NEONATAL LIFE SUPPORT

Cord Management at Birth for Preterm Infants

(NLS 5051: SysRev)

Rationale for Review

Adaptation to air breathing immediately after birth requires that several critical interdependent physiologic events occur rapidly.468

Air breathing reduces pulmonary vascu-lar resistance, which increases pulmonary blood flow. If the umbilical cord is clamped immediately, the increased pulmonary flow is initially from the aorta through the duc-tus arteriosus.

If cord clamping occurs after the onset of breathing, the increased pulmonary blood flow can come from the placenta through the umbilical vein and ductus ve-nosus, thereby maintaining left ventricular filling and output (vital for coronary and cerebral perfusion).469 Both milking the intact (not clamped or cut) umbilical cord and milking a long segment of clamped and cut cord have been pro-posed as alternatives to deferring clamping of the umbili-cal cord.

Decisions about umbilical cord management can critically influence the cardiorespiratory adaptation after birth,470,471 how and when other resuscitation interventions are provided, and mortality during subsequent hospitaliza-tion, particularly among preterm infants.472

The topic was last reviewed in by ILCOR in 2021.[473,474] Since then, additional RCTs have been completed and compiled into a very large pairwise individual patient data (IPD) meta-analysis and network meta-analysis (NMA), the iCOMP (Individual Participant Data on Cord Management at Preterm Birth) study,[475] which provided higher-certainty evidence for various methods of umbilical cord management than could have been achieved with study-level meta-analysis alone.[472,476] The Neonatal Life Support Task Force used the process of adolopment to appraise this evidence and develop updated treatment recommendations.[477] Task force members and content experts overlapped with the iCOMP study team, but assessment of suitability of the iCOMP analyses for adolopment was assessed by task force members and content experts who had no conflict of interest. The IPD meta-analysis is presented first and then the NMA, because the PICOST structure differs. The pairwise IPD meta-analysis was used for subgroup analyses, and the NMA was used for multiple between-intervention comparisons.

The iCOMP SysRev was registered before initiation (PROSPERO registration CRD42019136640). The full online CoSTR can be found on the ILCOR website.[477]

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

Individual Patient Data Pairwise Meta-Analysis

- Population: Preterm infants born at <37+0 weeks' gestation and their mothers[472,475]
- Interventions:
  - Deferred (delayed/later) cord clamping (>15 seconds)
  - Umbilical cord milking (cord milking or stripping immediately after birth or after deferred cord clamping)
- Comparators:
  - Immediate (early) cord clamping (≤15 seconds or as defined by the trialist) without cord milking and without initiation of respiratory support for any reason
  - Between-intervention comparisons

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Table 18. Summary of Pediatric Life Support Evidence Updates

Topic/PICO	Year last updated	Existing treatment recommendation	RCTs since last review	Observational studies since last review	Key findings	Sufficient data to warrant SysRev?
Prearrest care of the infant or child with dilated cardiomyopathy or myocarditis (PLS 4.030.19)	2020	2020 unchanged from 2015: The confidence in effect estimates is so low that the panel decided a specific recommendation was too speculative.	0	3	3 observational studies indirectly evaluated prearrest stabilization and intubation in patients with dilated cardiomyopathy or myocarditis.[465–467] Key findings: (1) Use of ketamine was associated with fewer adverse events (aOR, 0.74; 95% CI, 0.58–0.95).[465] (2) Given the high risk of cardiac arrest in children with acute myocarditis who demonstrate high-risk ECG changes (arrhythmias, heart block, ST segment changes) or low cardiac output, there should be early transfer to higher level of care for monitoring and therapy. (3) Where resources permit, prearrest use of ECLS may be beneficial. (4) Where resources permit, if cardiac arrest occurs, ECPR may be beneficial.	No
Ventilation rate when a perfusing rhythm is present (PLS 4.120.01)	2020	None	0	0	There was a SysRev in 2020 including 6 pediatric observational studies that examined oxygenation and ventilation targets, but not ventilation rate, after cardiac arrest.[231] For oxygenation, there was no association between hyperoxia and survival to hospital discharge or survival with favorable neurological outcome. For carbon dioxide levels, a single observational study rated as having less than critical risk of bias found both hypocapnia (OR, 2.71; 95% CI, 1.04–7.05) and hypercapnia (OR, 3.27; 95% CI, 1.62–6.61) to be associated with worse survival to hospital discharge compared with normocapnia. There remains insufficient evidence to make a recommendation on ventilation rates when a perfusing rhythm is present.	No

aOR indicates adjusted odds ratio; ECG, electrocardiogram; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; EvUps, evidence updates; PICO, population, intervention, comparator, outcome; RCTs, randomized controlled trials; SysRev, systematic review; and TR, treatment recommendation.

