Satellite Symposium Proceedings

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

Proceedings of a satellite symposium held at the 29th Annual Congress of the European Society for Intensive Care Medicine Milan, Italy, 3 October 2016

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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,[1] subarachnoid haemorrhage (SAH),[2] and intracerebral haemorrhage (ICH).[3] Deleterious effects of hyperthermia apply to focal and global ischaemia, as well as trauma and occur with delayed hyperthermia in addition to acute hyperthermia.[4] 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 (1–2ºC).[5–7] 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.[8] Elevated body temperature independently contributes to increased length of stay in the NICU.[9] 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.[9] 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).

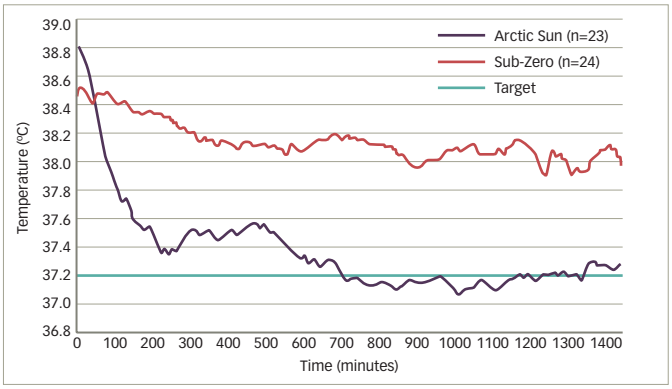
To identify risk factors for fever in consecutive patients treated within a NICU, frequency and causes of fever (defined as core temperature ≥38.3ºC on ≥2 consecutive days) were analysed in 584 consecutive patients with aneurysmal SAH.[10] Forty-five per cent of fevers were due to infection. According to univariate analysis, factors associated with poor outcome included days of fever, febrile load, and fever onset within 24 and 72 hours (all p<0.001), but subfebrile 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_{max} >37ºC during the first week was 1.1ºC (range 0–2.7ºC).[2] 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 >38.3ºC. 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 ≥38ºC 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.[11] 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 -3.55ºC-h, for ibuprofen was -4.05ºC-h; for the combination of acetaminophen and ibuprofen was -5.10ºC-h). In a case series investigating the use of a cooling blanket plus 30 cc/kg 4ºC saline bolus, a decline in temperature (39.2 ± 0.3 versus 37.1 ± 1.2ºC, p=0.006) at 2 hours and fever burden (97.3 ± 343.8 versus 734.3 ± 422.3ºC*min, p=0.02) at 12 hours was noted following the cold saline bolus.[12]

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 38ºC on at least two occasions.[13] Of these patients, 41% had SAH, 24% had TBI, 23% had intracerebral haemorrhage, and 13% had ischaemic stroke. Fever burden was 7.92 versus 2.87ºC-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

Figure 1: Sub-Zero cooling blanket versus Medivance Arctic Sun surface cooling system in neurocritical care patients: 24-hour fever burden[14]



Reproduced with permission from Mayer et al., 2004.[14]

Table 1: Columbia neuro-intensive care unit anti-shivering protocol[16]

0	Baseline	Acetominophen Buspirone Magnesium sulfate Skin counterwarming	650–1000 mg Q 4–6h 30 mg Q 8h 0.5–1 mg/h IV Goal (3–4 mg/dl) 43ºC/MAX Temp
1	Mild sedation	Dexemederomidine or opioid	0.2–1.5 mcg/kg/h Fentanyl starting dose 25 mcg/h Meperidine 50–100 mg IM or IV
2	Moderate sedation	Dexemederomidine and opioid	Doses as above
3	Deep sedation	Propofol	50–75 mcg/kg/min
4	Neuromuscular blockade	Vecuronium	0.1 mg/kg IV

IM = intramuscular; IV = intravascular
Reproduced with permission from Choi et al., 2011.[16]

was measured in 47 patients with fever ≥38.3ºC for >2 consecutive hours after receiving 650 mg of acetaminophen (60% SAH, 23% cerebral infarction, 11% ICH, and 4% TBI).[14] 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.[15] 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. To manage shivering, non-sedating strategies should be used initially, as has been laid out by the Columbia neurological ICU anti-shivering protocol, with neuromuscular blockade used as a last resort (see *Table 1*).[16] The Columbia neurological ICU anti-shivering protocol was based on prospective data from 213 patients who underwent 1,388 patient days of temperature modulation. Eighty-nine of the 213 patients underwent hypothermia and 124 underwent normothermia.

