Clinical question.
For infants and children who have ROSC after cardiac arrest (P), does the use of induced hypothermia (I) compared with normothermia (C) improve outcome (survival to discharge, survival with good neurologic outcome) (O)?

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 previous worksheets from 2000 and 2005

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).

MEDLINE: “Heart Arrest” [MeSH] AND “Hypothermia, Induced” [MeSH] limited to humans and clinical trials; limited to 2004-2008 22 hits 22 hits rejected VF only; rejected feasibility/technique articles; rejected hypothermic circulatory arrest in OR; rejected surrogate markers (evoked potentials, S100B, etc); rejected case reports and case series without comparators; rejected case series that lumped VF and other causes without separating them I considered further

Using similar limitations for the following searches, there were no additional articles identified
(“Drowning” [MeSH] OR “Near Drowning” [MeSH]) AND “Hypothermia, Induced” [MeSH]
(“Asphyxia” [MeSH] OR “Asphyxia Neonatorum” [MeSH]) AND “Hypothermia, Induced” [MeSH]
(“Brain Ischemia” [MeSH] OR “Hypoxia-Ischemia” [MeSH]) AND “Hypothermia, Induced” [MeSH]

MEDLINE: Asphyxia AND hypothermia 84 hits included only studies of neurologic outcome 3 animal studies

EMBASE: Heart Arrest AND Hypothermia,induced limited to 2004-2008 291 hits no additional articles identified

I also have an extensive file on hypothermia that I hand searched for additional articles.

There is a new Cochrane review for neonatal hypoxic encephalopathy that was not reviewed (see neonatal worksheet)
The Cochrane review for Hypothermia and CPR was last updated in 2003 (not reviewed)

Note: studies published in abstract form only were excluded as were any studies that were not peer reviewed.

After my initial search and submission of the WS, it was suggested that I add selected key human studies to the evidence evaluation grid that are not included in the above search and exclusion criteria. Accordingly, I have included the 2 human studies of adult VF (also included in the 2005 WS) and the 2 studies of neonatal birth asphyxia in the evidence evaluation grid.

State inclusion and exclusion criteria
See above (limited by date; excluded case reports and articles describing feasibility)

Number of articles/sources meeting criteria for further review:
4
Note: In addition to the above, there are 4 studies (extrapolation from studies in adults with cardiac arrest or neonates with birth asphyxia) that are also included in the evidence evaluation grid.

NOTE: search strategy was rerun on Dec 24, 2009. The Cochrane report has been updated but is not included in this worksheet because it excludes children. There is a new study describing hypothermia after pediatric arrest (Doherty et al) that has been added to the worksheet and the COS statement.
# Summary of evidence

## Evidence Supporting Clinical Question

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- **Good**
  - [Fink, 2005, 191-9] E (histology and behavior)
  - [Jia, 2006, 166-75] E (neurodeficit score)
  - [HACA, 2002, 549-56] D (extrapolation from study in adults)
  - [Bernard, 2002, 557-63] D (extrapolation from study in adults)
  - [Shankaran, 2005, 1574-84] (extrapolation from study in neonates)

- **Fair**
  - [Gluckman, 2005, 663-70] (extrapolation from study in neonates)

- **Poor**

### 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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<td>[Oddo, 2006, 1865-73]C,D (extrapolation from study in adults)</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*

## 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

*Italics = Animal studies*
In 2000 I completed a worksheet on induced hypothermia. At the time, there was a growing body of experimental animal data showing that it was safe, feasible, and improved outcome. However, human data was limited to small case series. During the evidence evaluation process, there was consensus that patients should not be actively warmed if they spontaneously developed mild hypothermia (and it was well-tolerated). There was also consensus that fever should be aggressively treated. However, opinion was divided on whether hypothermia ought to be induced. Approximately half of the invited experts were in favor of recommending induced hypothermia and the remainder thought the evidence was not yet persuasive enough and preferred to await the completion of ongoing clinical trials. Thus, permissive hypothermia and fever control received Class IIb and IIa recommendations, respectively, whereas induced hypothermia received an Indeterminate Class of Recommendation. Of note, the recommendations applied to all ages of victims and made no mention of the etiology of arrest.

