Targeted Temperature Management as the Standard of Care – Aligning Practice, Evidence and Guidelines

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Fever-related brain injury in the neurological intensive care unit (NICU) occurs in many indications, such as stroke, subarachnoid haemorrhage and intracerebral haemorrhage. The deleterious effects of elevated body temperature independently contribute to increased length of stay in the NICU and necessitates cautious management. Internationally agreed protocols to define the role of targeted temperature management (TTM) in the NICU setting are required. The European Society for Intensive Care Medicine has launched an important project to access actual TTM applications worldwide with the aim of creating an open-access TTM protocol library. Further, to access the value of prophylactic fever control, a randomised controlled trial looking at the potential benefits of fever prevention in critically ill stroke patients is now underway. These initiatives will throw light on how TTM can become optimised and standardised for best clinical practice.

Keywords
Fever control, targeted temperature management, normothermia, intensive care unit, intracranial pressure, traumatic brain injury, intracerebral haemorrhage, intracranial hypertension, stroke, subarachnoid haemorrhage

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**Fever Management and Hyperthermia**

**Presented by Stephan A Mayer**

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### Scope of the fever problem in the neurological intensive care unit

Fever-related brain injury in the neurological intensive care unit (NICU) has been reported across several indications, including stroke, subarachnoid haemorrhage (SAH), and intracerebral haemorrhage (ICH). Deleterious effects of hyperthermia apply to focal and global ischaemia, as well as trauma and occur with delayed hyperthermia in addition to acute hyperthermia. The effect is more pronounced after reversible (rather than permanent) ischaemia and can cause aggravation post-ischaemic brain oedema as well as cellular injury. These deleterious effects may occur even with small elevations of temperature (1–2°C). In 20 patients with elevated intracranial pressure (ICP) (10 with traumatic brain injury [TBI], eight with SAH and two with neoplasm), increases in brain temperature were associated with significant increases in ICP. Elevated body temperature independently contributes to increased length of stay in the NICU. This was observed in a cohort of 4,295 patients admitted to the NICU with length of stay longer than one day, in whom elevated body temperature was associated with a longer ICU and hospital length of stay, higher mortality rate, and worse hospital disposition. The most important predictor of ICU length of stay was the number of complications (beta=0.681) followed by elevated body temperature (beta=0.143).

To identify risk factors for fever in consecutive patients treated within a NICU, frequency and causes of fever (defined as core temperature ≥38.3°C on ≥2 consecutive days) were analysed in 584 consecutive patients with aneurysmal SAH. Forty-five per cent of temperatures were not associated with poor outcomes (p=0.56). Using a multivariate model, only days of fever were independently associated with poor outcome (odds ratio 1.14 of poor outcome per day of fever, 95% confidence interval 1.06–1.22; p=0.0006). In a consecutive cohort of 353 patients with SAH, studied over 10 days, the mean daily $T_{\text{max}}$ >37°C during the first week was 1.1°C (range 0–2.7°C). Fever was predicted by poor clinical grade, increased age, male sex and the Acute Physiology and Chronic Health Evaluation (APACHE-2) physiological subscore. Fever burden was independently associated with 3-month death and severe disability, instrumental activities of daily living (IADLs) and poor cognitive outcome, as measured by telephone interview for cognitive status scores. There was an even stronger association between death and disability and fever burden >38.3°C. Patient temperature at admission, however, did not affect outcome.

### Management strategies

In a prospective, randomised study exploring the antipyretic effect of the acetaminophen and ibuprofen combination, 79 NICU patients who developed a temperature ≥38°C were randomised to receive either a single dose of acetaminophen 975 mg, a single dose of ibuprofen 800 mg, or a combination of both acetaminophen 975 mg and ibuprofen 800 mg. The combination of ibuprofen and acetaminophen produced significantly greater fever control than acetaminophen alone, although there was no statistically significant difference in terms of fever control for the combination versus ibuprofen alone. The area under the curve (AUC) for temperature change for acetaminophen was -3.55°C-h, for ibuprofen was -4.05°C-h; for the combination of acetaminophen and ibuprofen was -5.10°C-h. In a case series investigating the use of a cooling blanket plus 30 cc/kg 4°C saline bolus, a decline in temperature (39.2 ± 0.3 versus 37.1 ± 1.2°C, p=0.006) at 2 hours and fever burden (97.3 ± 343.8 versus 734.3 ± 422.3°C*min, p=0.02) at 12 hours was noted following the cold saline bolus.

