



# TTM

## **Targeted Temperature Management (TTM) in Acute Neurologic Injury**

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Neurocritical Care Society.

# TTM

## Targeted Temperature Management (TTM) in Acute Neurologic Injury

### Program Overview

This activity is targeted to the multidisciplinary team treating and caring for patients undergoing Targeted Temperature Management (TTM) for acute neurological illnesses in the critical care setting, specifically post cardiac arrest, brain injury traumatic brain injury, acute ischemic and hemorrhagic stroke, hepatic encephalopathy and fever control. It provides detailed practical approaches on the delivery of TTM: induction, maintenance, rewarming and maintenance of normothermia in different settings and acute neurological illnesses. Complications and anticipated side effects of cooling are discussed to maximize the benefit of cooling for approved indications.

### Target Audience

This enduring program has been designed for practicing physicians, physicians in training, advanced practice and staff nurses, pharmacists, physician assistants, clinical nurse specialists, emergency care providers, including EMTs and paramedics; researchers, students, all professionals providing care in the critical care setting.

### Learning Objectives

Upon completion of the educational activity, participants should be able to:

- Examine the impact and benefit of temperature control in the Neuro population
- Compare the role of hypothermia in cardiac arrest, TBI, stroke and hepatic encephalopathy
- Define complications associated with TTM
- Explain how to implement a TTM program



**CME/CE Credit provided by AKH Inc., Advancing Knowledge in Healthcare**

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Activity is jointly-provided by  
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### Commercial Support

This activity is supported by an educational grant from The Global Science Center for TTM underwritten by Bard Medical.

## FEATURED FACULTY

### **Chad Miller, MD**

System Medical Chief  
Neurocritical Care and Cerebrovascular Diseases  
Columbus, Ohio

*Dr Miller discloses no financial relationships with pharmaceutical or medical product manufacturers.*

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### **Michelle Hill, MS, RN, AGCNS-BC, CNRN, CCRN, SCR**

Stroke Program Coordinator  
OhioHealth – Riverside Methodist Hospital  
Columbus, Ohio

*Dr Hill has disclosed the following relevant financial relationships: Speakers Bureau - Bard Medical*

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## STAFF/PLANNERS/REVIEWERS

### **Romergrzyko G Geocadin, MD, FNCS- Planning Committee**

*Discloses no financial relationships with pharmaceutical or medical product manufacturers.*

### **Alejandro Rabinstein MD- Peer Reviewer**

*Discloses no financial relationships with pharmaceutical or medical product manufacturers.*

### **Dorothy Caputo, MA, BSN, RN- Lead Nurse Planner**

*Discloses no financial relationships with pharmaceutical or medical product manufacturers.*

### **Bernadette Marie Makar, MSN, NP-C, APRN, BC- Nurse Planner**

*Discloses no financial relationships with pharmaceutical or medical product manufacturers.*

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NO CREDIT WILL BE GIVEN PAST THIS DATE.**

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## Targeted Temperature Management (TTM) in Acute Neurologic Injury

**Chad M. Miller, MD**

*System Medical Chief*

*Neurocritical Care and Cerebrovascular Disease*

*Columbus, Ohio*

**chad.miller2@ohiohealth.com**

**Michelle Hill, MS, RN, AGCNS-BC, CNRN, CCRN, SCRNI**

*Stroke Program Coordinator*

*OhioHealth – Riverside Methodist Hospital*

*Columbus, Ohio*

**Michelle.Hill@ohiohealth.com**

## INTRODUCTION

### History of Therapeutic Hypothermia and Targeted Temperature Management

Interest in induced hypothermia for medical purposes began in 1803 when Russian physicians documented covering patients with snow in order to assist with resuscitative efforts.<sup>1</sup> By the 1950's, therapeutic hypothermia was being intermittently used for neurologic patients to decrease intracranial pressure and preserve brain function. Unfortunately, the sophistication of critical care at that time lacked the capability to closely monitor the patient resulting in poor outcomes and unpredictable medical management.<sup>2</sup> The 1960's through the 1990's saw a subsequent decline in the use of therapeutic hypothermia as clinicians struggled to manage the multiple medical complications.<sup>1</sup>

In 2002, the *American Heart Association* released guidelines recommending use of therapeutic hypothermia for out-of-hospital cardiac arrest patients who remained comatose.<sup>3,4</sup> Subsequently, leading national and international professional organizations released guidelines recommending use of therapeutic hypothermia for this patient population.<sup>5,6</sup> Additionally, a wealth of data has been published describing the negative impact of fever in neurologic patients. These factors have renewed focus on exploring the potential benefits of targeted temperature management (TTM) across the spectrum of neurological injury.

## Concepts of Neuroprotection

Given the sensitivity of the brain and nervous system to insult and the devastating and permanent consequences of neurological injury, the last several decades have seen an exhaustive search for neuroprotective therapies. Specific physiologic pathways involved in injury have been defined and chemotherapeutics have been designed to impact these pathways of injury. The agents that have been studied to limit subsequent injury include ion channel blockers, NMDA and AMPA antagonists, magnesium, and aminobutyric acid agonists.<sup>7</sup> Many of these strategies experienced promising success in animal models of injury, but nearly all have failed to deliver similar therapeutic efficacy when applied to human disease. It was eventually discovered that the mechanisms of secondary injury are modulated by numerous pathways and attempts to inhibit any single mechanism of injury was circumvented by redundant biochemical pathways. In short, a search for a “silver bullet” to minimize injury was misguided. An effective neuroprotective therapy would have to simultaneously impact a multitude of pathways capable of mitigating secondary neurologic damage. To date, TTM has proven to be the most encouraging neuroprotective candidate.

