QUESTION

IMPACT OF DURATION OF INTENSIVE RESUSCITATION - NEONATES	
POPULATION:	Newly born infants presenting with at least 10 minutes of asystole, bradycardia (heart rate <60 beats per minute), or pulseless electrical activity after birth for which cardiopulmonary resuscitation is indicated.
INTERVENTION:	Ongoing cardiopulmonary resuscitation for incremental time intervals beyond 10 minutes after birth.
COMPARISON:	Cardiopulmonary resuscitation discontinued at 10 minutes after birth.
MAIN OUTCOMES:	– Survival to any age – Long term neurodevelopmental outcomes – Composite of survival to any age without moderate or severe neurodisability
SETTING:	In-hospital (delivery room)
PERSPECTIVE:	Population
BACKGROUND:	There has been an ongoing controversy as to how long after attempted cardiopulmonary resuscitation after birth for asystole, profound bradycardia (heart rate <60), or pulseless electrical activity, resuscitation should be continued in the face of poor or no response. The balance must be between ceasing too early, when return of spontaneous circulation (ROSC) and long-term survival may still be achievable, and continuing too long, when ROSC may occur, but at the risk of limiting parents' opportunity to have contact with and provide comfort to their dying infant, or when survival occurs but with an unacceptable degree of neurologic injury. Lack of detectable heart rate or other signs of life, typically reflected by an Apgar Score of zero, have classically a criterion for cessation of resuscitation. However, experience shows that ROSC and survival can occur after an Apgar Score of 0, either because of inadequacy of clinical detection of heart rate or due to the potential for neonatal organs to survive a prolonged pulseless, apneic state. Ongoing cardiopulmonary resuscitation is also indicated for profound bradycardia and pulseless electrical activity, states associated with both acidosis and impaired cardiac output from which recovery is sometimes, but not always, possible. The recommended duration of resuscitative efforts for newborns in the delivery room has variously been 10 or more minutes. According to the 2015 ILCOR CoSTR: "An Apgar score of 0 at 10 minutes is a strong predictor of mortality and morbidity in late-preterm and term infants. We suggest that, in babies with an Apgar score of 0 after 10 minutes of resuscitation, if the heart rate remains undetectable, it may be reasonable to stop resuscitation; however, the decision to continue or discontinue resuscitative efforts should be individualized (weak recommendation, very-low-quality evidence)." {Perlman 2015 S204}. The controversy has been generated from the following uncertainties: (1) It is often not clear whether resuscitation efforts have taken place or been optimal throughout the 10-minute period, (2) There may be questions about whether the infant has been pulseless or profoundly bradycardic throughout the 10 minutes and not just at 10 minutes, and (3) The timing of the onset of fetal bradycardia before birth is often unknown. (4) The 10-minute threshold has been subjected to further controversy, with published reports from therapeutic hypothermia trials of an increasing number of intact survivors after 10 minutes of an Apgar score of 0 {Laptook 2009 1619; Natarajan 2013, F473}.

CONFLICT OF INTERESTS:	The following Task Force members and other authors declared an intellectual conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees: Elizabeth E. Foglia and Myra H. Wyckoff authored studies cited in the CoSTR that were not included in the systematic review.

