviewer Comments:
The recommendation from the previous systematic review which included 10 RCTs enrolling 1502 participants stated that "for preterm newborn infants who receive positive pressure ventilation due to bradycardia or ineffective respirations at birth, we suggest against the routine use of initial sustained inflation(s) greater than 5 seconds (weak recommendation, low-certainty evidence). A sustained inflation may be considered in research settings."

This single RCT (which enrolled 160 participants, whereas the previous systematic review included 10 RCTs enrolling 1502 participants) would not change the direction of effect or certainty of the evidence for outcomes of the previous systematic review. There are no ongoing trials on sustained inflation in neonates in the clinical trial registries/Cochrane database. Therefore, the treatment recommendations of the previous review remain unchanged. There is also insufficient new evidence to recommend updating the systematic review at this time.

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Appendix – Search Strategy

Sources searched	Search strategy	Search time frame
Medline/Embase	#79 ((exp AND ('face mask'/exp OR 'face mask')) OR 'mechanical ventilator' OR 'manual ventilation' OR 'self inflating bag' OR 'flow-inflating bag' OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ab,ti) OR 'bag valve mask*':ab,ti OR 'ambu bag*':ab,ti OR 'manual resuscitator':ab,ti OR (('t piece':ab,ti OR tpiece:ab,ti OR t:ab,ti) AND piece:ab,ti AND resuscitator*:ab,ti)) AND ('peep':ab,ti OR 'positive end expiratory pressure':ab,ti OR 'positive pressure ventilation':ab,ti OR 'positive pressure respiration':ab,ti) AND (('newborn hypoxia'/exp OR 'newborn hypoxia') OR ('prematurity'/exp OR 'prematurity') OR ('newborn apnea attack'/exp OR 'newborn apnea attack') OR ('newborn disease'/exp OR 'newborn disease') OR ('neonatal stress'/exp OR 'neonatal stress') OR ('lung dysplasia'/exp OR 'lung dysplasia') OR ('newborn'/exp OR 'newborn') OR ('low birth weight'/exp OR 'low birth weight') OR ('newborn screening'/exp OR 'newborn screening') OR ('newborn monitoring'/exp OR 'newborn monitoring') OR ('newborn care'/exp OR 'newborn care') OR ('newborn period'/exp OR 'newborn period') OR ('birth weight'/exp OR 'birth weight') OR ('newborn morbidity'/exp OR 'newborn morbidity') OR ('live birth'/exp OR 'live birth') OR ('newborn death'/exp OR 'newborn death') OR ('newborn mortality'/exp OR 'newborn mortality') OR (('delivery'/exp OR delivery) AND room) OR ((((newborn*:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR post:ab,ti) AND mature:ab,ti) OR (newborn*:ab,ti OR 'low birth weight':ab,ti OR 'small for	2021 to 2 July 2024

	gestational age':ab,ti OR 'prematur*':ab,ti OR preterm:ab,ti OR postmature:ab,ti)) AND [2020-2024]/py 86 2 Jul 2024 #78 ('newborn hypoxia'/exp OR 'newborn hypoxia') OR ('prematurity'/exp OR 'prematurity') OR ('newborn apnea attack'/exp OR 'newborn apnea attack') OR ('newborn disease'/exp OR 'newborn disease') OR ('neonatal stress'/exp OR 'neonatal stress') OR ('lung dysplasia'/exp OR 'lung dysplasia') OR ('newborn'/exp OR 'newborn') OR ('low birth weight'/exp OR 'low birth weight') OR ('newborn screening'/exp OR 'newborn screening') OR ('newborn monitoring'/exp OR 'newborn monitoring') OR ('newborn care'/exp OR 'newborn care') OR ('newborn period'/exp OR 'newborn period') OR ('birth weight'/exp OR 'birth weight') OR ('newborn morbidity'/exp OR 'newborn morbidity') OR ('live birth'/exp OR 'live birth') OR ('newborn death'/exp OR 'newborn death') OR ('newborn mortality'/exp OR 'newborn mortality') OR (('delivery'/exp OR delivery) AND room) OR ((((newborn*:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR post:ab,ti) AND mature:ab,ti) OR (newborn*:ab,ti OR 'low birth weight':ab,ti OR 'small for gestational age':ab,ti OR 'prematur*':ab,ti OR preterm:ab,ti OR postmature:ab,ti) 29999192 Jul 2024 #77 newborn*:ab,ti OR 'low birth weight':ab,ti OR 'small for gestational age':ab,ti OR 'prematur*':ab,ti OR preterm:ab,ti OR postmature:ab,ti 593011 2 Jul 2024 #76 (((newborn*:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR post:ab,ti) AND mature:ab,ti 22865 2 Jul 2024 #75 ('delivery'/exp OR delivery) AND room 27238 2 Jul 2024 #74 'newborn mortality'/exp OR 'newborn mortality' 18126 2 Jul 2024 #73 'newborn death'/exp OR 'newborn death' 13526 2 Jul 2024 #72 'live birth'/exp OR 'live birth' 43593 2 Jul 2024 #71 'newborn morbidity'/exp OR 'newborn morbidity' 11833 2 Jul 2024 #70 'birth weight'/exp OR 'birth weight' 186542 2 Jul 2024 #69 'newborn period'/exp OR 'newborn period' 16934 2 Jul 2024 #68 'newborn care'/exp OR 'newborn care' 52601 2 Jul 2024 #67 'newborn monitoring'/exp OR 'newborn monitoring' 1192 2 Jul 2024 #66 'newborn screening'/exp OR 'newborn screening' 27098 2 Jul 2024 #65 'low birth weight'/exp OR 'low birth weight' 89125 2 Jul 2024 #64 'newborn'/exp OR 'newborn' 842778 2 Jul 2024 #63 'lung dysplasia'/exp OR 'lung dysplasia' 16792 2 Jul 2024 #62 'neonatal stress'/exp OR 'neonatal stress' 555 2 Jul 2024 #61 'newborn disease'/exp OR 'newborn disease' 2233978 2 Jul 2024 #60 'newborn apnea attack'/exp OR 'newborn apnea attack' 16 2 Jul 2024 #59 'prematurity'/exp OR 'prematurity' 160403 2 Jul 2024 #58 'newborn hypoxia'/exp OR 'newborn hypoxia' 8368 2 Jul 2024 #57 'peep':ab,ti OR 'positive end expiratory pressure':ab,ti OR 'positive pressure ventilation':ab,ti OR 'positive pressure respiration':ab,ti 24628 2 Jul 2024 #56 'positive pressure respiration':ab,ti 248 2 Jul 2024 #55 'positive pressure ventilation':ab,ti 9907 2 Jul 2024	

#54 'positive end expiratory pressure':ab,ti 9007 2 Jul 2024
#53 'peep':ab,ti 11709 2 Jul 2024
#52 (exp AND ('face mask'/exp OR 'face mask')) OR 'mechanical ventilator' OR 'manual ventilation' OR 'self-inflating bag' OR 'flow-inflating bag' OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ab,ti) OR 'bag valve mask*':ab,ti OR 'ambu bag*':ab,ti OR 'manual resuscitator':ab,ti OR (('t piece':ab,ti OR tpiece:ab,ti OR t:ab,ti) AND piece:ab,ti AND resuscitator*:ab,ti) 11859 2 Jul 2024
#51 ('t piece':ab,ti OR tpiece:ab,ti OR t:ab,ti) AND piece:ab,ti AND resuscitator*:ab,ti 173 2 Jul 2024
#50 'manual resuscitator':ab,ti 52 2 Jul 2024
#49 'ambu bag*':ab,ti 175 2 Jul 2024
#48 'bag valve mask*':ab,ti 904 2 Jul 2024
#47 'anesthesia bag*':ab,ti OR 'anaesthesia bag*':ab,ti 50 2 Jul 2024
#46 'flow-inflating bag' 41 2 Jul 2024
#45 'self-inflating bag' 257 2 Jul 2024
#44 'manual ventilation' 1324 2 Jul 2024
#43 'mechanical ventilator' 9038 2 Jul 2024
#42 exp AND ('face mask'/exp OR 'face mask') 170 2 Jul 2024
#41 ((exp AND ('face mask'/exp OR 'face mask')) OR 'mechanical ventilator' OR 'manual ventilation' OR 'self-inflating bag' OR 'flow-inflating bag' OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ab,ti) OR 'bag valve mask*':ab,ti OR 'ambu bag*':ab,ti OR 'manual resuscitator':ab,ti OR (('t piece':ab,ti OR tpiece:ab,ti OR t:ab,ti) AND piece:ab,ti AND resuscitator*:ab,ti)) AND ('peep':ab,ti OR 'positive end expiratory pressure':ab,ti OR 'positive pressure ventilation':ab,ti OR 'positive pressure respiration':ab,ti) AND (('newborn hypoxia'/exp OR 'newborn hypoxia') OR ('prematurity'/exp OR 'prematurity') OR ('newborn apnea attack'/exp OR 'newborn apnea attack') OR ('newborn disease'/exp OR 'newborn disease') OR ('neonatal stress'/exp OR 'neonatal stress') OR ('lung dysplasia'/exp OR 'lung dysplasia') OR ('newborn'/exp OR 'newborn') OR ('low birth weight'/exp OR 'low birth weight') OR ('newborn screening'/exp OR 'newborn screening') OR ('newborn monitoring'/exp OR 'newborn monitoring') OR ('newborn care'/exp OR 'newborn care') OR ('newborn period'/exp OR 'newborn period') OR ('birth weight'/exp OR 'birth weight') OR ('newborn morbidity'/exp OR 'newborn morbidity') OR ('live birth'/exp OR 'live birth') OR ('newborn death'/exp OR 'newborn death') OR ('newborn mortality'/exp OR 'newborn mortality') OR (('delivery'/exp OR delivery) AND room) OR ((((newborn*:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR post:ab,ti) AND mature:ab,ti) OR (newborn*:ab,ti OR 'low birth weight':ab,ti OR 'small for gestational age':ab,ti OR 'prematur*':ab,ti OR preterm:ab,ti OR postmature:ab,ti)) AND [2020-2024]/py 86 2 Jul 2024
#40 ((exp AND ('face mask'/exp OR 'face mask')) OR 'mechanical ventilator' OR 'manual ventilation' OR 'self inflating bag' OR 'flow-inflating bag' OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ab,ti) OR 'bag valve mask*':ab,ti OR 'ambu bag*':ab,ti OR 'manual resuscitator':ab,ti OR (('t piece':ab,ti OR tpiece:ab,ti OR t:ab,ti) AND piece:ab,ti AND resuscitator*:ab,ti)) AND ('peep':ab,ti OR 'positive end expiratory pressure':ab,ti OR 'positive pressure ventilation':ab,ti OR 'positive pressure respiration':ab,ti) AND (('newborn hypoxia'/exp OR 'newborn hypoxia') OR ('prematurity'/exp OR 'prematurity') OR ('newborn apnea attack'/exp OR 'newborn apnea attack') OR ('newborn disease'/exp OR 'newborn disease') OR ('neonatal stress'/exp OR 'neonatal stress') OR ('lung dysplasia'/exp OR 'lung dysplasia') OR ('newborn'/exp OR 'newborn') OR ('low birth weight'/exp OR 'low birth weight') OR ('newborn

	screening'/exp OR 'newborn screening') OR ('newborn monitoring'/exp OR 'newborn monitoring') OR ('newborn care'/exp OR 'newborn care') OR ('newborn period'/exp OR 'newborn period') OR ('birth weight'/exp OR 'birth weight') OR ('newborn morbidity'/exp OR 'newborn morbidity') OR ('live birth'/exp OR 'live birth') OR ('newborn death'/exp OR 'newborn death') OR ('newborn mortality'/exp OR 'newborn mortality') OR (('delivery'/exp OR delivery) AND room) OR ((((newborn*:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR post:ab,ti) AND mature:ab,ti) OR (newborn*:ab,ti OR 'low birth weight':ab,ti OR 'small for gestational age':ab,ti OR 'prematur*':ab,ti OR preterm:ab,ti OR postmature:ab,ti)) 253 2 Jul 2024 #39 ('newborn hypoxia'/exp OR 'newborn hypoxia') OR ('prematurity'/exp OR 'prematurity') OR ('newborn apnea attack'/exp OR 'newborn apnea attack') OR ('newborn disease'/exp OR 'newborn disease') OR ('neonatal stress'/exp OR 'neonatal stress') OR ('lung dysplasia'/exp OR 'lung dysplasia') OR ('newborn'/exp OR 'newborn') OR ('low birth weight'/exp OR 'low birth weight') OR ('newborn screening'/exp OR 'newborn screening') OR ('newborn monitoring'/exp OR 'newborn monitoring') OR ('newborn care'/exp OR 'newborn care') OR ('newborn period'/exp OR 'newborn period') OR ('birth weight'/exp OR 'birth weight') OR ('newborn morbidity'/exp OR 'newborn morbidity') OR ('live birth'/exp OR 'live birth') OR ('newborn death'/exp OR 'newborn death') OR ('newborn mortality'/exp OR 'newborn mortality') OR (('delivery'/exp OR delivery) AND room) OR ((((newborn*:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR post:ab,ti) AND mature:ab,ti) OR (newborn*:ab,ti OR 'low birth weight':ab,ti OR 'small for gestational age':ab,ti OR 'prematur*':ab,ti OR preterm:ab,ti OR postmature:ab,ti) 2999919 2 Jul 2024 #38 'macrosomia'/exp OR 'macrosomia' 11025 2 Jul 2024 #37 newborn*:ab,ti OR 'low birth weight':ab,ti OR 'small for gestational age':ab,ti OR 'prematur*':ab,ti OR preterm:ab,ti OR postmature:ab,ti 593011 2 Jul 2024 #36 (((newborn*:ab,ti OR low:ab,ti) AND birth:ab,ti AND weight:ab,ti OR small:ab,ti) AND for:ab,ti AND gestational:ab,ti AND age:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR post:ab,ti) AND mature:ab,ti 22865 2 Jul 2024 #35 ('delivery'/exp OR delivery) AND room 27238 2 Jul 2024 #34 'newborn mortality'/exp OR 'newborn mortality' 18126 2 Jul 2024 #33 'newborn death'/exp OR 'newborn death' 13526 2 Jul 2024 #32 'live birth'/exp OR 'live birth' 43593 2 Jul 2024 #31 'newborn morbidity'/exp OR 'newborn morbidity' 11833 2 Jul 2024 #30 'birth weight'/exp OR 'birth weight' 186542 2 Jul 2024 #29 'newborn period'/exp OR 'newborn period' 16934 2 Jul 2024 #28 'newborn care'/exp OR 'newborn care' 52601 2 Jul 2024 #27 'newborn monitoring'/exp OR 'newborn monitoring' 1192 2 Jul 2024 #26 'newborn screening'/exp OR 'newborn screening' 27098 2 Jul 2024 #25 'low birth weight'/exp OR 'low birth weight' 89125 2 Jul 2024 #24 'newborn'/exp OR 'newborn' 842778 2 Jul 2024 #23 'lung dysplasia'/exp OR 'lung dysplasia' 16792 2 Jul 2024 #22 'neonatal stress'/exp OR 'neonatal stress' 555 2 Jul 2024	

	#21 'newborn disease'/exp OR 'newborn disease' 2233978 2 Jul 2024 #20 'newborn apnea attack'/exp OR 'newborn apnea attack' 16 2 Jul 2024 #19 'prematurity'/exp OR 'prematurity' 160403 2 Jul 2024 #18 'newborn hypoxia'/exp OR 'newborn hypoxia' 8368 2 Jul 2024 #17 'neonatal respiratory distress syndrome'/exp OR 'neonatal respiratory distress syndrome' 11569 2 Jul 2024 #16 'peep':ab,ti OR 'positive end expiratory pressure':ab,ti OR 'positive pressure ventilation':ab,ti OR 'positive pressure respiration':ab,ti 24628 2 Jul 2024 #15 'positive pressure respiration':ab,ti 248 2 Jul 2024 #14 'positive pressure ventilation':ab,ti 9907 2 Jul 2024 #13 'positive end expiratory pressure':ab,ti 9007 2 Jul 2024 #12 'peep':ab,ti 11709 2 Jul 2024 #11 (exp AND ('face mask'/exp OR 'face mask')) OR 'mechanical ventilator' OR 'manual ventilation' OR 'self inflating bag' OR 'flow-inflating bag' OR ('anesthesia bag*':ab,ti OR 'anaesthesia bag*':ab,ti) OR 'bag valve mask*':ab,ti OR 'ambu bag*':ab,ti OR 'manual resuscitator':ab,ti OR (('t piece':ab,ti OR tpiece:ab,ti OR t:ab,ti) AND piece:ab,ti AND resuscitator*:ab,ti) 11859 2 Jul 2024 #10 ('t piece':ab,ti OR tpiece:ab,ti OR t:ab,ti) AND piece:ab,ti AND resuscitator*:ab,ti 173 2 Jul 2024 #9 'manual resuscitator':ab,ti 52 2 Jul 2024 #8 'ambu bag*':ab,ti 175 2 Jul 2024 #7 'bag valve mask*':ab,ti 904 2 Jul 2024 #6 'anesthesia bag*':ab,ti OR 'anaesthesia bag*':ab,ti 50 2 Jul 2024 #5 'flow-inflating bag' 41 2 Jul 2024 #4 'self inflating bag' 257 2 Jul 2024 #3 'manual ventilation' 1324 2 Jul 2024 #2 'mechanical ventilator' 9038 2 Jul 2024 #1 exp AND ('face mask'/exp OR 'face mask') 170 2 Jul 2024	
Results identified	**Results screened full text**	**Results included**
126	MISSING	1

2025 Evidence Update
NLS 5340 – Supraglottic Airway Devices for Neonatal Resuscitation

Worksheet Author(s): Yamada NK, Quek BH, Weiner GM
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest: None

PICOST:
Population: Newborn infants 34 0/7 weeks' or more gestation receiving intermittent positive pressure ventilation during resuscitation immediately after birth
Intervention: Supraglottic device
Comparison: Face mask
Outcomes:
- Failure to improve with the device
- Intubation during initial resuscitation
- Time to heart rate > 100 bpm during initial resuscitation
- Duration of positive pressure ventilation during initial resuscitation (OR) time to cessation of positive pressure ventilation
- Chest compressions or adrenaline (epinephrine) during initial resuscitation
- Soft tissue injury
- Admission to NICU
- Air leak during the initial hospital stay
- Mortality at hospital discharge
- Neurodevelopmental impairment at ≥ 18 months

Study Design: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) are excluded.
Timeframe: From inception of databases to November 13, 2020, updated on July 28, 2021 and December 9, 2021

Year of last full review*):* 2021 {Yamada 2022 e2022056568}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Wyckoff 2021 229}
The systematic review identified 5 RCTs {Feroze 2008 148, Pejovic 2020 2138, Pejovic 2018 255, Singh 2005 303, Trevisanuto 2015 286} and 1 quasi-RCT {Zhu 2011 1405}involving a total of 1857 newborn infants, and 2 retrospective cohort studies {Trevisanuto 2004 151, Zanardo 2010 327} involving 218 newborn infants. An additional study {Pejovic 2022 107} reported secondary outcomes from a subset of newborn infants enrolled in an included RCT. {Pejovic 2020 2138}

For the important outcome of **failure to improve with the device***, evidence of* **moderate certainty** *(downgraded for risk of bias and imprecision, upgraded for strong association) from* **6 trials** *involving 1823 newborn infants showed* **probable benefit** *from receiving positive-pressure ventilation with a supraglottic airway device compared to a face mask (risk ratio (RR) 0.24; 95% confidence interval (CI) 0.17 to 0.36; p <0.001; I^2 = 35%; Absolute risk difference (ARD) -11%, 95% CI -13% to -8%; number needed to treat (NNT) = 10).* {Feroze 2008 148, Pejovic 2020 2138, Pejovic 2018 255, Singh 2005 303, Trevisanuto 2015 286, Zhu 2011 1405}

For the important outcome of **endotracheal intubation during resuscitation***,* evidence of **low certainty** (downgraded for risk of bias, inconsistency, and imprecision; upgraded for strong association) from **4 trials** {Pejovic 2020 2138, Singh 2005 303, Trevisanuto 2015 286, Zhu 2011 1405} involving 1715 newborn infants showed **possible benefit** from receiving positive-pressure ventilation with a supraglottic airway device compared to a face mask (RR 0.34, 95% CI 0.20 to 0.56; p <0.001; I^2=78%; ARD -5%, 95% CI -6% to -3%; NNT 20). In sensitivity analysis, heterogeneity was not significantly decreased and the benefit remained (RR 0.19, 95% CI 0.09 to 0.37; p < 0.001; I^2 = 63%) after removing the study {Pejovic 2138} where intubation was only possible if a physician was available during the resuscitation. Heterogeneity was decreased and the risk reduction was no longer statistically significant (RR 0.65, 95% CI 0.36 to 1.19; p=0.17; I^2 =45%) when the single quasi-RCT {Zhu 2011 1405} was removed.

For the critical outcome of **chest compressions during resuscitation,** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **3 trials** {Pejovic 2020 2138, Singh 2005 303, Trevisanuto 2015 286} involving 1346 newborn infants **could not exclude benefit or harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 0.97, 95% CI 0.57 to 1.65; p=0.91; I^2=0%; ARD 1/1000 fewer newborn infants with chest compressions when receiving positive-pressure ventilation with a supraglottic airway device, 95% CI 17/1000 fewer to 26/1000 more).

For the critical outcome of **epinephrine (adrenaline) administration during resuscitation,** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 trials** {Singh 2005 303, Trevisanuto 2015 286} involving 192 newborn infants **could not exclude benefit or harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 0.67, 95% CI 0.11 to 3.87; p=0.65; I^2 not applicable; ARD 10 /1000 fewer newborn infants receive epinephrine (adrenaline) when receiving positive-pressure ventilation with a supraglottic airway device, 95% CI 28/1000 fewer to 90/1000 more). Statistical heterogeneity could not be calculated because events occurred in only one trial. {Trevisanuto 2015 286}

For the important outcome of **time to heart rate >100 bpm**, evidence of **low certainty** (downgraded for risk of bias and imprecision) from **1 trial** {Pejovic 2022 107} involving a subset of 46 newborn infants enrolled in a previously reported RCT {Pejovic 2020 2138} showed **possible benefit** from receiving positive-pressure ventilation with a supraglottic airway device compared to a face mask (mean difference -66 s, 95% CI -100 s to -31 s; p<0.001)

For the important outcome of **duration of positive-pressure ventilation***,* evidence of **low certainty** (downgraded for risk of bias and inconsistency) from **4 trials** {Pejovic 2020 2138, Singh 2005 303, Trevisanuto 2015 286, Zhu 2011 1405} involving 610 newborn infants showed **possible benefit** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (mean difference -18 s, 95% CI -24 s to -13 s; p < 0.001; I^2 = 94%. In sensitivity analysis, all of the heterogeneity was attributed to one study. {Trevisanuto 2015 286} This may reflect a different protocol or policy, in this single center trial, for when to remove the supraglottic airway device and discontinue positive-pressure ventilation. When removing this study, the beneficial effect was retained and statistical heterogeneity was significantly reduced (mean difference -30s, 95% CI -36 s to -24 s; p < 0.001; I^2 = 0%).

For the important outcome of **admission to the NICU,** evidence of **very low certainty** (downgraded for risk of bias, inconsistency, indirectness, and imprecision) from **4 trials** {Pejovic 2138, Pejovic 255, Singh 303, Trevisanuto 286} involving 1314 newborn infants showed **possible benefit and no likely harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 0.97, 95% CI 0.94 to 1.00; p=0.07; I^2=82%; ARD -3%, 95% CI -5% to 0%; NNT 34). In sensitivity analysis, all of the heterogeneity was attributed to the high rate of admission to the NICU (96% in both groups) in one study. {Pejovic 2020 2138} This may reflect heterogeneity in the population studied (sicker newborns) or in the policies/protocols for intensive care admission in this single center trial. When this study was removed, the treatment effect was increased and heterogeneity was significantly decreased (RR 0.60, 95% CI 0.40 to 0.90, p=0.01; I^2 =0%).

For the important outcome of **admission to the NICU**, evidence of **very low certainty** (downgraded for risk of bias, indirectness, and imprecision) from **2 retrospective cohort studies** {Singh 2005 303, Trevisanuto 2015 286} involving 218 newborn infants showed **possible benefit and no likely harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 0.65, 95% CI 0.43 to 1.00; p=0.05; I^2 =36%; ARD -13%; 95% CI -25% to 0%).

For the important outcome of **air leak during initial hospital stay***,* evidence of **very low certainty** (downgraded for risk of bias, indirectness, and imprecision) from **2 trials** {Singh 2005 303, Trevisanuto 2015 286}

involving 192 newborn infants **could not exclude benefit or harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR not estimable due to no events; I^2=0%; ARD 0%, 95% CI -3% to 3%).

For the important outcome of **air leak during initial hospital stay***,* evidence of **very low certainty** (downgraded for risk of bias, indirectness, and imprecision) from **2 retrospective cohort studies** {Trevisanuto 2004 151, Zanardo 2010 327} involving 218 newborn infants **could not exclude benefit or harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 0.32, 95% CI 0.05 to 1.99; p=0.22; I^2=0%; ARD -3%, 95% CI -7% to 1%).

For the important outcome of **soft tissue injury**, evidence of **low certainty** (downgraded for risk of bias and imprecision) from **4 trials** {Pejovic 2020 2138, Singh 2005 303, Trevisanuto 2015 286, Zhu 2011 1405} involving 1724 newborn infants **could not exclude benefit or harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 1.05, 95% CI 0.15 to 7.46; p=0.96; I^2 not applicable; ARD 0/1000 fewer newborn infants with soft tissue injury when receiving positive-

pressure ventilation with a supraglottic airway device, 95% CI 2/1000 fewer to 15/1000 more). Statistical heterogeneity could not be calculated for this outcome because there were no events recorded in 3 of 4 included studies. Soft tissue injury (2 events in each group) only occurred in one study. {Pejovic 2020 2138}

For the critical outcome of **survival to hospital discharge***, evidence of* **low certainty** *(downgraded for risk of bias and imprecision) from* **1 trial** *{Singh 303} involving 50 newborn infants* **could not exclude benefit or harm** *from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 1.00; 95% CI 0.93 to 1.08; p=1.0; I^2 not applicable; ARD, 0/1000 fewer newborn infants survive when receiving positive-pressure ventilation with a supraglottic airway device, 95% CI 70/1000 fewer to 80/1000 more).*

For the critical outcome of **survival to hospital discharge,** *evidence of* **low certainty** *(downgraded for risk of bias and imprecision) from* **2 retrospective cohort studies** {Trevisanuto 2004 151, Zanardo 2010 327} involving 218 newborn infants **could not exclude benefit or harm** from providing positive-pressure ventilation with a supraglottic airway device compared with a face mask (RR 0.99; 95% CI 0.96 to 1.02; p=0.58; I^2=0%; ARD 10/1000 fewer newborn infants survive when receiving positive pressure ventilation with a supraglottic airway device, 95% CI 40/1000 fewer to 20/1000 more).

For the critically important outcome of **neurodevelopmental impairment at ≥18 months of age**, no data were reported in the included studies.

Treatment Recommendation
Where resources and training permit, we suggest that a supraglottic airway device may be used in place of a face mask for newborn infants 34 0/7 weeks or more gestation receiving intermittent positive pressure ventilation during resuscitation immediately after birth (weak recommendation, low certainty of evidence).

Search Strategy for SysRev and EvUp: See Appendix
Database searched: Medline/Embase
Time Frame (EvUp): 1 October 2021 through 2 July 2024
Date Search Completed: 2 July 2024
Search Results:
Articles identified: 41
Full-text screening: 2
Included: 0

Summary of Evidence Update: The updated literature search found no new evidence. However, manual review revealed one quasi-randomized study that was not included in a prior literature search. This study is included below.
Relevant Guidelines or Systematic Reviews: none applicable
RCT: none applicable
Nonrandomized Trials, Observational Studies:

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Mathai 2014 {Mathai 2014 }	**Study Type:** Quasi-randomized: if born on odd day → supraglottic airway device (SGA device) If born on even day → face mask (FM) 67 babies were quasi-randomized to FM vs. SGA device as the primary mode of administering	**Inclusion Criteria:** >36 weeks and >2000gm Self-inflating bag Appropriate sized face masks Size 1 LMA which was inflated with 2-4mL after insertion **Exclusion Criteria:**	**1° endpoints:** Time to adequate chest rise = time from beginning of application of device to visual evidence of chest rise with ventilation - no difference between groups, mean (SD): FM = 20.26 (8.80) seconds vs. SGA device = 18.50 (3.04) seconds, p-value not reported	Authors' conclusion: "More babies achieved spontaneous respiration in the DR within the first 5 minutes in a shorter time and lesser needed intubation in the LMA group, as compared to babies resuscitated with bag and mask. This suggests that the LMA was a more effective

	positive pressure ventilation - 35 face mask - 32 supraglottic airway device Resuscitation was performed by 6 trained resident physicians in their 2nd or 3rd year of residency. "Training" consisted of simulation training on manikins and then supervised by a neonatologist for one month during actual resuscitations. N=67	- meconium stained amniotic fluid - congenital anomalies - no heart beat detected before delivery - infants that "looked smaller than 2kg" at delivery	Duration of PPV = onset of PPV until onset of spontaneous respirations - shorter duration of PPV in SGA device group, mean(SD): FM = 180 (37.83) seconds vs. SGA device 95.31 (23.22) seconds, p = 0.024 Timings were recorded by an assistant **2° endpoints:** Need for intubation - fewer intubated in SGA device group: FM = 12 vs. SGA device 5, p = 0.038 Need for chest compressions - no statistical difference between groups: FM = 3 vs. SGA device = 1, p = 0.054 Need for drugs (drugs not defined) - no statistical difference between groups: FM = 2 vs. SGA device = 1, p-value not reported	way of giving PPV in the DR. The long-term outcome, however, did not appear to be different in the two groups. There were no complications noted with the use of the LMA."

Reviewer Comments:
We found one additional study that was not included in the previous systematic review. {Mathai 2014 } This quasi-randomized study found that infants >36 weeks GA or >2kg estimated birth weight who received PPV using a supraglottic airway device required shorter duration of PPV and were less likely to require intubation when compared to infants who received PPV using a face mask. There was no difference between groups in time to adequate chest rise. There was no statistical difference between groups in need for chest compressions or drugs during resuscitation; this may be due in part to small sample size.

This evidence continues to support the current ILCOR recommendation: "Where resources and training permit, we suggest that a supraglottic airway device may be used in place of a face mask for newborn infants 34 0/7 weeks' or more gestation receiving intermittent positive pressure ventilation during resuscitation immediately after birth (weak recommendation, low certainty of evidence)." {Wyckoff 2022 208}

There is insufficient new evidence to elicit a new systematic or scoping review.

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Appendix 1 - **Search Strategy for EvUp**

Sources searched	**Search strategy**	**Search time frame**
Medline/EmBase	((supraglottic* AND (airway OR airways OR device*)) OR "LMA"[tiab] OR "Laryngeal masks"[Mesh] OR "laryngeal mask*"[tw] OR "Masks"[Mesh]) AND ("Infant, Newborn"[Mesh] OR infan*[tw] OR newborn* OR neonate OR neonates OR neonatal OR newborn*[tw] OR "new-born*"[tw] OR "infant, premature"[Mesh] OR "infant, low birth weight"[Mesh] OR (("preterm*" OR "pre-term*" OR "premature*" OR "low birth weight") AND birth) OR "LBW") AND ("positive pressure"[TW] OR "Positive-Pressure Respiration/instrumentation"[Mesh] OR resuscitat* OR "Resuscitation/instrumentation"[Mesh] OR "Resuscitation/methods"[Mesh] OR "Asphyxia Neonatorum/therapy"[Mesh] OR "airway management"[tw] OR ((airway*[tiab] OR respiratory[tiab] OR trachea*[tiab]) AND (management[tiab] OR control[tiab] OR obstruct*[tiab] OR restrict*[tiab] OR constrict*[tiab] OR stenosis[tiab])) OR "Airway Management/instrumentation"[Mesh] OR "Airway Management/methods"[Mesh] OR "airway obstruction/therapy"[Mesh]) AND (prospective[tw] OR "prospective studies"[Mesh] OR retrospective[tw] OR "case-	1 October 2021 through 2 July 2024

	control studies"[Mesh] OR "cohort studies"[Mesh] OR "controlled group*" OR "cohort stud*"[tw] OR "case-control" OR "retrospective studies"[Mesh] OR observational[tw] OR "clinical study"[tw] OR "clinical trial*"[tw] OR "clinical study"[PT] OR experimental[tw] OR "comparative study"[PT] OR "multicenter study"[PT] OR "comparative stud*"[TW] OR "randomized controlled"[tw] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [Mesh] OR randomly [tiab] OR trial [ti]) NOT (("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) Filters: from 2021/10/1 - 2024/7/2 Sort by: Most Recent	
Results identified	**Results screened full text**	**Results included**
41	2	0

2025 Evidence Update
NLS 5341 – Supraglottic Airway Devices vs. Endotracheal Tube for Neonatal Resuscitation

Worksheet Author(s): Yamada NK, Aly M, Quek BH, Weiner GM
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 28 November 2024
Conflicts of Interest: Gary Weiner is a co-author on the observational study identified {Zanardo 327}. He did not vote on inclusion or participate in data extraction.

PICOST:
Population: Newborn infants 34 0/7 weeks' or more gestation receiving intermittent positive pressure ventilation (PPV) during resuscitation immediately after birth
***Intervention*:** Supraglottic device
Comparison; Tracheal intubation
Outcomes:

- First attempt success
- Number of attempts required to successfully place the device
- Time to successful device insertion
- Failure to improve with the device
- Time to heart rate > 100 bpm during initial resuscitation
- Duration of positive pressure ventilation during initial resuscitation (OR) time to cessation of positive pressure ventilation
- Chest compressions or adrenaline (epinephrine) during initial resuscitation
- Soft tissue injury
- Admission to NICU
- Air leak during the initial hospital stay
- Mortality at hospital discharge
- Neurodevelopmental impairment at ≥ 18 months

***Study Design*:** Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) are excluded.
Timeframe: All years and languages to 2014.

Year of last full review: 2015 {Perlman 2015 S204}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
For the comparison of laryngeal mask to endotracheal tube as a secondary device (i.e., laryngeal mask or intubation when bag-mask ventilation has failed) for infants at term requiring positive pressure ventilation (PPV) for resuscitation, we identified the following evidence (1 randomized clinical trial with 40 patients) {Esmail 2002 115}

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 trial {Esmail 2002 115} 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 trial {Esmail 2002 115} 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 trial {Esmail 2002 115}; 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 trial {Esmail 2002 115} 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 trial {Esmail 2002 115} showing more trauma to tissue when comparing laryngeal mask versus endotracheal tube (OR, 2.43; 95% CI, 0.51–11.51).

Treatment Recommendation:
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).

Search Strategies – see appendix
Database searched: Medline/Embase and Cochrane
Time Frame: (existing PICOST) – updated from end of last search (please specify): 1 January 2014 through 4 November 2024
Date Search Completed: 4 November 2024 for PubMed/Embase, 26 April 2024 for Cochrane
Search Results (Number of articles identified and number identified as relevant):
Articles identified: 1,254
Full-text screening: 15
Included: 8 + 2 articles added by hand from the systematic reviews found in this search

Summary of Evidence Update: In addition to the articles summarized in the tables below, the updated literature search found 1 systematic review that did not provide statistical analysis of the specific comparison of supraglottic airway device vs. endotracheal tube {Schmölzer 722} and 3 narrative reviews of the literature. Note that hereafter, the term supraglottic airway device (SGA device) is used unless directly quoting authors because although used in the previous PICOST and Consensus on Science with Treatment Recommendations, 'Laryngeal Mask Airway' refers to one specific manufacturer's product. No studies comprehensively compared devices.