To study the effectiveness of a catheter-based heat exchange system in reducing elevated temperatures in critically ill neurological and neurosurgical cases, 296 patients were enrolled who had a temperature in excess of 38°C on at least two occasions. Of these patients, 41% had SAH, 24% had TBI, 23% had intracerebral haemorrhage, and 13% had ischaemic stroke. Fever burden was 7.92 versus 2.87°C-hours in the conventional and catheter groups (acetaminophen and cooling blankets), respectively (64% reduction, p<0.01). Shivering appeared to be a problem in four patients (3.7%). Twenty-four-hour fever burden...
was measured in 47 patients with fever ≥38.3°C for >2 consecutive hours after receiving 650 mg of acetaminophen (60% SAH, 23% cerebral infarction, 11% ICH, and 4% TBI). These patients were randomised to receive either a standard Sub-Zero cooling blanket or the Medivance Arctic Sun surface cooling system and the main outcome measure was 24-hour fever burden. The findings showed that the Arctic Sun Temperature Management System was superior to conventional cooling-blanket therapy for controlling fever (see Figure 1).

**Shivering management**

A simple tool, the Bedside Shivering Assessment Scale (BSAS), quantifies shivering using a scale of 0 to 3, describing no shivering to severe shivering, respectively. To assess accurately the BSAS score, the patient should be observed for 2 minutes, during which time they must be visually inspected and have their neck, thorax, arms and legs palpated.

**Establishing Guidelines – Broadening our Horizons**

Presented by Alain Cariou

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In addition to its current use in patients who are comatose after a cardiac arrest, hypothermia has been recognised as a promising treatment in other aspects of neurocritical care. There is, however, a plethora of possible side effects and adverse events. These include electrolyte abnormalities, worsening of haemodynamic status, exacerbation of the inflammatory response, requirement for muscle relaxants, reduced cytochrome P450 activity and an increase in infection rate. The benefit-risk ratio across indications other than cardiac arrest is not clear, therefore highlighting the need for guidelines. Strategies for targeted temperature management (TTM) fall broadly into two types: primary treatment, whereby TTM is used systematically in all patients with a given condition; or secondary treatment, in which TTM is used only in selected patients as a goal-directed strategy. However, TTM is still not recommended ubiquitously for patients following cardiac arrest. Indeed, in a large registry study of TTM in pulseless electric activity or asystole patients has not been significantly associated with good neurological outcome (adjusted odds ratio, 0.71; 95% confidence interval, 0.37–1.36).

**Severe traumatic brain injury**

The level of evidence supporting the use of TTM in patients with TBI is lower compared with post-cardiac arrest. Results regarding its ability to decrease pressure are quite consistent. In a systematic review of 18 studies involving hypothermia for control of ICP (13 were randomised controlled trials and five were observational studies), TTM was shown to be significantly superior to normothermia in controlling ICP. However, the effect on clinical outcomes remains unproven. Several teams reported its benefit when used as a salvage treatment. In a group of 136 TBI patients with a Glasgow Coma Scale score of ≤8 on admission, in whom ICP remained above 20 mmHg in spite of therapy according to a step-up protocol, those who responded to barbiturate coma formed the control group (n=72) whereas those who did not respond to barbiturate coma (n=64) were treated with moderate hypothermia (i.e. 32–34°C). Mortality rates were significantly lower in the hypothermia group compared with the control group (62% versus 72%, p<0.05). The number of patients with good neurological outcomes was also higher in the hypothermia group versus control: 15.7% versus 9.7%, respectively (p<0.02). However, this study was retrospective and monocentric, which results in several important biases. By contrast, in the recently published EUROtherm trial that included 387 patients with an ICP>20 mmHg following TBI, TTM in addition to standard care did not result in outcomes better than those with standard care alone.

**Future research in fever control**

A randomised controlled trial of prophylactic fever control for the prevention of fever in critically ill stroke patients (n=1,176), sponsored by CR Bard Inc., is currently underway and will be complete by 2019. The feasibility of the ‘temperature clamp’ (i.e. to normothermia) has been demonstrated, the methodology refined and initial results are expected by 2020.

**Other acute brain injuries**

Efficacy trials assessing TTM combined with reperfusion therapies in acute ischaemic stroke are ongoing. A multicentre, randomised controlled clinical trial, entitled Decompressive surgery Plus Hypothermia for Space-Occupying Stroke (DEPTH-SOS), is also underway. The DEPTH-SOS trial will provide data on the safety and feasibility of moderate, TTM in addition to decompressive hemicraniectomy in malignant middle cerebral artery infarction.

In an open-label, multicentre, randomised clinical trial in 49 intensive care units in France (n=130) moderate hypothermia did not improve outcomes in patients with severe bacterial meningitis. The results of the multicentre, randomised controlled HYBERNATUS trial, should be soon released. This trial was designed to determine whether 90-day outcomes in mechanically ventilated patients with convulsive status epilepticus requiring management in the ICU are improved by early TTM (32–34°C) for 24 hours.