- Outcomes:
  - Infant outcomes (importance assigned by task force consensus, in accordance with available guidelines[478,479]):
    - Mortality before hospital discharge (critical)
    - Major inpatient morbidities (including intraventricular hemorrhage), necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia) for preterm infants <32 weeks' gestation (critical)
    - Neurodevelopmental outcomes (critical)
    - Resuscitation and stabilization interventions (eg, receiving positive pressure ventilation, intubation, chest compressions, medications; important)
    - Blood transfusion (important)
    - Hematologic and cardiovascular status (in-hospital; important)
    - Hematologic status (in infancy; important)
    - Hyperbilirubinemia treated with phototherapy (important)
  - Maternal outcomes
    - Mortality (critical)
    - Maternal complications (postpartum hemorrhage and infection; critical)
- Study designs: iCOMP included RCTs comparing umbilical cord management strategies but excluded trials with missing data, integrity issues, those not fitting intervention categories, and cluster- and quasi-randomized trials.[475] ILCOR systematic reviews typically exclude unpublished studies (eg, conference abstracts, trial protocols), while the iCOMP analysis includes such studies. However, the iCOMP study "…conducted extensive data processing, quality, and integrity checks of all included data,"[472] ensuring a level of integrity not usually available for unpublished data. Given these measures, the reduced publication bias from including unpublished studies was considered advantageous.[480] All languages were included.
- Time frame: All years were included. Medical databases, including MEDLINE, Embase, and CENTRAL, and clinical trial registries, including ClinicalTrials.gov, were originally searched up to February 2022 and WHO International Clinical Trials Registry Platform up to March 2022. The search was updated on June 6, 2023, and no additional eligible studies were identified.[472]

Consensus on Science

Comparison 1: Deferred Cord Clamping Compared With Immediate Cord Clamping

The pairwise IPD meta-analysis[472] identified 21 eligible studies including 3292 infants.[481–499] The median

study sample size was 65 (IQR, 40–101). The median (IQR) gestational age at birth was 29 (27–33) weeks. Deferred cord clamping ranged from 30 to ≥180 seconds (some trials encouraging deferrals up to 5 minutes where feasible). For immediate cord clamping, most trials (14/21) 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.[500] For this review, we present odds ratios, aligning with the iCOMP statistical analysis plan.[472,475,476] Key results are summarized in Table 19.

For the subgroup of infants <32 weeks' gestation allocated to deferred cord clamping, higher hematocrit values were also demonstrated (moderate-certainty evidence). For the subgroup of infants ≥32 weeks' gestation allocated to deferred cord clamping, Hb and hematocrit values were also probably higher (low-certainty to moderate-certainty evidence). For other critical and important infant and maternal outcomes, clinical benefit or harm could not be determined.

Comparison 2: Umbilical Cord Milking Compared With Immediate Cord Clamping

The pairwise IPD meta-analysis[472] identified 18 trials including 1565 infants.[485,487,492,502–516] The median study sample size was 60 (IQR, 45–122). The median gestational age at birth was 29 (IQR, 27–31) weeks. The cord was milked intact 2 to 4 times in 12 trials (866 infants), whereas in 4 trials (340 infants) the cut cord was milked once, and in 2 trials (359 infants) there was a delay before intact-cord milking. Of all infants, 64% were born by cesarean delivery, 13% were multiples, and 56% were male. Trials were conducted in high-income (10/18), upper-middle-income (4/18), and lower-middle-income (4/18) countries. Key results are presented in Table 20.

For the subgroup of infants <32 weeks' gestation receiving umbilical cord milking, hematocrit values were also possibly higher (low-certainty evidence). For the subgroup of infants ≥32 weeks' gestation receiving umbilical cord milking, hemoglobin and hematocrit values were possibly higher, and body temperatures on admission were possibly lower (very low–certainty evidence) while red cell transfusions were possibly reduced (low-certainty evidence). For all other critical and important infant and maternal outcomes (for all included infants or either subgroup), clinical benefit or harm could not be determined.

Comparison 3: Umbilical Cord Milking Compared With Deferred Cord Clamping

The pairwise IPD meta-analysis[472] identified 15 trials including 1655 infants.[485,487,492,517–528] The median study sample size was 44 (IQR, 36–171). The median gestational age at birth was 30 (IQR, 28–33) weeks. The intact cord was milked 2 to 4 times in 14 studies including 1649 infants and once in 1 study including 6 infants. Deferral times in the deferred cord clamping group ranged from 30 to 120 seconds. Of 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. Results are summarized in Table 21.

Table 19. Comparison 1: Deferred Umbilical Cord Clamping Compared With Immediate Cord Clamping

Outcomes (importance)	Participants (studies)	Certainty of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effect	
				Risk or mean concentration (±SD) with ICC	RD (CI) or MD (CI) with DCC; NNTB or NNTH, if applicable
Mortality before hospital discharge (critical)	3263 (20 RCTs)[481–499,501]	High	0.68 (0.51–0.91)	81/1000	25 fewer infants died per 1000 (38–7 fewer); NNTB, 40 (26–143) infants
Hemoglobin concentration (g/dL) for infants <32 weeks' gestation (important)	523 (8 RCTs)[482,485–488,495,498,499]	Moderate	NA	16 (±2) g/dL	0.88 (0.52–1.24) g/dL
Red cell transfusion for infants <32 weeks' gestation (important)	1929 (13 RCTs)[482,484–486,488,489,491,493,495,496,498,499,501]	Moderate	0.59 (0.47–0.73)	571/1000	131 fewer infants received red cell transfusion per 1000 (186 fewer–78 fewer); NNTB, 7 (6–13) infants
Hypothermia on admission to NICU for infants <32 weeks' gestation (adverse effect: important)	1995 (8 RCTs)[484–486,493,495,498,499,501]	Moderate	1.28 (1.06–1.56)	449/1000	62 more infants were hypothermic per 1000 (14 more–111 more); NNTH, 16 (9–71) infants

DCC indicates deferred cord clamping; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ICC, immediate cord clamping; MD, mean difference; NA, not applicable; NICU, neonatal intensive care unit; NNTB, number needed to treat to benefit; NNTH, number needed to treat to harm; OR, odds ratio; RCT, randomized controlled trial; and RD, risk difference.

