Duration of Resuscitation at Birth, Mortality, and Neurodevelopment: A Systematic Review

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abstract

CONTEXT: The International Liaison Committee on Resuscitation Neonatal Life Support Task Force reviewed evidence for the duration of cardiopulmonary resuscitation (CPR) for newborns immediately after birth.

OBJECTIVE: To summarize evidence for ongoing CPR on the outcomes of survival, neurodevelopment, and the composite of survival without moderate or severe neurodevelopmental impairment (NDI).

DATA SOURCES: Medline, Embase, Evidence-Based Medicine Reviews, Cumulative Index to Nursing and Allied Health Literature, and Scientific Electronic Library Online were searched between inception and February 29, 2020.

STUDY SELECTION: Two independent reviewers selected studies of newborns with at least 10 minutes of asystole, bradycardia, or pulseless electrical activity for which CPR is indicated.

DATA EXTRACTION: Two independent reviewers extracted data and appraised the risk of bias.

RESULTS: In 16 eligible studies, researchers reported outcomes of 579 newborns born between 1982 and 2017. Within individual studies, 2% to 100% of infants survived to last follow-up (hospital discharge through 12 years). Summarized across studies, 237 of 579 (40.9%) newborns survived to last follow-up. In 13 studies, researchers reported neurodevelopmental outcomes of 277 newborns. Of these, 30 of 277 (10.8%) survived without moderate or severe impairment, and 240 of 277 (87%) met the composite outcome of death or NDI (191 died and 49 survived with moderate or severe impairment).

LIMITATIONS: There was very low certainty of evidence because of risk of bias and inconsistency.

CONCLUSIONS: Infants with ongoing CPR at 10 minutes after birth are at high risk for mortality and neurodisability, but survival without moderate or severe NDI is possible. One specified duration of CPR is unlikely to uniformly predict survival or survival without neuroimpairment.

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Drs Foglia and Guinsburg prepared the protocol, screened studies, abstracted data, assessed the risk of bias, completed the analysis, and prepared the first draft of the manuscript; Drs Weiner, de Almeida, Wyllie, Wyckoff, and Rabi were involved in reviewing the protocol, reviewing the analysis, and critically reviewing and editing the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Cardiopulmonary resuscitation (CPR) is recommended during delivery room resuscitation for newborns with asystole, profound bradycardia (heart rate <60 beats per minute), or pulseless electrical activity despite effective ventilation.[1] Persistent absence of detectable heart rate or other signs of life, typically recorded retrospectively as an Apgar score of 0, is used to guide the decision to cease resuscitative efforts. However, experience reveals that return of spontaneous circulation (ROSC) and survival can occur after Apgar scores of 0 at 5 and/or 10 minutes after birth, either because of inadequacy of clinical detection of heart rate leading to misclassification of the Apgar score[2–4] or because of fetal or neonatal adaptive responses to asphyxia.[5]

There is ongoing uncertainty as to how long it is appropriate to continue CPR for newborns who have an absent or incomplete response to interventions. A specific duration of resuscitation after birth that optimizes either survival or neurodevelopmental outcomes is not defined. This decision reflects a balance between stopping resuscitative efforts too early, when ROSC and long-term survival may still be achievable, and continuing too long, when ROSC may occur but with a significant burden of neurologic injury for the newborn.

The International Liaison Committee on Resuscitation (ILCOR) Neonatal Life Support Task Force provides consensus on science with treatment recommendations (CoSTR) for neonatal resuscitation to the international community. In 2015, ILCOR published a CoSTR suggesting it may be reasonable to discontinue resuscitation after 10 minutes of attempted resuscitation if the heart rate remains undetectable but highlighted the need to individualize decision-making.[1] This was a weak recommendation because of a low level of evidence, and subsequent studies in which authors address this topic have since been published.

In this review, we describe the scientific basis for the updated ILCOR CoSTR on this topic, which will be published in 2020. Our objective with this systematic review was to determine the impact of ongoing CPR beyond 10 minutes after birth on survival, neurodevelopment, and the composite outcome of survival without moderate or severe neurodevelopmental impairment (NDI) among newly born infants presenting with at least 10 minutes of asystole, bradycardia (heart rate <60 beats per minute), or pulseless electrical activity after birth.

