### WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

**Worksheet author(s)**

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Date Submitted for review:  
4/21/08 revised 10/8/09

**Clinical question.**

In term infants at risk for hypoxic-ischemic encephalopathy secondary to intra-partum hypoxia does selective/whole body cooling as opposed to standard care (without cooling) improve outcome?

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

**State if this is a proposed new topic or revision of existing worksheet.** Revision of an existing worksheet

**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).**

**Mesh terms** included hypothermia, induced hypothermia, body cooling, whole body cooling, selective head cooling, neonate, asphyxia, hypoxia ischemia, hypoxia, body temperature, animal, seizures brain diseases  
Medline: (1966-2009) Hypothermia + Hypoxia-ischemia – 69 hits of which 35 were reviewed, Hypoxia-Ischemia + Newborn +hypothermia- 20 hits-19 were reviewed, Asphyxia + hypothermia-7 hits- all reviewed, Induced hypothermia+ newborn-13 hits-all reviewed, whole body cooling –94 hits-10 reviewed, seizures +hypothermia+ newborn- 10 hits-4 reviewed  
Embase: Asphyxia+ hypothermia- 134 hits-27 reviewed, asphyxia+ body temperature- 27 hits-6 reviewed, asphyxia+newborn+hypothermia-58hits-22 were reviewed, induced hypothermia+ newborn- 114 hits-36 were reviewed, induced hypothermia + hypoxia-ischemia – 15 hits-11 were reviewed, hypothermia + hypoxia-ischemia- 57 hits- 29 were reviewed, newborn + neuroprotection + hypoxia-ischemia – 71 hits- 3 were reviewed, induced hypothermia+ neuroprotection +newborn- 18 hits – 14 were reviewed. Endnote library- 68 hits  
There is one relevant new Cochrane review Cooling for newborns with hypoxic ischaemic encephalopathy.[update of Cochrane Database Syst Rev. 2007;(4):CD003311; PMID: 14583966]

**State inclusion and exclusion criteria**

For this worksheet I included all the neonatal human studies that have been published since the last review and excluded any animal studies performed since the last worksheet completed in February 2005. The most recent search was through October 2009

**Number of articles/sources meeting criteria for further review:**

The previous worksheet contained 29 articles. Since that time there has been two large randomized studies, two small randomized studies, one of which was termed a pilot study that has both a safety and efficacy arm, an updated Cochrane review; all will be included in the worksheet grid. There have been 9 review articles on the subjects and several manuscripts using data from one of the randomized studies that were also reviewed but not included in the worksheet but will be available as a source of reference.
# Summary of evidence

## Evidence Supporting Clinical Question

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<thead>
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<th>Level of evidence</th>
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<td>Gluckman 2005 D</td>
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<td>Shankaran 2005 D</td>
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<td>Eicher B,D,E</td>
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<td>Lin C,D</td>
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<td><strong>Level of evidence</strong></td>
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<td>C = Survival to hospital discharge</td>
<td>E = Other endpoint</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  

*Italicics = Animal studies*

### Evidence Opposing Clinical Question

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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  

*Italicics = Animal studies*
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Modest systemic or selective cooling of the brain by as little as 2°-4°C has been shown to reduce the extent of tissue injury in experimental studies as well as in humans following brain injury events such as stroke, trauma or cardiac arrest {Bona, 1998 #167} {Gunn, 1997 #161} {Gunn, 1998 #162} {Laptook, 1997 #165} {Laptook, 1999 #166} {Thoresen, 2001 #243} {Thoresen, 2001 #244} {Tooley, 2003 #242} {Wagner, 2002 #230} LOE 6, {Bernard, 2002 #240} {The Hypothermia after Cardiac Arrest Study Group, 2002 #237} LOE 7 for neonates) and more recently in newborns. Three large randomized studies (Gluckman, 2005 #31 (selective head cooling), Shankaran, 2005#32 (whole body cooling)), one randomized pilot study (Eicher, 2005 #34) (whole body cooling) and one quasi randomized study (Lin, 2006 #30).