Relevant Guidelines or Systematic Reviews:

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Qureshi 2018 {Qureshi 2018 Cd003314}	Laryngeal mask airway (Supraglottic Airway Device; SGA device) versus bag-mask ventilation or endotracheal intubation for neonatal resuscitation	"(1) Among all newborns requiring positive pressure ventilation for cardiopulmonary resuscitation, is effective positive pressure ventilation and successful resuscitation achieved faster with the LMA compared to BMV? (2) When BMV is either	7 RCTs - 5 studies compared SGA device vs. face mask ventilation - 3 studies compared SGA device with tracheal intubation Total of 158 infants in the comparison of SGA device vs. tracheal tube	**1° Outcomes:** Time to correctly insert the device: Data from only 2 studies, no difference (MD 0.31 sec, 95% CI -0.27 to 0.88 sec) Failure to correctly insert the device: No difference (RR 0.95, 95% CI 0.17 to 5.42) **Successful insertion of device at first attempt**:	This review is consistent with the 2015 ILCOR recommendation that the SGA device is a reasonable alternative to tracheal tube based on no significant difference in insertion time, failure to correctly place the device, or first attempt success. Although death and HIE were reported, statistical analysis was not possible due to small sample size.

		insufficient or ineffective, is effective positive pressure ventilation and successful resuscitation achieved faster with the SGA device compared to tracheal intubation?"		Data from 2 studies, no difference (RR 1.01, 95% CI 0.89 to 1.14) **Ventilation time**: Data from two studies, slightly shorter in SGA device group, but not significant **Death or HIE**: Data from 1 study - 2 HIE events in each group, 1 death in tracheal tube group	
Diggikar 2022 {Diggikar 2023 156}	Laryngeal mask airway (SGA device) versus face mask ventilation or intubation for neonatal resuscitation in low-and-middle- income countries: a systematic review and meta-analysis	"To look at the efficacy of LMA as compared with face mask and tracheal tube for delivering PPV during neonatal resuscitation in LMIC. We used World Bank classification criteria based on Gross National Income (GNI) per capita (current US$). Countries were identified as low (GNI per capita ≤$1085) or middle-income (GNI per capita >$1086 but <$13 205)".	8 RCTs - 5 studies compared SGA device vs. FM ventilation - 2 studies compared SGA device with tracheal tube - 1 study included infants in each of SGA device, FM, and tracheal tube arms Total of 158 infants in the comparison of SGA device vs. tracheal tube	**1° Outcomes:** Failure to correctly insert the device: No difference (OR 1.20, 95% CI 0.34 to 4.18, I^2 0%) **Time taken to insert device:** No difference, 1.05 sec (95% CI -1.69 to 3.79, I^2 -94%) **Ventilation time:** Unable to perform statistical analysis **Soft tissue injury:** No difference (RR 1.36, 95% CI 0.30 to 6.20, I^2 -19%) Only one study reported HIE events: 2 HIE in each arm, and 1 death in tracheal tube arm	This review examined the same studies as the 2018 Cochrane review by Qureshi. It is consistent with that review and the 2015 ILCOR recommendation that the SGA device is a reasonable alternative to tracheal tube based on no significant difference in first attempt success, insertion time, or soft tissue injury. Although death and HIE were reported, statistical analysis was not possible due to small sample size.
Abbreviations: SGA device; supraglottic airway device, FM; face mask, PPV; positive pressure ventilation, HR; heart rate, OR; odds ratio, RR; relative risk, CI; confidence interval, GNI; gross national income, HIE; hypoxic ischemic encephalopathy					

RCT:

Study Acronym; Author;	Aim of Study; Study Type;	Patient Population	Study Intervention	Endpoint Results	Relevant 2° Endpoint (if any);

Year Published	Study Size (N)		(# patients) / Study Comparator (# patients)	(Absolute Event Rates, P value; OR or RR; & 95% CI)	Study Limitations; Adverse Events
Feroze 2008 {Feroze 2008 148}	**Study Aim:** "To evaluate the efficacy of laryngeal mask airway in neonatal resuscitation and artificial ventilation and to compare it with that of tracheal tube and FM" **Study Type:** Randomized, but randomization scheme is not detailed	**Inclusion Criteria:** - weight > 1.5kg - Apgar score <4 at birth - Newborns with elective or emergency C/S **Exclusion Criteria:** - weight <1.5kg - neonates with birth trauma	75 neonates selected on the basis of non-probability convenience sampling 25 neonates in each group: tracheal tube, FM, and SGA device	**1° endpoint:** **Insertion time**: SGA device = 9 sec vs. tracheal tube 9.5 sec **Number of attempts**: SGA device = 1-2 vs. tracheal tube = 2-3 Pink-up time (sec): SGA device = 30-35 vs. tracheal tube 35-40 **Time for effective resuscitation (min)**: SGA device = 1-2 vs. tracheal tube 1.5-2.5	**Study Limitations:** - No statistical analysis of any endpoints - Unclear randomization scheme - Only cesarean section deliveries - The following data are reported for LM group, but no comparison to tracheal tube or SGA device groups: insertion time, duration of PPV, and duration of CPAP
Yang 2016 {Yang 2016 17}	**Study Aim:** "To compare the feasibility, efficacy, and safety of laryngeal mask ventilation with tracheal tube during neonatal resuscitation". **Study Type:** Quasi-randomized: if born on odd day → tracheal intubation (tracheal tube) If born on even day → laryngeal mask airway (LM) "We involved 9 neonatal specialists from a baby-friendly zone for emergency endotracheal intubation." Infants in the SGA device group could	**Inclusion Criteria:** >34 weeks or >2000gm and HR <60bpm despite BMV for 30 seconds Self-inflating bag for PPV at 25-30, FiO2 100%, rate 40-60 breaths/min If meconium-stained fluid and non-vigorous at birth, tracheal suction through an endotracheal tube was performed before PPV – then infant was resuscitated according to the assigned method "LMA Classic Size 1" **Exclusion Criteria:**	68 newborns were quasi-randomized to tracheal tube vs. SGA device as the secondary mode of administering positive pressure ventilation (HR >60 bpm despite BMV for 30 seconds) - 35 tracheal tube - 36 SGA device Infants in the SGA device group could cross over to tracheal tube if HR remained <60bpm after 30 seconds of SGA device ventilation	**1° endpoints:** **First attempt at successful insertion** - tracheal tube 90.6% vs. SGA device 94.4%, p = 0.547 Effectiveness of resuscitation as characterized by: - **successful resuscitation (%):** tracheal tube 96.88% vs. SGA device 86.11%, p = 0.20 - **insertion time (sec):** tracheal tube 7.89 vs. SGA device 7.58, p = 0.34 - **response times (sec):** tracheal tube 41.38 vs. SGA device 34.06, p = 0.14	**2° endpoints:** Changes in arterial blood gas values and glucose levels (i.e. from cord blood immediately after birth and peripheral arterial samples 1 hour after resuscitation): - No statistical difference between groups in any values 1-min and 5-min Apgar scores: - No statistical difference between groups **Adverse effects:** No significant difference in incidence of adverse effects between tracheal tube vs. SGA

	cross over to tracheal tube if HR remained <60bpm	- absent heart rate at birth - "known major congenital malformations (e.g. congenital diaphragmatic hernia or cyanotic congenital heart disease)"		- **ventilation times (sec):** tracheal tube 171.09 vs. SGA device 137.19, p = 0.10	device groups: 12.5% vs. 8.33%, p > 0.05 **Adverse events** = tracheal tube group: laryngeal edema (n=1), tracheal bleeding (n=1), pneumothorax (n=2) SGA device group: vomiting (n=2), mild abdominal distension (n=1)
El-Ahmadi 2018 {El-Ahmadi 2018 1767}	**Study Aim:** "To evaluate the use of laryngeal mask airway in neonatal resuscitation among newborns in whom PPV by bag and mask has failed" **Study Type:** Single center, prospective, unblinded RCT	**Inclusion Criteria:** ≥ 34 weeks or ≥ 2000gm and Need for PPV determined by apnea or gasping, or HR <100bpm after warm/dry/stim, clear airway over first 30 seconds, and then ambu bagging for another 30 seconds by face mask In both groups, if 2 attempts to introduce the SGA device in the 1st group or the tracheal tube in the 2nd group failed, the other alternative was used. SGA device Classic Size 1 Exclusion Criteria: - lethal anomalies - hydrops - major malformations of the respiratory system	80 newborns were randomized 1:1 by simple randomization scheme to tracheal tube vs. SGA device as the secondary mode of administering positive pressure ventilation - 40 tracheal tube - 40 SGA device	**1° endpoints:** Proportion of infants needing endotracheal intubation after SGA device insertion - There was only 1 attempt of insertion for all patients except 2 patients who needed 2 attempts in the SGA device group	**2° endpoints:** **Insertion time (sec):** tracheal tube 18.08 vs. SGA device 9.7, p = 0.000 Post-resuscitation ABG: pH tracheal tube 7.34 vs. SGA device 7.28, p = 0.006 pO2 tracheal tube 58.39 vs. SGA device 52.74, p = 0.04

		- congenital heart disease - stillbirth - neonates who require chest compressions - severe fetal distress or meconium-stained fluid			

Abbreviations: SGA device; supraglottic airway device, FM; face mask, PPV; positive pressure ventilation, HR; heart rate, OR; odds ratio, RR; relative risk, CI; confidence interval, GNI; gross national income, HIE; hypoxic ischemic encephalopathy, ABG; arterial blood gas

Nonrandomized Trials, Observational Studies:

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Zanardo 2010 {Zanardo 2010 327}	**Study Type:** Observational study of 86 near-term infants (34+0 – 36+6 weeks) who received PPV in the delivery room - 34 face mask (39.5%) - 36 laryngeal mask (SGA device) (41.8%) - 16 tracheal tube (18.6%)	**Inclusion Criteria:** 34+0 to 36+6 weeks EGA who received PPV in the delivery room at Padua University Hospital (Padua, Italy), a tertiary teaching hospital with 4000 births/year and 350 NICU admissions/year Choice of FM, SGA device, or tracheal tube for initial airway management was left to the resuscitating physician's discretion SGA device was not used if: - no perceptible HR at birth - severe fetal distress or meconium-stained fluid - prenatal diagnosis of CDH or other	**1° endpoint:** **Decreased likelihood of NICU admission in SGA device group** compared to tracheal tube: OR 0.08 (0.02-0.33) **Decreased likelihood of developing RDS in SGA device group** compared to tracheal tube: OR 0.03 (0.003-0.26) **Shorter length of hospital stay in SGA device group** compared to tracheal tube: OR 12.2 days vs. 23.3 days, p <0.01 No statistical difference between groups for: - 1-min Apgar <5 - ventilator days Insufficient subjects to determine statistical difference between groups for the following outcomes: - 5-min Apgar <5 - ventilation unsuccessful - **pneumothorax** - **mortality**	This was a single unit study where SGA device usage was relatively high at baseline. There was only one outcome that aligned with this PICOST (likelihood of NICU admission), for which there was an advantage for the laryngeal mask group. There were insufficient subjects to determine statistical difference in other important outcomes of pneumothorax or mortality.

		major malformation		

Abbreviations: SGA device; supraglottic airway device, FM; face mask, tracheal tube; endotracheal tube, PPV; positive pressure ventilation, CDH; congenital diaphragmatic hernia, HR; heart rate, OR; odds ratio, CI; confidence interval, EGA; estimated gestational age

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
We found 2 systematic reviews {Diggikar 2023 156, Qureshi 2018 Cd003314} including a total of 158 patients, 3 new RCTs (2 of which were included in the systematic reviews) {El-Ahmadi 2018 1767, Feroze 2008 148, Yang 2016 17}, and 1 observational study {Zanardo 2010 327} that addressed the comparison for this PICOST. Consistent with the 2015 ILCOR CoSTR {Perlman 2015 S204} based on a single RCT {Esmail 2002 115} enrolling 40 patients, these new RCTs and meta-analyses support the previous recommendation that a supraglottic airway device can be used as an alternative to tracheal intubation when face mask ventilation is unsuccessful.

The evidence is not sufficient to change the current recommendation, or to elicit a new systematic or scoping review. The terms “laryngeal mask”, “PPV”, and “low-quality evidence” have been updated to the reflect current terminology (supraglottic airway device, ventilation, and low certainty evidence).

Updated Treatment Recommendation:
For resuscitation of the late-preterm and term newborn (more than 34 weeks’ gestation), we suggest a supraglottic airway device may be used as an alternative to tracheal intubation if ventilation via the face mask is unsuccessful (weak recommendation, low certainty evidence).

For resuscitation of the late-preterm and term newborn (more than 34 weeks’ gestation) where intubation is not feasible after failed face mask ventilation, a supraglottic airway device is recommended (strong recommendation, good clinical practice).

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sanuto D. Delivery room resuscitation of near-term infants: role of the laryngeal mask airway. Resuscitation. 2010;81(3)327-30.

Appendix – search strategy for EvUp

Sources searched	Search strategy	Search time frame
PubMed	((supraglottic* AND (airway OR airways OR device*)) OR "LMA"[tiab] OR "Laryngeal masks"[Mesh] OR "laryngeal mask*"[tw] OR "Masks"[Mesh]) AND ("Infant, Newborn"[Mesh] OR infan*[tw] OR newborn* OR neonate OR neonates OR neonatal OR newborn*[tw] OR "new-born*"[tw] OR “infant, premature”[Mesh] OR “infant, low birth weight”[Mesh] OR ((“preterm*” OR “pre-term*” OR “premature*” OR “low birth weight”) AND birth) OR “LBW”) AND ("positive pressure"[TW] OR "Positive-Pressure Respiration/instrumentation"[Mesh] OR resuscitat* OR "Resuscitation/instrumentation"[Mesh] OR "Resuscitation/methods"[Mesh] OR "Asphyxia Neonatorum/therapy"[Mesh] OR "airway management"[tw] OR ((airway*[tiab] OR respiratory[tiab] OR trachea*[tiab]) AND (management[tiab] OR control[tiab] OR obstruct*[tiab] OR restrict*[tiab] OR constrict*[tiab] OR stenosis[tiab])) OR "Airway Management/instrumentation"[Mesh] OR "Airway Management/methods"[Mesh] OR "airway obstruction/therapy"[Mesh]) AND (prospective[tw] OR "prospective studies"[Mesh] OR retrospective[tw] OR "case-control studies"[Mesh] OR "cohort studies"[Mesh] OR "controlled group*" OR "cohort stud*"[tw] OR "case-control" OR "retrospective studies"[Mesh] OR observational[tw] OR "clinical study"[tw] OR "clinical trial*"[tw] OR "clinical study"[PT] OR experimental[tw] OR "comparative study"[PT] OR "multicenter study"[PT] OR "comparative stud*"[TW] OR "randomized controlled"[tw] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [Mesh] OR randomly [tiab] OR trial [ti]) NOT (("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND 2010:2024[dp]	1 January 2014 through 4 November 2024
Embase	((supraglottic* NEAR/3 (airway OR airways OR device*)) OR 'lma':ti,ab,kw OR 'supraglottic airway device'/exp OR 'laryngeal mask'/exp OR 'laryngeal mask*':ti,ab,kw OR 'mask'/exp) AND ('infant'/exp OR infan*:ti,ab,kw OR newborn* OR neonate OR neonates OR neonatal OR newborn*:ti,ab,kw OR 'new-born*':ti,ab,kw OR 'prematurity'/exp OR 'low birth weight'/exp OR (('preterm*' OR 'pre-term*' OR 'premature*' OR 'low birth weight') NEAR/4 birth) OR 'lbw') AND ('positive pressure':ti,ab,kw OR 'positive pressure ventilation'/exp OR resuscitat* OR 'resuscitation'/exp OR 'newborn hypoxia'/exp OR ((airway* OR respiratory OR trachea*) NEAR/2 (management OR control OR obstruct* OR restrict* OR constrict* OR stenosis)) OR 'respiratory control'/exp) AND (prospective:ti,ab,kw OR 'controlled study'/exp OR 'observational study'/exp OR 'quality improvement study'/exp OR 'comparative study'/exp OR 'clinical study'/exp OR retrospective:ti,ab,kw OR 'controlled group*' OR 'cohort stud*':ti,ab,kw OR 'case-control' OR observational:ti,ab,kw OR 'clinical stud*':ti,ab,kw OR 'clinical trial*':ti,ab,kw OR experimental:ti,ab,kw OR 'comparative stud*':ti,ab,kw OR 'multicenter	

	stud*':ti,ab,kw OR 'randomized controlled':ti,ab,kw OR 'randomized controlled trial*':ti,ab,kw OR 'controlled clinical trial*':ti,ab,kw OR randomized:ti,ab OR placebo:ti,ab OR 'clinical trial (topic)'/exp OR 'double blind procedure'/exp OR 'cohort analysis'/exp OR 'control group'/exp OR 'single blind procedure'/exp OR randomly:ti,ab OR trial:ti) NOT ('animal experiment':kw OR 'animal model':kw) AND [2010-2024]/py	
Cochrane Library	ID Search #1 MeSH descriptor: [Laryngeal Masks] explode all trees #2 ((supraglottic* AND (airway OR airways OR device*)) OR "LMA" OR "laryngeal mask" OR "laryngeal masks") #3 MeSH descriptor: [Masks] explode all trees #4 #1 OR #2 OR #3 #5 infan* OR newborn* OR neonate OR neonates OR neonatal OR newborn* OR (new NEXT born*) OR "LBW" #6 MeSH descriptor: [Infant, Newborn] explode all trees #7 MeSH descriptor: [Infant, Low Birth Weight] explode all trees #8 MeSH descriptor: [Infant, Premature] explode all trees #9 (preterm* OR (pre NEXT term*) OR premature* OR “low birth weight”) AND birth #10 #5 OR #6 OR #7 OR #8 OR #9 #11 MeSH descriptor: [Positive-Pressure Respiration] explode all trees and with qualifier(s): [instrumentation - IS] #12 MeSH descriptor: [Resuscitation] explode all trees and with qualifier(s): [instrumentation - IS, methods - MT] #13 MeSH descriptor: [Airway Management] explode all trees and with qualifier(s): [instrumentation - IS, methods - MT] #14 MeSH descriptor: [Airway Obstruction] explode all trees and with qualifier(s): [therapy - TH] #15 "positive pressure" OR resuscitat* OR "airway management" OR ((airway* OR respiratory OR trachea*) AND (management OR control OR obstruct* OR restrict* OR constrict* OR stenosis)) #16 MeSH descriptor: [Asphyxia Neonatorum] explode all trees and with qualifier(s): [therapy - TH] #17 #11 OR #12 OR #13 OR #14 OR #15 OR #16 #18 #4 AND #10 AND #17 331 (24 SR, 3 protocol, 303 trials, 1 -clinical answer) Limit to 01/01/2014 and after (18 SR, 3 protocols, 161 trials, 1- clinical answer)	
Results identified	**Results screened full text**	**Results included**
1254	15	8 + 2 found by hand searching

2025 Evidence Update
NLS 5350 – Exhaled CO_2 to Guide Non-invasive Ventilation at Birth

Worksheet Authors: Monnelly, V, Josephsen, JB, Isayama T, de Almeida MF, Guinsburg R, Schmölzer GM, Rabi Y, Wyckoff MH, Weiner G, Liley HG, Solevåg AL.
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 24 October 2024
Conflicts of Interest:

- Tetsuya Isayama has been helping the company NIHON KODEN to develop a respiratory functioning monitoring (RFM) device for neonatal resuscitation. The RFM device does not have a CO_2 detector, which the PICOST assessed.
- Georg Schmölzer has written several papers on exhaled CO_2 in the delivery room, including two studies analyzed in this review {Kang 2014 e102729, Ngan 2017 F525}, and he was excluded from decisions about these studies.

These authors acknowledged their potential intellectual conflicts of interest and participated in the Task Force discussion of the consensus on science and treatment recommendations. None of the other authors have any conflict to declare.

PICOST:
Population: Newborn infants receiving intermittent positive pressure ventilation (IPPV) by any non-invasive interface at birth
Intervention: Use of exhaled CO_2 monitor in addition to clinical assessment, pulse oximetry and/or electrocardiogram (ECG)
Comparison: Clinical assessment, pulse oximetry and/or ECG only
Outcomes:
Primary outcome: Endotracheal intubation in the delivery room.
Secondary:

1) Resuscitation outcomes at birth
   - Survival to neonatal intensive care unit (NICU) admission (critical)
   - Time to heart rate >100 bpm (important)
   - Duration of IPPV (important); use of IPPV corrective actions (important)
   - Use of chest compressions (important)
2) Other major morbidities
   - Survival to hospital discharge (critical)
   - Bronchopulmonary dysplasia (BPD) (important) in infants born at <34 weeks' gestation
   - Severe intraventricular hemorrhage (IVH) (important) in infants born at <34 weeks' gestation
   - Periventricular leukomalacia (important) in infants born at <34 weeks' gestation
   - Unexpected admission to special or intensive care unit (important) in infants born at ≥34 weeks' gestation

Outcomes ratings using the GRADE classifications of critical or important were decided according to a consensus for international neonatal resuscitation guidelines {Strand 328}. Outcomes were converted into main outcomes and additional outcomes for submission to PROSPERO (CRD42022344849).
Potential subgroups were defined *a priori*: methods of exhaled CO_2 evaluation (capnography, capnometry, and colorimetric devices); non-invasive interfaces for IPPV (facemasks, supraglottic airways, and nasal cannulae); indication for IPPV (apnea/irregular respirations and/or bradycardia), and gestational age (<$28^{0/7}$; $28^{0/7}$ to $33^{6/7}$; and $34^{0/7}$ or more weeks).
Study Design: Randomized controlled trials (RCTs) and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, and cohort studies) were eligible for inclusion. Case series, case reports, animal studies and unpublished studies (conference abstracts, trial protocols) were excluded.
Timeframe: All years and all languages were included provided there was an English abstract. The literature was first searched on May 13, 2022, and updated on August 1, 2022.

Year of last full review: 2023 {Berg 2023 e187, Monnelly 2023 74}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Berg 2023 e187, Monnelly 2023 74}
Although no eligible studies were identified, those ineligible studies that may provide useful data relevant to non-invasive IPPV and CO_2 monitoring immediately after birth were summarized. Twenty-three studies discussed data on exhaled CO_2 in exhaled CO_2 monitoring. {Blank 2014 1568, Blank 2018 1, Ersdal 2020 71, Finer 2009 865, Hawkes 2017 74, Hawkes 2016 F62, Holte 2019 e000544, Hooper 2013 e70895, Hunt 2019 17, Hunt 2019 665, Kang 2014 e102729, Kong 2013 104, Linde 2018 1, Mizumoto 2015 186, Murthy 2015 235, Murthy 2012 783, Ngan 2017 F525, Pahuja 2018 1617, Palme-Kilander 1993

11, Thallinger 2017 66, van Vonderen 2015 F514} In eight of these studies, CO_2 presence or values were available to providers. {Blank 2014 1568, Blank 2018 1, Finer 2009 865, Hawkes 2017 74, Kang 2014 e102729, Kong 2013 104, Mizumoto 2015 186, Ngan 2017 F525} The main topics covered by these eight studies were: 1) Exhaled CO_2 and airway obstruction; 2) Exhaled CO_2 to assess lung aeration; 3) Exhaled CO_2 as a predictor of increase in heart rate (HR); and 4) Exhaled CO_2 and pCO_2 at NICU admission.

Exhaled CO_2 and airway obstruction:

Finer et al. reviewed data from 18 infants with GA <32 weeks' gestation that received IPPV by facemask from a trial that randomly assigned patients to resuscitation with room air or 100% oxygen. {Finer 2009 865} Colorimetric CO_2 detectors were used to assist with IPPV in all patients. These 18 infants received a median of 14 (range: 4-37) consecutive obstructed breaths delivered over a median duration of 45 seconds (range 10-220) diagnosed by no color change in the CO_2 detector. The interventions to correct the obstruction included repositioning of the head (n=10), checking the mask seal (n=5), a new operator (n=2), and increasing the pressure (n=1). The authors concluded that the use of a colorimetric detector provides the resuscitation team with a visible signal that can indicate airway patency.

Blank et al. reviewed the data of 41 preterm infants with bradycardia receiving PPV with T-piece and facemask at birth. {Blank 2014 1568} All infants were monitored with colorimetric CO_2 detectors. Although assessing airway obstruction and ventilation corrective actions was not the aim of the study, ventilation corrective actions were reported. The interventions performed preceding the change of color of the CO_2 detector were increasing the inspiratory pressure (37%) and readjusting the position of the infant's airway or the position of the mask (24%).

Exhaled CO_2 to assess lung aeration:

Kang et al. performed a pilot study in 51 infants <37 weeks' gestation and found that those on CPAP (n=31) had higher exhaled CO_2 values with lower tidal volumes compared to infants who received IPPV by T-piece and facemask (n=20). {Kang 2014 e102729} The authors concluded that exhaled CO_2 monitoring confirms that infants maintained on CPAP achieve better gas exchange (resulting from sufficient lung aeration) than infants requiring IPPV.

Ngan et al. randomized infants <33 weeks' gestation to IPPV (n=86) or a 20-second sustained inflation (n=76) with facemask at birth. {Ngan 2017 F525} Exhaled CO_2 increased more rapidly after the sustained inflation. The authors concluded that sustained inflation resulted in better lung aeration compared with IPPV.

Blank et al. used exhaled CO_2 to determine lung aeration prior to umbilical cord clamping in 44 infants $\geq$32 weeks' gestation. A T-piece with facemask was used in infants needing respiratory support, and gold/yellow color change (colorimetric devices) or an exhaled CO_2-value $\geq$15 mmHg (quantitative) was used as a measure of established gas exchange. {Blank 2018 1} The authors concluded that it is feasible to provide resuscitation and monitor infants during delayed cord clamping using physiologic targets to indicate when the infant is ready for umbilical cord clamping.

Exhaled CO_2 as a predictor of increase in HR in initially bradycardic infants:

Blank et al. reviewed the data of 41 preterm infants with bradycardia receiving IPPV with T-piece and facemask at birth. {Blank 2014 1568} All infants were monitored by colorimetric CO_2 detection. The median heart rate 10 seconds prior to CO_2 detector color change was 75 bpm (IQR 62-85) and increased to 136 bpm (IQR 113-158) 30 seconds after color change. The authors concluded that colorimetric CO_2 detection during mask IPPV at birth precedes a significant increase in HR.

Mizumoto et al. evaluated seven infants ventilated with flow-inflating bag and facemask. {Mizumoto 2015 186} They found that an exhaled CO_2 >15mmHg preceded a HR increase to >100 bpm by 8-73 seconds.

Exhaled CO_2 and pCO_2 at NICU admission:

Kong et al. randomized infants <34 weeks' gestation to receive respiratory support with continuous exhaled CO_2 values being visible (n=18) or not visible (n=19) to the resuscitation team at birth. {Kong 2013 104} All infants had a colorimetric CO_2 detector during ventilation with T-piece and facemask. Guiding delivery room ventilation with continuous exhaled CO_2 measurement did not result in more infants having the admission pCO_2 within the recommended range of 40-60 mmHg.

Hawkes et al. randomized 59 infants <32 weeks' gestation receiving IPPV by T-piece and facemask to be monitored with quantitative (n=33) or qualitative (n=26) exhaled CO_2. {Hawkes 2017 74} Health care providers were instructed to make ventilation corrective actions to prevent airway obstruction whenever exhaled CO_2 could not be detected. There was no difference in the rate of the admission pCO_2 within the target range between the two groups. Due to the lack of differences between study groups in

primary or secondary outcomes, the authors concluded that the use of either form of exhaled CO_2 monitoring should be considered during newborn stabilization.

No data were found on pre-specified subgroups: methods of exhaled CO_2 evaluation, types of non-invasive interface used in IPPV, indications of IPPV, and gestational age.

2023 Treatment Recommendation

There is insufficient evidence to suggest for or against monitoring the use of exhaled CO to guide noninvasive IPPV with noninvasive interfaces such as face masks, supraglottic airways, and nasal cannulas in infants immediately after birth.

Search Strategy for the original systematic review (same search strategy for 2024 evidence update) – See appendix

Database searched: Medline, Embase, Cochrane Central Register of Controlled Trials.
Time Frame: 1946 to August 1, 2022. Rerun from 2022 to July 3, 2024
Date Search Completed: July 3, 2024
Search Results (Number of articles identified and number identified as relevant):
Identified: 224
Full-text screening: 8
Included: 5

Summary of Evidence Update:
Only one pilot randomized control trial addressing the PICOST was found. No other eligible studies were identified. Therefore, we summarized also 4 observational ineligible studies that may provide useful data relevant to non-invasive IPPV and CO_2 monitoring immediately after birth.

Relevant Guidelines or Systematic Reviews: no included studies/articles

RCT:

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, p-value; OR/RR & 95% CI)	Relevant 2nd Endpoint (if any); Study Limitations; Adverse Events
Kong 2024 {Kong 2024 494}	**Study Aim:** "To evaluate the feasibility of a trial using colorimetric $ETCO_2$ device to improve mask ventilation among preterm newborns in the DR" **Study Type:** Pilot randomized controlled trial (n=47) Groups: Intervention (n=23) Control (n=24)	**Inclusion Criteria:** Newborns with 24+0 to 32+0 weeks gestation who required mask ventilation at birth	**Intervention:** PPV with colorimetric device **Comparison:** PPV without colorimetric device	**1st endpoint:** Bradycardia desaturation index Intervention: 276.7 ± 197.7 sec. Control: 322.7 ± 277.7 sec. (p = 0.6)	Proportion of participants with any bradycardia or desaturation at 5 min: Intervention: 38.1% Control: 56.5% (p = 0.2) There was no difference in mean duration of bradycardia and desaturation, and intubation in the DR between groups **Study Limitations:** Small sample size (underpowered) Single center
Abbreviations: $ETCO_2$: end-tidal carbon dioxide, DR; delivery room, PPV; positive pressure ventilation, wk; week(s)					

Nonrandomized Trials, Observational Studies (ineligible studies, but related to the topic):

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include p-value; OR/RR & 95% CI)	Summary/Conclusion Comments
	Study Type:	**Inclusion Criteria:**	**1st endpoint:**	
Gunawardana, 2023 {Gunawardana 2023 950}	Retrospective observational	GA <34 wk in need for stabilization (n=60)*	$ETCO_2$ levels were lower in infants who developed **IVH** or **died** compared to those that survived without IVH, which remained significant after adjustment for GA, Apgar score at 10 min, chorioamnionitis and coagulopathy (p=0.004)	Delivery room $ETCO_2$ and SpO_2 levels were associated with mortality and IVH
Kannan Loganathan 2023 {Kannan Loganathan 2023 110026}	Retrospective observational	GA ≤32 wk in need for stabilization (n=131; 91 with PPV)	**$ETCO_2$ increased in the first 3-4 minutes and reached a plateau of 3-4 kPa until 10 minutes** $ETCO_2$ could be reliably measured at a median of 14-16 sec. earlier than SpO_2 and pulse. There was no significant correlation between $ETCO_2$ and SpO_2, between $ETCO_2$ and pulse, or between $ETCO_2$ and 1st minute Apgar score. $ETCO_2$ rose at least as fast as the pulse, in particular in the infants who were not intubated	$ETCO_2$ could be measured at least as early as pulse, and earlier than SpO_2 The study provided $ETCO_2$ trends in the first 10 minutes after birth in preterm infants ≤32 wk needing stabilization
Shah 2023 {Shah 2023 652}	Retrospective observational	GA <30 wk in need for respiratory support (n=25) **	**Median (IQR) time (seconds) to achieve CO_2 of 5 mmHg** = 11.5 (2.0-23.7), **10 mmHg** = 15.5 (3.5-29.2), and **15 mmHg** = 18 (13-40). Median (IQR) of maximum $ETCO_2$ in mmHg: - 5.6 (1.3-12.6) - first 10 breaths - 12.6 (5.4-21.9) - 11-20 breaths - 18.0 (7.2-31.4) - 21-30 breaths No difference in maximum median $ETCO_2$ for the first 20 breaths $ETCO_2$ was lower in infants who were intubated vs. non-intubated (15.0 vs. 32.0 mmHg; p=0.018)	DR monitoring of $ETCO_2$ in infants with GA <30 weeks is feasible and may help guide resuscitation and ventilation of preterm infants
Shah 2023 {Shah 2023 e001768}	Retrospective observational	GA <30 wk in need for respiratory support (n=25) **	Mean $ETCO_2$ in mmHg: with vs. without **mask leak** 25.4 ± 10 vs. 30.9 ± 12.2; p=0.002 with vs. without **airway obstruction** 26.0 ± 10.4 vs. 30.8 ± 11.1; p=0.03	There was association of lower $ETCO_2$ in breaths associated with significant airway obstruction and mask leak

Abbreviations: $ETCO_2$: end-tidal carbon dioxide, IVH; intraventricular hemorrhage, GA; gestational age, IQR; interquartile range, PPV; positive pressure ventilation, wk; week(s)

* Same patients of Pahuja {Pahuja 2018 1617} who were included in Neonatal Life Support ILCOR Task Force systematic review {Monnelly 2023 74}

**Same patients in both studies {Shah 2023 652, Shah 2023 e001768}

Reviewer Comments:
This update of the evidence found one small pilot RCT addressing the PICOST and four ineligible retrospective observational studies that were narratively summarized because they were closely related to the topic. Although the five studies included in the EvUp provide additional useful data relevant to non-invasive IPPV and CO_2 monitoring immediately after birth, they do not include data that change the recommendations previously made for this subject, that there is insufficient evidence to suggest for or against using exhaled CO_2 to guide noninvasive IPPV with noninvasive interfaces such as face masks, supraglottic airways, and nasal cannulas, in infants immediately after birth.
Therefore, the evidence from the newer studies is not sufficient to change the current recommendation or to elicit a new systematic or scoping review.

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Appendix – Search Strategy

Ovid MEDLINE(R) ALL 1946 to August 1, 2022 and repeated on July 3rd, 2024

Sources searched	Search strategy	Search time frame

Medline	1 (Carbon Dioxide/ or (carbon dioxide or CO2 or "CO 2").ti.) and (Monitoring, Physiologic/ or (monitor* or measur* or detect* or record*).ti.) 2 ((non-invasive or noninvasive) adj4 (carbon dioxide or CO2 or "CO 2")).ti,ab,kf. 3 Colorimetry/ or colorimet*.ti,ab,kf. 4 Capnography/ or (capnograph* or capnomet* or capnogram*).ti,ab,kf. 5 Exhalation/ 6 ((exhal* or expir*) adj4 (carbon dioxide or CO2 or "CO 2")).ti,ab,kf. 7 ((endotracheal or end-tidal) adj (carbon dioxide or CO2 or "CO 2")).ti,ab,kf. 8 (etco2 or eco2).ti,ab,kf. 9 or/1-8 10 exp Infant, Newborn/ 11 Intensive Care, Neonatal/ 12 Intensive Care Units, Neonatal/ 13 Neonatology/ or Perinatology/ 14 exp Infant, Newborn, Diseases/ 15 Perinatal Care/ 16 Premature Birth/ 17 (newborn* or new born* or newly born* or neonat* or perinat* or peri-nat* or prematur* or preterm* or nicu* or postnat* or post-nat* or (low adj1 (weight or birthweight* or bodyweight*))).ti,ab,kf. 18 or/10-17 19 9 and 18 20 (Animal Experimentation/ or exp Animals/ or exp Models, Animal/) not Humans/ 21 ((veterinar* or animal or animals or rabbit or rabbits or rodent or rodents or rat or rats or mouse or mice or hamster or hamsters or pig or pigs or piglet or piglets or porcine or pigeon* or horse* or equine or cow or cows or bovine or goat or goats or sheep or lamb or lambs or monkey or monkeys or murine or ovine or dog or dogs or canine or cat or cats or feline or dolphin*) not (patient or patients or human or humans or infant*)).ti. 22 20 or 21 23 19 not 22 24 limit 23 to (abstracts or English language)	2021 to 30 2022 to July 3, 2024
Results identified	**Results screened full text**	**Results included**
224	8	5

2025 Evidence Update
NLS 5360 – Respiratory Function Monitoring for Neonatal Resuscitation

Worksheet Author(s): Thio M, Fabres FG, Fawke J, Fuerch J
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 8 November 2024
Conflicts of Interest: None

PICOST:
Population: In newborn infants receiving respiratory support at birth
Intervention: does the display of respiratory function monitoring (RFM)
Comparator: no display of RFM
Outcomes: Death before discharge (critical)
- Severe IVH (critical)
- Response to and characteristics of the resuscitation; achieving desired tidal volumes; percentage maximum mask leak; intubation in the DR; pneumothorax; duration of respiratory support during neonatal intensive care (important)
- Bronchopulmonary dysplasia (important)

Study Designs: RCTs, quasi-RCTs, and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Outcomes from observational studies were assessed if there were fewer than 2 included RCTs/quasi-RCTs or if the certainty of evidence from RCTs/quasi-RCTs was scored very low.
Timeframe: All years and all languages were included provided there was an English abstract. The literature search was updated to 25th August 2022.

Year of last full review*:* 2022. {Fuerch 2022 100327}

Consensus on Science: {Wyckoff 2022 e645}
The systematic review identified 3 RCTs {Schmölzer 2012 377, van Zanten 2021 317, Zeballos Sarrato 2021 145.e1} involving 443 newborns. One newborn infant died in the delivery room in the van Zanten et.al study which accounted for the total of 443 newborns, there is one less newborn reported in many of the longer-term outcomes due to this death.

For response to resuscitation:
For the important outcome ***intubation in the delivery room,*** evidence of **very low certainty** (downgraded for risk of bias, inconsistency and imprecision) from **3 randomized controlled trials (RCTs)** {Schmölzer 2012 377, van Zanten 2021 317, Zeballos Sarrato 2021 145.e1} involving 443 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.90, 95% CI 0.55 – 1.48; p=0.69; I^2 = 61%).

For the important outcome of ***achieving desired tidal volumes in the delivery room,*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {Schmölzer 2012 377, van Zanten 2021 317}involving 337 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.96, 95% confidence interval (CI) 0.69 – 1.34; p=0.8; I^2 = 0%).

For the important outcome of ***pneumothorax,*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {van Zanten 2021 317, Zeballos Sarrato 2021 145.e1} involving 393 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.54, 95% CI 0.26 – 1.13; p=0.10; I^2 = 0%).

For the important outcome of ***time to heart rate >100bpm in the delivery room***, no data were reported in the included studies.

For the outcome of ***face-mask leak***, the 3 RCTs could not be meta-analyzed as the measurement of leak was reported differently in each study. One trial reported median (IQR) percentage of leak per infant and found less leak when RFM was displayed (p=0.01). {Schmölzer 2012 377} Another trial reported percentage of leak >75% over all inflations and found less leak when RFM was displayed (p=0.001) {Zeballos Sarrato 2021 145.e1}. The third and largest trial reported median (IQR) percentage of leak >60% per infant and found no significant difference in leak (p=0.126) between RFM displayed and the RFM not displayed. {van Zanten 2021 317}

Longer-term clinical outcomes:
For the critical outcome of ***death before hospital discharge,*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **3** {Schmölzer 2012 377, van Zanten 2021 317, Zeballos Sarrato 2021 145.e1} involving 442 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 1.00 95% CI 0.66 – 1.52; p=0.99; I^2 = 0%).

For the critical outcome of ***severe intraventricular hemorrhage (grades 3 or 4),*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **1 RCT** {van Zanten 2021 317} involving 287 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.96 95% CI 0.38 – 2.42; p=0.93). Statistical heterogeneity could not be calculated because events occurred in only one trial. {van Zanten 2021 317}

For the important outcome of ***intraventricular hemorrhage (all grades),*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {van Zanten 2021 317, Zeballos Sarrato 2021 145.e1} involving 393 patients suggests **possible clinical benefit** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.69 95% CI 0.49-0.96; p=0.03; I^2 = 0%).

For the important outcome of ***bronchopulmonary dysplasia/chronic lung disease (any),*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {van Zanten 2021 317, Zeballos Sarrato 2021 145.e1} involving 393 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.85 95% CI 0.7 – 1.04; p=0.12; I^2 = 0%).

Treatment Recommendations
There is insufficient evidence to make a recommendation for or against the use of a respiratory function monitor in newborn infants receiving respiratory support at birth (low certainty evidence).

Search strategy for the Evidence Update Review: See appendix
Date Search Completed: 15th October 2024.
Search results:
Identified: 38
Included: none

Reviewers comments: There is no new evidence on this topic. Therefore, there is no indication to conduct a new systematic or scoping review.

References:

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Appendix; Search Strategy (EvUp)

Sources searched	**Search strategy** (Medline)	**Search time frame**

Ovid Medline, Embase, Cochrane Controlled Register of Trials, Cumulative Index to Nursing and Allied Health Literature (CINAHL), US National Library of Medicine (clinicaltrials.gov), International Standard Randomized Controlled Trial Number registry (isrctn.com) and the European Union Clinical Trials Register (clinicaltrialsregister.eu).	(infant*[ti] OR baby[ti] OR babies[ti] OR preemie*[ti] OR newborn*[ti] OR preterm[ti] OR neonat*[ti] OR “infant, newborn” [mesh]) AND ("respiratory rate"[tw] OR monitor*[ti] OR "heart rate" [mesh] OR "respiratory rate" [mesh] OR “respiratory support” [tw] OR “respiratory monitor*” [tw] OR "Monitoring, Physiologic"[Mesh:NoExp] OR "Hemodynamic Monitoring" [mesh] OR "Respiratory Function Tests" [mesh] OR “tidal volume” [mesh] OR “end tidal co2” [tw] OR “expiratory pressure” [tw] OR “inspiratory pressure” [tw] OR “tidal volume*” [tw] OR “mask leak” [tw] OR capnomet*[tw] OR "blood gas"[tw] OR "blood gases"[tw] OR abgs[tw] OR abg[tw] OR "Blood Gas Analysis"[Mesh]) AND (resuscitat*[tw] OR cpr[tw] OR "Cardiopulmonary Resuscitation"[Mesh:NoExp] OR "Resuscitation"[Mesh:NoExp] OR "Heart Massage"[Mesh] OR "Resuscitation Orders"[Mesh]) NOT ((“animals” [mesh] OR “humans” [mesh]) OR letter [pt] OR “case reports” [pt]) AND English [lang]	Start date missing to 15th October 2024.
Results identified	**Results screened full text**	**Results included**
38	Missing	None

2025 Evidence Update
NLS 5401 – Initial Oxygen Concentration for Term Newborn Resuscitation

Worksheet Authors: Solevåg AL, Schmölzer GM, Dawson JA, Roehr CC, Fawke J, Rüdiger M, Staffler A, Bua J, Ibarra D, Costa-Nobre DT, Trevisanuto D, Weiner G, Liley HG
Task Force: Neonatal Life Support
Date approved by SAC Representative: November 30, 2024
Conflicts of Interest:

PICOST:
Population*:* Newborn infants who receive respiratory support at birth (term or late preterm, ≥ 35 weeks' gestation)
Intervention: Lower initial oxygen concentration (FiO_2 <0.50)
Comparison*:* Higher initial oxygen concentration (FiO_2 ≥0.50)
Outcomes*:*

- All cause short-term mortality (in-hospital or 30 days) (Primary)
- All cause long-term mortality (1-3 years) (Secondary)
- Long-term neurodevelopmental impairment (1-3 years) (Secondary)
- Hypoxic-ischemic encephalopathy (Sarnat Stage 2-3) (Secondary)

Study Designs: Randomized controlled trials (RCT), quasi-randomized controlled trials (qRCT), and non-randomised cohort studies were included. Excluded animal studies, unpublished studies (e.g., conference abstracts).
Timeframe*:* 1980 to August 10, 2018.
A priori subgroups to be examined: gestational age (≥ 35 weeks, ≥37 weeks); grouped lower and higher oxygen concentrations; explicit oxygen saturation targeting vs no oxygen saturation targeting

Year of last full review: 2018 {Soar 2019 e826, Welsford 2019 1}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST {Soar 2019 e826}**:**
For the critical outcome of all cause short-term mortality (in-hospital or 30 days), the evidence of low certainty (downgraded for risk of bias and imprecision) from 7 RCTs (and quasi RCTs) involving 1469 term and late preterm newborns (≥ 35 weeks gestation) receiving respiratory support at birth showed benefit of starting with 21% compared to 100% oxygen (RR=0.73 95% CI 0.57-0.94, I^2=0%); 46/1000 fewer babies died when respiratory support at birth was started with 21% compared to 100% oxygen [95% CI: 73/1000 fewer to 10/1000 fewer] {Bajaj 2005 206, Ramji 1993 809, Ramji 2003 510, Saugstad 1998 e1, Toma 2006 33, Vento 2003 240, Vento 2005 1393}.

