

WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

Worksheet Author:	Taskforce/Subcommittee: __BLS __ACLS x PEDS __ID __PROAD __x_Other: NRP N
Author's Home Resuscitation Council: __x_AHA __ANZCOR __CLAR __ERC __HSFC __HSFC __RCSA __IAHF __Other:	Date Submitted to Subcommittee: 5/1/04

STEP 1: STATE THE PROPOSAL. State if this is a proposed new guideline; revision to current guideline; or deletion of current guideline.

Existing guideline, practice or training activity, or new guideline: Revision to current guideline

Existing guideline: Hyperthermia should be avoided because it is associated with perinatal respiratory depression (Class III (LOE))

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

Hyperthermia should be avoided because it is associated with perinatal respiratory depression, neonatal seizures increased mortality and cerebral palsy.

Step 1B: Gather the Evidence; define your search strategy. Describe search results; describe best sources for evidence.

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

Embase Hyperthermia + brain injury – 130 hits – 8 used, newborn + brain injury + hyperthermia – 10 hits – 1 used, fever + hypoxia-ischemia – 4 hits – 3 used, fever + newborn- 23 hits- 7 used

Medline Newborn+ brain injury_ hyperthermia – 10 hits- 2 used, Maternal fever + newborn- 23 hits – 4 used, Maternal fever + brain injury – 2 hits- both used

List electronic databases searched (at least AHA EndNote 7 Master library [<http://ecc.heart.org/>], Cochrane database for systematic reviews and Central Register of Controlled Trials [<http://www.cochrane.org/>], MEDLINE [<http://www.ncbi.nlm.nih.gov/PubMed/>], and Embase), and hand searches of journals, review articles, and books Medline(Pub Med), Embase, Cochrane Systemic reviews, ECC endnote library, review of references

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

Neonatal studies, Pediatric studies and adult stroke manuscripts were reviewed. Case reports were excluded. Animal studies including adult, pediatric and neonatal that evaluated the impact of elevated temperature at or following hypoxia-ischemia were reviewed. Review articles on hyperthermia were searched for additional references.

- Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Cummins-1"). If possible, please supply file of best references; EndNote 6+ required as reference manager using the ECC reference library.

There were 204 hits and 27 were included in the worksheet

STEP 2: ASSESS THE QUALITY OF EACH STUDY

Step 2A: Determine the Level of Evidence. For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)
Level 1	Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
Level 2	Randomized clinical trials with smaller or less significant treatment effects
Level 3	<u>Prospective</u> , controlled, non-randomized, cohort studies

Level 4	<u>Historic</u> , non-randomized, cohort or case-control studies Petrova (2001), Lieberman (2000), Lieberman (2000), Grether (1997), Adamson 1995, Badawi 1998, O Shea (1998)
Level 5	Case series: patients compiled in serial fashion, lacking a control group Perlman (1999)
Level 6	Animal studies or mechanical model studies Coimbra 1998, Dietrich 1996, Kim 1996, Baena 1997, Reglodi 2000, Chen 1991, Kuroiwa 1990, Shun, Tim 1998 Lundgren J 1996, Yager 1999, Kato H 1991
Level 7	Extrapolations from existing data collected for other purposes, theoretical analyses Sugita (1998), Fuguda 1999, Grau 1999, Castillo 1998, Azzimondi 1995, Hajat 2000
Level 8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and Rating	Excellent	Good	Fair	Poor	Unsatisfactory
Design & Methods	Highly appropriate sample or model, randomized, proper controls AND Outstanding accuracy, precision, and data collection in its class	Highly appropriate sample or model, randomized, proper controls OR Outstanding accuracy, precision, and data collection in its class	Adequate, design, but possibly biased OR Adequate under the circumstances	<i>Small or clearly biased population or model</i> OR <i>Weakly defensible in its class, limited data or measures</i>	<i>Anecdotal, no controls, off target end-points</i> OR <i>Not defensible in its class, insufficient data or measures</i>

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
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Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach
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Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction (ie, supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral* or *Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

Supporting Evidence

Hyperthermia should be avoided because it is associated with perinatal respiratory depression, neonatal seizures, increased mortality and cerebral palsy.

Quality of Evidence	Excellent						Coimbra 1996		
	Good				Petrova ^{B,E} 2001 Lieberman ^E 2000 Lieberman ^E 2000 Grether ^{DE} 1997 O'Shea ^{DE} 1998		Dietrich 1996 Kim 1996 Baena 1997 Reglodi 2000 Chen 1991 Kuroiwa 1990 Shum-Tim 1998 Lumgren 1994	Hajat 2000 ^D	
	Fair				Adamson ^E 1995 Badawi ^E 1998	Perlman ^E 1999		Fuguda ^D 1999 Grau 1999 ^D Castillo ^D 1998 Azzimondi ^D 1995 ^D Sugita	

STEP 3. DETERMINE THE CLASS OF RECOMMENDATION. Select from these summary definitions.

CLASS	CLINICAL DEFINITION	REQUIRED LEVEL OF EVIDENCE
<p>Class I <i>Definitely recommended.</i> Definitive, excellent evidence provides support.</p>	<ul style="list-style-type: none"> • Always acceptable, safe • Definitely useful • Proven in both efficacy & effectiveness • Must be used in the intended manner for proper clinical indications. 	<ul style="list-style-type: none"> • One or more Level 1 studies are present (with rare exceptions) • Study results consistently positive and compelling
<p>Class II: <i>Acceptable and useful</i></p>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Not yet confirmed definitively 	<ul style="list-style-type: none"> • Most evidence is positive • Level 1 studies are absent, or inconsistent, or lack power • No evidence of harm
<ul style="list-style-type: none"> • <i>Class IIa:</i> <i>Acceptable and useful</i> <p>Good evidence provides support</p>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered treatments of choice 	<ul style="list-style-type: none"> • Generally higher levels of evidence • Results are consistently positive
<ul style="list-style-type: none"> • <i>Class IIb:</i> <i>Acceptable and useful</i> <p>Fair evidence provides support</p>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered optional or alternative treatments 	<ul style="list-style-type: none"> • Generally lower or intermediate levels of evidence • Generally, but not consistently, positive results

<p>Class III: <i>Not acceptable, not useful, may be harmful</i></p>	<ul style="list-style-type: none">• Unacceptable• Not useful clinically• May be harmful.	<ul style="list-style-type: none">• No positive high level data• Some studies suggest or confirm harm.
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Indeterminate	<ul style="list-style-type: none"> • Research just getting started. • Continuing area of research • No recommendations until further research 	<ul style="list-style-type: none"> • Minimal evidence is available • Higher studies in progress • Results inconsistent, contradictory • Results not compelling
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STEP 3: DETERMINE THE CLASS OF RECOMMENDATION. State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class I, Class IIA, IIB, etc.; or **b) the condition**, and then whether the intervention is Class I, Class IIA, IIB, etc.

Indicate if this is a **Condition** or **Intervention**

Final Class of recommendation: **Class I-Definitely Recommended** **Class IIA-Acceptable & Useful; good evidence** **Class IIB-Acceptable & Useful; fair evidence** **Class III – Not Useful; may be harmful** **Indeterminate-minimal evidence or inconsistent**

Class II B- Acceptable and useful

REVIEWER’S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST: Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

Neonatologist with 25 years of postgraduate experience. My research training focused on cerebral blood flow and metabolism. I have served on the Neonatal Resuscitation Program (NRP) for six years and on the pediatric subcommittee of the AHA for four years. I have a potential conflict of interest in that I have written a manuscript on this subject that is part of the worksheet (LOE 5, evidence fair)

REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. “Mismatches” refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment.

The evidence supporting the association of fever either during or following ischemia and worse neurologic outcome has been observed in experimental models, in adult studies and in newborns. Supporting evidence for this association is summarized below

Experimental Evidence

There is an increasing body of experimental evidence indicating a worsening of cerebral injury during or following ischemia under conditions of elevations in temperature (Coimbra 1996, Dietrich 1996). This has been duplicated in different animal species (e.g., rat (Baena 1997, Chen 1991 Kim 1997, Reglodi 2000), gerbil (Kato 1991, Kuroiwa 1991) and piglet (Shum-Tim, Yager)). Worsening of brain injury has been observed with hyperthermia following induced seizures (Lundgren 1997), and in animals made febrile following deep hypothermic cardiac arrest in an infant swine model (Shum-Tim). Elimination of fever with an anti-inflammatory agent (Coimbra 1996) or with anesthesia (Kuroiwa 1991) prevents the progressive of brain injury. However a major limitation to almost all 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. One potential mechanism of injury is via excitotoxic neurotransmitter release (Castillo 1999). Transient pre-insult hyperthermia can be protective, consistent with other studies of pre-conditioning. However it is not clear that this is clinically relevant. There are two studies that fail to demonstrate an adverse neurologic effect of fever (Kato 1991, Yager 1999).