Upon publication of the two clinical trials of adults in VF, a Taskforce convened to re-examine the data. The resulting ILCOR advisory statement unequivocally recommended induced hypothermia for adults remaining comatose after resuscitation from out-of-hospital VF [Nolan, 2003, 231-5, Nolan, 2003, 118-21]. For other clinical scenarios the Taskforce advised, “Such cooling may (italics mine) also be beneficial for other rhythms of in-hospital cardiac arrest.” The pediatric section of the Advisory Statement recognized that the clinical trials did not enroll either children or patients with respiratory-related causes of arrest (the most common cause of pediatric arrest). Also, there was a history of failed neuroprotection using treatment regimens that included hypothermia in studies from the 1980s on children with near drowning. Thus, there would likely be controversy amongst pediatric intensivists regarding the use of hypothermia.

In 2005 I completed another worksheet on induced hypothermia (W22A) and fever (W22B). Dr. Elise van der Jagt also completed a worksheet on this topic (W22C). Worksheets can be viewed at www.C2005.org by selecting View the Evidence Evaluation Worksheet Data Supplement (http://circ.ahajournals.org/content/vol112/22_suppl/#APPENDIX). At the time, there was one clinical trial in neonates using a cooling cap for treatment of neonatal hypoxic encephalopathy showing a benefit in a subset of neonates [Gluckman, 2005, 663-70]. An additional study in neonates using whole-body cooling demonstrating a favorable effect was published subsequent to the 2005 Consensus Conference [Shankaran, 2005, 1574-84] (see the neonatal worksheet for discussion). In the 2005 worksheet I included a discussion of numerous animal studies (neonatal, maturing and mature animals with a variety of hypoxic-ischemic injuries; VF, asphyxia, etc) and basic laboratory studies demonstrating mechanistic benefits (reduced caspase activity and apoptosis, etc). However, there were no published studies of induced hypothermia in pediatric patients suffering cardiac arrest (excepting the studies in the 1980s). Thus, the 2005 COSTR treatment recommendation stated, “Induction of hypothermia (32°C to 34°C) for 12 to 24 hours should be considered (italics mine) in children who remain comatose after resuscitation from cardiac arrest.”

The review for 2010 has found 3 new animal studies of induced hypothermia for treatment of asphyxial cardiac arrest: 2 in mature rats [Jia, 2006, 166-75, Katz, 2004, 806-10] and one in a juvenile rat [Fink, 2005, 191-9]; all demonstrating an improvement in neurologic outcome. There is one new study in adults that examined induced hypothermia for treatment of non-VF cardiac arrest [Oddo, 2006, 1865-73]. This study is a single institute study (Lausanne University Hospital, Switzerland) that examined 55 cooled patients vs 44 non-cooled historic controls. Benefit to cooling was found in the 43 patients with VF (vs non-cooled, historic controls with VF). In the few cooled patients with PEA or asystole there was total neurologic recovery in 2 of 12 compared with 0 of the 11 control patients with PEA or asystole. The difference was not statistically significant, but the numbers are obviously small. The authors conclude, “the outcome after cardiac arrest due to nonventricular fibrillation rhythms was poor and did not differ significantly between the two groups.”

So, what is new since 2005?
-There remains an absence of studies in pediatric patients
-There are a number of studies in adults resuscitated from VF remain convincing and unchallenged
-There is limited human data on adults cooled after resuscitation from non-VF cardiac arrest comparing outcome with historic controls. They generally do not show a difference with treatment but they are small and underpowered. In general, non-VF patients are sicker and have poorer outcome than VF patients.
-There is an additional clinical trial in neonates demonstrating a benefit to cooling
-There are additional mechanistic laboratory studies showing a benefit to cooling
-There are additional studies in rats with asphyxial cardiac arrest (the most common cause of cardiac arrest in children) showing a benefit to cooling

It could be argued that the beneficial effects of induced hypothermia seen in a range of ages (neonatal, maturing, and mature) across a variety of species (rat, dog, squirrel, pig, sheep, and humans) with a variety of injuries (stroke, VF cardiac arrest, asphyxial cardiac arrest, neonatal hypoxia ischemia) combined with the substantial mechanistic benefits documented in basic science research is
sufficient evidence to recommend induced hypothermia for children resuscitated from cardiac arrest. This argument is supported by
the absence of any biologically plausible reason for a difference in response in maturing children compared with neonates and
adults. Even so, definitive studies are lacking and this will remain a controversial subject amongst pediatricians.

Other articles of interest:
The Amsterdam World Congress on Drowning in 2002 recommended the use of controlled hypothermia in comatose near-drowning
patients [Bieren, 2002, 578-86].