For the critical outcome of all cause long-term mortality (1-3 years), no evidence was identified.

For the critical outcome of long-term neurodevelopmental impairment (NDI, 1-3 years) among survivors who were assessed, evidence of very low certainty (downgraded for risk of bias and imprecision) from 2 RCTs (and quasi RCTs) involving 360 term and late preterm newborns (≥ 35 weeks' gestation) receiving respiratory support at birth showed no benefit or harm of starting with 21% compared to 100% oxygen (RR=1.41 95% CI 0.77-2.60, I^2=0%); 36/1000 more babies with NDI when respiratory support at birth was started with 21% compared to 100% oxgyen [95% CI: 20/1000 fewer to 142/1000 more] {Bajaj 2005 206, Saugstad 2003 296}

For the critical outcome of hypoxic-ischemic encephalopathy (Sarnat Stage 2-3) evidence of low certainty (downgraded for risk of bias and imprecision) from 5 RCTs (and quasi RCTs) involving 1359 term and late preterm newborns (≥ 35 weeks' gestation) receiving respiratory support at delivery showed no benefit or harm of 21% compared to 100% oxygen (RR=0.90 95% CI 0.71-1.14, I^2=8%); 20/1000 fewer babies with hypoxic-ischemic encephalopathy when respiratory support at birth was started with 21% compared to 100% oxygen [95% CI: 57/1000 fewer to 27/1000 more] {Bajaj 2005 206, Ramji 1993 809, Ramji 2003 510, Saugstad 1998 e1, Toma 2006 33}

No studies were identified that compared any intermediate oxygen concentrations.

Treatment Recommendations
For term and late preterm newborns (≥ 35 weeks' gestation) receiving respiratory support at birth, we suggest starting with 21% oxygen (weak recommendation, low certainty evidence). We recommend against starting with 100% oxygen (strong recommendation, low certainty evidence).

New and Previous Search strategies:
See appendix
Databases searched: PubMed, MEDLINE (Ovid), Embase (via Embase.com), CENTRAL (via the Cochrane Library), CINAHL (EBSCOHost), Clinicaltrials.gov, ISRCTN
Time Frame: (Previous review) – August 10, 2018
Time Frame: (Evidence Update) – July 1, 2018 to August 7, 2024
Date Search Completed: August 7, 2024

Search Results (Number of articles identified and number identified as relevant):
Identified: 2135
Full-text screening: 44 (includes search for preterm studies)
Included: 1

Summary of Evidence Update:

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Riley 2018 {Riley 2018 834}	**Study Type:** Retrospective cohort study including infants with CDH resuscitated with initial FiO_2 of 0.5 (n=68; 19.1% late preterm) and historical controls resuscitated with initial FiO_2 of 1.0 (n=45; 17.8% late preterm)	**Inclusion Criteria:** Infants with CDH born July 2011-December 2015 and were part of the Pulmonary Hypoplasia Program database at The Children's Hospital of Philadelphia	**1° endpoints:** Survival: No difference (p = 0.175) Duration of intubation: No difference (p = 0.0796) Need for ECMO: No difference (p = 0.0540) Duration of ECMO: No difference (p=0.446) Time to surgery: No difference (p=0.538) Multivariate regression controlling for gestational age, liver position, and lung volume–head circumference ratio demonstrated no difference in survival (p = 0.142), duration of intubation (p = 0.089), need for extracorporeal membrane oxygenation (ECMO) (p = 0.159), duration of ECMO (p = 0.744), or days to surgery (p = 0.345) **2° endpoint:**	An initial FiO_2 of 0.5 during resuscitation of infants with CDH is associated with similar outcomes compared to historical controls resuscitated with an initial FiO_2 of 1.0, suggesting that a starting FiO_2 of 0.5 may be safe in infants with CDH

			All cause long-term mortality (1-3 years): Not reported Long-term neurodevelopmental impairment (1-3 years): There was no differences in Bayley III scores—cognitive, language, or motor—at 6 or 12 months of age between historical controls and the study cohort Hypoxic ischemic encephalopathy: Not reported	
Abbreviations: CDH; congenital diaphragmatic hernia, ECMO; extracorporeal membrane oxygenation				

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
This update of the evidence found 1 retrospective cohort study in a very distinct patient population, i.e., infants with congenital diaphragmatic hernia. The starting FiO_2 was either 0.5 or 1.0 and not 0.21 as in the studies included in the current ILCOR Consensus on Science and Treatment Recommendation. Together with a non-randomized design, the indirectness of the study results lead us to conclude that the study does not influence the current recommendation, nor does it elicit a new systematic or scoping review.

*S*ubgroup analysis with regards to gestational age (≥ 35 weeks, ≥37 weeks); grouped lower and higher oxygen concentrations; explicit oxygen saturation targeting vs no oxygen saturation targeting could not be performed based on the data presented.

References:

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Riley JS, Antiel RM, Rintoul NE, Ades AM, Waqar LN, Lin N, et al. Reduced oxygen concentration for the resuscitation of infants with congenital diaphragmatic hernia. Journal of Perinatology. 2018;38(7)834-843.

Saugstad OD, Ramji S, Irani SF, El-Meneza S, Hernandez EA, Vento M, et al. Resuscitation of newborn infants with 21% or 100% oxygen: follow-up at 18 to 24 months. Pediatrics. 2003;112(2)296-300.

Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. Pediatrics. 1998;102(1)e1.

Soar J, Maconochie I, Wyckoff MH, Olasveengen TM, Singletary EM, Greif R, et al. 2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. Circulation. 2019;140(24)e826-e880.

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Vento M, Asensi MA, Sastre J, Lloret A, Garcįa-Sala F, Viųa J. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. The Journal of Pediatrics. 2003;142(3)240-246.

Vento M, Sastre J, Asensi MA, Vina J. Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. AmJRespirCrit Care Med. 2005;172(11)1393-1398.

Welsford M, Nishiyama C. Room Air for Initiating Term Newborn Resuscitation: A Systematic Review With Meta-analysis. Pediatrics. 2019;143(1)1-13.

Appendix; Search Strategies:

Sources searched	**Search strategy** (as run in PubMed)	**Search time frame**
PubMed, MEDLINE (Ovid), Embase (via Embase.com), CENTRAL (via the Cochrane Library), CINAHL (EBSCOHost), Clinicaltrials.gov, ISRCTN	("Infant"[Mesh] OR "Premature Birth"[MeSH] OR "Term Birth"[MeSH] OR "Live Birth"[MeSH] OR "Intensive Care, Neonatal"[MeSH] OR "Intensive Care Units, Neonatal"[Mesh] OR "Delivery Rooms"[MeSH] OR "Respiratory Distress Syndrome, Newborn"[MeSH] OR "Asphyxia Neonatorum"[MeSH] OR "Bronchopulmonary Dysplasia"[MeSH] OR "Infant, Premature, Diseases"[MeSH] OR "Neonatal Nursing"[MeSH] OR "Persistent Fetal Circulation Syndrome"[MeSH] OR "Gestational Age"[MeSH] OR "delivery room*"[tiab] OR newborn*[tiab] OR new-born*[tiab] OR neonat*[tiab] OR prematur*[tiab] OR preterm[tiab] OR pre-term[tiab] OR infant*[tiab] OR baby[tiab] OR babies[tiab] OR birth[tiab] OR "gestational age"[tiab]) AND ("Resuscitation"[Mesh] OR "Oxygen Inhalation Therapy"[Mesh] OR "Oxygen/administration and dosage"[Mesh] OR resuscitat*[tiab] OR "respiratory support"[tiab:~2] OR "cardiorespiratory support"[tiab:~2] OR "artificial respiration"[tiab:~2] OR "oxygen supplementation"[tiab:~2] OR "supplementing oxygen"[tiab:~2] OR "supplement oxygen"[tiab:~2]) AND ("high oxygen"[tiab:~2] OR "higher oxygen"[tiab:~2] OR "highflow oxygen"[tiab:~2] OR "100% oxygen"[tiab] OR "one hundred percent oxygen"[tiab] OR "100 percent oxygen"[tiab] OR "high O2"[tiab:~2] OR "higher O2"[tiab:~2] OR "highflow O2"[tiab:~2] OR "100% O2"[tiab] OR "one hundred percent O2"[tiab] OR "100 percent O2"[tiab] OR "high O(2)"[tiab:~2] OR "higher O(2)"[tiab:~2] OR "highflow O(2)"[tiab:~2] OR "100% O(2)"[tiab] OR "one hundred percent O(2)"[tiab] OR "100 percent O(2)"[tiab] OR "high Fio2"[tiab:~2] OR "higher Fio2"[tiab:~2] OR "highflow Fio2"[tiab:~2] OR "100% Fio2"[tiab] OR "one hundred percent Fio2"[tiab] OR "100 percent Fio2"[tiab] OR ((Air[MeSH] OR "room air"[tiab]) AND (oxygen[tiab] OR O2[tiab] OR "O(2)"[tiab] OR Fio2[tiab])) OR "low oxygen"[tiab:~2] OR "lower oxygen"[tiab:~2] OR "limited oxygen" [tiab:~2] OR "reduced oxygen" [tiab:~2] OR "reduction oxygen" [tiab:~2] OR "low O2"[tiab:~2] OR "lower O2"[tiab:~2] OR "limited O2" [tiab:~2] OR "reduced O2" [tiab:~2] OR "reduction O2" [tiab:~2] OR "low O(2)"[tiab:~2] OR "lower O(2)"[tiab:~2] OR "limited O(2)" [tiab:~2] OR "reduced O(2)" [tiab:~2] OR "reduction O(2)" [tiab:~2] OR "low Fio2"[tiab:~2] OR "lower Fio2"[tiab:~2] OR "limited Fio2" [tiab:~2] OR "reduced Fio2" [tiab:~2] OR "reduction Fio2" [tiab:~2] OR	30 July 1, 2018 to August 7, 2024

	"oxygen concentration"[tiab:~2] OR "oxygen concentrations"[tiab:~2] OR "oxygen fraction"[tiab:~2] OR "oxygen fractions"[tiab:~2] OR "target oxygen"[tiab:~2] OR "targets oxygen"[tiab:~2] OR "targeted oxygen"[tiab:~2] OR "oxygen saturation"[tiab:~2] OR "optimal oxygen"[tiab:~2] OR "oxygen differences"[tiab:~2] OR "O2 concentration"[tiab:~2] OR "O2 concentrations"[tiab:~2] OR "O2 fraction"[tiab:~2] OR "O2 fractions"[tiab:~2] OR "target O2"[tiab:~2] OR "targets O2"[tiab:~2] OR "targeted O2"[tiab:~2] OR "O2 saturation"[tiab:~2] OR "optimal O2"[tiab:~2] OR "O2 differences"[tiab:~2] OR "O(2) concentration"[tiab:~2] OR "O(2) concentrations"[tiab:~2] OR "O(2) fraction"[tiab:~2] OR "O(2) fractions"[tiab:~2] OR "target O(2)"[tiab:~2] OR "targets O(2)"[tiab:~2] OR "targeted O(2)"[tiab:~2] OR "O(2) saturation"[tiab:~2] OR "optimal O(2)"[tiab:~2] OR "O(2) differences"[tiab:~2] OR "Fio2 concentration"[tiab:~2] OR "Fio2 concentrations"[tiab:~2] OR "Fio2 fraction"[tiab:~2] OR "Fio2 fractions"[tiab:~2] OR "target Fio2"[tiab:~2] OR "targets Fio2"[tiab:~2] OR "targeted Fio2"[tiab:~2] OR "Fio2 saturation"[tiab:~2] OR "optimal Fio2"[tiab:~2] OR "Fio2 differences"[tiab:~2]) NOT (animals[MeSH] NOT humans[MeSH]) NOT (letter[pt] OR comment[pt] OR editorial[pt] OR "case reports"[pt] OR congress[pt] OR "clinical conference"[pt]) AND 2018/08/01:2024/12/31 [crdt]	
Results identified	**Results screened full text**	**Results included**
2135	44	1

2025 Evidence Update
NLS 5500 – Heart Rate for Starting Neonatal Chest Compressions

Worksheet Authors: Ramachandran S, Bruckner M, Schmölzer GM, Wyckoff MH
Task Force: Neonatal Life Support
Approved by SAC Representative: 4 November 2024
Conflicts of Interest: None of the Evidence Update Worksheet authors made any decision regarding inclusion of their own papers in the evidence update.

PICOST:
Population: In neonates being resuscitated with ventilation who have a slow heart rate
Intervention: does starting cardiac compressions at other heart rates
Comparators: versus starting cardiac compressions when the heart rate is < 60 bpm
Outcomes: impact any short- or long-term outcomes (increase survival rates, improve neurologic outcomes, decrease time to return of spontaneous circulation)
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded.
Timeframe: All years and all languages were included provided there was an English abstract; Initial search on Nov 22,2021. Recent updated search on June 16, 2024.

Year of last full review: 2022 {Berg, 2023 #182;Ramachandran, 2023 #173}

Current Search Strategy – see appendix

Inclusion and Exclusion Criteria
We included animal, manikin, and human studies if there was an abstract in English. Reviews, unpublished studies, or studies published in abstract only, and studies that did not specifically address the PICOST questions were excluded.

Database searched: Ovid Medline, Embase, Cochrane
Time Frame: (existing PICOST) – between Nov 22, 2021 and June 16, 2024
Date Search Completed: June 16, 2024
Search Results: 175 studies were screened, 42 full text studies were assessed for eligibility and no studies addressing this PICOST were found eligible for inclusion.

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
- No prior published treatment recommendation from ILCOR however ILCOR NLS algorithm has always said if HR <60/min after ensuring adequate ventilation, start compressions.
- Current recommendation of starting chest compressions for a heart rate cutoff of <60/min was originally selected based on expert opinion and a desire to simplify the resuscitation algorithm. (The earliest North American neonatal resuscitation recommendations included starting compressions when the heart rate was 60-80/min and not rising for example).
- This PICOST was addressed for the first time in 2021 when this topic was chosen for scoping review by the NLS Task Force because until then it was unknown what evidence existed regarding this important question.
- Initiation of cardiac compressions when the heart rate remains less than 60 bpm after successful inflation of the lungs has long been suggested in neonatal resuscitation algorithms. However, the evidence for using this cut-off has never been examined by the NLS Task Force via a systematic review with GRADE evaluation.

2. Narrative summary of evidence identified in initial search in November 2021
- No clinical studies were found that examined different heart rate thresholds to initiate chest compressions in newborn infants in the delivery room.
- One review article regarding strategies to prevent progression of bradycardia and the role of chest compressions for persistent neonatal bradycardia in the delivery room included some animal data which might be useful. {Agrawal 2019 119} Fetal lambs (n=14) were instrumented and asphyxiated until cardiac arrest. Heart rates were continuously monitored using an invasive

aortic line. Coronary, carotid and pulmonary flows were recorded and compared during asphyxia at different levels of bradycardia. Peak systolic carotid flows were significantly lower for heart rates <60/min compared to baseline.

3. Current search results and commentary

- No further studies addressing this PICOST were identified in the updated 2024 search.
- There is a significant gap in the published literature regarding the optimal threshold for which to initiate cardiac compressions as there were no studies that directly addressed this question.
- The information from this Evidence Update is insufficient to alter the current existing suggestion of starting compressions when the heart rate is < 60/min after successful inflation of the lung.
- The lack of clincial data makes it unnecessary to pursue a systematic review with meta-analysis at this time.
- Since the compression threshold of HR <60/min has only been noted in the algorithm for the past 2 decades, the NLS Task Force felt it was appropriate to issue the following good practice statement:

In neonates being resuscitated who have a slow heart rate even after optimizing ventilation, initiating cardiac compressions when the heart rate is < 60/min is reasonable (good practice statement).

References:

Agrawal V, Lakshminrusimha S, Chandrasekharan P. Chest Compressions for Bradycardia during Neonatal Resuscitation-Do We Have Evidence? Children. 2019;6(11)119.

Appendix – search strategy

Sources searched	Search strategy	Search time frame
PubMed	(((((compression:ventilation[Title/Abstract]) OR ((((((Heart Massage[MeSH Terms]) OR heart massage*[Title/Abstract]) OR cardiac massage*[Title/Abstract]) OR compression*[Title/Abstract])) AND (("Respiration, Artificial"[Mesh:NoExp]) OR ventilation*[Title/Abstract]))))) AND ((ratio [Title/Abstract]) OR ratios[Title/Abstract]))) NOT (("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp])) AND ("Respiratory Distress Syndrome, Newborn"[Mesh] OR "Bronchopulmonary Dysplasia"[Mesh] OR "Infant, Newborn"[Mesh] OR "Delivery Rooms"[Mesh] OR "Gestational Age"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Premature, Diseases"[Mesh:NoExp] OR "Term Birth"[Mesh] OR "Live Birth"[Mesh] OR "Neonatal Nursing"[Mesh] OR "Neonatal Screening"[Mesh] OR "Intensive Care, Neonatal"[Mesh] OR "Intensive Care Units, Neonatal"[Mesh] OR "Animals, Newborn"[Mesh] OR "Transient Tachypnea of the Newborn"[Mesh] OR "Persistent Fetal Circulation Syndrome"[Mesh] or newborn[TIAB] or neonatal[TIAB] or neonate[TIAB] or neonates[TIAB] OR "Low Birth Weight "[TIAB] or "Small for Gestational Age"[TIAB] or prematur*[TIAB] or preterm[TIAB] OR "Birth Injuries"[Mesh] OR "Birthing Centers"[Mesh] OR Postmature[TIAB] OR infants[TIAB] OR infant[TIAB] OR birth[TIAB]) Embase: (Search Completed:) ((‘Heart Massage’/de OR (heart NEAR/1 massage*):ab,ti OR (cardiac NEAR/1 massage*):ab,ti OR compression*:ab,ti) AND (‘Respiration, Artificial’/de OR ventilation*:ab,ti) OR ‘compression:ventilation’:ab,ti) AND (ratio:ab,ti OR ratios:ab,ti) NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [embase]/lim AND ('neonatal respiratory distress syndrome'/exp OR 'newborn hypoxia'/exp OR 'prematurity'/exp OR 'newborn apnea	Nov 22, 2021 to June 16, 2024

	attack'/exp OR 'newborn disease'/de OR 'neonatal stress'/exp OR 'lung dysplasia'/exp OR 'newborn'/exp OR 'low birth weight'/exp OR 'newborn screening'/exp OR 'newborn monitoring'/exp OR 'newborn care'/exp OR 'newborn period'/exp OR 'birth weight'/exp OR 'newborn morbidity'/exp OR 'live birth'/exp OR 'newborn death'/exp OR 'newborn mortality'/exp OR 'delivery room'/exp OR newborn OR 'low birth weight':ab,ti OR 'small for gestational age':ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR postmature:ab,ti OR 'macrosomia'/exp)	
Cochrane	(Search Completed:) (([mh “Heart Massage”] OR “heart massage*”:ab,ti OR “cardiac massage*”:ab,ti OR “compression*”:ab,ti) AND ([mh ^“Respiration, Artificial”] OR ventilation*:ab,ti) OR “compression:ventilation”:ab,ti) AND (ratio:ab,ti OR ratios:ab,ti) AND ([mh "Respiratory Distress Syndrome, Newborn"] or [mh "Bronchopulmonary Dysplasia"] or [mh "Infant, Newborn"] or [mh "Delivery Rooms"] or [mh "Gestational Age"] or [mh "Premature Birth"] or [mh ^"Infant, Premature, Diseases"] or [mh "Term Birth"] or [mh "Live Birth"] or [mh "Neonatal Nursing"] or [mh "Neonatal Screening"] or [mh "Intensive Care, Neonatal"] or [mh "Intensive Care Units, Neonatal"] or [mh "Animals, Newborn"] or [mh "Transient Tachypnea of the Newborn"] or [mh "Persistent Fetal Circulation Syndrome"] or newborn:ti,ab or neonatal:ti,ab or neonate:ti,ab or neonates:ti,ab or "Low Birth Weight ":ti,ab or "Small for Gestational Age":ti,ab or prematur*:ti,ab or preterm:ti,ab OR [mh "Birth Injuries"] OR [mh "Birthing Centers"] OR Postmature:ti,ab OR infant:ti,ab OR infants:ti,ab OR birth:ti,ab)	
Ovid Medline	1 resuscitation/ or cardiopulmonary resuscitation/ or advanced cardiac life support/ or heart massage 2 (resuscitation or CPR or cardiopulmonary resuscitation).tw,kf. 3 (ACLS or cardiac life support).tw,kf. 4 (heart massage or cardiac massage or closed chest massage).tw,kf. 5 1 or 2 or 3 or 4 6 compress*.tw,kf. 7 5 and 6 8 Infant/ 9 infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, postmature/ or infant, premature/ or infant, extremely premature/ 10 8 or 9 11 7 and 10 12 (infant or infants or neonate or neonatal or newborn).tw,kf. 13 7 and 12 14 11 or 13	
EMBASE	1 resuscitation/ 2 heart massage/ 3 (resuscitation or CPR or cardiopulmonary resuscitation).tw,kw. 4 (ACLS or cardiac life support).tw,kw. 5 (heart massage or cardiac massage or closed chest massage).tw,kw. 6 1 or 2 or 3 or 4 or 5 7 compress*.tw,kw. 8 6 and 7 9 infant/ or baby/ or high risk infant/ or hospitalized infant/ or newborn/ 10 8 and 9	

	11 (infant or infants or neonate or neonatal or newborn).tw,kw. 12 8 and 11 13 10 or 12	
Results identified	**Results screened full text**	**Results included**
175	42	none

2025 Evidence Update
NLS 5501 – Chest Compressions with Two Thumbs vs. Other Techniques

Worksheet Author(s): Ramachandran S, Bruckner M, Schmölzer GM, Wyckoff MH
Task Force: Neonatal Life Support
Approved by SAC Representative: 1 December 2024
Conflicts of Interest: None of the Evidence Update Worksheet authors made any decision regarding inclusion of their own papers in the evidence update.

PICOST:
Population: In neonates receiving chest compressions
Intervention: does use of any other technique (2-finger or other)
Comparators: versus the 2-thumb technique
Outcomes: increase survival rates (critical), improve neurologic outcomes (critical), decrease time to return of spontaneous circulation (important)
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion in the scoping reviews. Conference abstracts and unpublished studies (e.g., trial protocols) were excluded.
Timeframe: All years and all languages were included provided there was an English abstract between Nov 22,2021 and June 16, 2024.

Year of last full review: 2023 {Berg 2023 e187, Ramachandran 2023 442}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
The previous ILCOR ScopRev {Berg 2023 e187, Ramachandran 2023 442}identified 29 randomized crossover manikin studies, {Cheung 2019 559, Christman 2011 F99, Dorfsman 2000 1077, Huynh 2012 658, Jiang 2015 531, Jo 2017 462, Jo 2015 703, Jung 2019 261, Kim 2016 997, Ladny 2018 e9386, Lee 2020 e700, Lee 2018 372, Martin 2013 576, Na 2015 e70, Paek 2019 e0226632, Park 2019 74, Pellegrino 2019 530, Reynolds 2020 133, Rodriguez-Ruiz 2019 1529, Smereka 2017 e5915, Smereka 2017 589, Smereka 2019 761, Smereka 2018 159, Smereka 2017 1420, Udassi 2010 712, Whitelaw 2000 213, Yang 2019 1217} 1 observational study, {Jang 2018 36} and 1 randomized study {Saini 2012 690} comparing various finger/hand positions. The available data demonstrated that the 2-thumb technique resulted in greater chest compression depth, lower fatigue, and higher proportion of correct hand placement compared with the 2-finger technique.

The initial recommendation made in the 2015 ILCOR CoSTR {Perlman 2015 S204} remained unchanged in the most recent 2023 CoSTR {Berg 2023 e187} 'We suggest that chest compressions in newborn infants immediately after birth should be delivered by the 2-thumb, hands-encircling-the-chest method as the preferred option (weak recommendation, very low–quality evidence).'

Current Search Strategy – As for NLS 5500 – Heart Rate for Starting Neonatal Chest Compressions

Inclusion and Exclusion criteria
We included animal, manikin, and human studies if there was an abstract in English. Reviews, unpublished studies, or studies published in abstract only, and studies that did not specifically address the PICOST questions were excluded.

Database searched: Medline, Embase, Cochrane
Time Frame: (existing PICOST) – between Nov 22, 2021 and June 16, 2024
Date Search Completed: June 16, 2024
Search Results: 175 studies were screened, 42 were chosen for a full text review and 10 studies were identified that applied to this PICOST

Summary of Evidence Update

Relevant Guidelines or Systematic Reviews: None since the ILCOR scoping review published in 2022 {Ramachandran 2023 442} which concluded that the 2-thumb technique is superior to other techniques of administering chest compressions in newborn infants.

Randomized Controlled Trials (RCT):

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Aranda-García 2024 {Aranda-García 2024 100}	**Study Aim:** To compare single rescuer 2-thumb encircling the chest with provider at the head of the bed (OTH) CPR versus standard 2-thumb encircling the chest from the lateral position (LAT) **Study Type:** Randomized crossover simulation study **Study Size:** N=28	**Inclusion Criteria:** Lifeguards who were given a brief instructor-guided rolling refresher	**Intervention:** Single rescuer OTH CPR using 2-thumb encircling technique **Comparison:** LAT position using 2-thumb encircling technique	**1° endpoint:** CPR quality (assessment of depth, rate, and correct CC point) >70% achieved using both resuscitation techniques (OTH: 82%; IQR 54–88% vs. LAT: 79%; IQR 66–90%, p = 0.94)	**2° endpoints:** - OTH had higher values of correct recoil than LAT (OTH: 92%; IQR 62–99% vs. LAT: 62%; IQR 41–81%, p < 0.001). -No differences noted between groups in correct depth, rate and number of effective ventilations. -Participants indicated a pronounced preference for the OTH technique over the LAT technique in terms of perceived ease of performing CPR **Study Limitations:** -Small and local sample of trained lifeguards. -Controlled simulation scenario with manikins; real life scenarios may be more complex
Barcalas-Furelos 2022 {Barcala-Furelos 2022 910}	**Study Aim:** To compare the quality of CPR (Q-CPR), as well as the perceived fatigue and hand pain in a prolonged infant cardiopulmonary resuscitation (CPR) performed by	**Inclusion Criteria:** Professional lifeguards	**Intervention:** CPR in 15:2 cycles using TTF technique and TTE technique **Comparison:** CPR in 15:2 cycles using TFT	**1° endpoint:** All three techniques showed high Q-CPR results (TFT: 86 ± 9%/TTE: 88 ± 9%/TTF: 86 ± 16%), and the TTE showed higher	**2° endpoints: -** In a rate of perceived exertion (RPE) analysis, fatigue on a 10-point fatigue scale was not excessive with any of the three techniques (values 20 min

	lifeguards using three different techniques i.e. 2-finger technique (TFT), 2-thumb encircling technique (TTE) and 2-thumb-fist technique (TTF) **Study Type**: Randomized crossover simulation study **Study Size:** N=58			values than the TF (p = 0.03).	between 3.2 for TFT, 2.4 in TTE and 2.5 in TTF on a 10-point scale). TFT reached a higher value in RPE than TTF in all the intervals analyzed (p < 0.05) -In relation to hand pain numeric rating scale (NRS), TFT showed significantly higher values than TTE and TTF (NRS minute 20 = TFT 4.7 vs. TTE 2.5 & TTF 2.2; p < 0.001). **Study Limitations:** -Controlled simulation scenario with manikins; real life scenarios may be more complex -Not all CC quality variables such as compression depth were included.
Bruckner 2023 {Bruckner 2023 283}	**Study Aim:** To compare the hemodynamic effects of four different finger positions (2-thumb position, 2-finger, knocking fingers and 2-thumb OTH) during CC with sustained inflations in a piglet model of neonatal asphyxia **Study Type:** Randomized Controlled animal study **Study Size:** N=7	**Inclusion Criteria:** Asphyxiated post-transitional piglets	**Intervention:** 2-finger-, knocking-fingers-, and OTH 2-thumb-techniques used for CC for one minute at each technique **Comparison:** 2-thumb encircling technique used for CC for one minute	**1° endpoint:** The mean (SD) slope rise of carotid blood flow was significantly higher with the 2-thumb-technique and OTH 2-thumb-technique [118 (45) mL/min/s and 121 (46) mL/min/s, respectively] compared to the 2-finger-technique and knocking-finger-technique [75 (48) mL/min/s and 71 (67) mL/min/s, respectively) (p < 0.001)]	**2° endpoints:** The left ventricular function was significantly higher with the 2-thumb technique, [−1052 (369) mmHg/s, compared to −568 (229) mmHg/s and −578(180) mmHg/s (both p = 0.012) with the 2-finger-technique and knocking-finger-technique, respectively. **Study Limitations:** -CC+SI is not the recommended standard of treatment and

					may affect the results of this study -Post transitional piglets used which does not adequately match a delivery room scenario -Different shape and surface anatomy of the piglet chest might have generated different forces and a different hemodynamic response.
Cioccari 2021 {Cioccari 2021 e018050}	**Study Aim:** To compare the 2-finger and 2-thumb chest compression techniques on infant manikins in an out-of-hospital setting **Study Type** Randomized crossover manikin study **Study Size:** N=78	**Inclusion Criteria:** Medical students	**Intervention:** 2 minutes of single rescuer cardiopulmonary resuscitation with mouth-to-nose ventilation at a 30:2 rate on a Resusci Baby QCPR infant manikin using 2-finger technique **Comparison:** 2 minutes of single rescuer cardiopulmonary resuscitation with mouth-to-nose ventilation at a 30:2 rate on a Resusci Baby QCPR infant manikin using 2-thumb technique	**1° endpoint:** The 2-thumb technique resulted in a greater depth of chest compressions (42 versus 39.7 mm; P<0.01), and a higher percentage of chest compressions with adequate depth (89.5% versus 77%; P<0.01).	**2° endpoints:** No differences in ventilatory parameters or hands-off time between techniques. Pain and fatigue scores were higher for the 2-finger technique (5.2 versus 1.8 and 3.8 versus 2.6, respectively; P<0.01) **Study Limitations:** Chest wall distensibility and compressibility of infant manikins do not exactly mimic those in infants, so study results may not be directly translatable to human infants -Simulated CPR time was shorter than in reality
Gugelmin-Almeida 2021 {Gugelmin-Almeida 2021 100141}	**Study Aim:** to compare the 2-finger technique (TFT) performance using dominant	**Inclusion Criteria:** Participants from Bournemouth University including students,	**Intervention:** 3 min iCPR using the 2-finger technique with the non dominant hand	**1° endpoint:** No significant difference between DH and	**2° endpoints:** No significant correlation between iCPR metrics and

	hand (DH) and non-dominant hand (NH) during simulated infant CPR (iCPR). **Study Type**: Randomized crossover manikin study **Study Size:** N=24	staff and general public	**Comparison:** 3 min iCPR using the 2-finger technique with the dominant hand	NH for any iCPR metric	perception of fatigue for DH **Study Limitations:** -Participants were lay people with little or no CPR training. -Manikin based study in a simulated environment, lacks direct transferability -Simulated CPR time was shorter than in reality.
Hirayama 2022 {Hirayama 2022 e15118}	**Study Aim:** To compare TFT with real time visual feedback (RVF), one hand technique (OHT) without RVF and OHT with RVF **Study Type** Crossover manikin study **Study Size:** N=59	**Inclusion Criteria:** Nurses and doctors of a pediatric intensive care unit of a single tertiary pediatric center	**Intervention:** Group A Performed CC using TFT with RVF first, then OHT without RVF. Group B performed OHT without RVF first, then TFT with RVF. Both groups performed OHT with RVF at the end.	**1° endpoint:** Mean compression depth was 24 mm (interquartile range [IQR], 22–26 mm) in TFT with RVF and 43 mm (IQR, 38–48 mm) in OHT without RVF, $P < 0.001$. - The proportion of adequate CC depth was 0% (IQR, 0–0%) in TFT with RVF, 22% (IQR, 5–54%) in OHT without RVF, and 62% (IQR, 29–83%) in OHT with RVF.	**Study Limitations:** -Manikin study, so relationship between CC depth and objective patient outcomes such as coronary perfusion or neurological prognosis not analyzable. - Chest wall distensibility and compressibility of infant manikins do not exactly mimic those in infants. -Sample size not calculated in advance.
Jahnsen 2021 {Jahnsen 2021 1571}	**Study Aim:** To assess tidal volume (Vt) and minute ventilation (MV) during cardiopulmonary resuscitation (CPR) with two different chest compressions techniques: 2-finger (TFT) or 2-thumb technique (TTT) in a neonatal manikin	**Inclusion Criteria:** Neonatal resuscitation trained professionals including fellows, residents, neonatologists, nurses and respiratory therapists	**Intervention:** Two minutes of CPR in neonatal manikin using 2-finger technique (TFT) while performing positive pressure ventilation using a T-piece resuscitator (TPR) or a self-inflating bag (SIB) **Comparison:** Two minutes of CPR in neonatal	**1° endpoint:** -Vt during CPR with TFT was significantly higher than TTT with either TPR: 44.9 ± 4.3 vs 39.2 ± 5.4 ml ($p < 0.001$) or SIB: 39.2 ± 5.7 vs 35.6 ± 6.5 ml ($p < 0.023$). - MV was significantly higher in TFT than TTT with either mode: 1346 ± 130 vs 1175 ± 162 ml/min, respectively, with	**Study Limitations:** -Modified manikin used which likely has different chest wall compliance as compared to neonate. -CC depth and efficacy not evaluated

	Study Type: Prospective randomized crossover manikin trial **Study Size:** N=30		manikin using 2-thumb technique (TTT) while performing positive pressure ventilation using a T-piece resuscitator (TPR) or a self-inflating bag (SIB)	TPR ($p < 0.001$) and 1177 ± 170 vs 1069 ± 196 ml/min with SIB ($p < 0.03$).	
Jeon 2022 {Jeon 2022 e0271636}	**Study Aim:** To compare the quality of chest compression and brief hands-off times in 2-finger technique (TFT), 2-thumb technique (TTT), and crossed thumb technique (CTT) by a single rescuer using 30:2 ratio **Study Type:** Prospective randomized controlled simulation study **Study Size:** N=98	**Inclusion Criteria:** Participants who were already trained in Pediatric Basic Life Support.	**Intervention:** CC performed using TFT and TTT by a single rescuer with mouth to mouth ventilations **Comparison:** CC performed using TTT by a single rescuer with mouth to mouth ventilations	**1° endpoint:** -Depth of chest compression in TFT, TTT, and CTT were 40.0 mm (interquartile range [IQR] 39.0, 41.0), 42.0 mm (IQR 41.0, 43.0), and 42.0 mm (IQR 41.0, 43.0), respectively; $p<0.05$ TFT vs either TTT or CTT. -Chest compression fractions (CCF) in TFT, TTT, and CTT were 73.9% (IQR 72.2, 75.6), 71.2% (IQR 67.2, 72.2) and 71.3% (IQR 67.7, 74.1), respectively. CCF higher in TFT than in the other two techniques ($P<0.05$).	**2° endpoint:** -Correct location in TFT, TTT, and CTT were 99.0% (IQR 86.0, 100.0), 100.0% (IQR 97.0, 100.0) and 100.0% (IQR 99.0, 100.0), respectively with correct location in CTT and TTT being higher than that in TFT. -Subjective pain and fatigue score lower in CTT as compared to other two techniques. **Study Limitations:** -Manikin study results may not be directly translatable to human neonates. Crossover design is preferred in simulation studies. -Limited time of CC as compared to a real-life scenario
Kao 2024 {Kao 2024 81}	**Study Aim:** To determine whether CPR using a syringe plunger technique (SPT) could improve CPR quality measurements **Study Type:** Randomized	**Inclusion Criteria:** Healthcare providers with certificated ACLS licenses	**Intervention:** CPR for 2 minutes on manikin using TFT or SPT **Comparison:** CPR for 2 minutes on manikin using TTT	**1° endpoint:** **-**The median (IQR) compression depth in the TTT, TFT and SPT in the first minute were 41 mm (40–42), 40 mm (38–41) and 40 mm (39–41), respectively, $p < 0.001$.	**2° endpoint:** The fatigue scores were 6 (4–7), 7 (5–8) and 5 (3–7), in TTT, TFT and SPT groups respectively, with $p < 0.001$. **Study Limitations:**

	crossover manikin study **Study Size:** N=60			- The median (IQR) recoil in the TTT, TFT and SPT groups in the first minute was 15% (1–93), 64% (18–96) and 53% (8–95), respectively, with p = 0.003.	-Effect of ventilation was not evaluated -Manikin study, so may not be directly transferable to real life -CC only performed for 2 minutes, much less than actual CPR in a real-life scenario
Abbreviations: ACLS; advanced cardiac life support, CC; chest compressions, CCF; chest compression fraction, CC+SI; chest compressions with sustained inflation, CPR; Cardiopulmonary Resuscitation, CTT; crossed thumb technique, DH; dominant hand, iCPR; simulated infant CPR, IQR; interquartile range, LAT; lateral technique, MV; minute volume, NH; non-dominant hand, NRS; numeric rating scale, OHT; one hand technique, OTH; Over the head technique, Q-CPR; quality of CPR, RPE; rate of perceived exertion, RVF; real time visual feedback, SIB; self-inflating bag, SPT; syringe plunger technique, TFT; 2-finger technique, TPR; T-piece resuscitator, TTE; 2-thumb encircling technique, TTF; 2-thumb-fist technique, TTT; 2-thumb technique, Vt; tidal volume				

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
O'Connell 2023 {O'Connell 2023 109741}	**Study Aim:** To determine the effect of hand position on chest compression (CC) quality during CPR in young children. Four techniques were compared -TFT, TTT, one hand on sternum (1H) and two hands on sternum (2H). **Study Type:** Prospective observational exploratory study **Study Size:** N=47	**Inclusion Criteria:** Patients aged less than eight years receiving chest compressions in the ED as a continuation of ongoing care for out-of-hospital cardiac arrest, or for cardiac arrest and/or critical bradycardia while being cared for in the ED	**1° endpoint:** 1H achieved greater depth than 2 T in infants (p < 0.01), and 2H achieved greater depth than 1H in children > 1 (p < 0.001).	In infants, 1H resulted in greater CC depth than 2 T. In children 1 to 8 yo, 2H resulted in greater depth than 1H.
Abbreviations: CC; Chest compression, CI; confidence interval, CPR; cardiopulmonary resuscitation, ED; emergency department, OR; odds ratio, RR; relative risk, TFT; two finger technique, TTT; two thumb technique, 1H; one hand on sternum, 2H; two hand on sternum				

Ten studies were identified that evaluated different techniques for providing neonatal chest compressions, {Aranda-García 2024 100, Barcala-Furelos 2022 910, Bruckner 2023 283, Cioccari 2021 e018050, Gugelmin-Almeida 2021 100141, Hirayama 2022 e15118, Jahnsen 2021 1571, Jeon 2022 e0271636, Kao 2024 81, O'Connell 2023 109741} eight of which were simulation studies, }

{Aranda-García 2024 100, Barcala-Furelos 2022 910, Cioccari 2021 e018050, Gugelmin-Almeida 2021 100141, Hirayama 2022 e15118, Jahnsen 2021 1571, Jeon 2022 e0271636, Kao 2024 81} one was a randomized controlled animal study, {Bruckner 2023 283} and one was a prospective observational study in patients under eight years of age with cardiac arrest. {O'Connell 2023 109741}

Bruckner et al. evaluated the hemodynamic effects of four different finger positions used for chest compressions in a post-transitional neonatal piglet model. {Bruckner 2023 283} Carotid blood flow was higher when utilizing the 2-thumb lateral technique or the over-the-head 2-thumb technique. Left ventricular relaxation was also better while using these two techniques compared to the 2-finger technique and a knocking finger technique.