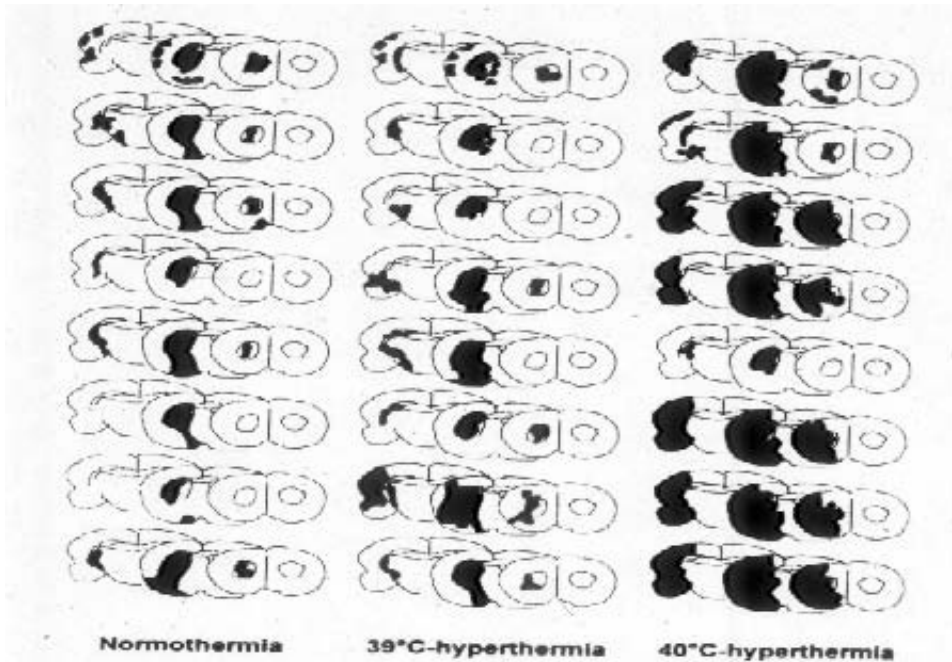


Figure- Note the increasing extent of brain injury during hypoxia-ischemia as a function of increasing temperature (From Kim et al)

Neonatal Evidence

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). It is important to note that for many of the studies that 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

- a) 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)

- b) 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

- a) 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)}

- b) 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^o 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 (1.11,1.56)(adjusted OR, 95% CI){Petrova, 2001 #102}(LOE 4).

4) Temperature > 38^o C in labor was associated with increased risk of unexplained cerebral palsy (CP) (OR, 9.3; 95% CI, 2.7-31.0) {Grether, 1997 (LOE 4), antepartum maternal temperature > 37.8^o 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 limited evidence linking fever to neonatal encephalopathy. This need further study.

Adult evidence

There is now highly consistent evidence, supported by a recent meta-analysis (Hajat 2000), that early onset fever following adult stroke (within the first 24 hours) is associated with a marked increase in neurological morbidity and mortality (Azzimondi, 1995, Castillo, 1998, Fukuda, 1999, Grau, 1999). Although plausible, there is no direct evidence currently, that this association is causal. An alternative hypothesis is that larger strokes cause fever. There are limited data examining pediatric cardiac arrest and fever. Of particular interest is a preliminary Japanese study that suggests an association between cardiac arrest at hot times of the year and adverse outcome (Sugita, 1998).

Summary

On balance these experimental data strongly suggest that hyperthermia of 2 to 3 degrees above normal during or following a cerebral insult can significantly worsen neurologic outcome, and that preventing hyperthermia is not deleterious. Moreover, there are some data to suggest that part of the adverse neurological impact of hyperthermia may represent a transient acceleration of damage. However there are no human intervention data to establish that the above clinical associations are causative. In view of these limitations, the current class IIb recommendation to avoid hyperthermia is appropriate.

Preliminary draft/outline/bullet points of Guidelines revision: Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Attachments:

Bibliography in electronic form using the Endnote Master Library. It is recommended that the bibliography be provided in annotated format. This will include the article abstract (if available) and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study.

Citation List

Citation Marker	Full Citation*
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{Adamson, 1995 #67}	Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal encephalopathy in full-term infants. <i>Bmj</i> . 1995;311:598-602.
{Badawi, 1998 #66}	Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. <i>Bmj</i> . 1998;317:1554-8.
{Grether, 1997 #65}	Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. <i>Jama</i> . 1997;278:207-11.
{Lieberman, 2000 #62}	Lieberman E, Eichenwald E, Mathur G, Richardson D, Heffner L, Cohen A. Intrapartum fever and unexplained seizures in term infants. <i>Pediatrics</i> . 2000;106:983-8.
{Lieberman, 2000 #63}	Lieberman E, Lang J, Richardson DK, Frigoletto FD, Heffner LJ, Cohen A. Intrapartum maternal fever neonatal outcome. <i>Pediatrics</i> . 2000;105 :8-13.
{O'Shea, 1998 #69}	O'Shea TM, Klinepeter KL, Meis PJ, Dillard RG. Intrauterine infection and the risk of cerebral palsy in very low-birthweight infants. <i>Paediatr Perinat Epidemiol</i> . 1998;12:72-83
Petrova, 2001 #102}	Petrova A, Demissie K, Rhoads GG, Smulian JC, Marcella S, Ananth CV. Association of maternal fever during labor with neonatal and infant morbidity and mortality. <i>Obstet Gynecol</i> . 2001;98:20-7
{Perlman, 1999 #60}	Perlman JM. Maternal fever and neonatal depression: preliminary observations. <i>Clin Pediatr (Phila)</i> . 1999;38:287-91.
{Sugita, 1998 #111}	Sugita M, Okamoto K, Terasaki H. Effect of the season on the neurological outcome in children with cardiac arrest. <i>Acta Paediatr Jpn</i> . 1998;40:20-5.
{Azzimondi, 1995 #109}	Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L, Re G, D'Alessandro R. Fever in acute stroke worsens prognosis. A prospective study. <i>Stroke</i> . 1995;26:2040-3.
{Castillo, 1998 #108}	Castillo J, Davalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. <i>Stroke</i> . 1998;29:2455-60.
{Fukuda, 1999 #106}	Fukuda H, Kitani M, Takahashi K. Body temperature correlates with functional outcome and the lesion size of cerebral infarction. <i>Acta Neurol Scand</i> . 1999;100:385-90.
{Grau, 1999 #107}	Grau AJ, Buggle F, Schnitzler P, Spiel M, Lichy C, Hacke W. Fever and infection early after ischemic stroke. <i>J Neurol Sci</i> . 1999;171:115-20.
{Hajat, 2000 #110}	Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome : a meta-analysis of studies in patients. <i>Stroke</i> . 2000;31:410-4.
{Baena, 1997 #72}	Baena RC, Busto R, Dietrich WD, Globus MY, Ginsberg MD. Hyperthermia delayed by 24 hours aggravates neuronal damage in rat hippocampus following global ischemia. <i>Neurology</i> . 1997;48:768-73.
	Castillo J, Davalos A, Noya M. Aggravation of acute ischemic stroke by hyperthermia is related to an excitotoxic mechanism. <i>Cerebrovasc Dis</i> . 1999;9:22-7.
	Chen H, Chopp M, Welch KM. Effect of mild hyperthermia on the ischemic infarct volume after middle cerebral artery occlusion in the rat. <i>Neurology</i> . 1991;41:1133-5.
	Coimbra C, Drake M, Boris-Moller F, Wieloch T. Long-lasting neuroprotective effect of postischemic hypothermia and treatment with an anti-inflammatory/antipyretic drug. Evidence for chronic encephalopathic processes following ischemia. <i>Stroke</i> . 1996;27:1578-85.
	Dietrich WD, Alonso O, Halley M, Busto R. Delayed posttraumatic brain hyperthermia

