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| Question |
| **Should rapid rewarming vs. slower rewarming be used for hypothermia immediately after birth in newborn infants?** |
| **Population:** | Newborn infants with hypothermia immediately after birth |
| **Intervention:** | Rapid rewarming |
| **Comparison:** | Slower rewarming |
| **Main outcomes:** | Mortality; need for respiratory support during the first week of life; hypoglycemia (<47 mg/dl, 2.6 mmol/L); hypoglycemia (<30 mg/dl, 1.6 mmol/L); convulsions/ seizures during hospital stay; length of hospital stay; neurodevelopmental impairment; intraventricular hemorrhage (IVH); periventricular leukomalacia; necrotizing enterocolitis (NEC) |
| **Setting:** | Locations where infants are born |
| **Perspective:** | Individual patients, their families and providers caring for those patients. |
| **Background:** | The rate of rewarming of newborn infants after unintentional hypothermia infants was last reviewed by ILCOR in 2015 and the level of evidence was considered so low that no recommendation could be made. {Perlman 2015 S204} A subsequent ILCOR evidence update in 2020 indicated that there was some new evidence. {Wyckoff 2020 S185} Slow rate of rewarming was defined as less than 0.5˚C per hour and rapid rate of rewarming was considered as 0.5˚C per hour or greater.  |
| **Conflict of interests:** | None |

# Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● **Yes**○ Varies○ Don't know | Newborn infants are at high risk of becoming hypothermic during resuscitation and in the immediate newborn period, leading to lower than desired body temperatures at admission to neonatal intensive care. Unintentional hypothermia should be corrected because of evidence of poor outcomes {Laptook 2018 53, Wilson 2016 61} A small case series of infants with severe hypothermia suggested that faster rewarming might result in fewer complications than slow rewarming.{Kaplan 1984 470}. In 2020, the NLS Task Force undertook an Evidence Update (NLS 858: EvUp). {Wyckoff 2020 S185} The update found that there was additional literature which might result (after systematic review) in a treatment recommendation, instead of the 2015 ILCOR conclusion that: “The confidence in effect estimates is so low that a recommendation for either rapid rewarming (0.5°C/h or greater) or slow rewarming (0.5°C/h or less) of unintentionally hypothermic newborn infants (temperature less than 36°C) at hospital admission would be speculative". {Perlman 2015 S204} |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial●**Small**○ Moderate○ Large○ Varies○ Don't know | Based on the available evidence rapid rewarming may not confer any significant advantage over slow rewarming other than achieving normothermia sooner. A higher rewarming rate was associated with a lower rate of respiratory distress syndrome in preterm infants. {Rech Morassutti 2015 557} However this was an observational study with low numbers (n=182 newborn infants) and a wide confidence interval (OR 0.39, 95% CI 0.17-0.87; p=0.02) for this outcome. For the outcome of hypoglycemia, one small randomized controlled trial (n=36 newborns), in whom 8 developed hypoglycemia (defined as glucose <30mg/dl), could not exclude clinical benefit or harm with rapid rewarming ((RR 0.3, 95% CI 0.09-1.05), ARD 292 fewer per 1000 (95% CI from 379 fewer to 21 more)), very low certainty evidence (downgraded for serious indirectness and very serious imprecision). {Motil 1974 546}. For the outcome of hypglycemia, an observational study (n=182 newborns, in whom 47 developed hypoglycemia (defined as glucose <47mg/dL), could not exclude clinical benefit or harm when comparing rapid with slow rewarming rates (OR 0.46, 95% CI 0.20-1.07), ARD 130 more per 1000 (95% CI from 211 fewer to 14 more)), very low certainty evidence (downgraded for serious indirectness and very serious imprecision. {Rech Morassutti 2015 557} | Whether or not the lower rates of respiratory distress syndrome were associated with lower rates of need for respiratory support was not reported. {Rech Morassutti 2015 557} |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate○ Large○ Varies**● Don't know** | The available evidence does not demonstrate undesirable effects of rapid rewarming; however, sample sizes are small and may be insufficient to detect uncommon, but potentially serious adverse outcomes.  | One additional retrospective observational study in which correlation between rate of rewarming and various outcomes was calculated was not included in the systematic review because a division into rapid rewarming and slower rewarming groups was not shown for all outcomes. {Rossi 2023 1113897} In this study, 43/344 (12.5%) infants developed hyperthermia (>37.5˚C). Rewarming rate was significantly correlated with hyperthermia (p=0.007). These findings may be clinically important because recent observational studies have confirmed an association between hyperthermia on NICU admission and adverse outcomes. {Brophy 2022 1706, Wilson 2016 61}Previous large studies have found an association between hypothermia in perterm and term infants and neonatal mortality and morbidity. {Boo 2013 447, Guinsburg 2016 1005, Laptook 2007 e643, Meyer 2001 395, Miller 2011 S49, Mullany 2010 650, S 2012 , Zayeri 2005 1367} It could be speculated that the more prolonged the hypothermia the greater the risk for mortality and morbidity. However, the included studies were too small to comprehensively assess the rate of rewarming on neonatal mortality and major morbidities.  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low**● Low**○ Moderate○ High○ No included studies | Overall, the certainty of evidence was low due to small sample size, wide confidence intervals and heterogeneity in populations and in some cases, outcome definition (e.g. hypoglycemia). No benefit of rapid rewarming compared to slow rewarming was found for the following outcomes, but the certainty of evidence was low or very low for each: * The critical outcome of mortality and intraventricular hemorrhage: (2 observational studies, n=280 neonates, **low certainty evidence** (downgraded for very serious imprecision) {Feldman 2016 295, Rech Morassutti 2015 557}
* The important outcomes of
	+ length of stay (1 observational study, n=182, **low certainty evidence** (downgraded for very serious imprecision) {Rech Morassutti 2015 557}
	+ hypoglycemia (1 small RCT, n=36, very low certainty evidence downgraded for serious indirectness and imprecision) {Motil 1974 546} and 1 observational study, n=182, **very low certainty evidence** (downgraded for serious indirectness and very serious imprecision), {Rech Morassutti 2015 557}
	+ convulsions/seizure (1 observational study, n=182, **low certainty evidence** (downgraded for very serious imprecision) {Rech Morassutti 2015 557}
	+ necrotizing enterocolitis (1 observational study, n=98, **low certainty evidence** (downgraded for very serious imprecision). {Feldman 2016 295}
* No data were found for the critical outcomes of neurodevelopmental impairment and periventricular leukomalacia and the important outcome of need for respiratory support during the first 48 hours of life.
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| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability**● Probably no important uncertainty or variability**○ No important uncertainty or variability | The value attributed to the main outcomes was based on consensus of the ILCOR NLS Task Force and a larger group of neonatal resuscitation experts. {Strand 2020 F328}  |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison ● **Does not favor either the intervention or the comparison**○ Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | The three included studies did not show clinical benefit or harm in either rewarming rate. However the overall certainty of evidence was low with wide confidence intervals and small numbers of participants. Based on low certainty evidence, rapid rates of rewarming may be associated with lower rate of RDS in preterm infants, but whether this resulted in a difference in the need for respiratory support was not reported. {Rech Morassutti 2015 557}.  |  |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings○ Varies● Don't know | No included studies assessed the resources required | Two of the three included studies used servo-controlled devices for rewarming. {Motil 1974 546, Rech Morassutti 2015 557} If future studies demonstrate superiority of servo-controlled devices, this could have important implications in resource limited settings. |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | No included studies assessed the certainty of resources required |  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | No included studies investigated cost-effectiveness.  |  |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced○ Probably no impact○ Probably increased○ Increased○ Varies● Don't know | No included studies addressed equity. However, unintended hypothermia after birth is a common problem in low-, middle- and high-income countries  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● **Probably yes**○ Yes○ Varies○ Don't know | No studies included in the review specifically addressed acceptability. However, the task force considered that rapid rewarming was likely to be an acceptable intervention.  |  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● **Probably yes**○ Yes○ Varies○ Don't know | While feasibility was not specifically addressed within the studies, the task force considered that rapid rewarming was a feasible intervention.  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Trivial | Small | Moderate | Large |  | Varies | **Don't know** |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | **●**  | ○  | ○  |