Table 20. Comparison 2: Umbilical Cord Milking Compared With Immediate Cord Clamping

Outcomes (importance)	Participants (studies)	Certainty of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effect	
				Risk or weighted mean concentration (±SD) with ICC	RD (CI) or MD (CI) with UCM; NNTB or NNTH, if applicable
Mortality before hospital discharge (critical)	1565 (18 RCTs)[485,487,492,502–516]	Low	0.73 (0.44–1.20)	56/1000	14 fewer infants died per 1000 (30 fewer–10 more) infants
Hemoglobin concentration (g/dL) for infants <32 weeks' gestation (important)	944 (12 RCTs)[502,504,506–508,510,512–515]	Low	NA	15 (±2) g/dL	0.45 (0.17–0.73) g/dL
Red cell transfusion for infants <32 weeks' gestation (important)	1163 (15 RCTs)[485,502–504,506–516]	Moderate	0.69 (0.51–0.93)	443/1000	92 fewer infants received red cell transfusion per 1000 (167 fewer–18 fewer); NNTB, 11 (6–56) infants

DCC indicates deferred cord clamping; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ICC, immediate cord clamping; NA, not applicable; NNTB, number needed to treat to benefit; OR, odds ratio; RCT, randomized controlled trial; RD, risk difference; and UCM, umbilical cord milking.

For all other critical and important infant and maternal outcomes, clinical benefit or harm could not be determined.

Subgroup analyses. For all 3 comparisons, subgroup analyses by gestational age at birth, multiple versus singleton birth, caesarean section versus vaginal birth, study start year, perinatal mortality rate of country where study was conducted, and sex of infant did not influence the effect on mortality (very low–certainty to low-certainty evidence).

Individual Patient Data Network Meta-Analysis

- Population: Preterm infants born at <37+0 weeks' gestation and their mothers.
- Interventions:
  - Immediate (early) cord clamping at ≤15 seconds, without cord milking or initiation of respiratory support or as defined by the trialist
  - Short deferral of cord clamping for >15 seconds to <45 seconds without milking, with or without respiratory support
  - Medium deferral of cord clamping for ≥45 to <120 seconds without milking, with or without respiratory support
  - Long deferral of cord clamping for ≥120 seconds without milking, with or without respiratory support
  - Intact cord milking immediately after birth (with the umbilical cord attached to the placenta)
- Comparisons: Between-intervention comparisons
- Outcomes:
  - Mortality before hospital discharge (critical)
  - Intraventricular hemorrhage (critical)
  - Blood transfusion (important)
- Study design: As for the pairwise IPD meta-analysis,[472] RCTs comparing umbilical cord management strategies at preterm birth were included. Interventions were grouped into the following nodes: immediate clamping, short deferral, medium deferral, long deferral, and intact cord milking.[476]

Table 21. Comparison 3: Umbilical Cord Milking Compared With Deferred Cord Clamping

Outcomes (importance)	Participants (studies)	Certainty of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effect	
				Risk or mean concentration (±SD) with DCC	RD or change with UCM; NNTB or NNTH, if applicable
Mortality before hospital discharge (critical)	1303 (12RCTs)[485,487,492,517,518,520,521,524–526,528,529]	Low	0.95 (0.59–1.53)	72/1000	3 fewer infants died per 1000 (28 fewer–34 more)
Severe IVH in preterm infants <32 weeks' gestation (critical)	860 (7 RCTs)[485,487,517,518,520,521,528]	Low	2.20 (1.13–4.31)	38/1000	42 more infants had severe IVH per 1000 (5 more–112 more); NNTH, 24 (9–200) infants
Maternal postpartum blood transfusion (critical)	653 (4 RCTs)[485,517,518,521]	Low	2.72 (1.11–6.65)	25/1000	39 more mothers received blood transfusion per 1000 (3 more–118 more); NNTH, 25 (8–333) mothers

DCC indicates deferred cord clamping; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ICC, immediate cord clamping; IVH, intraventricular hemorrhage; NNTB, number needed to treat to benefit; NNTH, number needed to treat to harm; OR, odds ratio; RCT, randomized controlled trial; RD, risk difference; and UCM, umbilical cord milking.

- Time frame: As for the pairwise IPD meta-analysis[472,476]

Certainty of evidence was assessed using the CINeMA framework (Confidence in Network Meta-Analysis), which is based on the GRADE framework but is adapted for network meta-analysis.[530]

Consensus on Science

The NMA[476] and the IPD meta-analysis identified 47 eligible studies including 6094 infants.[481–485,487–499,501,502,504–506,508,510,511,516,518–525,528,531–540] The median study sample size was 60 infants (IQR, 40–127). The median gestational age at birth was 29.6 weeks (IQR, 27.6–33.3). Of all infants, 61% were born by cesarean delivery, 17% were multiples, and 54% were male. The primary outcome was missing for 4 (<0.1%) infants.

