The document contains a worksheet titled "WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care." The worksheet includes the following sections:

**Worksheet author(s)**
Jeffrey Perlman MB Ch B

**Date Submitted for review:** 10/4/09

**Clinical question.**
Your worksheet tracking number is NRP-031A

**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 topic

**Conflict of interest specific to this question**
No

**Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?** No

**Search strategy (including electronic databases searched).**
Since this was a modified revision and the prior search was through December 2004, this search was conducted from January 05 through September 09.

Key words used included: hyperthermia, pyrexia, fever, cerebral ischemia, hypoxia-ischemia, asphyxia, maternal fever, newborn.

**Ovid** “MeSH Terms” hyperthermia (5602 hits), brain injury (8130 hits) hyperthermia and brain injury (72 hits), maternal pyrexia (4 hits) hyperthermia + fever + newborn (9 hits (one retrieved)), hypoxia ischemia + fever + infant (81 hits), maternal fever + labor (45 hits (two retrieved)), maternal fever + treatment (15 hits (two retrieved)).

**Embase** Newborn + Hyperthermia + brain injury – (37 hits – one used), maternal fever + newborn (16 hits) maternal fever + newborn + brain injury (one hit), maternal fever + labor (41 hits (two retrieved)), maternal fever + treatment (15 hits (two retrieved)).

**Cochrane library – terms – hyperthermia, Maternal Fever, 0 hits**

**Review articles** 2

**End note library – fever, encephalopathy, hyperthermia - 23 hits**

Last searched September 09

**State inclusion and exclusion criteria**
- Neonatal studies.
- Review articles on hyperthermia were searched for additional references.
- In the previous review animal studies were reviewed to determine the impact of elevated temperature on the extent of brain injury.
- Two of these are again included in this review. For the updated review only new human studies are included. Non English abstracts where found were reviewed.
- Excluded Case reports were excluded. No animal studies since 2005

**Number of articles/sources meeting criteria for further review:**
Identified five articles that directly or indirectly address the specific question.
## Summary of evidence

### Evidence Supporting Clinical Question

In neonates born to febrile mothers does intervention to normalize temperature compared to standard care improve outcome

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<th>Grether 1997&lt;sup&gt;DE&lt;/sup&gt;</th>
<th>O’Shea 1998&lt;sup&gt;DE&lt;/sup&gt;</th>
<th>Impey, 2001</th>
<th>Blume, 2008&lt;sup&gt;E&lt;/sup&gt;</th>
<th>Shalak 2005&lt;sup&gt;E&lt;/sup&gt;</th>
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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

In neonates born to febrile mothers does intervention to normalize temperature compared to standard care improve outcome

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### Evidence Opposing Clinical Question

In neonates born to febrile mothers does intervention to normalize temperature compared to standard care improve outcome

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A = Return of spontaneous circulation  
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Italics = Animal studies
There appears to be a reasonably consistent epidemiological association between maternal fever and adverse neonatal or infancy outcomes, both in preterm and term infants (Adamson, 1995, Badawi 1998, Lieberman, 2000, Lieberman, 2000, O'Shea, 1998, Petrova, 2001, Perlman, 1999, Impey 2002, Shalak 2005). It is important to note that for many of the studies the working definition for fever was clinical chorioamnionitis. All the studies are retrospective precluding any conjecture as to mechanism of injury. Thus it is unclear whether this association is mediated via infection, the fetal inflammatory reaction or other events.

Fever during labor at term has been associated with

1) **Neonatal Depression** - Infants whose mothers' maximum temperature was >101 degrees F as compared to infants of afebrile women were more likely to require bag and mask resuscitation (11.5% vs 3.0%) (Lieberman, 2000) (LOE 4). The perinatal event most commonly associated with a 5-minute Apgar score ≤ 5 was maternal fever in 19 infants (32%). By stepwise linear regression analysis, a 5-minute Apgar ≤ 5 was related only to the initial infant temperature (p = 0.009, r = 0.33) (Perlman, 1999 LOE 5).

