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Temperature Management in the ICU

Anne Drewry, MD, MS[1]
Nicholas M. Mohr, MD, MS, FCCM[2]

OBJECTIVE: Temperature abnormalities are recognized as a marker of human disease, and the therapeutic value of temperature is an attractive treatment target. The objective of this synthetic review is to summarize and critically appraise evidence for active temperature management in critically ill patients.

DATA SOURCES: We searched MEDLINE for publications relevant to body temperature management (including targeted temperature management and antipyretic therapy) in cardiac arrest, acute ischemic and hemorrhagic stroke, traumatic brain injury, and sepsis. Bibliographies of included articles were also searched to identify additional relevant studies.

STUDY SELECTION: English-language systematic reviews, meta-analyses, randomized trials, observational studies, and nonhuman data were reviewed, with a focus on the most recent randomized control trial evidence.

DATA EXTRACTION: Data regarding study methodology, patient population, temperature management strategy, and clinical outcomes were qualitatively assessed.

DATA SYNTHESIS: Temperature management is common in critically ill patients, and multiple large trials have been conducted to elucidate temperature targets, management strategies, and timing. The strongest data concerning the use of therapeutic hypothermia exist in comatose survivors of cardiac arrest, and recent trials suggest that appropriate postarrest temperature targets between 33°C and 37.5°C are reasonable. Targeted temperature management in other critical illnesses, including acute stroke, traumatic brain injury, and sepsis, has not shown benefit in large clinical trials. Likewise, trials of pharmacologic antipyretic therapy have not demonstrated improved outcomes, although national guidelines do recommend treatment of fever in patients with stroke and traumatic brain injury based on observational evidence associating fever with worse outcomes.

CONCLUSIONS: Body temperature management in critically ill patients remains an appealing therapy for several illnesses, and additional studies are needed to clarify management strategies and therapeutic pathways.

KEY WORDS: cardiac arrest; fever; hypothermia, induced; ICUs; sepsis

Temperature abnormalities have been recognized as markers of human disease since early civilization, and the value of temperature as a treatment target to cure disease has been hypothesized ever since (1–3). Temperature homeostasis is highly preserved throughout the animal kingdom (4–6). Even small changes in body temperature can lead to changes in inflammation and immune function, with variable-proposed effects on patient outcomes (7, 8). Hyperthermia also affects energy utilization. Among febrile critically ill patients, up to one-fifth of energy expenditures are channeled toward raising and maintaining body temperature (9). Any condition that extracts such a metabolic cost and influences so many physiologic pathways remains an attractive therapeutic target in the ICU.

The purpose of this Concise Definitive Review is to detail current evidence on the role of active temperature management in the ICU. We focus on adult ICU medical conditions, such as cardiac arrest, neurologic emergencies, and infection. In this review, we do not cover the role of thermal homeostasis in

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environmental emergencies (e.g., heat stroke, environmental hypothermia), drug-induced dysthermia (e.g., malignant hyperthermia, serotonin syndrome), or temperature management in children. For the purposes of this review, a core body temperature greater than 38.0°C is commonly used to define fever, and a body temperature less than 36.0°C often defines hypothermia (8).

POSTCARDIAC ARREST

Perhaps the best studied indication for temperature management in the critically ill is in adults after out-of-hospital cardiac arrest. Cardiac arrest survival is low, and in patients who regain spontaneous circulation, neurologic injury from anoxia is common (10–12). In animal models, mild therapeutic hypothermia was shown to decrease cerebral metabolism, reduce brain tissue inflammation, and prevent neuronal apoptosis (13–23). Therapeutic hypothermia has been used successfully during cardiac surgery as a neuroprotective strategy, leading some to hypothesize that therapeutic hypothermia after cardiac arrest may improve clinical outcomes (24).

Early Clinical Trials

In 2002, two separate, landmark randomized clinical trials in patients with witnessed out-of-hospital cardiac arrest and an initial shockable rhythm showed that mild therapeutic hypothermia (32–34°C) improved favorable neurologic survival (25, 26). Both trials were relatively small (combined 352 participants) and limited to patients with witnessed out-of-hospital arrest, but the effect size (absolute risk for favorable neurologic survival increased by 16% and 23%, respectively) was convincing.

Observational Studies Validating Results of Clinical Trials

Multiple observational studies over the next decade replicated the main finding of these trials—hospitals that implemented a postcardiac arrest therapeutic hypothermia protocol observed improvements in risk-adjusted survival (27, 28). Based on these findings, the International Liaison Committee on Resuscitation recommended mild therapeutic hypothermia based on level I evidence in 2002 (29).

Some contradictory findings, however, led some to question the mechanism and degree of hypothermia required for neuroprotection (30–32). Despite animal data suggesting that therapeutic hypothermia was highly time-sensitive, more rapid prehospital cooling in clinical trials did not result in incremental benefit (33–36). Patients also seemed to have similar outcomes even if they were cooled to different temperatures (37).