## Defining Hypothermia and Normothermia

Historically, therapeutic implementation of hypothermia has aimed to optimize clinical benefits while minimizing the adverse effects of cooling. As a result, most clinical trials have focused on attainment of mild hypothermia. Polderman and Herold define therapeutic hypothermia as a temperature reading between 32°C-35°C.<sup>8</sup> Prescutti, Bader and Hepburn reported therapeutic hypothermia as a temperature reading of 33°C.<sup>9</sup> Lyden, et al. define mild hypothermia as temperatures between 32°C-35°C, moderate hypothermia between 25°C-32°C, and severe hypothermia as temperatures below 25°C.<sup>10</sup> Considering the variation in nomenclature, it is recommended that cooling be described by the specific target range, rather than subjective terms such as mild and moderate.<sup>11</sup>

While normothermia is most accurately described by a physiologic temperature range, it has traditionally been defined as 98.6 °F or 37.0 °C. There is considerable debate regarding the temperatures at which normothermia transitions into fever or hypothermia. Mild elevations of temperature have been shown to have deleterious physiologic effects.<sup>12</sup> Maintenance of body temperature in the lower ranges of normothermia almost inevitably requires active TTM.

## Defining Fever

The majority of experts define fever as a temperature  $>38.3^{\circ}\text{C}$ .<sup>13, 14, 15</sup> There are two terms commonly used to describe an elevated temperature. The term fever is used when the cause is due to a reactive physiologic response.<sup>16</sup> The term central or neurogenic fever is used when the cause is thought to be related to damage to the centers and pathways of temperature regulation in the central nervous system (hypothalamus).<sup>17</sup> Several neurologic conditions have been associated with the development of neurogenic fevers; vasospasm, white matter diffuse axonal injury, intraventricular hemorrhage and intracranial hemorrhage.<sup>16</sup>

Badjatia reported that when fever develops during the ICU stay, there is a higher associated mortality than if fever is present on admission.<sup>18</sup> Therefore, constant observation of temperature trends is warranted when the patient is in the ICU setting. Uncertainty remains as to how and when to treat fevers.

There are several ways to measure a patient's temperature; oral, axillary, rectal, bladder, pulmonary artery catheter, tympanic membrane, esophageal and brain.<sup>16</sup> While invasive in nature, direct measurement of brain temperature provides the most reliable and direct method of temperature assessment in the brain injured patient. Differences of up to 2°C can be found when comparing core body temperature with brain temperature.<sup>19</sup> Recording temperature through a pulmonary artery catheter is considered the best assessment for core temperature when brain monitoring is not available.<sup>16</sup> Bladder measurements were found to be the closest to brain temperature when a pulmonary artery measurement was not available and are most commonly used.<sup>15</sup> Esophageal measurements were also found to be as reliable as pulmonary artery sources. Bladder sources are the next best option if esophageal measuring is not available, however, bladder sources are reliant on adequate urinary output.<sup>66</sup> When comparing esophageal and bladder temperature sources the esophageal temperature source responds more rapidly to temperature changes during initiation of TTM making this a better choice for accurate temperature modulation.<sup>67</sup> Considering the poor correlation with core temperature and susceptibility to vascular shunting during shivering, skin surface and axillary methods of temperature acquisition are not favored for TTM.

Fever is common in acute illness. Because the absolute value of TTM for fever is unproven, a reasonable approach to temperature monitoring must be taken to optimize potential treatment benefits while still remaining mindful of expense and resource utilization.

### **Impact of Fever**

Fever is an adaptive response by the body to fight infection. While it is protective and not routinely deleterious in many circumstances, the adverse effects of elevated temperature appear to be particularly pronounced in the brain injured patient.<sup>16</sup> Brain injury, regardless of its source, includes damage related to the initial insult and subsequent secondary injury. Fever is postulated to propagate secondary injury through a variety of pathophysiologic mechanisms. Release of excitatory amino acids and neurotransmitters are temperature dependent.<sup>18, 19</sup> Glutamate and dopamine release are modifiably dependent upon temperature and result in enhanced calcium cellular influx and lipid peroxidation during fever. Similarly, the inflammatory cytokine cascade and ion channels vital to cytoskeletal function and neuronal membrane integrity are temperature sensitive and exacerbated by fever. Conversely, reproduction of free radicals is reduced with fever control, and cooling, in experimental environments, has been shown to up-regulate genes that produce anti-apoptotic proteins.<sup>19</sup> Fever damages endothelial cells responsible for blood brain barrier integrity.<sup>18</sup> This fact, combined with augmented glutamate release, account for worsening of brain edema noted with fever. Furthermore, elevated brain temperatures result in and from increased metabolic demand. Adenosine triphosphate (ATP) production is accompanied by generation of heat during oxidative phosphorylation and electron transport in the cellular mitochondria. For every degree Celsius elevation in body temperature, brain metabolism is increased 6-8%.<sup>20</sup>

