NLS Appendix A – Evidence to decision tables

NLS 5050(a) Umbilical cord management at birth for non-vigorous term and late preterm infants

Question 1: Intact cord milking vs early cord clamping

Should intact cord milking vs. early cord clamping be used for non-vigorous newborn infants?	
POPULATION:	Term and late preterm infants (≥34 weeks' gestation) who are not vigorous at birth
INTERVENTION:	Intact cord milking (I-UCM)
COMPARISON:	Early cord clamping (ECC)
MAIN OUTCOMES:	Infant • Neonatal mortality (critical) • Moderate to severe neurodevelopmental impairment at 18-24 months (critical) • Any component of neurodevelopmental impairment at 18-24 months (critical) (cerebral palsy, significant mental developmental delay, blindness as defined by WHO (<20/200 visual acuity) or the author's definition, hearing deficit (aided or <60 dB on audiometric testing) • Moderate to severe hypoxic ischemic encephalopathy (HIE; Sarnat 2 or 3 {Sarnat 1976 696}) (critical) • Proportion of infants receiving chest compressions in the delivery room (DR) (important) • Admission to a neonatal intensive care unit (important) • Jaundice: treated with exchange transfusion (critical) or phototherapy (important) • Hematologic outcomes including peak hemoglobin or hematocrit concentration during hospital admission (important)and anemia or iron deficiency at 4-6 months (important) • Unintended hypothermia within the first hour of life (important) Mother: Postpartum hemorrhage, estimated as at least 1000 mL (critical), postpartum infection (critical), death or severe morbidity (composite), major surgery, organ failure, intensive care unit admission, (critical)
SETTING:	Delivery room

PERSPECTIVE:	Population
BACKGROUND:	Each of the 130 million babies born annually requires management of their umbilical cord. For term and near-term infants born in good condition there is now substantial evidence suggesting that deferred clamping of the cord for >60 seconds is the preferred strategy. {Wyckoff 229} This recommendation excludes an important group of infants at increased risk of death or long-term neurodevelopmental impairment i.e., those who are non-vigorous. These infants appear apneic, limp and pale and require early assistance, commonly in the form of assisted ventilation. Treatment of these infants has traditionally involved immediate clamping of the umbilical cord and transfer to a resuscitation trolley for the commencement of assisted ventilation. Immediate cord clamping greatly reduces preload for the left ventricle and cardiac output which are dependent on umbilical venous return until the lungs aerate and pulmonary blood flow increases. Two alternatives to maintain left ventricular preload exist; 1) deferred cord clamping with respiratory support to aerate and ventilate the lungs and 2) umbilical cord milking followed by clamping and transfer for ongoing ventilation. More effective cord management in the first minutes of life may translate into better short-term outcomes including avoidance of admission to the neonatal intensive care unit (and maternal-infant separation), reduction in the need for cardio-respiratory support and treatment for perinatal asphyxia (therapeutic hypothermia). {Te Pas 2016 455} Other benefits of enhancing the placental transfusion include higher hemoglobin levels and transfer of stem cells to the newborn infant. Whilst the physiological rationale for these strategies is very strong, they have potential downsides. Effective mask ventilation is challenging even on the standard platform of a resuscitation trolley. Resuscitation “on the cord” has the additional challenges of crowding of the operator amongst obstetric staff and parents, restriction of movement due to presence of the intact umbilical cord and maintenance of normal temperature and sterility. The transfusion of additional blood may increase the risk of polycythemia and neonatal jaundice. Concern for the baby or mother may serve as a barrier with a perceived need to initiate resuscitative measures rapidly at the expense of enhanced placental transfusion strategies. A range of equipment has been developed to support cord intact stabilisation and trials have shown that cord intact stabilisation is possible and further trials are ongoing. {Brouwer 2019 F396, Duley 2019 } Resuscitation before cord clamping may alter communications between the clinical team and the mother who will be much closer to the resuscitation than in a standard resuscitation.
CONFLICT OF INTERESTS:	Peter Davis and Stuart Hooper have published the BabyDUCC study and were excluded from study selection and bias assessment {Badurdeen 2022 e1004029}

	Anup Katheria and Walid El-Naggar have published the MINVI study and were excluded from study selection and bias assessment {Katheria 217.e1} Peter Davis, Susan Niemeyer and Walid El-Naggar published an ILCOR systematic review on the topic of umbilical cord management at term and late preterm birth {Gomersall 2021 e2020015404}

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Currently, there is clear evidence in term infants supporting deferring clamping of the umbilical cord for at least 60 seconds if the infant is vigorous. This is reflected in current ILCOR recommendations. {Wyckoff 2022 e645} The management of non-vigorous infants, particularly those requiring some form of respiratory support in the seconds following birth, has been identified as a gap in current recommendations. Three alternative strategies are possible in this situation. The standard approach has been to clamp the cord immediately and transfer the baby to a resuscitation trolley for ongoing care. Alternatives include milking the umbilical cord (either the intact cord or after cutting the cord, leaving a longer segment) and providing respiratory support to the baby whilst still attached to the cord. Non-vigorous infants are at increased risk of important adverse outcomes including mortality, hypoxic ischemic encephalopathy and admission to NICU. Therefore, the problem is a priority because of potential to influence these outcomes.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small	For the **critical primary outcome of mortality**, **clinical benefit or harm could not be excluded**, (RR 0.11, 95% CI 0.01 to 2.01), **low certainty evidence** (downgraded for	

○ Moderate ○ Large ○ Varies ○ Don't know	imprecision) from one clinical trial including 1730 participants. Rates of mortality were very low (4/1730), all occurred in the early cord clamping group. {Katheria 2023 217.e1} For the **critical outcome of moderate-to-severe encephalopathy,** there was **possible clinical benefit** for I-UCM [anticipated absolute risk difference 15 fewer per thousand (22 fewer to 1 fewer)], **moderate certainty evidence** from 1634 infants included in one RCT. This was associated with a reduction in the rate of infants receiving therapeutic hypothermia in the cord milking group (an outcome included post hoc). {Katheria 2023 217.e1} For the **important outcome of admission to NICU, clinical benefit or harm could not be excluded, moderate certainty evidence,** modelled OR 0.69 (0.14, 1.14) from one RCT including 1730 infants. {Katheria 2023 217.e1} For the **important outcome of hemoglobin at 24 hours of age**, **there was possible clinical benefit for intact cord milking** [modelled mean difference 0.7g/L (0.3 higher to 1.1 higher)] **moderate certainty evidence** from one RCT including 1730 infants. {Katheria 2023 217.e1} For the **critical outcome of survival with typical development, clinical benefit or harm could not be excluded,** [modelled OR 0.76 (0.54 to 1.08)] **low certainty evidence** from one RCT from which follow-up results were available for 971 of 1730 infants (56%). {Katheria 2024 e2416870}	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Early cord clamping	Risk difference with Intact cord milking
Mortality				Study population	

	1730 (1 RCT) {Katheria 2023 217.e1}[b]	⊕⊕◯◯ Low[a]	**RR 0.11** (0.01 to 2.03)	5 per 1,000	**4 fewer per 1,000** (5 fewer to 5 more)
Moderate to severe hypoxic ischemic encephalopathy (Sarnat stage 2 or 3)	1634 (1 RCT) {Katheria 2023 217.e1}[b]	⊕⊕⊕◯ Moderate[a]	**RR 0.49** (0.25 to 0.97)	Study population	
				30 per 1,000	**15 fewer per 1,000** (22 fewer to 1 fewer)
Admission to NICU	1730 (1 RCT) {Katheria 2023 217.e1} [b]	⊕⊕⊕◯ Moderate[a]	**mOR 0.69** (0.41 to 1.14)	Study population	
				279 per 1,000	**68 fewer per 1,000** (142 fewer to 27 more)
Hemoglobin (g/dL)	1730 (1 RCT) {Katheria 2023 217.e1}[c]	⊕⊕⊕◯ Moderate[a]	-	The median hemoglobin (g/dL) was **17.3** g/L	mMD **0.7 g/L higher** (0.3 higher to 1.1 higher)
				Study population	

Survival with typical development (ASQ domains normal range)	971 (1 RCT) {Katheria 2024 e2416870}[,c]	⊕⊕◯◯ Low[a,c,d]	**mOR 0.76** (0.54 to 1.08)	829 per 1,000	**42 fewer per 1,000** (105 fewer to 11 more)	

Abbreviations: RCT; randomized controlled trial, RR; relative risk, mOR; modelled odds ratio, mMD; modelled mean difference, CI; confidence intervals

Footnotes:
a Does not meet optimal information size
b Risk difference from RevMan used, not adjusted for clustering
c Odds ratio accounting for study design (clustering)published by authors
d Low follow-up rates (81% had data on death or neurodevelopmental assessment)
e Followup assessment not performed face to face (Ages and Stages Questionnaire rather than Bayley Scales of Infant Development)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For the important outcome of **rate of cardiac compressions, clinical benefit or harm could not be excluded,** [RR 1.27 (0.47 to 3.38)] **low certainty evidence** from one RCT including 1730 infants**.** {Katheria 2023 217.e1} For the important outcome of **jaundice treated with phototherapy, clinical benefit or harm could not be excluded,** [RR 1.16 (0.87 to 1.54)] **low certainty evidence** from one RCT for which this outcome was available for 1219 of 1730 infants (70.6%).{Katheria 2023 217.e1}	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Early cord clamping	Risk difference with Intact cord milking
Received cardiac compressions	1730 (1 RCT) {Katheria 2023 217.e1}[b]	⨁⨁◯◯ Low[a]	**RR 1.27** (0.47 to 3.38)	Study population	
				8 per 1,000	**2 more per 1,000** (4 fewer to 19 more)
Jaundice treated with phototherapy	1219 (1 RCT) {Katheria 2023 217.e1}[b]	⨁⨁⨁◯ Moderate[a]	**RR 1.16** (0.87 to 1.54)	Study population	
				126 per 1,000	**20 more per 1,000** (16 fewer to 68 more)

Abbreviations: RCT; randomized controlled trial, RR; relative risk, mOR; modelled odds ratio, mMD; modelled mean difference, CI; confidence intervals

Footnotes:
a Does not meet optimal information size

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ● Moderate ○ High ○ No included studies	Certainty of evidence was **low or moderate** for most outcomes (downgraded for imprecision); although large by neonatal standards the included trial did not reach optimal information size for any outcome. Evidence relating to long-term follow-up was of **low** certainty due to follow-up rates <90% and imprecision.	
Values Is 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 outcomes of death, long term neurodevelopment and moderate-to-severe encephalopathy were graded as critical and the remaining outcomes including admission to NICU as important, in accordance with consensus of the Neonatal Life Support Task Force {Strand 2020 328} and other expert and parent consensus. {Webbe 2020 425}	
Balance of effects Does 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 balance of effects favours cord milking as there is no evidence of harm and some evidence of benefit from this approach. A single, large cluster randomised trial (n=1730) provided moderate certainty evidence of a benefit in terms of a reduction in the rate of moderate-to-severe hypoxic ischemic encephalopathy. Non-RCTs: Only evidence from RCTs was used to derive treatment recommendations because of the low numbers of infants recruited and very low certainty of evidence from the non-randomized trials.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Cord milking does not require additional equipment or manpower.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ● Low ○ Moderate ○ High ○ No included studies	No economic analyses have been conducted but the intervention does not appear to have additional costs.	

Cost effectiveness
Does 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	Quantitating the cost effectiveness of the intervention is difficult because no economic outcomes are reported. However, it seems likely that the benefits experienced by infants undergoing the intervention and the lack of additional costs for the technique mean that cost effectiveness probably favours cord milking. The reduction of rates of moderate-to-severe hypoxic ischemic encephalopathy appear to translate into a reduction in the need for therapeutic hypothermia with its attendant additional staffing and equipment costs.	

Equity
What 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	Infants in lower resource settings may benefit more than those in well-resourced settings if the need for ongoing care in NICU is reduced with the simple, inexpensive technique of cord milking.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The technique of cord milking appears to be well accepted in most settings. There are no ethical concerns.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The technique of cord milking has been implemented in many settings around the world. It is simple to perform, not associated with additional costs and for infants 34 weeks' gestation and above not associated with harm. Extension of its use to infants below this gestational age, particularly below 28 weeks' is specifically recommended against in previous ILCOR statements.	

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	**Probably favors the intervention**	Favors the intervention	Varies	No included studies

			intervention or the comparison				
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

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

Recommendation

In term and late preterm infants who remain nonvigorous despite stimulation, we suggest intact cord milking in preference to early cord clamping (weak recommendation, low certainty evidence).

Justification

Overall justification

Certainty of evidence was low to moderate for most outcomes (downgraded for imprecision); although large by neonatal standards the included trial did not reach optimal information size for any outcome. Evidence relating to long-term follow-up was of low certainty due to follow-up rates <90% and imprecision.

The balance of effects favors cord milking as there is no evidence of short-term or long-term harm and some evidence of benefit from this approach. A single, large cluster randomized trial (n=1730) provided moderate certainty evidence of a benefit in terms of a reduction in the rate of moderate-to-severe hypoxic ischemic encephalopathy. The choice of a weak recommendation based on low quality evidence was influenced by the lack of replication of evidence obtained from the single published trial. Implementation of its results should be restricted to infants similar to those enrolled in the trial i.e. those with poor tone, pallor or lack of breathing despite stimulation in the first 15 seconds after birth. Likewise, the protocol used in the trial should be followed i.e. 20 cm of cord milked over two seconds, repeating three additional times.

The practice of stimulation of the infant before implementing a cord management strategy used in the included study {Katheria 2023 217.e1} is supported by evidence from a systematic review {Guinsburg 2022 e2021055067} and an observational study. {Kc 2021 e001207}

We refer to the following treatment recommendation in relation to tactile stimulation and suggest that this should apply immediately after birth regardless of the method of umbilical cord management:

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 }

Cord milking does not require additional equipment or manpower.

Quantitating the cost effectiveness of the intervention is difficult because no economic outcomes are reported. However, it seems likely that the benefits experienced by infants undergoing the intervention and the lack of additional costs for the technique mean that cost effectiveness probably favors cord milking. The reduction of rates of moderate-to-severe hypoxic ischemic encephalopathy appears to translate into a reduction in the need for therapeutic hypothermia with its attendant additional staffing and equipment costs.

Subgroup considerations

There were no pre-specified subgroup analyses for this review

Implementation considerations

Protocols and training similar to those used in this trial are required before implementation of cord milking.

Monitoring and evaluation

Research priorities

- Large multicenter RCTs evaluating both I-UCM and intact cord resuscitation are required
- High quality follow-up studies with formal assessment of cognition, motor development, hearing and vision are required
- Comparison of different devices to support resuscitation with an intact cord should be undertaken
- Economic analyses are required, especially to determine the feasibility of providing resuscitation with an intact cord in resource limited settings

REFERENCES SUMMARY

Badurdeen S, Davis PG, Hooper SB, Donath S, Santomartino GA, Heng A, et al. Physiologically based cord clamping for infants ≥32+0 weeks gestation: A randomised clinical trial and reference percentiles for heart rate and oxygen saturation for infants ≥35+0 weeks gestation. PLoS Medicine. 2022;19(6).

Brouwer E, Knol R, Vernooij ASN, van den Akker T, Vlasman PE, Klumper F, et al. Physiological-based cord clamping in preterm infants using a new purpose-built resuscitation table: a feasibility study. Arch Dis Child Fetal Neonatal Ed. 2019;104(4)F396-f402.