Sufficient data were found to include comparisons of the following 5 interventions in the NMA:

1. Immediate (early) cord clamping (as soon as possible or within 15 seconds)
2. Short deferral of cord clamping (≥15 seconds to <45 seconds)
3. Medium deferral of cord clamping (≥45 seconds to <120 seconds)
4. Long deferral of cord clamping (≥120 seconds)
5. Intact cord milking immediately after birth (milking the umbilical cord before the cord was clamped)

For the outcomes of death before discharge, any intraventricular hemorrhage, and blood transfusion, the number of trials for each comparison ranged from 0 to 8 and the number of infants varied from 29 to 1993.[476] The largest number of trials providing data for each outcome were for the cord milking compared with immediate cord clamping, for cord milking compared with medium deferral of cord clamping, and for immediate cord clamping compared with medium deferral of cord clamping. Note that in each case, the analysis was by intention to treat. Only 70% of the 47 trials reported treatment adherence.[476] Key results are presented in Table 22.

For comparisons and outcomes not included in Table 22, clinical benefit or harm could not be determined, and details are provided in the online CoSTR.[477]

When ranking probabilities were calculated, to prevent death before discharge, long deferred cord clamping had a 91% probability of being the highest ranked treatment; immediate cord clamping had <1% probability of being the best treatment and a 53% probability of being the worst treatment; and medium-length deferred cord clamping and intact umbilical cord milking had a high probability of being second or third best.[476]

Prior Treatment Recommendations (2021)

In infants born at <34 weeks' gestational age who do not require immediate resuscitation after birth, we suggest deferring clamping the cord for at least 30 seconds (weak recommendation, moderate-certainty evidence).[473,474]

In infants born at 28+0 to 33+6 weeks' gestational age who do not require immediate resuscitation after birth, we suggest intact-cord milking as a reasonable alternative to deferring cord clamping (weak recommendation, moderate-certainty evidence).[473,474]

We suggest against intact-cord milking for infants born at <28 weeks' gestational age (weak recommendation, very low–certainty evidence).[473,474]

In infants born at <34 weeks' gestational age who require immediate resuscitation, there is insufficient evidence to make a recommendation with respect to cord management.[473,474]

There is also insufficient evidence to make recommendations on cord management for maternal, fetal, or placental conditions that were considered exclusion criteria in many studies (in particular, multiple fetuses, congenital anomalies, placental abnormalities, alloimmunization, 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).[473,474]

Table 22. Network Meta-Analysis of Methods of Umbilical Cord Management

Comparison	Participants (studies)	Certainty of the evidence (GRADE)	OR (95% CI)	NNTB
Mortality before hospital discharge (critical)				
Long deferral (≥120 s) vs immediate cord clamping	469 (3 RCTs)[484,494,541]	Moderate	0.31 (0.11–0.80)	18 (4–143)
Red cell transfusion (important)				
Medium deferral vs immediate cord clamping	1933 (6 RCTs)[483,485,488,498,499,542]	Very low	0.45 (0.48–1.39)	NA
Short deferral vs immediate cord clamping	383 (5 RCTs)[481,482,489,491,501]	Moderate	0.44 (0.17–0.90)	NA
Intact cord milking vs immediate cord clamping	786 (9 RCTs)[502,504,506,508,511,516,535,543,544]	Very low	0.56 (0.31–0.97)	NA

GRADE indicates Grading of Recommendations, Assessment, Development, and Evaluation; NA, not applicable; NNTB, number needed to treat to benefit; and RCT, randomized controlled trial.

2024 Treatment Recommendations

In preterm infants born at <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 <28 weeks' gestation (weak recommendation, low-certainty evidence). There is insufficient evidence to make a recommendation concerning cut-cord milking in this gestational age group.

In preterm infants born at <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 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 clinicians and parents before delivery and should take into account individual maternal and infant circumstances (good practice statement).

Justification and Evidence-to-Decision Framework Highlights

The complete evidence-to-decision table can be found in Appendix A. A table summarizing key points of the treatment recommendations is presented in Table S1 in Appendix C.

The strong recommendation for deferring cord clamping for at least 60 seconds in preterm infants <37 weeks' gestation reflects the following considerations:

- Evidence for reduced mortality after deferred cord clamping compared with immediate cord clamping was rated high-certainty.[472,477] The reduction in mortality was robust across several participant-level and trial-level subgroups (including gestational age at birth, mode of birth, multiple birth, sex, trial year, and perinatal mortality rate) and consistent in all prespecified sensitivity analyses.
- We place high value on the outcome of mortality, and this has guided the strong treatment recommendation. The certainty of evidence for other outcomes varied from low to moderate, and, therefore, we concluded that the overall certainty of evidence is moderate.
- There was moderate-certainty evidence in infants <32 weeks' gestation for fewer red cell transfusions and in infants both < and ≥32 weeks' gestation for higher hemoglobin concentrations within the first 24 hours after birth after deferred cord clamping compared with immediate cord clamping.
- Sixty seconds or more was chosen as the recommended interval for deferred cord clamping because that threshold defined 80% of infants who received deferred clamping in the combined studies. The evidence for medium (60–119 seconds) or long (>120 seconds) deferral of cord clamping is based on fewer infants and trials. Moreover, the analysis was by intention to treat, many trials did not report actual interval from birth to cord clamping, and most trials allowed clinicians to clamp the cord when considered necessary to perform resuscitation. The reported adherence to long delay was lowest at 67% (compared with about 80% for medium deferral and 95% for immediate cord clamping, umbilical cord milking, and short deferred cord clamping), so the proportion and clinical characteristics of infants who benefited from medium or long delay are unclear. Furthermore, there were fewer than 121 extremely preterm infants in the trials of long delay.[493,494]
- Medium or long delay may be justified for infants who are coping well without resuscitation or where appropriate newborn stabilization can be provided before umbilical cord clamping (skilled team, proper training, appropriate equipment, enough space, and ability to provide measures to maintain normal temperature).
- The task force noted that there was moderate-certainty evidence for the adverse effect of an increase in the risk of hypothermia (body temperature <36.5 °C) on admission after deferred cord clamping compared with immediate cord clamping for infants <32 weeks' gestation. Refer to ILCOR recommendations concerning maintaining normal temperature immediately after birth in preterm infants.[146]
- Parents report that deferred cord clamping provides a positive experience, with the mothers feeling closer and more attached to their infants.[545]

