**Worksheet author(s)**

Ruth Guinsburg

**Date Submitted for review:** October 1, 2009

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

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**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

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

MEDLINE, Embase, Cochrane and SciELO databases were searched without any limit of period with the following strategies:

1. **MEDLINE and SciELO**
   - **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.

     **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.

     **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]} - 204 items.

     **MESH term:** Resuscitation AND words “Brady cardia” LIMITED by age group (newborn infant)
     

     **MESH term:** Cardiopulmonary Resuscitation AND word "Brady cardia" LIMITED by age group (newborn infant)
     

2. **EMBASE:**
   - withholding AND 'resuscitation'/exp AND apgar AND score: 0 items
   - withholding AND 'resuscitation'/exp AND [humans]/lim AND [newborn]/lim: 20 items
   - 10 AND minute AND low AND apgar AND score AND [newborn]/lim: 236 items
   - resuscitation AND 'brady cardia'/exp AND [newborn]/lim: 63 items

3. **COCHRANE LIBRARY:**
   - All systematic reviews provided by the Cochrane Neonatal Review Group in the address http://www.nichd.nih.gov/cochrane/ were manually searched to retrieve reviews related to prolonged resuscitation: 4 items were selected.

4. **ELIGIBLE ARTICLES IN REFERENCE LISTS OF ALL ARTICLES THAT MET INCLUSION CRITERIA**

   **State inclusion and exclusion criteria**

   **Inclusion criteria:** case series, cross-sectional, prospective or retrospective cohorts of infants born alive with any description of heart rate or Apgar score at 10 minutes of life or beyond, with any of the following outcomes: intrahospital survival, survival following hospital discharge, any developmental outcome after discharge (motor and/or cognitive and/or visual and/or hearing).
**Exclusion criteria:** animal studies, studies with cardiopulmonary arrest in any other age group beyond neonatal period and comments or personal opinions regarding ethic issues that surround withholding resuscitation in delivery room.

- **Number of articles/sources meeting criteria for further review:**
Abstracts of all retrieved items were used to select articles meeting inclusion criteria. After this first revision, 66 studies were fully evaluated:

A. 31 articles with some report of outcome after “perinatal asphyxia” based on low Apgar scores, but no data could be retrieved regarding Apgar or HR after 5 minutes of life.
B. 4 non systematic reviews of long term outcome of asphyxiated newborns
C. 5 personal comments about outcomes of severely asphyxiated infants
D. 2 recommendations that deals with Apgar after 5 minutes and outcomes
E. 25 articles with some report of outcome after at least 10 minutes of “depression”, as follows:
   E1-- 9 articles with some report of outcome and Apgar of 0 at 10 minutes of life (asystole)
   E2-- 6 articles with some report of outcome and bradycardia (Apgar of 1 or HR<100 or <60) at 10 min. life/arrest
   E3-- 8 articles with some report of outcome and Apgar of 0-3 at 10 minutes of life.

Observation: Literature search of all databases was done again at October 1st, 2009 with the same strategy described above but restricted to the previous year (October 2008 to October 2009). 17 studies were retrieved but none had relevant information to be added.

Therefore, the following worksheet is restricted to the six LOE 5 studies with some report of outcome after bradycardia at 10 minutes of life.

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**Summary of evidence**

**Evidence Supporting Clinical Question:**

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<td>(Chamnanvanakij and Perlman 2000) B, C, D</td>
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**Level of evidence**

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

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**Evidence Neutral to Clinical question:**

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|      |      | (Nelson and Ellenberg 1981) B, C, D  
(Haddad et al. 2000) B, C  
(Casalaz et al. 1998) B, C, D  
(Patel and Beeby 2004) B, C, D  
(Thornberg et al. 1995) B, E |

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**Level of evidence**
Evidence Opposing Clinical Question: NONE

| Good | | | | |
|------|------|------|------|
| Fair | | | | |
| Poor | | | | |
| 1    | 2    | 3    | 4    | 5    |