ASSESSEMENT

Problem -
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Previous ILCOR recommendations {Perlman 2015 S204}, as stated above, were based on 6 studies published between 1998 and 2015 {Casalaz 1998 112; Harrington 2007 463.e1; Kasdorf 2015 F102; Laptook 2009 1619; Patel 2004 136; Sarkar 2010 F423} that showed that 75 of 129 infants (58%) with an estimated gestational age of 36 weeks or greater and an Apgar score of zero at 10 minutes of life died before 22 months of age. After this review, some important issues continue to bring controversy to the question of timing of discontinuing resuscitation efforts: 1) most studies reported case series. Population-based studies were not available; 2) the adequacy of resuscitation procedures and whether prognosis differed after prolonged adequate resuscitation were not reported; 3) several of these studies were done prior to availability of therapeutic hypothermia and therefore they may not be representative of contemporary clinical care and advice regarding continuation of life support given to families; 4) the discussion in most was limited to late preterm and term infants, without any consideration of whether different recommendations were needed for more preterm infants {Perlman 2015 S204; McGrath 2016 102; Haines 2016 1305; Wilkinson 2020 Jan24}. New studies published since 2015, address some of these concerns. {Shah 2015 492; Ayrapetian 2017 545; Sproat 2017 F262; Zhang 2019 Jun15; Zhong 2019 77; Shibasaki 2020 64}	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	*For the critical outcome of* ***survival until last follow up****,* we identified very low certainty evidence (downgraded for risk of bias and inconsistency) from 15 studies {Ayrapetian 2017 545; Casalaz 1998 112; Haddad 2000 1210; Harrington 2007 463.e1; Jain 1991 778; Kasdorf 2015 F102; Natajaran 2013 F473; Patel 2004 136; Sarkar 2010 F423; Shah 2015 492; Shibasaki 2020 64; Socol 1994 991; Sproat 2017 F262; Zhang 2019 Jun15; Zhong 2019 77} reporting outcomes of 470 newborns to last known follow up (which ranged	Widening the time frame for continuation of resuscitative interventions after birth (despite a poor response) may have very important desirable effects, the most important being the possibility of survival without severe neurodevelopmental impairment for neonates

	from 4 months to 8 years of age). The number of enrolled newborns ranged from 3 to 177 per study. Across studies, reported survival rates to last follow up ranged from 1.7% to 100%. Among all 470 newborns reported in the literature, including studies that required survival to NICU admission or enrolment in a cooling protocol for inclusion, 187 (39.8%) survived to last follow up. The decision was made not to calculate confidence intervals due to the heterogeneity of included studies. *For the critical outcome of* ***neurodevelopmental outcomes among survivors,*** we identified very low certainty evidence (downgraded for risk of bias and inconsistency) from 13 studies including 277 infants {Ayrapetian 2017 545; Casalaz 1998 112; Harrington 2007 463.e1; Jain 1991 778; Kasdorf 2015 F102; Natajaran 2013 F473; Patel 2004 136; Sarkar 2010 F423; Shah 2015 492; Shibasaki 2020 64; Socol 1994 991; Sproat 2017 F262; Zhang 2019 Jun15}. Neurodevelopmental outcomes were assessed in 80 survivors. Thirty (37.5%) did not have moderate or severe neurodevelopmental impairment (range 0-100%). There was important heterogeneity between studies (and in some cases- within studies) regarding the timing and tools used to assess neurodevelopmental outcomes. The decision was made not to calculate confidence intervals due to the heterogeneity of included studies. *For the composite critical outcome of* ***survival without neurodevelopmental impairment***, we identified very low certainty evidence (downgraded for risk of bias and inconsistency) from 13 studies of 277 infants {Ayrapetian 2017 545; Casalaz 1998 112; Harrington 2007 463.e1; Jain 1991 778; Kasdorf 2015 F102; Natajaran 2013 F473; Patel 2004 136; Sarkar 2010 F423; Shah 2015 492; Shibasaki 2020 64; Socol 1994 991; Sproat 2017 F262; Zhang 2019 Jun15} reporting neurodevelopmental outcomes. Among all 277 infants reported in these studies, 69% died before last follow up, 18% survived with moderate to severe impairment, and 11% survived without moderate to severe impairment (2% lost to follow up). There was important heterogeneity between studies (and in some cases, within studies) regarding the timing and tools used to assess neurodevelopmental outcomes. The decision was made not to calculate confidence intervals due to the heterogeneity of included studies.	who otherwise would die. Because there is sometimes uncertainty about whether all resuscitation measures have been performed adequately, longer time intervals afford greater opportunity to summon additional team members or telephone advice, and for rechecking the adequacy of ventilation and drug delivery and that no reversible conditions have been missed. A longer duration may also allow greater communication among resuscitation team members and inclusion of the baby's parent(s) in the decision.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large ○ Moderate ○ Small ○ Trivial ○ Varies	Same as above.	Extending the duration of intensive resuscitation after birth may also have very important undesirable effects. Ongoing intervention may be futile and still result in

○ Don't know		failure to achieve return of circulation. This has the potential to increase moral distress for clinicians or parents without changing the outcome for the infant. More importantly, ongoing resuscitation may result in neonatal survival but with increased risk of moderate or severe neurodevelopmental impairment, increasing the burden on the affected infants and their families.