<p>{Castillo, 1999 #117}</p>	<p>worsens outcome after fluid percussion brain injury: a light and electron microscopic study in rats. <i>Neurosurgery</i>. 1996;38:533-41.</p>
<p>{Chen, 1991 #112}</p>	<p>Kato H, Araki T, Kogure K. Postischemic spontaneous hyperthermia is not a major aggravating factor for neuronal damage following repeated brief cerebral ischemia in the gerbil. <i>Neurosci Lett</i>. 1991;126:21-4.</p>
<p>{Coimbra, 1996 #71}</p>	<p>Kim Y, Busto R, Dietrich WD, Kraydieh S, Ginsberg MD. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. <i>Stroke</i>. 1996;27:2274-80.</p>
<p>{Dietrich, 1996 #73}</p>	<p>Kuroiwa T, Bonnekoh P, Hossmann KA. Prevention of postischemic hyperthermia prevents ischemic injury of CA1 neurons in gerbils. <i>J Cereb Blood Flow Metab</i>. 1990;10:550-6.</p>
<p>{Kato, 1991 #76}</p>	<p>Lundgren J, Smith ML, Blennow G, Siesjo BK. Hyperthermia aggravates and hypothermia ameliorates epileptic brain damage. <i>Exp Brain Res</i>. 1994;99:43-55.</p>
<p>Kim, 1996 #74}</p>	<p>Reglodi D, Somogyvari-Vigh A, Maderdrut JL, Vigh S, Arimura A. Postischemic spontaneous hyperthermia and its effects in middle cerebral artery occlusion in the rat. <i>Exp Neurol</i>. 2000;163:399-407.</p>
<p>{Kuroiwa, 1990 #113}</p>	<p>Shum-Tim D, Nagashima M, Shinoka T, Bucarius J, Nollert G, Lidov HG, du Plessis A, Laussen PC, Jonas RA. Postischemic hyperthermia exacerbates neurologic injury after deep hypothermic circulatory arrest. <i>J Thorac Cardiovasc Surg</i>. 1998;116:780-92.</p>
<p>{Lundgren, 1994 #115}</p>	<p>Yager JY, Asselin J. The effect of pre hypoxic-ischemic (HI) hypo and hyperthermia on brain damage in the immature rat. <i>Brain Res Dev Brain Res</i>. 1999;117:139-43.</p>
<p>{Reglodi, 2000 #75}</p>	
<p>{Shum-Tim, 1998 #114}</p>	
<p>{Yager, 1999 #116}</p>	

*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.

Neonatal Studies

Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal encephalopathy in full-term infants. *BMJ*. 1995;311:598-602. (LOE 4)

OBJECTIVE--Preliminary investigation of the contribution of adverse antepartum and intrapartum factors to neonatal encephalopathy in singleton neonates born full term. **DESIGN**--Matched case-control study based on incidence density sampling of controls. **SETTING**--Two major teaching hospitals (one paediatric and one obstetric) and three peripheral maternity hospitals in Perth, Western Australia (population 1.2 million). **SUBJECTS**--89 cases, all the full term singleton neonates born during an eight month period in 1992 who fulfilled one or more of six criteria during the first week of life (seizures, abnormal conscious state, persistent hypertonia or hypotonia, and feeding or respiratory difficulties of central origin). One full term control infant without neonatal encephalopathy was matched to each case by sex, hospital of delivery, time of day and day of the week of birth, and maternal health insurance status. **MAIN OUTCOME MEASURES**--Odds ratio estimates of relative risk of neonatal encephalopathy associated with antepartum and intrapartum factors. **RESULTS**--Estimated incidence of moderate or severe encephalopathy in first week of life was 3.75 per 1000 full term live births. Thirteen cases and no controls had evidence suggestive of important intrapartum hypoxia, and in only five of these cases was the neurological condition at birth attributed to events during the intrapartum period. **Univariate conditional logistic regression** analysis identified significant differences between cases and controls for maternal vaginal bleeding in pregnancy, maternal thyroxine treatment, congenital abnormalities, induction of labour, interval from membrane rupture to delivery, **maternal pyrexia in labour**, augmentation of labour, abnormal intrapartum cardiotocograms, and meconium in labour. Family history of convulsions also approached significance. **CONCLUSIONS**--Our preliminary results suggest that intrapartum hypoxia, according to currently used criteria, was not the cause of neonatal encephalopathy in most cases in this population. Our findings suggest that many aetiologies of neonatal encephalopathy originate in the antepartum period.

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

Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998;317:1554-8.

OBJECTIVE: To identify intrapartum predictors of newborn encephalopathy in term infants. **DESIGN:** Population based, unmatched case-control study. **SETTING:** Metropolitan area of Western Australia, June 1993 to September 1995. **Subjects:** All 164 term infants with moderate or severe newborn encephalopathy; 400 randomly selected controls. **MAIN OUTCOME MEASURES:** Adjusted odds ratio estimates. **RESULTS:** The birth prevalence of moderate or severe newborn encephalopathy was 3.8/1000 term live births. The neonatal fatality was 9.1%. **Maternal pyrexia (odds ratio 3.82)**, a persistent occipitoposterior position (4.29), and an acute intrapartum event (4.44) were all **risk factors for newborn encephalopathy**. More case infants than control infants were induced (41.5% and 30.5%, respectively) and fewer case infants were delivered by caesarean section without labour (3.7% and 14.5%, respectively). Operative vaginal delivery (2.34) and emergency caesarean section (2.17) were both associated with an increased risk. There was an inverse relation between elective caesarean section (0.17) and newborn encephalopathy. After

application of a set of consensus criteria for elective caesarean section only three (7%) eligible case mothers compared with 33 (65%) eligible control mothers were sectioned electively. Of all the case infants, 113 (69%) had only antepartum risk factors for newborn encephalopathy identified; 39 (24%) had antepartum and intrapartum factors; eight (5%) had only intrapartum factors; and four (2%) had no recognised antepartum or intrapartum factors. **Conclusions:** The causes of newborn encephalopathy are heterogeneous and many relate to the antepartum period. Elective caesarean section has an inverse association with newborn encephalopathy. Intrapartum hypoxia alone accounts for only a small proportion of newborn encephalopathy. These results question the view that most risk factors for newborn encephalopathy lie in the intrapartum period.

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

Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. *JAMA* 1997;278:207-11

CONTEXT: Exposure to maternal or placental infection is related to risk of preterm birth and, in premature infants, of brain lesions predictive of cerebral palsy (CP). Few studies have investigated whether maternal infection is associated with risk of CP in children of normal birth weight **Objective:** To investigate maternal infection during the admission for delivery as a possible risk factor for CP in infants born weighing 2500 g or more. **DESIGN:** Population-based case-control study. **SETTING:** All hospitals in 4 northern California counties, 1983 through 1985. **PARTICIPANTS:** A total of 46 children with disabling spastic CP who had no recognized prenatal brain lesions and 378 randomly selected control children weighing 2500 g or more at birth and surviving to age 3 years. **MAIN OUTCOME MEASURES:** Disabling spastic CP and signs of neonatal morbidity. **Results: Maternal fever exceeding 38 degrees C in labor was associated with increased risk of unexplained CP (odds ratio [OR], 9.3; 95% confidence interval [CI], 2.7-31.0),** as was a clinical diagnosis of chorioamnionitis. One or more indicators of maternal infection were present in 2.9% of control children, 22% of children with CP (OR, 9.3; 95% CI, 3.7-23.0), and 37% of those with the spastic quadriplegic subtype of CP (OR, 19.0; 95% CI, 6.5-56.0). Newborns exposed to maternal infection, both cases and controls, had 5-minute Apgar scores below 6 more often than those unexposed. Among children with CP, those born to infected women were more often hypotensive, needed intubation, had neonatal seizures, and received a clinical diagnosis of hypoxic-ischemic encephalopathy **Conclusion:** Intrauterine exposure to maternal infection was associated with a marked increase in risk of CP in infants of normal birth weight. Maternal infection was also linked with low Apgar scores, other evidence of hypotension [corrected] and need for resuscitation, and neonatal seizures-signs commonly attributed to birth asphyxia.

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

Level of Evidence 4

Quality of evidence-Good

Evidence - Supportive

Lieberman E, Eichenwald E, Mathur G, Richardson D, Heffner L, Cohen A. Intrapartum fever and unexplained seizures in term infants. *Pediatrics*. 2000;106:983-8.