Later Clinical Trials

In 2013, Nielsen et al (38) published the Targeted Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial, a randomized, controlled, dose-finding trial (n = 950) comparing outcomes for out-of-hospital cardiac arrest patients maintained at 33°C vs 36°C for 36 hours, followed by aggressive fever prevention for 72 hours. The TTM trial included patients with out-of-hospital arrest of presumed cardiac etiology, but it included patients with both shockable and nonshockable presenting rhythms. It also had a much larger sample size than prior trials, and it showed no difference in all-cause mortality (hazard ratio, 1.06; 95% CI, 0.89–1.23) or 6-month favorable neurologic outcome (relative risk [RR], 1.02; 95% CI, 0.88–1.16) (38). After the TTM trial was published, however, several observational studies suggested that changes in hospital protocols to allow for postarrest temperatures as high as 36°C were associated with higher prevalence of fever and a reduced percentage of patients with favorable neurologic outcome (39–42). Some questioned whether these observations resulted from heterogeneity of treatment effects or whether clinicians were implementing normothermia with less control than the TTM protocol had mandated. Additionally, severity of illness may have mediated heterogeneous treatment effects, with lower temperatures being associated with better outcomes in the most severely injured patients (43).

Two recent trials have continued to fuel controversy. The Therapeutic Hypothermia after Cardiac Arrest in Nonshockable Rhythm (HYPERION) trial was an open-label randomized controlled trial (RCT) assigning 584 comatose survivors of out-of-hospital or inhospital cardiac arrest with nonshockable rhythms to either mild therapeutic hypothermia (33°C) or induced normothermia (37°C). Prevalence of favorable neurologic outcome was higher in participants

allocated to therapeutic hypothermia (10.2% vs 5.7%; $p = 0.04$) (44). In 2021, the 1,850-participant Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospitals Cardiac Arrest (TTM2) trial was published, which also assigned comatose out-of-hospital cardiac arrest patients to 33°C versus 37°C. Both all-cause mortality (50% vs 48%; RR, 1.04; 95% CI, 0.95–1.23) and poor functional outcome (55% vs 55%; RR, 1.00; 95% CI, 0.92–1.09) at 6 months were similar (45). HYPERION was a study of patients in France with nonshockable arrest (27% inhospital), and a significant proportion of those in the control group had fever. In contrast, TTM2 was a larger trial that included only patients with out-of-hospital arrest, 74% had a shockable rhythm, and 79% had bystander cardiopulmonary resuscitation. These differences in patient population and management of fever in the control groups may have contributed to the seemingly disparate results between the two studies. Some have also questioned whether the fact that it took over 5 hours to achieve goal temperature in TTM2 may have attenuated any effect of therapeutic hypothermia (46). Others have pointed out that the lack of benefit in a superiority trial does not imply statistical equivalence.

At this point, multiple clinical trials have been conducted that lead to contradictory conclusions on the role and dose of therapeutic hypothermia in cardiac arrest, and observational data suggest benefit from standardized temperature management protocols. Based on the early trials, avoiding fever in comatose patients after cardiac arrest remains prudent, and some patients at high risk of poor neurologic outcome may benefit from more aggressive therapeutic hypothermia strategies (47). As an alternative, some centers may choose to use mild therapeutic hypothermia as a practical strategy to avoid fever; this has been shown to be no worse than aggressive, high-reliability maintenance of normothermia because the harm associated with unintentional fever is significant.

NEUROLOGIC INJURIES

Stroke

Hyperthermia is also common after stroke, and like cardiac arrest patients, stroke patients are susceptible to temperature-induced neurologic injury (48). Fever has been associated with secondary brain injury in patients with ischemic and hemorrhagic strokes, and hyperthermia increases cerebral oxygen consumption, worsens disruption of the blood-brain barrier, increases proinflammatory cytokine release, expands infarct size, and induces neuronal apoptosis (48–52). Fever has been associated with worsened neurologic outcome after ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage, but the effect of active temperature management is unclear (53–61). The degree and duration of fever are strongly linked to severity of brain injury, making it difficult to evaluate the role of fever in worsening outcomes from observational studies alone. In a cohort of 38,679 ICU patients with stroke or traumatic brain injury (TBI), patients with temperature over 37.4°C had higher hospital mortality, but increased mortality risk persisted after adjusting for illness severity only in those with peak temperature over 39°C (62). Whether fever is causal in the relationship or is simply an epiphenomenon related to injury severity presents an opportunity for future study.