**Methods for cooling**

According to the European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines, a cooling method with effective temperature monitoring that avoids temperature fluctuations is preferable for optimal temperature maintenance. To assess the quality of the evidence and the strength of the recommendations, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used in the development of these guidelines.

If TTM is used, a target temperature of between 32°C and 36°C should be maintained for at least 24 hours; fever should be prevented for at least 72 hours. This is achieved well with external or internal cooling devices that include continuous temperature feedback to reach a set target temperature. In a multicentre controlled study of patients...
with out-of-hospital cardiac arrest, participants were randomised between two cooling strategies: endovascular femoral (icy catheter, Coolgard™, Zoll, formerly Alsius, US, n=203) or basic external cooling using fans, a home-made tent, and ice packs placed on the main vascular accesses, torso and head (n=197). The target temperature was maintained close to 33°C for 24 hours, after which patients were re-warmed passively in the external group or actively in the endovascular group, with a targeted controlled re-warming speed of ≤0.5°C/h. Endovascular cooling was not associated with significantly superior outcomes in comparison with basic external; however, feedback-controlled cooling technology achieved better hypothermia induction and maintenance than ice and fans.

Sharing Protocols for Best Treatment – The European Society for Intensive Care Medicine Protocol Library

Presented by Katia Donadello

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Targeted temperature management (TTM) has potential applications in various intensive care medicine settings, yet has faced a non-uniform application in past years. Since the landmark trials showing improved neurological outcome in post-cardiac arrest patients who were cooled to 33–34°C, the practice became widespread, with intensive care units (ICUs) purchasing cooling devices such as surface blankets, intravascular cooling catheters and surface gel-coated pads. The landscape changed following the trial by Nielsen et al. in 2013, which indicated that induced hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C in unconscious survivors of out-of-hospital cardiac arrest. To assess the impact of this publication, a survey was performed using the database of the French Intensive Care Society, which included 3,229 physicians who were questioned between May 2014 to January 2015. The key TTM trial by Nielsen et al. seemed to have influenced a change in current practices in one-third of respondents, whereas for over half (56%) of them the target temperature remained unchanged. This highlighted a warranted educational need among clinicians in many ICUs, which could, in part, be met by the development of new international guidelines.

Despite the availability of local guidelines, there are no internationally agreed protocols for TTM that are shared among the intensive care community. To help address this deficiency, the European Society for Intensive Care Medicine (ESICM), with the support of CR Bard Inc., has embarked on a project to access actual TTM applications worldwide with the aim of creating an open-access TTM protocol library. The ESICM TTM Taskforce put together an online survey for critical care professionals practicing TTM. This survey covered the indications for TTM, methods, use of standard operating procedures (SOPs) and protocols. More than 700 responses were received from clinicians from more than 60 countries, the majority of which were European. University hospitals were most represented (more than 40% of respondents), followed by university-affiliated hospitals and non-university hospitals.

The survey results at the time of writing have not yet been fully analysed and released and therefore can only be discussed here in general terms. Interim analysis shows that the majority of respondents apply some form of TTM for patients with post-anoxic coma but not for TBI, sepsis nor perioperative medicine. Both TTM protocols and target temperature ranges are variable between different ICUs, although most respondents follow a SOP or protocol for implementing TTM. The majority of respondents have a SOP/protocol in place when commencing TTM, and these protocols are usually initiated in the ICU setting. Various methods are used, including basic ice packs and water blankets as well as more advanced technologies. Most respondents use much less invasive and simple procedures to initiate and maintain TTM, like gel-coated pads or water circulating blankets. Most respondents regularly assess sedation and shivering and utilise TTM also for the re-warming phase; the majority do increase temperature at a rate of 0.5°C/h or less.

With the objectives of knowledge sharing and discussion on TTM applications, an open-access TTM protocol library is being built. To date, more than 10 protocols have been received, mostly from European countries. Protocols submitted to the ESICM should be in their original form, together with visual material and a list of keywords. All submitted protocols will be evaluated by the ESICM TTM Task Force for language, content and form. If necessary, an English version may be requested.

The eventual development from the ESICM of a compendium of TTM SOPs and protocols will facilitate sharing and collaboration amongst the critical care community. Any clinician using a clinically established TTM protocol for one or more specific indications may submit their protocol to the ESICM. Completion and analysis of the ESICM survey is in progress and full publication of the results is expected during 2017.

For further information and to participate in building the TTM library, please visit: www.esicm.org/research/TTMlibrary

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