METHODS

Protocol

This systematic review was undertaken as part of the continuous evidence evaluation process for the production of the ILCOR CoSTR. This was a Neonatal Life Support Task Force–led review. An information specialist from Apex Information (Vancouver, British Columbia, Canada) assisted with the literature search. The protocol for this review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) on January 17, 2020 (CRD42020157370). The protocol included newborns immediately after birth presenting with at least 10 minutes of asystole, bradycardia, or pulseless electrical activity for which CPR is indicated. Older newborns and infants receiving CPR in the ICU or other settings were not the focus of this review.

Outcomes

Outcomes were selected in accordance with priority outcomes identified through consensus of the ILCOR Neonatal Life Support Task Force.[6] The primary outcome was survival to the latest follow-up reported by the authors of the study. Secondary outcomes included NDI and the composite outcome of survival without moderate or severe NDI. Neurologic outcomes were as defined by authors of individual studies, provided that age-appropriate assessment tools were used. A post hoc outcome was survival at hospital discharge.

Search Strategy

Ovid Medline, Embase, all Evidence-Based Medicine Reviews (including the Cochrane Central Register of Controlled Trials), Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full Text (EBSCOhost), and Scientific Electronic Library Online (SciELO) were searched. The search strategy is included in the Supplemental Information and in Supplemental Tables 7 through 11. There were no restrictions on year of publication or gestational age. The initial search was conducted October 17, 2019, and an updated search of the Medline, Embase, the Cochrane Central Register of Controlled Trials, CINAHL, and SciELO was performed on February 29, 2020. In addition, reference lists of included studies were hand screened for potential studies. One study was identified from public comments for the draft CoSTR posted on the ILCOR Web site.

We included randomized controlled trials (RCTs) and ancillary analyses of RCTs, non-RCTs, interrupted time series, and controlled before-and-after studies. Cross-sectional or cohort studies were eligible for inclusion if it was clear how the study population was generated (ie, population level studies or inclusive cohort of all deliveries within a given period).[7] Studies in all languages were eligible if there was an English abstract. Unpublished studies (eg, conference abstracts, trial protocols) and animal studies were excluded.

Study Selection and Data Extraction

Covidence systematic review software (Veritas Health Innovation,

Melbourne, Australia) was used for study selection in 2 steps. Two authors (E.E.F. and R.G.) independently screened titles and abstracts for all studies identified in the search. Selected studies were subject to full-text review and assessment. Differences were resolved through discussion and consensus. Two investigators (E.E.F. and R.G.) independently extracted the following data from all included studies: study author, location, year, study design, population, and outcome measures. Study authors were contacted to request missing data.

Risk of Bias

Two authors (E.E.F. and R.G.) assessed the risk of bias for all included studies. Authors of most included studies reported on single-arm cohorts without a comparison group. Therefore, the risk of bias was assessed for domains adapted from the Risk of Bias in Non-Randomized Studies - of Interventions tool.[8] These included subject selection, confounding, exposure measurement, outcome measurements, missing data, and selective reporting.

Statistical Analysis

When resuscitation efforts are discontinued before ROSC, newborns rarely survive. Thus, we did not generate risk ratios or other measures of comparison between infants with ongoing CPR beyond 10 minutes and those for whom resuscitation was discontinued. Because the data permitted the calculation of absolute risks at defined time intervals, we aggregated data from all included studies by simple, unweighted summation to describe the impact of ongoing duration of CPR on the probability of the primary and secondary outcomes at different time periods. Because of the heterogeneity of included studies, we did not calculate confidence intervals or attempt to calculate weighted summary estimates for these outcomes. Because not all researchers specified the neurodevelopmental assessment tools used, we performed a sensitivity analysis of neurodevelopmental outcomes excluding studies without a specified tool.

Prespecified subgroup analyses included therapeutic hypothermia postresuscitative care, gestational age ≥36 weeks versus <36 weeks, birth weight ≥2500 versus <2500 g, and infants enrolled in population-level cohort studies. We considered population-level cohort studies as those in which authors reported the outcome of all births, including unsuccessful resuscitations, within the defined population during the specified study period. In a post hoc subgroup analysis, we identified the primary and secondary outcomes for infants with first detectable heart rate or heart rate ≥100 beats per minute reported at or beyond 20 minutes after birth. Subgroups were defined using study-level characteristics, study-specific subgroups, or infant-level characteristics as reported in individual studies.