Three large randomized multicenter studies i.e. Cool Cap study (Gluckman, 2005 #31) whole body cooling (Shankaran, 2005#32 ) and Azzopardi # (TOBY) included infants with a gestational age ≥36 weeks treated at or before six hours of age with either severe acidosis or perinatal complications and resuscitation at birth and who had moderate or severe encephalopathy. In the Cool Cap and TOBY studies enrollment included an aEEG determination of moderate/severe encephalopathy + clinical whereas the whole body cooling utilized clinical criteria of moderate/severe encephalopathy (Sarnat classification). The Cool Cap study cooled to a rectal temperature of 34.5°C and whole-body cooling and TOBY studies to an esophageal or rectal temperature of 33.5°C; for 72 hours, followed by slow rewarming (hypothermia group). Neurodevelopmental outcome was assessed at 18 to 22 months of age with a primary outcome of a combined end point of death or severe disability (Cool Cap, TOBY) or death or moderate or severe disability (whole body cooling). The Cool-cap study failed to show an overall significant effect of cooling in reducing death and or severe neurodevelopmental deficits (OR 0.61 (95%CI 0.43-1.09), however for infants with moderate encephalopathy there was a significant effect OR 0.61 (95%CI 0.43-1.09) (p=0.02) whereas with severe encephalopathy and/or seizures no effect was noted (p=0.51). In the whole body study, a significant reduction in death and moderate/severe encephalopathy was noted (RR 0.72 (95%CI 0.54-.095) whereas there was no significant effect when these items were analyzed individually i.e. death (RR 0.68 (95%CI 0.44-.105), moderate encephalopathy (RR 0.68 (95%CI 0.44-.107) and severe encephalopathy (RR 0.85 (95%CI 0.64-.113). In the latter study the number needed to treat to show benefit in one infant was six. In the TOBY study in the cooled group, 42 infants died and 32 survived but had severe neurodevelopmental disability, whereas in the noncooled group, 44 infants died and 42 had severe disability (relative risk for either outcome, 0.86; 95% confidence interval [CI], 0.68 to 1.07; P=0.17). Infants in the cooled group had an increased rate of survival without neurologic abnormality (relative risk, 1.57; 95% CI, 1.16 to 2.12; P=0.003). Among survivors, cooling resulted in reduced risks of cerebral palsy (relative risk, 0.67; 95% CI, 0.47 to 0.96; P=0.03) and improved scores on the Mental Developmental Index and Psychomotor Developmental Index of the Bayley Scales of Infant Development II (P=0.03 for each) and the Gross Motor Function Classification System (P=0.01). In the pilot study of (Eicher, 2005 #34) whole body cooling was maintained at 33.5°C for 48 hours. At one year outcome, no different in cognitive scores were noted, however death and severe outcome was significantly less in infants who were cooled compared to comparison group (p=0.01). Importantly approximately 20 per cent in each group were lost to follow-up. In the study of (Lin, 2006 #30) a quasi randomized approach was used (alternate day) and whole body cooling to a temperature of 34 to 35°C was implemented. At seven day follow-up the CT scan showed significantly less severe disease and there was improved neurobehavioral scores in the hypothermic group. When the outcome data for the major studies are pooled and analyzed as a function of the severity of encephalopathy, the only significant effects were noted in those infants who presented with moderate encephalopathy as it related to death and moderate/severe encephalopathy (RR 0.72 (95%CI 0.58-.91) and severe cerebral palsy (RR 0.42 (95%CI 0.19-.92)(Shah, 2007 #4). Some adverse effects of hypothermia included an increase in the need for inotrope support and a significant increase in thrombocytopenia. (Jacobs, 2007 #35)

Acknowledgements:
**Citation List**

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*Type the citation marker in the first field and then paste the full citation into the second field. You can copy the full citation from EndNote by selecting the citation, then copying the FORMATTED citation using the short cut, Ctrl-K. After you copy the citation, go back to this document and position the cursor in the field, then paste the citation into the document (use Ctrl-V). For each new citation press Tab to move down to start a new field.

Comment: Although a randomized study the end points were side effects and the effect of cooling on CSF PAF concentrations. Moreover the study embraces very small numbers (n=20).

Level of Evidence: 1  
Quality: Fair  
Evidence: Supportive


Comments: Feasibility or pilot study demonstrating the safety of whole body cooling

Level of Evidence: 4  
Quality: Fair  
Evidence: Supportive


Comment: Randomized study with findings consistent with the two prior studies. Although the composite outcome i.e. death/severe disability was not different, secondary outcomes survival without neurologic disability and cerebral palsy was improved with cooling

Level of Evidence: 1  
Quality: Good  
Evidence: Positive treatment effect in the treated group of survivors


Comment: Outcome study Sequential design-small numbers-safety study

Level of Evidence: 2  
Quality: Fair  
Evidence: Supportive

Battin, M. R., J. Penrice, et al. Treatment of term infants with head cooling and mild systemic hypothermia (35.0 degrees C and 34.5 degrees C) after perinatal asphyxia. *Pediatrics* 2003 111(2): 244-51