Duley L, Dorling J, Ayers S, Oliver S, Yoxall CW, Weeks A, et al. Programme Grants for Applied Research. Improving quality of care and outcome at very preterm birth: the Preterm Birth research programme, including the Cord pilot RCT10.3310/pgfar07080. Southampton (UK): NIHR Journals Library; 2019.

Gomersall J, Berber S, Middleton P, McDonald SJ, Niermeyer S, El-Naggar W, et al. Umbilical Cord Management at Term and Late Preterm Birth: A Meta-analysis. Pediatrics. 2021;147(3).

Guinsburg R, de Almeida MFB, Finan E, Perlman JM, Wyllie J, Liley HG, et al. Tactile Stimulation in Newborn Infants With Inadequate Respiration at Birth: A Systematic Review. Pediatrics. 2022;149(4).

Katheria AC, Clark E, Yoder B, Schmölzer GM, Yan Law BH, El-Naggar W, et al. Umbilical cord milking in nonvigorous infants: a cluster-randomized crossover trial. American journal of obstetrics and gynecology. 2023;228(2)217.e1-217.e14.

Katheria AC, El Ghormli L, Clark E, Yoder B, Schmolzer GM, Law BHY, et al. Two-Year Outcomes of Umbilical Cord Milking in Nonvigorous Infants: A Secondary Analysis of the MINVI Randomized Clinical Trial. JAMA network open. 2024;7(7)e2416870.

Katheria AC, El Ghormli L, Clark E, Yoder B, Schmölzer GM, Law BHY, et al. Two-Year Outcomes of Umbilical Cord Milking in Nonvigorous Infants: A Secondary Analysis of the MINVI Randomized Clinical Trial. JAMA Netw Open. 2024;7(7)e2416870.

Kc A, Budhathoki SS, Thapa J, Niermeyer S, Gurung R, Singhal N. Impact of stimulation among non-crying neonates with intact cord versus clamped cord on birth outcomes: observation study. BMJ Paediatr Open. 2021;5(1)e001207.

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33(10)696-705.

Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. 2020;105(3)328-330.

Te Pas AB, Sobotka K, Hooper SB. Novel Approaches to Neonatal Resuscitation and the Impact on Birth Asphyxia. Clin Perinatol. 2016;43(3)455-67.

Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4)425-431.

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. Circulation. 2022;146(25)e483-e557.

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. Resuscitation. 2021;169229-311.

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.

Question 2 – Intact cord resuscitation vs early cord clamping

Should intact cord resuscitation vs. early cord clamping be used for non-vigorous newborn infants?	
POPULATION:	Non-vigorous newborn infants
INTERVENTION:	Intact cord resuscitation
COMPARISON:	Early cord clamping
MAIN OUTCOMES:	Infant • Neonatal mortality (critical) • Moderate to severe neurodevelopmental impairment at 18-24 months (critical) • Any component of neurodevelopmental impairment at 18-24 months (critical) (cerebral palsy, significant mental developmental delay, blindness as defined by WHO (<20/200 visual acuity) or the author's definition, hearing deficit (aided or <60 dB on audiometric testing) • Moderate to severe hypoxic ischemic encephalopathy (HIE; Sarnat 2 or 3 {Sarnat 1976 696}) (critical) • Proportion of infants receiving chest compressions in the delivery room (DR) (important) • Admission to a neonatal intensive care unit (important) • Jaundice: treated with exchange transfusion (critical) or phototherapy (important) • Hematologic outcomes including peak hemoglobin or hematocrit concentration during hospital admission (important)and anemia or iron deficiency at 4-6 months (important) • Unintended hypothermia within the first hour of life (important) Mother: • Postpartum hemorrhage, estimated as at least 1000 mL (critical), postpartum infection (critical), death or severe morbidity (composite), major surgery, organ failure, intensive care unit admission, (critical)
SETTING:	Delivery room
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	Each of the 130 million babies born annually requires management of their umbilical cord. This recommendation excludes an important group of infants at increased risk of death or long-term neurodevelopmental impairment i.e., those who are non-vigorous. These infants appear apneic, limp and pale and require early assistance, commonly in the form of assisted ventilation. Treatment of these infants has traditionally involved immediate clamping of the umbilical cord and transfer to a resuscitation trolley for the commencement of assisted ventilation. Immediate cord clamping greatly reduces preload for the left ventricle and cardiac output which are dependent on umbilical venous return until the lungs aerate and pulmonary

	blood flow increases. Two alternatives to maintain left ventricular preload exist; 1) deferred cord clamping with respiratory support to aerate and ventilate the lungs and 2) umbilical cord milking followed by clamping and transfer for ongoing ventilation. More effective cord management in the first minutes of life may translate into better short term outcomes including avoidance of admission to the neonatal intensive care unit, reduction in the need for cardio-respiratory support and treatment for perinatal asphyxia.
CONFLICT OF INTERESTS:	Peter Davis and Stuart Hooper have published the BabyDUCC study {Badurdeen 2022 e1004029} and were excluded from study selection and bias assessment Anup Katheria and Walid El-Naggar have published the MINVI study {Katheria 2023 217.e1} and were excluded from study selection and bias assessment Peter Davis, Susan Niemeyer and Walid El-Naggar were authors of the previous ILCOR systematic review on the topic of umbilical cord management at term and late preterm birth. {Gomersall 2021 e2020015404}

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Currently, there is clear evidence in term infants supporting deferring clamping of the umbilical cord for at least 60 seconds if the infant is vigorous. This is reflected in current ILCOR recommendations. The management of non-vigorous infants, particularly those requiring some form of respiratory support in the seconds following birth, has been identified as a gap in current recommendations. Three alternative strategies are possible in this situation. The standard approach has been to clamp the cord immediately and transfer the baby to a resuscitation trolley for ongoing care. Alternatives include milking the umbilical cord (either the intact cord or after cutting the cord, leaving a longer segment) and providing respiratory support to the baby whilst still attached to the cord.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate	For the **critical primary outcome of mortality (in hospital), clinical benefit or harm could not be excluded** (Relative risk (RR); 0.39 (0.03, 4.73); **very low certainty evidence** from 516 infants in 3 RCTs. {Andersson 2019 15, Badurdeen 2022 e1004029, Raina 2023 54} The evidence was	

○ Large ○ Varies ○ Don't know	downgraded for imprecision and high risk of bias (evidence that randomisation before birth may have altered management of enrolled infants in one trial). For the **critical outcome of moderate or severe hypoxic ischemic encephalopathy, clinical benefit or harm could not be excluded** (RR 0.47 (0.11, 1.96); **very low certainty evidence** from 285 infants in 2 RCTs. {Badurdeen 2022 e1004029, Raina 2023 54} The evidence was downgraded for imprecision and evidence that randomisation before birth may have altered management of enrolled infants in one trial. For the **important outcome of received cardiac compressions**, **clinical benefit or harm could not be excluded** (RR 0.26 (0.01, 5.24); **very low certainty evidence** from 285 infants in 2 RCTs. The evidence was downgraded for imprecision. {Badurdeen 2022 e1004029, Raina 2023 54} For the **important outcome of admission to NICU, clinical benefit or harm could not be excluded** (RR 0.88 (0.53, 1.48); **very low certainty evidence** from 516 infants in 3 RCTs. {Andersson 2019 15, Badurdeen 2022 e1004029, Raina 2023 54} The evidence was downgraded for imprecision and evidence that randomisation before birth may have altered management of enrolled infants in one trial. For the **important outcome of neurodevelopment at two years of age**, **clinical benefit or harm could not be excluded,** 138 infants in one RCT. {Isacson 2021 465} Analysis was not attempted because of low follow-up rates (59.7%), wide age range at time of assessment, instrument used (Indicators of Infant and Young Child Development which was still under development), and cut point used (15th centile) to define high risk.	

Outcomes	**№ of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with Early cord clamping	**Risk difference with Intact cord resuscitation**
Mortality				Study population	

	516 (3 RCTs) {Andersson 2019 15, Badurdeen 2022 e1004029, Raina 2023 54}	⊕◯◯◯ Very low[a,b]	**RR 0.39** (0.03 to 4.73)	16 per 1,000	**10 fewer per 1,000** (16 fewer to 60 more)
Moderate or severe hypoxic ischemic encephalopathy (Sarnat stage 2 or 3)	285 (2 RCTs) {Badurdeen 2022 e1004029, Raina 2023 54}	⊕◯◯◯ Very low[a,b]	**RR 0.47** (0.11 to 1.96)	Study population	
				40 per 1,000	**21 fewer per 1,000** (35 fewer to 38 more)
Received cardiac compressions	285 (2 RCTs) {Badurdeen 2022 e1004029, Raina 2023 54}	⊕◯◯◯ Very low[a,b]	**RR 0.26** (0.01 to 5.24)	Study population	
				13 per 1,000	**10 fewer per 1,000** (13 fewer to 56 more)
Admission to NICU	516 (3 RCTs) {Andersson 2019 15, Badurdeen 2022 e1004029, Raina 2023 54}	⊕⊕◯◯ Low[a,b]	**RR 0.88** (0.53 to 1.48)	Study population	
				234 per 1,000	**28 fewer per 1,000** (110 fewer to 112 more)
Abbreviations: RCT; randomized controlled trial, RR; relative risk, CI; confidence intervals					
Footnotes:					

a. Randomization before birth, treatment team aware of allocated treatment before enrolment decision made

b. Numbers studied well below optimal information size

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For the important outcome of **jaundice treated with phototherapy, clinical benefit or harm could not be excluded** (RR 1.30 (0.88, 1.90); **low certainty evidence** from 285 infants in 3 RCTs. {Andersson 2019 15, Badurdeen 2022 e1004029, Raina 2023 54} The evidence was downgraded for imprecision. For the important outcome of **maternal postpartum haemorrhage (>1L), clinical benefit or harm could not be excluded** (RR 0.95 (0.29, 3.12); **low certainty evidence** from 123 infants in 1RCT. {Badurdeen 2022 e1004029} The evidence was downgraded for imprecision.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Early cord clamping	Risk difference with Intact cord resuscitation
Jaundice treated with phototherapy	285 (3 RCTs) {Andersson 2019 15, Badurdeen 2022 e1004029, Raina 2023 54}	⨁⨁◯◯ Low[a,b]	**RR 1.30** (0.88 to 1.90)	Study population	
				232 per 1,000	**60 more per 1,000** (30 fewer to 150 more)
				Study population	

	Maternal postpartum haemorrhage (>1L)	123 (1 RCT) {Badurdeen 2022 e1004029}	⊕◯◯◯ Very low[c]	**RR 0.95** (0.29 to 3.12)	83 per 1,000	**4 fewer per 1,000** (59 fewer to 177 more)	
	Abbreviations: RCT; randomized controlled trial, RR; relative risk, CI; confidence intervals						
	Footnotes: a. Randomisation before birth, treatment team aware of allocated treatment before enrolment decision made b. Numbers studied well below optimal information size c. Single small study, well below optimal information size						

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence for neonatal outcomes is low to very low due to 1) the relatively small sample sizes of the three included studies, which fall well below optimal sample size for all outcomes and 2) randomisation before birth potentially leading to infants in the two allocated groups having different baseline risks of poor outcome in one study. {Andersson 2019 15} The allocated intervention was followed in <50% in the intact cord group and 100% in the early cord clamping group in one study. {Andersson 2019 15}	

Values
Is 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	The outcomes of death, long term neurodevelopment and moderate-to-severe encephalopathy were graded as critical and the remaining outcomes including admission to NICU as important. {Strand 2020 328, Webbe 2020 425}	

variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		
Balance of effects Does 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	**RCTs** The certainty of the available evidence is insufficient to recommend one strategy over the other. **Non-RCTs** The certainty of the available evidence is insufficient to recommend one strategy over the other.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Resuscitation of babies still attached to the umbilical cord can be done using a variety of techniques. Some centres use a purpose-built table to allow operators to resuscitate the baby close to the mother on a stable base and with the provision of warmth. They may be used for vaginal or caesarean section deliveries. These add considerable cost to that of conventional resuscitation equipment. Less expensive arrangements may be used, particularly for vaginal deliveries where strict asepsis is less critical.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	No economic analyses have been conducted and the costs of equipment used by the included studies are not reported.	

Cost effectiveness
Does 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	Quantitating the cost effectiveness of the intervention is difficult because no economic outcomes are reported. Since there were no important benefits of the intervention demonstrated, cost effectiveness is assumed to be greater in the less expensive control group.	

the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		
Equity What 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	Given the lack of effectiveness found, there are no implications for equity at present. Should larger, well conducted trials demonstrate a benefit for intact cord resuscitation in future, the cost implications will become important, particularly for resource limited settings.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Some centres in the developed world are currently practising intact cord resuscitation, many with purpose-built resuscitation trolleys. They may wish to continue to use this technique based on the physiological benefits demonstrated in studies performed in animal models. Other centres will await more robust evidence supporting or refuting this approach.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	As above, further evidence is required to justify widespread use of intact cord resuscitation. If proven safe and effective, more work is required to ascertain the range of equipment that should be used to enable its practice outside the context of a clinical trial.	

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

	JUDGEMENT						
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

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

Recommendation

There is currently insufficient evidence to recommend either for or against intact cord resuscitation for term and late preterm infants who are non-vigorous at birth (weak recommendation, low certainty evidence).

We refer to the following treatment recommendation in relation to tactile stimulation and suggest that this should apply immediately after birth regardless of the method of umbilical cord management:

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 }

Justification

Overall justification

The certainty of evidence for neonatal outcomes is low to very low due to 1) the relatively small sample sizes of the three included studies, which fall well below optimal sample size for all outcomes and 2) randomization before birth potentially leading to infants in the two allocated groups having different baseline risks of poor outcome in one study. The allocated intervention was followed in <50% in the intact cord group and 100% in the early cord clamping group in one study.{Andersson 2019 15}

Resuscitation of babies still attached to the umbilical cord can be done using a variety of techniques. Some centers use a purpose-built table to allow operators to resuscitate the baby close to the mother on a stable base and with the provision of warmth. They may be used for vaginal or caesarean section deliveries. These add considerable cost to that of conventional resuscitation equipment. Less expensive arrangements may be used, particularly for vaginal deliveries where strict asepsis is less critical.

Quantitating the cost effectiveness of the intervention is difficult because no economic outcomes are reported. Since there were no important benefits of the intervention demonstrated, cost effectiveness is assumed to be greater in the less expensive control group.

Some centers are currently practicing intact cord resuscitation, many with purpose-built resuscitation trolleys. They may wish to continue to use this technique based on the physiological benefits demonstrated in studies performed in animal models. Other centers will await more robust evidence supporting or refuting this approach.
Further evidence is required to justify widespread use of intact cord resuscitation. If proven safe and effective, more work is required to ascertain the range of equipment that is required.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Large multicenter RCTs evaluating both intact cord milking and intact cord resuscitation are required
- High quality follow-up studies with formal assessment of cognition, motor development, hearing and vision are required
- Comparison of different devices to support resuscitation with an intact cord should be undertaken
- Economic analyses are required, especially to determine the feasibility of providing resuscitation with an intact cord in resource limited settings

REFERENCES SUMMARY

Andersson O, Rana N, Ewald U, Malqvist M, Stripple G, Basnet O, et al. Intact cord resuscitation versus early cord clamping in the treatment of depressed newborn infants during the first 10 minutes of birth (Nepcord III) - a randomized clinical trial. Maternal health, neonatology and perinatology. 2019;515.

Andersson O, Rana N, Ewald U, Målqvist M, Stripple G, Basnet O, et al. Intact cord resuscitation versus early cord clamping in the treatment of depressed newborn infants during the first 10 minutes of birth (Nepcord III) - a randomized clinical trial. Matern Health Neonatol Perinatol. 2019;515.