RESULTS

Search Results

Using our search, we identified 761 studies (Fig 1). After duplicates were removed, 706 original references were screened and 92 full texts were reviewed for eligibility. Authors of 2 studies presented outcome data from the same cohort[9,10]; only the report from the latest follow-up was included. Sixteen eligible studies enrolling 579 newborns were included in this review.[10–25]

All studies were conducted in well-resourced settings, representing Australia, Canada, Japan, the United Kingdom, and the United States (Table 1). There was important clinical and methodologic heterogeneity among studies. Enrollment years ranged from 1982 to 2017 and the number of enrolled infants ranged from 3 to 177. Authors of 8 studies only included late preterm and/or term infants, whereas infants across the spectrum of gestation were assessed in the remaining 8 studies. When reported, resuscitation and postresuscitation interventions varied across studies.

Natarajan et al[10] reported on outcomes of a subset of infants enrolled in a trial of therapeutic hypothermia. The remaining studies were single-arm cohort studies that met specified enrollment criteria (Table 1). Six were population-based studies. Patients in the remaining 10 studies were included if they survived to neonatal unit admission or transfer or received an indicated treatment, such as therapeutic hypothermia. In 13 studies, the authors reported neurodevelopmental outcomes of survivors. There was important heterogeneity between, and in some cases within, studies regarding the timing and tools used for these assessments.

Risk of Bias

Overall, all studies were judged to have a high risk of bias (Table 2). Ten studies were considered to have high risk of bias for subject selection because enrolled patients had to survive resuscitation to a specific entry point to be included. This risk was unclear in the 6 population-level studies because these used variable or unspecified definitions of stillbirths for infants who did not respond to resuscitation. We considered all studies at high risk of bias caused by confounding because no authors provided specific information regarding the decision to discontinue resuscitation. There was potential differential use of cointerventions during resuscitation or postresuscitation, including withdrawal of intensive

