Journal of Athletic Training 2022;57(8):756–759
doi: 10.4085/1062-6050-366-19

www.natajournals.org

Persistent Knowledge Gaps Regarding Exertional Heat Stroke Treatment

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Individualized patient care is ideal for treating and rehabilitating patients with athletic illnesses and injuries. Exertional heat stroke (EHS) treatment best-practice recommendations state that all patients should undergo identical cold-water immersion (CWI) treatment for ideal outcomes. It is unknown, however, whether CWI can be optimized with individualized treatment plans, encouraging personalized medicine. To accomplish this task, clinicians and researchers need to better understand the factors affecting CWI effectiveness. In this short report, we will provide an update to the American College of Sports Medicine Roundtable on Exertional Heat Stroke, review research regarding EHS treatment, and identify knowledge gaps in EHS treatment.

Key Words: hyperthermia, body cooling, cold-water immersion

Key Points

- The "golden time frame" for treating patients with exertional heat stroke likely differs among patients and is influenced by a variety of individual factors.
- Individualized patient treatment plans may benefit patients with exertional heat stroke and optimize their care.

Exertional heat stroke (EHS) deaths in athletic and occupational settings continue despite a demonstrated 100% survival rate with standard-of-care recognition and treatment.[1] The EHS best practices state that immediate core body temperature assessment is required to confirm the EHS diagnosis (rectal temperature ≥40.5°C [104.9°F]) followed by aggressive whole-body cold-water immersion (CWI). Despite these best-practice recommendations, important knowledge gaps remain regarding treatment optimization for individual patients with EHS. Pertinent clinical questions regarding what is known and unknown about EHS treatment were asked in 2008 at an American College of Sports Medicine roundtable of experts.[2] In this short report, we provide an update on research answering these EHS treatment questions and discuss future research directions to continue improving and individualizing the care for patients with EHS.

TREATMENT AREA NO. 1: HOW LONG IS THE "GOLDEN HOUR" IN EHS RECOGNITION AND TREATMENT?

The *golden hour* represents a window of time in which effective cooling will determine the prognosis and stems from data[3] on rats indicating that EHS outcomes are predicted by the degree-minutes above 40°C (104°F). Comparative case reports,[4,5] mass participation race-event medical records,[1] and myriad high-profile EHS deaths highlight the consequences of delayed recognition and treatment. In practice, clinicians may not always observe the initial neuropsychiatric symptoms or collapse, resulting in an unknown start of the golden hour. Based on anecdotal evidence, physical collapse has been estimated to be associated with rectal temperatures ranging from 40°C to 43.9°C (104°F to 111°F); this suggests that degree-minutes >40°C (104°F) could be extensive, which is particularly worrisome given that rectal temperature remains dangerously high in hot conditions without active cooling.[6] The *time-to-treatment* (time between the onset of EHS and treatment initiation) is the most important factor related to EHS outcomes. Since the 2008 meeting,[2] several reports on EHS treatment timelines and associated outcomes have been published.

At the Falmouth Road Race, body cooling to <40°C (104°F) within 30 minutes of arriving at the finish-line medical tent is regularly achieved. As a result, almost all runners with EHS are discharged directly from the medical tent the same day without complications.[1] Runners at this race have reported to the medical tent with rectal temperatures as high as 42.8°C (109°F), causing us to speculate how many degree-minutes >40°C (104°F) were accumulated during the race. It is feasible that some runners, who were treated appropriately and discharged the same day without complications, may have endured an extensive number of degree-minutes >40°C (104°F), whereas others may have been above this threshold for only a short period of time. When patients spend an extensive amount of time at >40°C (104°F), the golden hour may also be prolonged, but how long is too long to achieve a positive outcome? In 28 cases of patients with

EHS who presented to an army hospital, 5 patients were cooled to <38°C (100.4°F) within 30 minutes of admission and reported no long-term morbidities.[7] Cooling time to 38°C (100.4°F) was associated with the number and severity of morbidities at a 3-month follow-up. Patients cooled to 38°C (100.4°F) in >3 hours sustained chronic brain and kidney injuries.[7] A comparative case report[4] from the Marine Corps Marathon described 2 runners with EHS. Rectal temperature was lowered to <39°C (102.2°F) within 30 minutes in 1 runner, whereas another did not reach <39°C (102.2°F) until 140 minutes after collapse. The time of medical discharge (same day versus 1 week later), return to exercise (approximately 3 weeks with no complications versus 5 weeks with activity restriction), and ability to return to their military activities (return to duty versus no return to duty) indicated that 2.5 hours to cool body temperature to <39°C (102.2°F) was too long to prevent sequelae.[4] In cases of EHS, the degree-minutes at >40°C (104°F) before core temperature assessment is unknown; therefore, when the golden hour stopwatch begins is also unknown. Thus, body cooling to <40°C (104°F) within the first 30 minutes of suspected EHS has been suggested.[8]