Hypothermia after cardiac arrest in rats alters cytochrome P450-mediated drug metabolism [Tortorici, 2007, 2196-204].

A review on fever control and its impact on neurologic disorders [Aiyagari, 2007, 39-46].

A survey of pediatric intensivists about attitudes and practice related to induced hypothermia [Haque, 2006, 7-14].

Selected recent articles on mechanisms of hypothermia not referenced in my previous worksheets [Gisselsson, 2005, 1346-55,

NOTE: The search strategy was rerun on Dec 24, 2009 and the article by Doherty et al was uncovered [Doherty, 2009, 1492-500].
Doherty et al developed a multicenter registry (5 centers) from Canada to examine the practice of hypothermia for treatment
of cardiac arrest (patients were NOT randomized). The method of data collection was good (research assistants were trained to
collect data). The main limitation is that patients treated with hypothermia were much sicker (median duration of arrest was 30 min
vs 10 min; they were given more drugs, had higher lactate, etc) and the hypothermic patients were much younger (75% <12 mo vs
44%). Furthermore, ECMO was used in 22/29 (76%) of hypothermia patients—so, in some sense this study is largely a study of the
use of ECMO for cardiac arrest. Also, 2 of 5 centers did not cool any patients. The authors performed a logistic regression to adjust
for these differences but I personally am skeptical of the ability of logistic regression to "adjust" two such disparate groups. With
respect to categorizing the quality of the study for the evidence evaluation grid: the quality of the data collection and the statistical
analysis of the data was Good but the heterogeneity of the patient groups made the overall quality Fair.

Treatment Recommendation:
Induction of hypothermia (32°C to 34°C) should be considered in children who remain comatose after resuscitation from cardiac
arrest.

Acknowledgements:
Dr. Elise van der Jagt completed a C2005 worksheet. Worksheets for C2010 addressing adult cardiac arrest are being completed by
the ALS Task Force.

Citation List


LOE=5, Quality=Good. Outcomes=survival to hospital discharge with good neurologic outcome. Studied only
adults.


LOE 2. Quality Fair. Multicenter registry (5 centers) from Canada. Good methods for data collection (research assistants were trained to collect data). The main limitation is that patients treated with hypothermia were much sicker (median duration of arrest was 30 min vs 10 min; they were given more drugs, had higher lactate, etc) and the patients were much younger (75% <12 mo vs 44%). Furthermore, ECMO was used in 22/29 (76%) of hypothermia patients---so, in some sense this study is largely a study of the use of ECMO for cardiac arrest. Also, 2 of 5 centers did not cool any patients. The authors performed a logistic regression to adjust for these differences but I personally am skeptical of the ability of logistic regression to "adjust" two such disparate groups. With respect to categorizing the quality of the study for the evidence evaluation grid: the quality of the data collection and the statistical analysis of the data was Good but the heterogeneity of the patient groups made the overall quality Fair.


LOE=5, Quality=Good. Outcomes=Histology and Behavior. Induced hypothermia in rats following asphyxial arrest is beneficial.


LOE=5, Quality=Fair. Neonates with neonatal encephalopathy. Outcome=death or severe disability at 18 mo. Subgroup analysis showed benefit.


LOE=5, Quality=Good. Adult cardiac arrest. Outcome=favorable neurologic outcome.


Tangential information. Not placed in WS grid. Survey of beliefs and practices regarding hypothermia within the pediatric critical care community.


LOE=5, Quality=Fair, Outcomes=histology and neurodeficit score. Rodent study demonstrating beneficial effect of permissive hypothermia.


LOE=5, Quality=Good, Outcomes=quantitative EEG. Hypothermia is associated with faster recovery of EEG.


LOE=5, Quality=Good, Outcomes=histology and behavior. Neurotensin-induced hypothermia improved neurologic outcome after asphyxial cardiac arrest in rats.


Tangential information. ILCOR advisory statement. Not placed in evidence evaluation grid.


Tangential information. ILCOR advisory statement. Not placed in evidence evaluation grid.


LOE=5, Quality=poor. Outcomes: feasibility of hypothermia protocol and CPC. Limitations: chart review with historic controls and small sample size.

LOE=5, Quality=Good, Outcomes=neurodevelopmental outcome. This neonatal trial was able to show a benefit to whole body cooling in the treated group (vs. the selected head cooling trial where a benefit was shown for only a subgroup).


Tangential information not included in evidence evaluation grid. Review article on the effect of hypothermia upon drug action, metabolism, etc.