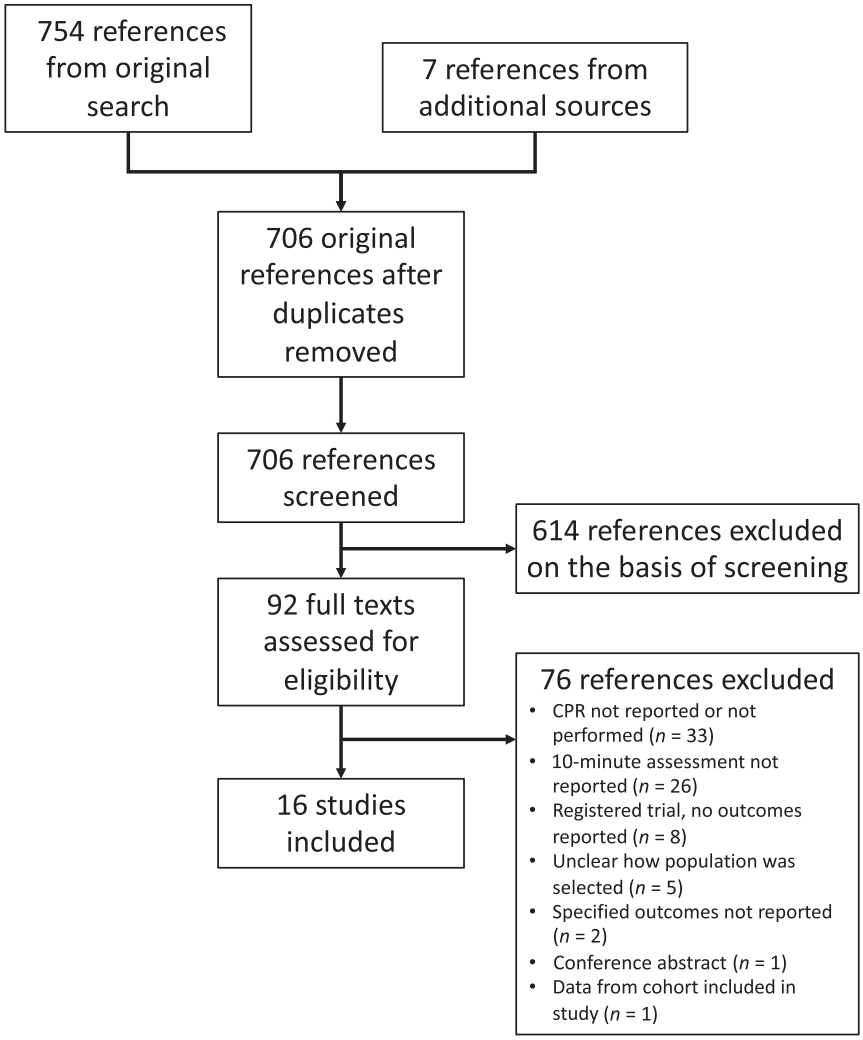

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

care, which may have been influenced by knowledge about the duration of resuscitation for enrolled infants.

Studies were at high risk of bias for exposure and outcome measurement. It is unclear how the duration of resuscitation and heart rate were measured. In most studies, authors reported duration of CPR in discrete time intervals instead of in minutes. In addition, infants were included on the basis of the Apgar score, which is subjective, prone to interobserver variability, and does not account for interventions in place.[4] It was unclear whether physiologic monitors were used for heart rate assessment, but many studies were conducted before 2010 when electronic physiologic monitoring was first recommended for the delivery room setting.[26] There was unclear risk of bias for outcome assessment. Although the primary outcome of survival is less susceptible to measurement bias, it is unclear whether assessors of secondary outcome measures were aware of the duration of resuscitation or hospital course. Except for the report by Natarajan et al,[10] the remaining studies were not prospectively registered, leading to unclear risk of bias from missing data or selective reporting. Finally, there is risk of publication bias because these studies may have preferentially represented centers with better outcomes among infants who receive ongoing CPR after birth.

Outcomes

For the primary outcome of survival until last follow-up, in all 16 studies, authors reported survival outcomes of 579 newborns (Table 3). The last documented follow-up ranged from hospital discharge through 12 years of age. Survival rates within studies ranged from 2% to 100%. Among all newborns included, 237 of 579 (40.9%) survived to last follow-up. The vast majority of deaths occurred before discharge. Across 13 studies in which authors reported specifically on survival at hospital discharge, 176 of 432 (40.7%) patients were alive at discharge.

There were 13 studies enrolling 277 infants that reported neurodevelopmental outcomes among survivors (Table 4); 86 (31.0%) infants survived and 79 were assessed for neurodevelopmental outcomes. Of these, 30 of 79 (38%) did not have moderate or severe NDI. When considering the composite outcome among all enrolled infants, 10.8% survived without moderate or severe NDI. In sensitivity analysis, excluding 4 studies in which authors did not specify the assessment tools used, 71 of 216 (33%) infants survived and 29 of 216 (13%) survived without moderate or severe NDI (Supplemental Table 6).

Subgroup Analysis

Results from subgroup analyses are shown in Table 5. Subgroup analyses based on birth weight were not conducted because this information was not reported in all studies. Among 131 infants enrolled in population-based studies with neurodevelopmental follow-up, 9 (7%) survived without moderate or severe NDI. Of 105 newborns who survived to NICU admission, received therapeutic hypothermia, and underwent