The clinical impact of fever on brain injured patients has been studied extensively. While fever is common in critical illness, brain temperature is often independent of and elevated above body temperature.<sup>19</sup> During fever, the gap between systemic and brain temperature increases.<sup>18</sup> Clearance of intracranial heat production is dependent upon cerebral blood flow (CBF) and compromises in regional perfusion may lead to local variations in temperature. Admission temperature is predictive of infarct size and outcome in acute ischemic stroke (AIS).<sup>21</sup> While this is true throughout the course of

acute stroke, fever that persists late into hospitalization appears to be even more damaging to clinical outcomes.<sup>22</sup> Fever complicates acute stroke in the first 48 hours in more than 25% of cases.<sup>23</sup> A large meta-analysis comprising nearly 3000 stroke patients concluded that fever early in the course of hospitalization doubles the 30 day mortality rate.<sup>24</sup> These findings have been corroborated by many other studies which have also correlated fever to length of stay and clinical outcomes assessed by various measures.<sup>25</sup> Fever within the first 72 hours following spontaneous intraparenchymal hemorrhage (IPH) impacts clinical recovery.<sup>18</sup> Cerebral edema follows a more protracted course after IPH compared to AIS. The escalation in metabolic rate attributable to fever increases local blood flow and exacerbates perihematomal edema. Aneurysmal subarachnoid hemorrhage (aSAH) appears to have a protracted sensitivity to fever, perhaps due to the extended risk of ischemic injury. Fever greater than 38.3 °C occurs in 72% of aSAH patients.<sup>26</sup> Every degree Celsius increase above 38.3 °C is associated with a 22-fold increase in mortality. Comparable effects have been demonstrated regarding morbidity and long term cognitive impairment.<sup>27</sup> Fever is common after severe traumatic brain injury (TBI) with over 2/3 of patients experiencing elevated temperatures in the first 72 hours of hospitalization. Fever in the first week appears to adversely impact recovery and can worsen edema and intracranial pressure control.<sup>27, 28</sup>

### **Benefits of Normothermia**

Despite extensive evidence regarding the impact of fever on neurological patients, there are no large randomized trials investigating the impact of fever control on clinical outcomes. Considering the relative acceptance and adoption of normothermic goals among the neuroscience community, this question may never be addressed in a randomized study with a comparative febrile cohort. In controlled animal models of stroke, fever reduction has been shown to reduce infarct size.<sup>29</sup> Maintenance of normothermia stabilizes the blood brain barrier, reduces cerebral metabolism, and lowers free radical production.<sup>18</sup> While this is not equivalent to improved outcome, per se, these are the chief mediators of secondary injury. A case-controlled series of aSAH patients showed that application of therapeutic normothermia for the first 2 weeks after aneurysm rupture led to improved 12 month outcomes.<sup>69</sup> aSAH is a desirable candidate for TTM since cooling can potentially begin prior to onset of vasospasm related ischemic risks. Prophylactic cooling has yielded the most promising results in animal models of hemorrhage.

Current guideline recommendations for control of fever provide restrained and non-specific recommendations for maintenance of normothermia in brain injured patients.<sup>30,31,32</sup> Given the compelling data equating fever with adverse outcome, the pathophysiologically sound premise supporting treatment, and the demonstrated safety of implementation, it is reasonable to aggressively pursue treatment of fever in the acute management of all severely brain injured patients.

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## **THERAPEUTICALLY INDUCED HYPOTHERMIA**

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### **Cardiac Arrest**

Much of the interest for induced hypothermia as a neuroprotective therapy for brain injured patients is derived from its proven success in the treatment of anoxic brain injury after cardiac arrest (CA). In 2002, two multicenter randomized trials were published demonstrating the efficacy of induced

hypothermia after cardiac arrest due to ventricular fibrillation (VF) or non-perfusing ventricular tachycardia (VT).<sup>3,4</sup> The Hypothermia After Cardiac Arrest (HACA) Working Group randomized 277 patients to either normothermia or surface cooled hypothermia (32-34 °C) within 6 hours after return of spontaneous circulation (ROSC).<sup>3</sup> Patients in the hypothermia group were treated for 24 hours and then slowly rewarmed. Patients were eligible for randomization if they were adult, had suffered a witnessed out of hospital arrest of presumed cardiac origin, had ROSC within 1 hour of arrest, and lacked a meaningful response to verbal stimuli after resuscitation. Subjects were excluded if they were hypothermic on presentation (< 30 °C), comatose prior to arrest, pregnant, persistently hypotensive (> 30 minutes MAP < 60 mm Hg), had a pre-existent coagulopathy, or were hypoxic (O2 saturation < 85% for > 15 minutes). Blinded assessment revealed improvement in 6 month mortality (41% vs. 55%) and good neurological outcome (55% vs. 39%) for the group treated with hypothermia.<sup>3</sup> A multi-center Australian trial demonstrated similar findings in 77 ventricular fibrillation patients treated within 2 hours of cardiac arrest. The mild hypothermia cohort underwent 12 hours of cooling at 33 °C with a favorable portion of patients achieving good outcome at discharge (home or rehabilitation: 49% vs. 26%).<sup>4</sup>

These two sentinel trials have been followed by numerous others that have corroborated their findings. As a result, mild hypothermia after out-of-hospital cardiac arrest has become standard of care and received the highest endorsement in the International Resuscitation Guidelines for patients successfully resuscitated from ventricular fibrillation or non-perfusing ventricular tachycardic arrest.<sup>5</sup> Treatment of six VF / VT arrest patients with induced hypothermia will result in 1 additional patient with a good neurological outcome.<sup>2</sup>