OBJECTIVE: Early-onset neonatal seizures are a strong predictor of later morbidity and mortality in term infants. Although an association of noninfectious intrapartum fever with neonatal seizures in term infants has been reported, it was based on only a small number of neonates with seizures. We therefore conducted

a case control study to investigate this association further. **METHODS:** All term infants with neonatal seizures born at Brigham and Women's Hospital between 1989 and 1996 were identified. For this study, cases consisted of all term neonates with a confirmed diagnosis of seizure born after a trial of labor for whom no proximal cause of seizure could be identified. Infants with sepsis or meningitis were excluded. Four controls matched by parity and date of birth were identified for each case. The rate of intrapartum maternal temperature >100.4 degrees F was compared for case infants and controls. Potential confounding was controlled in logistic regression analysis **Results:** Cases comprised 38 term infants with unexplained seizures after a trial of labor and 152 controls were identified. Infants with seizures were more likely to be born to mothers who were **febrile** during labor (31.6% vs 9.2%). In almost all cases, the fever developed during labor (94.7% cases, 97.4% controls). At admission, mothers of infants with seizures were not significantly more likely to have factors associated with concern about infection such as a white blood cell count >15 000/mm³ (28.9% vs 19.1%) and premature rupture of the membranes (15.8% vs 17.8%). 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 (odds ratio = 3.4, 95% confidence interval = 1.03-10.9).** **Conclusion** The data indicate that intrapartum fever, even when unlikely to be caused by infection, is associated with a fourfold increase in the risk of unexplained, early-onset seizures in term infants

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

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

Lieberman E, Lang J, Richardson DK, Frigoletto FD, Heffner LJ, Cohen A. Intrapartum maternal fever and neonatal outcome. *Pediatrics*. 2000;105:8-13.

OBJECTIVE: Much of fever during term labor may not be infectious but rather a consequence of the use of epidural analgesia. Thus the association of elevated maternal intrapartum temperature with neonatal outcome when the infant does not develop an infection was evaluated. **METHODS:** 1218 nulliparous women with singleton, term pregnancies in a vertex presentation and spontaneous labor were studied. Women were excluded if their temperature was >99.5 degrees F at admission for delivery, if they were diabetic or had an active genital herpes infection or if their infant developed a neonatal infection, had a congenital infection, or had a major malformation. Maximum intrapartum temperature was categorized as: <=100.4 degrees F (afebrile), 100.5 degrees F to 101 degrees F, and >101 degrees F. **RESULTS:** During labor, 123 women (10.1%) developed a fever >100.4 degrees F; 62 (5.1%) women had a maximum temperature of 100.5 degrees F to 101 degrees F and 61 (5.0%) women had a maximum temperature >101 degrees F. Of febrile women, 97.6% had received epidural analgesia for pain relief. Infants of women developing a fever >100.4 degrees F were more likely to have a 1-minute Apgar score <7 (22.8% for >100.4 degrees F vs 8.0% for afebrile) and to be hypotonic after delivery (4.8% for >100.4 degrees F vs.5% for afebrile). Compared with infants of afebrile women, infants whose mothers' maximum temperature was >101 degrees F were more likely to require bag and mask resuscitation (11.5% vs 3.0%) and to be given oxygen therapy in the nursery (8.2% vs 1.3%). A higher rate of neonatal seizure with fever (3.3% vs.2%), but the number of infants with seizure was small (n = 4). All associations remained essentially the same after controlling for confounding in logistic regression analyses. **CONCLUSIONS:** Intrapartum maternal fever, particularly if >101 degrees F, was associated with a number of apparently transient adverse effects in the newborn. Larger studies are needed to investigate the association of intrapartum fever with neonatal seizures and to determine whether any lasting injury to the fetus may occur

Critique Retrospective cohort study evaluating the impact of varying maternal fever on early neonatal outcomes. Fever was associated with a one minute Apgar < 7 and a greater likelihood that an infant will require BMV in the DR. An increase in seizures was noted although numbers were small. No long term outcome data.

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

O'Shea TM, Klinepeter KL, Meis PJ, Dillard RG. Intrauterine infection and the risk of cerebral palsy in very low-birthweight infants. *Paediatr Perinat Epidemiol.* 1998;12:72-83

Very low-birthweight infants constitute more than one-quarter of all new cases of cerebral palsy. A **case-control study** of associations between antenatal maternal infection and cerebral palsy in **very low-birthweight infants** was performed. Cases and controls were selected from a cohort of 1238 consecutive infants who: (1) had birthweights between 500 and 1500 g and no major congenital anomaly; (2) were born 1 January 1986 to 31 December 1993 to a mother residing in 1 of 17 counties in north-west North Carolina; and (3) were delivered at the only tertiary obstetric referral centre in those same 17 counties. A total of 984 of these infants (79%) survived to 1 year of age (adjusted for degree of prematurity) and were scheduled for a multidisciplinary examination; 815 (83%) came as scheduled. Excluding two cases attributable to post-neonatal events, 62 cases of cerebral palsy were identified. Controls were the two infants, without cerebral palsy, born closest in time to each case. Medical records were reviewed by a nurse who was not aware of which subjects were cases. **Among possible markers of intra-amniotic infection, those associated most strongly with cerebral palsy were chorioamnionitis** diagnosed by an obstetrician (odds ratio [OR] adjusted for gestational age [95% confidence limits] = 2.6 [1.0, 6.5]), **antepartum maternal temperature > 37.8 degrees C (OR = 2.6 [1.1, 6.0])**, uterine tenderness (OR = 2.6 [0.8, 9.3]), maternal receipt of antibiotics (OR = 2.2 [1.0, 4.7]) and neonatal sepsis in the first week of life (OR = 2.9 [0.9, 8.9]). All of these associations were stronger for diplegia than the other clinical subtypes of cerebral palsy. The association with chorioamnionitis and spastic diplegia persisted when adjusted for maternal magnesium sulphate receipt, maternal betamethasone receipt, method of delivery (vaginal vs. abdominal), acidosis on the neonate's initial arterial blood gas, systolic blood pressure < 30 mmHg and the diagnosis of major neonatal neurosonographic abnormality

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.

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

Petrova A, Demissie K, Rhoads GG, Smulian JC, Marcella S, Ananth CV. Association of maternal fever during labor with neonatal and infant morbidity and mortality. *Obstet Gynecol.* 2001;98:20-7

Objective To examine the association of intrapartum fever with infant morbidity and early neonatal (0-6 days) and infant (0-364 days) death. **Methods** A retrospective cohort analysis among singleton live births in the United States for the period 1995-1997 using the National Center for Health Statistics linked birth-infant death cohort data was carried out. **Results:** Among the 11,246,042 singleton live births during the study period, intrapartum **fever (at least 38C) was recorded in 1.6%**. Intrapartum fever was associated with early neonatal (adjusted odds ratio [OR], 95% confidence interval [CI] for preterm and term infants respectively: 1.32; 1.11, 1.56 and 1.67; 1.14, 2.46) and infant (OR, 95% CI for preterm and term, respectively: 1.31; 1.14, 1.51 and 1.27; 1.01, 1.59) death among nulliparous mothers. Among preterm infants of parous mothers, intrapartum fever was associated with early neonatal (OR 1.29, 95% CI 1.01, 1.64) death. In the combined analyses (infants of nulliparous and parous mothers), intrapartum fever was a strong predictor of infection-related death. These associations were stronger among term (OR 3.16, 95% CI 1.56, 6.40 for early neonatal; OR 1.75, 95% CI 1.20, 2.57 for infant death) than preterm infants (OR 1.52, 95% CI 1.15, 2.00 for early neonatal; OR 1.29, 95% CI 1.05, 1.57 for infant death). Intrapartum fever was also a risk factor for meconium aspiration syndrome, hyaline membrane disease, neonatal seizures, and

assisted ventilation. **CONCLUSION:** Intrapartum fever is an important predictor of neonatal morbidity and infection-related mortality.