TABLE 1 Characteristics of Included Studies

Author(s)	Country	Year(s) Enrolled	GA, wk	Inclusion Criteria	Population Study	Patients Included in This Review	*n*	Last Assessment	ND Assessment Tools
Ayrapetyan et al[11]	United States	2006–2015	≥35	Treated with TH	No	Apgar = 0 at 10 min	17	4 mo–5 y	BSID-III, WPPSI (third and fourth editions)
Billimoria et al[12]	United States	2005–2014	22–42	Apgar = 0 at 5 min	Yes	Apgar = 0 at 10 min	109	1 y	N/A[a]
Casalaz et al[13]	United Kingdom	1986–1994	≥24	Apgar = 0 at 1 min with resuscitation attempted	Yes	Apgar = 0 or 1 at 10 min or stillbirth with resuscitation attempted	8	20 mo–8 y	Not specified, data abstracted from pediatric case notes
Haddad et al[14]	United States	1986–1999	>22	Apgar = 0 at 1 and 5 min, admitted to NICU	No	Apgar = 0 or 1 at 10 min	16	3 mo–12 y	N/A[a]
Harrington et al[15]	United Kingdom	1991–2004	≥24	Apgar = 0 at 10 min	Yes	Apgar = 0 at 10 min, including failed resuscitation	12	11 mo–5 y	Not specified, follow-up data obtained through pediatric records
Jain et al[16]	United States	1982–1986	All	Apgar = 0 at 1 min and received CPR	Yes	Apgar = 0 at 10 min	58	4–60 mo	Cognitive: BSID, Stanford-Binet test; motor: Peabody Developmental Motor Scales, Milani-Comparetti Motor Development Screening Test
Kasdorf et al[17]	United States	2007–2012	≥36	Apgar = 0 at 10 min, eligible for TH	No	Apgar = 0 at 10 min, eligible for TH	9	15 mo–2 y	BSID-III
Natarajan et al[10]	United States	2000–2003	≥36	Enrolled in RCT for TH	No	Apgar = 0 or 1 at 10 min	35	6–7 y	WPPSI III, Wechsler Intelligence Scale for Children IV, GMFCS
Patel and Beeby[18]	Australia	1992–?	≥36	Apgar = 0 at 10 min, admitted to tertiary unit	No	Apgar = 0 at 10 min, admitted to tertiary unit	29	Not specified	Not specified, assessed in high-risk follow-up clinic
Sarkar et al[19]	United States	2003–2009	≥36	Treated with TH	No	Apgar = 0 at 5 and 10 min	12	9–24 mo	Not specified
Shah et al[20]	Australia	2007–2013	≥35	Apgar = 0 at 10, admitted to NICU	No	Apgar = 0 at 10, admitted to NICU	13	1–2 y	Griffiths Mental Development Scales, BSID-III
Shibasaki et al[21]	Japan	2012–2016	≥35	Apgar = 0 at 10 min, treated with TH	No	Apgar = 0 at 10 min, treated with TH	28	18–24 mo	KSPD, GMFCS
Socol et al[22]	United States	1984–1991	≥34	Apgar <4 at 10 min, admitted after resuscitation	No	Apgar = 0 or 1 at 10 min	3	1–7 y	BSID, Stanford-Benet Intelligence Scale (Fourth Edition), WPPSI (Revised), Wechsler Intelligence Scale for Children (Revised), neurologic examination
Sproat et al[23]	United Kingdom	2009–2013	All	No HR before 10 min and CPR performed	Yes	No HR before 10 min and CPR performed	22	2 y	BSID-III
Zhang et al[24]	United States	2010–2017	≥22	Apgar = 0 or 1 at 10 min and full resuscitation	Yes	Apgar = 0/1 at 10 min and full resuscitation	31	15–24 mo	BSID-III
Zhong et al[25]	Canada	2010–2016	All	Apgar = 0 at 10 min, admitted to NICU	No	Apgar = 0 at 10 min, admitted to NICU	177	Hospital discharge	N/A[a]

BSID, Bayley Scales of Infant Development; BSID-III, Bayley Scales of Infant Development, Third Edition; GMFCS, Gross Motor Functional Classification System; HR, heart rate; KSPD, Kyoto Scale of Psychological Development; N/A, not applicable; ND, neurodevelopment; TH, therapeutic hypothermia; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

[a] Did not report neurodevelopment assessment of survivors.

neurodevelopmental assessment, 21 (20%) survived without moderate or severe impairment.

Certainty in Estimates

Because of the high risk of bias and inconsistency, the evidence in this systematic review is considered to have low certainty. Given the heterogeneity of included studies and the lack of weighting, the summed outcome estimates should be interpreted cautiously.