The 2-thumb technique provides higher quality CPR {Barcala-Furelos 2022 910} with less fatigue and hand pain while performing CPR than the 2-finger technique.{Barcala-Furelos 2022 910, Cioccari 2021 e018050} Moreover, better depth of compressions was achieved with a higher percentage of chest compressions with adequate depth {Cioccari e018050, Jeon e0271636}.

While Cioccari et al. showed no difference in ventilatory parameters regardless of compression technique employed, {Cioccari 2021 e018050} Jahnsen et al., demonstrated higher tidal volumes and minute ventilation when utilizing the 2-finger technique compared to the 2-thumb technique. {Jahnsen 2021 1571}

One study demonstrated that use of a syringe plunger as a CPR assist device would significantly decrease fatigue scores when compared to either the 2-thumb or 2-finger technique. {Kao 2024 81}

Another study illustrated that the over the head 2-thumb technique generated better recoil as compared to the 2-thumb technique performed from a lateral position. {Aranda-García 2024 100} Additionally, there was a significant subjective preference (in terms of perceived ease of performing CPR) by the medical personnel participating in the study.

One prospective observational study in children under 8 years of age demonstrated that in infants undergoing CPR, use of a 1-hand CPR technique achieved better depth of compressions as compared to the 2-thumb technique. However, this comparison was not described in detail in the neonatal population. {O'Connell 2023 109741}

Reviewer Comments:

This 2025 evidence update confirmed the previous 2023 CoSTR that the 2-thumb-techniques resulted in improved chest compression depth, lower fatigue, and higher proportion of correct hand placement compared to the 2-finger-technique. Although studies also examined alternative finger and/or hand position techniques, none improved performance compared to the 2-thumb-technique.

There were no new randomized controlled trials that would prompt a systematic review of this PICOST at this time. The information from the studies identified is insufficient to alter existing recommendations.

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2025 Evidence Update
NLS 5503 – Supplemental Oxygen During Chest Compressions

Worksheet Author(s): Ramachandran S, Bruckner M, Schmölzer GM, Wyckoff MH
Task Force: Neonatal Life Support
Approved by SAC Representative: 1 December 2024
Conflicts of Interest: None of the Evidence Update Worksheet authors made any decision regarding inclusion of their own papers in the evidence update.

PICOST:
Population: Neonates receiving chest compressions
Intervention: Any lower concentration of oxygen
Comparator: 100% oxygen as the ventilation gas
Outcomes: survival rates (critical), improve neurologic outcomes (critical), decrease time to ROSC (important), or decrease oxidative injury (important)?
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded.
Timeframe: All years and all languages were included provided there was an English abstract; Literature search updated to between Nov 22, 2021 and June 16, 2024

Year of last full review: 2023 {Berg 2023 e187, Ramachandran 2023 442}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Berg 2023 e187, Ramachandran 2023 442}
The 2023 ILCOR CoSTR stated that no human studies that compared any other oxygen concentration with 100% O_2 during chest compressions were identified in the last full review conducted in 2021. Seven animal studies comparing 21% with 100% O_2 concentrations during chest compressions after asphyxial cardiac arrest were identified. Overall, the studies found no difference in time to ROSC, mortality, inflammation, or oxidative stress. {Dannevig 2012 89, Dannevig 2013 163, Linner 2017 1556, Linner 2009 391, Solevåg 2010 64, Solevåg 2020 102}

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 statement). If used, supplementary oxygen should be weaned as soon as the heart rate has recovered (weak recommendation, very-low-quality evidence). {Berg 2023 e187}

Current Search Strategy – As for NLS 5500 – HR for starting chest compressions

Inclusion and Exclusion criteria
We included animal, manikin, and human studies if there was an abstract in English. Reviews, unpublished studies, or studies published in abstract only, and studies that did not specifically address the PICOST questions were excluded

Database searched: Ovid Medline, Embase, Cochrane
Time Frame: (existing PICOST) – From November 21, 2021- June 16, 2024
Date Search Completed: June 16, 2024
Search Results (Number of articles identified and number identified as relevant): 175 studies were screened, 42 full text studies were assessed for eligibility and 3 studies addressing this PICOST were included

Summary of Evidence Update:
To date, no human studies that compared 21% oxygen versus 100% oxygen or any other oxygen concentration during chest compression were identified.

The previous ILCOR scoping review {Ramachandran 2023 442} reviewed all literature regarding chest compressions in neonates and found no evidence to change the previous recommendations for treatment. {Berg 2023 e187, Perlman 2015 S204} In this 2024 evidence update of the above scoping review, two animal studies comparing 21% with 100% inspired oxygen (O_2) concentrations during chest compression after asphyxial cardiac arrest were identified, {Nyame 2022 1601, Sankaran 2023 575} one of which was in pediatric piglets, {Nyame 2022 1601} rather than a transitional neonatal model.

The published literature identified by this evidence update reported no difference in time to return of spontaneous circulation, mortality, markers of injury or oxidative stress, hemodynamics or oxygen delivery.

None of the studies examined any longer-term outcomes.

Relevant Guidelines or Systematic Reviews: None since the ILCOR scoping review {Ramachandran 2023 442}

Randomized Controlled Trials (RCT):

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Nyame 2022 {Nyame 2022 1601}	**Study Aim:** To compare 21% O_2 vs. 100% O_2 during chest compressions in 20-23 day old pigs **Study Type:** Randomized controlled trial (blinded to O_2 level)	Pigs aged 20-23 days randomized to 5 groups- CC+SI with 21% O_2, CCaV with 21%O_2, CC+SI with 100% O_2, CCaV with 100%O_2, sham	**Intervention:**21% O_2 CC+SI or CCaV **Comparison:** 100% O_2 during chest compressions with sustained inflations CC+SI or CCaV	**1° endpoint:** Median (interquartile range) time to ROSC was 107 (90−440) and 140 (105−200) s with CC + SI 21% and 100% O_2, and 600 (50−600) and 600 (95−600) s with CCaV 21% and 100% O_2 (p = 0.27).	**2° endpoint:** No difference in injury marker ratios within the lung, myocardial tissues or brain between 21% and 100% O_2 with CC+SI or CCaV **Study Limitations:** -Study conducted in 20 to 23-day old pigs which represent a post-transitioned physiology. -Epinephrine administered 90 secs after CC initiated and then every 60 secs. The rapid succession of Epinephrine doses is different from current guidelines and possibly influenced results.
Sankaran 2023 {Sankaran 2023 575}	**Study Aim:** To compare the effects of 21% O_2 versus 100% O_2 during chest compressions and weaning strategies after ROSC	Newborn lambs randomized to 3 groups- 100% O_2 with CC-gradual wean, 100% O_2 with CC-abrupt wean and 21% O_2 with CC	**Intervention:**21% O_2 with CC; following ROSC O_2 titrated upwards to preductal SpO_2 per NRP™ guidelines as well as 100% O_2 with	**1° endpoint:** -No difference in PaO_2 (18.5±5.5 vs. 13.7±11 vs.10.7±4.3 mmHg; 100% O_2 CC gradual wean vs. 100% O_2 CC abrupt	**2° endpoint:** -No difference in mean carotid artery blood flow (3.1±0.9 vs.3.6±1.8 vs2.8±0.8 ml/kg/min; 100% O_2 CC gradual

	Study type: Randomized controlled trial		CC; following ROSC O_2 rapidly decreased to 21% O_2 and then titrated upwards to maintain SpO_2 per NRP™ guidelines **Comparison:**100% O_2 with CC; following ROSC, gradual weaning downwards of O_2 to keep SpO_2 per NRP guidelines	wean vs.21% O_2 CC) -No difference in cerebral O_2 delivery (0.07±0.07 vs. 0.08±0.07 vs.0.06±0.02ml/kg /min; 100% O_2 CC gradual wean vs. 100% O_2 CC abrupt wean vs.21% O_2 CC)	wean vs. 100% O_2 CC abrupt wean vs.21% O_2 CC) **Limitations:** -animal model
CC= chest compressions; ; CCaV, continuous chest compressions with asynchronized ventilations; CC+SI, chest compressions with sustained inflations; NRP™, Neonatal Resuscitation Program; O_2, oxygen; ROSC, return of spontaneous circulation;					

Nonrandomized Trials, Observational Studies: None

Reviewer Comments:

In the current Evidence Update, although most of the available animal evidence suggests that achieving ROSC using 21% O_2 during neonatal chest compressions is possible and that 100% O_2 as the resuscitation gas may increase oxidative injury, concern remains that there are no human data to confirm feasibility and none of the animal studies has evaluated use of 21% O_2 CPR for more than brief asystole. Value must be placed on balancing the desire to prevent ongoing hypoxic injury in these asphyxiated neonates with the determination to prevent subsequent hyperoxic injury.

The information from the studies identified in this evidence update is insufficient to alter existing recommendations and there were insufficient studies identified to support a full systematic review.

Additional research is required, i.e., studies in good transitional animal model of asphyxia-induced severe bradycardia or asystole and any clinical data for both preterm and term newborn infants.

Task Force Insights:

The available evidence from animal studies suggests that resuscitation using 21% O_2 during chest compressions is feasible and results in similar short-term outcomes. However, the animal studies examined only asphyxia-induced asystole of brief duration in animals lacking other underlying pathological conditions, and there are no human infant data.

Treatment Recommendation for 2025 CoSTR:

By the time resuscitation of a newborn infant has reached the stage of chest compressions, the steps of trying to achieve ROSC using effective ventilation should have been completed. It is reasonable to increase the supplementary oxygen concentration (good practice statement). Once the heart rate has recovered, supplementary oxygen should be titrated to oxygen saturation targets (good practice statement).

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2025 Evidence Update
NLS 5504 – Compression to Ventilation Ratio

Worksheet Author(s): Ramachandran S, Bruckner M, Schmölzer GM, Wyckoff MH
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 12 December 2024
Conflicts of Interest: None of the Evidence Update Worksheet authors made any decision regarding inclusion of their own papers in the evidence update.

PICOST
Population: In neonates receiving chest compressions
Intervention: does use of any other compression to ventilation ratio (5:1, 9:3,15:2, synchronous, etc)
Comparators: versus the standard 3:1 compression to ventilation ratio
Outcomes: impact any short- or long-term outcomes (survival rates (critical), time to return of spontaneous circulation (important), hemodynamic parameters (important), tissue oxygenation (important), lung/brain inflammatory markers (important), compressor fatigue (important)).
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded.
Timeframe: Literature search updated from November 22, 2021 to June 16, 2024.

Year of last full review: The 2015 ILCOR CoSTR suggested use of the 3:1 compression to ventilation (C:V) ratio during neonatal chest compressions (weak recommendation, very-low-certainty evidence). {Perlman 2015 S204} There was no clinical evidence for this suggestion and it was based on animal, mathematical modeling and manikin studies.

Use of the 3:1 C:V ratio was reaffirmed after an evidence update in 2020. {Wyckoff 2020 S185} Because the 2020 evidence update identified multiple new manikin studies, several animal studies, and one clinical pilot trial, the task force felt an in-depth scoping review was warranted.

The scoping review reported that the information from the identified studies was insufficient to alter existing recommendations. {Ramachandran 2023 442} The chest compressions superimposed with sustained inflations data was noted to be interesting and the task force was aware a larger trial was underway and awaited the results (which are now available).

Following the 2023 Scoping Review publication, the 2023 ILCOR CoSTR reaffirmed the use of the 3:1 C:V ratio for neonatal chest compressions. {Berg 2023 e187}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: The 2015 ILCOR CoSTR (upheld in 2020 and 2023) suggested a 3:1 C:V (compression: ventilation) ratio during chest compressions (weak recommendation, very-low-quality evidence).

Search Strategy- As for NLS 5500 – Heart rate for starting chest compressions
Database searched: Medline, Embase, Cochrane
Time Frame: (existing PICOST) – updated from end of last search November 22, 2021.
Date Search Completed: June 16, 2024
Search Results (Number of articles identified and number identified as relevant): 176 titles and abstracts screened, 42 selected for full text review, and eight new studies were selected for inclusion.

Summary of Evidence Update:
The updated literature search identified 8 (1 clinical and 7 animal) studies comparing 3:1 C:V (compression to ventilation) ratio, continuous chest compressions with asynchronized ventilation (CCaV), continuous chest compression superimposed with sustained

inflations (CC+SI), continuous chest compressions and high frequency percussive ventilation (CCC+HFPV), and different chest compression (CC) rates.

3:1 C:V ratio vs CC+SI:
A clinical study compared 3:1 C:V ratio with the CC+SI in newborn infants. {Schmölzer 2024 428} The authors found no statistically significant differences in time to return of spontaneous circulation (ROSC) and mortality between the groups. However, the trial was stopped early; thus the proposed sample size for adequate power was not obtained. An additional animal study investigating the difference between 3:1 C:V ratio and CC+SI was found. {Schmölzer 2022 488} However, the study focused primarily on whether cord clamping management affected outcomes during CPR with CC+SI (1 SI breath followed by PPV) and CC+SI (repetitive CC+SI) and found no differences in the time to ROSC between groups.

3:1 C:V ratio vs CCC+HFPV
A preterm lamb study described a high frequency ventilation approach during continuous chest compressions vs 3:1 compression to ventilation ratio. {Giusto 2024 160} The PaCO2 was lower and the PaO2 was higher in the CCC+HFPV group during resuscitation and at ROSC. The FiO2 need was lower in the CCC+HFPV group 15 minutes after ROSC. Incidence and time to ROSC were comparable between groups.

CCaV vs. CC+SI:
Two animal studies compared CCaV with the CC+SI approach. {Morin 2024 100629, Nyame 2022 1601} Both studies reported shorter time to ROSC in the CC+SI group, neither found differences in survival.

Different CC rates (60/min, 90/min, 120/min, 150/min, and 180/min) during CC+SI
Three animal studies investigating different CC rates during CC+SI were identified. An automated CC machine was used to vary the rates.{Bruckner 2022 1838, Bruckner 2023 200, Bruckner 2023 1214513} Two studies described no differences in time to ROSC comparing 60/min vs. 90/min and 90/min vs. 180/min. {Bruckner 2022 1838, Bruckner 2023 1214513} Piglets in the 180/min group received less epinephrine doses compared to the 90/min group. They also showed improved hemodynamics during CPR {Bruckner 1838}. The third study also reported improved hemodynamic parameters with higher CC rates.{Bruckner 2023 200}

Relevant Guidelines or Systematic Reviews: None since the ILCOR scoping review {Ramachandran 2023 442}

RCT:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
SURV1VE Trial; 2024 {Schmölzer 2024 428}	**Study Aim:** In newborn infants requiring CC in the DR does CC+SI compared with a 3:1 C:V ratio decreases time to ROSC? **Study Type:** International, multicenter, prospective, cluster cross-over randomized trial. **Study Size:** N=27	**Inclusion Criteria:** Preterm infants >28 weeks gestational age requiring CC in the DR	**Intervention (CC+SI group) n=11:** SIs with a PIP of 25–30 cmH_2O during continuous CC at 90/min. SI was delivered over 20s, followed by a PEEP of 5–8 cmH2O for 1 s. Then the next 20 s SI was started while CCs continued, then PEEP for 1s, then another SI for 20s.	**1° endpoint:** The median (IQR) time to ROSC was 90 (60–270) s and 615 (174–780) s (p=0.0502 (log rank), p=0.16 (cox proportional hazards regression)) with CC+SI and 3:1 C:V, respectively.	**2° endpoint:** Mortality was 2/11 (18.2%) with CC+SI versus 8/14 (57.1%) with 3:1 C:V (p=0.10 (Fisher's exact test), OR (95% CI) 0.17; (0.03 to 1.07)). CC+SI was not associated with adverse events. **Study Limitations:**

			HR was re-evaluated every 60s by auscultation. **Comparison (3:1 C:V group) n=14:** CC at 90/min and ventilations at 30/min in a 3:1 C:V ratio with HR re-evaluated every 60s by auscultation.		The trial was stopped early, thus the proposed sample size was not obtained.
CC, chest compressions; CCaV, continuous chest compressions with asynchronized ventilation; CC+SI, continuous chest compression superimposed with sustained inflations; CI, confidence interval; C:V, compression:ventilation; DR, delivery room; HR, heart rate; IQR, interquartile range; OR, odds ratio; ROSC, return of spontaneous circulation; RR, relative risk; SI, sustained inflation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure					

Animal studies:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Morin 2024 {Morin 2024 100629}	**Study Aim:** To compare neonatal and pediatric resuscitation approach by using either CCaV or CC + SI during infant CC. **Study Type:** Randomized controlled animal trial. **Study Size:** N=20	**Inclusion Criteria:** Mixed breed pediatric piglets with a current age of 5–10 days old (weighing 2.9–4.1 kg), approximately equivalent to infants 25– 35 days old.	**Intervention (CC+SI group) n=10:** 120/min compression rate, ventilations for 30 sec each with PIP 30cmH2O, PEEP 5cmH2O, and gas flow of 10 L/min. There was a 1 sec pause between successive inflations using a T-Piece resuscitator **Comparison (CCaV) n=10:** 120/min compression rate, asynchronous ventilations with 30 inflations per minute, PIP 30cmH2O, self-inflating bag	**1° endpoint:** The median (IQR) duration of resuscitation with CC + SI compared to CCaV was 179 (104–447) vs 660 (189–660), p = 0.05. Survival rate with CC + SI vs CCaV was not different	**2° endpoint:** CC + SI required fewer epinephrine doses compared to CCaV (0 (0–2.3) vs 3 (0.8–3), respectively, p = 0.039) **Study Limitations:** Started CC after a simulated delay in recognition of the need for resuscitation, no neurological outcome in surviving piglets were assessed.
Giusto 2023 {Giusto 2024 160}	**Study Aim:**	**Inclusion Criteria:**	**Intervention (CCC with HFPV) n=7:**	**1° endpoint:**	**2° endpoint:**

	To compare 3:1 C:V to CCC with HFPV in a perinatal asphyxial cardiac-arrest preterm lamb model. **Study Type:** Randomized controlled animal trial. **Study Size:** N=14	Time-dated preterm (124–126 days gestation, equivalent to a human gestation of 25–26 weeks) lambs.	Following 30 s of PPV, CCC were given at a rate of 120/min, ventilator settings: frequency 200 breaths/min, amplitude 50, I:E ratio 1:2, Paw 15cmH2O. **Comparison (3:1 C:V ratio) n=7:** Following 30s of PPV, start CC with C:V ratio of 3:1 (90 compressions and 30 breaths/min).	PaCO2 in the intervention group were significantly lower throughout resuscitation and at 15 min post-ROSC compared to the control group. PaO2 in the intervention group were significantly higher during resuscitation and at ROSC.	There was a significantly lower FiO2 need in the intervention group compared to the control group at 15min after ROSC. Incidence and time to ROSC were comparable to the 3:1 C:V resuscitation **Study Limitations:** Since the control group had a 100% ROSC success rate, it's not possible to assess a higher success rate in the intervention group. It's unclear if the higher compression rate contributed to the observed results or if it was the HFPV. HFPV ventilator is needed and is currently not in wide-spread use.
Bruckner 2023 {Bruckner 2023 1214513}	**Study Aim:** To compare CC rates of 60/min with 90/min and their effect on the time to ROSC, survival, hemodynamic, and respiratory parameters in asphyxiated newborn piglets. **Study Type:** Randomized controlled animal trial. **Study Size:** N=14	**Inclusion Criteria:** Newborn mixed-breed piglets (0–3 days of age).	**Intervention (CC rate 60/min) n=7:** CC provided with a rate of 60/min using an automated CC machine and ventilated with CC+SI. **Comparison (CC rate 90/min) n=7:** CC provided with a rate of 90/min using an automated CC machine and ventilated with CC+SI.	**1° endpoint:** The number of piglets that achieved ROSC was 5 (71%) and 5 (71%) with 60/min and 90/min CC rates, respectively (p =1.00). The median (IQR) resuscitation time was 132 (71–600) s for CC rate of 60/min and 189 (96–600) s for CC rate of 90/min (p =0.46),	**2° endpoint:** Hemodynamic and respiratory parameter were not different between the groups. **Study Limitations:** Piglets had already undergone the fetal-to-neonatal transition, were sedated/ anesthetized. The compression ranges were tested using a technique (CC+SI) which is not currently recommended. Thus, whether same results would

					be obtained if altering compression rates while using the traditional chest compression technique is unknown.
Nyame 2022 {Nyame 2022 1601}	**Study Aim:** To determine if 21% O2 during CPR with either CC+SI or CCaV will reduce time ROSC compared to 100% O2 in infant piglets with asphyxia-induced cardiac arrest. **Study Type:** Randomized controlled animal trial. **Study Size:** N=28	**Inclusion Criteria:** Infant piglets aged 20–23 days were included	**Factorial Design** Intervention 1 (CC+SI + 21%O2) n=7: Intervention 2 (CC+SI + 100%O2) n=7: Comparison 1 (CCaV + 21%O2) n=7: Comparison 2 (CCaV + 100%O2) n=7:	**1° endpoint:** CC+SI reduced time to ROSC compared to CCaV.	**Study Limitations:** Piglets were 20-23 days, 7-9kg, (thus not a newborn model) as well as sedated/ anesthetized and intubated .
Bruckner 2022 {Bruckner 2022 1838}	**Study Aim:** To compare CC rates of 90/min with 180/min and their effect on the time to ROSC, survival, hemodynamic, and respiratory parameters in asphyxiated newborn piglets. **Study Type:** Randomized controlled animal trial. **Study Size:** N=14	**Inclusion Criteria:** Newborn mixed-breed piglets (0–3 days of age).	**Intervention (CC rate 180/min) n=7:** CC provided with a rate of 180/min using an automated CC machine and ventilated with CC+SI. **Comparison (CC rate 90/min) n=7:** CC provided with a rate of 90/min using an automated CC machine and ventilated with CC+SI.	**1° endpoint:** The number of piglets that achieved ROSC was 7 (100%) and 5 (71%) with 180/min and 90/min CC rates, respectively (p=0.46). The median (IQR) time to ROSC was 103 (79–170) s for CC rate of 180/min and 189 (96–600) s for CC rate of 90/min (p=0.12).	**2° endpoint:** During CC+SI with a CC rate of 180/min less epinephrine administration, higher blood pressure, carotid blood flow, and significantly improved left ventricular function minute ventilation and thereby oxygen delivery was observed. **Study Limitations:** Piglets had already undergone the fetal-to-neonatal transition, were sedated/ anesthetized, CC+SI was used which might have

					contributed to the results.
Bruckner 2023 {Bruckner 200}	**Study Aim:** To compare the hemodynamic effects of CC rates of 60/min, 90/min, 120/min, 150/min and 180/min during CPR in asphyxiated newborn piglets. **Study Type:** Randomized study with each animal as own control and randomized order of interventions **Study Size:** N=6	**Inclusion Criteria:** Newborn mixed-breed piglets (0–3 days of age).	The sequence of all CC rates was randomized in all piglets and was mechanically performed using the automated CC machine. **Intervention and comparison:** 60/min vs. 90/min vs. 120/min, vs. 150/min vs. 180/min	**1° endpoint:** There was an optimized stroke volume, end-diastolic volume, minimum and maximum rate of left ventricle pressure change, and carotid blood flow with a CC rate of 150/min, while cardiac output was highest with a CC rate of 180/min.	**Study Limitations:** CC+SI might positively or negatively affect venous return, cardiac transmural and thoracic pressure gradient. CCC were used because the current recommended CC approach of 3:1 C:V ratio made it impossible to examine rates as high as 180/min. Unknown if humans could achieve the high CC rates while maintaining adequate depth.
Schmölzer 2022 {Schmölzer 2022 488}	**Study Aim:** To determine whether physiological based cord clamping (PBCC) combined with SI_{cont} during CCs provides physiological benefit over ICC and a SI_{sing} followed by standard 3:1 C:V in asphyxiated lambs. **Study Type:** Randomized controlled animal trial. **Study Size:** N=35	**Inclusion Criteria:** Asphyxiated asystolic near-term lambs.	**Four groups being studied:** ICC+SI_{sing} (n=12) ICC+SI_{cont} (n=7) PBCC+SI_{sing} (n=9) PBCC+SI_{cont} (n=7) PBCC had maternal iliac artery compression to induce asphyxia. whereas ICC animals had umbilical cord occlusion. No differences in blood gas variables at conclusion of asphyxia prior to resuscitation. CCs were initiated using an asynchronous technique at a 3:1	**1° endpoint:** There were no differences in the time taken to achieve ROSC between groups. There was no difference in the number of doses of epinephrine required to achieve ROSC between the groups.	**Study Limitations:** Lambs were sedated/anaesthe-tized and intubated with a endotracheal tube with no leak. Previous studies have found that continuous CC provides better minute ventilation, however, the study was not designed to explicitly detect potential differences due to CC technique

			ratio in the SI_{sing} groups, with continuous CCs used in the SI_{cont} groups.		

Abbreviations: CC; chest compressions, CCaV; continuous chest compressions with asynchronized ventilation, CCC; continuous chest compressions, CC+SI; continuous chest compression superimposed with sustained inflations, CI; confidence interval, C:V; compression to ventilation, DR; delivery room, FiO_2; fraction of inspired oxygen, HFPV; high frequency percussive ventilation, HR; heart rate, ICC; immediate cord clamping, I:E; inspiratory:expiratory, IQR; interquartile range, OR; odds ratio, PBCC; physiologic based cord clamping, ROSC; return of spontaneous circulation, RR; relative risk, SI; sustained inflation, SI_{cont}; continuous sustained inflation, SI_{sing}; single sustained inflation, Paw; mean airway pressure, PEEP; positive end-expiratory pressure, PIP; peak inspiratory pressure, PPV; positive pressure ventilation

Nonrandomized Trials, Observational Studies: None applicable

Reviewer Comments:
Despite evidence from animal studies and a small clinical pilot trial indicating that CC+SI and CCaV may offer advantages over a 3:1 C:V ratio in terms of time to ROSC, survival, and the optimization of hemodynamic parameters, these findings were not replicated in the randomized controlled trial "SURV1VE". {Schmölzer 2024 428} This RCT was terminated before the calculated sample size was reached. The task force is aware that a new multi-center clinical trial SURV1VE-2 is planned.

This evidence update found no need to change the current treatment recommendation and that a Systematic Review is not needed at this time. The task force upholds the prior suggestion to use a 3:1 C:V (compression: ventilation) ratio during chest compressions (weak recommendation, very-low-certainty evidence).

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2025 Evidence Update
NLS 5505 – Use of Feedback CPR Devices for Neonatal Cardiac Arrest

Worksheet Author(s): Ramachandran S, Bruckner M, Schmölzer GM, Wyckoff MH
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 2 December 2024
Conflicts of Interest: None of the Evidence Update Worksheet authors made any decision regarding inclusion of their own papers in the evidence update.

PICOST:
Population: In neonates receiving chest compressions
Intervention: does use of any feedback devices such as end-tidal carbon dioxide monitors, pulse oximeters or automated compression feedback devices
Comparators: compared with clinical assessments of compression efficacy
Outcomes: decrease hands-off time (important), decrease time to return of spontaneous circulation (ROSC) (important), improve perfusion (important), increase survival rates (critical) or improve neurologic outcomes (critical)?
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded.
Timeframe: From inception to Nov 22, 2021.

Year of last full review: 2023 {Berg 2023 e187, Ramachandran 2023 442}

Current ILCOR Consensus on Science and Treatment Recommendation (CoSTR) for this PICOST:
2015 CoSTR: The current neonatal CoSTRs suggest against the routine use of feedback devices during chest compressions (weak recommendation and limited data). {Perlman 2015 S204}

2023 Scoping review: The Task Force found that the available studies did not warrant a new systematic review given the paucity of clinical data. {Ramachandran 2023 442}

Current treatment recommendation:{Berg 2023 e187, Ramachandran 2023 442}
In asystolic/bradycardic newborn infants, we suggest against the routine reliance on any single feedback device such as $ETCO_2$ monitors or pulse oximeters for detection of ROSC until more evidence becomes available (weak recommendation, very low–certainty evidence).

Search strategy: See appendix
Database searched: Medline, Embase, Cochrane
Time Frame: Literature search updated from November 22, 2021 to June 16, 2024.
Date Search Completed: June 16, 2024
Search Results: 175 titles and abstracts screened, 42 selected for full text review, and three new studies were selected for inclusion.

Summary of Evidence Update:
Three studies compared chest compression (CC) feedback devices including one animal study {O'Reilly 2024 156} and two manikin studies. {Lee 2021 35, Wagner 2022 1762} Two were randomized {O'Reilly 2024 156, Wagner 2022 1762} and one was a small observational pilot trial. {Lee 2021 35}

Studies assessed a CC machine, {O'Reilly 2024 156} real time visual feedback, {Wagner 2022 1762} and a new smart-ring-based CC depth feedback device . {Lee 2021 35}

The animal study compared hemodynamic parameters by using a CC machine or CC provided by a human. Improved stroke volume and left ventricular contractile function were described for the CC machine group, whereas there were no differences in carotid blood flow, arterial blood pressure and end diastolic volume. {O'Reilly 2024 156}

A manikin study reported improvements in several CC parameters (e.g., total CC score, CC rate compliance) when provided with visual compared to no feedback. {Wagner 2022 1762}

One study describes a novel smart-ring-based CC depth feedback device and compared it to a smartwatch. This study describes many technical aspects and tested the accuracy of the novel feedback device, however, the experimental manikin data are very limited (n=4). {Lee 2021 35}

Relevant Guidelines or Systematic Reviews: None since the ILCOR scoping review {Ramachandran 2023 442}

RCT: None applicable

Animal studies:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
O'Reilly 2024 {O'Reilly 2024 156}	**Study Aim:** To compare the hemodynamic effects of machine versus human CC during CPR in a neonatal piglet model of cardiac arrest induced by asphyxia. **Study Type:** Randomized controlled animal study **Study Size:** N=12	**Inclusion Criteria:** Term newborn mixed breed, post-transitional piglets.	**Intervention:** Machine CC during CPR (n=6) **Comparison:** Human CC during CPR (n=6)	**1° endpoint:** Piglets in the machine group had improved hemodynamic outcomes (CC stroke volume, dp/dtmax, and dp/dtmin) during CC compared to piglets receiving human CC.	**Study Limitations:** Piglets had already undergone the fetal-to-neonatal transition, were sedated/ anesthetized, and used tracheostomy with a tightly sealed endotracheal tube to prevent leak, which does not occur in the delivery room.
Abbreviations: dp/dtmax; maximum rate of change in left ventricular pressure, dp/dtmin; minimum rate of change in left ventricular pressure, CC; chest compressions, CI; confidence interval, CPR; cardiopulmonary resuscitation, OR; odds ratio, RR; relative risk					

Manikin studies

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Wagner 2022 {Wagner 2022 1762}	**Study Aim:** To study the impact of feedback devices on resuscitation quality with eye-tracking to analyze	**Inclusion Criteria:** Medical students in their final year, fellows, nurses, and consultants from the local Neonatal Intensive	**Interventions:** Participant performing CC with real-time visual feedback (CC rate, percentage of correct CC rate,	**1° endpoint:** Participants showed significant improvements in several CC parameters when provided with real-	**2° endpoint:** Self-reported CC quality increased by 7% (p= 0.03), mean CC depth increased by 0.9 mm with feedback

	participants' performance when supported with feedback devices. **Study Type:** Prospective randomized cross-over simulation-based trial **Study Size:** N=40	Care Unit were eligible for enrolment.	depth, percentage of correct CC depth, complete release, and hand position). **Comparison:** Participant performing CC without feedback.	time feedback: 22% higher total CC score and a 25% higher CC rate compliance than in the no-feedback condition (both P < 0.001). In both conditions, participants significantly reduced attention from the infant's chest and mask (72.9 vs. 32.6% and 21.9 vs. 12.7%). Participants' subjective workload increased by 3.5% (P = 0.018) and 8% (P < 0.001) when provided with a feedback device.	(p= 0.01), without influencing CC depth compliance. **Study Limitations:** The clinical relevance of the secondary endpoints is unknown. Simulation-based trial not involving any real patients, no blinding, no other feedback routes such as voice or sound cues could be evaluated, scenarios were limited to 3 min
Abbreviations: CC; chest compressions, CI; confidence interval, OR; odds ratio, RR, relative risk					

Nonrandomized Trials, Observational Studies:

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results**	**Summary/Conclusion Comment(s)**
Lee 2021 {Lee 2021 35}	**Study Aim:** Report the accuracy of a new smart-ring-based CC depth feedback device for CPR and comparing the performance of the proposed ring system to a smartwatch system. **Study Type:** Observational study (small pilot trial of a new feedback device) **Study Size:**N=4 4 participants wore both a smart ring and a smartwatch and performed CCs on an infant mannequin.	**Inclusion Criteria:** Emergency medical professionals with actual CPR experience in adults and infants participated in this experiment.	**1° endpoint:** For the estimated CPR depth of the smart ring, the compression depth error on the infant mannequin (2.9 ± 1.8 mm) were similar to those of the estimated depth of ring-based CC depth feedback system (1.9 ± 1.1 mm).	This is primarily a report of proof-of-concept, of a new smart-ring- based CC depth feedback device. Clinical trials must be conducted. The main focus of the report is on describing the many technical aspects of the smart ring CC depth feedback device.

Abbreviations: CC; chest compressions, CI; confidence interval, OR; odds ratio, RR, relative risk

Reviewer Comments:
No studies assessed whether feedback devices result in improvements in resuscitation practice or outcomes in human infants.

Further research is justified, including assessing whether improvements measured in simulation settings result in improvement in clinical performance or outcomes and to assess the role of capnography and other types of clinical measurements in improving outcomes in infants who receive chest compressions.

The available studies in this 2025 Evidence Update do not warrant a new systematic review given the paucity of clinical data.

Knowledge gaps include:

- There is a need for large studies powered for important clinical outcomes to determine the role of capnography in improving response to and outcomes of newborn infant CPR
- Does continuous monitoring of flow and volume or exhaled CO_2 levels compete with other essential auditory and visual cues that need to be appreciated and responded to by resuscitation teams?
- Does use of feedback devices during CPR have negative impacts on medical provider cognitive load?

Task Force Insights:
The task force concluded that the treatment recommendation in the 2023 CoSTR should still apply; {Berg 2023 e187}

In asystolic/bradycardic newborn infants, we suggest against the routine reliance on any single feedback device such as $ETCO_2$ monitors or pulse oximeters for detection of ROSC until more evidence becomes available (weak recommendation, very low–certainty evidence).

References:

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Lee S, Song Y, Lee J, Oh J, Lim TH, Ahn C, et al. Development of Smart-Ring-Based Chest Compression Depth Feedback Device for High Quality Chest Compressions: A Proof-of-Concept Study. Biosensors. 2021;11(2)35.

O'Reilly M, Lee TF, Cheung PY, Schmölzer GM. Comparison of hemodynamic effects of chest compression delivered via machine or human in asphyxiated piglets. Pediatr Res. 2024;95(1)156-159.

Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal Resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2015;132(suppl 1)(16)S204–S241.

Ramachandran S, Bruckner M, Wyckoff MH, Schmolzer GM. Chest compressions in newborn infants: a scoping review. Arch Dis Child Fetal Neonatal Ed. 2023;108(5)442-450.

Wagner M, Gröpel P, Eibensteiner F, Kessler L, Bibl K, Gross IT, et al. Visual attention during pediatric resuscitation with feedback devices: a randomized simulation study. Pediatr Res. 2022;91(7)1762-1768.

2025 Evidence Update
NLS 5506 – Depth of Chest Compressions

Worksheet Author(s): Ramachandran S, Bruckner M, Schmölzer GM, Wyckoff MH
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 2 December 2024
Conflicts of Interest: None of the Evidence Update Worksheet authors made any decision regarding inclusion of their own papers in the evidence update.

PICOST:
Population: In neonates receiving chest compressions
Intervention: does use of any other chest compression depth
Comparators: versus compressing 1/3 the anteroposterior diameter of the chest
Outcomes: increase survival rates (critical), improve neurologic outcomes (critical), decrease time to return of spontaneous circulation (important)
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion in the scoping reviews. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded.
Timeframe: All years and all languages were included provided there was an English abstract between Nov 22,2021 and June 16, 2024;

Year of last full review: The last published CoSTR that reviewed this topic was the 2010 CoSTR publication {Perlman 2010 S516} before ILCOR adopted GRADE methods of evidence evaluation. The level of evidence (LOE) in 2010 was considered LOE 5 which meant the available data came from case series where patients were compiled in a serial fashion and a control group was lacking. A recent ILCOR scoping review examined the topic {Ramachandran 2023 442} but the findings were not included in the 2023 CoSTR.

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
Compressions should be centered over the lower third of the sternum and should compress the chest one third the anterior-posterior diameter. {Perlman 2010 S516}

EvUp Search Strategy – As for NLS 5500 – Heart rate for starting chest compressions

Inclusion and Exclusion criteria
We included animal, manikin, and human studies if there was an abstract in English. Reviews, unpublished studies, or studies published in abstract only, and studies that did not specifically address the PICOST questions were excluded.

