**Clinical question:** In term neonates with a heart rate < 60 and no other signs of life (P), is ten minutes (I) as opposed to 15 minutes or longer (C) of effective resuscitation a reliable measure of outcome (abnormal neurologic examination and/or death) (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis?  Prognosis

State if this is a proposed new topic or revision of existing worksheet: New topic

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? NO

**Search strategy (including electronic databases searched).**

AHA Endnote, Medline, Embase, Cochrane and Pubmed databases were searched without any limit of period with the following strategies:

1. **MESH terms: Withholding resuscitation AND Apgar score**  
   "{"resuscitation orders"[MeSH Terms] OR ("resuscitation"[All Fields] AND "orders"[All Fields]) OR "resuscitation orders"[All Fields] OR ("withholding"[All Fields] AND "resuscitation"[All Fields]) OR "withholding resuscitation"[All Fields]) AND ("apgar score"[MeSH Terms] OR ("apgar"[All Fields] AND "score"[All Fields]) OR "apgar score"[All Fields]) - 4 items.

2. **MESH term: Withholding resuscitation LIMITED by age group (newborn infant)**  
   "{"resuscitation orders"[MeSH Terms] OR ("resuscitation"[All Fields] AND "orders"[All Fields]) OR "resuscitation orders"[All Fields] OR ("withholding"[All Fields] AND "resuscitation"[All Fields]) OR "withholding resuscitation"[All Fields]) AND "infant, newborn"[MeSH Terms]} - 204 items.

3. **Words “10 minute low Apgar score” LIMITED by age group (newborn infant)**  
   "{10[All Fields] AND minute[All Fields] AND low[All Fields] AND "apgar score"[MeSH Terms] OR ("apgar"[All Fields] AND "score"[All Fields]) OR "apgar score"[All Fields]) AND "infant, newborn"[MeSH Terms]} - 107 items.

4. **MESH term Resuscitation AND words “Bradycardia” LIMITED by age group (newborn infant)**  
   "{"resuscitation"[MeSH Terms] OR "resuscitation"[All Fields]) AND ("bradycardia"[MeSH Terms] OR "bradycardia"[All Fields]) AND "infant, newborn"[MeSH Terms]} - 124 items.

5. **MESH term Cardiopulmonary Resuscitation AND word "Bradycardia " LIMITED by age group (newborn infant)**  
   "{"cardiopulmonary resuscitation"[MeSH Terms] OR ("cardiopulmonary"[All Fields] AND "resuscitation"[All Fields]) OR "cardiopulmonary resuscitation"[All Fields]) AND ("bradycardia"[MeSH Terms] OR "bradycardia"[All Fields]) AND "infant, newborn"[MeSH Terms]} - 233 items.

**State inclusion and exclusion criteria**

**Inclusion criteria:** case series, cross-sectional, prospective or retrospective cohorts of infants of any gestational age born without signs of life but with no obvious signs of prolonged fetal death (maceration, dependent lividity) in whom resuscitation was attempted; outcomes included Apgar scores at 5 and 10 minutes and beyond, intra-hospital survival, survival following hospital discharge, any developmental outcome after discharge (motor and/or cognitive and/or visual and/or hearing). Studies of depressed infants at birth with low Apgar scores were reviewed to see if babies in the case list fit the PICO criteria.

**Exclusion criteria:** animal studies, studies with cardiopulmonary arrest in any other age group beyond neonatal period, studies of only preterm infants, abstracts, commentaries or ethics opinions.

**Number of articles/sources meeting criteria for further review:** 23
23 articles reported outcomes after at least 10 minutes of “depression”, as follows:
- 9 articles with some report of outcome and Apgar of 0 at 10 minutes of life (asystole) - these articles comprise the worksheet on “Discontinuation of Resuscitation at 10 minutes with no ROSC”
- 6 articles with some report of outcome and bradycardia (Apgar of 1 or HR<100 or <60 at 10 min. life/arrest)
- 8 articles with some report of outcome and Apgar of 0-3 at 10 minutes of life.

This reviewer hand searched the 23 articles looking for some signs of life at 10 minutes after the initiation of resuscitation to extract babies meeting the PICO criteria. Five of these report outcome after bradycardia at 10 minutes of life: one with LOE P4 and five with LOE P5. Eight others report outcomes of infants with 0-3 Apgars and these were hand searched for infants whose only sign of life was a HR<60 at 10 minutes and their outcomes. Data in only 5 of these articles was sufficient to include in the summary of evidence, and this comprised very few patients.