DISCUSSION

The duration of resuscitation that optimizes either survival or neurodevelopmental outcomes after prolonged CPR after birth has not been identified. In this systematic review of 16 studies including 579

TABLE 2 Risk of Bias for Included Studies

Author	Selection Bias	Confounding	Exposure Measurement	Outcome Measurement	Missing Data	Selective Reporting	Overall Risk of Bias
Ayrapetyan et al[11]	High	High	High	Unclear	High	Unclear	High
Billimoria et al[12]	Unclear	High	High	Unclear	High	Unclear	High
Casalaz et al[13]	High	High	High	Unclear	High	Unclear	High
Haddad et al[14]	Unclear	High	High	Unclear	High	Unclear	High
Harrington et al[15]	Unclear	High	High	Unclear	High	Unclear	High
Jain et al[16]	Unclear	High	High	Unclear	High	Unclear	High
Kasdorf et al[17]	High	High	High	Unclear	High	Unclear	High
Natarajan et al[10]	High	High	High	Unclear	High	Low	High
Patel and Beeby[18]	High	High	High	Unclear	High	Unclear	High
Sarkar et al[19]	High	High	High	Unclear	High	Unclear	High
Shah et al[20]	High	High	High	Unclear	High	Unclear	High
Shibasaki et al[21]	High	High	High	Unclear	High	Unclear	High
Socol et al[22]	High	High	High	Unclear	High	Unclear	High
Sproat et al[23]	Unclear	High	High	Unclear	High	Unclear	High
Zhang et al[24]	Unclear	High	High	Unclear	High	Unclear	High
Zhong et al[25]	High	High	High	Unclear	High	Unclear	High

newborns with ongoing need for CPR at 10 minutes after birth, 237 (40.9%) patients survived to last follow-up. Among 277 newborns included in 13 studies in which authors reported neurodevelopmental outcomes, 49 (17.6%) survived with moderate or severe NDI, and 30 (10.8%) survived without moderate or severe impairment.

TABLE 3 Survival Outcomes

Author	*n*	Survival at Discharge, *n* (%)	Time of Last Follow-up	Survival at Last Follow-up, *n* (%)
Ayrapetyan et al[11]	17	8 (47)	4 mo–5 y	7 (41)
Billimoria et al[12]	109	Not reported	1 y	50 (46)
Casalaz et al[13]	8	1 (13)	20 mo–8 y	1 (13)
Haddad et al[14]	16	2 (13)	3 mo–12 y	2 (13)
Harrington et al[15]	12	3 (25)	11 mo–5 y	2 (17)
Jain et al[16]	58	1 (2)	4–60 mo	1 (2)
Kasdorf et al[17]	9	9 (100)	15 mo–2 y	8 (89)
Natarajan et al[10]	35	Not reported	6–7 y	15 (43)
Patel and Beeby[18]	29	9 (31)	Not specified	9 (31)
Sarkar et al[19]	12	5 (42)	9–24 mo	3 (25)
Shah et al[20]	13	5 (38)	1–2 y	5 (38)
Shibasaki et al[21]	28	21 (75)	18–24 mo	19 (68)
Socol et al[22]	3	Not reported	1–7 y	3 (100)
Sproat et al[23]	22	8 (36)	2 y	8 (36)
Zhang et al[24]	31	5 (16)	15–24 mo	5 (16)
Zhong et al[25]	177	99 (56)	Discharge	99 (56)
Total	579	176 of 432 (40.7)	—	237 of 579 (40.9)

—, not applicable.

The 2015 ILCOR Neonatal Life Support Task Force reviewed the available evidence on this topic and suggested it may be reasonable to discontinue resuscitation after 10 minutes of resuscitation if the heart rate remains undetectable.[1] Eight studies reviewed in the present analysis, including the single largest population-level cohort study,[12] were published in 2015 or later. In the present review, the number of survivors without moderate or severe NDI at or beyond 10 minutes of resuscitation suggests that cessation of resuscitation before 10 minutes may preclude survival of some infants who may survive without moderate or severe neurodisability.

Factors that may influence a provider's decision to discontinue CPR include whether optimal resuscitative efforts were performed throughout the 10-minute period and whether the infant was pulseless or profoundly bradycardic throughout the 10 minutes or just at 10 minutes. No studies included in this review were used to report specific details about the timing or efficacy of resuscitative interventions or information about the presenting cardiac rhythm. In addition, because the onset of bradycardia or pulseless state is frequently before birth, the total duration of compromise may or may not be known but could influence the outcome of resuscitation. Finally, advances in postresuscitative care may improve the probability of survival without neurologic impairment after prolonged CPR after birth.