The decision to enroll VF and VT patients with witnessed out of hospital arrest in the early trials were based upon the desire to select patients most capable of survival and demonstration of improved neurologic recovery. The vast majority of out of hospital arrests (60-80%) are due to non-shockable rhythms whose victims are likely to suffer similar mechanisms of anoxic brain damage.<sup>33</sup> A retrospective study of induced hypothermia (32-33 °C for 24 hours) for non VF/VT arrest showed benefit compared to results in a non-cooled cohort. Six month mortality (61% vs. 75%; OR 0.51 95% CI 0.33-0.80) and favorable functional outcomes (35% vs. 23%, OR 1.84, 95% CI 1.08-3.13) were improved in the hypothermic group.<sup>33</sup> Other retrospective and prospective studies assessing non-VF / VT and in-hospital arrest have revealed similar findings leading to the conclusion that induced hypothermia may also be beneficial for these clinical scenarios.<sup>5</sup>

There has been recent interest in exploring the temperature thresholds responsible for the neuro-protective effects of hypothermia after cardiac arrest. A recent multicenter trial randomized 939 out-of-hospital unconscious cardiac arrest patients of presumed cardiac origin to receive hypothermia at either 33 or 36 °C for 28 hours (intravenous or surface cooling). Patients in each cohort underwent a slow rewarming protocol with maintenance of normothermia for an additional 72 hours after rewarming. Immediate and 180 day mortality and poor neurological function rates were similar for the two groups.<sup>34</sup> While this study showed that the effective temperature range for induced hypothermia requires further definition, the benefits of targeting a higher temperature are not readily apparent. In fact, shivering is often more difficult to control at higher temperature targets. Prolonged continuance of normothermia after rewarming represented a novel protocol variation that may prove beneficial regardless of goal target temperatures.

The increasing use of induced hypothermia after cardiac arrest has challenged prior established timelines and protocols for determination of prognosis. Classical prognostic methodology developed prior to widespread TTM suggested that 24 hour post arrest pupil and 72 hour motor exams were highly predictive of recovery potential.<sup>35</sup> Early prognosis is commonly delivered after cardiac arrest, yet a fair number of patients regarded as having a poor prognosis for recovery had been noted to have outcomes better than anticipated,<sup>36</sup> particularly after completing hypothermic treatment. Mounting evidence is challenging the prognostic reliability of 72 hour post arrest examinations in cooled patients.<sup>37</sup> New paradigms recommend assessing the clinical exam at least 72 hours after rewarming and encourage liberal use of supporting tests to assist in clinical projection (SSEP, EEG, brain MRI, biomarkers). Rendering prognosis after longer delays in patients undergoing TTM appear to improve the sensitivity and accuracy of the prediction.<sup>38</sup> Of the available supporting data, continuous EEG (cEEG) is particularly valuable in the assessment of the cardiac arrest patient. Seizures have been reported to occur in 19-34% of patients after arrest,<sup>39</sup> the majority of which are non-convulsive and clinically unapparent.<sup>40</sup> Refractory seizures are associated with poor outcome after CA.<sup>40</sup> While data associating the treatment of CA associated seizures with improved outcome is not available, some patients with status epilepticus have achieved good outcomes. cEEG is required to guide management of this sub-group. Furthermore, cEEG is valuable in distinguishing post anoxic myoclonus from seizure activity and provides insight regarding the physiologic persistence of sedating medications that may be affecting the clinical exam. Irrespective of the identification of seizure activity, background cEEG rhythm and reactivity has prognostic value. Appropriate care of the non-responsive post cardiac arrest patient requires cEEG monitoring.

### **Traumatic Brain Injury**

The multitude and complexity of injury mechanisms characteristic of TBI has fueled the notion that induced hypothermia might provide neuroprotective benefit for this patient population. In fact, a 2009 review by Polderman, 13 of the 18 randomized trials addressing induced hypothermia after TBI reported improved outcomes.<sup>2</sup> These trials differed considerably regarding the type and number of patients enrolled, temperature targets, treatment duration and several other characteristics. A 2001 multi-center randomized trial attempted to uniformly assess the clinical impact of TTM on TBI. The trial showed no clear benefit of induced hypothermia, but was limited by significant inter-facility variance in efficacy and overall late attainment of target temperatures.<sup>41</sup> More recently, the National Acute Brain Injury Study (NABISH) II trial assessed ultra-early (< 2.5 hours) induction of hypothermia (33-35 °C) in 232 TBI patients through a protocol designed to correct some of the concerns of earlier trials. Nonetheless, no difference was seen in 6 month outcomes with the possible exception of benefit in a small cohort of patients with evacuated hematomas.<sup>42</sup> The disparity of results from early and more recent trials has been discouraging. Post-hoc analyses and subsequent single center trials have identified rate of rewarming and duration of induced hypothermia as pivotal determinants of efficacy. Whereas the clinical benefit of hypothermia as a neuroprotectant remains unproven, essentially all trials of hypothermia in TBI appear to show significant lowering of intracranial pressure<sup>2</sup> (See Table 1). Most recently, the Eurotherm trial explored benefits of TTM in the clinical outcome of severe TBI patients with elevated intracranial pressures.<sup>68</sup> Despite the demonstrated benefits on intracranial hypertension for this cohort, cooling was not associated with improved 6 month outcomes.