# Conclusions

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| Recommendation |
| In newborn infants who are unintentionally hypothermic after birth, rewarming should be commenced, but there is insufficient evidence to recommend either rapid (≥0.5 ˚C per hour) or slow (<0.5 ˚C per hour) rates of rewarming. (Low certainty evidence) Irrespective of the rewarming rate chosen, a protocol for rewarming should be used. Frequent or continuous monitoring of temperature should be undertaken while rewarming, particularly if using a supraphysiological set temperature point to accelerate the rewarming rate, due to potential risk of hyperthermia. In any hypothermic infant, monitoring of blood glucose should occur due to risk of hypoglycemia. (Good practice point) |
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| Justification |
| The available evidence does not confirm clinical benefit or harm in either rewarming rate; however, the overall certainty of evidence was low with wide confidence intervals and small numbers. We are aware of the increased risk of mortality associated with hypothermia, however the present studies are too small to find an impact of rewarming rate on mortality. One small randomized controlled trial showed an association of slow rewarming with occurrence of asymptomatic hypoglycemia. {Motil 1974 546} However, a somewhat larger observational study did not show an effect on hypoglycemia. {Rech Morassutti 2015 557} Finally, one study showed an association with a reduced rate of respiratory distress syndrome (RDS) in preterm infants. However, numbers were small with wide confidence intervals. {Rech Morassutti 2015 557} Furthermore, the authors did not report whether there was a clinical difference in need for respiratory management related to RDS. Both intervention and control are considered to be acceptable and feasible, however two out of the three studies used servo control to monitor rate of rewarming. If servo control is in an important factor in regulating rewarming, then this could be an important consideration in resource limited settings. The rate of rewarming varied widely in the rapid rewarming groups in the included studies. Furthermore, none of the studies included hyperthermia as an outcome. However, one observational study which did not meet the inclusion criteria found that 43 out of 344 (12.5%) infants developed hyperthermia (>37.5˚C). {Rossi 2023 1113897} In this study, rapid, compared to slow rewarming rate was significantly associated with hyperthermia (p=0.007). It is unclear whether this related to specific settings of the devices (radiant warmers and inclubators in manual mode) used for rewarming in this particular study. Future studies should consider this important outcome. |

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| Subgroup considerations |
| The three included studies did not provide sufficient evidence for any subgroup analysis. Two of the three included studies considered only preterm and very low birthweight infants. {Feldman 2016 295, Rech Morassutti 2015 557} Further studies are needed to analyse according to varying gestational age and birthweight, and to address methods and outcomes in high- and low-resource settings.  |

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| Implementation considerations |
| Rapid or slower rates of rewarming may be accomplished with similar cost, personnel, or equipment resources. Both approaches require close monitoring of temperature. In two of the three included studies, monitoring and rewarming were accomplished using servo-controlled devices. If demonstrated to be preferable, the use of servo control may have implications in resource limited settings.  |

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| Monitoring and evaluation |
| Continued monitoring of rewarming practices and short- and long-term clinical outcomes are suggested. The monitoring should include monitoring for and attempting to avoid hyperthermia.  |

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| Research priorities |
| Research priorities include identification of the optimal method of rewarming. Research gaps include: * impact of rate of rewarming on:
* critical short and long term neonatal outcomes
* risk of hyperthermia
* metabolic markers such as metabolic and lactic acidosis, blood glucose level
* cost-effectiveness considerations, including equipment, need for NICU admission, length of stay
* parental separation
* breastfeeding rates
* subgroup analysis according to:
* gestational age and birthweight
* degree of hypothermia at initiation of rewarming
* location of birth (e.g., in or out of hospital/birthing centre) and resource setting
* superiority/inferiority of servo versus manual control of rewarming
* safety and effectiveness of skin-to-skin care for rewarming
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