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 studies included in this systematic review are 14 case series and one cohort nested in an RCT with clinical heterogeneity in population (gestational age), setting, cointerventions and time period. All the studies have a high risk of bias: selection bias, confounding bias, bias in exposure measurement, in outcome measurement and in reporting results, and missing data. The methodological quality of the studies makes the certainty of evidence very low.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT		ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Providers value the outcomes included in this systematic review {Strand 2019 F1}. Parents have not been extensively surveyed but are considered likely to have similar views about the importance of survival and of moderate to severe neurodevelopmental disability.	Individual parents and providers may hold different values regarding the relative importance of survival and neurologic impairment.

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 between desirable and undesirable effects probably favors the intervention since there is a possibility of survival and survival without moderate to severe neurodevelopmental impairment after prolonged resuscitation. Overall 11% (30/277) of infants with an Apgar zero or one at 10 minutes survive without moderate or severe neurodevelopmental impairment. Moreover, if the infant survives resuscitation, 35% will not develop moderate or severe neurodevelopmental impairment. However, how long cardiopulmonary resuscitation should be provided is still unanswered. The small group of reported infants who have a detectable HR only at or after 20 minutes from birth shows that intact survival is still possible (survival 15/38 = 38%; survival without moderate or severe neurodevelopment impairment 6/39 =15%). However, selection bias of the reported case series and cohorts markedly limits the external validity of these findings.	

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	We did not identify any studies specifically reporting costs of prolonged resuscitation after birth.	Although costs are not objectively reported, it inherently costs more to care for a survivor than a non-survivor. All neonates that survive prolonged resuscitation will need intensive post-resuscitation care, which may include neuroprotective strategies, for a variable duration. Neonatal intensive care is expensive and the additional resources may include a wide range of diagnostic and therapeutic interventions, such as ventilation, EEG monitoring, eventually NIRS monitoring, image resources, with emphasis on MRI imaging, and therapeutic interventions (hypothermia and adjuncts, such as seizure control medication), as well as ongoing resources after hospital discharge. Therefore, the cost of treatment of neonates who survive aggressive and prolonged resuscitation is expected to be higher than the cost of a non-survivor, even if the outcome is good. An adverse outcome can have lifelong costs to the family and to society. Nevertheless, the absolute number of affected infants is small.

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	We did not identify any studies specifically reporting costs of prolonged resuscitation after birth.	

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	We did not identify any studies specifically assessing the cost effectiveness of prolonged resuscitation after birth.	

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	We did not identify studies addressing health equity.	Health equity was not objectively reported for prolonged neonatal resuscitation; however, one should consider that a possibility of reduced equity exists. In the first place, extensive neonatal resuscitation is generally not recommended in low resource settings, where face mask ventilation with 21% oxygen for non-breathing neonates is the focus of the intervention {Kamath-Rayne 2018 538}. Secondly, availability of intensive care resources for post-resuscitation care differs between high and low resource settings. Finally, availability of neuroprotective strategies also differs among high, medium and low resource settings. Therefore, it is likely that