Badurdeen S, Davis PG, Hooper SB, Donath S, Santomartino GA, Heng A, et al. Physiologically based cord clamping for infants ≥32+0 weeks gestation: A randomised clinical trial and reference percentiles for heart rate and oxygen saturation for infants ≥35+0 weeks gestation. PLoS Medicine. 2022;19(6).

Gomersall J, Berber S, Middleton P, McDonald SJ, Niermeyer S, El-Naggar W, et al. Umbilical Cord Management at Term and Late Preterm Birth: A Meta-analysis. Pediatrics. 2021;147(3).

Isacson M, Gurung R, Basnet O, Andersson O, Ashish KC. Neurodevelopmental outcomes of a randomised trial of intact cord resuscitation. Acta Paediatrica, International Journal of Paediatrics. 2021;110(2)465-472.

Katheria AC, Clark E, Yoder B, Schmölzer GM, Yan Law BH, El-Naggar W, et al. Umbilical cord milking in nonvigorous infants: a cluster-randomized crossover trial. American journal of obstetrics and gynecology. 2023;228(2)217.e1-217.e14.

Raina JS, Chawla D, Jain S, Khurana S, Sehgal A, Rani S. Resuscitation with Intact Cord Versus Clamped Cord in Late Preterm and Term Neonates: A Randomized Controlled Trial. The Journal of pediatrics. 2023;25454-60.e4.

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33(10)696-705.

Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. 2020;105(3)328-330.

Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4)425-431.

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. Circulation. 2022;146(25)e483-e557.

NLS 5351 - Video vs traditional laryngoscope for neonatal intubation

NLS 5351 - Video vs traditional laryngoscopy for neonatal intubation	
POPULATION:	Infants receiving tracheal intubation at birth or on a neonatal unit
INTERVENTION:	Tracheal intubation using video laryngoscopy
COMPARISON:	Tracheal intubation using traditional laryngoscopy
MAIN OUTCOMES:	Primary: • Successful tracheal intubation (Yes/No) (Important) Secondary: • Successful tracheal intubation at the first attempt (Important) • Number of attempts to achieve successful tracheal intubation (Important) • Time taken to successfully intubate (Important) • Adverse events around the time of laryngoscopy e.g., airway trauma, bradycardia, desaturation, esophageal intubation, pneumothorax (Important) • Perception of intubating clinician e.g., intubation difficulty (as defined by author) (Important) • Mortality in-hospital (Critical) • Any intraventricular hemorrhage (IVH) (preterm only) (Important) Outcomes ratings using the GRADE classifications of critical or important were decided according to a consensus for international neonatal resuscitation guidelines {Strand 328}.
SETTING:	At the time of birth or on a neonatal unit
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	Ventilation of the lungs are key for a successful resuscitation at birth. Around 5% of newborn infants receive positive pressure ventilation in the delivery room and the great majority of them improve with ventilation applied by non-invasive interfaces. {Ersdal 2012 869} However, around 0.4-1.2% of neonates may require rapid tracheal intubation to secure the airway, optimize oxygenation and achieve adequate ventilation immediately after birth. {Bjorland 2020 175, Niles 2017 102} Several aspects of the neonatal anatomy, such as the small size of the mouth and airway, the disproportionately large tongue, epiglottis and arytenoids, and the keyhole appearance of the glottis complicate the process of tracheal intubation. In

addition, low pulmonary reserve and high oxygen consumption in preterm infants limit the time for the procedure. {Lingappan 2023 Cd009975}

According to an international registry, 46% of tracheal intubations are successful on the first attempt in the delivery room. {Foglia 2019 e20180902} There is great concern that changes in the clinical practice are negatively impacting current physicians' competency in the procedure {Johnston 2021 434}, including the fact that tracheal aspiration is no longer recommended for infants born through meconium-stained amniotic fluid {Wyckoff 2020 S185} and there is a greater emphasis on the utilization of non-invasive ventilation strategies for preterm infants.

Besides the concern with unsuccessful tracheal intubation, the frequency of adverse events associated with the procedure has been increasingly studied. In an international registry, among 598 tracheal intubations in the delivery room, adverse events occurred in 103 (17%). In 27 procedures, the events were classified as severe, such as late recognition of esophageal intubation, laryngospasm, air leaks and airway trauma, among others. Severe desaturations occurred in 134 of 426 procedures (31%) and they were defined as ≥20% decrease in oxygen saturation from the highest level achieved immediately before the first attempt.{Foglia 2019 e20180902}

Therefore, health professionals face a stressful scenario of a life-saving procedure that may be unsuccessful and/or lead to important adverse events, requiring skilled providers, in a context of few opportunities to practice tracheal intubation. The availability of video laryngoscopy could facilitate the training and the procedure in the clinical setting. It may also be useful in infants who are perceived to have a difficult airway. {Gupta 2021 14}

To accomplish tracheal intubation using traditional laryngoscopy, there must be an unobstructed view from the eye of the practitioner to the laryngeal inlet. Video laryngoscopes allow for visualization of the glottis without the need to align the site of vision in a linear fashion with the laryngeal inlet. The blade of a video laryngoscope has a video camera and a light source at its tip enabling the transmission of glottis' image to the operator. A liquid crystal display screen is mounted on the handle of the device or as a separate screen for visualization of the glottis. {Balaban 2017 477}

The first attempt to elucidate the advantages of video laryngoscopy in adults was reported in 2003. {Kaplan 2003 E025} Around the same time, new types of video laryngoscopes, suitable for pediatric use, were introduced and they have shown encouraging results in randomized controlled trials. {Riva 2023 101} However, their exact role at present remains unclear in this population. {Gupta 2021 14} Video laryngoscopy is a heterogeneous term covering a range of different devices and effectiveness might vary. Besides the devices themselves, the age of the patients, type of intubation (oral vs. nasal) and the experience of the providers also influence the performance of the video laryngoscopes during tracheal intubation. {de Carvalho, 2022 #1094}

The first report of the use of video laryngoscopy in newborn infants occurred in 2009.{Vanderhal 2009 e339} The authors described the video laryngoscopy equipment and the technique for tracheal intubation and airway evaluation in the delivery room and in the neonatal intensive care unit (NICU) in 47 patients who weighed 530-6795g and concluded that the new equipment showed promise to improve airway management, evaluation, and teaching. Since then, tracheal intubation

	assisted by video laryngoscopy has been increasingly used. In a research involving NICU (n=2009) and delivery room (n=598) tracheal intubations from 10 international centers, the use of video laryngoscopy occurred in, respectively, 21% and 11%. {Foglia 2019 e20180902} An UK survey of 169 neonatal units showed that 63% (107/169) of them have a video laryngoscope and 31% (33/107) of these units use it as first-line equipment when intubating. {Thomas 2015 } A Cochrane systematic review compared video to traditional laryngoscopy in decreasing the time and attempts required for tracheal intubation and increasing the success rate at first intubation in neonates. {Lingappan 2023 Cd009975} The authors collected information on newborn infants who required tracheal intubation in the delivery room, operating room or in the intensive care unit. They found eight studies: three of them enrolled newborns in the neonatal unit {Bartle 2019 195, Moussa 2016 e20152156, Volz 2018 1074}, one enrolled infants both in the delivery room and in the neonatal unit {O'Shea 2015 912} and four of them studied infants in the operating room. {Kamath 2020 S24, Salama 2019 28, Singh 2009 338, Tao 2019 482} The systematic review concluded that video laryngoscopy may increase the success of tracheal intubation on the first attempt and may result in fewer intubation attempts but may not reduce the time required for successful intubation in newborn infants (low-certainty evidence). {Lingappan 2023 Cd009975} In the literature, intubation competency has been defined as provider success intubating on the first or second attempt ≥80% of the time.{Falck 2003 1242} Video laryngoscopy has been increasingly applied in health professionals' training as it allows the supervisor to see what the provider is viewing. {Antoine, 2024 #229;Dias, 2021 #1101} In a systematic review of studies that compared the performance of trainees, video laryngoscopy and real-time supervisor feedback was more effective for supporting the development of neonatal intubation skills, compared with traditional laryngoscopy. {MacKinnon, 2023 #1102} However, there is conflicting evidence in the simulation setting as to whether video laryngoscopy is superior to traditional laryngoscopy when used as a teaching tool. {Antoine, 2024 #229;Dias, 2021 #1101;Nair, 2017 #1103;Parmekar, 2017 #1104} Based on the available information, the European Resuscitation Council guidelines concluded that the effectiveness of video laryngoscopy in the context of resuscitation at birth has not been fully evaluated. {Madar, 2021 #1105} The American Academy of Pediatrics' Neonatal Resuscitation Program (NRP), in 2021, stated that "a videolaryngoscope may be a helpful device for training novice operators and for intubating a baby with a difficult airway". {Weiner 2021 } There are no recommendations about video laryngoscope use by any of the ILCOR Task Forces. Therefore, as part of its continuous evaluation process, the ILCOR Neonatal Life Support Task Force prioritized this topic for a systematic review.
CONFLICT OF INTERESTS:	Jasmine Antoine is completing a PhD on neonatal intubation training that includes video laryngoscopy {Antoine 100776} and does not have any conflict of interest regarding the use of the tool in the clinical practice. The following Task Force members have no conflicts of interest to declare: Joe Fawke, Ruth Guinsburg, Maria Fernanda de Almeida and Daniela Testoni Costa-Nobre.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○Probably yes ● Yes ○ Varies ○ Don't know	There are concerns about physicians' opportunities to gain intubation skills given the greater use of non-invasive ventilation and the move away from inspecting the airway at births through meconium stained amniotic liquid. {Johnston 2021 434} A Cochrane systematic review with 8 studies considered infants intubated in the delivery room, neonatal unit or operating room. {Lingappan 2023 Cd009975} It concluded that video laryngoscopy may increase the success of intubation on the first attempt and may result in fewer intubation attempts but may not reduce the time required for successful intubation (low-certainty evidence). In the literature, intubation competency has been defined as provider success intubating on the first or second attempt ≥80% of the time. {Falck 2003 1242} Video laryngoscopy has been increasingly applied in health professionals' training as it allows the supervisor to see what the provider is viewing. {Dias, 2021 #1101} In a systematic review of studies that compared the performance of trainees, video laryngoscopy and real-time supervisor feedback was more effective for supporting the development of neonatal intubation skill, compared with traditional laryngoscopy. {MacKinnon, 2023 #1102}	Video laryngoscopy has been recommended as a useful tool in managing the difficult airway. This applies to all age groups including neonatal. A number of organizations have issued guidance including The Difficult Airway Society {Black, 2024 #1108} and the British Association of Perinatal Medicine {Tinnion, 2021 #1107} The 2021 European Resuscitation Council guidelines concluded that the effectiveness of video laryngoscopy in the context of resuscitation at birth has not been fully evaluated. {Madar, 2021 #1105} The American Academy of Pediatrics Neonatal Resuscitation Program (NRP), in 2021, stated that "a video laryngoscope may be a helpful device for training novice operators and for intubating a baby with a difficult airway". {Weiner 2021 } There are no recommendations about video laryngoscope use by any of the ILCOR Task Forces. Therefore, as part of its continuous evaluation process, the ILCOR Neonatal Life Support Task Force prioritized this topic for a systematic review.

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The main desirable effects were: • Moderate certainty evidence from 6 RCTs (862 tracheal intubations) showing greater tracheal intubation success rate with video laryngoscopy vs traditional laryngoscopy. {Bartle 2019 195, Geraghty 2024 1885, Moussa 2016 e20152156, O'Shea 2015 912, Tippmann 2023 , Volz 2018 1074}High certainty evidence from 4 RCTs (610 tracheal intubations) showing greater intubation success rate at the first attempt with video laryngoscopy vs traditional laryngoscopy {Geraghty 2024 1885; O´Shea 2015 912; Tippmann 2023 e001958; Volz 2018 1074}. {Geraghty 2024 1885, O'Shea 2015 912, Tippmann 2023 , Volz 2018 1074} • Very low certainty evidence from 4 observational trials (3342 intubations) also showed greater first pass tracheal intubation success rates with video laryngoscopy {Lacquiere 2024 476, Moussa 2016 e20152156, O'Shea 2015 912, Tippmann 2023 } • Higher confidence in tracheal tube placement among trainees, trainers and supporting staff when using a video laryngoscope compared to a traditional laryngoscope intubations. {Bartle 2019 195, Moussa 2016 e20152156} • One RCT reported in cases of intubation failure there were lower rates of problems visualizing the glottis when intubating with a video laryngoscope 8/101 (8%) vs a traditional laryngoscope 19/112 (17%). {Moussa 2016 e20152156} There were no differences in the following outcomes between video and traditional laryngoscopy {Geraghty 2024 1885, Moussa 2016 e20152156, O'Shea 2015 912, Tippmann 2023 , Volz 2018 1074} • Mortality in-hospital (critical outcome) • Adverse events associated with intubation including ○ Esophageal intubation ○ Airway trauma ○ Oxygen desaturation <80% ○ Bradycardia (either <100 bpm or <60 bpm) ○ Pneumothorax	Video laryngoscopy may help with visual issues such as reduced visual acuity and/or speed of accommodation when intubating. Much of the evidence in this systematic review is derived from less experienced intubators. The desirable effects among experienced intubators are less certain.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	A Cochrane systematic review suggested that intubation with a video laryngoscope may take longer than with a traditional laryngoscope. {Lingappan 2023 Cd009975} There was a lack of clarity among the studies in this systematic review over how time to intubate was measured. However, the raw data from 4 RCTS showed that video laryngoscopy took slightly longer than traditional in two studies whilst traditional laryngoscopy took slightly longer in the other two studies. The time differences in both cases were small. {Geraghty 2024 1885, Moussa 2016 e20152156, O'Shea 2015 912, Volz 2018 1074}	

Study	Time to intubate in seconds	
	Video laryngoscopy	Traditional laryngoscopy
Geraghty 2024	61 (52-66)*	51 (43-60)*
Moussa 2016	57 (14-85)*	45 (33-63)*
O'Shea 2015	51 (39-63)*	53 (41-70)*
Volz 2018	28.1 (11.9)**	30.6 (18.8)**
*median (IQR); **mean (SD)		

One RCT reported that, in cases of intubation failure, a reason given was that the laryngoscope blade was too big in 5/101 video laryngoscopy tracheal intubations vs. 0/112 with the traditional laryngoscopy. {Moussa 2016 e20152156}

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The certainty of evidence from RCTs varied across different outcomes as follows: Primary:	

	Successful tracheal intubation: **Moderate** {Bartle 2019 195, Geraghty 2024 1885, Moussa 2016 e20152156, O'Shea 2015 912, Tippmann 2023 , Volz 2018 1074}
	Secondary:
	• Successful tracheal intubation at the first attempt: **High** {Geraghty 2024 1885, O'Shea 2015 912, Tippmann 2023 , Volz 2018 1074}
	• Number of attempts to achieve successful tracheal intubation: **Moderate** {Bartle 2019 195, Geraghty 2024 1885, Moussa 2016 e20152156, O'Shea 2015 912, Tippmann 2023 }
	• Time taken to successful tracheal intubation: **Very Low** {Geraghty 2024 1885, Moussa 2016 e20152156, O'Shea 2015 912, Volz 2018 1074}
	• Adverse events related to laryngoscopy:
	  ○ airway trauma: **Very Low** {Geraghty 2024 1885, Moussa 2016 e20152156, Tippmann 2023 , Volz 2018 1074}
	  ○ bradycardia (heart rate <100 bpm or <60 bpm): **Moderate** {Geraghty 2024 1885, Tippmann 2023 }
	  ○ desaturation (oxygen saturation <80%): **Moderate** {Geraghty 2024 1885, Tippmann 2023 }
	  ○ esophageal intubation: **Low** {Moussa 2016 e20152156, Tippmann 2023 , Volz 2018 1074}
	  ○ pneumothorax: **Low** {Tippmann 2023 , Volz 2018 1074}{Tippmann 2023 e001958, Volz 2018 1074}
	• Mortality in-hospital: {Geraghty 2024 1885, Tippmann 2023 }
	All outcomes were rated as important except mortality in-hospital, which was rated as critical.
	The main outcomes of interest (successful tracheal intubation, successful tracheal intubation at first attempt, mortality in-hospital) provided high or moderate certainty evidence.	