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

Level of Evidence 4

Quality of evidence-Good

Evidence - Supportive

Perlman JM. Maternal fever and neonatal depression: preliminary observations. *Clin Pediatr (Phila)*. 1999;38:287-91

The objectives of this study were to determine in term infants: (1) the importance of maternal fever (maternal temperature > 38 degrees C) as a risk factor for neonatal depression and (2) the clinical course of infants admitted to the Neonatal Intensive Care Unit (NICU) born to mothers with fever. For 2 years, 59 (0.24%) of 25,000 term infants had a 5-minute Apgar score < or = 5 and 22 (0.08%) infants were administered chest compressions with or without epinephrine as part of cardiopulmonary resuscitation (CPR) in the delivery room. The perinatal event most commonly associated with a 5-minute Apgar score < or = 5 was maternal fever in 19 infants (32%), with meconium + fetal heart rate (FTHR) abnormalities in 15 (25%), and FTHR abnormalities only in 13 (22%), additional associations (n = 13). By stepwise linear regression analysis, a 5-minute Apgar < or = 5 was related only to the initial infant temperature (p = 0.009, r = 0.33). Maternal fever noted in six infants (27%) was also commonly associated with CPR, as was the presence of meconium + FTHR abnormalities in seven (32%), and FTHR abnormalities only in four (18%). One hundred thirteen (7.5%) of the approximately 1,500 term infants born to mothers with maternal fever were admitted to the NICU. In addition to fever, the labor was complicated by meconium (in 16 infants), meconium + FTHR abnormalities (in 19 infants), and FTHR abnormalities only (in 11 infants). Resuscitative interventions in the delivery room included oxygen only in 43 infants, bag and mask ventilation in 38, continuous positive airway pressure in 10, intubation in 16, and CPR in six infants. Forty-nine infants (43%) had an initial temperature > 38 degrees C including 13 (11%) with an initial temperature > 39 degrees C. Twelve (10%) infants remained intubated on admission and five required ventilator support > 24 hours. One blood culture was positive although all mothers were pretreated with antibiotics. One infant developed hypoxic ischemic encephalopathy including seizures. Maternal fever is the perinatal event most frequently associated with a 5-minute Apgar score < or = 5 and a common association with the need for CPR. Clinicians attending the delivery of a mother with fever should anticipate the potential for neonatal depression; such awareness should facilitate appropriate preparation before delivery and potentially reduce the need for more intensive resuscitation

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

Pediatric

Sugita M, Okamoto K, Terasaki H. Effect of the season on the neurological outcome in children with cardiac arrest. *Acta Paediatr Jpn*. 1998;40:20-5.

Twenty children who were successfully resuscitated after cardiac arrest (CA) were retrospectively studied to examine the hypothesis that children with CA may have a worse neurological outcome in hot weather than in cold weather. Of 7 children with CA in the cold season (atmospheric temperature < 14 degrees C), 4

in the warm season (14-24 degrees C) and 9 in the hot season (> 24 degrees C), 5 (71%), 2 (50%), and 1 (11%), respectively, recovered consciousness (P < 0.05). Postresuscitative hyperthermia tended to be frequently observed in the group of children who suffered CA in the hot season, and it appeared to be associated with neurological damage. This preliminary study suggests that the neurological outcome of children with CA changes with the seasons, with a worse neurological outcome for CA in hot weather than in cold weather. A prospective study is required to determine whether, in a hot season or area, cooling of pediatric cardiac arrest victims during cardiopulmonary resuscitation on the scene improves the neurological outcome.

Critique- Worse outcome was noted during the hot season than during the cold seasons –the association with neurologic outcome was weak

Level of Evidence 7

Quality of evidence-Fair

Evidence - Supportive

Adult Studies

Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L, Re G, D'Alessandro R. Fever in acute stroke worsens prognosis. A prospective study. Stroke. 1995;26:2040-3.

BACKGROUND AND PURPOSE: No definitive data are yet available on the effects of body temperature on neurological damage after cerebral ischemia in humans. Experimental animal models have provided much evidence, but to our knowledge, only two studies on the relationship between fever and prognosis of stroke in humans have been published. The aim of our study was to investigate the prognostic role of fever in the first 7 days of hospitalization in a cohort of patients admitted to our hospital for acute stroke. **METHODS:** We analyzed the data of 183 patients included in a prospective observational prognostic study. Vital status at 30 days was considered the main outcome and was obtained for all patients. Age, level of consciousness, and glycemia at the time of hospitalization were considered covariates for an exact logistic regression analysis. The maximum temperature recorded during the first 7 days dichotomized as "no or low fever" versus "high fever" was added to the model. Death within 10 days, taken as a secondary outcome suggestive of death from neurological causes, was analyzed with exact permutation tests. **RESULTS:** Of the 183 patients analyzed in this study, 43% had fever during the first 7 days after hospitalization. The mean value of the maximum temperature recorded during the first 7 days in the 78 febrile patients was 38.3 degrees C, and the median was 37.9 degrees C. Onset of fever occurred in only 15% of febrile patients during the first day and in 49% on the second. The prognostic roles of age, level of consciousness, and glycemia were confirmed by exact logistic regression. Degree of consciousness impairment was the strongest prognostic variable, with an odds ratio (OR) of 11.4 (95% confidence interval [CI], 4.4 to 31.6). High fever (maximum temperature recorded during the first 7 days > or = 37.9 degrees C) was an independent factor for a worse prognosis, with an OR of 3.4 (95% CI, 1.2 to 9.5). The OR of dying within 10 days versus dying between 11 and 30 days was 4.9 (95% CI, 1.2 to 25.2) in patients with high fever with respect to all other patients. **CONCLUSIONS: Fever in the first 7 days was an independent predictor of poor outcome during the first month after a stroke. No data were available on the underlying causes of fever, but the higher risk of death in the first 10 days, most frequently attributed to neurological mechanisms, suggested that high temperature was an independent component of poor prognosis and not only an epiphenomenon of other complications in the course after a stroke. In agreement with animal studies, we found that patients with higher temperature had a worse stroke outcome**

Level of Evidence 7

Quality of evidence-Fair

Evidence - Supportive

Castillo J, Davalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. Stroke. 1998;29:2455-60.

BACKGROUND and PURPOSE: The association between hyperthermia and early neurological deterioration, increased morbidity, and mortality in acute ischemic stroke is well known. However, the timing at which the cerebral lesion may be aggravated by high temperature has not been firmly established. The aim of this study was to determine the prognostic value of body temperature measured at different times after onset of stroke. **METHODS:** Axillary temperature was recorded every 2 hours for 72 hours in 260 patients with a hemispheric cerebral infarction of <24 hours' duration. A potential infectious focus was examined in all patients with hyperthermia (temperature >37.5 degreesC in any of the assessments). Stroke severity was quantified with the Canadian Stroke Scale on admission. The relationship between the highest temperature recorded in each 6-hour interval from stroke onset and stroke outcome (Canadian Stroke Scale and Barthel Index at 3 months) or infarct volume was evaluated by correlation analyses. The importance of the time at which hyperthermia was first detected was assessed by logistic regression analysis. **RESULTS:** During the first 72 hours, 158 patients (60.8%) had hyperthermia, and in 57.6% of them an infectious cause was identified. Mortality rate at 3 months was 1% in normothermic patients and 15.8% in hyperthermic patients (P<0.001). The correlation coefficients between the final infarct volume, Canadian Stroke Scale and Barthel Index scores at 3 months, and each temperature recording decreased progressively over time from symptom onset. **Hyperthermia initiated within the first 24 hours from stroke onset, but not afterward, was independently related to larger infarct volume (odds ratio [OR]=3.23, 95% CI=1.63 to 6.43; P<0.001) and higher neurological deficit (OR=3.06, 95% CI=1.70 to 5.53; P<0.001) and dependency (OR=3.41, 95% CI=1.69 to 6.88; P=0.002) at 3 months.** The infectious origin of hyperthermia was not associated with poorer outcome or greater infarct volume. **CONCLUSIONS:** The relationship between brain damage and high temperature is greater the earlier the increase in temperature occurs. However, only body temperature within the first 24 hours from stroke onset is associated with poor outcome and large cerebral infarcts

Level of Evidence 7

Quality of evidence-Fair

Evidence – Supportive

Fukuda H, Kitani M, Takahashi K. Body temperature correlates with functional outcome and the lesion size of cerebral infarction. *Acta Neurol Scand.* 1999;100:385-90.

INTRODUCTION: Experimental studies have demonstrated that mild hyperthermia exacerbates ischemia-induced neuronal injury. **MATERIAL AND METHODS:** The relationship between body temperature and functional outcome in 183 patients suffering from cerebral infarction, and admitted within 24 h from the onset of stroke was examined. Patients' functional capacities in daily life were evaluated by Rankin's score before the attack (RS0), on the day of admission (RS1), and 3 months after the onset of stroke (RS90). **RESULTS:** RS90 showed an independent correlation with RS0, RS1, age, infarct size and maximum body temperature recorded within the first 7 days from the onset of stroke by multivariate analysis. History of previous cerebrovascular accidents, atrial fibrillation, hemorrhagic transformation, infection, and a hypothalamic lesion showed significant associations with RS90 by the Mann-Whitney U-test, but not by multivariate analysis. Infarct size correlated with body temperature, atrial fibrillation, and hemorrhagic transformation. **CONCLUSION: Body temperature correlated well with both functional outcome and infarct size in patients with an acute cerebral infarction.**

Level of Evidence 7

Quality of evidence-Fair

Evidence - Supportive

Grau AJ, Buggle F, Schnitzler P, Spiel M, Lichy C, Hacke W. Fever and infection early after ischemic stroke. *J Neurol Sci.* 1999;171:115-20.