		prolonged resuscitation would be offered to a higher proportion of infants in higher-resource settings; outcomes may also be better in settings with full availability of neuroprotective strategies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not identify studies addressing acceptability of recommendations on prolonged resuscitation of newly born infants.	The inability to predict the individual outcome of an infant who receives prolonged resuscitation leads to uncertainty on the decision-making process in the delivery room. Cultural and religious differences, including different perceptions on the value of extending life, the quality of life, and the acceptance of comfort care as an option, also influence medical decisions. {Cuttini 2000 212; Fanaroff 2014 701; Schijvers 2018 1710}. Therefore, we expect that acceptability of the treatment recommendation on a matter that ultimately deals with the limits of life and death will be modulated by cultural differences, which includes individual moral and ethical beliefs.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	All reported studies show that prolonged resuscitation is feasible, although the success assessed by survival or by survival without moderate or severe neurodevelopmental impairment varies according to several factors that include patient characteristics (such as gestational age, timing and cause of arrest), timing and procedures performed during resuscitation, availability of post-resuscitation care and neuroprotective strategies.{Ayrapetian 2017 545; Casalaz 1998 112; Haddad 2000 1210; Harrington 2007 463.e1; Jain 1991 778; Kasdorf 2015 F102; Laptook 2009 1619; Natajaran 2013 F473; Patel 2004 136; Sarkar 2010 F423; Shah 2015 492; Shibasaki 2020 64; Socol 1994 991; Sproat 2017 F262; Zhang 2019 Jun15; Zhong 2019 77}	

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	**Large**	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			
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

Failure to achieve return of spontaneous circulation in newborn infants after 10-20 minutes of intensive resuscitation is associated with a high risk of mortality and a high risk of moderate to severe neuroimpairment among survivors. However, there is no evidence that any specific duration of resuscitation consistently predicts mortality or moderate or severe neurodevelopmental impairment. If a newborn infant requires ongoing cardiopulmonary resuscitation (CPR) despite completing all the recommended steps of resuscitation and excluding reversible causes, we suggest initiating discussion of discontinuing resuscitative efforts with the clinical team and family. A reasonable timeframe for this change in goals of care is around 20 minutes after birth. (Weak recommendation, very low certainty of evidence).

Justification

In making this recommendation, we recognize the need to balance the risk of ceasing resuscitation too early, when return of spontaneous circulation and long-term survival may still be achievable, and continuing resuscitation for too long, when return of spontaneous circulation may occur but survival is associated with a high risk of severe neurologic injury. The appreciable number of survivors who do not have moderate or severe neurodevelopmental impairment after ≥10 minutes of resuscitation suggests that early cessation of resuscitation may preclude survival of some infants who may have had a good prognosis.

While an Apgar score of 0 or 1 at 10 minutes is a strong predictor of mortality and morbidity, recent case reports and series have reported favorable outcomes among newborn infants with Apgar scores of 0 or 1 at 10 minutes after birth who achieved return of spontaneous circulation and received therapeutic hypothermia. In this subgroup of newborns with severe depression at birth, both survival and survival without moderate to severe impairment have been reported. Among 105 such infants reported in the literature with Apgar scores 0 or 1 who were successfully resuscitated, were treated with therapeutic hypothermia, and assessed after discharge, 20% survived without moderate to severe impairment and 37% of survivors did not have moderate or severe neurodisability {Ayrapetian 2017 545; Kasdorf 2015 F102; Natajaran 2013 F473; Sarkar 2010 F423; Shah 2015 492; Shibasaki 2020 64; Sproat 2017 F262; Zhang 2019 Jun15}.

The evidence supporting this recommendation is of very low certainty. However, we value the possibility of survival and intact survival following ongoing resuscitation. In a large multisite cohort of 659 newborn infants who survived to discharge following >1 minute chest compressions in the delivery room, 25% of survivors received 10 minutes or more of CPR {Foglia 2020 pii: S0300-9572(20)30031-9}. This study did not specifically report on infants with 10-minute Apgar scores of zero or one. While these data indicate that survival to discharge is possible following a prolonged duration of CPR, neurodevelopmental outcomes among survivors in this study were not reported.

Extremely limited data are available regarding outcomes of infants who received 20 or more minutes of CPR after birth. Six studies included in this systematic review {Ayrapetian 2017 545; Shah 2015 492; Shibasaki 2020 64; Sproat 2017 F262; Zhang 2019 Jun15} reported results for 39 patients in which first detectable heart rate or heart rate ≥100 beats per minute occurred at or beyond 20 minutes after birth. Of these patients, 15/39 (38%) survived until last follow up and 6/15 (40%) survivors did not have moderate or severe neuroimpairment.