In making the suggestion to consider umbilical cord milking as an alternative to immediate cord clamping in infants born at 28+0 to 36+6 weeks' gestation, the task force considered the following:

- Low-certainty evidence that umbilical cord milking may not reduce the critical outcome of death before discharge compared with immediate cord clamping

- Moderate-certainty evidence for reduced red cell transfusion after umbilical cord milking compared with immediate cord clamping in infants both <32 weeks' gestation and ≥32 weeks' gestation
- Low-certainty evidence for higher hemoglobin after umbilical cord milking compared with immediate cord clamping in infants, both <32 weeks' gestation and ≥32 weeks' gestation.
- No evidence for adverse effects in preterm infants <37 weeks' gestation or their mothers after umbilical cord milking compared with immediate cord clamping
- No evidence for adverse effects after umbilical cord milking compared with deferred cord clamping in preterm infants born at 28+0 to 36+6 weeks' gestation
- The IPD meta-analyses did not distinguish between the 2 methods of cord milking (intact-cord and cut-cord). The intact cord was milked 2 to 4 times in most trials, while a few trials milked the cut cord once; therefore, no specific recommendations are made for either method.

In making the suggestion against intact umbilical cord milking in infants <28 weeks' gestation, but not in infants of higher gestational age, the task force considered the following:

- Low-certainty evidence for increased severe intraventricular hemorrhage after intact-cord milking compared with deferred cord clamping
- One trial was stopped early because of increased rates of severe intraventricular hemorrhage in the prespecified subgroup of preterm infants born at <28 weeks' gestation[520]
- The same RCT has subsequently reported that for infants born at 28 to 32 weeks' gestation there was no increase in severe intraventricular hemorrhage, mortality, or other adverse clinical outcomes after umbilical cord milking compared with deferred cord clamping.[546] This study was not included in the analysis because it was published after the iCOMP meta-analysis was completed and the CoSTR development process was started.

There was insufficient evidence to make a recommendation concerning cord management of preterm infants who are deemed to require resuscitation at birth. This conclusion reflected the following:

- Adherence to deferred cord clamping was low (<75% in those trials reporting adherence), in most cases because health care professionals chose immediate cord clamping or cord milking in preference to deferred cord clamping when they judged that the infant required assisted ventilation.[472] Some studies did not report adherence. Taken together, these factors led to a conclusion that the benefits and risks of deferred cord clamping remain unclear for nonvigorous preterm infants and those who require resuscitation at birth.[472]
- The evidence from animal studies and feasibility studies in human infants increasingly supports provision of some resuscitation measures while deferring cord clamping (variously described in studies as resuscitation with intact cord, physiologic cord clamping, or baby-directed cord clamping). Results of studies currently underway that evaluate these strategies may lead to changes in recommendations in the future, but there was insufficient evidence to make a recommendation now.

The suggestion for individualized decision-making in the context of maternal, fetal, or placental conditions that were exclusion criteria is unchanged from 2021 and took into account that similar constraints applied to the results of the iCOMP systematic reviews.

In suggesting discussion before birth (whenever possible) about the plan for umbilical cord management, the task force considered that this approach is most likely to lead to the best decisions about what plan of cord management to use and how to coordinate the steps in care of the infant among different care professionals and the parents.

Knowledge Gaps

- Long-term neurodevelopment and health outcomes after different cord management strategies
- Effectiveness of optimized cord management as a public health strategy to improve child health and development
- Optimal cord management of preterm infants who are not breathing after initial steps of resuscitation
- Optimal cord management for preterm infants born with specific maternal, fetal, and placental conditions that led to exclusion from RCTs
- Optimal measures to prevent hypothermia during deferred cord clamping
- Optimal duration of deferred cord clamping, and the criteria to determine that duration
- Circumstances where cut-cord milking represents best-available management
- Impact of cord management on vertical transmission of infectious diseases
- Widely agreed-upon nomenclature and definition of different interventions, including delayed, deferred, later, optimal, and physiologic cord clamping as well as milking, stripping, intact-cord milking, and cut-cord milking

Effect of Rewarming Rate on Outcomes for Newborns Who are Unintentionally Hypothermic After Delivery (NLS 5700: SysRev)

Rationale for Review

Both term and preterm newborn infants are at high risk of hypothermia during and immediately after resuscitation in high-, middle-, and low-income countries.[547–549]

Previous large observational studies have found an association between hypothermia and neonatal mortality and morbidity.[550–557] The optimal rate of rewarming for unintentionally hypothermic infants has not been defined. Slow rewarming could prolong metabolic demands and increase adverse outcomes of hypothermia such as apnea, respiratory distress, and hypoglycemia,[550,558,559] but there is a suggestion from a few preclinical and clinical studies in other age groups and contexts (such as after therapeutic hypothermia) that rapid rewarming could be harmful.[560] In 2020, the Neonatal Life Support Task Force undertook an evidence update which concluded that there were sufficient new studies to consider updating the systematic review.[561] The SysRev was registered before initiation (PROSPERO registration CRD42022359005). The full online CoSTR can be found on the ILCOR website.[562]

