Deleterious effects of hyperthermia: cellular injury increased

Background: study of 387 patients in neurologic intensive care unit (ICU) found 23% had fever ≥38.3°C; risk factors included length of stay and coma; fevers categorized as infectious and unexplained (designated neurogenic or essential); intubation additional risk factor for infectious fever; external ventricular drain risk factor for essential fever (indicates blood in ventricles); diagnosis of subarachnoid hemorrhage (SAH) additional risk for fever, because it suggests abnormal regulation of body temperature

Deleterious effects of hyperthermia: cellular injury increased in focal and global ischemia and trauma; occur with delayed and acute hyperthermia; damage more pronounced after reversible ischemia (eg, cardiac arrest, global ischemia with reperfusion injury, thrombolysis); aggravates postischemic brain edema (increased cerebral blood volume leads to leaking of blood-brain barrier, exacerbation of vasogenic brain edema, brain shifts, and increased intracranial pressure [ICP]); occur even with elevations of only 1°C to 2°C; studies of patients with cerebral infarction, SAH, and intracerebral hemorrhage (ICH) found increased temperature associated with poor outcome; among patients with ischemic stroke, temperature elevation more important during first 24 hr (phase of temperature-modifiable brain injury); among patients with poor grade SAH or ICH with intraventricular hemorrhage, fevers after first day more important; fever burden defined as area under curve of maximum temperature (Tmax) over period of 7 to 10 days

After SAH: in study (Fernandez et al, 2007) of 353 patients with SAH, fever burden predicted by coma or poor clinical grade, increased age, male sex, and more acute physiologic derangement on admission (eg, white count elevation, blood pressure instability); among patients with poor grade, average Tmax 1.5°C and average fever 38.5°C; fever burden correlated with death, disability, and poor cognitive outcome, especially with high degrees of fever

Intracranial pressure: Rossi et al (2001) found ≥8 mm Hg difference in ICP between patients with and without fever; patients with fever had luxury perfusion and brain hyperemia with higher oxygen saturation

Length of stay: Deringer et al (2004) showed elevated body temperature associated with longer ICU and hospital stays, higher mortality, and worse hospital disposition

Antipyretic medications: oral acetaminophen or ibuprofen reduces temperature by only ≤0.5°C; act by inhibiting cyclooxygenase and prostaglandin synthesis in hypothalamus (controls set-point temperature of brain); administration of intravenous (IV) indomethacin more effective than oral administration at lowering temperature; studies under way evaluating 400 mg every 4 hr or 83 mg/hr as continuous infusion to determine correct dosing and safety profile; effects of tendency to inhibit platelets need further evaluation

Refrigerated saline and cooling catheters: administration of ≥2 L of saline at 4°C cools body temperature over 2 hr from ≥39°C to <37°C; head cooling — reduces brain and core body temperature simultaneously; cooling catheters — multicenter study of 300 patients treated with endovascular heat exchange catheter plus cooling blankets found 64% relative reduction in fever burden >38°C; assessment of shivering limited

Arctic Sun Temperature Management System: study of cooling pads vs cooling blanket found temperature of patients with blankets remained ≥38°C; cooling pads reduced temperature to ≤37°C more rapidly; other end points (eg, percentage of time normothermic, number who ever attained normothermia, speed of attaining normothermia) all superior with pads; group with cooling pads also had 1-point increase in Glasgow Coma Scale score after 24 hr; reducing temperature to normal may also improve level of consciousness; patients may need sedation for treatment with pads or catheter

Diagnosing infection without fever: to determine whether patient undergoing therapeutic temperature management (TTM) has infection, check hourly temperature of water (TOW) circulating through cooling device; if TOW >20°C, active cooling absent or minimal and patient not febrile; if TOW <10°C, active cooling intense and patient febrile (consider culturing)

Shivering: counteracts efforts to induce hypothermia or reduce fever; uncontrolled shivering during use of TTM has worse effect than allowing patient to remain febrile; brain monitoring showed that uncontrolled shivering reduced oxygen levels in brain tissue, increased cerebral metabolic demand, and increased lactate levels; to defeat shiver reflex, use nonsedating strategies first; paralyze as last resort (brain remains hypermetabolic);
Bedside Shivering Assessment Scale (BSAS) — quantifies shivering with 4-point scale from no shivering (1), slight shivering in masseter or neck (2), shivering in arms (3), to shivering that involves all 4 extremities (4)