Level of evidence

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

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

After extensive search of literature, only reports of scattered patients with presumptive low heart rate following 10 minutes of resuscitation were found, except for one article related to prolonged resuscitation in the NICU (Chamnanvanakij, 2000). With the exception of this last article, none of the studies reported how resuscitation was managed. “Fishing” for data of patients with presumptive persistent bradycardia in studies not focused on this specific population led to important information gaps. The result was finding 3 patients that survived an Apgar score of 1 at 10 minutes (that is not equal to HR<60 after 10 minutes of resuscitation) with disabilities and 14 patients with audible heart rate between 11 and 15 minutes of life without reported outcomes. Regarding neonatal arrests outside delivery room, 1 retrospective study with LOE4 (Chamnanvanakij, 2000) suggests that resuscitation after 10 minutes of chest compressions results in death of term infants that have associated clinical conditions such as congenital malformations.

Due to paucity of data regarding HR<60 at 10 or 15 minutes as a measure of outcome, evaluation of severe depression at 10 minutes after birth and outcome was also analyzed. A systematic review of 368 patients with Apgar 0-3 at 10 minutes (van de Riet, 1999) showed 250 deaths, 116 alive (14 with major impairment) and 104 (28%) with minor disabilities or normal development. These results imply that almost a third of patients with 0-3 Apgar score at 10 minutes can survive without major sequelae. But, it is impossible to extend this data to HR values, since an Apgar score of 0-3 may indicate either an asystolic baby or one with normal HR and some respiratory effort.

Therefore, based on available studies, it is impossible to make any recommendation based on HR levels after 10 minutes of effective resuscitation. It is desirable to use prospectively collected databases with documented responses of neonates to adequate resuscitation management and with outcomes evaluated by reliable methods in order to assess futility or not of prolonging resuscitation in neonates with extended bradycardia. Some databases collected for neonatal neuroprotection with hypothermia may be useful for this purpose.

Acknowledgements: to Allan Chiaratti de Oliveira, MD, for helping with the literature search.
**Citation List**


**Level 5 - Neutral (insufficient data).**

**Comment:** authors identified 454 newborn infants with Apgar=0 at 1st minute among 94,511 deliveries in Bristol, UK (1986-94). 45 (26 fullterm) received full resuscitation by trained staff. Out of the 45, 1 infants (GA 31 weeks, BW 1710g) had Apgar of 1 at 10 minutes (HR<100bpm??) and this patient died. The main problems with this case series is: retrospective collection of perinatal data and selection bias (409 babies non-resuscitated - decision at discretion of attending staff); study did not aim to evaluate persistent bradycardia after adequate resuscitation; Apgar score of one does not equals HR<60 and finally it is not stated how HR was assessed for Apgar scoring and how exact was timing of assessment. Therefore one PT dying with Apgar score of one at 10 minutes does not drive to any conclusion.


**Level 5 - Supporting (selection bias for proposed question)**

**Comment:** authors identified 39 newborn infants among 1485 admitted to Parkland Hospital in TX (119-97) who had 62 episodes of persistent bradycardia needing chest compressions and/or epinephrine. Among the 39 infants 3 were fullterm (all had malformations) and 4 were late preterm infants (3 had malformations and 1 had congenital infection). Five of them had ≥9 minutes of heart rate <60 bpm (duration of chest compressions). All of them died. This retrospective case series of neonatal arrest after admission to NICU is interesting (paucity of data regarding this issue) and indicates that prolonged resuscitation of term and late preterm infants with medical problems have bad outcomes, probably related to the severity of baseline condition. It indicates that prolonged chest compression or epinephrine in this specific situation is futile.