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

- Population: Newborn infants who are hypothermic (<36.0 ˚C) on admission
- Intervention: Rapid rewarming (≥0.5 °C/hour)
- Comparators: Slow rewarming (<0.5 °C/hour)
- Outcomes (importance assigned by task force consensus, in accord with available guidelines[478,479]):
  - Mortality rate (critical)
  - Neurodevelopmental impairment (critical)
  - Need for respiratory support during the first 48 hours of life (important)
  - Hypoglycemia during the first week of life (important)
  - Convulsions/seizures during hospital stay (important)
  - Length of hospital stay (important)
  - In addition, for preterm infants born at <34 weeks:
    - Intraventricular hemorrhage (all grades—important; severe [III or IV]—critical)
    - Periventricular leukomalacia (critical)
    - Necrotizing enterocolitis (important)
- Study designs: RCTs and nonrandomized studies (nonrandomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (eg, conference abstracts, trial protocols), case series, case reports, and animal studies were excluded.
- Time frame: All years and all languages were included if there was an English abstract. The search strategy designed for the 2020 evidence update was rerun in July 2022 and updated in July 2023.

Consensus on Science

The review identified 1 RCT of 42 infants comparing maximum temperature set points for the servo-controlled radiant warmers used for rewarming; rates of rewarming depended on these set points.[563] The study enrolled only otherwise well, term newborn infants of normal birth weight. The review also identified 2 observational studies including a total of 280 infants, one of which included only infants born at ≤28 weeks' gestation or birth weight ≤1000 g[564] while the other enrolled only infants with birthweight <1500 grams.[565] For the critical outcome of mortality, these 2 studies could not exclude benefit or harm from rapid rewarming compared with slow rewarming (RR, 1.09 [95% CI, 0.7–1.71]; absolute risk difference, 17 fewer deaths per 1000 infants [95% CI, from 58 fewer–138 more]; low-certainty evidence).[564,565]

For other critical and important outcomes, either data were inconclusive or there were no data.

Prior Treatment Recommendations (2015)

The confidence in effect estimates is so low that a recommendation for either rapid rewarming (0.5 °C/h or greater) or slow rewarming (0.5°C/h or less) of unintentionally hypothermic newborn infants (temperature <36 °C) at hospital admission would be speculative.[566]

2024 Treatment Recommendations

In newborn infants who are unintentionally hypothermic after birth, rewarming should be started, but there is insufficient evidence to recommend either rapid (≥0.5˚C/h) or slow (<0.5˚C/h) rates of rewarming.

Regardless of the rewarming rate chosen, a protocol for rewarming should be used. Frequent or continuous monitoring of temperature should be undertaken, particularly if using a supraphysiological set temperature point to accelerate the rewarming rate, because of the risk of causing hyperthermia. In any hypothermic infant, monitor blood glucose because there is a risk of hypoglycemia (good practice statement).

Justification and Evidence-to-Decision Framework Highlights

The complete evidence-to-decision table can be found in Appendix A.

- Although hypothermia after birth is associated with increased mortality and morbidity, the included studies were too small to determine the effect of rate of rewarming on mortality and other outcomes. One observational study showed an association of rapid rewarming with a reduced rate of respiratory distress syndrome in preterm infants.[564] However, numbers were small, the absolute risk difference was not shown, and the authors did not report whether this resulted in a clinical difference in need for respiratory support for respiratory distress syndrome.
- The task force considered that both the intervention and control treatment were acceptable and feasible. Two of the 3 included studies used servo-controlled devices to monitor and control the rate of rewarming. Regarding equity, servo-controlled devices

(eg, servo-controlled radiant warmers, incubators, or thermal mattresses) have not yet been demonstrated to improve outcomes of rewarming. The cost of devices capable of operating in servo mode and disposable temperature probes may be unaffordable in resource-limited settings.

- The rate of rewarming varied widely in the rapid rewarming groups in the included studies. The task force noted that a safe maximum rate of rewarming has not been identified. Furthermore, none of the included studies reported hyperthermia as an outcome. One observational study that did not meet inclusion criteria found that 43 (12.5%) of 344 included infants developed hyperthermia (>37.5 ˚C).[567] In this study, a rapid rewarming rate, compared with a slow rewarming rate, was associated with hyperthermia. It is unclear whether this related to specific settings of the devices used for rewarming (which were radiant warmers and incubators in manual mode) in this study or to other characteristics of the included infants. These findings may be clinically important because recent observational studies have confirmed an association between hyperthermia on neonatal ICU admission and adverse outcomes.[568,569] Future studies should consider this important outcome.