Ischemic Stroke. Multiple small RCTs in ischemic stroke have been conducted to measure the impact of mild therapeutic hypothermia (33–35°C) on improving stroke outcomes. Unfortunately, the trials have been small (18–98 participants), and although none showed clinical benefit, they were underpowered to detect improvement associated with therapeutic hypothermia (63–70). Two large RCTs of cooling in stroke were planned, but the European Multicentre, Randomised, Phase III Clinical Trial of Therapeutic Hypothermia for Acute Ischaemic Stroke was stopped for slow recruitment and withdrawal of funding (98 of 1,500 planned participants), and the Intravascular Cooling in the Treatment of Stroke trial was stopped because of overlap with thrombectomy trials (120 of 1,600 planned participants) (64, 70).

Hemorrhagic Stroke. Two observational studies with historical controls in hemorrhagic stroke have resulted in limited evidence for benefit, with one study ($n = 50$) reporting that perihemorrhage edema increased less over the first 2 weeks in patients with large intracerebral hemorrhage (≥25 mL) and induced normothermia but a second study ($n = 80$) with more variation in hemorrhage size showing no difference in neurologic outcome or survival (71, 72).

Antipyretic Therapy. In patients for whom induced normothermia is used, the impact of

pharmacologic antipyretic therapy is modest. Hyperthermia in the context of neurologic injury is different from infectious fever, and physical cooling methods may be required (73–77). The Paracetamol In Stroke trial compared early prophylactic acetaminophen therapy with placebo in 1,400 patients with acute ischemic or hemorrhagic stroke, and neither neurologic improvement (adjusted odds ration [aOR], 1.20; 95% CI, 0.96–1.50) nor favorable neurologic outcome (aOR, 1.02; 95% CI, 0.78–1.32) improved with acetaminophen therapy.

Current guidelines from the American Heart Association (AHA)/American Stroke Association (ASA) recommend treating hyperthermia over 38.0°C (class 1 recommendation), but the role of induced therapeutic hypothermia is uncertain (78). The European Stroke Organization concludes that insufficient evidence exists to recommend either induced hypothermia or treatment of hyperthermia, but antipyretics do not improve functional outcome after stroke (79).

Traumatic Brain Injury

Fever occurs in nearly 70% of patients with TBI and has been associated with increased cerebral blood volume, elevated intracranial pressure, increased metabolism, and worsening of ischemic damage (80–84). A meta-analysis of the impact of fever on outcomes in patients with TBI demonstrated a consistent association between presence of fever and poor outcomes including higher mortality, more disability, and longer ICU and hospital length of stay (48). Thus, although there are no clinical trials showing superiority of fever control, the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) recommendations for the management of severe TBI recommend fever control in patients with TBI as a tier 0 intervention (85, 86), meaning that fever should be controlled regardless of intracranial pressure readings.

Clinical studies of therapeutic hypothermia in TBI have yielded mixed results, and meta-analyses have reached contradictory conclusions (87–93). To date, the largest clinical trial of therapeutic hypothermia in patients with TBI, the Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury—Randomized Clinical Trial, which randomized 511 patients with Glasgow Coma Score less than 9 to normothermia versus prophylactic hypothermia (33–35°C) for 72 hours, found no neurologic benefit (94). Favorable outcomes occurred in 48.8% of patients treated with prophylactic hypothermia versus 49.1% in the normothermia group (risk difference, 0.4%; 95% CI, –9.4% to 8.7%). The most recent Brain Trauma Foundation guidelines for management of severe TBI do not recommend therapeutic hypothermia to improve outcomes (95). The SIBICC consensus treatment algorithms for the management of elevated intracranial pressure, which are based on expert interpretation of available evidence, recommend mild therapeutic hypothermia (35–36°C) as a tier 3 intervention to reduce intracranial pressure in patients with ongoing intracranial hypertension after other tier 1 and tier 2 interventions have been exhausted (85, 86).

SEPSIS

The benefit of fever control in sepsis has also been debated. Fever is an adaptive response to infection and has both potential beneficial and adverse effects in patients with severe infections (8). Elevated temperatures have been shown to augment innate and adaptive immunity through their effect on macrophage function, heat shock protein response, antibody production, and T cell activation (96–100). Febrile-range hyperthermia also inhibits microorganism growth, reduces viral replication, and enhances antibiotic effectiveness (101–105). Pyrogenic cytokines (e.g., interleukin-1, interleukin-6, tumor necrosis factor-α, and interferon-γ) produced during febrile episodes have been shown to directly potentiate the immune system and provide protection against pathogens (8). However, fever also raises metabolic burden, increases oxygen consumption, and can depress myocardial function (106, 107). These deleterious physiologic effects may counter the benefit of increased pathogen clearance and immune effects, especially in patients with septic shock with sepsis-associated hypoperfusion.