Database searched: Medline, Embase, Cochrane
Time Frame: All years and all languages were included provided there was an English abstract; Literature search updated to June 16, 2024
Date Search Completed: June 16, 2024
Search Results (Number of articles identified and number identified as relevant):
1031 studies screened, 290 were chosen for full text review and 7 were found to address this PICOST

Summary of Evidence Update:
Five studies were identified. {Bruckner 2022 262, Bruckner 2021 , Ikeyama 2024 720, Lee 2021 e26122, Meyer 2010 544} Two were retrospective neonatal clinical studies that examined computed tomography (CT) scans that had been obtained for other purposes, {Lee 2021 e26122, Meyer 2010 544} and one study utilized CT scans to investigate best chest compression depth in critically ill children under 8 years of age but which included 127 infants who were 0-2 months of age. {Ikeyama 2024 720}
In a randomized animal trial, time to ROSC was similar with CC depths of 25%, 33% and 40% of the antero-posterior diameter of the chest. A CC depth of 12.5% did not achieve ROSC. {Bruckner 2022 262}

Meyer et al. concluded that the recommended 1/3 AP diameter is more effective than ¼ AP diameter compression

and safer than ½ AP diameter compressions. {Meyer 2010 544}

Bruckner et al. compared CC depths of 12.5%, 25%, 33% and 40% during CPR of asphyxiated piglets and reported the highest carotid blood flow and systemic mean blood pressure was achieved with 40% CC depth (19.3±7.5mL/min/kg and 58±32mm, respectively). {Bruckner 2021 }

Lee et al. compared CC depths of 25, 30 and 35mm with the 1/3 the anterior-posterior diameter of the chest using computed tomography by assessing the heart compression fraction. A proper depth for sufficient and safe CC during CPR in newborn infants could be determined to be 30 mm, which was one-third of the depth of the external chest AP diameter. {Lee 2021 e26122}

Ikeyama et al. measured anterior- the posterior (AP) chest diameter with a laser distance meter and calculated target CC depth in critically ill infants and children which corresponds to 1/3 the AP chest diameter. They demonstrated that in the 0-2 month age groups, the target CC depth was shallower than the recommended depth of 4cm in infants; thus suggesting that compressing to 4cm in this age group would result in over-compression during cardiopulmonary resuscitation. {Ikeyama 2024 720}

No neonatal survival outcomes or long term outcomes were reported in any studies.

Relevant Guidelines or Systematic Reviews: None since the ILCOR scoping review {Ramachandran 2023 442}

Randomized Controlled Trials:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Bruckner 2022 {Bruckner 2022 262}	**Aim:** To determine the optimal AP depth of CC to reduce time to ROSC and improve survival. **Study Type:** Randomized controlled animal study	**Inclusion Criteria:** Asphyxiated neonatal piglets	**Intervention:** CC administered with 40% AP diameter, 25% AP diameter, 12.5% AP diameter **Comparison:** CC administered with 33% AP diameter	**1° endpoint:** -Time to return of spontaneous circulation was 600 (600–600) s, 135 (90–589) s, 85 (71–158)* s and 116 (63–173)* s for the 12.5%, 25%, 33% and 40% depth groups, respectively (*p<0.001 vs 12.5%). -The number of piglets that achieved ROSC was 0 (0%), 6 (75%), 7 (88%) and 7 (88%) in the 12.5%, 25%, 33% and 40% AP depth groups, respectively. -12.5% AP compression depth was discontinued to avoid unnecessary sacrifice of piglets due to no ROSC seen in the first 4.	**2° endpoints:** Hemodynamic and respiratory parameters improved with increasing AP depth of CC suggesting improved organ perfusion and oxygen delivery with 33%–40%. **Study Limitations:** -Model uses piglets that have already undergone transition from fetal to neonatal life. -Tightly sealed ET tubes were utilized which may not occur in the DR where uncuffed tubes are commonly used.
Abbreviations: AP; anterior-posterior, CC; chest compression, DR; delivery room, ET; endotracheal, OR; odds ratio, ROSC; return of spontaneous circulation, RR; relative risk					

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Meyer 2010 {Meyer 2010 544}	**Aim:** To compare the efficacy and safety of neonatal CC depths of 1/4, 1/3, and 1/2 AP chest diameter during CPR. **Study type:** Retrospective observational study	**Inclusion criteria:** CT scans of neonates <28 days **Exclusion criteria:** babies with anatomical chest abnormalities e.g. Pulmonary hypoplasia, chest wall deformities	**1° endpoint:** Estimated chest compression induced EF increased incrementally with increasing chest compression depth (EF was 51 ± 3% with 1/4 AP chest depth vs 69 ± 3% with 1/3 AP chest depth, and 106% with 1/2 AP chest depth, $p < 0.001$).	Mathematical modeling based upon neonatal chest CT scan dimensions suggests that current NRP chest compression recommendations of 1/3 AP CC depth should be more effective than 1/4, and safer than 1/2 AP compression depth.
Bruckner 2021 {Bruckner 2021 }	**Aim:** To investigate the hemodynamic effects of different CC depths in a neonatal piglet model. **Study Type:** Observational piglet study	**Inclusion Criteria:** Asphyxiated neonatal piglets	**1° endpoint:** CBF and systolic blood pressure were the highest using a CC depth of 40% AP chest diameter (19.3±7.5 mL/min/kg and 58±32 mm Hg).	CC depth influences hemodynamic parameters in asphyxiated newborn piglets during cardiopulmonary resuscitation. The highest CBF and systolic blood pressure were achieved using a CC depth of 40% AP chest diameter.
Lee 2021 {Lee 2021 e26122}	**Study Aim:** To assess whether a 30-mm depth of chest compression (CC) is sufficient and safe for neonatal CPR. **Study type:** Retrospective observational study	**Inclusion criteria:** Medical records of neonatal infants ≤ 28 days who underwent CT scan of the chest in the NICU between Jan 2004 to Dec 2018 **Exclusion criteria:** Twin or multiple births, extremely low birth weight infants(<1000g), babies with anatomical chest abnormalities e.g. pectus excavatum, total atelectasis	**1° endpoint:** -When the patients were divided into term (n = 53) and preterm (n = 10) groups, the equivalent depth (when compared to 1/3 AP diameter)was 30 ± 3 mm in the term group (P<.001) and 25±2.5mm in the preterm group (P=.004). -When simulated CCs with a 30-mm depth were performed, over-compression occurred more frequently in the preterm group (20%) compared to the term group (1.9%) (P=.014).	A proper depth for sufficient and safe CC during CPR in neonates could be determined to be 30mm, which was one-third of the depth of the external chest AP diameter. This was true for normal birth weight term newborn infants. When performing CCs in preterm or low-birth-weight babies, a shallower depth should be considered. .
Ikeyama 2024 {Ikeyama 2024 720}	**Aim:** To examine measurements of AP chest diameter with a laser distance meter and calculate CC depth targets in	**Inclusion Criteria:** All critically ill children admitted to the PICU under 8 years of age (total n=555 of which	**1° endpoint:** Target CC depth for neonates < 1 month of age was 2.7cm (2.5-2.9cm and for 2 month old infants was 2.9cm (2.7-3.2cm)	Using Japanese pediatric guideline-recommended absolute CC depth targets of 4cm for infants, 49% of infants between 0-2 months would be

	critically ill infants and children. **Study Type:** Retrospective observational study	n=127 were 0-2 months of age)		over compressed during cardiopulmonary resuscitation
AP, anterior-posterior; CBF, carotid blood flow; CC, chest compression; CPR, cardiopulmonary resuscitation; CT, computed tomography; DR, delivery room; ET, endotracheal; NICU, neonatal intensive care unit; OR, odds ratio; ROSC, return of spontaneous circulation; RR, relative risk				

Reviewer Comments:
There were insufficient studies identified to support a doing a systematic review at this time, and the information from the studies identified is insufficient to alter existing recommendations.
This evidence update reaffirms the 2010 suggestion:

Compress the chest one third the anterior-posterior diameter during neonatal chest compressions.

Additional research is required, i.e., further studies in good transitional animal model of asphyxia-induced severe bradycardia or asystole and any neonatal human data describing short- and long-term outcomes when compressions of different depths are provided. More information regarding appropriate depth in different gestational ages is needed.

Task Force Insights: Given the limited new evidence available, it is reasonable to confirm the 2010 treatment recommendation as a good practice statement.

References:

Bruckner M, Kim SY, Shim GH, Neset M, Garcia-Hidalgo C, Lee TF, et al. Assessment of optimal chest compression depth during neonatal cardiopulmonary resuscitation: a randomised controlled animal trial. Arch Dis Child Fetal Neonatal Ed. 2022;107(3)262-268.

Bruckner M, O'Reilly M, Lee TF, Neset M, Cheung PY, Schmölzer GM. Effects of varying chest compression depths on carotid blood flow and blood pressure in asphyxiated piglets. Arch Dis Child Fetal Neonatal Ed. 2021;106(5)553-556.

Ikeyama T, Hozumi T, Kikuyama K, Niles D, Nadkarni V, Ito K. Chest Compression Depth Targets in Critically Ill Infants and Children Measured With a Laser Distance Meter: Single-Center Retrospective Study From Japan, 2019-2022. Pediatr Crit Care Med. 2024;25(8)720-727.

Lee J, Lee DK, Oh J, Park SM, Kang H, Lim TH, et al. Evaluation of the proper chest compression depth for neonatal resuscitation using computed tomography: A retrospective study. Medicine. 2021;100(26)e26122.

Meyer A, Nadkarni V, Pollock A, Babbs C, Nishisaki A, Braga M, et al. Evaluation of the Neonatal Resuscitation Program's recommended chest compression depth using computerized tomography imaging. Resuscitation. 2010;81(5)544-8.

Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, et al. Part 11: neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010;122(suppl 2)(16)S516–S538.

Ramachandran S, Bruckner M, Wyckoff MH, Schmolzer GM. Chest compressions in newborn infants: a scoping review. Arch Dis Child Fetal Neonatal Ed. 2023;108(5)442-450.

2025 Evidence Update
NLS 5507 – Chest Compression Location on Sternum

Worksheet Author(s): Wyckoff MH, Ramachandran S, Bruckner M, Schmölzer GM
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 6 December 2024
Conflicts of Interest: None of the Evidence Update Worksheet authors made any decision regarding inclusion of their own papers in the evidence update.

PICOST:
Population: In neonates receiving chest compressions
Intervention: does use of any other location on the sternum
Comparators: versus compressing over the lower 1/3 of the sternum
Outcomes: increase survival rates (critical), improve neurologic outcomes (critical), decrease time to return of spontaneous circulation (important)
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion in the scoping reviews. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded.
Timeframe: All years and all languages were included provided there was an English abstract between Nov 22,2021 and June 16, 2024;

Year of last full review: The last published CoSTR that reviewed this topic was the 2010 CoSTR publication {Perlman 2010 S516} before ILCOR adopted GRADE methods of evidence evaluation. The level of evidence (LOE) in 2010 was consider LOE 5 which meant the available data came from case series where patients were compiled in a serial fashion and a control group was lacking.

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: From the 2010 CoSTR {Perlman 2010 S516}: Compressions should be centered over the lower third of the sternum and should compress the chest one third the anterior-posterior diameter.

EvUp Search Strategy – As for NLS 5500 – Heart rate for starting chest compressions

Inclusion and Exclusion criteria
We included animal, manikin, and human studies if there was an abstract in English. Reviews, unpublished studies, or studies published in abstract only, and studies that did not specifically address the PICOST questions were excluded.

Database searched: Medline, Embase, Cochrane
Time Frame: All years and all languages were included provided there was an English abstract; Literature search all dates to June 16, 2024
Date Search Completed: June 16, 2024
Search Results (Number of articles identified and number identified as relevant):
1031 studies screened, 290 were chosen for full text review and 8 were found to address this PICOST.

Summary of Evidence Update:
Eight studies were identified {Clements 2000 43, Moya 1962 798, Orlowski 1986 667, Phillips 1986 1024, Shah 1992 49, Thaler 1963 606, You 2009 1378}
The first study to report successful external CC newborns described survival in two of five infants after compressions applied to the mid-sternum using either a 2-finger or two-thumbs-with-hands encircling the chest technique. {Moya 1962 798} After noting severe liver injury in some infants and children who had received external CC, a study compared abdominal compressions vs xiphoid versus middle sternum vs simultaneous chest/abdominal compression in fresh cadavers of infants and young children with subsequent autopsy examination. {Finholt 1986 646} No rupture of liver was produced when pressure was applied to the chest alone at mid-sternum. Superficial tears of the liver capsule were produced when pressure was applied to the xiphoid process and all patients with simultaneous chest/abdomen compressions had liver rupture. In an additional 20 fresh cadavers of infants and

young children with an induced free circulatory system obtained by intracardiac injection of heparin within 15 minutes of death followed by 10 min of CC, compression of the middle part of the sternum (above the xiphoid) produced effective circulatory pressures. {Finholt 1986 646}

Subsequent studies using chest radiographs taken with lead markers placed at the suprasternal notch and xiphoid concluded that the lower one-third of the sternum, above the xiphoid would result in more effective compressions for infants and young children. {Finholt 1986 646, Orlowski 1986 667, Phillips 1986 1024} These results were confirmed in vivo in 10 one-month to three-year-old children who had arterial lines in place at time of arrest, with compressions applied over the lower one-third of the sternum resulting in significantly better systolic and mean blood pressures ($p<0.001$) than when applied over the mid-sternum, {Orlowski 1986 667} providing the only clinical data that available confirming the optimal site of compression in infants.

A more recent study assessed chest radiographs with radio-opaque markers in 210 healthy children from birth to 12 years (of whom 48 were < 6 months of age). The heart was found to descend with age, its center lying beneath the mid-sternum during the first 6 months of life and beneath the lower sternum after infancy ($p<0.0001$). {Shah 1992 49} The authors recommended using the mid-sternal location for CC of infants and that the nipple line should not be taken into account. {Shah 1992 49}

A further study of chest radiographs in 30 infants concluded that using the then-recommended method of CC one finger-breadth below the nipple line would cause pressure on the abdomen or xiphisternum. {Clements 2000 43} The authors recommended using sternal anatomy alone to determine location, rather than the position of the nipples.

A chest computed tomography study concluded that in infants, the left ventricle was located beneath the lower quarter of the sternum, not the lower one-third, but the author recommended clinical correlation before changing treatment recommendations. {You 2009 1378}

Relevant Guidelines or Systematic Reviews – none available since {Perlman 2010 S516}

Randomized Controlled Trials:

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Orlowski 1986 {Orlowski 1986 667}	Convenience sample randomized to whether CC were given first at mid-sternal location or lower sternal location above the xiphoid. Each patient served as own control.	N=10 patients between 1 month and 3 years of age in cardiac arrest who had arterial lines in place at time of arrest	All CC over the lower one-third resulted in significantly better SBP and mean BPs ($P<0.001$). No instances of liver or organ injury either at autopsy or in surviving children were found.	CC performed over the lower 1/3 of the sternum but above the xiphoid is superior to mid-sternal CC in infants and young children. Comment: No newborn infants included.
Abbreviations: CC; chest compressions, SBP; systolic blood pressure, BPs; blood pressures				

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Moya 1962 {Moya 1962 798}	**Design:** Case series of term newborns **Aim:** to report for the first time physiologic and pathologic findings after use of closed chest CC in the newborn infant.	N=5 Full term babies in CA at birth who received CC after ventilation via ET tube failed to restore the heart rate	CC with 2 fingers on the mid-sternum and 2 thumbs with hands encircling the chest were provided. 1 of 5 infants survived with normal outcome at 18 months. In 1 infant with lines in place at the time of CC, physiologic pressures were generated with external CC.	External CC should be used only after the newborn infant's lungs are properly ventilated via an ET tube and the diagnosis of CA confirmed by auscultation. The newborn infant should be placed upon a firm surface. Effective massage is obtained with vigorous compression of the

				middle 1/3 of the sternum using only 2 fingers.
Thaler 1963 {Thaler 1963 606}	**Design:** Cadaveric case series **Aim 1)** To determine if variation in the point of application of manual pressures affected liver injury (abdominal vs Xiphoid vs middle sternum vs simultaneous chest and abdominal compression **Aim 2)** To determine whether effective circulatory pressures can be produced by mid-sternal compression in infants and young children	**1)** N=15 fresh cadavers of infants and young children **2)** N=20 fresh cadavers of infants and young children with an induced free circulatory system obtained by intracardiac injection of heparin within 15 minutes of death followed by 10 min of CC	**1)** No rupture of liver was produced when pressure was applied to the chest alone at mid-sternum. Superficial tears of the liver capsule were produced when pressure was applied to the xiphoid process and all patients with simulataneous chest/abdomen compressions had liver rupture. **2)** Compression of the middle part of the sternum (above the xiphoid) produces effective circulatory pressures Autopsies on all 20 showed no injury to the liver or other structures	**1)**Simultaneous abdominal and chest compression and compression of the xiphoid must be avoided to prevent catastrophic liver injury during CC in infants and young children. **2)**The technique of external CC should be compression of the mid-sternum with superimposed thumbs while the fingers are linked behind the patient for additional support.
Finholt 1986 {Finholt 1986 646}	**Design**: Case series of pediatric patients who had CXR with no control group **Aim:** To verify that the heart lies under the midsternum in infancy and descends with age	N=55 patients aged 1 day to 19 yrs who had routine CXR (n=30) or right-sided heart Angiography (n=25). 8 were preterm infants and 16 were less than 1 yo.	The center of the heart lies ~25% of the distance from the xyphoid to the suprasternal notch in all age groups. The nipple line bisects the sternum at a significantly higher location than the center of the cardiac silhouette. The heart lay under the lower third of the sternum in all age groups. Analysis of variance indicated that there was no significant difference in this location between age groups.	The nipple line cannot be taken as an estimation of the heart's intrathoracic location. CC at the mid-sternum may not be optimal in infants and children. Altering the prior midsternal CC recommendation for infants and children should be considered. Comment: It is possible that decreases in volume of air in the lung and volume of blood in the heart may raise the heart to a more cephalad position in the cadaver than a living child.
Orlowski 1986 {Orlowski 1986 667}	**Design:** Case series **Aim:** To determine where the geometric center of the heart lies under the sternum	N=187 (majority under 1 yr of age, 14 <1 month) undergoing routine upright CXR in the PA projection and n=	The position of the geometric center of the cardiac silhouette in relation to the sternum was recorded as a percentage of the distance along	CC performed on infants and young children over the lower one-third of the sternum, above the xiphoid, is superior to CC

		90 with supine AP CXR who had lead markers placed at the suprasternal notch and xiphoid prior to taking the CXR.	the sternum. The heart lies under the lower one-third of the sternum in the majority of infants under 1 year of age.	performed at the midsternum
Philips 1986 {Phillips 1986 1024}	**Design:** Case series **Aim:** To establish the true position of the heart in the infant chest.	N=55 patients of 27 weeks' gestation to 13 months post-term	The center of the heart was positioned under the lower third of the sternum in 48 cases. In 4 infants the position was slightly more cephalad, but still below the lower half of the sternum. In 3 infants, the position was below the xiphosternal junction	CC guidelines for infant resuscitation (*which at the time recommended mid-sternal CC*) should be revised in view of these findings.
Shah 1992 {Shah 1992 49}	**Design:** Case Series **Aim:** To determine the location of the heart in relation to the nipples and sternum	N=210 (of which n-48 were < 6 months of age) healthy children from birth to 12 years who had CXR with radio-opaque markers at sternal ends and both nipples	The heart was found to descend with age, its center lying beneath the mid-sternum during the first 6 months of life and beneath the lower sternum after infancy ($p<0.0001$). The position did not vary with age in relation to inter-nipple line ($p>0.05$).	The inter-nipple line is a poor landmark for where to give CC. External CC should be applied in relation to the sternum and at different locations according to age. Comment: There findings were different from that of Philips, Orlowski and Finholt whose data suggested that the heart lies primarily under the lower 1/3 of the sternum in infants and young children. {Finholt 1986 646, Orlowski 1986 667, Phillips 1986 1024}
Clements 2000 {Clements 2000 43}	**Aim:** To determine whether the recommended method of locating finger position for chest compression in infant cardiac arrest can cause pressure on the abdomen or xiphisternum	N= 30 infants, under the age of 1 year of which 7 infants were < 4 weeks old	At the time of the study, The ERC and AHA recommended that the CC position for infants be located by placing two fingers on the sternum, one finger's breadth below the inter-nipple line. If any infant in this study had received chest compressions using the recommended method, pressure would have been exerted on the xiphisternum or abdomen.	The method of locating finger position one finger breadth below the nipple line should be changed to one using sternal anatomy alone.

You 2009 {You 2009 1378}	**Design:** Retrospective chart review of infants who had chest CT **Aim:** To evaluate the optimal CC site for 2-rescuer infant CPR	N=75 infants with a mean age of 4.43±3.55 months. Of the infants studied, 47 were boys (62.7%).	The left ventricle was located in the lower quarter of the sternum, lower than the lower 1/3 (the ratio of the length from the xiphoid process to the point of maximal anterior–posterior heart diameter).	More studies are needed to validate the efficiency and safety of compressing the lower quarter of the sternum in 2-rescuer infant CPR.
Abbreviations: AP; antero-posterior, CA; cardiac arrest; CC; chest compressions, CPR; cardiopulmonary resuscitation, CXR; chest x-ray, ET; endo-tracheal; OR; odds ratio, PA; Postero-Anterior, RR; relative risk				

Reviewer Comments: There were insufficient new studies identified to warrant a systematic review but since the older papers have never been evaluated using GRADE, this should be considered in the coming years.

The information from the identified studies is insufficient to alter the existing recommendation. This evidence update reaffirms the prior 2010 suggestion as follows: *Neonatal chest compressions should be centered over the lower third of the sternum but above the xiphoid.*

Additional human newborn infant research may be helpful. Due to species differences in thoracic shape and sternal anatomy, animal model data is not particularly helpful for this PICOST. Newborn infant cohort data from different gestational ages with accurate determinations of where the heart is located under the sternum could be helpful.

Task Force Insights: Given the limited new evidence available, it is reasonable to confirm the 2010 treatment recommendation as a good practice statement.

References:

Clements F, McGowan J. Finger position for chest compressions in cardiac arrest in infants. Resuscitation. 2000;44(1)43-6.

Finholt DA, Kettrick RG, Wagner HR, Swedlow DB. The heart is under the lower third of the sternum. Implications for external cardiac massage. Am J Dis Child. 1986;140(7)646-9.

Moya F, James LS, Burnard ED, Hanks EC. Cardiac massage in the newborn infant through the intact chest. Am J Obstet Gynecol. 1962;84798-803.

Orlowski JP. Optimum position for external cardiac compression in infants and young children. Ann Emerg Med. 1986;15(6)667-73.

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Phillips GW, Zideman DA. Relation of infant heart to sternum: its significance in cardiopulmonary resuscitation. Lancet. 1986;1(8488)1024-5.

Shah NM, Gaur HK. Position of heart in relation to sternum and nipple line at various ages. Indian Pediatr. 1992;29(1)49-53.

Thaler MM, Stobie GH. An improved technic of external cardiac massage in infants and young children. N Engl J Med. 1963;269606-10.

You Y. Optimum location for chest compressions during two-rescuer infant cardiopulmonary resuscitation. Resuscitation. 2009;80(12)1378-81.

2025 Evidence Update
NLS 5600 – Dose, Route, and Interval of Epinephrine (Adrenaline) for Neonatal Resuscitation

Worksheet Author(s): Cunningham P, Isayama T, Mildenhall L, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 28 October 2024
Conflicts of Interest: None

PICOST:
Population: Among neonates (of any gestation) < 28 days of age who have no detected cardiac output or who have asystole or heart rate < 60 bpm despite ventilation and chest compressions
Intervention: Any non-standard dose, interval or route of epinephrine (adrenaline)
Comparators*:* Epinephrine (adrenaline) doses of 0.01-0.03 mg/kg intravenously at intervals of every 3-5 minutes
Outcomes:

- Mortality before hospital discharge (critical)
- Survival to neonatal unit admission (critical)
- Return of spontaneous circulation (ROSC - incidence and time until) (critical)
- HIE Stage moderate-severe (term infants only)
- Intraventricular hemorrhage grades III-IV (preterm infants only)
- Other morbidities in early infancy (e.g., necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia) (important)
- Neurodevelopmental outcomes (important)

Study Designs*:* Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. Cohort studies may compare different interventions or include only one arm receiving one intervention. They were eligible for this review if they were considered representative of a defined population (e.g. infants born at a hospital between specified dates). Otherwise, they were considered to be (ineligible) case series. All languages were eligible if there was an English abstract. Unpublished studies (e.g., conference abstracts, trial protocols) were excluded.
Timeframe: From inception of the searched databases to March 6, 2019

Year of last full review: 2020 {Isayama 2020 586}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST {Wyckoff 2020 S185}:
Consensus on Science:

- Only two observational studies (both in term and preterm infants) were found that addressed any of the comparisons for the PICOST question. {Barber 2006 1028, Halling 2017 232} They were from a single neonatal unit, although the participants were from different epochs. The overall certainty of evidence was rated as very low for all outcomes primarily due to a very serious risk of bias and very serious imprecision. The individual studies were at a critical risk of bias due to confounding.
- For the critical outcome of **mortality before hospital discharge** (O), we have identified very-low-certainty evidence (downgraded for very serious risk of bias and very serious imprecision) from one observational study in which 50 neonates were treated with epinephrine (P), that showed no significant difference between the initial administration via the endotracheal tube (I) compared to initial intravenous administration (C) (relative risk [RR], 1.03; 95%CI, 0.62, 1.71; Absolute Risk Difference [ARD]; 17 more, 95%CI, 209 fewer to 391 more deaths per 1000 infants). {Halling 2017 232} This was despite larger doses given via the endotracheal route (0.03-0.05 vs. 0.01 mg/kg/dose).
- For the critical outcome of **failure to achieve ROSC** (O), we have identified very-low-certainty evidence (downgraded for very serious risk of bias and very serious imprecision) from two observational studies in which 97 neonates (P) were treated with epinephrine, that showed no significant difference between the initial administration of epinephrine via the endotracheal tube (I) compared to initial intravenous administration (C) (RR, 0.97; 95%CI, 0.38, 2.48; P=0.96; ARD; 7 fewer, 95%CI, 135 fewer to 322 more per 1000 neonates failed to achieve ROSC). {Barber 2006 1028, Halling 2017 232} This was despite the infants in one of the studies receiving larger doses given via the endotracheal route. Halling 2017 232}

- For the important outcome of **time to ROSC** (O), we have identified very-low-certainty evidence (downgraded for very serious risk of bias and serious imprecision) from one observational study in which 50 neonates were treated with epinephrine (P), that showed no significant difference in the time to ROSC after initial administration of epinephrine via the endotracheal tube (I) when compared to initial intravenous administration (C) (mean difference 2.00 minutes later, 95%CI, 0.60 minutes earlier to 4.60 minutes later). {Halling 232} This was despite larger doses given via the endotracheal route (0.03-0.05 vs. 0.01 mg/kg/dose).
- In a post-hoc analysis , we have identified very-low-certainty evidence (downgraded for very serious risk of bias and very serious imprecision) from two observational studies {Barber 1028, Halling 232} in which 97 neonates were treated with epinephrine (P), that showed no significant difference in the **receipt of an additional dose** after the initial administration of epinephrine via endotracheal tube (I) when compared to intravenous administration (C) (RR, 1.94; 95%CI, 0.18, 20.96; P=0.59; ARD, 654 more neonates, 95%CI, 570 fewer to 1000 more per 1000 infants would receive additional epinephrine dose or doses after the first). {Barber 2006 1028, Halling 2017 232} This was despite infants having receiving larger doses given via the endotracheal route in one of the studies {Halling 2017 232}
- No studies specifically reported the critical outcome of survival to neonatal unit admission, but this is likely to have been similar to the inverse of the outcome 'failure to achieve ROSC' which was reported. We did not find any eligible studies comparing **different doses of intravenous epinephrine**, but one study {Halling 232} in which 30 neonates received initial ET epinephrine allowed a post hoc comparison of 30 infants who received two **different doses of endotracheal epinephrine** (0.03 vs 0.05 mg/kg/dose) in different epochs of the study. Although no statistically significant difference was found there is such serious imprecision as to prevent any conclusion.
- Except for the comparison between intravenous vs. endotracheal epinephrine, we did not find any eligible studies comparing **different routes of administration**.

We did not find any eligible studies comparing **different intervals of epinephrine administration.**
We did not find any eligible studies that allowed comparison of any other pre-specified important outcomes (HIE Stage moderate-severe (term infants only); intraventricular hemorrhage grades III-IV (preterm infants only); other morbidities in early infancy (e.g., necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia) or neurodevelopmental outcomes).

Treatment Recommendations:

- If the heart rate has not increased to > 60 beats per minute after optimizing ventilation and chest compressions, we suggest the administration of intravascular epinephrine (0.01 to 0.03 mg/kg). (Weak recommendation, very low certainty of evidence).
- If intravascular access is not yet available, we suggest administering endotracheal epinephrine at a larger dose (0.05 to 0.1 mg/kg). (Weak recommendation, very low certainty of evidence). The administration of endotracheal epinephrine should not delay attempts to establish vascular access. (Weak recommendation, very low certainty of evidence).
- We suggest the administration of further doses of epinephrine every 3-5 minutes, preferably intravascularly, if the heart rate remains less than 60 beats per minute. (Weak recommendation, very low certainty of evidence).
- If the response to endotracheal epinephrine is inadequate, we suggest that an intravascular dose be given as soon as vascular access is obtained, regardless of the interval. (Weak recommendation, very low certainty of evidence).

Current Search Strategy – See appendix

New Search strategy: Not applicable (same as previous review)
Database searched: Medline Embase Cochrane
Time Frame: (existing PICOST) – updated from end of last search to 20 August 2024
Time Frame: (new PICOST) – not applicable
Date Search Completed: 20 August 2024
Search Results (Number of articles identified and number identified as relevant): 739 titles and abstracts screened, 41 full text articles assessed for eligibility, 12 included.

Summary of Evidence Update:
This evidence update found 4 new human infant observational studies and 8 animal studies that addressed questions relevant to the PICOST.

Relevant Guidelines or Systematic Reviews: None identified

RCT: None identified

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population Inclusion Criteria:	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Holmberg 2020 {Holmberg 2020 180}	Cohort study (N=2977 neonates) (in larger study of infants and children) Survival of newborn subgroup also reported. (N=1345) (Note: 'neonatal' and 'newborn' not defined in detail, but likely to mean: • Neonatal; <28 days (including newborns) • Newborn; immediately after birth)	Get With The Guidelines Resuscitation registry (GWTG-R). Patients ≤ 18 y who received in-hospital cardiopulmonary resuscitation for bradycardia with poor perfusion (non-pulseless event) N=6762. Subgroup of neonates; 1514 in No Epinephrine group, 1463 in Epinephrine group, Subgroup of newborns; 708 in No Epinephrine group, 637 in Epinephrine group.	Survival to discharge: Neonate subgroup: No Epinephrine 41.4% vs Epinephrine 28.5%; RR 0.69 (0.61-0.78 95% CI)) Newborn subgroup: No Epinephrine 37.4% vs Epinephrine 20.0%; RR 0.53 (0.45-0.64 95% CI))	Study reports better survival to discharge for those who don't receive epinephrine, including in neonatal and newborn subgroups. However, study uses propensity scoring system for adjustment. The variables used for this system may not have ensured low confounding within the neonatal or newborn subgroups. For example, gestation and birthweight not among variables for propensity matching. Most baseline characteristics for neonatal and newborn subgroups not provided. Some results reported separately for neonates and for newborns, but baseline characteristics only provided for the neonates, so presume the newborns are a subgroup of neonates but this is not explicitly stated.
Alsaleem 2021 {Alsaleem 2021 490}	Cohort study (N=96)	Infants admitted to John R. Oishei Children's Hospital, Buffalo, NY, with heart rate (HR) < 100/minute at 1 min and requiring positive pressure ventilation (PPV) at resuscitation. Compared group who received epinephrine with group who received just PPV.	For the whole group of 96 participants, blood glucose levels were generally higher in the epinephrine group than the no epinephrine group over the first 24 h with statistical significance at 12 hours after birth ($p < 0.01$, ANOVA repeated measures; $p < 0.05$, unpaired t-test vs. PPV group. However, trends were opposite in those ≤ 32 weeks and those >32 weeks (higher blood glucoses in those who received epinephrine if >32 weeks, but other way round in those ≤ 32 weeks.	Only infants who survived to admission were included, so cannot estimate survival difference, or any other outcomes relevant to the PICOST. There were major differences in baseline characteristics in epinephrine group vs no epinephrine group (e.g. cord pH (mean ±SD) 7.14 ± 0.16 in no epinephrine vs 6.95 ± 0.10 in epinephrine group). There were also baseline differences in 5 min Apgar scores and chest compressions (14% vs

				100%). Therefore, major potential for confounding by indication.
Halling 2021 {Halling 2021 236}	Cohort study (N=1553)	All newly born infants who received chest compressions in the DR submitted to the GWTG-R registry.	Decreased odds of achieving ROSC in the DR was associated with epinephrine administration, greater number of epinephrine doses and longer time to receive the first epinephrine dose. The first dose of epinephrine was administered earlier among infants who achieved ROSC compared to those who did not achieve ROSC (4 vs 7 min). Mortality prior to discharge was associated with an increased epinephrine administration and increased number of epinephrine doses.	The contribution of this study is to illustrate in a large registry of infants who received chest compressions is that (1) administration of epinephrine within 4-7 minutes of birth may be possible and (2) that achieving ROSC is less likely in those who received epinephrine than those who didn't. However, there is a high likelihood of confounding by indication (sicker infants more likely to receive epinephrine). Also, those who did not receive ROSC had a later time to first dose, but it is unknown whether there were confounding factors that might have affected both time to first dose and likelihood of achieving ROSC.
Halling 2024 {Halling 2024 114058}	Cohort study (N=408)	Newly born infants from 142 centers who received chest compressions and at least 1 dose of epinephrine in the delivery room. From AHA's GWTG-R registry.	Comparing initial ET with initial IV epinephrine, ROSC was achieved in 70.1% vs 58.3% (adjusted risk difference 10.02; 95% CI 0.05-19.99). ROSC was achieved in 58.3% with IV epinephrine alone, and 47.0% with ET epinephrine alone, with 40.0% receiving subsequent IV epinephrine.	The authors' conclusion is that initial use of ET epinephrine is reasonable because overall rates of ROSC were higher in those who received ET epinephrine (with or without subsequent IV doses) than those who received IV epinephrine alone. The time to first dose of epinephrine was much shorter for ET epinephrine than for IV epinephrine (median 6 vs 8 min) Study seems likely to have some of the same risks of bias due to confounding as {Halling 2017 232} (included in the previous systematic review) which was assessed as very serious, (this concern is acknowledged in

				the methods section of the paper). Small overlap with {Halling 2017 232} (which was included in the previous systematic review{Liley 2020 }) which enrolled from January 2006 to July 2014, all from Parkland Hospital in Dallas Tx and also examined IV vs ET epinephrine. A few of the same patients likely included in this Registry paper, for which inclusion dates were October 2013 to July 2020).
Abbreviations: AHA; American Heart Association, DR; delivery room, ET; endotracheal, IV; intravenous, HR; heart rate, BG; blood glucose, RR; relative risk, CI; confidence intervals, GWTG-R; Get with the Guidelines registry, ROSC; return of spontaneous circulation, PPV; positive pressure ventilation, GWTG-R; American Heart Association Get With The Guidelines Resuscitation Registry.				