### Summary of evidence

#### Evidence Supporting Clinical Question:

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<td>Chamnanvanakij 2000, ABCD</td>
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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*

#### Evidence Neutral to Clinical Question:

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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
Evidence Opposing Clinical Question: NONE

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Level of evidence

A = Return of spontaneous circulation  
C = Survival to hospital discharge  
E = Other endpoint  
B = Survival of event  
D = Intact neurological survival  
*Italicics*= Animal studies

REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Review of the literature produced no reports that directly answered this PICO question. Analysis of papers which looked at depressed or asphyxiated newborns, apparent stillborns or infants with prolonged low Apgar Scores revealed occasional data which allowed the reviewer to abstract a few patients who met this criteria. Even manuscripts reporting infants with Apgar of 1 at 10 or 15 minutes did not define why the score was given and the reviewer had to make the assumption that the single point was given for heart rate < 100. If the search is expanded to include babies with Apgars 0-3 at 10 to 15 minutes, more data is available (van de Riet, 1999 and Nelson, 1981), but it is impossible to draw conclusions from these two studies which reliably address the situation of an infant who is being effectively and vigorously resuscitated but has only a terminal bradycardia of <60 at 10 minutes. Laptook et al. (2009) did a secondary analysis of term and near-term infants entered into the NICHD hypothermia trial. Of 188 infants for whom data was available, 11 had an Apgar score of 1 at 10 minutes, presumably for a heart rate <100 bpm. Follow up was done at 18-22 months of age. Of these infants, 7 died, 2 had moderate/severe disability, and 2 (18%) had mild or no disability. It should be noted that this population starts off with a distinct selection bias, since these are infants who are capable of being resuscitated and possibly transported to the hypothermia centers.

Terminal bradycardia (HR <60) is known to be associated with inadequate organ perfusion and often heralds the final stage of heart failure in a neonate (unlike the terminal rhythms or lack of spontaneous circulation of older children or adults). The data from the Laptook study for the 10 minute Apgar 1 infants does not differ statistically from the 10 minute Apgar 0 infants. It would therefore seem that this rhythm should be equated to asystole in a newborn. However, the data at present does not justify such an assumption. Therefore based on the lack of data, no recommendation can be made at this time.
Citation List

LOE P4 – Fair, Neutral (retrospective cohort, insufficient data).

Comment: The authors reviewed 454 newborn infants with Apgar=0 at 1st minute among 94,511 deliveries in 2 institution in the UK between 1986-94. The rate of successful resuscitation (42 of 45 = 93%) is much higher than reported in other studies (for example, Jain reports that 31 of 93 died in the DR). Among the 45 (26 full term) infants, 93 % were anticipated and received full resuscitation by trained staff. Out of the 45, 4 infants (GA 36-42 weeks) were still asystolic at 10 minutes (Apgar = zero at 10 minutes): 3 of them died in the first week of life and 1 had documented CP (quadriplegic) at more than 18 months of life. A poorer outcome was associated with late return of spontaneous circulation, but we do not know whether this was due to prolonged fetal asphyxia, the cause of the asphyxia or the effectiveness of the resuscitation.
Similar problems to other series although there is more confidence that with trained staff the resuscitation was performed adequately. Only one baby is described with an Apgar of 1 at 10 minutes(assumed to be for HR <100, but not stated) and this infant died (31 weeks gestation). There is inadequate data to classify this study according to the PICO of this worksheet.

LOE P4 - Fair, Supporting (selection bias for proposed question)

Comment: The infants in this retrospective review were already admitted to the NICU at Parkland in Dallas and were intubated on assisted ventilation. Thus the usefulness of this data in regards to babies in the delivery room should be questioned. However, important data can be abstracted from the study when looking at the duration of the persistent bradycardia (PB). When the bradycardia was brief (< 2 minutes), the outcomes were determined by the underlying medical condition. However, of the infants who had > 9 minutes of HR <60 (n=5) in this relatively controlled situation (i.e. endotracheal tube and iv access already in place), all died. This study emphasizes the importance of persistent bradycardia in relationship to outcomes and that even with chest compression, ventilation and drugs, the outcomes are poor. The study emphasizes that terminal bradyarrhythmias are the sign of cardiac failure in neonates and that prolonged PB is a very poor prognostic sign.

LOE P5 - Fair, Neutral (retrospective cohort, insufficient data).