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. ❑

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.[17] 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.[18] 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).[19]

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.[20] 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. 32–34ºC).[21] 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.[22]

Other acute brain injuries

Efficacy trials assessing TTM combined with reperfusion therapies in acute ischaemic stroke are ongoing.[23] 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.[24]

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 (32–34ºC) for 24 hours.[25]

Methods for cooling

According to the European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines,[26,27] 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 32ºC and 36ºC should be maintained for at least 24 hours; fever should be prevented for at least 72 hours.[26,27] This is achieved well with external or internal cooling devices that include continuous temperature feedback to reach a set target temperature.[26,27] 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 33ºC 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 ≤0.5ºC/h. Endovascular cooling was not associated with significantly superior outcomes in comparison with basic external;[28] 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.[30,31] Since the landmark trials showing improved neurological outcome in post-cardiac arrest patients who were cooled to 33–34ºC,[32,33] 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 33ºC did not confer a benefit as compared with a targeted temperature of 36ºC in unconscious survivors of out-of-hospital cardiac arrest.[34] 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.[35] 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 0.5ºC/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 ❑

Suggested protocol elements

- Indication for TTM
- Inclusion criteria
- Exclusion criteria checklist
- Neurological assessments before TTM
- Medical information and risk stratification
- Step-by-step preparation instructions to initiate therapy
  - Target temperature range
  - Length of cooling period
  - Re-warm rate
  - Definition and length of normothermia period
  - Patient preparation
  - Cooling device preparation
  - Documentation preparation
- Location, timing, method
  - Type of used device (multiple choices)
  - Cooling instructions – induction and maintenance phase
  - Induction phase (device, attitude, monitoring)
  - Maintenance phase (device, attitude, monitoring)
  - Device monitoring procedure and adjustments
  - Handling alerts and alarms
  - Patient transport instructions
  - Re-initiating therapy
  - Feeding criteria
- Guidelines for sedation and shiver control
  - Drugs
  - Scale and algorithm for sedation
  - Scale and algorithm for neuromuscular blockade, if existing
- Pharmacotherapy attitude during TTM (if available)
- Re-warm phase (instructions and preparation)
- Normothermia phase
  - Length and target temperature
  - Means to control and maintain
- Discontinuing therapy
  - System shut down criteria and instructions
- Monitoring during TTM
  - Neurological assessment
  - Haemodynamic
  - Ventilation management
  - Metabolic
  - Infections
- Cost evaluation (if available)

Conclusions

Fever in the NICU setting is very common and has a negative impact on all clinical outcomes. Fever-related brain injury in the NICU occurs in many indications such as stroke,[1] SAH[2] and intracerebral haemorrhage,[3] highlighting the need for effective fever control strategies within the NICU. Beyond cardiac arrest, in which guidelines have been published and updated on a regular basis, evidence exists to support the use of targeted temperature control in SAH and the management of ICP. Early results of a randomised controlled trial of prophylactic fever control in critically ill stroke patients (n=1,176) are expected shortly. The benefit–risk ratio is currently unclear for TTM in TBI; there is a need for more clinical trial data and high-quality guidelines to guide clinical decisions. In addition, there are currently no internationally agreed protocols for TTM that are used consistently across the intensive care community. There is a need for internationally agreed protocols to define the role of TTM in the NICU setting and to reflect current practice. To this purpose, 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. ❑