Values Is 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	Intubation skills are a key part of advanced neonatal resuscitation and can be a lifesaving technique. Patient centered intubation measures that are pragmatic include successful intubations on the first attempt, overall success, number of attempts, time taken to intubate, and rates of complications.{Geraghty 2024 1885, Tippmann 2023 }	In considering the importance of this topic, we note a recent Cochrane review {Lingappan Cd009975} and a meta-analyses {MacKinnon 2023 111} agreeing on the value of the outcomes of successful intubation and successful intubation at first attempt. Additionally, the American Academy of Pediatrics' Neonatal Resuscitation Program (NRP), in 2021, stated that "a video laryngoscope may be a helpful device for training novice operators and for intubating a baby with a difficult airway" {Weiner }.
Balance of effects Does 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	The review found evidence of clinical benefit for intubation with video laryngoscope compared to intubation with traditional laryngoscope in two outcomes, successful tracheal intubation and successful tracheal intubation at the first attempt. These outcomes are described in the context of the majority of clinicians being junior doctors. RCTs: • {Bartle 195} - 40 junior doctors • {Geraghty 1885} - 12 neonatologists, 67 neonatal trainees, 135 pediatric trainees • {Moussa e20152156} - 34 residents • {O´Shea 2015 912} - 72 residents • {Tippmann } - 51 residents, 21 neonatologists • {Volz 1074} - 48 residents Observational studies:	

intervention ○ Varies ○ Don't know	• {Lacquiere 476}: videolaryngoscopy (VL) was performed by advanced medical trainees (55%) and neonatologists (45%), and traditional laryngoscopy (TL) was performed by advanced medical trainees (48%) and neonatologists (52%) • {Moussa 1210}: VL - 43% nurse practitioner, 33% fellow, 13% resident, 5% neonatologist, 1% respiratory therapist, 6% other vs. TL - 36% nurse practitioner, 30% fellow, 17% resident, 8% neonatologist, 6% respiratory therapist, 4% other • {O´Shea 2021 168}: mixture of advanced neonatal nurse practitioners, residents, and fellows • {Tippmann 2021 675238}: first attempt VL - 74% pediatric resident and 26% neonatologist vs. first attempt TL - 62% pediatric resident and 38% neonatologist	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No included studies measured the difference in resources required for video laryngoscopes compared to traditional laryngoscopes.	The review group looked at the costs of video laryngoscopes. Video laryngoscopes are expensive (>10-15 times higher than traditional laryngoscopes) and this applies to all settings, so it is likely that the costs involved would be large. Maintenance and video laryngoscope blades would be more expensive than traditional laryngoscopes. Training costs exist for both video and traditional laryngoscopy. However, it is unclear if video laryngoscopy use would require additional training and incur additional training costs. An electrical supply is needed to charge video laryngoscopes.
Certainty of evidence of required resources What 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 described the cost incurred with purchase, implementation, training or maintenance of video laryngoscopes.	The costs of video laryngoscopes will likely be site specific and depend on the brand, type and number of devices required.
Cost effectiveness Does 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 performed a health economic analysis and measured the cost effectiveness of video laryngoscopes.	The costs of video laryngoscopes will likely be site specific and depend on the brand, type and number of devices required. Some devices have single use blades versus reusable blades.
Equity What 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	The cost of purchasing and ongoing maintenance of video laryngoscopes is likely to be unaffordable in low-income settings.	Not all health systems could afford video laryngoscopes. Video laryngoscopes are more expensive than traditional laryngoscopes.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The acceptability of video laryngoscopy in neonatal intubation has been reflected by increasing purchase and use of video laryngoscopes. {Thomas 2023 89}	We do not know the acceptability of video laryngoscopes among more experienced staff. Video laryngoscopes are used in other age groups (adult, pediatric) and by other professional groups (anesthesiologists). Cost issues and the allocation of limited resources may impact the acceptability of video laryngoscopes in low-resource settings. Not all models of video laryngoscopy have size 00 blades and this might limit their acceptability in some settings.
Feasibility Is the intervention feasible to implement?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Infant tracheal intubation with video laryngoscopy is feasible in well-resourced healthcare settings. Cost issues related to overall resource availability may restrict feasibility of implementation in low resource settings.	Dependent on costs, available resources, and suitable clinicians to provide training.

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**

	JUDGEMENT						
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

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

Recommendation

Where resources and training allow, in infants being intubated at birth or on a neonatal unit, we suggest the use of video laryngoscopy in comparison to traditional laryngoscopy, especially in settings where less experienced staff are intubating (conditional recommendation, high certainty of evidence).

Traditional laryngoscopy remains a reasonable option as no increased harm was shown compared to video laryngoscopy (weak recommendation, very low certainty of evidence).

A traditional laryngoscope should be available as a backup device (good practice statement).

Justification

In making this conditional recommendation, the NLS Task Force considered the systematic review evidence from 6 RCTs {Bartle 2019 195; Geraghty 2024 1885; Moussa 2016 e20152156; O´Shea 2015 912; Tippmann 2023 e001958; Volz 2018, 1074} with 862 tracheal intubations and moderate to high certainty evidence that favored video laryngoscopy over traditional laryngoscopy for the outcomes of successful tracheal intubation and successful tracheal intubation at first attempt. These findings are supported by 4 observational studies {Lacquiere 2024 476; Moussa 2022 1210;

O´Shea 2021 168; Tippmann 2021 675238} with 3342 tracheal intubations and very low certainty evidence that favored video laryngoscopy over traditional laryngoscopy for the outcome of successful intubation at the first attempt.

There was no difference in a range of adverse events when using a video laryngoscope compared to a traditional laryngoscope. The RCTs mainly enrolled infants who were intubated by less experienced staff or in training neonatologists in the neonatal unit or in the delivery room, in newborns without airway congenital anomalies, excluding all studies that reported intubations by anesthesiologists. The reason for this was to provide focused information about the use of video laryngoscopes by neonatal staff. The observational studies included a wider range of experience among intubators.

It should be recognized that video laryngoscopes are expensive and will not be available in all settings. Traditional laryngoscopy remains a good alternative for neonatal tracheal intubations on neonatal units and delivery rooms and should always be available.

Subgroup considerations

Regarding subgroups analysis, no data were reported to perform subgroup analysis by location of tracheal intubation (delivery room or neonatal unit), type of intubation (emergency vs. elective), gestational age (≥37+0, 28+0 to 36+6 and < 28+0 weeks), experience of the person handling the laryngoscope and type of laryngoscope. Although two RCTs used one brand of video laryngoscope {O´Shea 2015 912; Tippmann 2023 e001958} and 4 RCTs {Bartle 195, Geraghty 1885, Moussa e20152156, Volz 2018 1074} used another brand, they lacked sufficient details regarding models, screen size or whether screens were attached to the laryngoscope handle or separate. As a result, subgroup analysis of brands could not be made.

Implementation considerations

Video laryngoscopes for infant intubation requires resources and training. Care needs to be taken to ensure that a wide range of staff are trained, who can effectively use the devices and trouble shoot. Consideration should also be given to the order of tasks during intubation with video laryngoscopes. It has been highlighted that intubating with video laryngoscopy differs from traditional laryngoscopy.

Monitoring and evaluation

We recommend ongoing evaluation of the rates of successful tracheal intubation, successful tracheal intubation at the first attempt and adverse events following tracheal intubation with video laryngoscopy compared to traditional laryngoscopy.

Research priorities

Studies are needed to advance knowledge regarding the use of videolaryngoscopy, in comparison with traditional laryngoscopy, such as:

- Efficacy, effectiveness and safety in decreasing number of intubation attempts
- Efficacy, effectiveness and safety in decreasing time to successful intubation
- Efficacy, effectiveness and safety in different gestational ages

- Efficacy, effectiveness and safety at birth, in the delivery room
- Efficacy, effectiveness and safety in emergent tracheal intubations
- Efficacy, effectiveness and safety of the different types of video laryngoscopes (e.g., different blade shape, whether video screen attached to handle or detached, size of screen)
- Benefits of video laryngoscopy among more experienced intubators
- Cost effectiveness of video laryngoscope use
- Feasibility of video laryngoscope use in different settings

References

Antoine J, Dunn B, McLanders M, Jardine L, Liley H. Approaches to neonatal intubation training: A scoping review. Resusc Plus. 2024;20100776.

Balaban O, Tobias JD. Videolaryngoscopy in Neonates, Infants, and Children. Pediatr Crit Care Med. 2017;18(5)477-485.

Bartle DG, Powell R, Pearson K, Adeboye TS. Video vs direct laryngoscopy. Success rates and confidence: a feasibility study. Infant. 2019;15(5)195-198.

Bjorland PA, Ersdal HL, Øymar K, Rettedal SI. Compliance with Guidelines and Efficacy of Heart Rate Monitoring during Newborn Resuscitation: A Prospective Video Study. Neonatology. 2020;117(2)175-181.

Ersdal HL, Mduma E, Svensen E, Perlman JM. Early initiation of basic resuscitation interventions including face mask ventilation may reduce birth asphyxia related mortality in low-income countries: a prospective descriptive observational study. Resuscitation. 2012;83(7)869-73.

Falck AJ, Escobedo MB, Baillargeon JG, Villard LG, Gunkel JH. Proficiency of pediatric residents in performing neonatal endotracheal intubation. Pediatrics. 2003;112(6 Pt 1)1242-7.

Foglia EE, Ades A, Sawyer T, Glass KM, Singh N, Jung P, et al. Neonatal Intubation Practice and Outcomes: An International Registry Study. Pediatrics. 2019;143(1).

Geraghty LE, Dunne EA, CM NC, Vellinga A, Adams NC, O'Currain EM, et al. Video versus Direct Laryngoscopy for Urgent Intubation of Newborn Infants. N Engl J Med. 2024;390(20)1885-1894.

Gupta A, Sharma R, Gupta N. Evolution of videolaryngoscopy in pediatric population. J Anaesthesiol Clin Pharmacol. 2021;37(1)14-27.

Johnston L, Sawyer T, Ades A, Moussa A, Zenge J, Jung P, et al. Impact of Physician Training Level on Neonatal Tracheal Intubation Success Rates and Adverse Events: A Report from National Emergency Airway Registry for Neonates (NEAR4NEOS). Neonatology. 2021;118(4)434-442.

Kamath N, Dogra N, Gupta A. Comparison of ease of intubation with airtraq optical laryngoscope versus Miller laryngoscope in neonates – a randomised interventional study. Ind J Anaesth 2020;64S24-5.

Kaplan MB, Ward DS, Berci G. A New Video Laryngoscope - An Aid in Intubation and Teaching. J Educ Perioper Med. 2003;5(1)E025.

Lacquiere D, Smith J, Bhanderi N, Lockie F, Pickles J, Steere M, et al. Early experience in use of videolaryngoscopy by a neonatal pre-hospital and retrieval service. Emerg Med Australas. 2024;36(3)476-478.

Lingappan K, Neveln N, Arnold JL, Fernandes CJ, Pammi M. Videolaryngoscopy versus direct laryngoscopy for tracheal intubation in neonates. Cochrane Database Syst Rev. 2023;5(5)Cd009975.

Moussa A, Luangxay Y, Tremblay S, Lavoie J, Aube G, Savoie E, et al. Videolaryngoscope for Teaching Neonatal Endotracheal Intubation: A Randomized Controlled Trial. Pediatrics. 2016;137(3)e20152156.

Moussa A, Sawyer T, Puia-Dumitrescu M, Foglia EE, Ades A, Napolitano N, et al. Does videolaryngoscopy improve tracheal intubation first attempt success in the NICUs? A report from the NEAR4NEOS. J Perinatol. 2022;42(9)1210-1215.

Niles DE, Cines C, Insley E, Foglia EE, Elci OU, Skare C, et al. Incidence and characteristics of positive pressure ventilation delivered to newborns in a US tertiary academic hospital. Resuscitation. 2017;115102–109.

O'Shea JE, Thio M, Kamlin CO, McGrory L, Wong C, John J, et al. Videolaryngoscopy to Teach Neonatal Intubation: A Randomized Trial. Pediatrics. 2015;136(5)912-9.

Riva T, Engelhardt T, Basciani R, Bonfiglio R, Cools E, Fuchs A, et al. Direct versus video laryngoscopy with standard blades for neonatal and infant tracheal intubation with supplemental oxygen: a multicentre, non-inferiority, randomised controlled trial. Lancet Child Adolesc Health. 2023;7(2)101-111.

Salama ER, El Amrousy D. GlideScope(®) cobalt video laryngoscope versus direct Miller laryngoscope for lateral position-tracheal intubation in neonates with myelodysplasia: A prospective randomized study. Saudi J Anaesth. 2019;13(1)28-34.

Singh R, Singh P, Vajifdar H. A comparison of Truview infant EVO2 laryngoscope with the Miller blade in neonates and infants. Paediatr Anaesth. 2009;19(4)338-42.

Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. 2020;105(3)328-330.

Tao B, Liu K, Zhao P, Wang D, Liu Y, Yin H. Comparison of GlideScope Video Laryngoscopy and Direct Laryngoscopy for Tracheal Intubation in Neonates. Anesth Analg. 2019;129(2)482-486.

Thomas H, Lugg R, James B, Geeroms C, Risbridger A, Bell R, et al. Survey of the use of videolaryngoscopy in neonatal units in the UK. Arch Dis Child Fetal Neonatal Ed. 2023;108(1)89-90.

Thomas N, Chakrapani Y, Rebekah G, Kareti K, Devasahayam S. Phase changing material: an alternative method for cooling babies with hypoxic ischaemic encephalopathy. Neonatology. 2015;107(4)266–70.

Tinnion R, Powell S, Bew S, Gilpin D, Cusack J, Patel R, et al. A Framework for Practice. 2020.

Tippmann S, Schäfer J, Winter J, Mühler AK, Schmitz K, Schönfeld M, et al. Video versus direct laryngoscopy to improve the success rate of nasotracheal intubations in the neonatal intensive care setting: a randomised controlled trial. BMJ Paediatr Open. 2023;7(1).

Vanderhal AL, Berci G, Simmons CF, Jr., Hagiike M. A videolaryngoscopy technique for the intubation of the newborn: preliminary report. Pediatrics. 2009;124(2)e339-46.

Volz S, Stevens TP, Dadiz R. A randomized controlled trial: does coaching using video during direct laryngoscopy improve residents' success in neonatal intubations? J Perinatol. 2018;38(8)1074-1080.

Weiner G, Zaichkin J. Textbook of Neonatal Resuscitation. 8th ed. Weiner G, Zaichkin J, editors: American Academy of Pediatrics; 2021 2021.

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.