Knowledge Gaps

- The optimal method and rate of rewarming, including equipment and settings
- Effect of rewarming rate on short-term and long-term outcomes, for both preterm and term infants
- Effect of rewarming rate on metabolic markers such as acidosis and glycemic status
- Cost-effectiveness of rewarming strategies, including equipment and the need for and duration of neonatal ICU admission
- The effects of protocols for rewarming on parental separation and the establishment of breastfeeding and on the safety and effectiveness of skin-to-skin care for rewarming

Therapeutic Hypothermia in Limited-Resource Settings (NLS 5701: SysRev)

Rationale for Review

Therapeutic hypothermia is now standard care in high-income countries for the treatment of moderate or severe hypoxic ischemic encephalopathy in term and near-term infants.[570] However, uncertainty persists about the efficacy of therapeutic hypothermia in low-resource settings or in low- and middle-income countries. Because asphyxia is a leading cause of neonatal mortality and morbidity in low- and middle-income countries, it is critical to determine whether therapeutic hypothermia improves mortality and neurodevelopmental outcomes in this setting. The treatment shown to be effective in high-income countries generally consists of cooling to 33.5 °C commencing within 6 hours of birth and for a duration of 72 hours. Servo-controlled cooling devices are increasingly used in high-income countries because they achieve more consistent adherence to target temperatures,[571] although effective cooling can be accomplished by removal of heat sources and clothing and by applying refrigerated gel packs, making the treatment feasible in low-resource settings.[572] The topic was last reviewed by the task force in 2015, with an emphasis on the use of passive hypothermia or cold packs.[468] An evidence update in 2020[561] identified new studies and an ongoing large multicenter RCT that has since been published.[573]

The SysRev was registered before initiation (PROSPERO registration CRD42022360554). The full online CoSTR can be found on the ILCOR website.[574]

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

- Population: Late preterm and term infants (34+0 or more weeks' gestation) with moderate or severe hypoxic ischemic encephalopathy managed in low-resource settings
- Intervention: Therapeutic hypothermia to a specified target temperature for a defined duration
- Comparators: Standard care
- Outcomes (importance assigned by task force consensus, in accord with available guidelines[478,479]):
  - Death or neurodevelopmental impairment at 18 months to 2 years: composite outcome (critical)
  - Death at hospital discharge (critical)
  - Neurodevelopmental impairments at 18 months to 2 years (critical)
  - Cerebral palsy (critical)
  - Blindness (critical)
  - Deafness (critical)
  - Persistent pulmonary hypertension of the newborn or other adverse outcome (as defined by the study authors)

Neurodevelopmental impairment was defined as abnormal motor, sensory, or cognitive function using an appropriate standardized test.

- Study designs: RCTs and nonrandomized studies (nonrandomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (eg, conference abstracts, trial protocols) were excluded. All languages were included if there was an English abstract.
- Time frame: Databases were searched from inception until September 2022, and the search was updated to July 2023.

Consensus on Science

The systematic review identified 21 RCTs involving 2145 infants with hypoxic ischemic encephalopathy.[575–595] Most

studies were single site, but 3 were multicenter.[585,592,594] Key results are summarized in Table 23.

Apart from persistent pulmonary hypertension, reporting of adverse events during therapeutic hypothermia was inconsistent between studies. Subgroup analysis suggested that non–servo-controlled methods were more efficacious, although the task force considered that these results were more likely due to other aspects of study design than to a benefit of non–servo-controlled methods.

Prior Treatment Recommendations (2015)

We suggest that newborn infants at term or near term with evolving moderate-to-severe hypoxic-ischemic encephalopathy in low-income countries and/or other settings with limited resources may be treated with therapeutic hypothermia (weak recommendation, low-quality evidence).[566]

Cooling should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care and availability of adequate resources to offer intravenous therapy, respiratory support, pulse oximetry, antibiotics, antiseizure medications, and pathology testing. Treatment should be consistent with the protocols used in the randomized clinical trials in developed countries, that is, cooling to start within 6 hours, strict temperature control at 33 °C to 34 °C for 72 hours, and rewarming over at least 4 hours.[566]

2024 Treatment Recommendations

We suggest the use of therapeutic hypothermia in comparison with standard care alone for term (≥37+0 weeks' gestational age) newborn infants with evolving moderate-to-severe hypoxic-ischemic encephalopathy in low- and middle-income countries in settings where a suitable level of supportive neonatal care is available (weak recommendation, low-certainty evidence).

For late preterm infants, 34+0 to 36+6 weeks' gestational age infants, a recommendation cannot be made due to insufficient evidence.

Therapeutic hypothermia should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care and availability of adequate resources to offer intravenous therapy, respiratory support, pulse oximetry, antibiotics, antiseizure medication, transfusion services, radiology (including ultrasound), and pathology testing, as required. Treatment should be consistent with the protocols used in RCTs. Most protocols included the starting of cooling within 6 hours after birth, strict temperature control to a specified range (typically 33 °C–34 °C) and most commonly for a duration of 72 hours with rewarming over at least 4 hours. Adoption of hypothermia techniques without close monitoring, without protocols, or without availability of comprehensive neonatal intensive care may lead to harm (good practice statement).

Justification and Evidence-to-Decision Framework Highlights

The complete evidence-to-decision table can be found in Appendix A.

Table 23. Use of Therapeutic Hypothermia for Infants With Moderate or Severe Hypoxic Ischemic Encephalopathy in Low- or Middle-Income Countries