Comment: The authors identified 103 newborn infants with Apgar=0 at 1 minute among 81,603 deliveries >22 weeks and >500g in the University of Tennessee Hospital over a 14 year period (1986-1999). Among the 103,
33 with Apgar=0 at 1 and 5 minutes were successfully resuscitated. Out of the 33, 16 infants were still asystolic at 10 minutes (Apgar = zero at 10 minutes): 14 of them died and 2 had hypoxic ischemic encephalopathy at neonatal period and non-documented follow-up. Only 63% of the survivors (7 of 11) were examined at follow-up. The significance of gestational age on survival is noteworthy here as none of the babies less than 26 weeks who had Apgar 0 at 1 and 5 minutes survived. Similar issues to all other series of severely depressed babies at birth include questions regarding efficacy of resuscitation and poor follow up percentage. With regards to this PICO, the authors do not disclose how many newborns had Apgar of 1 at 10 minutes or who had HR<60 at 10 minutes and how many of them died. In the survivor list, 2 babies had Apgar of 1 at 10 minutes. The assumption is that this score is given for a HR < 100. Follow up of these patients is not reported separately from the other survivors. This paper has numerous issues with regard to the PICO question. Given the paucity of data on only 2 newborns with Apgar of 1 at 10 minutes, no conclusions can be drawn from this study.


LOE P4: Good, Opposing (secondary analysis of a prospective cohort trial)

Comment: This was a retrospective secondary analysis of the NICHD hypothermia trial with developmental follow-up of survivors at 18-22 months. With an Apgar of 0 at 10 minutes, death or disability was very high (76%) which is similar but not as overwhelming as other similar retrospective reports. Of 188 infants for whom data was available, 11 had an Apgar score of 1 at 10 minutes, presumably for a heart rate <100 bpm. Of these infants, 7 died, 2 had moderate/severe disability, and 2 (18%) had mild or no disability. It should be noted that this population starts off with a distinct selection bias, since these are infants who are capable of being successfully resuscitated and possibly transported to the hypothermia centers. The outcome for Apgar 1 babies, though more heterogeneous than previously thought, was not statistically different than those infants with Apgar 0 at 10 minutes.


LOE P5 - Fair, Neutral (insufficient data).

Comment: This is a very old study since the cohort was recruited prospectively from 1959-1961 in 12 US centers. The study evaluated a total of 49,000 births (45,000 at term) and reported outcomes for babies who had Apgars of 0-3 after 10 minutes. This study is often quoted as the reason why low Apgar scores do not correlate with poor neurologic outcomes since 80% of infants with Apgars of 0-3 at 10 minutes of age were free of major handicap at the 7 year evaluation. Trying to abstract some embedded data to answer this PICO question, this reviewer found only 2 babies who had Apgar score of 1 at 10 minutes (assuming only for HR < 100). Both of these infants survived but had significant disabilities (CP in one and severe MR in the other). The paucity of this data does not allow for any conclusions.

LOE P4 - Fair, Neutral (insufficient data).

**Comment:** The authors identified all newborn infants with Apgar=0 at 1 and 5 minutes in 10 Level 3 NICUs of New South Wales, Australia (1992-2002). Among the 60 identified neonates with gestational age >36 weeks, 29 were still asystolic at 10 minutes (Apgar = zero at 10 minutes): 20 of them died, 8 developed cerebral palsy (not stated age and type of disability) and 1 had minor fine motor dysfunction. Of these 29 patients, 28 had an audible heart rate at 15 minutes (time to have HR: 11-40 minutes). No outcome differences are reported for the patients who had HR at 10-15 minutes vs those who took longer to establish ROSC. These findings support the dismal outcome of resuscitation regardless of how it is performed. The search strategy would not identify infants not transferred to these units if they were successfully resuscitated (doubt there would be many). Similar problems with this case series: retrospective collection of data and selection bias (asystolic babies non-resuscitated at discretion of the staff) and developmental assessment is not clear. The authors do not provide enough details regarding the babies who did have a HR from 11-40 minutes after resuscitation was begun to draw any conclusions regarding this PICO question.

LOE - Not assessed- additional citation not directly related to PICO

**Comment:** Data from this report reveals that 11 term newborns received full CPR (intubation and positive pressure ventilation, chest compression, adrenaline) and of these 8 died, 2 had significant neurologic sequelae and 1 was normal at follow up. The assumption is that this degree of resuscitation was necessitated by no or very low heart rate. However, the paper does not give details on the condition of these babies at 10 minutes and whether a heart rate was present or there were other signs of successful resuscitation. Therefore this data cannot be included in the evaluation.

LOE – not assessed – additional citation not directed related to PICO

**Comment:** A systematic review of the literature of a similar theme, but one that does not address the proposed worksheet question. It is interesting however that among 368 patients of 42 different studies with a 10 minute Apgar score of 0-3, 250 (68%) died and 14 (12% of survivors) had CP. Among 178 patients of 42 different studies with a 20 minute Apgar score of 0-3, 156 (88%) died and 9 (41% of survivors) had CP. The study does not help to evaluate the importance of low heart rate as a predictor of bad outcome during neonatal resuscitation but does show trends of outcomes with poor response to resuscitation, not just babies who are asystolic at 10 minutes. The study is not included in the evaluation.