The Task Force considered that as well as duration of resuscitation, it was important to consider whether all recommended resuscitation interventions had been provided. Studies suggest that the time taken to accomplish steps of a resuscitation up to the point of administration of one or more doses of epinephrine varies widely across studies but may take as long as 20 minutes {Barber 2006 1028; McKinsey 2016 F244; Halling 2017 232; Sprout 2017 F262}. The variation in the interval from birth to completion of these steps may depend on the characteristics and time to attendance of the resuscitation team. Thus,

using a single time interval after birth to discontinue intensive resuscitation for all newborns implies might mean that in some cases, the full repertoire of recommended resuscitation interventions had not yet been provided before cessation of resuscitation.

Another issue considered by the Task Force is the potential impact for infants and their families. Among the included studies, most deaths occurred either in the delivery room/birth suite or during the initial hospitalization. In this systematic review, rates of survival to discharge were similar to rates of survival to last follow up. For those infants who ultimately die in early infancy, achieving even this short-term survival may provide the family the time and opportunity to participate in decision making and care of their infant. Moreover, intact survival is possible among surviving infants. In this systematic review, 38% of surviving infants did not have moderate or severe impairment.

Given these considerations, we do not recommend a specific duration of resuscitation after which point resuscitative efforts should be ceased. Instead, we suggest that providers consider changing the goals of care if a newborn infant has not responded to all recommended steps of resuscitation that are appropriate to the given setting. We acknowledge that cultural and religious differences, including different perceptions on the value of extending life, the quality of life, and the acceptance of comfort care as an option, may influence the decision {Cuttini 2000 212; Fanaroff 2014 701; Schijvers 2018 1710}.

Ultimately, the decision to initiate and continue resuscitative efforts should be individualized and informed by factors such as gestational age, the presence of congenital anomalies, the timing of perinatal insult (if known), the perceived adequacy of resuscitative interventions performed, the family's stated preferences and values, and the availability of post-resuscitative resources such as neonatal intensive care and neuroprotective strategies, such as therapeutic hypothermia. Finally, in low resource settings, where emphasis is given to face mask ventilation with 21% oxygen for non-breathing neonates {Kamath-Rayne 2018 538}, advanced resuscitation procedures and prolonging resuscitation may not be an option. Therefore, caution must be taken to globally adopt this treatment recommendation, and local/regional discussion and customization are necessary.

Subgroup considerations

Subgroup Analyses for Specified Outcomes

Subgroup	Studies contributing	Infants	Survival to last follow up	Assessed for NDI	No moderate or severe NDI	Survivors assessed without moderate or severe NDI	Composite: Survival without Moderate or Severe NDI
Population level studies	5	131	17/131 (13%)	15	9	9/15 (60%)	9/131 (7%)
Therapeutic hypothermia	9	206	122/206 (60%)	57	21	21/57 (37%)	21/105 (20%)*
Gestational Age ≥36 weeks	12	286	146/286 (51%)	73	23	23/73 (32%)	23/166 (14%)**
Gestational Age <36 weeks	6	99	34/99 (34%)	8	5	5/8 (63%)	5/42 (12%)***

* 8 studies with 105 infants reported post-discharge outcomes; **11 studies with 166 infants reported post-discharge outcomes; ***5 studies with 42 infants reported post-discharge outcomes