Previous studies showed that elevated body temperature early after ischemic stroke is associated with severe neurological deficit and a poor outcome. The aim of this study was to analyse the prevalence and putative etiology of febrile body temperature (≥ 38.0 degrees C) early after stroke and to investigate the association between body temperature, stroke severity and outcome. We investigated 119 consecutive patients who were admitted within 24 h after ischemic stroke. Patients were examined for infection before ischemia using a standardized questionnaire and received daily clinical examination after stroke. In case of

fever, standardized radiological and microbiological examinations were performed. Fever within 48 h after stroke was observed in 30 (25.2%) patients. The probable cause of fever was infective or chemical aspiration pneumonia (n=12), other respiratory tract infection (n=7), urinary tract infection (n=4), viral infections (n=3) or insufficiently defined (n=5). (One patient had two potential causes of fever.) In thirteen of these patients, infection was most probably acquired before stroke. Fever newly developed more often during day 1 to 2 than day 3 to 7 after stroke (P=0.016). Fever was associated with a more severe deficit on admission independent from age, vascular diseases and risk factors (odds ratio 9.6; 95% confidence interval 3.1-29). Fever is a frequent complication early after stroke and in the majority of cases, it can be explained by infection or chemical aspiration pneumonia. In about half of the infected patients, infection was most probably acquired before stroke. **Fever was associated with a more severe neurological deficit on admission.**

Level of Evidence 7

Quality of evidence-Fair

Evidence - Supportive

Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome : a meta-analysis of studies in patients. *Stroke*. 2000;31:410-4.

BACKGROUND AND PURPOSE: The effect of pyrexia on cerebral ischemia has been extensively studied in animals. In humans, however, such studies are small and the results conflicting. We undertook a **meta-analysis** using all such published studies on the effect of hyperthermia on stroke outcome. **METHODS:** Three databases were searched for all published studies that examined the relationship of raised temperature after stroke onset and eventual outcome. Combined probability values and odds ratios were obtained. A heterogeneity test was performed to ensure that the data were suitable for such an analysis. Morbidity and mortality were used as outcome measures. **RESULTS: Nine studies were identified totaling 3790 patients**, providing the study with 99% power to detect a 9% increase in morbidity and 84% power to detect a 1% increase in mortality for the pyrexial group. The combined odds ratio for mortality was 1.19 (95% CI, 0.99 to 1.43). A heterogeneity test was highly nonsignificant (P>0.05) for mortality, suggesting that the data were sufficiently similar to be meta-analyzed. Combined probability values were highly significant for both morbidity (P<0.0001) and mortality (P<0.0000001). **CONCLUSIONS: The results from this meta-analysis suggest that pyrexia after stroke onset is associated with a marked increase in morbidity and mortality.** Measures should be taken to combat fever in the clinical setting to prevent stroke progression. The possible benefit of therapeutic hypothermia in the management of acute stroke should be further investigated.

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 7

Quality of evidence-Good

Evidence - Supportive

Animal Studies

Baena RC, Busto R, Dietrich WD, Globus MY, Ginsberg MD. Hyperthermia delayed by 24 hours aggravates neuronal damage in rat hippocampus following global ischemia. *Neurology*. 1997;48:768-73. We investigated whether moderate, transient whole-body hyperthermia (approximately 39.6 degrees C), if imposed 1 day following a brief episode of forebrain ischemia, would affect the neuropathologic outcome. Forty-two Wistar rats were subjected to either a 5- or 7-minute period of bilateral common carotid artery occlusion plus hypotension (50 mm Hg), or to the equivalent sham procedure. Twenty-four hours later, rats of one subgroup were placed into a hyperthermic chamber containing high-intensity lamps designed to elevate rectal temperature to 39 to 40 degrees C for 3 hours. Normothermic subgroups received the same procedures, but the heating lamps were turned off. Eight days after brain ischemia or the sham procedure, brains were perfusion-fixed, and numbers of ischemic-appearing CA1 pyramidal neurons were counted. **In**

rats with 7-minute forebrain ischemia, delayed hyperthermia increased mean numbers of ischemic neurons by 2.6- to 2.7-fold in all subsectors of area CA1 ($p < 0.05$, ANOVA). Delayed hyperthermia in 5-minute ischemic rats also tended to increase mean numbers of ischemic neurons (by 11-fold in lateral, 6-fold in middle, and 5-fold in medial CA1 subsectors), but these differences were not statistically significant. We conclude that moderate, transient hyperthermia, even if occurring 1 day after a 7-minute global ischemic insult, exacerbates the extent of ischemic neuronal injury

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

Level of Evidence 6
Quality of evidence-Good
Evidence - Supportive

Castillo J, Davalos A, Noya M. Aggravation of acute ischemic stroke by hyperthermia is related to an excitotoxic mechanism. *Cerebrovasc Dis.* 1999;9:22-7.

OBJECTIVE: To examine whether hyperthermia aggravates cerebral injury in acute ischemia by an excitotoxic mechanism, we studied the relationship between body temperature on admission and CSF concentrations of neuroexcitatory amino acids in 128 patients with acute ischemic stroke of less than 24 h duration. **METHODS:** Stroke worsening was defined as the percent change between the Canadian Stroke Scale (CSS) at 48 h and the CSS on admission. Infarct volume was measured on days 4-7 on cranial computed tomography. Excitatory amino acids were analyzed using HPLC. **RESULTS:** Glutamate concentration [median (min.-max.)] was 11 (2-19) micromol/l in hyperthermic patients (body temperature >37.5 degreesC) and 5 (2-22) micromol/l in normothermic patients ($p < 0.0001$). Glycine concentration in hyperthermic and normothermic patients was 16 (3-21) micromol/l and 9 (3-50) micromol/l, respectively ($p < 0.0001$). Glutamate was significantly higher in patients with hyperthermia only during the first 12 h after the onset of symptoms. The CSF concentrations of glutamate ($r = 0.52$; $p < 0.0001$) and glycine ($r = 0.62$; $p < 0.0001$) correlated with body temperature. Body temperature was significantly related to stroke worsening and infarct size, but this effect was dependent on the glutamate effect. **CONCLUSION:** Glutamate and glycine release during the acute phase of cerebral ischemia could be responsible for the increased brain damage in hyperthermia.

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 6
Quality of evidence-Good
Evidence - Supportive

Chen H, Chopp M, Welch KM. Effect of mild hyperthermia on the ischemic infarct volume after middle cerebral artery occlusion in the rat. *Neurology.* 1991;41:1133-5.

We investigated the effect of mild whole-body hyperthermia (40 degrees C) on a permanent middle cerebral artery occlusion (MCAo) model in Fisher rats by subjecting them to MCAo under the following conditions: (1) normothermia ($n = 20$); (2) hyperthermia ($n = 14$) before (1 hour), during, and after (1 hour) MCAo; and (3) post-MCAo hyperthermia ($n = 14$) for 1 hour. We measured brain and body temperatures during the experiment using micro-thermocouples and blood-brain-barrier (BBB) permeability using Evans blue staining of the brain. We measured the volume of the infarcted brain tissue 4 days after MCAo. We detected no differences in BBB permeability among three groups. The volume of infarcted tissue was significantly greater ($p < 0.05$) for the two groups of hyperthermic animals than the normothermic animals. Our data suggest that mild hyperthermia, both during and after induction of ischemia, has a detrimental effect on the ischemic infarct volume in this model

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

Level of Evidence 6

Quality of evidence-Good

Evidence - Supportive

Coimbra C, Drake M, Boris-Moller F, Wieloch T. Long-lasting neuroprotective effect of postischemic hypothermia and treatment with an anti-inflammatory/antipyretic drug. Evidence for chronic encephalopathic processes following ischemia. *Stroke*. 1996;27:1578-85.