Equally important is whether all recommended resuscitation interventions have been provided. The time taken to perform all recommended steps, including the administration of ≥1 doses of epinephrine, varies but may be as long as 20 minutes.[23,27–29] The variation in the interval from birth to completion of these steps may depend on the availability,

TABLE 4 Neurodevelopmental Outcomes

Author	*n*	Survivors, *n* or *n* (%)	Assessed for Neurodevelopment, *n*	Survival Without Moderate or Severe NDI	
				n (% of Survivors Assessed)	*n* (% of All Enrolled)
Ayrapetyan et al[11,a]	17	7	4	4 (100)	4 (24)
Casalaz et al[13,b]	8	1	1	0 (0)	0 (0)
Harrington et al[15,b]	12	2	2	1 (50)	1 (8)
Jain et al[16]	58	1	1	0 (0)	0 (0)
Kasdorf et al[17,a]	9	8	7	4 (57)	4 (44)
Natarajan et al[10]	35	15	15	6 (40)	6 (17)
Patel and Beeby[18,b]	29	9	9	0 (0)	0 (0)
Sarkar et al[19,a,b]	12	3	2	0 (0)	0 (0)
Shah et al[20,c]	13	5	5	3 (60)	3 (23)
Shibasaki et al[21]	28	19	19	3 (16)	3 (11)
Socol et al[22]	3	3	3	1 (33)	1 (33)
Sproat et al[23]	22	8	7	5 (71)	5 (23)
Zhang et al[24]	31	5	4	3 (75)	3 (10)
Total	277	86 of 277 (31.0)	79	30 of 79 (38)	30 of 277 (10.8)

[a] Survivors who were only assessed in infancy or by report were considered lost to follow-up.
[b] Tools used for neurodevelopmental follow-up not specified.
[c] One survivor with a Bayley Scales of Infant Development, Third Edition score of 110 was classified as impaired because of bilateral deafness.

composition, and procedural skill of the resuscitation team. As a result, recommending a single time interval after birth to cessation of intensive resuscitation for all newborns might mean that the full repertoire of resuscitation interventions has not yet been provided before CPR is discontinued.

Extremely limited data are available regarding outcomes after specific durations of CPR beyond 10 minutes after birth. The duration of CPR after which continued efforts no longer improve the probability of intact survival has not been defined. In a retrospective multicenter analysis of registry data including 659 newborns who survived delivery room CPR, lower gestational age and prolonged duration of CPR were independently associated with decreased odds of survival to hospital discharge; however, 25% of survivors received ≥10 minutes of CPR.[30] In the present review, we identified outcomes for 39 infants with ROSC or increase in heart rate at or beyond 20 minutes of life. Within this small cohort, 15 (38%) survived to last follow-up and 6 of 15 (40%) survivors did not have moderate or severe NDI. Although these limited data may be influenced by selective reporting, the potential for survival without moderate or severe NDI after 20 minutes of intensive resuscitation is noteworthy.

Another concern is the potential burden of adverse outcomes on infants and their families after hospital discharge. The discharge survival rates were similar to survival rates at last follow-up, suggesting that most deaths occurred in the delivery room or during the initial hospitalization. For those infants who ultimately die during their initial hospitalization, achieving even short-term survival may provide the family the time and opportunity to participate in decision-making and care of their infant. Moreover, among those infants who do survive, survival without moderate or severe NDI is possible. In this systematic review, 38% of survivors assessed in follow-up did not have moderate or severe NDI.