2) **Neonatal Seizures** - In a logistic regression analysis controlling for confounding factors, intrapartum fever was associated with a 3-4-fold increase in the risk of unexplained neonatal seizures (OR = 3.4, 95% CI = 1.03-9) (Lieberman, 2000 (LOE 4)). Intrapartum fever was also a risk factor for neonatal seizures in a retrospective cohort analysis amongst 11,246,042 singleton live births (Petrova, 2001 (LOE 4))

3) **Increased Mortality** - A retrospective cohort analysis among 11,246,042 singleton live births in the United States for the period 1995-1997 revealed intrapartum fever (at least 38°C) in 1.6% of cases. Intrapartum fever was associated with early neonatal mortality for both term 1.32(1.14,1.51) and preterm infants 1.32 (1.1,1.56)(adjusted OR, 95% CI) (Petrova, 2001 #102)(LOE 4).

4) **Association with Cerebral Palsy (CP)** - temperature > 38°C in labor was associated with increased risk of unexplained CP (OR, 9.3; 95% CI, 2.7-31.0) (Grether, 1997 (LOE 4), antepartum maternal temperature > 37.8°C was associated with CP (OR = 2.6 [1.1, 6.0]) in preterm infants (O'Shea, 1998 (LOE 4)

5) **Neonatal Encephalopathy** - There is a three reports linking fever to neonatal encephalopathy. (Impey, 2001 LOE 4 Blume 2008 LOE 4.)

The mechanism/s contributing to the brain injury with fever remain unclear limiting a specific therapeutic intervention. Experimental elimination of fever with an anti-inflammatory agent (Coimbra LOE 5 1996) or with anesthesia (Koroiwa LOE 5 1991) prevents the progressive of brain injury. However a major limitation to these studies is a short duration of follow up. In one study, a substantial protective effect was observed after a few days but this was greatly attenuated after two months recovery.

There are two clinical studies (Goetz 2004 LOE 1, Goetzl, 2006 LOE 1) that have attempted to examine the effect of an intervention to lower maternal temperature on outcome. In the first study, mothers who were randomized to high or low dose corticosteroids, the fetal exposure to hyperthermia was significantly reduced as was the extent of inflammation (IL-6) with the high dose. However, maternal high-dose corticosteroids increased the rate of neonatal asymptomatic bacteremia. In a second small randomized study the administration of acetaminophen as compared to placebo do not prevent maternal fever. Neither study was powered to address any of the morbidities mentioned previously. Importantly newborns with fever at birth normalize temperature without any intervention with an hour following delivery.

On balance the clinical data suggest that maternal fever during labor is associated with an increased risk of neonatal mortality and morbidity. However in one study Goetzl 195; 1031:2006 the use of corticosteroids to lower temperature was associated with increased occurrence of asymptomatic bacteremia in the neonates.

**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.

Red indicates new studies since last review

**Neonatal Studies**


Comment: Retrospective case control study. Maternal fever was one of several factors associated with neonatal encephalopathy

Level of Evidence 4
Quality of evidence - Fair
Evidence - Supportive


Comment: Case control retrospective study from same authors as above. Maternal fever was one of several risk factors associated with neonatal encephalopathy

Level of Evidence 4
Quality of evidence - Fair
Evidence - Supportive


Comment: Population based study that showed an independent risk of encephalopathy with isolated intrapartum fever

Level of Evidence 4
Quality of evidence - Fair
Evidence - Supportive


Comment: Retrospective case control study-maternal fever was associated with 9.3 fold increased risk for unexplained CP. Also maternal infection was associated with lower 5 minute Apgar score and neonatal seizures
Goetzl, Laura, Rivers, Jose, Evans, Tracy, Citron, Deborah R. Richardson, Barbara E.Lieberman, Ellice, Suresh, Maya S. Prophylactic Acetaminophen Does Not Prevent Epidural Fever in Nulliparous Women: A Double-Blind Placebo-Controlled Trial J Perinatol 24; 471-475 2004

Comment: Small randomized study that showed that acetaminophen did not prevent maternal fever – small study