Comment: Non randomized study with control group. A safety study

Level of Evidence: 2  
Quality: Fair  
Evidence: Supportive


Comment: Adult study with important protective effects of hypothermia

Level of Evidence: 5  
Quality: Good  
Evidence: Supportive

**Comment**  Well conducted animal study with histopathologic data

**Level of Evidence:** 5  
**Quality:**  Good  
**Evidence:** Supportive


**Comments**  Small numbers, historical controls. No side effects of hypothermia

**Level of Evidence:** 3  
**Quality:**  Fair  
**Evidence:** Supportive


**Level of Evidence:** 3  
**Quality:**  Fair  
**Evidence:** Supportive


**Comments**  Small numbers, serial patients without a control group. Problems in maintaining temperature- thrombocytopenia developed in 12 infants

**Level of Evidence:** 4  
**Quality:**  Fair  
**Evidence:** Supportive but possible side effects


**Comments**  Pilot study showing a longer dependent on pressors, higher PTT,PT, lower platelets and more requiring FFP and platelets

**Level of Evidence:** 1  
**Quality:**  Fair  
**Evidence:** Increased side effects in the hypothermia group


**Comments**  Large multicenter study that did not show an overall treatment effect but in infants with moderate encephalopathy and no seizures at enrollment there was a significant effect

**Level of Evidence:** 1  
**Quality:**  Good  
**Evidence:** Positive treatment effect in a subcategory of patients


**Comments**  Seminal large animal study demonstrating the effectiveness of hypothermia in reducing brain injury

**Level of Evidence:** 5  
**Quality:**  Excellent  
**Evidence:** Supportive

**Comments**  Important timing study in a large animal model suggesting implementation of an intervention prior to six hours

**Level of Evidence:** 5  
**Quality:**  Good  
**Evidence:** Supportive


**Comments**  Important timing study showing no effect with delayed intervention

**Level of Evidence:** 5  
**Quality:**  Good  
**Evidence:** Negative study


**Comments**  While a randomized study it was in essence a pilot study with a randomized but sequential design. With minimal hypothermia (rectal temperature 35.7°C), no adverse effects were noted

**Level of Evidence:** 2  
**Quality:**  Fair  
**Evidence:** Supportive study


**Level of Evidence:** 5  
**Quality:**  Fair  
**Evidence:** Supportive study


**Level of Evidence:** 4  
**Quality:**  Fair  
**Evidence:** Supportive study


**Comments**  Overall a good review however included small pilot studies in the overall review. Did not address the issue of different temperature used in the two major studies and the two different modes of cooling and its impact when performing a meta-analysis

**Level of Evidence:** 1  
**Quality:**  Good  
**Evidence:** Supportive study


**Level of Evidence:** 5  
**Quality:**  Fair  
**Evidence:** Supportive study

Level of Evidence: 5  
Quality: Good  
Evidence: Supportive review


Level of Evidence: 5  
Quality: Good  
Evidence: Negative

Lin ZL, Yu HM et al Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: an experience from a single neonatal intensive care unit

Level of Evidence: 1  
Quality: Good  
Evidence: Negative


Comment Safety study in animals (n=3) and term infants (n=19) who were randomized to modest hypothermia versus normothermia. This study was designed to assess the feasibility of using whole body cooling and for preliminary safety issues.

Level of Evidence: 5  
Quality: Fair  
Evidence: Supportive study

Shankaran S, Laptook AR et al Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy

Comments Large multicenter study that shows a beneficial effect of whole body cooling in reducing death and/or moderate/severe neurodevelopmental deficits at 18 month followup. However when these items were evaluated individually, there were no significant differences

Level of Evidence:1  
Quality: Good  
Evidence: Supportive study


Level of Evidence: 1  
Quality: Good  
Evidence: Supportive analysis


Abstract
**Comment**  Non randomized study and using asphyxiated non cooled babies as controls-the latter poorly defined. Using the method of cool caps, no side effects were noted

Level of Evidence: 4  
Quality: Fair  
Evidence: Supportive study

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Level of Evidence: 5  
Quality: Fair  
Evidence: Supportive study


Comment  Seminal study in adults  

Level of Evidence: 5  
Quality: Excellent  
Evidence: Supportive study


Level of Evidence: 5  
Quality: Fair  
Evidence: Supportive study


Level of Evidence: 5  
Quality: Good  
Evidence: Opposing


Level of Evidence: 5  
Quality: Fair  
Evidence: Supportive study


Level of Evidence: 5  
Quality: Fair  
Evidence: Supportive study

**Comments** Randomized controlled study to address the question of hypothermia for neuroprotection. Numbers in this study too small to show an effect. Intervention was not associated with untoward side effects.

Level of Evidence: 1  
Quality: Fair  
Evidence: Supportive study


Level of Evidence: 5  
Quality: Fair  
Evidence: Supportive study