**Table 1.** Evidence for benefit of Targeted Temperature Management (TTM) in various neurological injuries.

| Type of Neurological Injury and TTM            | Evidence for Efficacy                                                                                       |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Fever Control after Neurological Injury *      | No RCT<br>Clinical benefits seen in animal studies<br>Favorable results seen in human case series           |
| TIH Out-of-Hospital Cardiac Arrest (VF / VT)   | Mortality and morbidity benefit shown in multiple multi-center RCT                                          |
| TIH Cardiac Arrest (non-shockable or in house) | Clinical benefit shown in retrospective and small single center trials                                      |
| TIH Severe TBI (neuroprotection)               | Multiple single center trials with clinical benefit<br>No multi-center RCT with benefit                     |
| TIH Severe TBI (ICP control)                   | Numerous single and multi-center RCT suggest benefit with ICP control with no benefit to patient outcome.   |
| TIH Hemorrhagic Stroke (aSAH / IPH)            | Small studies have demonstrated feasibility<br>Case series have shown reduced edema                         |
| TIH Ischemic Stroke                            | Feasibility shown in numerous trials<br>Reduced stroke volume in animal studies<br>Multi-center RCT ongoing |
| TIH Hepatic Failure                            | Case series have shown metabolic improvement and ICP control                                                |

RCT = Randomized Clinical Trial, TIH = therapeutic induced hypothermia, VF / VT = ventricular fibrillation / pulseless ventricular tachycardia, TBI = traumatic brain injury, ICP = intracranial pressure, aSAH = aneurysmal subarachnoid hemorrhage, IPH = intraparenchymal hemorrhage,

\* refers to TTM target goal of normal temperature.

### Hemorrhagic Stroke

Evaluation of TTM after spontaneous IPH is relatively limited compared to CA and TBI. A small trial of prolonged mild hypothermia (35 °C for 10 days) demonstrated stability in hematoma size in the cooled cohort, while 25 age-matched controls experienced doubling of the edema volume.<sup>43</sup> A similar study of 25 IPH patients undergoing endovascular cooling (8-10 days at 35 °C) showed less perihematoma edema that became significant at 3 days and persisted throughout the duration of the study. Three month (8.3% vs. 16.7%) and 1 year mortality rates (28% vs. 44%) were better in the cooled patients.<sup>44</sup>

Use of TTM in aSAH is limited to small case series. Reduction of brain edema after aneurysm rupture has been shown by Gasser and colleagues.<sup>45</sup> Several animal studies have demonstrated improved ICP control with induced cooling.<sup>46</sup>

### **Ischemic Stroke**

TTM holds potential benefit in complicated acute ischemic stroke both as a neuroprotectant and as a treatment for malignant edema.<sup>47, 48</sup> Hypothermic rats have attenuated infarct volumes compared to normothermic animals.<sup>49</sup> Feasibility for cooling humans was demonstrated by both the Cooling for Acute Ischemic Brain Damage (COOL-AID) and Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTus-L) studies.<sup>50, 51</sup> In the latter trial, post IV-tPA patients were randomized to 24 hours of cooling at 33 °C within 6 hours after stroke onset. While safety was demonstrated, pneumonia rates were elevated in the cooled patients, raising concerns for the practicality of cooling non-intubated patients with large strokes. Neither trial was powered to assess clinical outcomes, but a larger multi-center ICTus 2/3 trial is currently enrolling patients. In the Reperfusion and Cooling in Cerebral Acute Ischemia (RECCLAIM 1) trial, the safety and feasibility of intravascular cooling was demonstrated in patients undergoing endovascular therapy.<sup>52</sup> Interestingly, reperfusion hemorrhage risks did not appear to be increased.

### **Hepatic Failure**

Acute hepatic failure can result in life threatening diffuse cerebral edema.<sup>52</sup> Numerous case series have shown the value of TTM in controlling intracranial hypertension.<sup>53</sup> Induced hypothermia may delay disease progression to allow for identification of a suitable transplant donor.<sup>54</sup> TTM also decreases splanchnic ammonia production and lowers oxidative brain metabolism. Many of the potential side effects of TTM, such as coagulopathy and thrombocytopenia, mirror those associated with acute liver failure. Nonetheless, increased risk of bleeding has not been consistently reported among those patients treated with hypothermia. A randomized trial is needed to establish benefits of TTM for this indication.

### **Implementation of Therapeutic Temperature Management**

Various approaches and devices exist for the induction, maintenance, and rewarming phases of TTM. For most hypothermia indications, the rapidity of cooling is vital for clinical efficacy. Traditionally, ice packs and surface cooling measures have been used due to their low cost and widespread availability. More recently, chilled saline (4 °C) boluses have been adjunctively used to facilitate cooling induction. A pilot study of 2 L 4 °C saline infusion over 20-30 minutes lowered core temperatures in CA patients by 1.4 °C within 30 minutes without adverse effects.<sup>55</sup> A similar study in stroke patients reported a 2.1 °C drop with a 30 cc / kg 4 °C saline bolus.<sup>56</sup> For ventilated patients, the temperature of the humidified air may be lowered to 34 °C with infrequent adverse effects on volume of pulmonary secretions. This is a particularly useful approach to assist cooling considering the expansive alveolar surface area of the lung. Aspirin, acetaminophen, and non-steroidal agents have been used adjunctively for TTM. These agents chiefly work through the cyclooxygenase pathway to modify the hypothalamic temperature set point. Acetaminophen has been shown to be effective in reducing fever burden in the stroke population.<sup>18</sup> Ibuprofen, diclofenac sodium, and other anti-pyretics are less well studied, and may not be safe in the patient with intracranial hemorrhage. When thermoregulation is impaired due to brain injury, the medicinal approach to fever control is seldom effective.<sup>18</sup> Cold water baths and alcohol rubs are often used to promote evaporation and cooling from the skin surface. Local head cooling, utilizing nasal catheters and helmet cooling