**Level 5 - Neutral (insufficient data).**

**Comment:** authors identified 103 newborn infants with Apgar=0 at 1st minute among 81,603 deliveries ≥22 weeks and >500g in the University of Tennessee Hospital (1996-1999). Among the 103, authors do not inform how many had Apgar of 1 at 10 minutes or who had HR<60 at 10 minutes and how many of them died. In the list of surviving babies it can be extracted that 2 NB with Apgar=1 at 10 minutes survived neonatal period. Follow up of these patients is not reported. The main problems with this case series is: retrospective collection of perinatal data and selection bias; study did not aim to evaluate persistent bradycardia after adequate resuscitation; Apgar score of one does not equals HR<60 and finally it is not stated how HR was assessed for Apgar scoring and how exact was timing of assessment. Therefore 2 NB alive after an Apgar score of one at 10 minutes does not lead to any conclusion.


**Level 5 - Neutral (insufficient data).**
**Comment:** this prospective cohort study evaluated 49,000 births (around 45,000 full term births) in 12 USA centers from 1959 to 1961 and reported death or major neurological disabilities at 7 years old. Among prolonged resuscitated babies with birthweight > 2500, the following outcomes were reported:

- 66 babies with Apgar 0-3 after 10 minutes: 12 deaths, 2 with cerebral paralysis (CP) and 41 alive without disabilities.
- 23 babies with Apgar 0-3 after 15 minutes: 11 deaths, 1 with CP and 10 alive without disabilities.
- 39 babies with Apgar 0-3 after 20 minutes: 23 deaths, 8 with CP and 6 alive without disabilities.

Regarding HR<60 at 10 minutes or beyond, authors list 2 babies among 10 infants with low Apgar scores and CP that have Apgar score at 10 minutes of 1 (HR<100?): one with CP and seizures and the other one with severe mental retardation.

The main problems with this classical study is that the data needed for the worksheet is extracted and incomplete in the published paper that did not aim to evaluate outcomes after HR<60 and adequate resuscitation. Therefore the presence of 2 NB alive with major disabilities after an Apgar score of one at 10 minutes does not lead to any conclusion.


**Level 4 - Neutral (insufficient data).**

**Comment:** authors identified all newborn infants with Apgar=0 at 1st and 5th minutes in 10 3rd level NICUs of New South Wales, Australia (1992-2002). Among the 60 identified neonates with gestational age >36weeks, 29 were still asystolic at 10 minutes (Apgar = zero at 10 minutes) and 14 of them had audible heart rate at 10-15 minutes of life. For the whole cohort (29 infants): 20 died, 8 developed cerebral paralysis and 1 minor fine motor dysfunction. No outcome is reported for the patients who had HR at 10-15 minutes vs those who took longer. The main problems with this case series is: retrospective collection of part of data and selection bias (asystolic babies non-resuscitated at discretion of the staff) and study did not aim to evaluate persistent bradycardia after adequate resuscitation. Finally it is not stated how HR was assessed for Apgar scoring and how exact was timing of assessment. Therefore the presence of 2 NB alive after an Apgar score of one at 10 minutes does not lead to any conclusion.


**Level 5 - Neutral (insufficient data).**

**Comment:** authors studied 42,203 live infant in a Swedish city from 1985-1991. 292 were full term infants with 5 minutes Apgar less than 7. It can be extracted from the text that 11 NB received positive pressure ventilation plus chest compressions plus intubation plus adrenaline (prolonged resuscitation? How long the babies had low heart rate?): 8 died, 2 developed disabilities and only one was normal at follow up. Among the 292 infants with 5th minute Apgar <7, 10 babies had neurological sequelae and one of these 10 infants had Apgar score of 1 at 10 minutes of life. It is not stated how many babies had Apgar=1 at 10 minutes and how many of them died. Also heart rate status through resuscitation is not reported. Therefore it is difficult to conclude anything since the study was done aiming other objectives.

Level of evidence – not assessed – extra citation not directed related to the question

Comment: A systematic review of the literature of a correlated theme, but 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 hear rate as a predictor of bad outcome during neonatal resuscitation.