Outcomes (importance)	Participants (studies)	Certainty of the evidence (GRADE)	RR (95% CI)	Anticipated absolute effect	
				Risk with standard care	RD with therapeutic hypothermia; NNTB, if applicable
Death or NDI at 18–24 mo (critical)	813 (5 RCTs)[576,585,592,594,595]	Moderate	0.67 (0.45–0.99)	458/1000	151 fewer infants died or had NDI per 1000 (5 fewer–252 fewer); NNTB, 7 (4–200) infants
Death or NDI at any time of follow-up (critical) (post-hoc outcome)	1168 (9 RCTs)[576,578,581,582,585,590,592,594,595]	Low	0.50 (0.35–0.71)	474/1000	237 fewer infants died or had NDI per 1000 (138 fewer–308 fewer); NNTB, 5 (4–8) infants
Death at hospital discharge (critical)	1488 (15 RCTs)[576–580,584,586–593,595]	Moderate	0.70 (0.47–1.02)	215/1000	64 fewer infants died per 1000 (114 fewer–4 more)
Cerebral palsy (critical)	919 (6 RCTs)[576,583,585,590,592,594]	High	0.52 (0.37–0.72)	186/1000	89 fewer infants had cerebral palsy per 1000 (52 fewer–117 fewer); NNTB, 12 (9–20) infants
Blindness (critical)	718 (4 RCTs)[581–583,592]	Moderate	0.48 (0.22–1.03)	53/1000	28 fewer infants were blind per 1000 (41 fewer–2 more)
Deafness (critical)	718 (4 RCTs)[581–583,592]	Moderate	0.42 (0.21–0.82)	72/1000	42 fewer infants were deaf per 1000 (57 fewer–13 fewer); NNTB, 24 (18–77) infants
PPHN (adverse effect: critical)	564 (3 RCTs)[575,591,592]	High	1.31 (0.76–2.25)	74/1000	23 more infants had PPHN per 1000 (18 fewer–92 more)

GRADE indicates Grading of Recommendations, Assessment, Development, and Evaluation; NDI, neurodevelopmental impairment; NNTB, number needed to treat to benefit; PPHN, persistent pulmonary hypertension; RCT, randomized controlled trial; RD, risk difference; and RR, risk ratio.

- The largest included (multicenter) RCT found that therapeutic hypothermia significantly increased mortality and did not reduce the combined outcome of death or disability at 18 months.[592]
- Nevertheless, the combined (moderate certainty) evidence from all RCTs that assessed death plus disability at 18 to 24 months or cerebral palsy found that therapeutic hypothermia reduced neurodevelopmental impairment without increasing mortality. For several of the critical outcomes, there was high heterogeneity, which together with the preponderance of smaller, single-center trials mostly reporting benefit, raised the possibility of publication bias. For some studies, concerns have been raised about study methodology underlying participant heterogeneity, including methods of patient selection, as well as consistency of diagnosis and pathogenesis.[596] Therefore, the task force concluded that the overall certainty of evidence was low. Furthermore, for adverse effects of therapeutic hypothermia, there was heterogeneity and inconsistency of reporting among the included studies, precluding meta-analysis.
- Although the PICOST intended to evaluate infants ≥34+0 weeks of gestational age, 15 of the 21 included studies specified ≥37 weeks of gestational age as an inclusion criterion, making the data for late preterm infants insufficient to support a treatment recommendation.
- Distinction between low- and middle-income countries versus high-income countries, based on World Bank determinations, is straightforward.[597] However, the hospitals in the included studies (all in low- and middle-income countries) could provide neonatal ICU care, including advanced respiratory support, indicating a high level of resources despite their location in low- and middle-income countries. Therefore, the recommendation is made in relation to low- and middle-income countries rather than to the low-resource settings intended by the PICOST.
- In high-income countries, adequate follow-up assessment and care are also considered necessary to optimize neurodevelopmental outcomes and to monitor the effectiveness of treatment.

Knowledge Gaps

- The minimum intensive care resources required for safe and effective provision of therapeutic hypothermia in low- and middle-income countries
- Cost-effectiveness of therapeutic hypothermia in low- and middle-income countries
- Resource implications for safe and effective care of infants during provision of therapeutic hypothermia in low- and middle-income countries
- Strategies for optimal case selection of infants who may benefit from or may be harmed by therapeutic hypothermia in countries at all income levels

EDUCATION, IMPLEMENTATION, AND TEAMS

Cardiac Arrest Centers (EIT 6301: SysRev)

Rationale for Review

Specialized post–cardiac arrest care at a cardiac arrest center (CAC) may improve long-term survival from OHCA. Previous studies have reported an association between survival to hospital discharge and transport to a CAC, but there is inconsistency in the hospital factors that are most related to patient outcome.[598]

In 2020, ILCOR reviewed the evidence on CACs despite a lack of high-quality data to support their implementation.[232] Since then, new evidence on CACs has been published, triggering this update of the SysRev SysRev (PROSPERO number CRD42018093369). CACs are defined as specialized institutions offering treatment or services for patients with OHCA, including a coronary angiography laboratory with 24/7 percutaneous coronary intervention, post–cardiac arrest temperature control, extracorporeal membrane oxygenation, mechanical ventilation, and neurologic prognostication.[599] For this review, we defined CAC as having the capability for 2 or more of the above interventions and explicitly referred to by study authors as CACs (or synonymous terms such as critical care medical center, tertiary heart center, or regional center).[600] We excluded studies that used high volume (number of cases/patients) or percutaneous coronary intervention capability as the only distinguishing characteristics. The full CoSTR can be found online.[601]

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

- Population: Adults and children with attempted resuscitation after nontraumatic IHCA or OHCA
- Intervention: Care at a specialized CAC
- Comparator: Care in an institute not designated as a specialized CAC
- Outcome:
  - Critical: Survival at 30 days with favorable neurological outcome, survival at hospital discharge with favorable neurological outcome, survival at 30 days, and survival at hospital discharge
  - Important: ROSC after hospital admission for patients with ongoing CPR
- Study design: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (eg, conference abstracts, trial protocols) were excluded. All relevant publications in any language were included as long as there was an English abstract available.
- Time frame: The literature search included all years to June 23, 2023.