devices, has been attempted to circumvent the burden of whole body cooling. In the RhinoChill study, a perfluorocarbon was perfused through a two pronged nasal catheter for 1 hour to facilitate cooling induction.<sup>16</sup> A 1.4 °C drop in brain temperature was seen with good patient tolerability. Maintenance of temperature is achievable by several different methods. External cooling exerts its effects without dependence upon manipulation of the hypothalamic set point.<sup>18</sup> Basic exposure of the skin results in loss of heat through radiation. Convective heat loss can be achieved by circulating air cooling blankets or fans blowing across the surface of the patient's body. Evaporation of fluid from the skin surface may be accomplished with sponge baths. Axillary and groin ice packs and water circulating cooling blankets remove body heat by conduction. All surface cooling strategies risk shivering and peripheral vasoconstriction which may undermine cooling efforts.<sup>18</sup> A variation on surface cooling is the development of adhesive gel pads which circulate chilled saline whose temperature is managed by a temperature probe feedback. These devices have been shown to be more effective than traditional surface cooling methods in some comparative studies.<sup>57</sup> In a prospective study of a novel gel pad cooling device with direct feedback thermoregulation in CA patients, use of the device resulted in a nearly one hour reduction in target temperature attainment compared to cooling with standard blankets and ice packs.<sup>58</sup>

Cooling may also be achieved by placement of an intravascular cooling catheter. These catheters cool the surrounding blood by conduction via a metallic tip on the end of the catheter or by oscillating balloons through which cooled saline is perfused. Various models of cooling catheters exist, each having a different size or location of venous access. In a two center critical care study of 102 patients with aSAH, ICH, and complicated stroke, use of a cooling catheter resulted in an 83% reduction in the hourly fever burden compared to an aggressive preventative protocol utilizing conventional cooling measures.<sup>59</sup>

Special clinical circumstances afford the opportunity for other TTM approaches. Extracorporeal Membrane Oxygenation (ECMO) is occasionally used for resuscitation from cardiac arrest, albeit with poor outcomes.<sup>60</sup> Body temperature may be regulated with the ECMO device without the need for additional cooling devices.

Numerous single center studies have compared adhesive surface cooling and intravascular cooling devices.<sup>61</sup> In general, the times to cooling and clinical outcomes are similar between devices. Some studies report less temperature variation with use of the intravascular catheters.<sup>61</sup> Choice of device should consider institutional familiarity with the commercial products and availability of personnel to minimize delays in cooling initiation. Cooling products possessing automated temperature feedback can be used to limit overshoot and fluctuations in body temperature.

Rewarming after TTM should be slow and controlled ( $\leq 0.25$  °C per hour) for all indications. When the indication for TTM is ICP or edema control, a slower rewarming rate may be indicated and careful monitoring is required.

Infection reconnaissance is challenging during TTM. Many practitioners look at trends in the water cooling temperature ( $< 10$  °C) to determine the thresholds for culture.<sup>18</sup> White blood cell trends and intermittent chest radiograph imaging are also useful.

## COMPLICATIONS AND SIDE EFFECTS OF TTM

### Shivering

Shivering has been defined as “the presence of high frequency shaking that is palpable in the masseter, deltoid, or pectoralis muscles” and it is one of the most common complications seen in temperature management.<sup>13</sup> Shivering is an involuntary response to a temperature decrease of 1°C below the patient’s shivering threshold.<sup>9</sup> The metabolic rate is increased 2-5 times normal as a result of vasoconstriction and muscle contraction accompanying shivering.<sup>9, 16</sup> Shivering is the body’s attempt at increasing core temperature, but can also have an adverse effect of increasing systemic oxygen consumption, decreasing brain tissue oxygenation and increasing intracranial pressure.<sup>14</sup> Control of shivering is important to decrease these unintended consequences, especially when temperature control is used for neuroprotection.

### Shivering assessment tools

Shivering can be a subjective term. To enable a more consistent approach to treatment, assessment tools and scales are important to standardize examination and documentation techniques. Badjatia, et.al. developed a simple and effective assessment scale for shivering.<sup>62</sup> The Bedside Shivering Assessment Scale (BSAS) is widely used to assess shivering for both hypothermia and normothermia (See Figure 1).

**Figure 1. Bedside Shivering Assessment Score (BSAS). The BSAS is a 4 point scale that allows objective assessment of the degree of shivering to guide therapy.<sup>14</sup>**

| SCORE 0            |                                                                                              |
|--------------------|----------------------------------------------------------------------------------------------|
| No shivering       | No shivering is detected on palpation of the masseter, neck, or chest muscles.               |
| ↓                  |                                                                                              |
| SCORE 1            |                                                                                              |
| Mild shivering     | Shivering is localized to the neck and thorax only.                                          |
| ↓                  |                                                                                              |
| SCORE 2            |                                                                                              |
| Moderate shivering | Shivering involves gross movement of the upper extremities (in addition to neck and thorax). |
| ↓                  |                                                                                              |
| SCORE 3            |                                                                                              |
| Severe shivering   | Shivering involves gross movements of the trunk and upper and lower extremities.             |