Fever Control (Observational Studies)

Observational studies in sepsis patients have demonstrated that fever is associated with improved outcomes. A meta-analysis of 42 studies evaluating body temperature in patients with sepsis showed than mean

body temperature was higher in the lowest mortality quartile versus the highest (38.1°C vs 37.1°C) (108). Fever was associated with decreased mortality in patients with CNS infections, despite being associated with worse outcomes in noninfectious neurologic injuries (62). Altogether, these observational data suggest fever could be uniquely beneficial to infected hosts. However, the role of fever in improving outcomes may also mean that patients with more robust immune response and pathogen killing have the greatest febrile response.

Fever Control (Clinical Trials)

Several randomized trials have assessed whether antipyretic therapy improves outcomes (23, 109–114). These studies have evaluated pharmacological treatment with acetaminophen and/or ibuprofen, physical cooling to normothermia, and combinations of pharmacological and physical cooling methods. The largest and most recent trial, Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in the ICU, randomized 700 patients with fever greater than 38.3°C and infection to treatment with IV acetaminophen or placebo. There was no difference in 90-day mortality (RR, 0.96; 95% CI, 0.66–1.39) or 28-day ICU-free days (absolute difference, 0; $p = 0.07$) (114). Similar findings were seen in a trial of 200 severely ill (median norepinephrine dose 0.5 and 0.65 μg/kg/min in the intervention and control groups, respectively) patients with septic shock randomized to external cooling to normothermia (36.5–37.0°C) for 48 hours versus no cooling (112). Due to severity of their illness, these patients were hypothesized to be the type of patients most likely to benefit from fever control and the concomitant reduction in metabolic burden. Patients who were cooled to normothermia had lower risk of death at 14 days (odds ratio [OR], 0.36; 95% CI, 0.16–0.76), but there was no difference in mortality at ICU or hospital discharge (112).

A meta-analysis subsequently demonstrated no effect of antipyretic therapy on 28-day or hospital mortality in pooled data from eight randomized studies (RR, 0.93; 95% CI, 0.77–1.13) and six observational studies (OR, 0.90; 95% CI, 0.54–1.52), although only five of eight clinical trials and six of eight observational studies had low risk of bias (115). A second, individual patient-level meta-analysis showed no impact of active fever management even in subgroups of patents with higher illness severity or age (116). Therefore, current evidence does not suggest a mortality benefit of routine treatment of fever in patients with sepsis, and individualized treatment based on symptom relief may be preferred.

Induced Hypothermia

Induced therapeutic hypothermia has also been hypothesized as a treatment for patients with sepsis due to potential protective effects on the heart, lungs, and liver, and encouraging results in animal models of sepsis (117–119). A randomized trial of 24 hours of therapeutic hypothermia (32–34°C) followed by 48 hours of normothermia versus no temperature management performed in 432 patients with sepsis was stopped early for futility (120). Therapeutic hypothermia did not improve 30-day mortality (44.2% in induced hypothermia vs 35.5% in control; absolute difference, 8.4%, 95% CI, –0.8% to 18%). Therefore, there is no current role for therapeutic hypothermia in patients with sepsis.

Warming

Spontaneous hypothermia in sepsis is common, occurring in 15–35% of patients, and spontaneous hypothermia is associated with higher mortality than normothermia or fever, although the reasons for this relationship are unclear (108, 121–125). Most clinicians actively warm hypothermic patients with sepsis to normothermia (126), but strong data do not exist to clarify the causal role of temperature on outcomes. In a small pilot trial of 56 afebrile patients with sepsis, therapeutic hyperthermia seemed to be associated with improved survival, but imbalances between the groups and the lack of difference in immune outcomes suggest that further research should be done prior to clinical practice change (127). If spontaneous hypothermia represents a sepsis phenotype, the role of active temperature management to change physiologic pathways and clinical outcomes remains uncertain and is an opportunity for future investigation.

CONCLUSIONS

Fever and spontaneous hypothermia are common in critically ill patients, and observational studies have consistently demonstrated that body temperature predicts clinical outcomes in multiple diseases of the critically ill (48, 62, 108, 121–125, 128). The

strongest data supporting the use of targeted temperature management exist in comatose survivors of cardiac arrest, although more recent trials suggest that aggressive maintenance of normothermia may be adequate to improve neurologic outcomes. Currently, there is little evidence for the routine use of moderate therapeutic hypothermia in patients with acute neurologic injury, and clinical studies of pharmacologic antipyretic therapy have failed to show clinical benefit. Current AHA/ASA guidelines recommend treatment of fever in these patients, largely based on observational association between fever and poorer outcomes. Future work on temperature management in the critically ill may elucidate new signaling mechanisms and therapeutic pathways to inform the more personalized care of critically ill patients in the future.

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1 *Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO.*

2 *Departments of Emergency Medicine, Anesthesia, and Epidemiology, University of Iowa Carver College of Medicine, Iowa City, IA.*

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For information regarding this article, E-mail: nicholas-mohr@uiowa.edu

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