Finally, interpretation of these results should be influenced by the local and regional context. All studies included in this review occurred in high-resource settings. In low-resource settings, where resuscitation may include only face mask ventilation,[31] advanced resuscitation procedures and prolonging resuscitation may not be an option. In addition, the quality of available antenatal and neonatal care as a whole and access to neuroprotective strategies in particular are likely to influence outcomes after delivery room CPR.[32]

Given these considerations, it is unlikely that 1 uniform time interval or duration of CPR after birth will be appropriate for all newborns. Relevant contextual factors include gestational age, the presence of congenital anomalies, the timing of perinatal insult, the perceived adequacy of resuscitative interventions performed, the family's stated preferences and values, and the availability of postresuscitative resources such as neonatal intensive care and neuroprotective strategies. In addition, 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 this decision.[33–35] ILCOR treatment recommendations based on this evidence are available online,[36] and authors of previous work have proposed a practical approach for discontinuing resuscitation.[37]

This systematic review includes a comprehensive assessment of the best available evidence; however, the

TABLE 5 Subgroup Analyses for Survival and Neurodevelopmental Outcomes

Subgroup	Studies Contributing	Infants, *N*	Survival to Last Follow-up, *n* (%)	Infants Assessed for Neurodevelopment, *n*	Survival Without Moderate or Severe NDI	
					n (% of Survivors Assessed)	*n* (% of All Enrolled)
Population level studies	6[12,13,15,16,23,24]	240	67 of 240 (28)	15	9 of 15 (60)	9 of 131[a] (7)
Therapeutic hypothermia treatment	9[10,11,17,19–21,23–25]	206	122 of 206 (59)	57	21 of 57 (37)	21 of 105[b] (20)
Gestational age ≥ 36 wk	13[10–13,15,17–21,23–25]	350	189 of 350 (54)	73	23 of 73 (32)	23 of 166[c] (14)
Gestational age <36 wk	7[12,13,15,20,23–25]	144	41 of 144 (28)	8	5 of 8 (63)	5 of 42[d] (12)
Heart rate detection reported ≥ 20 min after birth	5[11,20,21,23,24]	39	15 of 39 (38)	15	6 of 15 (40)	6 of 39 (15)

[a] In 5 studies enrolling 131 infants, authors reported neurodevelopmental outcomes.
[b] In 8 studies enrolling 105 infants treated with therapeutic hypothermia, authors reported neurodevelopmental outcomes.
[c] In 11 studies enrolling 166 infants ≥36 wk' gestation, authors reported neurodevelopmental outcomes.
[d] In 5 studies enrolling 42 infants <36 wk' gestation, authors reported neurodevelopmental outcomes.

certainty of evidence is considered very low. The most significant weakness is the potential for selection bias. Only 6 studies included in this review were population-level cohort studies. In the remaining studies, authors reported outcomes of infants who survived resuscitation, were admitted or transferred to the NICU, and in some cases met criteria for therapeutic hypothermia treatment. Because infants who died in the delivery room were not included in those studies, mortality estimates likely underestimate the actual probability of death when all resuscitations in a defined birth cohort are considered.

In addition, the details, efficacy, and timing of resuscitation procedures were not reported in most studies. Furthermore, the impact of prolonged resuscitation in preterm infants is uncertain because of limited data. We reported results of only 144 infants <36 weeks' gestation, of whom 41 survived and only 8 were assessed for NDI; results should be cautiously applied to preterm infants. Last, in most available studies, authors characterized the infant's response to resuscitation with the 10 minute Apgar score, which is subjective and does not provide information about ongoing assessments or response to resuscitation beyond 10 minutes.[4] To address these gaps, additional cohort studies in which authors report outcomes of all infants who present without signs of life and receive intensive resuscitation are needed. Ideally, these would include consistent definitions of the at-risk population, standardized definitions of stillbirths, objective physiologic assessments during CPR, detailed information about the occurrence and timing of resuscitation and postresuscitative interventions, and accurate and consistent assessments of outcomes among survivors.

CONCLUSIONS

Infants with ongoing need for CPR at 10 minutes after birth are at high risk for mortality and neurodisability, but survival without NDI is possible. Exposure to 1 specified duration of CPR is unlikely to uniformly predict survival or survival without NDI for all newborns.

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ABBREVIATIONS

CINAHL: Cumulative Index to Nursing and Allied Health
CoSTR: consensus on science with treatment recommendations
CPR: cardiopulmonary resuscitation
ILCOR: International Liaison Committee on Resuscitation
NDI: neurodevelopmental impairment
RCT: randomized controlled trial
ROSC: return of spontaneous circulation
SciELO: Scientific Electronic Library Online

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