NLS 5362 – Near infrared spectroscopy during positive pressure ventilation

Should Delivery room monitoring of cerebral oxygen saturation with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or electrocardiogram (ECG) vs. Clinical assessment, pulse oximetry and/or ECG only be used for Newborn infants receiving CPAP and/or IPPV (any interface) during stabilization/resuscitation at birth?	
POPULATION:	Newborn infants receiving continuous positive airway pressure (CPAP) and/or intermittent positive pressure ventilation (IPPV) (any interface) during stabilization/resuscitation at birth
INTERVENTION:	Delivery room monitoring of cerebral oxygen saturation with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or electrocardiogram (ECG)
COMPARISON:	Clinical assessment, pulse oximetry and/or ECG only
MAIN OUTCOMES:	Survival without neurodevelopmental impairment (Critical) Survival (Critical) Neurodevelopmental impairment (Critical) Regional cerebral tissue oxygen saturation ($crSO_2$) <10th percentile or >90 percentile (Important – Task Force defined) Maximum FiO_2 used (Important – Task Force defined) Total oxygen exposure (Important – Task Force defined) In infants < 34 weeks: • Severe intraventricular hemorrhage (Papile grade III or IV) {Papile 1978 834} (Critical) • Periventricular leukomalacia (Critical) • Severe intraventricular hemorrhage <28 weeks (Critical) • Severe intraventricular hemorrhage ≥28 weeks (Critical) • Periventricular leukomalacia <28 weeks (Critical) • Periventricular leukomalacia ≥28 weeks (Critical) Survival <28 weeks (Critical) Survival ≥28 weeks (Critical) Important and Critical according to {Strand 2020 328} and {Webbe 2020 425} unless otherwise specified
SETTING:	Delivery room
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	Up to five percent of newborn infants require positive pressure respiratory support {Skåre 2018 394}, with a higher incidence in preterm infants and those receiving CPAP. As the use of near infrared spectroscopy (NIRS) may help optimizing the delivery of respiratory support (CPAP and/or IPPV) to avoid both cerebral hypoxia and hyperoxia {Pichler

	2017 29}, the International Liaison Committee on Resuscitation (ILCOR) Neonatal Life Support (NLS) Task Force (TF) considered that the effectiveness of monitoring $crSO_2$ with NIRS and a dedicated treatment guideline in addition to standard care should be evaluated. The topic was prioritized by the NLS TF for consideration after the publication of a recent multicenter randomized controlled trial (RCT) {Pichler 2023 }. A systematic review and knowledge synthesis may impact existing ILCOR recommendations for respiratory support at birth and identify knowledge gaps to be addressed in future research.
CONFLICT OF INTERESTS:	Georg Schmölzer is co-author of RCTs on the use of NIRS during respiratory support at birth, and he was excluded from decisions about these studies. This author acknowledged his potential intellectual conflicts of interest and participated in the Task Force discussion of the consensus on science and treatment recommendations.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Preterm birth may have lifelong consequences for neurodevelopmental outcomes such as cerebral palsy and learning difficulties with resulting social and health economic implications. Initial oxygenation is a determinant of morbidity and mortality in preterm infants. There is evidence that suggests that although the preterm infants reach early target peripheral oxygen saturations (SpO_2), $crSO_2$ may be low. A low $crSO_2$ may be a risk factor for intraventricular hemorrhage {Baik 2015 }. Severe intraventricular hemorrhage (Papile grade III or IV) {Papile 1978 } and/or periventricular leukomalacia may impact the outcome survival without neurodevelopmental impairment, all defined as critical outcomes. If the intervention reduces severe intraventricular hemorrhage and/or periventricular leukomalacia in preterm infants, this would be of anticipated substantial benefit to the target population.	

	The question whether monitoring of $crSO_2$ with a dedicated treatment guideline in addition to standard care improves outcomes when compared to standard care alone has not been reviewed by ILCOR previously.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The systematic review identified 2 RCTs {Pichler 2023 , Pichler 2016 73} with a similar intervention, but only some of the same outcomes. {Pichler 2016 73} included 60 infants <34 weeks (pilot study) and {Pichler 2023 } included 607 preterm infants <32 weeks (phase 3 RCT). Briefly, the intervention was using $crSO_2$-values to provide respiratory support or to adjust FiO_2 provided that SpO_2 was between the 10th and 90th percentile. In the control group, respiratory support and FiO_2 was guided by SpO_2 only. For the critical outcome of **survival clinical benefit or harm could not be excluded** (relative risk (RR) 1.02, 95% CI 0.99 to 1.05), **low certainty evidence** from 667 infants included in 2 RCTs {Pichler 2023 , Pichler 2016 73}. The certainty of evidence was downgraded for very serious imprecision due to OIS not being met. For the critical outcome of **severe intraventricular hemorrhage clinical benefit or harm could not be excluded** (RR 0.76, 95% CI 0.38 to 1.54), **very low certainty evidence** from 667 infants included in 2 RCTs {Pichler 2023 , Pichler 2016 73}. The certainty of evidence was downgraded for risk of bias and very serious imprecision. For the critical outcome of **periventricular leukomalacia clinical benefit or harm could not be excluded** (RR 1.93, 95% CI 0.66 to 5.70), **very low certainty evidence** from 667 infants included in 2 RCTs infants {Pichler 2023 , Pichler 2016 73}. The certainty of evidence was downgraded for risk of bias and very serious imprecision. For the important outcome of **$crSO_2$<10th percentile {Pichler 2013 1558} clinical benefit or harm could not be excluded** (RR 1.00, 95% CI 0.78 to 1.29), **very low certainty evidence** from 60 infants included in one RCT {Pichler 2016 73}. The certainty of evidence was downgraded for risk of bias and very serious imprecision.	Only the pilot study performed neurological assessment of 29 infants from one of two centres: General movement assessment was performed between 36 and 40 weeks of corrected gestational age. The task force does not consider this a representation of neurodevelopmental impairment.

The important outcome **maximum FiO_2** (one RCT involving 607 infants {Pichler 2023 }, was "slightly higher", 0.48 (0.45-0.50) vs. 0.44 (0.42-0.46) in the intervention vs. control group, respectively. The highest FiO_2 was at 5 min in both groups with a corresponding SpO_2 of 77.6 (76.1-79.2) and 78.3 (76.7-79.8), respectively. Thus, **clinical benefit or harm could not be excluded.**

Outcomes	№ of participants (studies) Follow-up [1,2]	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects: Risk with Clinical assessment, pulse oximetry and/or ECG only	Anticipated absolute effects: Risk difference with Delivery room monitoring of cerebral oxygen saturation with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or electrocardiogram (ECG)
Survival (Survival)	[1] 667 (2 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.02** (0.99 to 1.05)	946 per 1 000	**19 more per 1 000** (9 fewer to 47 more)
Regional cerebral tissue oxygen saturation (crSO2) <10th percentile (crSO2 <10th percentile)	[1,2] 60 (1 RCT)	⨁◯◯◯ Very low[c,d]	**RR 1.00** (0.78 to 1.29)	800 per 1 000	**0 fewer per 1 000** (176 fewer to 232 more)
In infants < 34 weeks: Severe intraventricular hemorrhage (Papile grade III or IV) (Severe IVH) assessed with: Cranial ultrasound	[1,2] 667 (2 RCTs)	⨁⨁◯◯ Low[b,e]	**RR 0.76** (0.38 to 1.54)	51 per 1 000	**12 fewer per 1 000** (32 fewer to 28 more)
In infants < 34 weeks: Periventricular leukomalacia (PVL) assessed with: Cranial ultrasound	667 (2 RCTs)	⨁◯◯◯ Very low[b,e]	**RR 1.93** (0.66 to 5.70)	15 per 1 000	**14 more per 1 000** (5 fewer to 71 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. The study was underpowered for the main outcome "Survival without NDI" and the optimal information size was not met for the outcome "Survival"
b. Low sample size with an infrequently occurring outcome
c. There was a potential incomplete outcome reporting for this outcome
d. Only 60 infants in a pilot trial
e. Potential bias as it is unclear if the assessor was actually unaware of group allocation

1. Pichler G et al J Pediatr. 2016;170:73-8.e1-4.
2. Pichler G et al Bmj. 2023;380:e072313.

	No data were found for the critical outcomes survival without neurodevelopmental impairment and neurodevelopmental impairment; and no data were found for the important outcomes $crSO_2$>90th centile {Pichler 2013 1558} and total oxygen exposure. Thus, based on the available evidence, clinical benefit or harm associated with delivery room monitoring of $crSO_2$ with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or ECG over clinical assessment, pulse oximetry and/or ECG only could not be excluded. This includes the critical outcomes severe intraventricular hemorrhage (Papile grade III or IV) and periventricular leukomalacia. However, due to the low sample sizes and imprecision of the results, the desirable effects are presently uncertain.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Neither of the 2 RCTs reported any undesirable clinical effects from monitoring of $crSO_2$ with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or ECG.	Intravenous fluid administration and intubation have been mandated by $crSO_2$ -values. However, the appropriateness of these interventions cannot be determined.
Certainty of evidence What 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 very low due to unclear risk of bias, small sample size, and wide confidence intervals. The phase 3 RCT {Pichler 2023 } was underpowered for the main outcome of survival without cerebral injury (measured in this study as abnormalities on imaging studies) as only 607 infants (304 and 303 in the intervention and control group, respectively) out of a planned 724 infants were included. In addition, to detect a clinically important 2% improvement in survival rates from 95% to 97% with a 95% confidence level and 80% power in a two-sided hypothesis test, the optimal information size {Guyatt 2008 924} would be 1,506 infants per group (3,012 infants in total). For the outcomes severe intraventricular hemorrhage and periventricular leukomalacia, there was a potential/unclear risk of bias resulting from uncertainty as to whether the outcome assessor was blinded to the intervention. For the outcome cerebral hypoxia ($crSO_2$ <10th centile) (small pilot study n=60 {Pichler 2016 73}) there was incomplete outcome reporting resulting in potential reporting bias. For all outcomes, imprecision resulted in further downgrading of the certainty of evidence. IMPORTANT NOTE: The prespecified primary outcome in the systematic review was survival without neurodevelopmental impairment, and a secondary outcome survival. However, the included studies did not report the critical primary outcome, but did report survivial. {Pichler 2023 , Pichler 2016 73}	

Values Is 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	Interventions that improve survival without neurodevelopmental impairment are universally valued by stakeholders including families, healthcare and society in general {Strand 2020 328} and {Webbe 2020 425}.	

uncertainty or variability ● No important uncertainty or variability		
Balance of effects Does 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	Clinical benefit or harm could not be excluded for delivery room monitoring of $crSO_2$ with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or ECG vs. clinical assessment, pulse oximetry and/or ECG only in newborn infants receiving CPAP and/or IPPV (any interface) during stabilization/resuscitation at birth. No undesirable or adverse effects were reported, so the balance of desirable/undesirable effects does not favor the intervention or the comparison. $crSO_2$-measurement has not been associated with serious adverse reactions or serious adverse device related events.	Intravenous fluid administration (n=4) and intubation (n=9) have been mandated by $crSO_2$-values (phase 3 RCT). However, it cannot be determined whether these interventions resulted in overall clinical benefit. FiO2 was also slightly higher in the NIRS group than the control group in the first minutes after birth, indicating that NIRS results may have changed oxygen management. It is unclear whether this was beneficial to the infant or not.
Resources required How 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	None of the included studies included data on costs related to NIRS-monitoring and use of a dedicated treatment guideline. There are increased costs associated with the introduction of NIRS into the delivery room (equipment, maintenance, supplies, training of personnel).	Purchasing NIRS equipment and training of personnel in its use and interpretation are expected to increase costs. The costs are anticipated to differ in different contexts/parts of the world. Using NIRS with a dedicated treatment guideline may alter other aspects of care (such as increased use of IV fluids and mechanical ventilation) that have additional cost implications.

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	None of the included studies included data on costs related to monitoring of $crSO_2$ with the use of a dedicated treatment guideline, or training. However, there are moderate to high costs associated with purchasing and implementing new devices.	

Cost effectiveness Does 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	None of the included studies included data on cost effectiveness of monitoring of $crSO_2$ with the use of a dedicated treatment guideline. However, as the intervention did not have effect (clinical benefit), it cannot be judged as cost effective.	
Equity What 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	Purchasing NIRS equipment and training of personnel in its use and interpretation are expected to increase costs. The cost of equipment and training may be higher in low- and middle resource settings, so health equity may be potentially reduced and the gap between well-resourced and resource-limited environments may become larger. None of the included studies specifically addressed equity.	The availability of equipment can vary – further leading to inequity

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Interventions that improve survival without neurodevelopmental impairment are universally valued by stakeholders including families, healthcare and society in general. NIRS is non-invasive and monitoring of $crSO_2$ does not cause harm or pain. To healthcare personnel, acceptability may be influenced by the added workload in the delivery room management associated with monitoring of $crSO_2$ with the use of a dedicated treatment guideline. The ease/difficulty of applying the NIRS sensor immediately after birth and acquiring a signal may represent a challenge. There were no surveys looking into staff acceptability in the included studies.	Additional monitoring equipment may distract healthcare professionals from focusing on the infant and/or other monitoring equipment. Human factors should be considered when new technology is incorporated in delivery room management. Anchoring bias and fixation may be a problem.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	In both studies a research team member was present at det included deliveries. In the phase 3 RCT {Pichler 2023 }, it was specified that the research team member either covered/turned the NIRS monitor away and documented the $crSO_2$ values every minute for the control group infants. I.e., the research team member did not assist in the use and interpretation of NIRS. The studies were performed in highly resourced settings under study conditions. In the phase 3 RCT {Pichler 2023 }, the NIRS sensor was applied "within three minutes after birth" by the clinical team members who were trained to apply the NIRS sensors, interpret the $crSO_2$-values and -targets, and apply the trial interventions. In the pilot trial {Pichler 2016 73}, NIRS-values were	

	available by minute 2 after birth in 48/60 neonates. None of the studies mentioned whether additional staff was needed to be present to deliver the intervention. The pilot study {Pichler 2016 73} reported that "despite technical challenges in measurement of $crSO_2$, approximately 50% of study neonates had $crSO_2$ data (no missing data) for every minute", indirectly stating that $crSO_2$ may be technically challenging, reducing feasibility. None of the studies reported protocol adherence/non-compliance, or protocol withdrawals, indicating feasibility in the study setting.	

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	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
REQUIRED RESOURCES							
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

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

Recommendation

In newborn infants receiving continuous positive airway pressure and/or positive-pressure ventilation immediately after birth, there is insufficient evidence to recommend for or against use of delivery room monitoring of regional cerebral oxygen saturation with a dedicated treatment guideline in addition to (and compared with) clinical assessment and pulse oximetry with or without ECG (very low–certainty evidence).

Justification

In making this recommendation, the Neonatal Life Support Task Force acknowledges the following:

No specific device cost or training cost were reported in the trials. However, the cost of purchasing and implementing new devices is significant. In addition, there are several human factor issues that should be addressed if monitoring of cerebral oxygen saturation is being implemented in clinical practice.

The lack of clinical benefit and the lack of cost-effectiveness data, contributed to the recommendation statement.

We place value on not allocating human and financial resources to an intervention yet to be proven to be associated with a benefit for critical or important outcomes.

Subgroup considerations

Both studies used the same method for monitoring of $crSO_2$, and neither study reported data stratified by CPAP versus IPPV, cord management strategy, or infant sex. The final pre-planned subgroup analysis was by gestational age (weeks): $<28^{0/7}$; $28^{0/7}$-$33^{6/7}$; and $34^{0/7}$ or more. We identified only two studies in preterm infants. One of the studies provided separate data om infants $<28^{0/7}$. There was no difference in the outcomes severe intraventricular hemorrhage and periventricular leukomalacia when results were stratified by $<28^{0/7}$ or $28^{0/7}$ or more. No study of term infants and addressing the PICO was identified.