BACKGROUND AND PURPOSE: It has been recognized that postischemic pharmacological interventions may delay the evolution of neuronal damage rather than provide long-lasting neuroprotection. Also, fever complicates recovery after stroke in humans. Here we report the effects of late postischemic treatment with hypothermia and an antipyretic/anti-inflammatory drug, dipyron, on cell damage at 1 week and 2 months of survival. **METHODS:** Rats were subjected to 10 minutes of forebrain ischemia. Hypothermia (33 degrees C) was induced at 2 hours of recovery and maintained for 7 hours. Dipyron (100 mg.kg-1IP) was given every 3 hours from 14 to 72 hours of recovery. Temperature was measured every 6 hours for 60 days. Neuronal damage was assessed at 7 days and 2 months of recovery. **RESULTS:** From 17 to 72 hours of recovery, a period of hyperthermia was observed, which dipyron abolished but postischemic hypothermia treatment did not. Dipyron treatment diminished neuronal damage by 43% at 7 days, and at 2 months of survival, a minor (16%) protection was seen. Postischemic hypothermia treatment alone delayed neuronal damage. In contrast, combined treatment of hypothermia followed by dipyron markedly diminished neuronal damage by more than 50% at both 7 days and 2 months of recovery. **CONCLUSIONS:** Neuronal degeneration may be ongoing for months after a transient ischemic insult, and prolonged protective measures need to be instituted for long-lasting neuroprotective effects. Hyperthermia during recovery worsens ischemic damage, and processes associated with inflammation may contribute to the development of neuronal damage. An early and extended period of postischemic hypothermia provides a powerful and long-lasting protection if followed by treatment with anti-inflammatory/ antipyretic drug.

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 6

Quality of evidence-Good

Evidence - Supportive

Dietrich WD, Alonso O, Halley M, Busto R. Delayed posttraumatic brain hyperthermia worsens outcome after fluid percussion brain injury: a light and electron microscopic study in rats. *Neurosurgery*. 1996;38:533-41; discussion 541.

The morphological consequences of **delayed posttraumatic** brain hyperthermia (39 degrees C) after fluid percussion brain injury were assessed in rats. Sprague-Dawley rats anesthetized with 4% halothane and maintained on a 70:30 mixture of nitrous oxide:oxygen and 0.5% halothane underwent moderate (1.5-2.0 atm) traumatic brain injury with the injury screw positioned parasagittally over the right parieto-occipital cortex. At 24 hours after traumatic brain injury, the rats were reanesthetized and randomized into two groups in which either a 3-hour period of brain normothermia (36.5 degrees C, n = 18) or hyperthermia (39 degrees C, n = 18) was maintained. Sham-operated controls (n = 10) underwent all surgical and temperature-monitoring procedures. After the 3-hour monitoring period, the rats were allowed to survive for 3 days for light microscopic analysis or were injected with the protein tracer horseradish peroxidase and were perfusion-fixed 15 minutes later for light and electron microscopic analysis. At 4 days after traumatic

brain injury, delayed posttraumatic hyperthermia (n = 12) significantly increased mortality (47%) and contusion volume (1.7 +/- 0.69 mm³, mean +/- standard error of the mean), compared to normothermia (n = 12) (18% mortality and 0.13 +/- 0.21 mm³ contusion volume) (P < 0.01, analysis of variance). At 15 minutes after the 3-hour hyperthermic period, the area of hemorrhage and horseradish peroxidase extravasation overlying the lateral external capsule was significantly increased (2.52 +/- 0.71 mm², mean +/- standard error of the mean, versus 0.43 +/- 0.16 mm²) (P < 0.01), compared to normothermic rats. Examination of toluidine blue-stained plastic sections demonstrated a higher frequency of abnormally swollen myelinated axons per high microscopic field with hyperthermia. For example, numbers of swollen axons within the sixth layer of the right somatosensory cortex, corpus callosum, and internal capsule were 7.3 +/- 1.3, 4.2 +/- 1.4, and 3.0 +/- 1.2 axons (mean +/- standard error of the mean) with normothermia, respectively, compared with 24.7 +/- 12.1, 33.1 +/- 4.2, and 27.3 +/- 3.1 axons with hyperthermia, respectively (P < 0.01). An ultrastructural examination of the swollen axons demonstrated a severely thinned myelin sheath containing axoplasm devoid of cytoskeletal components. These experimental results indicate that posttraumatic brain hyperthermia might increase morbidity and mortality in patients with head injury by aggravating axonal and microvascular damage.

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

Level of Evidence 6

Quality of evidence-Good

Evidence - Supportive

Kato H, Araki T, Kogure K. Postischemic spontaneous hyperthermia is not a major aggravating factor for neuronal damage following repeated brief cerebral ischemia in the gerbil. *Neurosci Lett*. 1991;126:21-4.

Brief and non-lethal cerebral ischemia produces most severe neuronal damage when such ischemia is induced repeatedly at 1-h intervals. We examined whether spontaneous postischemic hyperthermia is an aggravating factor for the cumulative damage following repeated ischemia in the gerbil. We maintained body and cranial temperature at normothermia throughout the initial reperfusion period, but could not observe an amelioration of histopathological brain damage following two 2-min bilateral carotid artery occlusions at a 1-h interval as compared to hyperthermic conditions. The results suggest that postischemic hyperthermia is not a major aggravating factor for the cumulative damage following repeated ischemic insults

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

Level of Evidence 6

Quality of evidence-Good

Evidence - Neutral

Kim Y, Busto R, Dietrich WD, Kraydieh S, Ginsberg MD. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. *Stroke*. 1996;27:2274-80; discussion 2281.

BACKGROUND AND PURPOSE: Over the past several years, it has been demonstrated that mild intraischemic or immediate postischemic hyperthermia worsens ischemic outcome in models of global and focal ischemia. Periods of hyperthermia are commonly seen in patients after stroke and cardiac arrest. The hypothesis tested in this study was that a brief hyperthermic period, even when occurring days after an ischemic insult, has detrimental effects on the pathological outcome of focal ischemia. **METHODS:** Rats were subjected to 60 minutes of transient middle cerebral artery occlusion by insertion of an intraluminal filament. Twenty-four hours after reperfusion, awake rats were subjected to temperature modulation for 3 hours in a heating chamber. The brain temperature was equilibrated to either 37 degrees C to 38 degrees C,

or 40 degrees C. Changes in rectal temperature and blood glucose concentration were evaluated during and just after temperature modulation. Behavioral tests were also assessed. Three days after temperature modulation, brains were perfusion-fixed, and infarct volumes were determined. RESULTS: In animals with 40 degrees C hyperthermia, cortical and total infarct volumes were markedly greater (92.2 +/- 63.1 and 126.5 +/- 72.3 mm³ [mean +/- SD], respectively) than in normothermic rats (14.4 +/- 12.7 and 42.4 +/- 19.2 mm³) and in animals with 39 degrees C hyperthermia (16.5 +/- 28.7 and 40.9 +/- 34.3 mm³) (P < .05), whereas there was no significant difference between normothermic and 39 degrees C hyperthermic animals. In addition, animals with 40 degrees C hyperthermia displayed worsened neurological scores compared with normothermic and 39 degrees C hyperthermic rats. In the 39 degrees C hyperthermia group, rectal temperatures were significantly lower (by 0.2 degree C to 0.5 degree C) than brain temperatures throughout the modulation period. CONCLUSIONS: The present findings provide evidence that, after a transient focal ischemic insult, the postischemic brain becomes abnormally sensitive to the effects of delayed temperature elevation, even of moderate degree. The threshold for aggravation of ischemic injury by delayed hyperthermia appears to be approximately 40 degrees C. Body-temperature measurements, in both awake and anesthetized animals, may not accurately reflect brain temperature under these conditions. The present study stresses that fever of even moderate degree in the days following brain ischemia may markedly exacerbate brain injury.

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

Level of Evidence 6
Quality of evidence-Good
Evidence - Supportive

Kuroiwa T, Bonnekoh P, Hossmann KA. Prevention of postischemic hyperthermia prevents ischemic injury of CA1 neurons in gerbils. *J Cereb Blood Flow Metab.* 1990;10:550-6.