Antishivering protocol: standard protocol — Arctic Sun TTM

Mechanisms of neuroprotection: hypothermia effectively protects brain after cardiac arrest; previously, only ~1.4% of patients with out-of-hospital cardiac arrest discharged alive because of severe brain injury; among patients who recover from cardiac arrest after resuscitation, global ischemia occurs for ~5 min, reperfusion for ~20 min, and then reperfusion injury takes place over period of hours as oxygen delivered and free radicals generated; neurons excrete cytokotic neurotransmitters, activate pathways for secondary programmed cell death, and shed inflammatory mediators; large window for intervention after cardiac arrest because reperfusion injury lasts ~72 hr; in contrast, window in persistent focal ischemia only 3 to 4 hr

Protocol for emergency department (ED): ability to perform TTM in ED and ICU increased safety; administer 2 L refrigerated saline; may help with systemic inflammatory response (ie, postresuscitation syndrome); administer large induction dose of fentanyl, propofol, or meperidine; monitor blood pressure (50% of patients on infusion of vasopressor); temperature should decrease ≥1°C/hr; if shivering observed, give single induction paralytic dose of vecuronium or cisatracurium

Toxicity of hypothermia: cardiovascular toxicity — occurs at 33°C with bradycardia, reduced cardiac output, reduced left ventricular performance, and inotropy; shivering increases blood pressure and heart rate; at <30°C, bradycardia converts into ventricular ectopy, tachycardia, or fibrillation; 10% to 20% of patients resuscitated before admission have acute coronary syndrome; catheter stenting of lesions needed despite absence of classic ST-segment elevation myocardial infarction findings on electrocardiography; cooling can lead to platelet dysfunction and prolong prothrombin time and partial thromboplastin time (effect not clinically important even in patients with ICH); immunosuppression — studies of trauma and stroke show cooled patients have more hospital-acquired infections (especially pneumonia); general metabolic derangements — include hypokalemia, insulin resistance, ileus, cold diuresis, and amylose elevation

Indications for cooling: 
- early — effective for neuroprotection against reperfusion injury after hypoxic ischemic coma from out-of-hospital arrest; not effective for traumatic brain injury (TBI); effects unknown for stroke: delayed — for mass effect and brain edema, delayed cooling lowers ICP after TBI and coma and for middle cerebral artery infarction (but hemicraniectomy more effective for space-occupying brain infarction); may also reduce perihematodal edema in ICH

Trials of cooling: European Hypothermia after Cardiac Arrest (HACA) Trial, Australian Trial, and others showed that among patients selected for cooling, rate of recovery 15% for those with nonshockable cardiac arrest, and 40% for those with ventricular fibrillation and pulseless ventricular tachycardia cardiac arrest

Adoption of therapeutic hypothermia: requires standing protocol and team of clinicians; New York mandates that any patient who achieves return of spontaneous circulation must be taken to hospital with hypothermia protocol (ie, 60% of hospitals in New York City); overall survival increased 5% in first year after initiation of mandate (single biggest one-year increase in survival from out-of-hospital cardiac arrest among patients admitted to ICUs)

Trauma: pediatric trial showed more harm produced by hypothermia; second study found early hypothermia produced poor outcome in adults; possibly because rewarming occurs at days 2 and 3 when effects of brain edema peak

Acute Encephalopathy

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Case example: how to evaluate “change in mental status” in patient for whom little other information available

Mental status: term used to describe patients whose condition may range from obtunded to confused; important to distinguish content vs level of consciousness

Agitated vs withdrawn delirium: patients with agitated delirium require more time and effort from staff; outcome decrement identical between withdrawn and agitated patients

Anatomy: level of consciousness — maintained in brainstem, ie, reticular activating system (RAS); starts in medulla; ends at end of thalamus (intralaminar nucleus of thalamus on both sides); and projects throughout brain; network throughout cortex also responsible; content of consciousness — maintained in memory circuit, ie, Papez circuit; includes thalamus, amygdala, fornix, hippocampus, and cingulate gyrus (area highly susceptible to many medications); changes in content of consciousness often associated with medications

Delirium: underlying neural basis unclear; associated with poor outcome for unknown reasons; study (Girard et al, 2010) showed number of days of delirium predicted outcome among overall population but not individual patients; treatments alleviate symptoms but do not reverse delirium; another study showed patients with delirium have decreased brain volumes later in life (unknown whether smaller volumes preceded delirium); also unknown whether symptoms attributed to delirium actually caused by medications, eg, benzodiazepines (especially midazolam [Versed]); recent decrease in incidence of delirium appears to correlate with decrease in use of benzodiazepines

Evaluation of delirium: diagnostic gold standard unknown; Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) questionnaire administered once (spot check); Intensive Care Delirium Screening Checklist (ICDSC) filled out at end of shift covering period of shift; study compared metrics with evaluation according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition; DSM-IV) criteria and judgment of neurointensivist; 44% of patients considered delirious according to DSM-IV criteria, ≥29% considered delirious according to CAM-ICU and ICDSC, and ≥25% diagnosed as delirious by neurointensivist; delirium represents subset of encephalopathy (“brain failure”)

Encephalopathy: causes include acute metabolic disarray (eg, hypoxia, hypoglycemia, acidosis, thyrotoxicosis), seizures, effects of medication (especially polypharmacy and errors); other underlying causes, eg, N-methyl-D-aspartic acid (NMDA) receptor antibody encephalitis (associated with ovarian teratomas; manifests as psychiatric symptoms and seizures followed by frank encephalopathy and inflammation of brain)
Differential diagnosis: for alterations in level of consciousness, consider ischemia, infection, neoplasm, vasculitis, conversion, and malingering; for alterations in content of consciousness, consider epileptic, metabolic, toxic, and infectious disorders.