- ✓ Population-level studies: { Casalaz 1998 112; Harrington 2007 463.e1; Jain 1991 778; Sproat 2017 F262; Zhang 2019 Jun15}
- ✓ Studies with any infants treated with therapeutic hypothermia: {Ayrapetian 2017 545; Kasdorf 2015 F102; Natajaran 2013 F473; Sarkar 2010 F423; Shah 2015 492; Shibasaki 2020 64; Sproat 2017 F262; Zhang 2019 Jun15; Zhong 2019 77}
- ✓ Studies with any infants born at gestational age >=36 weeks: {Ayrapetian 2017 545; Casalaz 1998 112; Harrington 2007 463.e1; Kasdorf 2015 F102; Natajaran 2013 F473; Patel 2004 136; Sarkar 2010 F423; Shah 2015 492; Shibasaki 2020 64; Sproat 2017 F262; Zhang 2019 Jun15; Zhong 2019 77}
- ✓ Studies with any infants born at gestational age < 36 weeks {Casalaz 1998 112; Harrington 2007 463.e1; Shah 2015 492; Sproat 2017 F262; Zhang 2019 Jun15; Zhong 2019 77}.

Insufficient details about birthweight precluded the planned subgroup analysis based on birthweight.
Given the small sample sizes and heterogeneity of study characteristics, there is no strong evidence on which to base any variation in recommendations for specific subgroups of infants.

Implementation considerations

Acceptability of the intervention should be thoroughly discussed in the different settings according to cultural, ethical and moral standards that prevail in each country or region. Optimal resuscitation should be available for infants in need, and training of skills and team performance is critical to achieve it. Communication with families should be optimized, and whenever possible, parents' wishes and values must be considered even in urgent and stressful situations. Availability of neonatal intensive care and neuroprotective strategies for post-resuscitation care is another aspect that may be considered in the decision process.

Monitoring and evaluation

Monitoring and evaluation of prognosis of infants that receive prolonged resuscitation at birth is extremely important. In addition, although health equity was not objectively reported for prolonged neonatal resuscitation, it is possible that prolonged resuscitation may be offered to a higher proportion of infants in higher-resource settings; outcomes may also be better in settings with full availability of intensive care and neuroprotective strategies. Since prolonged CPR after birth is relatively rare, an international registry of events, with detailed description of procedures and their timing in the delivery room, post-resuscitation care and neurologic outcomes assessed in follow-up would provide essential evidence to inform the discussion of "how long is too long." Such a registry would also provide valuable information on variations in practice regarding duration of resuscitation in different settings.

Research priorities

Many studies only reported outcomes of infants who survived resuscitation and met a specific study eligibility criterion, such as neonatal intensive care unit admission or initiation of therapeutic hypothermia. Therefore, estimates of mortality following prolonged resuscitation likely underestimate the actual incidence of death when failed resuscitations are considered. Studies accounting for the full population of newborn infants who receive CPR after birth, using consistent definitions of stillbirths and resuscitation failures, are needed to identify the incidence of mortality and neurodevelopmental impairment after prolonged resuscitation of term and preterm infants.

In addition, the extent and timing of resuscitation procedures were not reported in most studies; therefore, prognosis of newborn infants after prolonged resuscitation at birth is inferred from the available data. Further, most available studies characterized the infant's response to resuscitation using the Apgar score at 10 minutes, which is prone to subjective assessment and does not provide information about ongoing assessments or response to resuscitation beyond 10 minutes. More granular information about the interval from birth to detectable heart rate using objective measures such as electrocardiogram (ECG) and time to return of circulation is needed to inform more precise recommendations regarding the duration of intensive resuscitation after birth. Additionally, as ECG has become more frequently used in the delivery room environment, additional information about the presenting rhythm (bradycardia, asystole, pulseless electrical activity) preceding chest compressions will be helpful to identify outcomes following these varied presentations.
Therefore, studies that report outcomes on the full population of infants who present without signs of life and receive intensive resuscitation are needed with:

- A priori definitions of stillbirths and complete resuscitation attempts
- Complete description of co-interventions (resuscitation procedures), timing of procedures at birth, and interventions in post-resuscitative care
- Description of methods to assess the heart rate during resuscitation using objective measures, such as ECG, and report of timing for detection of heart rate and heart rate >60 and >100 beats per minute
- Complete follow up of survivors with accurate and consistent methods of assessment of neurodevelopment, comparable across studies and population

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