Comment: Two phase study that showed that corticosteroid (high dose) reduced maternal fever and IL-6 levels but was associated with an increased rate of asymptomatic bacteremia. The effect on other adverse neonatal outcomes was not examined. Supportive as well as a negative study


Comment: Cohort study showing an independent association between neonatal encephalopathy and maternal fever


Comment: Case controlled retrospective study. Fever was associated with 4 fold-increased risk of unexplained seizures


Comment: Case control retrospective study in very low birthweight infants. Maternal fever OR = 2.6 was amongst other markers associated with CP at one year (mainly diplegia). Data does not distinguish fever from other putative markers of clinical infection.


Critique: Retrospective cohort national study of singletons born over two years. Intrapartum fever was associated with increased mortality and morbidity including seizures. Clearly not a cause and effect relationship

Comment  Case series. Maternal fever was associated with a low 5 minute Apgar score and the need for CPR
Level of Evidence  5
Quality of evidence-Fair
Evidence - Supportive


Comment  Cohort study that infants born to mothers with chorioamnionitis were an elevated rectal temperature at 30 minutes of life were more likely to be admitted to intensive care, were more likely to have birth depression. Temperature declined within 60 minutes spontaneously. Was not associated with neurologic morbidity but was not powered to address this question
Level of Evidence  4
Quality of evidence-Good
Evidence - Supportive

Pediatric


Critique  Worse outcome was noted during the hot season than during the cold seasons—the association with neurologic outcome was weak
Level of Evidence  5
Quality of evidence-Fair
Evidence - Supportive

Adult Studies


Level of Evidence  5
Quality of evidence-Fair
Evidence - Supportive


Level of Evidence  5
Quality of evidence-Fair
Evidence – Supportive


Level of Evidence  5
Quality of evidence-Fair
Evidence - Supportive


Level of Evidence  5
Quality of evidence-Fair
Evidence - Supportive


Comment  Meta analysis showing high probability values for both mortality and morbidity with fever following a stroke. Again no cause and effect
Level of Evidence  5
Quality of evidence-Good
Evidence - Supportive

Animal Studies


Comment  Global ischemic model showing the delayed adverse effect (24 hours) of hyperthermia in a rat model

Comment Data suggest that temperature elevation results in glutamate and/or glycine release from neurons that may represent one mechanism of injury.

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


Comment This study demonstrates the adverse effect of hyperthermia both during and following the hypoxic-ischemic insult

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


Comment The effect of post-ischemic hyperthermia was partly transient. Long lasting and clinically important protection required a combination of early and extended post-ischemic hypothermia in combination with antipyretic treatment. Speaks directly to the issue of fever and brain injury

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


Comment Hyperthermia worsened the extent of brain injury in a post-traumatic brain model.

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


Comment Gerbil model demonstrating no adverse effect of hyperthermia following brief global hypoxia-ischemia

Level of Evidence 5
Quality of evidence-Good
Evidence - Neutral


Comment Focal ischemic model demonstrating the delayed adverse effects of hyperthermia- a threshold of 40°C is suggested

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


Comment Another example of when hyperthermia is prevented, this time with anesthesia, that delayed neuronal death is prevented

Level of Evidence 5
Quality of evidence-Good
Evidence – Supportive

Comment Rat model demonstrating aggravated neocortical and hippocampal injury with hyperthermia during seizures, an effect that was ameliorated by hypothermia

Level of Evidence 5
Quality of evidence-Good
Evidence – Supportive

Comment Study demonstrating the worsening of brain injury including the incorporation of the penumbral areas into necrotic areas in a spontaneous hyperthermia model

Level of Evidence 5
Quality of evidence-Good
Evidence – Supportive

Comment Piglet model demonstrating the adverse effects of hyperthermia following deep hypothermia

Level of Evidence 5
Quality of evidence-Good
Evidence – Supportive

Comment Newborn model indicating that hyperthermia prior to hypoxia-ischemia protects the immature brain.

Level of Evidence 5
Quality of evidence-Good
Evidence – Opposing