Implementation considerations

Purchasing NIRS equipment and training of personnel in its use and interpretation are expected to increase costs and require personnel resources.

Implementing monitoring of $crSO_2$ with a dedicated treatment guideline into routine clinical practice is expected to require significant training and cost. Human factor issues also need to be addressed should monitoring of $crSO_2$ with a dedicated treatment guideline be more widespread (see Research priorities section below)

Monitoring and evaluation

Where resources, training and staff permit, monitoring of cerebral oxygen saturation with a dedicated treatment guideline should be monitored, evaluated and documented for research purposes and closing knowledge gaps.

Additional monitoring equipment might distract healthcare professionals from focusing on the infant. Human factors should be taken into account when new technology is incorporated in delivery room management. Units that implement monitoring of cerebral oxygen saturation in the delivery room could consider monitoring and evaluating acceptability amongst staff, as well as resource requirements including a potential need for more people attending deliveries, as well as training requirements.

Research priorities

Research priorities should include human factors, opportunities to reduce inequity, and cost-benefit analysis.

Potential research questions are listed below:

What are the training requirements to achieve and maintain competency in interpretation of cerebral oxygen saturation monitoring during neonatal resuscitation?

What is the cost effectiveness for monitoring of cerebral oxygen saturation during neonatal resuscitation?

Monitoring cerebral oxygen saturation alone versus monitoring cerebral oxygen saturation with a dedicated treatment guideline should also potentially be explored, as well as the optimal treatment guideline. No studies addressed the critical outcomes survival without neurodevelopmental impairment and neurodevelopmental impairment. Future studies should address these outcomes. Sufficiently powered trials to investigate a difference in the critical outcomes severe intraventricular hemorrhage and periventricular leukomalacia should also be considered.

NLS 5400 – Oxygen concentration for commencing positive pressure ventilation in preterm infants

Should lower initial oxygen concentration (FiO2 ≤0.5) vs. higher initial oxygen concentration (FiO2 >0.5) be used for newborn infants <35 weeks' estimated gestational age who receive respiratory support at delivery?	
POPULATION:	Newborn infants <35 weeks' estimated gestational age who receive respiratory support at delivery
INTERVENTION:	Lower initial oxygen concentration (FiO2 ≤0.5)
COMPARISON:	Higher initial oxygen concentration (FiO2 >0.5)
MAIN OUTCOMES:	All-cause mortality in-hospital or 28 days (critical); All-cause mortality before 1-3 years (critical); Neurodevelopmental impairment at 1 to 3 years of age (critical); Major IVH (grade III or IV) (critical); Retinopathy of prematurity (critical); Necrotizing enterocolitis stage II or III (critical); Bronchopulmonary dysplasia (Chronic Neonatal Lung Disease) (important); Number with HR > 100 at 5 mins; Time from birth to SpO2 ≥80% (important); Advanced resuscitation (chest compressions with or without epinephrine (adrenaline)) (important);
SETTING:	Delivery room or other locations where preterm infants are born
PERSPECTIVE:	Population
BACKGROUND:	A previous ILCOR systematic review {Welsford 2019 1} reported; "Ten *randomized controlled studies and 4 cohort studies included 5697 patients. There are no statistically significant benefits of or harms from starting with lower compared with higher FiO2 in short-term mortality (n = 968; risk ratio = 0.83 [95% confidence interval 0.50 to 1.37]), long-term mortality, neurodevelopmental impairment, or other key preterm morbidities. A sensitivity analysis in which 1 study with a high RoB was excluded failed to reveal a reduction in mortality with initial low FiO2 (n = 681; risk ratio = 0.63 [95% confidence interval 0.38 to 1.03])".* As a result of these findings, the Task Force recommended that; "*We suggest starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks' gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence)*" {Soar 2019 e826} A recent network meta-analysis and individual patient data meta-analysis (IPD NWMA - NetMotion) {Sotiropoulos 2024 774} included 8 {Armanian 2012 25, Boronat 2016 e 20161405, Kapadia 2013 e1488, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}of the 12 RCTs included in {Welsford 2019 1} and 4 additional trials {Dekker 2019 10.3389/fped.2019.00504, Finer 2018 , Kaban 2022 104, Liyakat 2023 794} NetMotion obtained patient data for 1055 infants concluded that; *"High initial FiO2 (0.90) may be associated with reduced mortality in preterm infants born*

at less than 32 weeks' gestation compared to low initial FiO2 (low certainty). High initial FiO2 is possibly associated with reduced mortality compared to intermediate initial FiO2 (very low certainty) but more evidence is required".

Three of the 4 additional trials included in NetMotion were not published at the time of the previous ILCOR systematic review. {Dekker 2019 10.3389/fped.2019.00504, Kaban 2022 104, Liyakat 2023 794} For an additional study, the NetMotion investigators obtained unpublished results (not eligible for inclusion in the ILCOR systematic review) from study authors. {Finer 2018 } One additional trial that enrolled 42 infants was not included in the previous ILCOR systematic review, {Escrig 2008 875} because it was a pilot/feasibility study and most data were reported in subsequent larger trial that was included in the review. {Vento 2009 e439}

The previous ILCOR systematic review {Welsford 2019 1} also included 4 observational studies {Dawson 2009 F87, Kapadia 2017 35, Rabi 2015 252, Soraisham 2017 1141} that were ineligible for NetMotion. {Sotiropoulos 2023 372}

Due to the discordance between the conclusions of these two systematic reviews (conducted at different times and using different methods) the Task Force concluded that an updated ILCOR systematic review was required, to consider three types of evidence:

1. Evidence from eligible randomized controlled trials included in {Welsford 2019 1} and any published since the last search date for that review (10th August 2018)

2. Evidence from any large (preferably population-based) observational studies that is adjudicated using GRADE methods to provide similar or higher certainty of evidence to the RCTs

3. Results of the IPD NWMA NetMotion {Sotiropoulos 2024 774}, by adolopment, considering the evidence therein but using it to develop the Task Force's own conclusions about the Consensus on Science and Treatment recommendations, in combination with the evidence from study level metanalysis of RCTs and observational studies.

The combined results of these are considered in this Evidence to Decision Table to determine whether the previous treatment recommendations are still applicable or need to be superseded.

The updated systematic literature search identified for inclusion in the study-level meta-analysis the 3 RCTs that had been included in NetMotion {Sotiropoulos 2024 774}) that had been published too recently for inclusion in the previous ILCOR systematic review. {Welsford 2019 1} The search found one additional RCT {Law 2021 942}) which had not been included in NetMotion because it was cluster-randomized. The study-level meta-analysis therefore included 1289 infants (compared to the 1007 included in the previous ILCOR meta-analysis. Welsford 2019 1} Of the included studies, three reported aspects of a single two-country trial {Aguar 2013 , Boronat 2016 e 20161405, Rook 2014 1322}, one included most data from a previous pilot study {Escrig 2008 875, Vento 2009 e439}, and one reported neurodevelopmental follow-up data and late mortality {Thamrin 2018 55} from another trial. {Oei 2017 26}

CONFLICT OF INTERESTS:	Co-author Schmölzer is a co-author on the NetMotion study {Sotiropoulos 2024 774}and was excluded from decisions about adolopment and bias assessment of this study. Co-author Schmölzer is a co-author on one study eligible for inclusion {Law 2021 942} and was excluded from decisions about inclusion and risk of bias assessment for this study.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Preterm infants are at risk for the toxic effects of oxygen that can have adverse effects on the lungs (leading to increased risk of bronchopulmonary dysplasia or neonatal chronic lung disease, eyes (leading to retinopathy of prematurity), brain and other organs. Although neonatal intensive care after birth may expose infants to much of their ongoing risk, studies demonstrating high levels of oxygen free radicals after resuscitation in high inspired oxygen concentrations suggests that exposure soon after birth may also impose clinically important risk. {Vento 2009 e439} Conversely, delivery room hypoxia adversely affects outcomes, and morbidity and mortality are increased in preterm infants with a gestational age less than 32 weeks who fail to achieve a peripheral oxygen saturation higher than 80% at 5 min of life, especially if combined with bradycardia. {Torrejón-Rodríguez 2023 244} Adverse outcomes of hypoxia and hyperoxia may be reduced if resuscitators rapidly and effectively titrate the inspired oxygen concentration during resuscitation. However, their responses may be limited by latencies in measurement and slow reactions to high or low oxygen saturation levels. In addition, in settings with very limited resources, the only choice may be air (FiO2 0.21) or in other resource-limited settings, air or pure oxygen (FiO2 1.00). Before any aeration of the newborn's lungs, the oxygen concentration provided may briefly make little difference. However, as soon as aeration commences and pulmonary blood flow starts to increase, a higher inspired oxygen concentration could provide benefits including enhanced respiratory drive and pulmonary arteriolar vasodilation. Potential benefits could include an enhanced response to resuscitation, reduced need for resuscitation interventions and improved survival without short- and long-term morbidity.	

	Therefore, the problem is a priority because of potential to influence survival and important adverse consequences of prematurity, and also because of implications for resources to blend and titrate oxygen.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**From the individual patient network meta-analysis:** NetMotion evaluated IPD for 1055 participants from 12 of 13 eligible studies. Eligibility included gestation <32 weeks at birth. {Sotiropoulos 2024 774} See description in background for overlap with the previous and updated study level meta-analysis. For the **critical primary outcome of all-cause mortality** (in hospital or by 28 days) the NetMotion IPD NWMA) compared low (≤0.3), intermediate (0.5-0.65) and high (≥0.9) initial FiO2. • **High initial FiO2 (≥ 0.90) reduced all-cause mortality (in hospital or within 28 days) compared to low initial FiO2 (0.21-0.30)** (adjusted odds ratio (aOR) 0.45, 95% credible interval (CrI) 0.23-0.86, number needed to benefit (NNTB) 16 (95% CrI 10-66) ARD 67 more infants per 1000 survived with high initial FiO2 (95% CrI 15 more to 100 more), **low certainty** evidence from direct comparison of 833 patients included in 8 studies. {Dekker 2019 10.3389/fped.2019.00504, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083} • For **intermediate initial FiO2 (0.50-0.65) compared to low FiO2 (0.21-0.30)** clinical benefit or harm could not be excluded (aOR 1.33, 95% CrI 0.54-3.15), **very low certainty** evidence from direct comparison of 352 participants in 4 studies. {Aguar 2013 , Finer 2018 , Kaban 2022 104, Rook 2014 1322} • For **high (≥0.90) compared to intermediate initial FiO2 (0.50-0.65) there was possible clinical benefit** (aOR 0.34; 95% CrI 0.11-0.99; number needed to treat, 11; 95% CrI, 4-1514) **very low certainty** evidence from an indirect comparison. (No studies compared high vs intermediate FiO2). {Sotiropoulos 2024 774} For the critical outcome of **severe intraventricular hemorrhage clinical benefit or harm could not be excluded** (OR 0.56, 95% CrI 0.10-1.82), **very low certainty evidence** from 809 infants included	

	in 8 studies. {Dekker 2019 10.3389/fped.2019.00504, Escrig 2008 875, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083} **From the study-level meta-analysis:** ***Randomized controlled trials*** **For the comparison between lower (FiO_2 ≤0.5) vs higher initial oxygen concentration (FiO_2 >0.5)** • For the **critical primary outcome of all-cause mortality (in hospital or by 28 days) clinical benefit or harm could not be excluded** (Relative risk (RR); 1.12, 95% confidence intervals (95% CI); 0.84 to 1.49), **very low certainty evidence** from 1289 infants included in 14 RCTs {Aguar 2013 , Armanian 2012 25, Dekker 2019 10.3389/fped.2019.00504, Harling 2005 F401, Kaban 2022 104, Kapadia 2013 e1488, Law 2021 942, Liyakat 2023 794, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Rook 2014 1322, Vento 2009 e439, Wang 2008 1083} The certainty of evidence was downgraded for risk of bias and imprecision. • For the critical secondary outcome of **long term all-cause mortality (1-3 years) clinical benefit or harm could not be excluded** (RR 1.04, 95% CI 0.42-2.58) **very low certainty evidence** from 515 infants included in 2 RCTs. {Boronat 2016 e 20161405, Thamrin 2018 55} The certainty of evidence was downgraded for serious risk of bias and very serious imprecision. (These results are essentially the same as those reported in the previous ILCOR systematic review, but are replicated with updated assessment using Cochrane RoB2 and GRADE CoE, and using the denominator of infants included in each study, rather than the denominator of only those for whom follow-up was achieved). • For the critical secondary outcome of **neurodevelopmental impairment** (1-3 years) **clinical benefit or harm could not be excluded** (RR;1.14, 95% 95% CI; 0.78 to 1.67), **very low certainty evidence** from 389 infants who were able to be followed up from 2 RCTs. {Boronat 2016 e 20161405, Thamrin 2018 55} The certainty of evidence was downgraded for risk of bias and imprecision. (These results are essentially the same as those reported in the previous ILCOR systematic review, but are replicated with updated assessment using Cochrane RoB2 and GRADE CoE). • For the critical secondary outcome of **major IVH (grade III or IV) clinical benefit or harm could not be excluded** (RR; 1.10, 95%; 0.81 to 1.49), **very low certainty evidence** from 1129 infants included in 11 RCTs. {Boronat 2016 e 20161405, Dekker 2019 10.3389/fped.2019.00504, Harling 2005 F401, Kaban 2022 104, Kapadia 2013 e1488, Law 2021 942, Liyakat 2023 794, Lundstrøm 1995 F81, Oei 2017 26, Vento 2009 e439, Wang	

2008 1083} The certainty of evidence was downgraded for very serious risk of bias and for imprecision.