Animal Studies

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population Inclusion Criteria:**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Polglase 2020 {Polglase 2020 902}	Compare the cardiovascular response to chest compressions prior to or after umbilical cord clamping in asystolic lambs. (N=28)	Near-term lambs. Asphyxia induced by clamping of the umbilical cord for lambs undergoing ICC or occlusion of the maternal internal iliac artery for lambs undergoing 'physiological based cord clamping' (PBCC).	PBCC1 - ventilation commenced and CPR initiated while the lamb was still attached to the umbilical cord with UCC occurring 1 min after ROSC; Epinephrine (0.1 mg/kg bodyweight) was given IV 1 min after CCs were initiated, and every 3 min thereafter for a maximum of three doses. (n=8) PBCC10 - ventilation commenced and CPR initiated while the lamb was still attached to the	Determine whether it was feasible to undertake CC prior to UCC - No differences in diastolic pressures between a clamped and an open umbilical cord during CCs, or upon ROSC.	Doesn't directly address PICOST question but does address an identified gap in knowledge by comparing responses to chest compressions plus epinephrine by timing of cord clamping. No differences in the ability to obtain ROSC or the time that it took to achieve ROSC between ICC and PBCC groups. If UCC was delayed for 10 min after ROSC there were significant reductions in post-asphyxial rebound

			umbilical cord with UCC occurring 10 min after ROSC; Epinephrine (0.1 mg/kg bodyweight) was given IV 1 min after CCs were initiated, and every 3 min thereafter for a maximum of three doses. (n=8) ICC - Cord clamped and CPR initiated within 30s; Epinephrine (0.1 mg/kg bodyweight) was given IV 1 min after CCs were initiated, and every 3 min thereafter for a maximum of three doses. (n = 12)		hypertension, cerebral blood flow and cerebral oxygenation. The authors comment in the discussion that administering CC on an intact umbilical cord is technically challenging.
Songstad 2020 {Songstad 2020 262}	Compare IV, endotracheal (ET), and intranasal (IN) routes for epinephrine administration during resuscitation of asphyxiated newborn lambs. (N=22)	Near-term lambs, delivered by caesarean section. Severe asphyxia induced by clamping the umbilical cord while delaying ET ventilation until blood flow in the carotid artery ceased.	IV Epinephrine (50ug; n=6) ET Epinephrine (500 microg; n=5) Intranasal (IN) Epinephrine (250 microg to each nostril, 50 microg total; n=6) IV saline receiving 5.0 mL of saline via the jugular vein (n=5)	Number of lambs to achieve ROSC after one treatment dose - IV-Epinephrine (5/6, all after 1 or 2 doses), ET-Epinephrine (1/5), IN-Epinephrine (1/6), IV-Saline (0/5). Time to ROSC was significantly shorter using IV-Epinephrine (2.4 ± 0.4 min) compared with ET-Epinephrine (10.3 ± 2.4 min), IN-Epinephrine (9.2 ± 2.2 min), and IV-saline (11.2 ± 1.2 min).	At 3 mins (after a single dose via respective route), circulating epinephrine concentrations were significantly higher in IV-Epi- and ET-Epi-administered lambs than in IN-Epi- and saline-treated lambs. Lambs that did achieve ROSC in the ET and IN groups mostly received multiple doses and, in some cases, rescue IV doses so total cumulative dose was considerably higher. A result likely attributable to this was that at 15 mins, plasma

					epinephrine concentrations were increased further in ET-Epi-treated lambs but were similar in IV-Epi-, IN-Epi-, and saline-treated lambs. Note that ET and IN each dose was approximately 0.125 mg/kg for these approximately 4 kg lambs (at the high end of an ET dose cf. current recommendations), and IV dose was 0.0125 mg/kg (within current recommended range).
Sankaran 2021 {Sankaran 2021 1}	To evaluate the effect of 1mL and 2.5mL flush volumes after UVC epinephrine administration on the incidence and time to achieve return of spontaneous circulation (ROSC) (N=22)	Near-term lamb model of perinatal asphyxia induced cardiac arrest.	IV epinephrine (0.03 mg/kg) followed by 2.5mL saline flush (n=15) IV epinephrine (0.03 mg/kg) followed by 1.0mL saline flush (n=7)	Twelve out of fifteen (80%) and three out of seven (43%) lambs had ROSC after the first dose of epinephrine with 2.5-mL and 1-mL flush respectively (p = 0.08)	Larger flush volume following low UVC epinephrine may increase the incidence of ROSC with the first dose of epinephrine. However, the time to achieve ROSC from the time of epinephrine administration was not different (p = 0.71), and nor was the cumulative epinephrine dose required to achieve ROSC or the plasma epinephrine concentrations at 1 min after epinephrine plus flush administration. Heart rates, arterial blood pressures, and carotid blood flows

					at 10 min after ROSC were also similar.
Andersen 2023 {Andersen 2023 511}	Evaluate the effect of epinephrine in a piglet model of neonatal hypoxic cardiac arrest Post-perinatal transition model (N=25)	Term piglets - hypoxia induced by endotracheal tube clamping until cardiac arrest	CPR + IV Epinephrine (n=13) CPR + placebo (n=12)	Animals that received epinephrine had significantly higher rate of ROSC (epinephrine 10/13 vs placebo 4/12, RR 2.31; 95% CI: 1.09 to 5.77, p = 0.047). We found no difference between the groups in median time-to-ROSC (epinephrine: 160 (113-211) vs placebo 153 (116-503) s, p = 0.66), and no difference in 6-h survival (7/13 vs 3/12, p = 0.23)	Epinephrine improved rate of ROSC. Animals treated with epinephrine had significantly higher aortic systolic blood pressure (96.0 ± 8.5 vs 55.2 ± 5.5 mm Hg, p < 0.0001), aortic diastolic blood pressure (54.1 ± 4.5 vs 24.8 ± 1.6 mm Hg, p < 0.0001), and mean arterial blood pressure (68.8 ± 5.8 vs 33.9 ± 2.5 mm Hg, p < 0.0001) compared to animals treated with placebo. No difference in the composite endpoint of death or severe brain MRS/MRI abnormality between animals resuscitated with epinephrine compared to placebo.
Berkelhamer 2022 {Berkelhamer 2022 828130}	Investigate bioavailability of intramuscular (IM) epinephrine in asphyxia. (N=4)	Term fetal lambs delivered by cesarean section and asphyxiated by umbilical cord occlusion with resuscitation after 5 min of asystole.	Four lambs treated with IM epinephrine. No control group treated via other route or with no epinephrine.	There was no significant increase in plasma concentrations prior to ROSC with IM epinephrine administration. Increased concentrations were observed in 2 animals several minutes after ROSC.	Cannot say whether the IM epinephrine contributed to achieving ROSC, i.e. whether it had any effect. Study compares with results from other studies to conclude that rise in plasma epinephrine concentrations is much later than IV and somewhat

					later than ET dosing, therefore unlikely to be as efficacious.
Roberts 2022 {Polglase 2020 902}	Compare intraosseous with intravenous epinephrine administration during resuscitation of severely asphyxiated lambs at birth. (N=21)	Near-term lambs. Intrapartum asphyxia induced by umbilical cord clamping until asystole. All animals instrumented before inducing asphyxia so may not resemble times to administration of IV or IO epinephrine achievable in human infants.	Intraosseous Epinephrine (10ug/kg, n=9) Intravenous Epinephrine (10ug/kg, n=12)	ROSC was successful in 7 of 9 IO epinephrine lambs and in 10 of 12 IV epinephrine lambs.	The time and number of epinephrine doses required to achieve ROSC were similar between the groups, as were the achieved plasma epinephrine levels. Lambs in both groups displayed a similar marked overshoot in systemic blood pressure and carotid blood flow after ROSC. Blood gas parameters improved more quickly in the IO lambs in the first 3min but were otherwise similar over the 30min after ROSC.
Polglase 2024 {Polglase 2024 }	Assess whether endotracheal epinephrine achieved return of spontaneous circulation (ROSC), and maintained physiological stability after ROSC, at standard and higher doses (N=33)	Near-term fetal lambs asphyxiated until asystole All animals instrumented before inducing asphyxia so may not resemble times to administration of IV or ET epinephrine achievable in human infants.	IV Epinephrine (20ug/kg, n=9) Standard-dose ET Epinephrine (100ug/kg, n=9) High-dose ET Epinephrine (1mg/kg, n=9) IV Saline (n=6)	ROSC in response to allocated treatment (without rescue IV Epinephrine) occurred in 1/6 Saline, 9/9 IV Epinephrine, 0/9 Standard-dose ET Epinephrine, and 7/9 High-dose ET Epinephrine.	Cortex microbleeds were more frequent in High-dose ET Epinephrine lambs (8/8 lambs examined, versus 3/8 in IV Epinephrine lambs) Lambs that did achieve ROSC initially in the ET groups received multiple doses and, in some cases, rescue IV doses so total cumulative dose and plasma levels after ROSC were considerably higher, probably accounting for higher systolic and diastolic pressures

					after ROSC. Unclear whether the higher rate of microbleeds was due to higher post-ROSC epinephrine levels or more prolonged asphyxia due to longer time to ROSC or both.
Vali 2024 {Vali 2024 527}	Compare current practice of epinephrine administration through a low-lying UVC followed by a saline flush (UVC Epinephrine) with an initial dose via a direct umbilical vein injection followed by the milking of a 20cm length of cut umbilical cord (DUV + UCM) (N=18)	Near-term asphyxiated lambs All animals instrumented before inducing asphyxia except for establishment of vascular access.	Direct injection of epinephrine into the umbilical vein followed by milking a ~20 cm segment of cut umbilical cord to flush the epinephrine (0.02mg/kg, n=5; 0.03mg/kg, n=5) Epinephrine given through a UVC (0.02mg/kg, n=4; 0.03mg/kg, n=4)	Achieving ROSC - 9/10 of lambs in the DUV + UCM group, 7/8 in the UVC group. Time the first epinephrine dose (from asystole, including the time taken to establish route of access and administer epinephrine) similar between the two groups (2.97 ± 0.48 min in the DUV + UCM group compared with 4.23 ± 0.58 in the control group; p = 0.12). Time to ROSC similar between the groups (4.67 ± 0.67 min vs. 3.99 ± 0.58 min for DUV + UCM vs. UVC Epinephrine, respectively; p = 0.58). No difference in the time to ROSC from the first epinephrine administration (1.25 ± 0.20 min vs. 0.75 ± 0.17 min in DUV + UCM vs. UVC epinephrine, respectively; p = 0.12).	Plasma epinephrine concentrations between the two methods of administration were similar for each dose of 0.02 and 0.03 mg/kg throughout the study period. Direct injection with cord milking was not faster than insertion of an umbilical catheter, although authors comment on differences between lamb and human umbilical cords and that human umbilical cords might be easier or more difficult.

Abbreviations: PBCC; physiological based cord clamping, UCM; umbilical cord milking, ICC; immediate cord clamping, DUV; direct UV injection, UVC; umbilical venous catheter, IN; intranasal, ROSC; return of spontaneous circulation, IV; intravenous, RR; relative risk, CI; confidence intervals, CPR; cardiopulmonary resuscitation, UCC; umbilical cord clamping,

Reviewer Comments:)
This evidence update found 4 new human infant observational studies. {Alsaleem 2021 490, Halling 2024 114058, Halling 2021 236, Holmberg 2020 180} Two compared infants who received epinephrine with those who did not among infants who received chest compressions. {Halling 2021 236, Holmberg 2020 180} One study compared ET vs IV epinephrine, {Halling 2024 114058} and one study examined blood glucose levels after epinephrine vs no epinephrine. {Alsaleem 2021 490} Both epinephrine vs no epinephrine studies found lower survival rates among infants who received epinephrine, but the likelihood of confounding by indication and by other factors is so high that it cannot be concluded that epinephrine is, in and of itself, harmful. {Halling 2021 236, Holmberg 2020 180}

The study of ET vs IV epinephrine (vs both) concluded that initial ET epinephrine may be reasonable because overall rates of ROSC were higher in those who received ET epinephrine (although the majority needed subsequent intravenous doses prior to achieving ROSC) than those who received IV epinephrine alone. However, the authors acknowledge that the study is also at risk of confounding by various factors that could not be assessed because of missing data. {Halling 2024 114058}

In the study of glucose levels, the two study arms had such different baseline characteristics that no conclusions can be reached about the specific effects of epinephrine. {Alsaleem 2021 490}

The 8 animal studies examined various comparisons including epinephrine vs no epinephrine as well as dose and route (IV, ET, IN, IM , IO and direct injection into the umbilical cord followed by cord milking) as well as flush volume. {Andersen 2023 511, Berkelhamer 2022 828130, Polglase 2024 , Polglase 2020 902, Roberts 2022 311, Sankaran 2021 1, Songstad 2020 262, Vali 2024 527}

The Evidence Update authors noted an additional animal study that was published just after the literature search completion date, that examined ET vs intranasal (IN) vs IV epinephrine in bradycardic newborn lambs and also concluded that IN has similar efficacy to ET (though IV remained the most effective). {de Jager 2024 327348}

The overall results of these studies continue to confirm that:

- Epinephrine administered via a UVC at a dose within the currently recommended range (0.01-0.03 mg/kg) is more effective than a standard (0.05-0.10 mg/kg) or higher dose administered via tracheal tube. {Polglase 2024 , Songstad 2020 262}
- IO doses are similarly effective to UVC doses. {Roberts 2022 311}

New evidence from the animal studies suggests:

- There may be risk of harm from high cumulative doses (which may be irrespective of route of administration). {Polglase 2024 }
- IN doses are similarly effective to ET doses. {de Jager 2024 327348, Songstad 2020 262}
- IM dosing achieves much lower plasma concentrations and at later times than either IV or ET and therefore this route is unlikely to be effective. {Berkelhamer 2022 828130}
- A larger flush volume (2.5 mL compared to 1mL) after IV administration increased the proportion of lambs that achieved ROSC but no difference to other measured outcomes. {Sankaran 2021 1}

In many of the animal studies, the animals were instrumented (including intubation and insertion of vascular cannulas) before inducing asphyxia, so do not take into account the time taken to perform these procedures, which can be quite prolonged in human infant resuscitation.

Overall conclusions:
There are few new human infant studies and none that seems likely to change the direction of effects or level of certainty of evidence found in the previous review.

There are several new animal model studies that refine understanding of dose, route and potential harms of epinephrine, particularly when given in high cumulative doses. These include studies examining routes of administration not considered in the

previous review, such as intranasal and direct IV injection into the umbilical cord with subsequent cord milking, and intramuscular. {Berkelhamer 2022 828130, de Jager 2024 327348, Songstad 2020 262, Vali 2024 527}

IN dosing may be similarly effective to ET dosing (one very small, included animal study and one additional animal study that was published after the last search date) and deserves further investigation because it may provide an option in circumstances where endotracheal intubation is unattainable. {de Jager 2024 327348, Songstad 2020 262} IO dosing may be similarly effective to UVC dosing, suggesting that remains a valid treatment option. {Roberts 2022 311}

The PICOST question deserves an updated systematic review, mainly to assess additional indirect evidence (i.e., from animal studies). While unlikely to change the current treatment recommendations, formulation of one or more good practice statements may ensue. The timing of this review could be determined by when the VERSE trial, {Schmolzer 2023 } comparing IV or ET epinephrine to IV or ET vasopressin is completed, or could be accomplished earlier because that study addresses a somewhat different PICOST question.

A new knowledge gap was identified in the Task Force discussion of this question: Whether administration of epinephrine via a supraglottic airway device is effective, or whether another route (e.g. IV, ET, IN) should be used

Meanwhile, the the 2020 treatment recommendations are unchanged. {Wyckoff 2020 S185}

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Appendix: Search strategy

MEDLINE SEARCH STRATEGY
Search strategies used for search update August 20 2024

Sources searched	Search strategy	Search time frame
Medline	1 exp Infant, Newborn/ 2 Delivery Rooms/ 3 exp Respiratory Distress Syndrome, Newborn/ 4 Premature Birth/ 5 Gestational Age/ 6 Term Birth/ 7 Live Birth/ 8 Infant, Newborn, Diseases/ 9 Persistent Fetal Circulation Syndrome/	March 6, 2019 to 20 August 2024

	10 Infant, Premature, Diseases/ 11 Intensive Care, Neonatal/ 12 Intensive Care Units, Neonatal/ 13 Neonatal Nursing/ 14 Nurses, Neonatal/ 15 Neonatology/ 16 Neonatologists/ 17 Perinatology/ 18 exp Perinatal Care/ 19 Perinatal Death/ 20 Perinatal Mortality/ 21 newborn*.tw,kf. 22 neonat*.tw,kf. 23 prematur*.tw,kf. 24 preterm.tw,kf. 25 delivery room*.tw,kf. 26 low birth weight.tw,kf. 27 gestational age.tw,kf. 28 perinat*.tw,kf. 29 antenat*.tw,kf. 30 NICU.tw,kf. 31 postnat*.tw,kf. 32 newly born.tw,kf. 33 or/1-32 34 exp Heart Arrest/ 35 Ventricular Fibrillation/ 36 exp Resuscitation/ 37 Asphyxia/ 38 Asphyxia Neonatorum/ 39 Bradycardia/ 40 cardi* arrest*.tw,kf. 41 heart arrest*.tw,kf. 42 asystol*.tw,kf. 43 pulseless electrical activity.tw,kf. 44 Advanced Cardiac Life Support.tw,kf. 45 advanced life support.tw,kf. 46 acls.tw,kf. 47 resuscitat*.tw,kf. 48 ventricular fibrillation*.tw,kf. 49 return of spontaneous circulation.tw,kf. 50 ROSC.tw,kf. 51 bradycardi*.tw,kf. 52 asphyxia*.tw,kf. 53 or/34-52 54 exp Epinephrine/ 55 epinephrinenephrin*.tw,kf. 56 Epienalin*.tw,kf 57 54 or 55 or 56 58 33 and 53 and 57 59 58 not (animals/ not human/) 60 limit 59 to (comment or editorial or letter) 61 59 not 60 62 remove duplicates from 61	

	63 (202210* OR 202211* OR 202212* OR 2023* OR 2024*).dt. 64 62 AND 63	
Cochrane Register of controlled trials	#1 [mh "Infant, Newborn"] #2 [mh ^"Delivery Rooms"] #3 [mh "Respiratory Distress Syndrome, Newborn"] #4 [mh ^"Premature Birth"] #5 [mh ^"Gestational Age"] #6 [mh ^"Term Birth"] #7 [mh ^"Live Birth"] #8 [mh ^"Infant, Newborn, Diseases"] #9 [mh ^"Persistent Fetal Circulation Syndrome"] #10 [mh ^"Infant, Premature, Diseases"] #11 [mh ^"Intensive Care, Neonatal"] #12 [mh ^"Intensive Care Units, Neonatal"] #13 [mh ^"Neonatal Nursing"] #14 [mh ^"Nurses, Neonatal"] #15 [mh ^Neonatology] #16 [mh ^Neonatologists] #17 [mh ^Perinatology] #18 [mh "Perinatal Care"] #19 (newborn*:ti,ab OR neonat*:ti,ab OR prematur*:ti,ab OR preterm:ti,ab OR (delivery NEXT room*):ti,ab OR "low birth weight":ti,ab OR "gestational age":ti,ab OR perinat*:ti,ab OR antenat*:ti,ab OR NICU:ti,ab OR postnat*:ti,ab OR "newly born":ti,ab) #20 {Halling 542-#19} #21 [mh "Heart Arrest"] #22 [mh ^"Ventricular Fibrillation"] #23 [mh Resuscitation] #24 [mh ^Asphyxia] #25 [mh ^"Asphyxia Neonatorum"] #26 [mh ^Bradycardia] #27 ((cardi* NEXT arrest*):ti,ab OR (heart NEXT arrest*):ti,ab OR asystol*:ti,ab OR "pulseless electrical activity":ti,ab OR "Advanced Cardiac Life Support":ti,ab OR "advanced life support":ti,ab OR acls:ti,ab OR resuscitat*:ti,ab OR (ventricular NEXT fibrillation*):ti,ab OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR bradycardi*:ti,ab OR asphyxia*:ti,ab) #28 {Halling 232-#27} #29 [mh Epinephrine] #30 epinephrinenephrin*:ti,ab #31 Epienalin*:ti,ab #32 {Polglase 326047-#31} #33 #20 AND #28 AND #32	
Cochrane Database of Systematic Reviews	#1 (newborn*:ti,ab OR neonat*:ti,ab OR prematur*:ti,ab OR preterm:ti,ab OR (delivery NEXT room*):ti,ab OR "low birth weight":ti,ab OR "gestational age":ti,ab OR perinat*:ti,ab OR antenat*:ti,ab OR NICU:ti,ab OR postnat*:ti,ab OR "newly born":ti,ab) #2 ((cardi* NEXT arrest*):ti,ab OR (heart NEXT arrest*):ti,ab OR asystol*:ti,ab OR "pulseless electrical activity":ti,ab OR "Advanced Cardiac Life Support":ti,ab OR "advanced life support":ti,ab OR acls:ti,ab OR resuscitat*:ti,ab OR (ventricular NEXT fibrillation*):ti,ab OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR bradycardi*:ti,ab OR asphyxia*:ti,ab) #3 epinephrinenephrin*:ti,ab	

	#4 Epienalin*:ti,ab #5 #3 OR #4 #6 #1 AND #2 AND #5	
Embase	1 newborn/de 2 "delivery room"/de 3 "gestational age"/de 4 "term birth"/de 5 "live birth"/de 6 "newborn disease"/de OR "low birth weight"/exp OR "neonatal respiratory distress syndrome"/de OR "neonatal stress"/de OR "newborn apnea"/de OR "newborn apnea attack"/de OR "newborn hypoxia"/de OR "perinatal asphyxia"/de OR "perinatal stress"/de OR prematurity/de 7 "neonatal intensive care unit"/de 8 "newborn period"/de 9 "newborn care"/exp 10 "neonatal nurse"/de OR "neonatal nurse practitioner"/de 11 neonatologist/de OR neonatology/exp 12 "perinatal care"/de 13 "birth weight"/exp 14 "lung dysplasia"/de 15 "persistent pulmonary hypertension"/de 16 "perinatal morbidity"/exp 17 "perinatal morbidity"/exp 18 "newborn death"/de 19 (newborn* OR neonat* OR prematur* OR preterm OR "delivery room*" OR "low birth weight" OR "gestational age" OR perinat* OR antenat* OR NICU OR postnat* OR "newly born"):ti,ab 20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 21 "heart arrest"/exp 22 "heart ventricle fibrillation"/de 23 resuscitation/exp 24 asphyxia/exp 25 bradycardia/de 26 ("cardi* arrest*" OR "heart arrest*" OR asystol* OR "pulseless electrical activity" OR "Advanced Cardiac Life Support" OR "advanced life support" OR acls OR resuscitat* OR "ventricular fibrillation*" OR "return of spontaneous circulation" OR ROSC OR bradycardi* OR asphyxia*):ti,ab 27 #21 OR #22 OR #23 OR #24 OR #25 OR #26 28 epinephrine/de 29 epinephrinenephrin*:ti,ab 30 Epienalin*:ti,ab 31 #28 OR #29 OR #30 32 #20 AND #27 AND #31 33 #32 NOT ((animal/exp OR nonhuman/de) NOT human/exp) 34 #33 AND ('editorial'/it OR 'letter'/it) 35 #33 NOT #34 36 #35 AND [embase]/lim	
CINAHL	S36 S34 AND S35 S35 EM 20221001- S34 S32 NOT S33 S33 S30 NOT S31 S32 S30 NOT S31	

	S31 ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human)) S30 S17 AND S25 AND S29 S29 S26 OR S27 OR S28 S28 Epienalin* S27 epinephrinenephrin* S26 (MH "Epinephrine") S25 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 S24 TI ((cardi* arrest* or heart arrest* or asystol* or pulseless electrical activity or Advanced Cardiac Life Support or advanced life support or acls or resuscitat* or ventricular fibrillation* or return of spontaneous circulation or ROSC or bradycardi* or asphyxia*)) OR AB ((cardi* arrest* or heart arrest* or asystol* or pulseless electrical activity or Advanced Cardiac Life Support or advanced life support or acls or resuscitat* or ventricular fibrillation* or return of spontaneous circulation or ROSC or bradycardi* or asphyxia*)) S23 (MH "Bradycardia") S22 (MH "Asphyxia Neonatorum") S21 (MH "Asphyxia") S20 (MH "Resuscitation+") S19 (MH "Ventricular Fibrillation") S18 (MH "Heart Arrest+") S17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 S16 TI ((newborn* or neonat* or prematur* or preterm or delivery room* or low birth weight or gestational age or perinat* or antenat* or NICU or postnat* or newly born)) OR AB ((newborn* or neonat* or prematur* or preterm or delivery room* or low birth weight or gestational age or perinat* or antenat* or NICU or postnat* or newly born)) S15 (MH "Perinatal Death") S14 (MH "Perinatal Nursing") S13 (MH "Perinatal Care") S12 (MH "Neonatologists") S11 (MH "Neonatology") OR (MH "Perinatology") S10 (MH "Neonatal Nurse Practitioners") S9 (MH "Neonatal Nursing+") S8 (MH "Intensive Care Units, Neonatal") S7 (MH "Intensive Care, Neonatal") S6 (MH "Infant, Newborn, Diseases") OR (MH "Infant, Premature, Diseases") OR (MH "Bronchopulmonary Dysplasia") OR (MH "Apnea of Prematurity") OR (MH "Respiratory Distress Syndrome+") OR (MH "Persistent Fetal Circulation Syndrome") S5 (MH "Term Birth") S4 (MH "Gestational Age") S3 (MH "Childbirth, Premature") S2 (MH "Delivery Rooms+") S1 (MH "Infant, Newborn+")	
Results identified	**Results screened full text**	**Results included**
739	41	12 (4 human infant studies, 8 animal studies)

2025 Evidence Update
NLS 5601 – Sodium Bicarbonate During Neonatal Resuscitation

Worksheet Author(s): Wyllie J, Oldham S, Mildenhall L, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 1 November 2024
Conflicts of Interest: None

PICOST:
Population: Neonates who are requiring resuscitation in the hospital
Intervention: Sodium bicarbonate administration
Comparator: No sodium bicarbonate
Outcomes:
- Survival (to hospital discharge or as defined by authors) (Critical)
- Return of spontaneous circulation (Critical)
- HIE Stage moderate-severe (term infants only) (Important)
- IVH Grades III-IV (preterm only) (Important)
- Other morbidities in early infancy (e.g., necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia) (Important)
- Neurodevelopmental outcomes (Important)

Study types: (not reported for original PICOST)
Timeframe: (Not reported for original PICOST)

Year of last full review: Last review 2005 {2006 e955}, Evidence Update 2020 {Wyckoff 2020 S185}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
2005 CoSTR: Sodium bicarbonate is discouraged during brief CPR but it may be useful during prolonged arrests after adequate ventilation is established and there is no response to other therapies. {2006 e955}
2005, 2010: The results were not presented in the ILCOR CoSTR reports because there was insufficient evidence relating to sodium bicarbonate for prolonged resuscitation. {ILCOR 2006 e989, Perlman 2010 e1319}
2020: The evidence update concluded that; "There is no new compelling evidence found for this Evidence Update to suggest any change in recommendations on use of sodium bicarbonate in newborn resuscitation, or to justify a new Systematic Review". {Wyckoff 2020 A156}
Previous Search Strategy (for 2019 Evidence Update): see appendix
New Search Strategy: see appendix
Database searched: Medline/Embase
Time Frame: January 1st 2020 to June 17th 2024
Date Search Completed: June 17th 2024
Search Results::
Identified: 206
Full text articles assessed: 30
Included: 3

Summary of Evidence Update:
No new studies were directly relevant to the PICOST. The updated literature search found the following studies that were assessed for their contribution to indirect evidence;

- One observational paediatric study that included infants and reported that sodium bicarbonate might have differential effects depending on chloride level – suggests that bicarb might be beneficial for hyperchloremic metabolic acidosis but may be harmful when chloride level is normal. {Liu 2023 473}
- One human infant observational study of infants >32 weeks and <2 months of age in a mixed NICU/PICU population – compared 4.2% vs 8.4% solutions of sodium bicarbonate. The main purpose of the study was to examine the effect of the concentration of the bicarbonate solution. {Spilios 2023 446}

- One animal study which contributes to understanding of potential method of brain injury (during a 4-hour bicarbonate infusion) in anaesthetised but not asphyxiated newborn piglets. {Chilakala 2022 729}

Relevant Guidelines or Systematic Reviews: None applicable
RCT: None applicable
Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Liu 2023 {Liu 2023 473}	**Study Type:** Retrospective cohort (single centre) observational study N = 5865 newborns and children, 2462 exposed to sodium bicarbonate *Note – population was not newborn infants needing resuscitation immediately after birth*	**Inclusion Criteria:** • Admitted to any type of PICU between 2010 and 2018 • Metabolic acidosis defined as a pH <7.35 and a bicarbonate level <22 mmol/L	**1° endpoint:** • In-hospital death Secondary outcomes: • 28-day death • length of ICU stay	Sodium bicarbonate treatment did not reduce in-hospital or 28 day mortality. In a subgroup analysis by baseline chloride level: • Chloride level <107 mmol/L: higher in-hospital mortality if treated with sodium bicarbonate than if no sodium bicarbonate (adjusted OR 2.065 (95% CI, 1.435–2.97)). Also higher 28-day mortality. • Chloride >113 mmol/L: in-hospital mortality lower if treated with sodium bicarbonate than if no sodium bicarbonate (adjusted OR 0.515 (95% CI, 0.337–0.788)). Also lower 28-day mortality and shorter stay in PICU Sodium bicarbonate treatment increased mortality in those without hyperchloremia but may have a role in treating hyperchloremic acidosis.
Spilios 2023 {Spilios 2023 446}	Retrospective observational study (chart review) N = 351 screened, 135 met inclusion criteria	• Neonates and infants gestation >32 weeks and postnatal age <2 months who received sodium bicarbonate in an intensive care unit at an academic tertiary children's hospital. • Had at least one cranial imaging examination (not specified whether ultrasound, CT or MRI for each group)	Intracranial hemorrhage (ICH)	Incidence of ICH in term neonates and infants was not significantly different in those receiving 4.2% vs 8.4% sodium bicarbonate. Major risk of confounding (e.g., newborns much more likely to receive 4.2% solution). No subgroup analysis or adjustment for indication for bicarbonate treatment. Study underpowered for the primary outcome, as only one patient in each group had an intracranial hemorrhage.

Animal Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Chilakala 2022 {Chilakala 2022 729}	**Study Type:** Non-randomized intervention study, each piglet as its own control.	**Inclusion Criteria:** 2-5 day old piglets of either sex. • Anaesthetised, not asphyxiated • Not a resuscitation model • Closed cranial window established for topical application of vasodilators or vasoconstrictors	**1° endpoint:** • Changes in pial arteriolar diameters (proxy for cerebral blood flow) • Pial arteriolar responses to vaso-active drugs	Intravenous infusion of sodium bicarbonate over 4 h caused progressive vasoconstriction of pial arterioles. Cerebrovascular function evaluated by the responses of pial arterioles to physiologically relevant vasoconstrictors and vasodilators was preserved during NaHCO3 infusion. A notable additional reduction of pial arteriolar diameters was observed during NaHCO3 infusion in the presence of vasoconstrictors.
Abbreviations: ICU; Intensive Care Unit, PICU; Pediatric Intensive Care Unit, ICH; intracranial hemorrhage, MRI; magnetic resonance imaging, CT; computed tomography, NaHCO3; sodium bicarbonate, OR; odds ratio, CI; confidence interval, h; hour(s)				

Reviewer Comments:
This PICOST was assessed using evidence worksheets in 2005 and 2010, before ILCOR adopted GRADE standards for evidence evaluation.

The ILCOR 2010 reports of the Consensus on Science of Resuscitation with Treatment Recommendations {Perlman 2010 S516, Wyllie 2010 e260} included evidence worksheets on sodium bicarbonate as appendices and while one of the two manuscripts did not mention sodium bicarbonate. The other made a statement that; "*Very rarely a narcotic antagonist (naloxone), sodium bicarbonate, or vasopressors may be useful after resuscitation"* {Wyllie 2010 e260}

The worksheets summarised that in the 1960s sodium bicarbonate had first been introduced into resuscitation practice for adults based on the logic that acidosis, common during cardiac arrest, impairs the action of epinephrine (adrenaline). The worksheet referred to evidence at the time for a lack of benefit and potential harm from using sodium bicarbonate in adult cardiac arrest. The worksheet also addressed evidence for paradoxical worsening of intracellular acidosis in the presence of hypercarbia, the potential to worsen, not improve myocardial function and cerebral blood flow.

The worksheets noted that in infants at birth, the physiology differs, and physiological experiments in asphyxiated newborn animals found that concurrent administration of an alkalinising agent and glucose could prolong or restart the 'gasping' phase of asphyxia.

- Animals (newborn lambs or macaque monkeys) were asphyxiated to apnea and then infusions of alkali or glucose or both were commenced after asphyxia but before (or without) commencing assisted ventilation or chest compressions {Adamsons 1963 679, Adamsons 1964 807, Dawes 1964 801, Dawes 1963 167, Dawes 1963 43}
- The studies utilised a mild to moderate (not severe) model of asphyxia and examined prolongation or restoration of gasping, or how long blood pressure and pH were sustained, rather than addressing ROSC in asystolic animals.

- Results were generally obtained using a combination of sodium carbonate and glucose, or Tris-hydroxymethylaminomethane (Tris) buffer plus glucose, with alkali and glucose each being ineffective as monotherapy. The studies that utilized sodium bicarbonate found that much higher infusion volumes were needed.
- The prolongation of gasping was relatively short (13% increase in lambs, 24% increase in monkeys).
- The infusion volumes were large enough as to be a potential form of confounding, since control animals generally received no infusion, so the temporary expansion of intravascular volume may have contributed to the effects.
- Overall, these studies do not directly address any of the critical or important outcomes of the PICOST question, and if anything, in the setting of mild asphyxia, indicate ineffectiveness of sodium bicarbonate alone and compared to other alkalinising agents for restoring or maintaining gasping activity.
- They do not address the circumstance of the previous treatment recommendation (after prolonged arrest after adequate ventilation is established and there is no response to other therapies).

In the 2010 worksheets, a single randomized, controlled trial in asphyxiated newborn infants was identified. {Lokesh 2004 219} This RCT (N=55) compared sodium bicarbonate (1.8mmol/kg) vs 5% glucose (both infused at ~ 4 mL/kg over 3-5 min) and found no difference in survival or neurological abnormality (or the combination of either) at discharge. No further randomized controlled trials have been published since then. A Cochrane systematic review in 2006, which has not been updated since, confirmed the solitary status of this study. {Beveridge 2006 Cd004864}

In 2015 this question was not reviewed due to a conclusion that there would be insufficient evidence. The last formal evidence update was undertaken in 2019 for the 2020 CoSTR using a search devised by a university librarian and based on previous worksheet searches. The PICOST was revised at the time for compatibility with contemporary NLS Task Force PICOST questions. Because of the paucity of eligible human infant studies, evidence from animal studies was included.

In the 2020 Evidence Update used a search devised by a university librarian and based on previous worksheet searches. The PICOST was revised at the time for compatibility with contemporary NLS Task Force PICOST questions. Because of the paucity of eligible human infant studies, evidence from animal studies was included.

This evidence update concluded that: "*Sodium bicarbonate has historically been used during cardiopulmonary resuscitation based upon animal evidence but has been removed from most regional guidelines. Although serum acid base status may improve with intravenous sodium bicarbonate, there is evidence that rapid infusion of sodium bicarbonate may cause a paradoxical intracellular acidosis, cardiac impairment, and variations in cerebral blood flow, {Graf 1985 754, van Alfen-van der Velden 2006 122} and some historical studies have shown an association between intraventricular hemorrhage in preterm neonates and use of sodium bicarbonate for correction of base deficit during intensive care. {Funato 1992 614, Papile 1978 834}*

The observational trials identified in this Evidence Update provide indirect evidence suggesting that there may be detrimental physiological effects and clinical outcomes associated with intravenous sodium bicarbonate infusion in different neonatal and pediatric populations. {Buckley 2013 668, Glatstein 2011 463, Katheria 2017 518, Mok 2016 534, Moler 2011 141} An observational study of neonatal intensive care found an association of sodium bicarbonate administration with intraventricular hemorrhage, {Szpecht 2016 1399} and an additional study in infants undergoing surgery for hypoplastic left heart syndrome found an association with periventricular leukomalacia, {Jalali 2012 5931} but neither could establish whether the sodium bicarbonate was causative.

A single randomized, controlled trial of sodium bicarbonate therapy in a newborn piglet model of hypoxia-reoxygenation demonstrated a reduction in cortical reactive oxygen species, specifically hydrogen peroxide in the sodium bicarbonate treated group. {Liu 2012 e39081} This small animal study is certainly not sufficient evidence to change recommendations, but it is a reminder that the pathophysiology of hypoxic-ischemic injury is complex and highlights the importance of ongoing intermittent evidence updates in this area of resuscitation".

In this 2024 Evidence Update we again considered both animal and human newborn studies and found **no new evidence** to support the use of sodium bicarbonate in neonatal resuscitation, although the study in piglets suggests a possible mechanism of harm in a 2-5 day old, anaesthetised, non-asphyxiated model, particularly in the setting of prior administration of vasoconstrictors. {Chilakala 2022 729} One study also suggested that benefits of sodium bicarbonate treatment for paediatric acidosis in intensive care may depend on context, with possible benefit in the setting of hyperchloremia but harm if the chloride level is normal (as will usually be the case in newborn infants). {Liu 2023 473} The study examining 4.2% vs 8.4% solutions is underpowered, at risk of confounding by indication and inconclusive. {Spilios 2023 446}

Conclusions:

- The overall evidence from the current and the previous evidence update is insufficient to justify a new systematic review.
- As in 2005, 2010, 2015 and 2020, there is insufficient evidence to make a recommendation in relation to treatment with sodium bicarbonate during resuscitation in neonates.
- **The previous treatment recommendation (2005)** was not supported by a systematic review using contemporary ILCOR methods of evidence appraisal. The conditions suggested in the previous treatment recommendation for the use of sodium bicarbonate (after adequate ventilation is established and there is no response to other therapies) are rare and unexpected in human infants needing resuscitation immediately after birth, meaning that human infant trials would be difficult to conduct and might take many years to complete.
- **Animal studies in contemporary models of asphyxia requiring resuscitation immediately after birth are supported,** in order to define benefits and harms of sodium bicarbonate (or other alkalinizing agent) treatment.
- **If an updated systematic review is undertaken in the future, the evidence update authors suggest revising the PICOST as follows:**

  Population: Newborn infants requiring resuscitation immediately after birth
  Intervention: sodium bicarbonate (or other alkalinizing agent) administration
  Comparator: no bicarbonate (or other alkalinizing agent)
  Outcomes:
    - Survival (to hospital discharge or as defined by authors) (critical)
    - Return of spontaneous circulation (critical)
    - HIE Stage moderate-severe (term infants only) (important)
    - IVH Grades III-IV (preterm only) (important)
    - Other morbidities in early infancy (e.g., necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia)i(Important)
    - Neurodevelopmental outcomes (important)

Task Force Insights: As a result, the Task Force makes a statement as follows:
Although a treatment recommendation related to the use of sodium bicarbonate during prolonged arrests was included in previous consensus statements (2005 – 2020), this treatment recommendation can no longer be supported. Based on current methods of evaluating the certainty of evidence, the Task Force has concluded there is neither direct nor indirect evidence to inform a treatment recommendation. As a result, the previous (2005) treatment recommendation has been withdrawn and will be reconsidered if new evidence becomes available.

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Appendix A: Previous search strategy (2019 evidence update)

The following search strategy for updating NRP 606 was developed for the EMBASE.com platform, which includes both the Medline and Embase bibliographic databases (See Table). The approach includes identifying the newborn population, then refining with limits for publication types (conference abstracts were excluded) and publication dates (from last ILCOR search). Then the intervention (sodium bicarbonate) was specified and combined with the above search.

A low number of records was identified by this approach, so no further filtering of records was necessary. This batch of records was split into two groups, depending on whether they included any terms that indicated animal studies:

- _'human' set; and
- _'animal' set.

Explanation of search strategy approach for updating NRP 606 #	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
#1	'newborn'/exp 'infant'/exp neonat* in title or abstract newborn$ in title or abstract baby in title or abstract babies in title or abstract infant$ in title or abstract child in title or abstract birth in title or abstract	Population – Newborns Newborns should be the focus of the article, so all newborn terms (neonates; newborns; babies; infants; child) must appear in either the title or the abstract, or the article must be tagged with EMTREE terms for newborn or infant.
#2	#1 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de)	Exclude publication types Conference abstracts and other ineligible study types were removed here.
#3	#2 AND [2009-2020]/py	Date limit The last ILCOR search was run to some point in 2008, so the publication date range was limited to 2008 or later.

		This search string can be combined with intervention strings or other population strings to produce a final number of records.
#4	sodium bicarbonate in title or abstract or keyword nahco in title or abstract or keyword 'na hco3' in title or abstract or keyword 'na hco' in title or abstract or keyword ‘bicarbonate' in title or abstract or keyword	Intervention – sodium bicarbonate Sodium bicarbonate must appear in the title, abstract or the list of keywords allocated by the study authors.
#5	#3 AND #4	Newborn + sodium bicarbonate Records for use of sodium bicarbonate in newborns. This string identified the checklist studies.
#6	#5 NOT ('animal'/exp NOT 'human'/exp OR 'nonhuman'/exp OR 'rodent'/exp OR 'animal experiment'/exp OR 'experimental animal'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR dog$:ti,ab OR pig$:ti,ab OR porcine:ti,ab OR swine:ti,ab OR chick$:ti,ab)	Newborn + sodium bicarbonate: Human studies The search results were stratified using this filter for animal studies.

Appendix B: New Search strategy: 2024 Evidence Update

Sources searched	**Search strategy**	**Search time frame**
Ovid Medline	Query'newborn'/exp AND 'infant'/exp NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de) AND [2020-2024]/py AND ('bicarbonate' OR 'nahco' OR 'na hco3' OR 'na hco' OR 'sodium bicarbonate')	January 1st 2020 to June 17th 2024
Results identified	**Results screened full text**	**Results included**
206	30	3

2025 Evidence Update
NLS 5650 – Blood Volume Expansion During Neonatal Resuscitation

Worksheet Author(s): Wyckoff, MH and Nakwa FL
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 8 December 2024
Conflicts of Interest: none

PICOST:
Population: Term and preterm newborn infants who receive resuscitation immediately after birth and who have a heart rate <60 beats per minute after chest compressions and epinephrine and/or suspected hypovolemia based on history and examination
Intervention: Blood volume expansion with blood (red cells or whole blood), colloid (e.g. albumin, plasma), crystalloid (e.g. 0.9% sodium chloride) or other solution
Comparators: No blood volume expansion
Outcomes:
Critical
- Survival (to any stage)
- Neurodevelopmental outcomes (with age-appropriate, validated tools)

Important
- Time to return of spontaneous circulation (or heart rate >60 beats per minute)
- Subsequent use of vasopressor infusion(s)
- Blood pressure at specified time by the study authors
- Pulmonary edema
- Serious neonatal morbidity (including IVH, NEC, PPHN, HIE, pulmonary hemorrhage)

Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), and case series were eligible for inclusion. Manikin, computer model and animal studies were eligible for inclusion. Conference abstracts and unpublished studies (e.g. trial protocols) were excluded.
Timeframe: Literature search updated from 5/1/2020 through 7/2/24

Year of last full review: The last full review for this PICOST was the 2010 ILCOR CoSTR. {Perlman 2010 S516} This was before ILCOR adopted use of the GRADE evidence evaluation system. The level of evidence (LOE) in 2010 was considered LOE 4 which meant that the data came from historic non-randomized cohort or case-control studies.