The patient's age can play a significant role in how quickly the patient will begin shivering. Elderly patients begin shivering at lower core temperatures than younger patients.<sup>9</sup> A greater incidence of shivering is seen in men and patients with hyponatremia or hypomagnesemia.<sup>13</sup> The BSAS has been validated and proven to have inter-rater reliability across a diverse group of practitioners.<sup>9,63</sup> The BSAS is scored from 0-3 with 0 representing no shivering and 3 denoting severe shivering. The assessment should be performed regularly and is assessed by palpating the patient's neck masseter and chest muscles for up to two minutes.<sup>9</sup> There are other methods to assess for shivering, including the use of EMG electrodes on the pectoralis muscles. However, the use of EMG requires specialized equipment and data interpretation and can be less practical for routine use.<sup>9</sup>

### Controlling Shivering

Early treatment of shivering is important. Implementation of anti-shivering measures prior to the initiation of cooling can decrease the amount of shivering experienced.<sup>14</sup> Counterwarming is an effective early strategy to limit shivering which can be achieved by placing mittens on the hands or socks on the feet, warm blankets wrapped around the patient's extremities, or a warm air conduction blanket. The shivering set point receives 20% of its input from the skin. Additionally, hands and feet have a disproportionate concentration of temperature receptors, so counterwarming of these regions is particularly useful. Warming the skin to temperatures higher than core body temperatures will alter the perception of actual temperature and decrease the amount of counterproductive shivering.<sup>9</sup>

Acetaminophen is a central temperature modulator which acts to lower the hypothalamic set point.<sup>8</sup> Little effect may be seen if the source of the increased temperature is related to damage of the central nervous system.<sup>8</sup> Scheduled doses up to 650mg every 4 hours can be started at the beginning of temperature management. Daily laboratory assessment should include liver function tests to observe for hepatic injury related to systemic hypoperfusion or acetaminophen dosing. Buspirone hydrochloride is a neurotransmitter agonists that causes vasodilation of the peripheral vasculature through stimulation of the vagus nerve. It works synergistically with other anti-shivering medications, particularly meperidine.<sup>14</sup> Buspirone should be started at the beginning of temperature management and given around the clock. The recommended dose of Buspirone is 30 mg every 8 hours.

Magnesium is a known vasodilator that facilitates the cooling process. It can also cause hypotension and magnesium serum concentration and blood pressure should be monitored.<sup>9</sup> An effective dose of magnesium is 0.5-1mg/hr intravenously and the goal should target serum concentrations of 3-4mg/dl.<sup>14</sup>

Mild sedation with dexmedetomidine or opioid agents is effective in reduction of shivering. Choice of medication should consider the clinical situation. Dexmedetomidine has been observed to cause bradycardia and mild hypotension, but is effective for a patient with agitation.<sup>14</sup> Opioids are an alternative to dexmedetomidine for patients who are not agitated. Meperidine is an effective anti-shivering narcotic but the metabolic byproducts of meperidine may lower the seizure threshold in a dose dependent fashion. As with any critically ill patient, the hemodynamic and metabolic state needs to be considered when contemplating the best tactics for shivering control. Sedation during hypothermia should always be targeted to an objective level of measured sedation. The Richmond Agitation Sedation Score (RASS) is commonly used with a target sedation goal of -3 to -4 (See Figure 2).<sup>64</sup>

## Figure 2. Richmond Agitation Sedation Scale (RASS).<sup>64</sup>

The RASS may be used to assess alertness during therapeutic temperature management. Verbal stimulation should be completed by stating the patient's name and asking the patient to open his/her eyes and direct gaze toward the examiner. Tactile stimulus is required if there is no response to verbal stimulation and involves shaking of the shoulder or rubbing of the patient's sternum.

| Score | Term              | Description                                                                                |
|-------|-------------------|--------------------------------------------------------------------------------------------|
| +4    | Combative         | Overtly combative, violent, immediate danger to staff                                      |
| +3    | Very Agitated     | Pulls or removes tubes or catheters, aggressive                                            |
| +2    | Agitated          | Frequent non-purposeful movement, fights ventilator                                        |
| +1    | Restless          | Anxious, but movements are not aggressive                                                  |
| 0     | Alert and Calm    |                                                                                            |
| -1    | Drowsy            | Not fully alert, sustained awakening to voice (eye-opening / eye contact for > 10 seconds) |
| -2    | Light Sedation    | Briefly awakens with eye contact to voice (<10 seconds)                                    |
| -3    | Moderate Sedation | Movement or eye opening to voice, but no eye contact                                       |
| -4    | Deep Sedation     | No response to voice, but movement or eye opening to physical stimulation                  |
| -5    | Unarousable       | No response to voice or physical stimulation                                               |

Refractory shivering may be treated with the use of propofol. Many TTM patients will already be on a propofol infusion for sedation. The doses used for sedation are lower than the dose recommended for shivering control. The latter recommended dose for propofol is 50-75mcg/kg/min infusion. At this dosing level, propofol causes peripheral vasoconstriction and lower shivering thresholds.<sup>14</sup> Daily monitoring of serum creatine kinase, pH, and triglyceride levels are appropriate due to concerns of propofol infusion syndrome.

The most aggressive and definitive step to control shivering is use of neuromuscular blockade. While remarkably effective, this approach compromises the ability to complete a neurologic exam. As a result, anytime neuromuscular blockade agents (NMBA) are utilized, adequate sedation and pain management are required. NMBA effectiveness can be monitored by a train of four (TOF), however there is some concern that a TOF is an unreliable measure of paralysis in the setting of hypothermia.