Although best practices are available, individual and environmental factors may mediate the golden hour treatment window. We have observed that some elite athletes experienced potentially detrimental rectal temperatures (40°C to 41°C [104°F to 105.8°F]) for a short period of time without EHS symptoms, whereas others presented with impaired thermoregulatory ability and EHS symptoms at 40°C (104°F), sparking the idea of different thermoregulatory tolerances and golden hour windows among patients. The *golden hour* may be appropriately renamed the *golden time frame* because this treatment window likely differs among patients and is not exactly 1 hour in length. Such anecdotal evidence spurred us to consider what environmental, genotypic, or phenotypic factors explain the individual resilience to dangerously high core temperatures. In clinical practice, this question is critical because understanding the factors that mediate high core temperature resilience could influence the golden time frame.

Important questions regarding the golden time frame remain:

- Is the golden time frame longer when EHS occurs in cooler conditions?
- Could individual factors such as illness, heat acclimatization, heat shock protein expression, certain genetic mutations, or fitness level mediate extreme core-temperature resiliency and mediate the golden time frame?
- How does dehydration influence the golden time frame?

TREATMENT AREA NO. 2: HOW ARE THE COOLING RATES OF PATIENTS WITH EHS INFLUENCED BY INDIVIDUAL ANTHROPOMETRIC CHARACTERISTICS?

Clinicians must understand the discrete and combined influences of individual characteristics on CWI cooling rates to optimize and individualize care for patients with EHS. However, the relationships between some of these factors and cooling rates during CWI remain unclear, and no consensus in the literature has been apparent since the 2008 American College of Sports Medicine meeting.[2] Researchers focusing on the cooling responses of normothermic individuals, such as those stranded at sea, found that cooling rates were greater in those with less body mass, muscle mass, and body fat as well as a high surface area-to-mass ratio, although these results were not consistent between studies.[9,10] In hyperthermic exercising individuals, differences in body fat percentage and the surface area-to-mass ratio did not influence the CWI cooling rate[11] and cooling was not related to body surface area, body mass, or fat mass.[12] In this investigation, the cooling rate was related to the body surface area-to-mass ratio[12]; the latter is a patient characteristic that can be quickly and broadly estimated during EHS treatment as either high or low, creating a starting point for individualized EHS management plans. Whereas body morphology and composition influence CWI cooling rates, we are not yet able to predict appropriate cooling needs based on these characteristics. For example, although lean body mass may be related to the cooling rate, it only explained 14% of the variation in cooling time when assessed in healthy hyperthermic individuals.[13]

High school and collegiate athletes regularly report their height and weight on preparticipation examinations, allowing for an approximation of body surface area-to-mass ratio. Road race organizers could modify race entry paperwork and require this information before participation in endurance events. However, it is important to remember that the relationship between body morphology and cooling efficacy was identified in healthy hyperthermic individuals, not patients with EHS, potentially limiting its applicability. Excluding overall body characteristic differences, a study[14] documenting the cooling rates of hyperthermic individuals and patients with EHS demonstrated consistent mean cooling rates when the same modality was used. In summary, prediction of the CWI cooling-rate in patients with EHS has yet to be achieved and requires further exploration by investigators and clinicians in translational field research.

Important questions regarding factors influencing the cooling rate remain:

- How does hydration status influence CWI cooling rates?
- Do the anthropometric characteristics of patients with EHS predict CWI cooling rates and hypothermic overshoot after immersion?

TREATMENT AREA NO. 3: WHAT IS THE OPTIMUM BODY COOLING ENDPOINT FOR TREATING EHS?