Treatment: administer oxygen if patient hypoxic; administer naloxone (Narcan) and check glucose if needed; use collar until spinal cord injury ruled out; do not use flumazenil initially because of increased seizures; rule out or treat conditions that could kill patient within 24 hr, eg, meningitis, status epilepticus, infection, bleeding.

General recommendations: for difficult-to-manage patients, speaker uses neuroleptics and haloperidol (Haldol); lower doses (eg, 1 mg) not effective; begin treatment at same time as evaluation; perform directed examination specifically for brainstem function, global cortical function, and mental status; treat problems that affect outcome immediately (eg, oxygen, glucose level, electrolytes); review serum bicarbonate levels for acidosis; keep looking until cause found; examine all encephalopathic patients personally to make better physical examinations and diagnoses; assume loss of consciousness usually structural; focus on medical portion of examination in addition to neurologic portion; start eliminating medications as soon as possible; do not treat with antibiotics unless infectious source identified (antibiotics cause much delirium); if dementia or sundowning likely (diagnosis of exclusion), speaker uses antipsychotics; avoid sedating or mind-altering drugs.

Suggested Reading


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1. All the following statements about fever and hyperthermia are correct, except:
   (A) Risk factors for fever ≥38.3°C in the neurologic intensive care unit (ICU) include length of stay and coma
   (B) Presence of an external ventricular drain is a risk factor for essential fever
   (C) Damage caused by hyperthermia is more pronounced after reversible ischemia
   (D) Diagnosis of subarachnoid hemorrhage (SAH) is not an independent risk factor for fever

2. Choose the correct statements about fever and outcomes after brain injury.
   1. Patients with increased temperature after cerebral infarction, SAH, or intracerebral hemorrhage (ICH) have poorer outcomes than those with normal temperature
   2. Among patients with ischemic stroke, temperature elevation was more important after the first 36 hr
   3. A study found ≈8 mm Hg difference in intracranial pressure between patients with and without fever
   4. A study showed elevated body temperature was associated with longer ICU and hospital stays
   5. Deleterious effects occur with elevations of 1°C to 2°C
   (A) 3,4,5 (B) 1,2,3,4 (C) 1,3,4,5 (D) 1,2,3,4,5

3. Administration of ≈2 L of saline at 4°C can cool the body temperature over a period of 2 hr from 39°C to <37°C.
   (A) True (B) False

4. All the following changes have been shown by brain monitoring to be associated with uncontrolled shivering, except:
   (A) Increased oxygen levels in brain tissue
   (B) Increased cerebral metabolic demand
   (C) Increased lactate levels

5. Therapeutic hypothermia is beneficial during a period of approximately _______ after out-of-hospital cardiac arrest.
   (A) 3 to 4 hr (B) 24 hr (C) 48 hr (D) 72 hr

6. Which of the following is an indication for early therapeutic hypothermia?
   (A) Traumatic brain injury
   (B) Middle cerebral artery infarction
   (C) Hypoxic ischemic coma from out-of-hospital arrest
   (D) Brain edema

7. Patients with agitated delirium have poorer outcomes than those who show withdrawn delirium.
   (A) True (B) False

8. Choose the correct statement(s) about delirium.
   (A) Changes in the level of consciousness are often associated with injuries to the brainstem
   (B) Changes in the content of consciousness are often caused by medications
   (C) A study showed the number of days of delirium predicted overall outcome among a population of patients
   (D) A, B, and C

9. Which of the following conditions is least likely to cause an isolated alteration in content of consciousness?
   (A) Hypoglycemia (B) Acidosis (C) Vasculitis (D) Infection

10. Which of the following treatments should not be given initially to a patient with delirium and there is no information or evidence about its cause?
    (A) Oxygen (if patient hypoxic) (C) Glucose (if patient hypoglycemic)
    (B) Naloxone (D) Flumazenil

Answers to Audio-Digest Neurology Volume 04, Issue 06: 1-B, 2-D, 3-D, 4-D, 5-B, 6-C, 7-B, 8-D, 9-C, 10-B