## Electrolyte Disturbances

Electrolyte disturbances are commonly seen during TTM and rewarming. Many electrolytes shift in and out of cells changing their serum levels and renal excretion.<sup>8</sup> Hypokalemia, caused by potassium

shifting into the cell, is common during cooling. However, with rewarming, the potassium will shift back out of the cell, placing the patient at risk of profound hyperkalemia. Therefore, potassium should be replaced carefully, and rewarming should occur slowly. Hypothermic patients may become hyperglycemic due to reduced insulin secretion in the pancreas.<sup>8</sup> Response to insulin infusion may also be blunted due to temperature related insulin resistance.<sup>65</sup> Markedly elevated levels of serum glucose can exacerbate secondary ischemic brain injury. Close monitoring and implementation of continuous insulin drips may be necessary.

### **Cardiac Abnormalities**

Cardiac abnormalities may occur as a result of hypothermia or electrolyte abnormalities. The most common cardiac abnormalities are mild sinus tachycardia during induction, and sinus bradycardia, prolonged PR interval, widened QRS interval and increased QT interval during the maintenance phase.<sup>8</sup> The bradycardia that occurs during hypothermia is a normal physiologic response and does not require specific treatment if blood pressure is preserved. Treatment of the bradycardia can result in a decrease in the myocardial contractility.<sup>8</sup> Hemodynamic instability can also result from hypovolemia and may occur during the TTM induction phase.<sup>8</sup> A simple way to determine if hypovolemia is present is to assess the response to fluid boluses. More malignant cardiac arrhythmias can be seen with greater depths of induced hypothermia. For this reason, it is important to avoid overshooting the target temperature during hypothermia induction.

### **Laboratory Values, Drug Clearance, Infection Rates**

Certain laboratory values, such as arterial oxygen and carbon dioxide content, may be altered during hypothermia, and the lab should be alerted to 'temperature adjust' the values reported. Considering the changes in physiology resulting from cooling and the dynamic nature of electrolyte concentrations, routine serum chemistry assessment is advised during TTM. Clearance of specific medications can be decreased due to altered function of select liver enzymes and may require regular monitoring.<sup>8</sup>

### **TTM Implementation**

In order to implement a successful TTM program, a group of key stakeholders are necessary. The group will need to clarify specific treatment objectives:

- ... Who will be responsible for managing these patients?*
- ... How will TTM patients be identified?*
- ... What methods will be used for achieving TTM?*
- ... What temperature target and duration will be sought?*
- ... During what circumstances will TTM be aborted.*
- ... Who will be monitoring outcomes?*
- ... Who will be assessing for success or adjustments that might be needed?*

Active involvement of key nursing and physician leaders within the unit are essential to the success of any program.

Identifying patients who are eligible for TTM can be simplified with an algorithm for practitioners to reference. Clearly defined criteria and triggers will help ensure that no patients are eliminated or missed. There are many different process improvement methods an organization could utilize; 7-step process improvement, DRIVE (define, review, identify, verify and execute), Six Sigma, Lean Management, and Kaizen. Each of these implementation strategies requires reassessment to determine if success has occurred.

Once the process has been developed by the multi-disciplinary group and defined in a written policy and procedure, the next step is development of a standardized set of orders that will be used by all practitioners (See Appendix A and B). These orders should include any assessment scales or scoring systems to ensure standardization of assessments. If electronic order entry is utilized, the order set will need to be incorporated. Examples of TTM policy and procedures and order sets can be found in the addendum of this monograph.

Training is an important part of any new process. Everyone learns differently and having the education presented in multiple formats is important. Demonstration, verbal instruction and written material should all be available for everyone who will be using the protocol. Competencies should be demonstrated before the protocol is put into place and can be assessed with hands-on demonstration at the bedside or through the use of a simulation lab. The organization needs to determine how often competency assessment will take place. Education and competency demonstration should occur in a non-threatening environment to ensure staff feels comfortable asking questions and discussing the intricate details of the protocol.

Physicians, residents and Advanced Practice Nurses need to be educated on the order set and protocol. Practitioners may already be familiar with the concept of hypothermia for cardiac arrest. Therefore, education may need to focus on normothermia and the value of TTM for the neurologic patient. Joint education with the nursing staff will further solidify the roles of the two disciplines and the collaborative environment necessary for successful implementation.

Reassessing the protocol frequently after initiation is important. Often changes will be necessary or education may need to be reinforced with practitioners and nursing staff. Catching these issues early and implementing corrections will keep everyone on the same page and help minimize protocol deviations.

It is reasonable to assess competency during orientation and annually either at the bedside or in a simulation lab. TTM may be frequently utilized in some organizations and seldom in others. Infrequent use makes TTM a high risk low usage care item. Ensuring staff are able to appropriately implement the protocol should take place on a regular basis.

## CONCLUSIONS

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Induced hypothermia has proven value as a neuroprotectant for survivors of cardiac arrest and can be useful to lower ICP in patients with refractory intracranial hypertension. Numerous other neurologic indications continue to be explored. Avoidance of fever is probably beneficial in any patient with acute brain injury, but its value remains unproven despite widespread implementation of normothermia protocols throughout neurocritical care units. Optimization of the benefits of TTM requires a coordinated multi-disciplinary effort with careful organization, education, and monitoring.

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