ILCOR 2010 CoSTR: {Perlman 2010 S516}
<u>Consensus on Science</u>
Multiple case series support the use of volume expansion in babies with a history of blood loss, including some who are unresponsive to chest compressions (LOE 4 {Kirkman 1959 92}). Many with pallor and tachycardia responded to volume expansion without having received chest compressions. In the absence of a history of blood loss there is limited evidence of benefit from administration of volume during resuscitation unresponsive to chest compressions/epinephrine (LOE 4 {Wyckoff 2005 950}) and some suggestion of potential harm from animal studies (LOE 5 {Mayock 2004 395, Wyckoff 2007 415})
<u>Treatment Recommendation</u>
Early volume replacement with crystalloid or red cells is indicated for babies with blood loss who are not responding to resuscitation. There is insufficient evidence to support the routine use of volume administration in the infant with no blood loss who is refractory to ventilation, chest compressions, and epinephrine. Because blood loss may be occult, a trial of volume administration may be considered in babies who do not respond to resuscitation.

The neonatal life support volume resuscitation treatment recommendation was reaffirmed after an evidence update in 2020 {Wyckoff 2020 S185} that included 6 additional studies since the review in 2010. {Conway-Orgel 2010 241, Finn 2017 163, Keir 2016 201, Keir 2019 632, Mendler 2015 73, Shalish 2017 328}

Current Search Strategy (for an existing PICOST) – see appendix

Database searched: Medline, Embase, Cochrane

Time Frame: (existing PICOST) – updated from end of last search January 1, 2021.
Date Search Completed: Jul 2, 2024

Search Results:
Identified: 242
Full text review: 2
Included: 1

Summary of Evidence Update:

Sankaran et al. published a narrative review of the causes and consequences of acute fetal blood loss and available evidence on volume replacement during neonatal resuscitation of asphyxiated neonates. {Sankaran 2022 1484} The review included some previously unpublished animal data that examined the physiologic responses of a well described fetal lamb model of asphyxia when acute volume loss is added. Acute blood loss hastened bradycardia, hypotension, left carotid arterial blood flow, and cardiac arrest in the hypovolemic compared to normovolemic lambs. The mean left carotid arterial blood flow decreased drastically at the end of exsanguination although the heart rate and blood pressure did not significantly change when compared to baseline.

Relevant Guidelines or Systematic Reviews: None applicable

RCT: None applicable

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Sankaran 2022 {Sankaran 2022 1484}	Design: non-randomized asphyxiated fetal lamb study Aim: To validate a lamb hypovolemic asphyxial cardiac arrest model, hemodynamics during asphyxia with cord occlusion alone vs asphyxia plus acute volume loss were compared Study Size: N=5	2 fetal lambs were asphyxiated via cord occlusion. 3 lambs had exsanguination (acute volume loss via removal of 45 mL/kg of blood) in addition to asphyxia	Acute blood loss hastened bradycardia, hypotension, left carotid arterial blood flow, and cardiac arrest in the hypovolemic compared to normovolemic lambs. The mean left carotid arterial blood flow decreased drastically (30.5 ± 3.7 to 10.6 ± 2.3 mL/kg/min) at the end of exsanguination although the HR and BP did not significantly change with exsanguination when compared to baseline.	These findings suggest that fetal HR may not be a reliable measure of moderate fetal volume loss.

Reviewer Comments:
- There were insufficient new clinical studies identified to warrant a systematic review but since the older papers have never officially been evaluated using GRADE, this should be considered in the coming years.
- The information from the one new publication identified in the evidence update is insufficient to alter the existing recommendation but the treatment recommendation language has been updated to reflect current standards
- This evidence update reaffirms the prior 2010 suggestion:

    - Early volume replacement with crystalloid or packed red blood cells is indicated for newborn infants with blood loss who are not responding to resuscitation (strong recommendation, good practice statement).
    - There is insufficient evidence to support the routine use of volume administration in the newborn infant with no blood loss who is refractory to ventilation, chest compressions, and epinephrine. Because blood loss may be occult, a trial of volume administration may be considered in newborn infants who do not respond to resuscitation (good practice statement).
- Knowledge gaps include risks and benefits for infusing volume during resuscitation in situations of occult versus obvious blood and differences for various gestational ages.

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Appendix – search strategy

Sources searched	Search strategy	Search time frame
PubMed	14 #4 AND #8 AND #13 from 2020/1/1 - 2024/7/2 ((("infant, newborn"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("neonat*"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("newborn"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication])) AND 2020/01/01:2024/07/02[Date - Publication] AND ((("resuscitation"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("cardiopulmonary resuscitation"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("resuscitation"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication])) AND 2020/01/01:2024/07/02[Date - Publication]) AND ((("blood volume"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("fluid therapy"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("blood substitutes"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("fluid bolus"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication])) AND 2020/01/01:2024/07/02[Date - Publication])) AND (2020/1/1:2024/7/2[pdat])	January 1, 2021 to July 2, 2024

	13 #9 OR #10 OR #11 OR #12 from 2020/1/1 - 2024/7/2 (("blood volume"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("fluid therapy"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("blood substitutes"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("fluid bolus"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication])) AND (2020/1/1:2024/7/2[pdat]) 12 fluid bolus [tiab] from 2020/1/1 - 2024/7/2 ("fluid bolus"[Title/Abstract]) AND (2020/1/1:2024/7/2[pdat]) 11 blood substitutes [mh] from 2020/1/1 - 2024/7/2 ("blood substitutes"[MeSH Terms]) AND (2020/1/1:2024/7/2[pdat]) 10 fluid therapy [mh] from 2020/1/1 - 2024/7/2 ("fluid therapy"[MeSH Terms]) AND (2020/1/1:2024/7/2[pdat]) 9 volume, blood [mh] from 2020/1/1 - 2024/7/2 ("blood volume"[MeSH Terms]) AND (2020/1/1:2024/7/2[pdat]) 8 #5 OR #6 OR #7 from 2020/1/1 - 2024/7/2 (("resuscitation"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("cardiopulmonary resuscitation"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("resuscitation"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication])) AND (2020/1/1:2024/7/2[pdat]) 7 resuscitation [tiab] from 2020/1/1 - 2024/7/2 ("resuscitation"[Title/Abstract]) AND (2020/1/1:2024/7/2[pdat]) 6 cardiopulmonary resuscitation [mh] from 2020/1/1 - 2024/7/2 ("cardiopulmonary resuscitation"[MeSH Terms]) AND (2020/1/1:2024/7/2[pdat]) 5 resuscitation [mh] from 2020/1/1 - 2024/7/2 ("resuscitation"[MeSH Terms]) AND (2020/1/1:2024/7/2[pdat]) 4 #1 OR #2 OR #3 from 2020/1/1 - 2024/7/2 (("infant, newborn"[MeSH Terms] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("neonat*"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication]) OR ("newborn"[Title/Abstract] AND 2020/01/01:2024/07/02[Date - Publication])) AND (2020/1/1:2024/7/2[pdat]) 3 newborn [tiab] from 2020/1/1 - 2024/7/2 ("newborn"[Title/Abstract]) AND (2020/1/1:2024/7/2[pdat]) 2 neonat* [tiab] from 2020/1/1 - 2024/7/2 ("neonat*"[Title/Abstract]) AND (2020/1/1:2024/7/2[pdat]) 1 Infant, Newborn [MH] from 2020/1/1 - 2024/7/2 ("infant, newborn"[MeSH Terms]) AND (2020/1/1:2024/7/2[pdat])	
EMBASE	#20 (('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn') AND (('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')) AND (('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti) AND [2020-2024]/py AND ([newborn]/lim OR [infant]/lim) AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND ([medline]/lim OR [pubmed-not-medline]/lim) #19 (('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn') AND (('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')) AND	

	(('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti) AND [2020-2024]/py AND ([newborn]/lim OR [infant]/lim) AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim	
	#18 (('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn') AND (('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')) AND (('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti) AND [2020-2024]/py AND ([newborn]/lim OR [infant]/lim) AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim)	
	#17 (('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn') AND (('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')) AND (('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2020-2024]/py AND ([newborn]/lim OR [infant]/lim)	
	#16 (('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn') AND (('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')) AND (('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2020-2024]/py	
	#15 (('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn') AND (('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')) AND (('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti) AND ([article]/lim OR [article in press]/lim OR [review]/lim)	
	#14 (('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn') AND (('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')) AND (('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti)	
	#13 ('resuscitation'/exp OR resuscitation) OR ('cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation') OR 'resuscitation':ab,ti	
	#12 ('blood volume'/exp OR 'blood volume') OR (('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy)) OR ('blood substitute'/exp OR 'blood substitute') OR ('fluid bolus therapy'/exp OR 'fluid bolus therapy')	

	#11 'fluid bolus therapy'/exp OR 'fluid bolus therapy' #10 'blood substitute'/exp OR 'blood substitute' #9 ('fluid'/exp OR fluid) AND ('therapy'/exp OR therapy) #8 'blood volume'/exp OR 'blood volume' #7 'resuscitation':ab,ti #6 'cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation' #5 'resuscitation'/exp OR resuscitation #4 ('infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))) OR neonat* OR 'newborn' #3 'newborn' #2 neonat* #1 'infant, newborn'/exp OR 'infant, newborn' OR (('infant,'/exp OR infant,) AND ('newborn'/exp OR newborn))	
Results identified	**Results screened full text**	**Results included**
242	2	1

2025 Evidence Update
NLS 5652 – Intraosseous vs. Intravenous Administration of Drugs during Cardiac Arrest

Worksheet Author(s): de Almeida MF, Guinsburg R, Kawakami MD, Thio M, Trevisanuto D, Yamada NK, Weiner GM, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 24 October 2024
Conflicts of Interest: None

PICOST

Population: Newborn infants in any setting (in hospital or out-of-hospital) with cardiac arrest (includes severe bradycardia and inadequate perfusion requiring chest compressions)

Intervention: Placement of an IO cannula with drug administration through this IO site during cardiac arrest

Comparator: Placement of an IV cannula (umbilical vein in newborn infants) and drug administration through this IV during cardiac arrest

Outcomes:

- Death during event, within 24 hours and before hospital discharge (critical)
- Long-term neurodevelopmental outcomes (critical)
- ROSC: any signs of cardiac output with heart rate 60/min or greater, and time to ROSC (critical)
- Brain injury (HIE Stage 2-3 Sarnat) {Sarnat 1976 696} [term only] (critical)
- Intraventricular hemorrhage Grades 3-4 {Papile 1978 }, periventricular leukomalacia [preterm only] (critical)
- Time to secure access (important)
- Morbidity related to IO (osteomyelitis, fracture, epiphyseal plate injury, compartment syndrome) or to IV (extravasation, embolic phenomenon, phlebitis) (important)

Study design:

– Inclusion criteria: Randomized trials, non-RCTs, and observational studies (cohort studies and case-control studies) comparing IO with IV administration of drugs; randomized trials assessing the effect of specific drugs (e.g., epinephrine [adrenaline]) in subgroups related to IO versus IV administration; studies assessing cost-effectiveness for a descriptive summary

– Exclusion criteria: Ecological studies, case series, case reports, reviews, abstracts, editorials, comments, letters to the editor, or unpublished studies

Timeframe: All years and languages were included if there was an English abstract. MEDLINE (Ovid interface), Embase (Ovid interface), and Cochrane Central Register of Controlled Trials literature search, as well as ongoing trials on International Clinical Trials Registry Platform.

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

Year of last full review*:* 2020 {Foglia 2020 e20201449}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST {Wyckoff 2020 S185}

Consensus on Science:

Although small clinical series and case reports suggest that medications and fluids can be successfully delivered by the IO route during neonatal resuscitation {Ellemunter 1999 , Wagner 2018 }, case series also report complications with IO catheter insertion or use. {Carreras-González 2012 , Ellemunter 1999 , Katz 1994 , Oesterlie 2014 , Suominen 2015 , Vidal 1993 } To determine if IO or intravascular access is more effective for neonatal resuscitation, evidence from neonatal literature was sought and considered by the NLS Task Force as part of a joint effort with the Adult Life Support and Pediatric Life Support Task Forces. No studies meeting the a priori inclusion criteria were found for newborn infants, precluding meta-analysis in this population. A draft CoSTR was developed that reflected the lack of data and was posted on the ILCOR website; the draft was viewed more than 2600 times, and more than 50 comments were posted. The majority were supportive of the conclusions. No evidence was identified for newborn infants comparing use of IO and IV cannulas for drug administration in any setting (in-hospital or out-of-hospital) for any prespecified outcome of the review. In 2010, the NLS Task Force said that temporary IO access to provide fluids and medications to resuscitate critically ill neonates may be indicated after unsuccessful attempts to establish IV vascular access or when caregivers are skilled at securing IO access. The 2020 SysRev identified reports of serious complications after use of IO access in neonates.{Carreras-González 2012 , Ellemunter 1999 , Katz 1994 , Oesterlie 2014 , Suominen 2015 , Vidal 1993 } As a result, the

2020 treatment recommendations are stronger in support of the umbilical venous route as the primary route for vascular access during delivery room resuscitation but continue to allow that in some circumstances the IO route is acceptable.

Treatment Recommendation:

We suggest umbilical venous catheterization as the primary method of vascular access during newborn infant resuscitation in the delivery room. If umbilical venous access is not feasible, the intraosseous route is a reasonable alternative for vascular access during newborn resuscitation (weak recommendation, very low-certainty evidence). Outside the delivery room setting, we suggest that either umbilical venous access or the IO route may be used to administer fluids and medications during newborn resuscitation (weak recommendation, very low-certainty evidence). The actual route used may depend on local availability of equipment, training, and experience.

Search strategy for the evidence update review: Dec 1st, 2019, to July 15, 2024 0- see appendix

Database searched: Ovid MEDLINE ALL, Embase (via Embase.com), Cochrane CENTRAL (via the Cochrane Library)

Time Frame: (existing PICOST) – 1946 until December 17, 2019. Rerun from December 2019 to July 15, 2024
Date Search Completed: July 15, 2024
Search Results:
Identified: 35
Full text articles assessed: 10
Included: 2 studies included {Mileder 571285, Schwindt 952632}. Searching NLS monthly updated literature, we found 6 more references; 6 full texts accessed for eligibility; one study was included {Joerck 853}. Therefore, this evidence update summarizes the data of 3 observational studies. {Joerck 2023 853, Mileder 2020 571285, Schwindt 2022 952632}

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews: None identified

RCT: None identified

Nonrandomized Trials, Observational Studies: 3

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results**	**Summary/Conclusion Comment(s)**
	Study Type:		**1st endpoint**	
Joerck 2923 Australia {Joerck 2023 853}	Cohort retrospective review of prospectively collected data before interhospital transfer service of 102 newborns with IO access from 2006 to 2020	**Inclusion Criteria:** 102 newborns with IO inserted to receive volume expansion and/or medications Mean GA 39±3 wk (range 24-44) Median weight 3.25 kg (IQR 2.71-3.78) Median age 10 days **Setting:** 53 in ED, 7 in prehospital setting, 13 in the birthing suite 19/102 (19%) newborns received resuscitation medications and 54/102 (53%) received fluid bolus via IO	**Death before hospital discharge:** 19/102 (19%) **Success IO access at 1st attempt:** 88 (86.2%); total number of IO attempts not reported **IO site:** not reported in the neonates **Morbidity related to IO:** 11/102 (11%): - subperiosteal infusion 6 (6%) - tibial fracture in 1 (1%), in a 9-day-old newborns	**Authors conclusion:** Early insertion of IO in a critically unwell NB facilitates early volume expansion and delivery of resuscitation drugs. Complications of IO in this cohort is similar to that previously reported in the literature. This large observational study showed that: - IO insertion was feasible in most emergency situations in pre-transferred newborns. - The high mortality of this cohort may be due to the diagnoses preceding IO access. - Serious morbidities related to IO were reported

Abbreviations: IO; intraosseous				

Mileder 2020 Austria {Mileder 2020 571285}	Questionnaire-based survey of IO use followed by retrospective electronic patient chart review of 12 NB from Apr/2015 to Apr/2020 in a single center	12 NB with 15 IO access attempts: 8 term, 3 late PT, 1 former extremely PT 5 NB received adrenaline, and 3 NB received fluid and/or blood **Setting:** 10 in neonatal resuscitation suite and 2 in NICU (the extreme PT NB had the IO placed at 121 days of age). Team: 8/9 physicians (88.9%) previously trained IO access with a battery device using simulation-based method	**Death before hospital discharge:** 8/12 (67%); 5 died within 24h **Successful IO access:** 9/12 (75%) **Successful IO access at 1st attempt:** 6/12 (50%); at 2nd attempt: 3/12 (25%) **IO site:** 12/12 (100%) with proximal tibial access **Morbidity related to IO:** 3/9 patients with successful IO access: extravasation, local skin reactions and/or local soft tissue infections	Authors conclusion: IO access was rarely attempted during neonatal resuscitation. Despite offering regular simulation-based training, our success rate was lower than reported by other groups. Short-term complications were reported in a third of patients, no severe complications occurred. This small study with few cases shows the rare use of IO in DR and the presence of complications
Schwindt 2022 Germany {Schwindt 952632}	Prospective surveillance to investigate safety and frequency of IO access from Jul/2017 to Jun/2019 nationwide	161 NB (145 term and 16 PT) with 206 IO access attempts 98/161 (61%) had perinatal asphyxia 92/161 (57%) required CPR Mean GA 39+0 wk (range 25+6 to 42+0) Postnatal age at IO attempt: 113 NB <24h and 48 NB 24h-28 days Medication administered out of 146 successful access: crystalloids in 139 (95%) and adrenaline in 81 (56%) **Setting:** reporting hospital (n=102) and out of reporting hospital (n=59)	**Death before hospital discharge:** 58/161 (36%) **Successful IO access:** 146/161 (91%) **Success at 1st attempt:** 109/161 (68%); at 2nd attempt: 33/161 (20%); at 3rd attempt: 3/161 (2%); at 4th attempt: 1/161 (<1%) In 71 infants with successful IO access, the estimated duration of placement was < 3 minutes **IO site:** Among 202 IO attempts with information available, 192 (95%) in the proximal tibia **Morbidities related to IO-access:** 55/155 (35%) - Minor: 46/155 (30%) - misplacement in soft tissue and mild extravasation (n=44); healing deficiency (1); local swelling (1) - Severe: 9/155 (6%) - necrosis (n=3); peripheral perfusion problems (2); fracture (1), broken IO needle (1); osteomyelitis (1); soft tissue infection (1) Two misplacements in soft tissue and 1 extravasation in 3/15 (20%) PT	**Authors conclusion:** IO access in NB was feasible and safe. IO access is an important alternative for vascular access in NB - This is the largest observational study regarding IO insertion in NB. - IO access was successful in 68% at 1st attempt in NB, most of them term infants - High mortality in this cohort may be due to the diagnoses preceding IO access (57% of this cohort required CPR) - Serious morbidities related to IO were reported
Abbreviations: CPR; cardiopulmonary resuscitation, DR; delivery room, ED; emergency department, GA; gestational age, IO; intraosseous, IQR; interquartile range, NB; newborn, NICU; neonatal intensive care unit, PT; preterm, wk; weeks				

Reviewer Comments:

This update of the evidence found 3 observational studies {Mileder 571285, Schwindt 952632}; {Joerck 853} that were narratively summarized because there is no comparison between neonates who received IO vs intravenous (umbilical vein) administration of drugs (Table).

Table: Characteristics of the three studies that reported any outcome of intraosseous insertion in newborn infants in any setting (in hospital or out-of-hospital) with cardiac arrest (includes severe bradycardia and inadequate perfusion requiring chest compressions), according to patients, intervention, control, and outcomes

	Patients	**Intervention**	**Control**	**Outcomes**						
	NB infants in any setting with cardiac arrest	Drug administration through IO site during cardiac arrest	Drug administration through umbilical vein catheter during cardiac arrest	Death during event, within 24h and before hospital discharge	Long-term ND outcomes	ROSC and time to ROSC	HIE 2/3 [term only]	IVH 3/4 and PVL [PT only]	Time to secure access	Morbidity related to IO
Joerck Australia 2023	14 with cardiac arrest among 102 NB included	YES	NO	YES	NO	NO	NO	NO	NO	YES
Mileder Austria 2020	12 with cardiac arrest among 12 NB included	YES	NO	YES	NO	NO	NO	NO	NO	YES
Schwindt Germany 2022	92 with cardiac arrest among 161 NB included	YES	NO	YES	NO	NO	NO	NO	YES	YES

Abbreviations: CPR; cardiopulmonary resuscitation, HIE; hypoxic-ischemic encephalopathy grades 2 or 3, IO; Intraosseous, IVH 3-4; intraventricular hemorrhage grades 3-4, NB; newborn, ND; neurodevelopment, PVL periventricular leukomalacia, ROSC; return of spontaneous circulation (any signs of cardiac output with heart rate 60/min or greater).

The 3 studies included in the EvUp provide useful data regarding the success at 1st attempt of IO access: 86% in 102 pre-transferred newborns over 15 years, {Joerck 2023 853} 50% in 12 neonates reported over 5 years {Mileder 2020 571285} and 68% in 161 newborns {Schwindt 952632} with several emergency clinical conditions in a nationwide report over two years, including the need for resuscitation.

Only 23 patients {Joerck 2023 853, Mileder 2020 571285} received IO administration of drugs in the delivery room, and 113 neonates received volume expansion or medications <24h after birth {Schwindt 952632}, but outcomes are not reported. Regarding the IO site, two studies {Mileder 2020 571285, Schwindt 2022 952632} reported that proximal tibia access was predominant: 100% of the 12 patients in the Austrian study {Mileder 2020 571285) and 192 (95%) of 202 IO attempts in the German study.{Schwindt 952632}

This EvUp also found important morbidities related to IO access, varying from 10.8% {Joerck 853} to 35% {Schwindt 952632} such as extravasation, necrosis, compartment syndrome, subperiosteal infusion, tibial fracture, broken IO needle, osteomyelitis, and soft tissue infection. These complications were the same complications reported in the previous ILCOR consensus on science. {Wyckoff 2020 S185} The high mortality before discharge noted in the studies {Joerck 853, Mileder 571285, Schwindt 952632} was expected due to the diagnoses preceding IO access and was not due to complications of the IO procedure. Neither the original review {Granfeldt 2020 150} nor this evidence update has yielded studies reporting on success rates for umbilical vein catheter placement in the resuscitation setting.

The evidence retrieved from the new studies is not sufficient to change the current recommendation {Wyckoff 2020 S185} :
"We suggest umbilical venous catheterization as the primary method of vascular access during newborn infant resuscitation in the delivery room. If umbilical venous access is not feasible, the intraosseous route is a reasonable alternative for vascular access during newborn resuscitation (weak recommendation, very low-certainty evidence). Outside the delivery room setting, we suggest that either umbilical venous access or the IO route may be used to administer fluids and medications during newborn resuscitation (weak recommendation, very low-certainty evidence). The actual route used may depend on local availability of equipment, training, and experience."

Therefore, the evidence from the new studies is not sufficient to elicit a new systematic or scoping review.

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Appendix – Search Strategy for this Evidence Update

Sources searched	**Search strategy** Ovid MEDLINE ALL, Embase (via Embase.com), Cochrane CENTRAL (via the Cochrane Library)	**Search time frame**
Ovid/Medline	(exp Heart Arrest/ OR Ventricular Fibrillation/ OR Resuscitation/ OR Heart Massage/ OR exp Cardiopulmonary Resuscitation/ OR cardi* arrest*.tw,kf. OR heart arrest*.tw,kf. OR OHCA.tw,kf. OR IHCA.tw,kf. OR CPR.tw,kf. OR advanced cardiac life support.tw,kf. OR ACLS.tw,kf. OR basic life support.tw,kf. OR BLS.tw,kf. OR asystol*.tw,kf. OR pulseless electrical activity.tw,kf. OR pulseless ventricular tachycardia.tw,kf. OR (return of circulation or return of spontaneous circulation or ROSC).tw,kf. OR resuscitat*.tw,kf. OR ventricular	Dec 1st, 2019, to July 15, 2024

	fibrillation*.tw,kf. OR chest compression*.tw,kf.) AND (((Infusions, Intraosseous/ OR Intraosseous.tw,kf. OR Intra-osseous.tw,kf.) AND (Infusions, Intravenous/ OR Intravenous.tw,kf. OR Intra-venous.tw,kf. OR Umbilical Veins/ OR (umbilical vein or umbilical veins or umbilical venous).tw,kf. OR (venous adj3 catheter*).tw,kf. OR (vascular adj3 catheter*).tw,kf. OR catheterization/ or catheterization, central venous/ or catheterization, peripheral/ OR catheters/ or catheters, indwelling/ or exp vascular access devices/ OR central venous.tw,kf. OR vascular access.tw,kf.)) OR (IO adj15 IV).tw,kf.) AND (newborn*.tw. OR "new born*".tw. OR exp "Infant, Newborn"/ OR infant*.tw. OR neonat*.tw. OR neo-nat*.tw. OR "newly born".tw. OR premature.tw. OR prematurity.tw. OR preterm.tw. OR "pre term".tw. OR exp "Premature Birth"/ OR "low birth weight".tw. OR "low birthweight".tw. OR VLBW.tw. OR LBW.tw. OR postnatal.tw. OR post-natal.tw. OR "golden hour".tw. OR exp "Perinatal Care"/ OR exp "Intensive Care, Neonatal"/ OR exp "Intensive Care Units, Neonatal"/ OR exp "Neonatal Nursing"/ OR NICU.tw.) NOT (animals/ not humans/) NOT ("case reports".pt. OR comment.pt. OR editorial.pt. OR letter.pt.) AND (201912* or 2020* or 2021* or 2022* or 2023* or 2024*).dt.	
EMBASE	(resuscitation/exp OR 'heart arrest'/exp OR 'heart ventricle fibrillation'/de OR (Resuscitat* OR CPR OR 'code blue'):ti,ab OR 'cardi* arrest*':ti,ab OR 'heart arrest*':ti,ab OR 'advanced cardi* life support':ti,ab OR ACLS:ti,ab OR 'basic life support':ti,ab OR BLS:ti,ab OR OHCA:ti,ab OR IHCA:ti,ab OR asystol*:ti,ab OR 'pulseless electrical activity':ti,ab OR 'pulseless ventricular tachycardia':ti,ab OR ('return of circulation' OR 'return of spontaneous circulation' OR ROSC):ti,ab OR 'ventricular fibrillation*':ti,ab OR 'chest compression*':ti,ab) AND (((('intraosseous drug administration'/exp OR 'intraosseous infusion system'/de OR (Intraosseous OR Intra-osseous):ti,ab OR ((bone OR intrabone OR intratibial OR intra-tibial OR intraulnar OR intra-ulnar OR IO) NEAR/2 (infusion* OR injection* OR administ*)):ti,ab) AND ('intravenous drug administration'/exp OR Intravenous:ti,ab OR Intra-venous:ti,ab OR 'umbilical vein'/de OR ('umbilical vein' OR 'umbilical veins' OR 'umbilical venous'):ti,ab OR (venous NEAR/3 catheter*):ti,ab OR 'intravenous catheter'/de OR (vascular NEAR/3 catheter*):ti,ab OR catheterization/de OR 'central venous catheterization'/exp OR catheter/de OR 'central venous catheter'/de OR 'indwelling catheter'/de OR 'vascular access device'/de OR 'central venous':ti,ab OR 'vascular access':ti,ab)) OR (IO NEAR/15 IV):ti,ab) AND (newborn*:ti,ab OR 'new born*':ti,ab OR 'newborn'/exp OR infant*:ti,ab OR neonat*:ti,ab OR neo-nat*:ti,ab OR 'newly born':ti,ab OR premature:ti,ab OR prematurity:ti,ab OR preterm:ti,ab OR 'pre term':ti,ab OR 'prematurity'/exp OR 'low birth weight':ti,ab OR 'low birthweight':ti,ab OR VLBW:ti,ab OR LBW:ti,ab OR postnatal:ti,ab OR post-natal:ti,ab OR 'golden hour':ti,ab OR 'perinatal care'/exp OR 'newborn intensive care'/exp OR 'newborn intensive care nursing'/exp OR 'neonatal intensive care unit'/exp OR 'newborn nursing'/exp OR 'newborn care'/exp OR NICU:ti,ab) NOT ((animal/exp or nonhuman/de) NOT human/exp) NOT ('editorial'/it OR 'letter'/it) NOT 'case report'/de AND [embase]/lim AND [01-12-2019]/sd	
Cochrane CENTRAL	**(**[mh "Heart Arrest"] OR [mh ^"Ventricular Fibrillation"] OR [mh ^Resuscitation] OR [mh ^"Heart Massage"] OR [mh "Cardiopulmonary Resuscitation"] OR (cardi* NEXT arrest*):ti,ab OR ("heart" NEXT arrest*):ti,ab OR OHCA:ti,ab OR IHCA:ti,ab OR CPR:ti,ab OR ("advanced" NEXT cardi* NEXT "life support"):ti,ab OR ACLS:ti,ab OR "basic life support":ti,ab OR BLS:ti,ab OR asystol*:ti,ab OR "pulseless electrical activity":ti,ab OR "pulseless ventricular tachycardia":ti,ab OR "return of circulation":ti,ab OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR resuscitat*:ti,ab OR ("ventricular" NEXT fibrillation*):ti,ab OR ("chest" NEXT compression*):ti,ab) AND ((([mh ^"Infusions, Intraosseous"] OR Intraosseous:ti,ab OR Intra-osseous:ti,ab OR ((bone:ti,ab OR intrabone:ti,ab OR intratibial:ti,ab OR intra-tibial:ti,ab OR intraulnar:ti,ab OR intra-ulnar:ti,ab) NEAR/3 (infusion*:ti,ab OR injection*:ti,ab OR administ*:ti,ab))) AND ([mh	

	"Administration, Intravenous"] OR Intravenous:ti,ab OR Intra-venous:ti,ab OR [mh ^"Umbilical Veins"] OR "umbilical vein":ti,ab OR "umbilical veins":ti,ab OR "umbilical venous":ti,ab OR (venous:ti,ab NEAR/3 catheter*:ti,ab) OR (vascular:ti,ab NEAR/3 catheter*:ti,ab) OR [mh ^catheterization] OR [mh ^"catheterization, central venous"] OR [mh ^"catheterization, peripheral"] OR [mh ^catheters] OR [mh ^"catheters, indwelling"] OR [mh "vascular access devices"] OR "central venous":ti,ab OR "vascular access":ti,ab)) OR (IO NEAR/15 IV):ti,ab) AND (newborn*:ti,ab OR ("new" NEXT born*):ti,ab OR [mh "Infant, Newborn"] OR infant*:ti,ab OR neonat*:ti,ab OR neo-nat*:ti,ab OR "newly born":ti,ab OR premature:ti,ab OR prematurity:ti,ab OR preterm:ti,ab OR "pre term":ti,ab OR [mh "Premature Birth"] OR "low birth weight":ti,ab OR "low birthweight":ti,ab OR VLBW:ti,ab OR LBW:ti,ab OR postnatal:ti,ab OR post-natal:ti,ab OR "golden hour":ti,ab OR [mh "Perinatal Care"] OR [mh "Intensive Care, Neonatal"] OR [mh "Intensive Care Units, Neonatal"] OR [mh "Neonatal Nursing"] OR NICU:ti,ab)	
Search 2 (for RCTs on relevant drugs)		
Ovid MEDLINE ALL	(exp Heart Arrest/ OR Ventricular Fibrillation/ OR Resuscitation/ OR Heart Massage/ OR exp Cardiopulmonary Resuscitation/ OR cardi* arrest*.tw,kf. OR heart arrest*.tw,kf. OR OHCA.tw,kf. OR IHCA.tw,kf. OR CPR.tw,kf. OR advanced cardiac life support.tw,kf. OR ACLS.tw,kf. OR basic life support.tw,kf. OR BLS.tw,kf. OR asystol*.tw,kf. OR pulseless electrical activity.tw,kf. OR pulseless ventricular tachycardia.tw,kf. OR (return of circulation or return of spontaneous circulation or ROSC).tw,kf. OR resuscitat*.tw,kf. OR ventricular fibrillation*.tw,kf. OR chest compression*.tw,kf.) AND (exp Epinephrine/ OR (epinephrine or adrenaline or adrenalin).tw,kf.) AND (newborn*.tw. OR "new born*".tw. OR exp "Infant, Newborn"/ OR infant*.tw. OR neonat*.tw. OR neo-nat*.tw. OR "newly born".tw. OR premature.tw. OR prematurity.tw. OR preterm.tw. OR "pre term".tw. OR exp "Premature Birth"/ OR "low birth weight".tw. OR "low birthweight".tw. OR VLBW.tw. OR LBW.tw. OR postnatal.tw. OR post-natal.tw. OR "golden hour".tw. OR exp "Perinatal Care"/ OR exp "Intensive Care, Neonatal"/ OR exp "Intensive Care Units, Neonatal"/ OR exp "Neonatal Nursing"/ OR NICU.tw.) AND (randomized controlled trial.pt. OR controlled clinical trial.pt. OR (randomized or randomised).ab. OR placebo.ab. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti.) NOT (exp animals/ not humans.sh.) NOT ("case reports".pt. OR comment.pt. OR editorial.pt. OR letter.pt.) AND (201912* or 2020* or 2021* or 2022* or 2023* or 2024*).dt.	
EMBASE	(resuscitation/exp OR 'heart arrest'/exp OR 'heart ventricle fibrillation'/de OR (Resuscitat* OR CPR OR 'code blue'):ti,ab OR 'cardi* arrest*':ti,ab OR 'heart arrest*':ti,ab OR 'advanced cardi* life support':ti,ab OR ACLS:ti,ab OR 'basic life support':ti,ab OR BLS:ti,ab OR OHCA:ti,ab OR IHCA:ti,ab OR asystol*:ti,ab OR 'pulseless electrical activity':ti,ab OR 'pulseless ventricular tachycardia':ti,ab OR ('return of circulation' OR 'return of spontaneous circulation' OR ROSC):ti,ab OR 'ventricular fibrillation*':ti,ab OR 'chest compression*':ti,ab) AND (epinephrine/de OR (epinephrine OR adrenaline OR adrenalin):ti,ab) AND (newborn*:ti,ab OR 'new born*':ti,ab OR 'newborn'/exp OR infant*:ti,ab OR neonat*:ti,ab OR neo-nat*:ti,ab OR 'newly born':ti,ab OR premature:ti,ab OR prematurity:ti,ab OR preterm:ti,ab OR 'pre term':ti,ab OR 'prematurity'/exp OR 'low birth weight':ti,ab OR 'low birthweight':ti,ab OR VLBW:ti,ab OR LBW:ti,ab OR postnatal:ti,ab OR post-natal:ti,ab OR 'golden hour':ti,ab OR 'perinatal care'/exp OR 'newborn intensive care'/exp OR 'newborn intensive care nursing'/exp OR 'neonatal intensive care unit'/exp OR 'newborn nursing'/exp OR 'newborn care'/exp OR NICU:ti,ab) AND ((double NEAR/1 blind*):de,ab,ti OR placebo*:ti,ab OR blind*:ti,ab) NOT ((animal/exp or nonhuman/de) NOT human/exp) NOT ('editorial'/it OR 'letter'/it) AND [embase]/lim AND [01-12-2019]/sd	

Cochrane CENTRAL	([mh "Heart Arrest"] OR [mh ^"Ventricular Fibrillation"] OR [mh ^Resuscitation] OR [mh ^"Heart Massage"] OR [mh "Cardiopulmonary Resuscitation"] OR (cardi* NEXT arrest*):ti,ab OR ("heart" NEXT arrest*):ti,ab OR OHCA:ti,ab OR IHCA:ti,ab OR CPR:ti,ab OR ("advanced" NEXT cardi* NEXT "life support"):ti,ab OR ACLS:ti,ab OR "basic life support":ti,ab OR BLS:ti,ab OR asystol*:ti,ab OR "pulseless electrical activity":ti,ab OR "pulseless ventricular tachycardia":ti,ab OR "return of circulation":ti,ab OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR resuscitat*:ti,ab OR ("ventricular" NEXT fibrillation*):ti,ab OR ("chest" NEXT compression*):ti,ab) AND ([mh Epinephrine] OR (epinephrine:ti,ab OR adrenaline:ti,ab OR adrenalin:ti,ab)) AND (newborn*:ti,ab OR ("new" NEXT born*):ti,ab OR [mh "Infant, Newborn"] OR infant*:ti,ab OR neonat*:ti,ab OR neo-nat*:ti,ab OR "newly born":ti,ab OR premature:ti,ab OR prematurity:ti,ab OR preterm:ti,ab OR "pre term":ti,ab OR [mh "Premature Birth"] OR "low birth weight":ti,ab OR "low birthweight":ti,ab OR VLBW:ti,ab OR LBW:ti,ab OR postnatal:ti,ab OR post-natal:ti,ab OR "golden hour":ti,ab OR [mh "Perinatal Care"] OR [mh "Intensive Care, Neonatal"] OR [mh "Intensive Care Units, Neonatal"] OR [mh "Neonatal Nursing"] OR NICU:ti,ab)	
Results identified	**Results screened full text**	**Results included**
35	10	2 plus 1 identified by manual searching

2024 Evidence Update
NLS 5800 – Impact of Duration of Intensive Resuscitation

Worksheet Author(s): Foglia EE, Guinsburg R, de Almeida MF, Weiner G, Wyllie J, Wyckoff MH, Rabi Y
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 24 October 2024
Conflicts of Interest: none

PICOST:
Population: Newborn infants presenting with at least 10 minutes of asystole, bradycardia (heart rate less than 60 bpm), or pulseless electrical activity after birth for which CPR is indicated
Intervention: Ongoing CPR for incremental time intervals beyond 10 minutes after birth
Comparator: CPR discontinued at 10 minutes after birth
Outcomes:
- Survival (to any age) (critical)
- Neurodevelopmental outcomes (critical)
- Composite of survival to any age without moderate or severe neurodisability (critical)

Study design*:* Cross-sectional or cohort studies were eligible for inclusion. Ancillary analyses of RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies, case series) were eligible for inclusion. All years and languages were included if there was an English abstract. Conference abstracts and trial protocols were excluded.
Time frame: All years were included from inception of the searched databases to October 17, 2019.
A priori subgroups to be examined: Hypothermia post resuscitative care among newborn infants 36 weeks' or greater gestational age; 36 weeks' or greater gestational age versus less than 36 weeks; birthweight 2500 grams or greater; infants enrolled in population-level cohort studies

Year of last full review: 2020 {Foglia 2020 e20201449}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Wyckoff 2020 S185}
For the critical outcome of ***survival until last follow up****,* we identified very low certainty evidence (low quality evidence downgraded for risk of bias and inconsistency) from 15 studies {Ayrapetyan 2019 428, Casalaz 1998 F112, Haddad 2000 1210, Harrington 2007 463.e1, Jain 1991 778, Kasdorf 2015 F102, Natarajan 2013 F473, Patel 2004 136, Sarkar 2010 F423, Shah 2015 F492, Shibasaki 2020 64, Socol 1994 991, Sproat 2017 F262, Zhang 2019 933, Zhong 2019 77} reporting survival outcomes of 470 newborns to last known follow up. The number of enrolled newborns ranged from 3 to 177. The duration of follow up in the studies ranged from 4 months to 8 years old. Across studies, reported survival rates to last follow up ranges from 1.7% to 100%. Among all 470 newly-born infants reported in the literature and included in this review, 187 (39.8%) survived to last follow up.