1. 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.
2. Fernandez A, Schmidt JM, Claassen J, et al., Fever after subarachnoid hemorrhage: risk factors and impact on outcome, *Neurology*, 2007;68:1013–9.
3. Schwarz S, Hafner K, Aschoff A, Schwab S, Incidence and prognostic significance of fever following intracerebral hemorrhage, *Neurology*, 2000;54:354–61.
4. Ginsberg MD, Busto R, Combating hyperthermia in acute stroke: a significant clinical concern, *Stroke*, 1998;29:529–34.
5. Laptook AR, Corbett RJ, The effects of temperature on hypoxic-ischemic brain injury, *Clin Perinatol*, 2002;29:623–49.
6. Minamisawa H, Smith ML, Siesjo BK, The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia, *Ann Neurol*, 1990;28:26–33.
7. Wass CT, Lanier WL, Hofer RE, et al., Temperature changes of > or = 1 degree C alter functional neurologic outcome and histopathology in a canine model of complete cerebral ischemia, *Anesthesiology*, 1995;83:325–35.
8. Rossi S, Zanier ER, Mauri I, et al., Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage, *J Neurol Neurosurg Psychiatry*, 2001;71:448–54.
9. Diringer MN, Reaven NL, Funk SE, Uman GC, Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients, *Crit Care Med*, 2004;32:1489–95.
10. Kramer CL, Pegoli M, Mandrekar J, et al., Refining the association of fever with functional outcome in aneurysmal subarachnoid hemorrhage, *Neurocrit Care*, 2016;26:41–7.
11. Mullins ME, Empey M, Jaramillo D, et al., A prospective randomized study to evaluate the antipyretic effect of the combination of acetaminophen and ibuprofen in neurological ICU patients, *Neurocrit Care*, 2011;15:375–8.
12. Badjatia N, Bodock M, Guanci M, Rordorf GA, Rapid infusion of cold saline (4 degrees C) as adjunctive treatment of fever in patients with brain injury, *Neurology*, 2006;66:1739–41.
13. Diringer MN, Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system, *Crit Care Med*, 2004;32:559–64.
14. Mayer SA, Kowalski RG, Presciutti M, et al., Clinical trial of a novel surface cooling system for fever control in neurocritical care patients, *Crit Care Med*, 2004;32:2508–15.
15. Badjatia N, Strongilis E, Gordon E, et al., Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale, *Stroke*, 2008;39:3242–7.
16. Choi HA, Ko SB, Presciutti M, et al., Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol, *Neurocrit Care*, 2011;14:389–94.
17. Polderman KH, Induced hypothermia and fever control for prevention and treatment of neurological injuries, *Lancet*, 2008;371:1955–69.
18. Soleimanpour H, Rahmani F, Golzari SE, Safari S, Main complications of mild induced hypothermia after cardiac arrest: a review article, *J Cardiovasc Thorac Res*, 2014;6:1–8.
19. Dumas F, Grimaldi D, Zuber B, et al., Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry, *Circulation*, 2011;123:877–86.
20. Sadaka F, Veremakis C, Therapeutic hypothermia for the management of intracranial hypertension in severe traumatic brain injury: a systematic review, *Brain Inj*, 2012;26:899–908.
21. Polderman KH, Tjong Tjin Joe R, Peerdeman SM, et al., Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury, *Intensive Care Med*, 2002;28:1563–73.
22. Andrews PJ, Sinclair HL, Rodriguez A, et al., Hypothermia for intracranial hypertension after traumatic brain injury, *N Engl J Med*, 2015;373:2403–12.
23. Wu TC, Grotta JC, Hypothermia for acute ischaemic stroke, *Lancet Neurol*, 2013;12:275–84.
24. Neugebauer H, Kollmar R, Niesen WD, et al., DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke (DEPTH-SOS): a protocol of a multicenter randomized controlled clinical trial and a literature review, *Int J Stroke*, 2013;8:383–7.
25. Legriel S, Pico F, Tran-Dinh YR, et al., Neuroprotective effect of therapeutic hypothermia versus standard care alone after convulsive status epilepticus: protocol of the multicentre randomised controlled trial HYBERNATUS, *Ann Intensive Care*, 2016;6:54.
26. Nolan JP, Soar J, Cariou A, et al., European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: Section 5 of the European Resuscitation Council guidelines for resuscitation 2015, *Resuscitation*, 2015;95:202–22.
27. Nolan JP, Soar J, Cariou A, et al., European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care, *Intensive Care Med*, 2015;41:2039–56.
28. Deye N, Cariou A, Girardie P, et al., Endovascular versus external targeted temperature management for patients with out-of-hospital cardiac arrest: a randomized, controlled study, *Circulation*, 2015;132:182–93.
29. French Intensive Care Society, Targeted temperature control in resuscitation. Available at: www.srlf.org/referentiels/cardio-circulatoire/controle-cible-de-temperature-reanimation-rfe-commune-sfar-srlf/ (accessed 28 November 2016).
30. Abella BS, Rhee JW, Huang KN, et al., Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey, *Resuscitation*, 2005;64:181–6.
31. Merchant RM, Soar J, Skrifvars MB, et al., Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest, *Crit Care Med*, 2006;34:1935–40.
32. Bernard SA, Gray TW, Buist MD, et al., Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia, *N Engl J Med*, 2002;346:557–63.
33. The Hypothermia after Cardiac Arrest Study Group, Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest, *N Engl J Med*, 2002;346:549–56
34. Nielsen N, Wetterslev J, Cronberg T, et al., Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest, *N Engl J Med*, 2013;369:2197–206.
35. Deye N, Vincent F, Michel P, et al., Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey, *Ann Intensive Care*, 2016;6:4.

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