Clinicians treating patients with EHS require a reputable cooling endpoint for positive outcomes. The most recent National Athletic Trainers' Association (NATA) position statement[8] recommended a cooling endpoint of 38.9°C (102°F). However, it is interesting that the only citation for this recommendation involved 10 healthy participants without EHS.[15] The lack of research support is not a fault of the expert writing team but instead reflects the need for evidence and thorough documentation of patient outcomes after successful EHS treatment. After EHS, myriad physiological impairments are likely individual in nature. Therefore, the optimal cooling endpoint may differ based on individual characteristics, although we currently have no evidence for treatment to avoid certain EHS consequences (eg, hypothermic overshoot, hyperthermic rebound, organ dysfunction). Two case examples of EHS patients were directly witnessed by one of us (B.P.M.):

1. A female distance runner (peak rectal temperature of 41.4°C [106.5°F]) was cooled via CWI to 39.4°C (103°F) before being dried with towels. She was removed early (before 38.9°C [102°F]) secondary to her lucid behavior and appropriate verbal responses during CWI. Upon removal, her body temperature returned to normal without consequence, appropriately resulting in her discharge from the medical tent.
2. A male patient with EHS (peak rectal temperature 41.7°C [107.1°F]) was cooled via CWI to 39.2°C (102.5°F) and promptly removed and dried. His cognitive responses worsened and were abnormal within 5 minutes. Upon reassessment, his rectal temperature had climbed back to 40.3°C (104.5°F).

These situations raise concern over the standard removal (at 38.9°C [102°F]) from CWI for all patients. The influence of the following individual or combination of factors on optimal removal from CWI is unknown:

- Ambient conditions (ie, air temperature, solar load, wind speed) during or immediately after treatment
- Heat production just before treatment onset
- Temperature of the CWI
- Cooling rate toward the end of cooling
- Maximum rectal temperature reached
- Time above a threshold temperature
- Predispositions contributing to EHS onset (eg, illness, fever, medication, previous EHS)

After EHS, there may be a temporary abnormal response of the median preoptic nucleus of the hypothalamus, the area of the brain responsible for thermoregulatory responses to maintain core temperature at the set point (37°C [98.6°F]).[16] A temporary alteration in the hypothalamic input or process may help explain individual responses of hyperthermic rebound and hypothermic overshoot after treatment. Alterations in the peripheral nociceptive (warm) thermoreceptors, peripheral cold receptors, central thermoreceptors, thermal inertia, or central processing could influence post-EHS acute thermoregulatory recovery. Any, or a combination, of these factors may explain shivering during CWI despite the rectal temperature remaining >40.6°C (105°F), as we have observed in multiple patients. After treatment, the hypothalamus responds to a persistently elevated core temperature (eg, 38.9°C [102°F]) and cool or cold periphery and must recover from the EHS insult. Therefore, it seems that temporary impairments are expected, but the patient may recover in an individual fashion (ie, symptoms may or may not occur).

Another facet of EHS recovery devoid of evidence is the need for emergency transport and physician follow-up as suggested in the NATA position statement,[8] although these instructions may be related to cooling decisions and endpoints, as discussed previously. Experienced medical teams often determine the need for immediate referral based on common sense and expected patient responses. However, these decisions have not been studied with respect to patient outcomes immediately after EHS and during the return to activity. Investigators and clinicians should work together on translational field research with enhanced EHS patient documentation to inform the medical community about effectively individualizing EHS management and follow-up care.

Important questions regarding the body cooling endpoint remain:

- Which individual factor or combination of factors influences optimal removal from CWI?
- Can the duration of CWI be individually optimized to minimize hypothermic overshoot?
- What are the incidences of hypothermia, rhabdomyolysis, liver dysfunction, renal failure, and the like after efficient EHS treatment?
- Do CWI cooling specifications influence patient outcomes, including the return to activity?

CONCLUSIONS

Individualized medicine is the criterion standard: treating patients on the basis of individual presentation and characteristics. Although the NATA best-practice recommendations[8] are a good starting point for treating patients with EHS, there may be room for improvement in individualized patient treatment plans for optimizing care. Aggressive CWI is clearly the best treatment option available to patients, but some individuals may benefit from variations in this treatment (eg, varied cooling times, concomitant hydration or medications). Before individualized medicine in EHS treatment can be achieved, the questions highlighted throughout this report must be answered. Whereas a lack of human randomized controlled trials of EHS is a barrier to EHS treatment research, useful data may stem from high-quality medical documentation at recreational endurance races (eg, road races, cycling races, triathlons) where patients with EHS are commonly treated. Detailed information regarding patient presentation, assessment, treatment, and return to activity may lead to retrospective analysis of treatment strategies for optimally individualizing EHS treatment.

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