For the critical outcome of ***neurodevelopmental outcomes among survivors****,* we identified very low certainty evidence (low quality evidence downgraded for risk of bias and inconsistency) from 13 studies {Ayrapetyan 2019 428, Casalaz 1998 F112, Haddad 2000 1210, Harrington 2007 463.e1, Jain 1991 778, Kasdorf 2015 F102, Natarajan 2013 F473, Patel 2004 136, Sarkar 2010 F423, Shah 2015 F492, Shibasaki 2020 64, Socol 1994 991, Sproat 2017 F262, Zhang 2019 933, Zhong 2019 77} reporting neurodevelopmental outcomes for 277 newly-born infants. The number of infants assessed in each study was small (1-19 infants), with reported rates of moderate to severe neuro-impairment ranging from 0 to 100%. Across all 13 studies, 86/277 infants survived, and 80 were assessed for neurodevelopmental outcomes. Of these, 50 were diagnosed with moderate or severe neuroimpairment, and 30 (38%) survivors did not have moderate or severe neuroimpairment. There was important inconsistency between studies (and in some cases- within studies) regarding the timing and tools used to assess neurodevelopmental outcomes. Hence, the impact of ongoing resuscitation on neurodevelopmental impairment remains uncertain.

For the critical outcome of ***the composite of survival without neurodevelopmental outcome***, we identified very low certainty evidence (low quality evidence downgraded for risk of bias and inconsistency) from 13 studies reporting neurodevelopmental outcomes. {Ayrapetyan 2019 428, Casalaz 1998 F112, Haddad 2000 1210, Harrington 2007 463.e1, Jain 1991 778, Kasdorf 2015 F102, Natarajan 2013 F473, Patel 2004 136, Sarkar 2010 F423, Shah 2015 F492, Shibasaki 2020 64, Socol 1994 991, Sproat 2017 F262, Zhang 2019 933, Zhong 2019 77} Among 277 reported infants, 69% died before last follow up, 18% survived with moderate to severe impairment, and 11% survived without moderate to severe neuroimpairment (2% lost to follow up). There was important

inconsistency between studies (and in some cases- within studies) regarding the timing and tools used to assess neurodevelopmental outcomes. Hence, the impact of ongoing resuscitation on survival without neurodevelopmental impairment remains uncertain.

Treatment Recommendations: Failure to achieve return of spontaneous circulation after 10-20 minutes of intensive resuscitation is associated with a high risk of morbidity and mortality among newly born infants. However, no single time interval has been demonstrated to universally predict mortality or morbidity. If the newly born infant requires ongoing CPR despite completing all the recommended steps of resuscitation and excluding reversible causes, we suggest initiating discussion of discontinuing resuscitative efforts with the team and family. A reasonable timeframe for this change in goals of care is around 20 minutes after birth. (weak recommendation, very low certainty of evidence).

Search Strategy for the original systematic review (same search strategy for 2024 evidence update) (see appendix)

Database searched: Medline, Cochrane database of systematic reviews
Time Frame: 1946 until October 17, 2019. Rerun from 2019 to July 4, 2024
Date Search Completed: July 4, 2024
Search Results:
Identified: 290
Full Text articles assessed; 8
Included: 2 studies included {Shukla e2021054992, Tylleskär 421}.{Shukla 2022 e2021054992, Tylleskär 2022 421} Searching NLS monthly updated literature, we found 2 eligible studies: one cohort study {Schmölzer 2024 428} and 1 systematic review.{Khorram 2022 669} In the references of this systematic review, we found 1 more eligible study. {Cnattingius 2020 49} Therefore, this evidence update summarizes the data of 1 systematic review {Khorram 2022 669} and 4 observational studies. {Cnattingius 2020 49, Schmölzer 2024 428, Shukla 2022 e2021054992, Tylleskär 2022 421}

Summary of Evidence Update:
Relevant Systematic Reviews

Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Khorram 2022 {Khorram 2022 669}	Systematic review with meta-analysis of the proportion of outcomes for studies published after year 2000 with >5 NB. Meta-regression using the median year of the study period and subgroup analyses by use of therapeutic hypothermia and GA was applied	Survival and survival without moderate-to-severe NDI of NB with a 10-min Apgar score of zero	28 studies of 820 NB with moderate risk of bias were included	*Survival:* 40% (95% CI 30–50%, 16 studies, 646 NB, I_2 = 83%) Survival increased by 2.3% per year (95%CI 1.3–3.2%, p<0.001) *Survival without moderate-to-severe NDI:* 19% (95%CI 11–27%, 13 studies, 211 NB, I_2 = 62%). Survival was higher for: - - NB who received therapeutic hypothermia vs no hypothermia - NB with GA ≥32 wk vs. GA <32 wk	Authors conclude that: "Approximately 2 in 5 NB with a 10-min Apgar score of zero survive, and 1 in 5 survive without moderate to-severe NDI. Survival has improved over the years, especially since the era of therapeutic hypothermia"

CI: confidence interval; GA: gestational age; NB: newborns; NDI: neurodevelopmental impairment; wk: weeks.

RCT: None

Observational Studies

Author; Year, Country	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)

Cnattingius 2020 Sweden {Cnattingius 2020 49}	Population-based study Born from 1992 to 2016	**Inclusion Criteria:** NB with GA <37 wk without malformations, with Apgar at 10 minutes of zero (n=137) or 1 (n=302)	**1° endpoint:** *Alive at 28 days:* - Apgar 0 at 10 min: 35/137 (25.5%) - Apgar 1 at 10 min: 63/302 (20.9%) *Alive at 28 days by GA strata* (neonates with Apgar score of 0/1 at 10 minutes): - 210 NB 22-24 wk: 7 (3.3%) - 50 NB 25-27 wk: 4 (8.0%) - 52 NB 28-31wk: 15 (28.8%) - 61 NB 32-34 wk: 33 (54.1%) - 66 NB 35-36 wk: 39 (59.1%)	Authors conclude that "In this nationwide study, 5-minute and 10-minute Apgar scores and changes in the score between 5 minutes and 10 minutes were associated with neonatal mortality" Data shows that it is possible to survive if Apgar at 10 minutes = zero, but the chance of survival is higher as gestational age increases
Schmölzer 2024 Canada & Austria {Schmölzer 2024 428}	Cohort nested in RCT in 4 centers Born from 2017 to 2022	NB with GA > 28 we without malformations with adverse effects on breathing/ventilation who required cardiac compressions	*Alive at hospital discharge* - Apgar 0 at 10 min: 3/3 (100%; discharge at 20, 29 and 44 days) - Apgar 1 at 10 min: 2/4 (50%; two infants discharged alive at 12 and 70 days; 1 died in the delivery room and one died with 6 days))	The objective of the RCT was to compare two different strategies of ventilation + chest compressions for time to return of spontaneous circulation. This study adds that survival to hospital discharge of infants with Apgar scores of 0/1 at 10 minutes is possible: 5/7 (71%) infants survived
Shukla 2022 USA {Shukla 2022 e2021054992}	Cohort nested in RCT in 18 centers Born from Oct/2010 to Nov/2013	NB with GA ≥36 wk, admitted to NICU <6 hours after birth with moderate to severe HIE and Apgar of zero at 10 min. (n=26). All NB received therapeutic hypothermia	*Alive without moderate/severe NDI at 18-22 months:* - 13/26 (50%) were alive at 18-22 months - 8/13 survivors (62%) without moderate or severe disabilities Among the 13 NB with Apgar 0 at 10 min who survived: - 6 (46%) had no disability - 2 (16%) had mild disabilities - 5 (38%) had moderate/ severe disabilities	Authors conclude that: "A 10-minute Apgar score of 0 alone does not predict the risk of death or moderate or severe disability well. The current study provides evidence in support of the 2020 ILCOR recommendation for continuing resuscitative efforts for infants who need cardiopulmonary resuscitation at 10 minutes after birth"
Tylleskar 2022 Uganda {Tylleskär 2022 421}	Cohort nested in RCT in a single center Born from May/2018 to Aug/2019	NB with GA ≥34 wk, expected birth weight ≥2000g, in need of PPV, without malformations, with Apgar at 10 minutes of 0/1 and with (n=21) or without (n=28) advanced resuscitation **Advanced resuscitation is not defined by the authors*	*Alive 7 days after birth:* - 0/21 with advanced resuscitation - 1/28 (4%) without advanced resuscitation	The authors conclude that "Our study adds information from a low-resource setting to the recent evidence from high-resource settings about prolonging the resuscitation in infants with Apgar scores of 0/1 at 10 min. The vast majority died in the delivery room despite prolonged resuscitative efforts. We confirm that duration of resuscitation should be tailored to the setting, while the focus in low-resource settings should be improving the quality of antenatal and immediately after birth care

Abbreviations: GA: gestational age; HIE: hypoxic-ischemic encephalopathy; min: minutes; NB: newborns; NICU: neonatal intensive care unit; NDI: neurodevelopmental impairment; PPV: Positive pressure ventilation; RCT: randomized control trial; wk: weeks.

Reviewer Comments:
We identified one metanalysis {Khorram 2022 669} with 28 studies and 820 neonates showing that around two in 5 neonates with a 10-min Apgar score of zero survive, and one in 5 survive without moderate to-severe neurodevelopmental impairment. The risk of bias in this study was concluded to be moderate but was evaluated by the Newcastle-Ottawa scale and there are some concerns that this assessment may underestimate it compared to ROBINS-I tool. {Losilla 2018 61} Among the 28 studies, 16 were included in the previous ILCOR review {Foglia e20201449}, 7 were excluded from the previous ILCOR review {Foglia 2020 177} because individual data of interest could not be retrieved, 4 studies were excluded from the previous ILCOR review {Foglia 2020 177} because they were case reports, and 1 population-based study was published after the previous ILCOR review and is included in the present evidence update.{Cnattingius 2020 49} Therefore, the majority of studies of the recent metanalysis {Khorram 669} were included in the previous ILCOR systematic review.{Foglia 2020 177} The results of this recent metanalysis, with meta-regression, do not change the previous ILCOR conclusions that the use of a rigid timeframe (10 minutes) for discontinuing resuscitation is questionable and that it is possible for neonates to survive, and to survive without moderate-to-severe neurodevelopmental impairment, after prolonged resuscitation at birth.

We identified one population-based study {Cnattingius 49} showing that, in a high income setting, 20-25% of preterm neonates with an Apgar score of 0/1 (asystolic or bradycardic) are alive at 28 days after birth, but the chance of survival is higher as gestational age increases. {Cnattingius 2020 49} We identified one cohort study, nested in a multicenter randomized controlled trial of two strategies to apply positive pressure ventilation and chest compressions in newborns with gestational age >28 weeks who required chest compressions, that showed 71% of survival at hospital discharge among 7 neonates with Apgar score of zero or one at 10 minutes. {Schmölzer 2024 428} Another cohort study, nested in a multicenter randomized controlled trial of prolonged/more intense hypothermia in the USA, that showed, among 26 newborn infants asystolic at 10 minutes after birth (Apgar score of zero at 10 minutes), that 8/26 (31%) were alive without severe or moderate disabilities at 18-22 months after birth. {Shukla 2022 e2021054992} Another cohort study, nested in a randomized controlled trial of upper airway devices in Uganda, a low resource setting, showed that, among 49 newborn infants at least 34 weeks gestational age with an Apgar score of 0/1 at 10 minutes, only one was alive at 7 days. {Tylleskär 2022 421} Overall, these studies indicate that survival without severe neurodevelopmental impairment is possible following prolonged asystole or bradycardia. However, it is dependent on several factors, including gestational age, the availability of therapeutic hypothermia, resuscitation practices, and access to other intensive or complex care.

It should be noted that the method of heart rate detection at birth was not reported in most studies and that Apgar scores are subjective and have inter-rater variability.{Rüdiger 2020 321} This limitation may have had influence on selection of infants for inclusion in each study and should be considered in the interpretation of the results.

The evidence retrieved from the new studies and the systematic review is not sufficient to change the current recommendation: “Failure to achieve return of spontaneous circulation after 10-20 minutes of intensive resuscitation is associated with a high risk of morbidity and mortality among newly born infants. However, no single time interval has been demonstrated to universally predict mortality or morbidity. If the newly born infant requires ongoing CPR despite completing all the recommended steps of resuscitation and excluding reversible causes, we suggest initiating discussion of discontinuing resuscitative efforts with the team and family. A reasonable timeframe for this change in goals of care is around 20 minutes after birth. (weak recommendation, very low certainty of evidence)”.

The evidence retrieved from the new studies and the systematic review is not sufficient to elicit a new systematic or scoping review.

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Appendix: Search Strategy

Sources searched	Search strategy	Search time frame
Ovid Multi-Database Search	1 "Infant, Newborn"/ or "newborn"/ or (newborn* or "newly born" or neonat* or "full term infant" or "full term infants").ti,ab,kf,kw. [NEWBORN] 2 ("Apgar Score"/ or Apgar.ti,ab,kf,kw.) and ("0" or zero or "1" or one).ti,ab,kf,kw. [APGAR] 3 "Heart Arrest"/ or "Bradycardia"/ or exp "bradycardia"/ or ("heart arrest" or "cardiac arrest" or "cardiopulmonary arrest" or "cardio-pulmonary arrest" or asystol* or bradycardi* or bradyarrhythmi* or pulseless or pulse-less or "no pulse" or "no detectable pulse" or "undetectable pulse" or "un-detectable pulse" or "no heartbeat*" or "no detectable heartbeat*" or "no heart beat*" or "no detectable heart beat*" or "no heart rate*" or "no detectable heart rate*" or "lack of detectable heart rate*" or "lack of detectable heartbeat*" or "lack of detectable heart beat*" or "lack of heartbeat*" or "lack of heart beat*" or "undetectable heart beat*" or "undetectable heartbeat*" or "undetectable heart rate*" or "un-detectable heart beat*" or "un-detectable heartbeat*" or "un-detectable heart rate*" or "respiratory failure" or hypoxia or hypoxic or apnea* or apneic or anoxia or anoxic).ti,ab,kf,kw. [CONDITION #1] 4 "Asphyxia Neonatorum"/ or "newborn hypoxia"/ [CONDITION #2] 5 1 and 2 [NEWBORN + APGAR] 6 (1 and 3) or 4 [NEWBORN CONDITION] 7 ("10 minute*" or "ten minute*" or "10 min" or "ten min" or "10 mins" or "ten mins").ti,ab,kf,kw. [TIME INTERVAL] 8 5 and 7 [NEWBORN + APGAR + TIME INTERVAL] 9 5 and 6 [NEWBORN + APGAR + CONDITION] 10 8 or 9 [NEWBORN + APGAR + (TIME INTERVAL OR CONDITION)] 11 exp "Resuscitation"/ or exp "Ventilators, Mechanical"/ or "mechanical ventilator"/ or (resuscitat* or "heart massag*" or "cardiac massag*" or	Jan 1 2019 to July 4, 2024

	"heart compression*" or "cardiac compression*" or "chest compression*" or "artificial respiration*" or "positive pressure respiration*" or "continuous positive airway pressure*" or "positive end expiratory pressure*" or ventilation* or ventilator* or CPAP or CPR or "cardiac life support" or ACLS).ti,ab,kf,kw. 12 "Epinephrine"/ or (epinephrine or adrenalin or adrenalina or adrenaline or epitrate or lyophrin or epifrin or adnephrin or adnephrine or adrenamine or adrenapax or adrenazin or adrenine or adrin or adrine or advaradin or asthmahaler or balmadren or biorenine or bosmin or chelafrin or drenamist or dylephrin or epiglaufrin or epimephrine or epinefrina or epinephran or epirenamine or epirenan or exadrin or glaucon or glaucosan or glaufrin or "glin epin" or glycirenan or haemostatin or hemisine or hemostasin or hemostatin or hypernephrin or "isopto epinal" or levoadrenalin or levoadrenaline or levoepinephrine or levorenin or levorenine or methylaminoethanolcatechol or methylarterenol or mucidrina or myosthenine or nephridine or nieraline or paranephrin or posumin or primatene or renaglandin or renaglandulin or renaleptine or renalina or renaline or renoform or renostypticin or renostyptin or scurenaline or simplene or soladren or sphygmogenin or styptirenal or supracapsulin or supranephrane or supranephrin or supranol or suprarenaline or suprarenin or suprarenine or suprel or surenine or surrenine or "sus phrine" or susphrine or symjepi or sympathin or takamina or tonogen or trenamist or vasoconstrictine or vasodrine or vasotonin or weradren).ti,ab,kf,kw,nm,du,dy. 13 11 or 12 [INTERVENTION] 14 10 and 13 [NEWBORN + (APGAR OR CONDITION) + INTERVENTION] 15 (Animals/ or "Animal Experimentation"/ or "Models, Animal"/ or "Disease Models, Animal"/) not (Humans/ or "Human Experimentation"/) 16 (exp "animal model"/ or exp "animal experiment"/ or "nonhuman"/ or exp "vertebrate"/) not (exp "human"/ or exp "human experiment"/) 17 14 not (15 or 16) [ANIMAL STUDIES REMOVED] 18 (comment or letter or "newspaper article" or news or note).pt. 19 (conference or "conference abstract" or "conference paper" or "conference review" or congresses).pt. 20 17 not (18 or 19) [PUBLICATION TYPES REMOVED] EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 9, 2019> EBM Reviews - ACP Journal Club <1991 to September 2019> EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> EBM Reviews - Cochrane Clinical Answers <August 2019> EBM Reviews - Cochrane Central Register of Controlled Trials <September 2019> EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> EBM Reviews - Health Technology Assessment <4th Quarter 2016> EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> Embase <1974 to 2019 October 16> Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 16, 2019> 21 remove duplicates from 20 EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 9, 2019> EBM Reviews - ACP Journal Club <1991 to September 2019>	

	EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> EBM Reviews - Cochrane Clinical Answers <August 2019> EBM Reviews - Cochrane Central Register of Controlled Trials <September 2019> EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> EBM Reviews - Health Technology Assessment <4th Quarter 2016> EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> Embase <1974 to 2019 October 16> Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 16, 2019> 22 from 21 keep 1-212 23 from 21 keep 213-338 24 from 21 keep 339-617	
Results identified	**Results screened full text**	**Results included**
290	8	2 plus 3 identified from other sources (literature surveillance, reference lists of included studies etc.)

2025 Evidence Update
NLS 5900 – Family Presence During Neonatal Resuscitation

Worksheet Author(s): Wyllie J, Aly M, Monnelly V, Liley HG
Task Force: Neonatal Life Support
Date Approved by SAC Representative: 19 November 2024
Conflicts of Interest: None

PICOST:
Population: Children with cardiac arrest, in any setting,
Intervention: Family presence during resuscitation
Comparator: No family presence during resuscitation
Outcomes:

- Improved patient outcomes (short- and long-term)
- Family-centered outcomes (short- and long-term, perception of the resuscitation)
- Healthcare provider–centered outcomes (perception of the resuscitation, psychological stress)

Note that this PICOST was designed for a nodal review with the Pediatric Life Support Task Force, but after discussion with the PLS TF, this evidence update was intended to focus only on newborn infants immediately after birth receiving resuscitation.

Year of last full review: 2019 {Dainty 2021 20}

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: {Wyckoff 2021 229}
Consensus on Science:
For the critical outcome of improved patient outcomes (short and long term) there were no useful data to inform practice. Only one study reported Apgar scores in demographic data. {Zehnder 2020 559}

For the important outcome of family-centered outcomes there were 7 studies reporting on 144 people, all from high resource settings. The studies included 4 surveys of parents or family members who were present during stabilization or resuscitation (Arnold 2012 e002487, Harvey 2012 F439, Lindberg 2007 142, Sawyer 2015 e008495}, 2 surveying the opinions of health care providers {Harvey 2012 F439, Yoxall 2015 e008494} and 1 surveying both health care providers and parents . {Katheria 2018 100} Overall, the findings in these mainly qualitative studies reflected a positive experience for families who were present during the stabilization or resuscitation of their newborn babies. Qualitative themes included:

- The unique experience and perspective of fathers/partners particularly around their knowledge of what happened.
- Fathers/partners focused on their partner at the time of the resuscitation/stabilisation event.
- Parents felt that being present provided reassurance and opportunities for involvement and communication, but parents also reported some reservations about the emotional toll of witnessing a resuscitation.
- The need for staff training in support and debriefing of parents.
- Parental presence at birth was characterised by intense but polarized emotions ranging from desperation to see the baby immediately, to fear of witnessing a situation involving their baby they would rather have avoided.

For the important outcome of health care provider outcomes, we identified 4 studies. Two of the papers surveyed opinions of health care providers who had participated in a resuscitation with family presence or delivery of the baby with all immediate care beside the mother for delayed clamping of the umbilical cord {Harvey 2012 F439, Yoxall 2015 e008494} One paper surveyed parental opinion (Sawyer 2015 e008495). One paper surveyed health care providers and found that the presence of a family member reduced perceived workload. {Zehnder 2020 559}

Overall, health care provider participants were professionals who were used to having parents in attendance and did not report any major detrimental effects. However, some expressed concern that less experienced professionals may feel under increased pressure while being observed. {Harvey 2012 F439, Yoxall 2015 e008494} This finding was not reported in the one study assessing workload. {Zehnder 2020 559} The potential impact on staff performance was also raised as a concern by parents in one study. {Sawyer 2015 e008495}

Treatment Recommendation:
We suggest it is reasonable for mothers/fathers/partners to be present during the resuscitation of neonates where circumstances, facilities and parental inclination allow. This is a weak recommendation based on very low certainty of evidence.

There is insufficient evidence to indicate an interventional effect on patient or family outcome. Being present during the resuscitation of their baby seems to be a positive experience for some parents but concerns about an adverse effect upon performance exist among both healthcare providers and family members.

Current Search Strategy – See appendix
New Search strategy: Not applicable
Database searched: Medline Embase Cochrane, CENTRAL, PsychInfo, CINAHL
Time Frame: (existing PICOST) – 1st September 2019 to 5th September 2024
Time Frame: (new PICOST) – Not applicable
Date Search Completed: 5 September 2024
Search Results:
Identified: 1390
Full text articles assessed: 45
Included: 5
Other full text articles considered for this Evidence Update were 24 studies that were excluded because they only addressed resuscitation of a pediatric, adult or mixed age people in settings such as in intensive care units, operating rooms or emergency departments. An additional four studies addressed antenatal counselling, consent and decision-making for extreme prematurity, one was a needs-assessment of education, policy and opinion in Canada, one was a study of simulation training for parental presence during critical situations in pediatric ICUs and one was a protocol for a Cochrane review. One was a study of training for intubation using video laryngoscopy that included trainees' comments on parental presence. These studies may reveal useful indirect evidence relating to family presence during newborn resuscitation, but they were excluded from this evidence update because they do not address the unique circumstances at the time of birth.

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews: There have been several systematic reviews and scoping reviews relevant to family presence during adult and pediatric resuscitation, but none addressed newborn resuscitation.

RCTs: None relevant

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion Comment(s)
Patriksson 2024 (a) {Patriksson 2024 255}	**Study Type:** Semistructured interviews of midwives using reflexive thematic analysis (qualitative method). (Convenience sample; N= 13) Study was of midwives' experiences of managing resuscitation with umbilical cord intact (included 'stabilisation' and	**Inclusion Criteria:** • 1 of 4 labour wards in various parts of Sweden • Participants 33-59 years of age • 18 mo to 30 yrs experience • Varying experiences related to performing/initiating CPR	**1° endpoint:** One of 3 themes explored was "Zero separation – a big advantage"	Responses included that the necessity for parental presence imposed by the trial to conduct resuscitation with an intact cord was positive in reducing parental trauma, making them better informed and more trusting, and improving communication. Midwives reported that parents expressed gratitude and found the experience empowering.

	resuscitation of non-vigorous neonates, during a clinical trial (SAVE study).			
Patriksson 2024 (b) {Patriksson 2024 362}	Interview study with an inductive, interpretative approach was chosen and analysed according to reflexive thematic analysis by Braun & Clark (qualitative methods). Purposive sampling (N=20) Study was of health care professionals' experiences of managing resuscitation with umbilical cord intact (included 'stabilisation' and resuscitation of non-vigorous neonates, during a clinical trial (SAVE study).	Neonatal healthcare professionals (including paediatric nurses, regional nurses, midwives, and physicians)	Questions included those about avoiding separation of mother and infant, as well as how to manage the environment, and the agreement or disagreement of team members about course of action.	Themes relevant to this PICOST included managing mothers' vulnerability and dignity. Benefits of not separating mothers and infants highlighted, including avoiding the anxiety associated with physically separating mother and infant. Issues of how to cope with disagreements about best course of action, and also how to manage the environment (crowding, access etc.)
Zehnder 2020 {Zehnder 2020 559}	Prospective observational study. Over 3 months, "Perceived workload was measured using the multidimensional retrospective National Aeronautics and Space Administration Task Load Index survey". (Raw-TLX)	204 anonymous survey responses (not clear whether 204 unique participants)	Raw-TLX score was lower when at least one parent was present (33; 16–47) compared with when no parents were present (46; 29–57) during the resuscitation (p=0.0004). Raw-TLX score was similar when parents were or were not present during resuscitation in both the low 5 min Apgar group (≤3) (54 (48–61) vs 53 (48–59), p=0.8103) and the medium 5 min Apgar group (4–7) (44 (36–54) vs 49 (42–58), p=0.7143) in the subgroup analysis. In the high 5 min Apgar group (≥8), however, Raw-TLX score was lower when parents were present compared with when they were not (23 (11–40) vs 38 (24–56), p=0.0023	Workload was perceived by clinicians to be lower, (but with most of the difference contributed by a subgroup where 5-min Apgar scores were ≥8). Wide, overlapping ranges for each group so cannot exclude that in some cases, workload was increased. Subjective comments included "HCPs reported benefits including (1) feeling more appreciated, (2) acting more professionally, and (3) increased rapport between HCPs and family members, resulting in a more humanistic experience". **<u>Limitations:</u>** • The anonymous and self-administered survey distribution prohibited the

				calculation of response rates. • The analysis was limited by the inability to pair survey responses to specific deliveries. Therefore, each survey response was treated as an independent variable. • No information about the length of time a parent was present or how many parents were present, which both may have affected results. • Recall bias might have resulted in inaccuracies when reporting perceived workload.
Karlsson 2023 {Karlsson 2023 220}	A retrospective qualitative interview study using critical incident technique. Registered nurses asked to recall a recent (no time frame specified) resuscitation situation (defined as 'the time span from when the team was alerted that a critically ill infant had been born or was about to be born, to the moment when the infant was either stable or declared dead and/or when the team gathered afterward for debriefing event')	N = 16 Participants were recruited from NICUs (level III and IV units with 16-24 bed capacity) at 4 university hospitals in Sweden. Participant selection limited to pediatric nurses with at least 1 year of clinical experience in a NICU /neonatal resuscitation.	Thematic analysis performed and categorized into experiences and actions. 577 behavioral quotations were identified (306 experiences and 271 actions) Experiences were individual or team. Individual experiences included parental presence. Actions included adopting a professional attitude toward parents	**<u>Regarding Parental Presence:</u>** pRNs reported; • Frustration when in a situation where no one on the team had time to take responsibility for parents • Challenging to include and support parents early in the neonatal resuscitation process due to medical priority • Perception that it was stressful for parents to watch the resuscitation procedure, although it was even harder for parents if they were not allowed to attend • Nevertheless the presence of parents in resuscitation situations was perceived as important and positive. **Limitations:** • Retrospective nature and risk of recall bias (no time frame was used, therefore could be recalling

				resuscitation situation from years before)
denBoer 2021 {den Boer 2021 346}	Qualitative explorative study (part of a wider project studying ethical aspects of recording and reviewing neonatal resuscitation). The study combined participant observations during parental review of recordings with retrospective semi-structured interviews.	Characteristic observations (n=20 occasions reviewing recordings of 31 infants) Characteristic interviews (n=13 interviews with 25 parents of 19 infants)	Parental review of recordings of neonatal resuscitation was observed on 20 occasions, reviewing recordings of 31 children (12 singletons, 8 twins and 1 triplet), of whom 4 died during admission. Median gestational age at birth was 27+5 (24+5–30+3) weeks. 25 parents (13 mothers and 12 fathers) were interviewed.	Interviewed parents consider reviewing recordings of neonatal resuscitation of their very or extremely preterm infant as valuable. Parents reported that reviewing recordings can help them cope with the trauma of neonatal resuscitation. Reviewing recordings resulted in appreciation for the child, the father and the medical team. Moreover, parents considered a copy of the video recordings of the resuscitation of their infant as a valuable keepsake. These positive parental experiences could allay concerns about sharing recordings of neonatal resuscitation with parents. **Limitations**: • A retrospective witnessing of the resuscitation or stabilisation of preterm infant. Parent not physically present. Retrospective nature means the parent is witnessing and processing events knowing the outcome for their baby. Might not be a true reflection of prospective parental presence at resuscitation. • All preterm infants, mostly stabilisation rather than resuscitation

				• Majority of infants had continuous positive airway pressure or positive pressure ventilation. Only 4 newborns were intubated (13%) and 1 newborn received CPR (3%)

Reviewer Comments:
We found five studies that specifically addressed parental presence during resuscitation at birth. Two were qualitative studies nested within a multicenter clinical trial of initiating resuscitation with the umbilical cord intact (a situation where proximity of mother and infant during resuscitation is inevitably very close). {Patriksson 2024 255, Patriksson 2024 362} Both reported results of structured interviews using slightly different methods, one addressing midwives' responses and the other reporting the responses of a variety of caregivers who were involved in the resuscitation. Both reported that the resuscitation with the umbilical cord intact reduced separation of mother and baby at a critical time, and that this was generally positive. There were some concerns expressed by resuscitation clinicians about how to protect the mothers' vulnerability and dignity. Themes of improved communication and building of trust were also noted.

One study used anonymous questionnaires of a variety of clinicians involved in newborn resuscitation at a single maternity hospital that assessed perceived workload using a validated scale. {Zehnder 2020 559} The study found that workload was perceived to be decreased overall by parental presence compared to no parental presence although there was a large overlap in scores for the two groups. The largest contribution to this decrease was in a subgroup with high 5-minute Apgar scores. Reported subjective comments were generally positive and included that the clinicians felt more appreciated, acted more professionally and experienced more rapport between the clinicians and families.

One study interviewed 16 paediatric nurses, who were asked to recall newborn resuscitation situations they had encountered and a thematic analysis was performed. {Karlsson 2023 220} One theme that emerged related to parental presence. The main recollections were feelings of frustration at not having the time to be responsible for the parents, and the challenges associated with trying to involve parents early but balancing this with meeting the medical needs of the baby. They perceived that it was stressful for the parents watching a resuscitation. However, it was noted to be harder for parents if they were not present, and family presence was generally acknowledged as being important and positive.

The final study involved retrospective viewing of 31 videos of preterm stabilization or resuscitation followed by structured interviews for 25 parents. {den Boer 2021 346} This study used observation at the time of viewing the videos and structured interviews. These videos were rated by parents as very or extremely valuable to them. Four infants died during their neonatal admission; none died in the delivery room. The majority had ventilatory support in the form of CPAP or IPPV, with only 4 infants being intubated and 1 infant receiving chest compressions. Parents reported that seeing the videos helped them deal with the trauma associated with preterm resuscitation, and an increased appreciation of both their baby and the healthcare team. Parents frequently reported the importance of having a provider present during the review to explain the medical context even when this was retrospective and they were aware of the outcome.

The previous Task Force Treatment recommendation is still valid (although we have changed the terminology slightly to use contemporary terms): "*We suggest it is reasonable for parents and caregivers to be present during the resuscitation of neonates where circumstances, facilities and parental inclination allow. This is a weak recommendation based on very low certainty of evidence. There is insufficient evidence to indicate an interventional effect on any patient or family outcome. Being present during the resuscitation of their baby seems to be a positive experience for some parents but concerns about an adverse effect upon performance exist among both healthcare providers and family members".*

The five new studies support that parental presence is a positive experience for parents. Four addressed clinicians' views and the one that interviewed parents involved a retrospective viewing of video recording of the resuscitation. All included studies mitigate some concerns about effects on resuscitator performance. We note that all studies are from high income countries (Canada,

Sweden, Netherlands) and there is a need for studies in culturally diverse settings and where resources are limited. The small number of new studies does not appear to justify a new systematic or scoping review at this time, but an updated systematic or scoping review may be considered based on on-going surveillance of the literature.

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Appendix – Search strategy

This was an update of a search previously performed on 1-8-2019. This search retrieved new material added to the databases from 1-7-2019 to 5-9-2024, so the search is now up to date to 5-9-2024.

The previous search strategies were adapted to the database platforms available at the University of Queensland in 2024 but were otherwise unchanged.

Summary of Results per Database

Database	Number of Results
MEDLINE (OVID)	365
Embase (Embase.com)	970
Cochrane Central Register of Controlled Trials (Cochrane Library)	138
Cochrane Database of Systematic Reviews (Cochrane Library)	3
CINAHL (EBSCOhost)	275
PsycINFO (EBSCOhost)	56
Total Number of Results (before deduplication)	1807

Sources searched	**Search strategy** Medline Embase Cochrane, CENTRAL, PsychInfo, CINAHL	**Search time frame**
Ovid Medline	1 advanced trauma life support care/ or resuscitation/ or exp cardiopulmonary resuscitation/ or heart massage/ 2 exp Heart Arrest/ 3 Ventricular Fibrillation/ 4 (Resuscitat* or CPR or code blue).tw,kf. 5 cardi* arrest*.tw,kf. 6 heart arrest*.tw,kf. 7 advanced cardiac life support.tw,kf. 8 ACLS.tw,kf. 9 basic life support.tw,kf. 10 BLS.tw,kf. 11 asystol*.tw,kf. 12 pulseless electrical activity.tw,kf. 13 (return of circulation or return of spontaneous circulation or ROSC).tw,kf. 14 ventricular fibrillation*.tw,kf. 15 chest compression*.tw,kf. 16 or/1-15 17 exp Parents/ or Grandparents/ 18 Family Relations/ 19 Family/ or Siblings/ 20 (family or families or parent or parents or parental or relative or relatives or father or fathers or mother or mothers or guardian* or sibling* or brother* or sister*).tw,kf. 21 17 or 18 or 19 or 20 22 16 and 21 23 Visitors to Patients/ 24 (Presence or present or witness* or participat* or watch* or observe*).tw,kf. 25 23 or 24 26 22 and 25 27 (Infan* or newborn* or new-born* or perinat* or neonat* or baby* or babies or toddler* or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child* or schoolchild* or adolescen* or juvenil* or youth* or teen* or under age* or pubescen*).mp. or exp pediatrics/ or (pediatric* or paediatric* or peadiatric*).mp. or school*.tw. or (prematur* or preterm*).mp. 28 26 and 27 29 28 not (animals/ not humans/) 30 limit 29 to (comment or editorial or letter) 31 29 not 30 32 limit 31 to case reports 33 case series.tw,kf. 34 32 and 33 35 31 not (32 not 34) 36 remove duplicates from 35 37 (201907* OR 201908* OR 201909* OR 201910* OR 201911* OR 201912* OR 2020* OR 2021* OR 2022* OR 2023* OR 2024*).dt. 38 36 and 37	1st September 2019 to 5th September 2024
EMBASE	#1 'resuscitation'/exp #2 'heart arrest'/exp #3 'heart ventricle fibrillation'/de #4 (Resuscitat* or CPR or "code blue"):ti,ab	

	#5 "cardi* arrest*":ti,ab #6 "heart arrest*":ti,ab #7 "advanced cardiac life support":ti,ab #8 ACLS:ti,ab #9 "basic life support":ti,ab #10 BLS:ti,ab #11 asystol*:ti,ab #12 "pulseless electrical activity":ti,ab #13 ("return of circulation" or "return of spontaneous circulation" or ROSC):ti,ab #14 "ventricular fibrillation*":ti,ab #15 "chest compression*":ti,ab #16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #17 'first-degree relative'/exp #18 'family'/de or 'extended family'/de or 'grandparent'/exp or 'great-grandparent'/exp or 'parenthood'/de #19 'nuclear family'/de or 'parent'/exp or 'sibling'/exp #20 'family relation'/de #21 'family stress'/de #22 'family interaction'/exp or 'family attitude'/de or 'family coping'/de #23 'family interaction'/de or 'family attitude'/de or 'family coping'/de #24 'family centered care'/de #25 (family or families or parent or parents or parental or relative or relatives or father or fathers or mother or mothers or guardian* or sibling* or brother* or sister*):ti,ab #26 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 #27 #16 AND #26 #28 (Presence or present or witness* or participat* or watch* or observe*):ti,ab #29 #27 AND #28 #30 (Infan* or newborn* or new-born* or perinat* or neonat* or baby* or babies or toddler* or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child* or schoolchild* or adolescen* or juvenil* or youth* or teen* or "under age*" or pubescen*) #31 (pediatric* or paediatric* or peadiatric*) #32 school*:ti,ab #33 (prematur* or preterm*) #34 'pediatrics'/de or 'neonatology'/exp or 'pediatric emergency medicine'/de #35 #30 OR #31 OR #32 OR #33 OR #34 #36 #29 AND #35 #37 #36 not (('animal'/exp or 'nonhuman'/de) not 'human'/exp) #38 #37 AND ('editorial'/it OR 'letter'/it) #39 #37 NOT #38 #40 'case report'/de #41 'case study'/de or case series:ti,ab #42 #40 AND #41 #43 39 not (40 not 42) #44 #43 AND [embase]/lim #45 #44 AND [01-07-2019]/sd	
PsycInfo (EBSCOHost)	S28 S26 AND S27 S27 RD 20190701- S26 S24 NOT S25	

	S25 DE "Case Report" S24 S22 NOT S23 S23 S20 AND S21 S22 S20 AND S21 S21 Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby* OR babies OR toddler* OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child* OR schoolchild* OR adolescen* OR juvenil* OR youth* OR teen* OR "under age*" OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR TI school* OR AB school* OR prematur* OR preterm* S20 S18 AND S19 S19 TI Presence OR AB Presence OR TI present OR AB present OR TI witness* OR AB witness* OR TI participat* OR AB participat* OR TI watch* OR AB watch* OR TI observe* OR AB observe* S18 S14 AND S17 S17 S15 OR S16 S16 16 TI family OR AB family OR TI families OR AB families OR TI parent OR AB parent OR TI parents OR AB parents OR TI parental OR AB parental OR TI relative OR AB relative OR TI relatives OR AB relatives OR TI father OR AB father OR TI fathers OR AB fathers OR TI mother OR AB mother OR TI mothers OR AB mothers OR TI guardian* OR AB guardian* OR TI sibling* OR AB sibling* OR TI brother* OR AB brother* OR TI sister* OR AB sister* S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 S13 TI "chest compression*" OR AB "chest compression*" S12 TI "ventricular fibrillation*" OR AB "ventricular fibrillation*" S11 TI "return of circulation" OR AB "return of circulation" OR TI "return of spontaneous circulation" OR AB "return of spontaneous circulation" OR TI ROSC OR AB ROSC S10 TI "pulseless electrical activity" OR AB "pulseless electrical activity" S9 TI asystol* OR AB asystol* S8 TI BLS OR AB BLS S7 TI "basic life support" OR AB "basic life support" S6 TI ACLS OR AB ACLS S5 TI "advanced cardiac life support" OR AB "advanced cardiac life support" S4 TI "heart arrest*" OR AB "heart arrest*" S3 TI "cardi* arrest*" OR AB "cardi* arrest*" S2 TI Resuscitat* OR AB Resuscitat* OR TI CPR OR AB CPR OR TI "code blue" OR AB "code blue" S1 DE "cpr"	
Results identified	**Results screened full text**	**Results included**
1390	45	5