Halothane-anesthetized Mongolian gerbils were submitted to 5-min bilateral carotid artery occlusion. After ischemia, halothane anesthesia was continued for various periods of up to 85 min, and the degree of CA1 neuronal injury was estimated 7 days later by counting the number of surviving pyramidal cells. During ischemia and postischemic halothane anesthesia, rectal and cranial temperature was kept at control level (37.7 and 37.0 degrees C, respectively) using a feedback-controlled heating system. When anesthesia was discontinued after ischemia, transient hyperthermia occurred. In animals with 0- and 15-min postischemic halothane anesthesia, both cranial and rectal temperature rose by approximately 1.5 degrees C, and the number of surviving CA1 neurons amounted to less than 25% of control. After 45- or 85-min postischemic anesthesia, hyperthermia was significantly reduced and the number of surviving neurons increased to 65 and 89%, respectively. The protective effect of postischemic anesthesia was lost when anesthetized animals were submitted to the same hyperthermic profile as nonanesthetized ones, using a feedback-controlled heating system (16% surviving neurons in hyperthermia vs. 89% in normothermia, respectively). These observations demonstrate that postischemic anesthesia with 1% halothane protects against delayed neuronal death by preventing postischemic hyperthermia and not by its anesthetic effects

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

Level of Evidence 6
Quality of evidence-Good
Evidence – Supportive

Lundgren J, Smith ML, Blennow G, Siesjo BK. Hyperthermia aggravates and hypothermia ameliorates epileptic brain damage. *Exp Brain Res.* 1994;99:43-55.

The influence of hyperthermia and hypothermia on epileptic brain damage was studied in rats, in which status epilepticus was induced by flurothyl. Histopathological changes were examined by light microscopy after 1 or 7 days of recovery. Two series of animals were studied. In the first, short periods of seizures (20 and 25 min) were employed to examine whether moderate hyperthermia (39.5 degrees C) would aggravate epileptic brain damage, and a longer period (45 min) was used to investigate whether moderate hypothermia (32.5 degrees C) would ameliorate the damage. The second series investigated whether brief periods of status epilepticus (10 min) would cause brain damage if hyperthermia were high or excessive. For this series, animals with body temperatures of 37.0, 39.0, and 41.0 degrees C were studied. Data from normothermic animals (37.5 degrees C) confirmed previously described neuronal damage. Although hyperthermic animals failed to show increased damage in the CA1 sector, or in the hilar region of the dentate gyrus, they showed enhanced damage in the neocortex and globus pallidus (GP). In substantia nigra pars reticulata (SNPR) four out of five hyperthermic animals had bilateral infarcts after 20 min of status epilepticus, whereas no normothermic animal showed such damage. Hypothermia seemed to ameliorate epileptic brain damage in the neocortex (n.s.) and GP ($P < 0.05$) following status epilepticus for 45 min. Three out of seven hypothermic animals had mild SNPR involvement compared to severe infarction of the nucleus in five out of six normothermic animals ($P < 0.05$). Thus, hyperthermia aggravated and hypothermia ameliorated epileptic brain damage both in regions showing selective neuronal necrosis (neocortex) and in regions developing pan-necrosis (GP and SNPR). The second series displayed an unexpected result of excessive hyperthermia. Animals subjected to only 10 min of status epilepticus at a temperature of 41 degrees C showed not only neocortical lesions, but also moderate to extensive damage to the hippocampus (CA1, subiculum, and dentate gyrus). It is concluded that at high body and brain temperature, brief periods of status epilepticus can yield extensive brain damage, primarily affecting the hippocampus.

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

Level of Evidence 6

Quality of evidence-Good

Evidence – Supportive

Reglodi D, Somogyvari-Vigh A, Maderdrut JL, Vigh S, Arimura A. Postischemic spontaneous hyperthermia and its effects in middle cerebral artery occlusion in the rat. *Exp Neurol.* 2000;163:399-407.

This study examined the time course and effects of postischemic spontaneous hyperthermia after transient and permanent focal ischemia. Rats underwent a 90-min, 120-min, or permanent middle cerebral artery occlusion (MCAO). Body temperatures started rising 15-20 min after MCAO and reached 39-40.5 degrees C during the first hour. Sustained hyperthermia was observed during the rest of the first 24 h. In another experiment, rats were subjected to the same interventions, but a normothermic body temperature was maintained. Spontaneous hyperthermia significantly increased the infarct volumes measured 48 h after MCAO in all groups. Reperfusion 2 h after the onset of ischemia was not beneficial in the hyperthermic animals in contrast to the normothermic group. We also examined the effect of spontaneous hyperthermia on the temporal progression of infarcted and penumbral areas 4, 12, or 48 h after MCAO. During spontaneous hyperthermia, penumbral areas became infarcted areas more rapidly, which was most expressed at 4 h. These findings demonstrate that severe spontaneous hyperthermia can occur in rats after MCAO and that it not only increases the infarct volumes in both transient and permanent ischemia, but also accelerates the incorporation of penumbral areas into necrotic areas, which significantly decreases the window of opportunity for therapeutic interventions

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 6

Quality of evidence-Good

Evidence – Supportive

.Shum-Tim D, Nagashima M, Shinoka T, Bucarius J, Nollert G, Lidov HG, du Plessis A, Laussen PC, Jonas RA. Postischemic hyperthermia exacerbates neurologic injury after deep hypothermic circulatory arrest. *J Thorac Cardiovasc Surg.* 1998;116:780-92.

BACKGROUND: Aggressive surface warming is a common practice in the pediatric intensive care unit. However, recent rodent data emphasize the protective effect of mild (2 degrees - 3 degrees C) hypothermia after cerebral ischemia. This study evaluates different temperature regulation strategies after deep hypothermic circulatory arrest with a survival piglet model. **METHODS:** Fifteen piglets were randomly assigned to 3 groups. All groups underwent 100 minutes of deep hypothermic circulatory arrest at 15 degrees C. Brain temperature was maintained at 34 degrees C for 24 hours after cardiopulmonary bypass in group I, 37 degrees C in group II, and 40 degrees C in group III. Neurobehavioral recovery was evaluated daily for 3 days after extubation by neurologic deficit score (0, normal; 500, brain death) and overall performance category (1, normal; 5, brain death). Histologic examination was assessed for hypoxic-ischemic injury (0, normal; 5, necrosis) in a blinded fashion. **RESULTS:** All results are expressed as mean +/- standard deviation. Recovery of neurologic deficit score (12.0 +/- 17.8, 47.0 +/- 49.95, 191.0 +/- 179.83; P = .05 for group I vs III), overall performance category (1.0 +/- 0.0, 1.4 +/- 0.6, 2.8 +/- 1.3; P < .05 for group I vs III), and histologic scores (0.0 +/- 0.0, 1.0 +/- 1.2, 2.8 +/- 1.8; P < .05 for group I vs III cortex) were significantly worse in hyperthermic group III. These findings were associated with a significantly lower cytochrome aa3 recovery determined by near-infrared spectroscopy in group III animals (P = .0041 for group I vs III). No animal recovered to baseline electroencephalographic value by 48 hours after deep hypothermic circulatory arrest. Recovery was significantly delayed in the hyperthermic group III animals, with a lower amplitude 14 hours after the operation, which gradually increased with time (P < .05 for group III vs groups I and II). **CONCLUSIONS:** Mild postischemic hyperthermia significantly exacerbates functional and structural neurologic injury after deep hypothermic circulatory arrest and should therefore be avoided.

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

Level of Evidence 6

Quality of evidence-Good

Evidence – Supportive

Yager JY, Asselin J. The effect of pre hypoxic-ischemic (HI) hypo and hyperthermia on brain damage in the immature rat. *Brain Res Dev Brain Res.* 1999;117:139-43.

To determine the effect of pre-hypoxic-ischemic (HI) hypo and hyperthermia on neuropathologic outcome in the immature brain, groups of 7-day rat pups underwent unilateral common carotid artery ligation and exposure to hypoxia in 8% oxygen at 37 degrees C for 3 h. Prior to HI, rat pups were divided into three groups and received either: (a) 3-1 h periods, at 8-h intervals, 24 h prior to HI, (b) 1-3 h period, 24 h prior to HI, or (c) 1-3 h period, immediately prior to HI, of exposure to environmental temperatures of 28 degrees C, 31 degrees C, 34 degrees C, 37 degrees C, or 39 degrees C. Following HI, all animals were returned to their dams for neuropathologic assessment at 30 days of age. Mortality was highest among those animals exposed to pre-HI hypothermia at 28 degrees C. Only those animals who were pre-conditioned with hyperthermia at either 37 degrees C or 39 degrees C, immediately prior to HI, displayed a significant reduction in brain damage compared to control ($p < 0.01$). These results indicate that hyperthermia induced prior to HI protects the immature brain from damage. This study further emphasizes the importance of a cautionary approach in implementing systemic hypothermia during clinical trials, and the need to further understand the timing and effects of thermoregulation on the immature brain

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

Level of Evidence 6

Quality of evidence-Good

Evidence – Opposing