- For the important secondary outcome of **advanced resuscitation** (chest compressions with or without epinephrine (adrenaline)) **clinical benefit or harm could not be excluded** (RR; 0.84, 95% CI; 0.24 to 2.90), **very low certainty evidence** from 772 infants included in 7 RCTs {Escrig 2008 875, Kaban 2022 104, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Wang 2008 1083} The certainty of evidence was downgraded for serious risk of bias, and extremely serious imprecision.
- For other important outcomes of the review, they were not reported or there was insufficient evidence for meaningful analysis (e.g. outcome reported in only one small study with high risk of bias for the outcome).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Higher initial oxygen concentration (FiO2 >0.5)	Risk difference with Lower initial oxygen concentration (FiO2 ≤0.5)
All-cause mortality in-hospital or 28 days (critical)	1289 (14 RCTs)[1,10,11,12,13,14,2,3,4,5,6,7,8,9]	⨁◯◯◯ Very low[a,b,c]	**RR 1.12** (0.84 to 1.49)	Study population	
				103 per 1,000	**12 more per 1,000** (16 fewer to 50 more)
				Study population	

All cause mortality before 1-3 years (critical)	515 (2 RCTs)[15,16]	⊕◯◯◯ Very low[b,d,e]	**RR 1.04** (0.42 to 2.58)	104 per 1,000	**4 more per 1,000** (60 fewer to 164 more)
Neurodevelopmental impairment at 1 to 3 years of age (critical)	389 (2 RCTs)[15,16]	⊕◯◯◯ Very low[b,d,f]	**RR 1.14** (0.78 to 1.67)	Study population	
				192 per 1,000	**27 more per 1,000** (42 fewer to 129 more)
Major IVH (grade III or IV) (critical)	1130 (11 RCTs)[1,12,13,16,2,4,5,6,7,8,9]	⊕◯◯◯ Very low[b,g,h]	**RR 1.10** (0.81 to 1.49)	Study population	
				113 per 1,000	**11 more per 1,000** (21 fewer to 55 more)
Advanced resuscitation (chest compressions with or without epinephrine (adrenaline)) (important)	772 (7 RCTs)[1,13,17,3,5,6,7]	⊕◯◯◯ Very low[b,i,j]	**RR 0.84** (0.24 to 2.90)	Study population	
				17 per 1,000	**3 fewer per 1,000** (13 fewer to 32 more)

1. {Wang 2008 1083}
2. {Vento 2009 e439}
3. {Rabi 2011 e374}

4. {Lundstrøm 1995 F81}
5. {Liyakat 2023 794}
6. {Kaban 2022 104}
7. {Kapadia 2013 e1488}
8. {Harling 2005 F401}
9. {Dekker 2019 10.3389/fped.2019.00504}
10. {Armanian 2012 25}
11. {Aguar 2013 }
12. {Law 2021 942}
13. {Oei 2017 26}
14. {Rook 2014 1322}
15. {Thamrin 2018 55}
16. {Boronat 2016 e 20161405}
17. {Escrig 2008 875}

a. For this outcome, 8 trials were at low overall risk of bias, 3 had some concerns in one domain, and 3 had high risk. Less than half the data came from studies rated as low risk.
b. $I^2 = 0\%$
c. OIS not met for control group event rate 0.104
d. For this outcome, one study had low overall risk of bias, one was high
e. OIS not met for control group event rate 0.059
f. OIS not met for control group event rate 0.19
g. For this outcome, 2 trials at low overall risk of bias, 3 had some concerns and 2 were high
h. OIS not met for control group event rate 0.11
i. For this outcome, 4 trials at high overall risk of bias, 2 with some concerns
j. OIS not met for control group event rate 0.01

Observational studies:

There were no new observational studies found for inclusion in this updated review. The previous ILCOR systematic review included 4 observational studies and reported for **long-term mortality** that "two observational cohort studies involving 1225 preterm newborns receiving respiratory support at birth revealed **a statisticially significant benefit of starting with lower compared to higher FiO2** (RR 0.77, 95% CI 0.59 to 0.99; I 2 =6%)". {Kapadia 2017 35, Soraisham 2017 1141} These studies were deemed to be at **"unclear" overall risk of bias** using ROBINS-I assessment. {Welsford 2019 1} For **neurodevelopmental impairment**, two studies including 930 infants

	"revealed **no statistically significant difference in starting with lower compared with higher FiO2** (RR = 0.89 [95% CI 0.66 to 1.20]; I2 = 59%. {Kapadia 2017 35, Soraisham 2017 1141} These studies were deemed to be at **"unclear" overall risk of bias** using ROBINS-I assessment {Welsford 2019 1}	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**From the individual patient network meta-analysis:** For the following important outcomes, **the comparison between high (>0.90) and low (≤0.30) FiO2 could not exclude benefit or harm:** • **chronic lung disease** (aOR 1.17, 95% CrI 0.55-2.52) from 783 infants included in 8 studies {Dekker 2019 10.3389/fped.2019.00504, Escrig 2008 875, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083} • **retinopathy of prematurity** (OR 1.17, 95% CrI 0.58-2.20), 767 infants included in 8 studies {Dekker 2019 10.3389/fped.2019.00504, Escrig 2008 875, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083} In each case, the evidence was of **very low certainty.** The comparisons between high (>0.90) and intermediate (0.50 to 0.65) FiO2 included 483, 519 and 480 infants respectively from 4 included studies and have even greater imprecision due to smaller numbers of included infants, so are not presented. {Sotiropoulos 2024 774} Other critical and important outcomes of the PICOST were not reported. **From the study-level meta-analysis:** **For the comparison between lower (FiO_2 ≤0.5) vs higher initial oxygen concentration (FiO_2 >0.5)** • For the critical secondary outcome of **severe retinopathy of prematurity clinical benefit or harm could not be excluded** (RR; 1.06, 95% CI; 0.62 to 1.82), **very low certainty evidence** from 1046 infants included in 9 RCTs. {Boronat 2016 e 20161405, Harling 2005 F401, Kaban 2022 104, Kapadia 2013 e1488, Law 2021 942, Liyakat 2023 794, Lundstrøm 1995 F81, Oei	

2017 26, Vento 2009 e439}The certainty of evidence was downgraded for risk of bias and for imprecision.

- For the critical secondary outcome of **necrotizing enterocolitis (grade 2 or 3) clinical benefit or harm could not be excluded** (RR; 1.07, 95% CI; 0.58 to 2.00), **very low certainty evidence** from 1007 infants included in 9 RCTs. {Boronat 2016 e 20161405, Harling 2005 , Kaban 2022 104, Kapadia 2013 e1488, Law 2021 , Liyakat 2023 794, Lundstrøm 1995 , Oei 2017 26, Vento 2009 e439The certainty of evidence was downgraded for very serious risk of bias and serious imprecision.
- For the important secondary outcome of **bronchopulmonary dysplasia clinical benefit or harm could not be excluded** (RR; 1.04, 95% CI; 0.70 to 1.56), **very low certainty evidence** from 921 infants included in 8 RCTs. {Boronat, 2016 #60;Harling, 2005 #57;Kaban, 2022 #28;Kapadia, 2013 #47;Law, 2021 #31;Lundstrøm, 1995 #55;Oei, 2017 #50;Vento, 2009 #45} The certainty of evidence was downgraded for very serious risk of bias, and for inconsistency and imprecision.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Higher initial oxygen concentration (FiO2 >0.5)	Risk difference with Lower initial oxygen concentration (FiO2 ≤0.5)
Retinopathy of prematurity (critical)	1046 (9 RCTs)[1,2,3,4,5,6,7,8,9]	⨁◯◯◯ Very low[a,b,c]	**RR 1.06** (0.62 to 1.82)	Study population	
				49 per 1,000	**3 more per 1,000** (19 fewer to 40 more)
				Study population	

Necrotizing enterocolitis stage II or III (critical)	1007 (9 RCTs)[1,10,2,4,5,6,7,8,9]	⨁◯◯◯ Very low[c,d,e]	**RR 1.07** (0.58 to 2.00)	47 per 1,000	**3 more per 1,000** (20 fewer to 47 more)
Bronchopulmonary dysplasia (Chronic Neonatal Lung Disease) (important)	921 (8 RCTs)[1,2,3,4,6,7,8,9]	⨁◯◯◯ Very low[f,g,h]	**RR 1.04** (0.70 to 1.56)	Study population	
				239 per 1,000	**10 more per 1,000** (72 fewer to 134 more)

1. {Law 2021 942}
2. {Oei 2017 26}
3. {Vento 2009 e439}
4. {Lundstrøm 1995 F81}
5. {Liyakat 2023 794}
6. {Kaban 2022 104}
7. {Kapadia 2013 e1488}
8. {Boronat 2016 e 20161405}
9. {Harling 2005 F401}
10. {Wang 2008 1083}

a. For this outcome, 3 trials had overall low risk of bias, 3 had some concerns and 3 were high
b. $I^2 = 0\%$
c. OIS not met for control group event rate 0.05
d. For this outcome, 2 trials at low overall risk of bias, 3 had some concerns and 2 were high
e. $I^2 = 3\%$
f. For this outcome, 2 trials were at high overall risk of bias, 3 had some concerns and 3 were low
g. $I^2 = 56\%$, likely due to variations between studies in criteria for outcome
h. OIS not met for control group event rate 0.24

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**From the individual patient network meta-analysis:** The results for "high vs. low" and "intermediate vs. low" were based on direct comparisons, whereas "intermediate vs. high" was an indirect comparison as no included study compared "intermediate vs. high". {Sotiropoulos 2024 774} Using the AMSTAR2 checklist {Shea 2017 j4008}, we concluded that the NETMOTION IPD NWMA was of **overall high quality**. The only shortcomings included a lack of information about the included studies as the paper did not report individual study outcomes, funding etc. The authors did not justify including only RCTs and only papers written in English and did not provide a list of excluded studies. (The study level meta-analysis also excluded papers not written in English and no additional non-RCTs were found). NetMotion used IPD which allowed adjustment for various important modifiers such as gestation at birth and birthweight, so should have greater precision of estimates than the study level meta-analysis. {Sotiropoulos 2023 372} There is such extensive overlap of included data that it is unlikely that differences in the results of NetMotion and the updated study level meta-analysis are accounted for by study exclusions. There is some indirectness of NetMotion compared to our PICOST, because it included only infants <32 weeks' gestation, and therefore does not inform a decision about infants 32 to 34+6 weeks' gestation. However, for infants <32 weeks' gestation, the results were considered by the Task Force to be more precise than those of the study level meta-analysis even though the overall certainty of evidence was similar. Nevertheless, NetMotion is subject to the same concerns as the study-level meta-analysis about overall sample size being well below the optimal information size for all critical and important outcomes. The certainty of evidence in the NetMotion study was upgraded for large effect size, but this is a consideration usually applied in GRADE to observational, not intervention studies. Current guidance from GRADE for systematic review authors is to consider a fully contextualized approach, in which “thresholds for decision-making are determined with considerations across all important and critical outcomes before rating the final certainty in the evidence. This includes considering the range of possible effects on all critical outcomes, bearing in mind the decision(s) that need to be made, and, as for the partially contextualized approach, the importance (value) of	

	these outcomes. For each outcome, certainty ratings represent our confidence that the direction of the net effect (positive or negative) and decision will not differ from one end of the certainty range to the other". {Schünemann 2022 225} On this basis, the Task Force judged that the certainty, considered across all critical and important outcomes in the IPD NMA was **very low**. We concluded that the certainty of evidence relating to mortality is, at best **low** for the comparison between low and high FiO2 for short-term mortality, **very low** for the comparison between intermediate and high categories, **very low** for all for morbidity outcomes and receipt of chest compressions and **low** for the overall ranking of FiO2 categories. NetMotion did not examine long-term outcomes (mortality or neurodevelopmental impairment). The prediction intervals (i.e., range between which results of a future study would be expected to fall) crossed the line of no effect for both the high vs. low comparison (prediction interval 0.44, 95% CrI 0.15-1.34) and high vs. intermediate comparison (prediction interval 0.33, 95% CrI 0.08-1.40), which may be considered to further reduce the certainty of evidence. {Sotiropoulos 2024 774} **From the study-level meta-analysis:** For comparisons between any lower and any higher FiO2, the certainty of evidence was **very low** for all mortality and morbidity outcomes and receipt of chest compressions. There was insufficient evidence for meaningful meta-analysis of other resuscitation outcomes. The most frequent reasons for downgrading of certainty were risk of bias and very serious imprecision. Contributions to the risk of bias included that it was inevitable in nearly all the trials that the study group allocation could not be masked, which we considered most likely to affect determination of resuscitation outcomes. Many did not report whether outcome assessors for major morbidity were blinded to treatment group allocation, and earlier trials were less likely to have pre-registered protocols to allow determination of whether there was selective outcome reporting, or to report the method of random sequence generation. Very serious imprecision was determined because the combined sample size did not meet the Optimal Information Size for any outcome. Of note, two included studies used a method of cluster randomization, which was considered to have the potential to increase risk of bias in domains 1 and 2 of the RoB 2 tool. However one of these {Liyakat 2023 794} randomized oxygen and air cylinders and the days on which they were used and may have resulted in better concealment of randomization and blinding of the	

	intervention than patient level randomization. It is not stated in the paper whether there were any actual clusters (which would only have occurred if two eligible infants were born on the same day). The other study randomly allocated different 2-month time periods and there were unquestionably clusters. {Law 2021 942} Because it was a small pilot study that contributes very little weight to the analysis, no adjustment for clustering has been applied. (This study was excluded from NetMotion). For **long term mortality,** as in the previous ILCOR systematic review, {Welsford 2019 1} there were only two papers included {Boronat 2016 e 20161405, Thamrin 2018 55}, which reported the 1-3 year outcomes of {Aguar 2013 } plus {Rook 2014 1322}, and {Oei 2017 26} respectively. The missing proportions from the follow-up in these trials were 7.5% and 17.6% respectively. Missing mortality data or mis-attribution for as few as 2-3 infants who died could have changed the statistical significance of the effect estimate. Of note, there were inconsistencies in the CONSORT diagrams in the follow-up paper by {Thamrin 2018 55}, and the original Torpido study paper {Oei 2017 26} that were not fully resolved by enquiry of study authors. In the follow-up study, {Thamrin 2018 55}, a higher total number of babies is shown as included in the study, the number of babies attributed to the high oxygen group was higher than the number originally allocated to that group, and the number in the low oxygen group was lower.	
Values Is 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	Consistent with previous ILCOR systematic reviews, the importance of outcomes has been assigned in accord with consensus of the Neonatal Life Support Task Force {Strand 2020 328} and other expert and parent consensus. {Webbe 2020 425}	

uncertainty or variability		
Balance of effects Does 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	**From the individual patient data network meta-analysis:** From direct comparisons, NetMotion found benefit to high vs. low oxygen for commencing resuscitation for the critical primary outcome for the review, **short-term mortality** (low certainty evidence), with no evidence of benefit for other critical or important outcomes. The study also suggested benefit for **high vs intermediate oxygen** for short term mortality but with very low certainty evidence. {Sotiropoulos 2024 774} **From the study-level meta-analysis:** **RCTs** For all critical and important outcomes that were reported in the included studies, there was low or very low certainty evidence that could not exclude benefit or harm from the use of a low compared to a high level of oxygen for initiating resuscitation in preterm infants <35 weeks' gestation. Most studies included detailed provisions for titrating or changing FiO2 depending on response to oxygen saturation (SpO2) measured using pulse oximetry and utilising early and frequent observations and adjustments. The remaining studies had provisions for crossover or adjustments in certain circumstances, or after a specified time interval. It seems likely that the better the adherence to these strategies, the greater the likelihood that any differential in study outcomes between high and low initial oxygen concentrations would be reduced. However, the effect on short-term mortality of low oxygen vs high oxygen in those studies that used no or late titration (RR 1.10, 95% CI 0.81 to 1.60) {Harling 2005 F401, Law 2021 942, Liyakat 2023 794, Rabi 2011 e374, Wang 2008 1083} was very similar to that in studies that used early titration (RR 1.25, 95% CI 0.65-2.40). {Armanian 2012 25, Boronat 2016 e 20161405, Dekker 2019 10.3389/fped.2019.00504, Kaban 2022 104, Kapadia 2013 e1488, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Vento	In clinical care outside clinical trials, there may be latencies in obtaining accurate measurements of saturation and heart rate and in the responses of resuscitation personnel.

