**Clinical question.**

In term neonates at risk for hypoxic-ischemic encephalopathy secondary to intra-partum hypoxia (P) does selective / whole body cooling (I) versus standard therapy (C), result in improved outcome (O)?

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

**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).**

PubMed: Infant, newborn (MeSH) AND Hypoxia-Ischemia, Brain (MeSH) AND Hypothermia, induced (MeSH). 94 hits.
Embase (OVID): hypothermia AND asphyxia AND infant; all as keywords. 65 hits.
Cochrane Library and Cochrane Central database of clinical trials: hypothermia AND infant as textwords. 36 hits.
AHA Endnote Master Library: hypothermia AND infant as textwords. 24 hits.

**State inclusion and exclusion criteria**

Randomised studies involving term infants with evidence of hypoxic ischemic encephalopathy (HIE) will be eligible for inclusion. Studies involving any method of cooling (e.g. whole body or selective head cooling), any duration of cooling, and any time of initiation of cooling will be eligible.

Human cohort and case-control studies and animal studies will be included.

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

Of these 9 were LOE 1 (1Cochrane Review, 8 RCTs); 4 were LOE 2 (non-randomized, concurrent controls); 3 were LOE 3 (historical controls); 3 were LOE 4 (no controls) and 3 were LOE 5 (animal studies)

Search strategy repeated on 21st August 2009: no additional trials located
# Summary of evidence

## Evidence Supporting 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
- **Italics** = Animal studies
### Evidence Neutral to Clinical question

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

The benefits shown in animal and human cohort studies have been confirmed by the results of RCTs of therapeutic hypothermia for HIE in newly born infants.

Meta-analysis of the eight available RCTs (638 infants) shows that hypothermia significantly reduces the risk of death or major disability following moderate or severe HIE [relative risk 0.76 (0.65, 0.89); risk difference -0.15 (-0.07, -0.24); number needed to treat 7 (4, 14)] (Jacobs, 2007, Cochrane Review). The Cochrane meta-analysis included Akisu 2003, Eicher 2005, Gluckman 2005, Wyatt 2007, Gunn 1998, Battin 2001, Battin 2003, Inder 2002, Lin 2006, Shankaran 2002 and Shankaran 2005. When analysis is restricted to infants with severe encephalopathy the reduction in death or disability remains statistically significant (NNT=6). For infants with moderate encephalopathy the reduction is of borderline statistical significance. Cooling reduces mortality and if an infant survives, also decreases the risk of major disability.

The results of RCTs are consistent. In spite of differences in techniques of cooling there was little statistical evidence of heterogeneity for any of the important outcomes. The implication for clinicians is that they may apply whichever technique is locally available. Future studies should directly compare different available techniques as well as refining the timing, duration and degree of cooling.

Increased rates of thrombocytopenia and hypotension were seen in cooled infants but these were outweighed by the survival and neurodevelopmental benefits.

Three trials (829 infants) are yet to be published. Future recommendations will need to take these trials into account.

Caution should be exercised in the application of these recommendations. The trials on which they are based were conducted at centres experienced in this new therapy and according to strict protocols. Centres wishing to offer therapeutic hypothermia should adopt similar protocols.

Acknowledgements:
**Citation List**


*Level 1 study, small numbers, short term outcomes only, selective head cooling*


*Level 4 study, no controls, indicated feasibility of cooling.*


*Level 1 study, selective head cooling, short term outcomes only, includes same patients as reported in Gunn 1998 and Battin 2003.*


*Level 1 study, selective head cooling, short term outcomes only, includes same patients as reported in Gunn 1998 and Battin 2001.*


*Level 3 evidence, historical controls, whole body hypothermia*


*Level 3 evidence, historical controls, whole body cooling*


*Level 4 evidence, no controls, feasibility study of whole body cooling*


LOE 1, earlier follow-up (12 months) than other RCTs and less complete follow-up (82%)


**LOE 1, Large international multicentred RCT of selective head cooling. Included patients also published in Wyatt (2007).**


*Level 1 study, selective head cooling, short term outcomes only, includes same patients as reported in Battin 2001 and Battin 2003.*


*Level 5 evidence, animal study.*


*Level 5 evidence, animal study.*


*Level 1 evidence, publication of MRI outcomes of subset of infants enrolled in international RCT of whole body cooling (trial ongoing)*


*LOE 1, Cochrane systematic review.*


*Level 2 evidence, concurrent controls, selective head cooling*


*LOE 1, single centre RCT, short term outcomes only*

**Level 2 evidence, concurrent controls evaluated both whole body and selective head cooling**


**LOE 1, small single centre trial, short term outcomes only, whole body cooling.**


**LOE 1, single centre RCT, short term outcomes only**


**LOE 3, historical controls**


**Level 5 evidence, animal study**


**LOE 5, animal study**


**Level 4 study, no controls indicating feasibility of therapeutic cooling**


**LOE 1, Large international multicentred RCT of selective head cooling. Included patients also published in Gluckman (2005)**


**LOE 5, Animal study**