	2009 e439} The test for subgroup differences was not significant: Chi2 = 0.14 df = 1, p = 0.71 I2 = 0%. (Note that in this comparison, one study is included twice and the low FiO2 group is represented twice because it was a 3-arm study, one high FiO2 group with titration (managed by the study investigator) and one with no titration. {Rabi 2011 e374}). One trial compared FiO2 0.30 to 0.50, both of which are within our definition of "low", and the difference between these oxygen concentrations may have been small enough to mask an overall difference between low and high. {Kaban 2022 104} However, removing this trial from the analysis resulted in confidence intervals that still crossed the line of no effect. There was also no apparent influence of the level of oxygen used in the low oxygen group; with effect sizes being: • RR 1.12, 95% CI 0.76 to1.64 for studies that used FiO2 0.21 as the low oxygen group. {Kapadia 2013 e1488, Liyakat 2023 794, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Wang 2008 1083} • RR 1.46 95% CI 0.73 to 2.88 for studies that used FiO2 0.30 as the low oxygen group {Aguar 2013 , Armanian 2012 25, Dekker 2019 10.3389/fped.2019.00504, Kaban 2022 104, Law 2021 942, Rook 2014 1322, Vento 2009 e439} • RR 0.80 95% CI 0.24 to 2.65 for the one study that used FiO2 0.50 as the low oxygen group. {Harling 2005 F401} The test for subgroup differences was not significant: Chi2 = 11.76, df = 11, p = 0.47, I2 = 0%. Thus for short term mortality, the results did not show differences by or pre-specified subgroup analyses, (or by gestation - see Subgroup Considerations below). In a study level post-hoc analysis by NetMotion subgroups: • RR 1.73, 95%CI 0.53-5.58 for studies that compared intermediate vs low initial FiO2 (0.5-0.65 vs ≤0.3) {Aguar 2013 , Harling 2005 F401, Kaban 2022 104, Law 2021 942, Rook 2014 1322} • RR 1.29 95% CI 0.89 to 1.87 for studies that used high vs low initial FiO2 (≥0.9 vs ≤0.3) {Armanian 2012 25, Dekker 2019 10.3389/fped.2019.00504, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}	

	The test for subgroup differences was not significant; Chi2 = 0.21, df = 1, p = 0.65 I2 = 0% **Non-RCTs** These studies (included in the previous meta-analysis) could not exclude benefit or harm for short term mortality, and are at high risk of bias. For long term mortality they suggested benefit for long term mortality but not neurodevelopmental impairment, but the risk of bias due to incomplete outcome data was sufficiently high that we do not think they should influence the estimate of balance of effects.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No studies specifically addressed the required resources.	The Task Force concluded that there was unlikely to be a difference in resources, beyond those needed for training in any new strategy.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No studies specifically addressed the required resources.	

Cost effectiveness Does 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 addressed cost-effectiveness.	

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased	No direct evidence from included studies. There were included studies from both high- and middle-income countries.	

○ Varies ○ Don't know		
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The rate of deviations from study protocols was low in studies that reported it.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

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

	JUDGEMENT						
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

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

Recommendation

Among newborn infants <32 weeks' gestation, it is reasonable to begin resuscitation with 30% oxygen or more (weak recommendation, low-certainty evidence).

For infants born at 32 to 34+6 weeks' gestation, there is insufficient evidence to make a recommendation.

Justification

Overall justification

The previous ILCOR treatment recommendation (2020) was:

*We **suggest** starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks' gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence).* {Soar 2019 e826}

This was based on (1) evidence from RCTs appraised at the time that for all critical and important outcomes of the review, there was no benefit or harm of using either lower or higher oxygen concentrations for commencing resuscitation, (2) evidence from observational studies suggesting benefit of lower oxygen concentrations for long term mortality and (3) the evidence from "*decades of research (that) demonstrate that oxygen exposure is a determinant of critical neonatal outcomes in preterm infants. Concern remains that oxygen concentrations to which preterm infants are exposed if they need resuscitation immediately after birth may be a critical contributor to outcomes regardless of subsequent oxygen exposure*". {Soar 2019 e826}

The updated study level meta-analysis found that benefit or harm could not be excluded for lower vs. higher concentrations of oxygen for commencing resuscitation, with low certainty of evidence for all outcomes. The NetMotion individual patient network meta-analysis suggested benefit of higher concentrations and that 90-100% may result in the lowest mortality {Sotiropoulos 2024 774}, but the Task Force concluded that the overall certainty of evidence is still very low.

Concerns persist regarding unmeasured adverse effects of hyperoxia and hypoxia, and most very preterm infants whose resuscitation has started in 21% or 100% will need prompt adjustments of inspired oxygen concentration, and as a result, two pending multicenter trials are utilizing 30% vs 60% oxygen for their treatment arms.

Among the included trials, 6 (all of which allowed early/frequent titration of oxygen concentration) included measurements of various different markers of oxidative stress, inflammation and cerebral blood flow after resuscitation. Three of these six found differences in markers. {Kapadia 2013 e1488, Lundstrøm 1995 F81, Vento 2009 e439} This may be because of differences in study protocols or differences in the sensitivity of the different biomarkers. However, taken together, the studies do not establish conclusively the extent to which oxygen concentration for commencing resuscitation, (provided there are subsequent adjustments in response to oxygen saturation monitoring and other clinical events) affects biomarkers for injury caused by hypoxia or hyperoxia.

Whichever initial oxygen concentration was used, oxygen saturation monitoring and individualized adjustments of inspired oxygen concentration were used in most of the clinical trials and are likely to be needed to optimize outcomes.

Detailed justification

Certainty of evidence

In determining the relative importance of evidence from the study level meta-analysis vs the IPD NWMA the Task Force noted the following: Both the study-level meta-analysis (according to usual ILCOR default) (and NetMotion) used Random Effects for calculation of confidence intervals, but even using the less conservative Fixed Effects for the study level meta-analysis, all confidence intervals in the study level meta-analysis crossed the line of no effect.

The combined sample size did not meet the 'optimal information size' for any outcome (and was well below this level for several of them) the IPD NWMA. For this reason, the "prediction intervals" (the estimate of where results might lie in future studies) for the IPD NMA all cross the line of no effect. {Sotiropoulos 2024 774} The use of individual patient data for network meta-analysis allows adjustment for important baseline characteristics of participants as well as differences in protocol-driven differences such as titration strategy, but there remains the possibility of unmeasured effect modifiers within and between studies. The Task Force noted that at the study level, there was no apparent dose-effect (subgroup interaction) for analysis by either the protocol-prespecified definitions of categories for low oxygen, or by the NetMotion categories of low, intermediate and high.

Subgroup considerations

Oxygen level used for low oxygen group and titration strategy:

See section on Balance of Effects.

Gestation groups:

The effect size for short term mortality was similar for studies reporting infants (or subgroups) < 28 weeks' (or mostly <28 weeks') gestation or 28 to 34+6 weeks' gestation.

- <28 weeks' gestation RR 1.67 95% CI 0.88 to 3.15 {Escrig 2008 875, Law 2021 942, Oei 2017 26, Vento 2009 e439}
- 28 - 34+6 weeks gestation RR 1.19 95% CI 0.77 to 1.83 {Armanian 2012 25, Liyakat 2023 794, Oei 2017 26}

The test for subgroup differences was not significant; Chi2 = 0.75, df = 1, p = 0.339, I2 = 0%.

Note - one study is listed twice because a breakdown was provided by gestation subgroups. {Oei 2017 26} For the higher gestation group, the analysis attached heavy weighting to a study done in a low-resource setting where no titration of oxygen was possible and overall mortality was high. {Liyakat 2023 794}

Method of umbilical cord management:

There were insufficient data distinguishing infants by method of umbilical cord management to conduct this preplanned subgroup analysis.

Implementation considerations

Whichever initial oxygen concentration is chosen, protocols and training to ensure subsequent titration may be very important to achieving good outcomes, although the optimal titration targets and strategy have not yet been determined. Following the titration strategies derived from one or more of the included clinical trials may suffice until there is an evidence basis for the choice.

Monitoring and evaluation

Monitoring of the mortality, morbidity and resuscitation outcomes that were the pre-specified outcomes of this review is recommended.

Research priorities

- Human factors aspects of resuscitation performance depending on initial oxygen concentration for commencing resuscitation.
- Comparison of targets and strategies for oxygen saturation levels in the first 10-20 min after birth in preterm infants.
- Optimal oxygen concentration for commencing resuscitation in preterm newborn infants (noting that two trials comparing FiO2's of 0.30 to 0.60 are expected).
- Effect of initial oxygen concentrations and titration strategies on biomarkers of both hypoxic and hyperoxic injury to organs including the brain, lungs and retina.

The Task Force concluded that the uncertainty over the optimal initial oxygen concentration means that it is reasonable to study a full range of oxygen concentrations (21% to 100%) within a research protocol.

REFERENCES SUMMARY

Aguar M, Brugada M, Escobar J. Resuscitation of ELBW infants with initial FiO2 of 30% vs. 60%, a randomized, controlled, blinded study: the REOX trial. x. Pediatric Academic Societies Annual Meeting; Washington DC2013.

Armanian AM, Badiee Z. Resuscitation of preterm newborns with low concentration oxygen versus high concentration oxygen. Journal of research in pharmacy practice. 2012;1(1)25-29.

Baik N, Urlesberger B, Schwaberger B, Schmolzer GM, Avian A, Pichler G. Cerebral haemorrhage in preterm neonates: does cerebral regional oxygen saturation during the immediate transition matter? Arch Dis Child Fetal Neonatal Ed. 2015;100(5)F422-7.

Boronat N, Aguar M, Rook D, Iriondo M, Brugada M, Cernada M, et al. Survival and Neurodevelopmental Outcomes of Preterms Resuscitated With Different Oxygen Fractions. Pediatrics. 2016;138(6)e 20161405.

Dawson JA, Kamlin CO, Wong C, te Pas AB, O'Donnell CP, Donath SM, et al. Oxygen saturation and heart rate during delivery room resuscitation of infants <30 weeks' gestation with air or 100% oxygen. Arch Dis Child Fetal Neonatal Ed. 2009;94(2)F87-91.

Dekker J, Martherus T, Lopriore E, Giera M, McGillick EV, Hutten J, et al. The Effect of Initial High vs. Low FiO2 on Breathing Effort in Preterm Infants at Birth: A Randomized Controlled Trial. Frontiers in Pediatrics. 2019;7.

Escrig R, Arruza L, Izquierdo I, Villar G, Saenz P, Gimeno A, et al. Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. Pediatrics. 2008;121(5)875-81.

Finer N, Vento M, Saugstad OD. Study of room air versus 60%oxygen for resuscitation of premature infants (PRESOX). NCT01773746 2018 [

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650)924-6.

Harling AE, Beresford MW, Vince GS, Bates M, Yoxall CW. Does the use of 50% oxygen at birth in preterm infants reduce lung injury? Arch Dis Child Fetal Neonatal Ed. 2005;90(5)F401-5.

Kaban RK, Aminullah A, Rohsiswatmo R, Hegar B, Sukadi A, Davis PG. Resuscitation of very preterm infants with 30% vs. 50% oxygen: a randomized controlled trial. Paediatrica Indonesiana. 2022;62(2)104-114.

Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. Resuscitation of preterm neonates with limited versus high oxygen strategy. Pediatrics. 2013;132(6)e1488-96.

Kapadia VS, Lal CV, Kakkilaya V, Heyne R, Savani RC, Wyckoff MH. Impact of the Neonatal Resuscitation Program-Recommended Low Oxygen Strategy on Outcomes of Infants Born Preterm. J Pediatr. 2017;19135-41.

Law BHY, Asztalos E, Finer NN, Yaskina M, Vento M, Tarnow-Mordi W, et al. Higher versus Lower Oxygen Concentration during Respiratory Support in the Delivery Room in Extremely Preterm Infants: A Pilot Feasibility Study. Children (Basel). 2021;8(11).

Liyakat NA, Kumar P, Sundaram V. Room air versus 100% oxygen for delivery room resuscitation of preterm neonates in low resource settings: A randomised, blinded, controlled trial. J Paediatr Child Health. 2023;59(6)794-801.

Lundstrøm KE, Pryds O, Greisen G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1995;73(2)F81-6.

Oei JL, Saugstad OD, Lui K, Wright IM, Smyth JP, Craven P, et al. Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial. Pediatrics. 2017;139(1)26-26.

Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4)529-34.

Pichler G, Binder C, Avian A, Beckenbach E, Schmolzer GM, Urlesberger B. Reference ranges for regional cerebral tissue oxygen saturation and fractional oxygen extraction in neonates during immediate transition after birth. J Pediatr. 2013;163(6)1558-63.

Pichler G, Goeral K, Hammerl M, Perme T, Dempsey EM, Springer L, et al. Cerebral regional tissue Oxygen Saturation to Guide Oxygen Delivery in preterm neonates during immediate transition after birth (COSGOD III): multicentre randomised phase 3 clinical trial. BMJ. 2023;380e072313.

Pichler G, Schmolzer GM, Urlesberger B. Cerebral Tissue Oxygenation during Immediate Neonatal Transition and Resuscitation. Front Pediatr. 2017;529.

Pichler G, Urlesberger B, Baik N, Schwaberger B, Binder-Heschl C, Avian A, et al. Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial. J Pediatr. 2016;17073-8 e1-4.

Rabi Y, Lodha A, Soraisham A, Singhal N, Barrington K, Shah PS. Outcomes of preterm infants following the introduction of room air resuscitation. Resuscitation. 2015;96252-9.

Rabi Y, Singhal N, Nettel-Aguirre A. Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. Pediatrics. 2011;128(2)e374-81.

Rook D, Schierbeek H, Vento M, Vlaardingerbroek H, van der Eijk AC, Longini M, et al. Resuscitation of preterm infants with different inspired oxygen fractions. J Pediatr. 2014;164(6)1322-6.e3.

Schünemann HJ, Neumann I, Hultcrantz M, Brignardello-Petersen R, Zeng L, Murad MH, et al. GRADE guidance 35: update on rating imprecision for assessing contextualized certainty of evidence and making decisions. J Clin Epidemiol. 2022;150225-242.

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358j4008.

Skare C, Boldingh AM, Nakstad B, Calisch TE, Niles DE, Nadkarni VM, et al. Ventilation fraction during the first 30s of neonatal resuscitation. Resuscitation. 2016;10725-30.

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.

Soraisham AS, Rabi Y, Shah PS, Singhal N, Synnes A, Yang J, et al. Neurodevelopmental outcomes of preterm infants resuscitated with different oxygen concentration at birth. J Perinatol. 2017;37(10)1141-1147.

Sotiropoulos JX, Oei JL, Schmölzer GM, Libesman S, Hunter KE, Williams JG, et al. Initial Oxygen Concentration for the Resuscitation of Infants Born at Less Than 32 Weeks' Gestation: A Systematic Review and Individual Participant Data Network Meta-Analysis. JAMA Pediatr. 202410.1001/jamapediatrics.2024.1848.

Sotiropoulos JX, Schmolzer GM, Oei JL, Libesman S, Hunter KE, Williams JG, et al. PROspective Meta-analysis Of Trials of Initial Oxygen in preterm Newborns (PROMOTION): Protocol for a systematic review and prospective meta-analysis with individual participant data on initial oxygen concentration for resuscitation of preterm infants. Acta Paediatr. 2023;112(3)372-382.

Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. 2020;105(3)328-330.

Thamrin V, Saugstad OD, Tarnow-Mordi W, Wang YA, Lui K, Wright IM, et al. Preterm Infant Outcomes after Randomization to Initial Resuscitation with FiO2 0.21 or 1.0. Journal of Pediatrics. 2018;20155-61.e1.

Torrejón-Rodríguez L, Solaz-García A, Lara-Cantón I, Pinilla-González A, Aguar M, Vento M. Clinical Parameters in the First 5 Minutes after Birth Have a Predictive Value for Survival of Extremely Preterm Infants. Maternal-Fetal Medicine. 2023;05(04)244-247.

Vento M, Moro M, Escrig R, Arruza L, Villar G, Izquierdo I, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. Pediatrics. 2009;124(3)e439-49.

Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN. Resuscitation of preterm neonates by using room air or 100% oxygen. Pediatrics. 2008;121(6)1083-9.

Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4)425-431.

Welsford M, Nishiyama C. Initial Oxygen Use for Preterm Newborn Resuscitation: A Systematic Review With Meta-analysis. Pediatrics. 2019;143(1)1-17.