External Cooling in the Management of Fever

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Although physical methods of cooling are the treatment of choice for hyperthermia, their value in the treatment of fever remains uncertain. Methods involving convection and evaporation are more effective than those involving conduction for the treatment of hyperthermia. These same methods, combined with antipyretic medication, are preferable to immersion as treatment for fever in young children but are generally not practical in adults. Febrile children treated with tepid-water sponging plus antipyretic drugs are more uncomfortable than those treated with antipyretic drugs alone, although they exhibit slightly more rapid reductions in temperature. When febrile, seriously ill patients are externally cooled and are sedated or paralyzed with drugs that suppress shivering, they may have a more rapid reduction of fever and reduced energy expenditure than if treated with antipyretic drugs alone. A risk/benefit assessment of the consequences of such treatment is not yet possible.

Although clinicians have used conductive, convective, and evaporative methods of cooling to lower body temperature for >2500 years, the benefits of such treatments are uncertain even to this day. More than 100 years ago, the German surgeon Frederick von Esmarch wrote that some surgeons favored application of cold to inflamed tissues as a means of diminishing blood flow to such tissues, whereas others recommended against the practice because of concern that cold might have deleterious effects on the skin [1]. One of the most commonly used physical methods of treating fever before the advent of antipyretic drugs was phlebotomy [2]. In 170 A.D., Galen wrote, “...for I know in some, up to 6 pints of blood were removed, so that the fever was immediately extinguished and no impairment of strength ensued” [3].

Today, the two lingering questions regarding physical methods of antipyresis are whether the discomfort of physical cooling in young children is justified by a concomitant reduction in complications of high fever, such as febrile seizures, and whether external cooling of seriously ill, febrile patients is associated with lower morbidity than is treatment with antipyretic drugs alone. The latter question arises because of the unwanted side effects of physical methods of cooling, including induction of shivering, hypermetabolism, sympathetic activation, and, possibly, pneumonia, pressure sores, and other complications that arise when sedating and paralyzing drugs are used for the suppression of shivering.

Hyperthermia

External cooling is the treatment of choice for hyperthermia. In contrast to fever, hyperthermia is characterized by a core temperature that exceeds the thermoregulatory set point. During fever, shivering, cutaneous vasoconstriction, and behavioral responses raise core temperature to coincide with an elevated thermal set point dictated by the action of endogenous pyrogens in the thermoregulatory center. During hyperthermia, decreased heat production, vasodilation, sweating, and behavioral cooling responses work to lower body temperature [4]. Thus, when external cooling is used to treat hyperthermia, it is not opposed by the counterregulatory processes that are evoked by the use of such treatment for fever.

Exercise-induced hyperthermia is generally most effectively managed by rapid cooling methods employing evaporation and convection. An early study by Wyndham et al. [5] raised the rectal temperatures of volunteers to 40°C by means of exercise in a hot environment. When subjects were cooled by wetting the skin surface and blowing warm air across the body, the mean rectal temperature decreased by 0.071°C/min; when they were exposed to continuous sprays of water without forced air, temperature fell at a rate of 0.068°C/min. Exposure to an ambient temperature of 21°C resulted in a decrease of 0.061°C/min; immersion in cold water (14°C), a decrease of 0.044°C/min; and exposure to ambient temperature of 33.9°C, a decrease of 0.020°C/min. In this study, immersion in cold water not only failed to produce an optimal rate of cooling but was also the only treatment to induce significant shivering. It was also the only treatment that caused a drop in temperature after the cessation of therapy (known as an “afterfall”), despite subjects having taken a hot shower. Shivering persisted for as long as 1 h after immersion, and afterfalls ranged from 0.6°C to 1.7°C.

Weiner and Khogali [6] compared combined evaporation and convection (a continuous spray of finely atomized water under pressure combined with blown warm, cool, or cold air) with cooling done by use of either a water mattress (20°C) or a water bath (15°C) for the treatment of heatstroke. The combined method that used warm air was the most effective, cooling at a mean rate of 0.31°C/min, compared with mean rates of
0.13°C/min with the use of atomized water and cool air, 0.12°C/min with atomized water and cold air, 0.11°C/min with the cold water bath, 0.10°C/min with the water mattress, and 0.06°C/min when no treatment was given. The water bath caused continuous shivering and marked discomfort. Less-severe shivering was seen among subjects treated with the water mattress and among those treated with atomized water and cool air. The authors concluded that the combination of evaporation and convection was superior to conduction (cold immersion and cooling blanket) for the treatment of hyperthermia, and that treatment with cold air or water was counterproductive because it induced shivering and cutaneous vasoconstriction. A more recent study by Kielblock et al. [7] showed that ice packs placed on the neck, axillae, and groin are ineffective in the treatment of hyperthermia.

Few randomized trials of the treatment of heat stroke exist [8]. Observational studies have established the efficacy of both combined evaporation and convection and ice water immersion. However, both the age and the underlying conditions of the patients studied have varied. Yaqub et al. studied 30 patients who developed heatstroke during a pilgrimage to Mecca [9]. The age range of the patients was 32–80 years. Some had coronary artery disease and/or were obese. The group had a mean rectal temperature of 42.3°C (range, 40.5°C–43.9°C) before initiation of therapy, which consisted of sprays of water and air at an ambient temperature of 20°C. After initiation of therapy, a mean time of 1 h was required to lower rectal temperature to 38.5°C. Ninety percent of subjects survived, and 83% did not have sequelae. These results are equivalent to or better than any results previously achieved for patients with illnesses of similar severity [8, 10, 11].

In an observational study of heatstroke among runners participating in summertime races, Armstrong et al. [12] observed more rapid cooling among subjects treated with ice water immersion than among those treated with wet towel wrappings (both of which are essentially conductive cooling methods). The subjects, all of whom were conditioned athletes (mean age, 35 years; range, 23–65 years), were generally less ill than those studied by Yaqub et al. [9]. Although iced peritoneal lavage has been successfully used to treat a patient with hyperthermia unresponsive to evaporative cooling and iced gastric lavage [13], the preferred treatment continues to be the use of cooling measures that involve a combination of evaporation and convection [8].

Adverse Metabolic and Physiologic Consequences of External Cooling

In febrile patients, the capacity of external cooling to lower core temperature may be limited because it induces both cutaneous vasoconstriction and shivering. The former effect has been documented in a study of 19 healthy volunteers exhibiting significant reductions in cutaneous fingertip blood flow in response to cooling blankets [14]. A study of anesthetized volunteers also confirmed that when cutaneous vasoconstriction is induced by external cooling, core body heat is conserved because of diminution in normal cutaneous heat loss [15]. Numerous studies have shown that shivering in response to external cooling raises core temperature by increasing generation of heat [16].

External cooling lowers skin temperature to a much greater extent than it lowers core temperature, and it appears to initiate vasoconstriction and shivering through its effect on skin temperature. Cheng et al. [17] have studied the relative contributions of core temperature and skin temperature to cutaneous vasoconstriction and shivering. In their investigation, core temperature was controlled by adjusting the temperature of infused iv fluids, and skin temperature was controlled by varying the temperatures of air blown across the skin. As skin temperature dropped, both vasoconstriction and shivering occurred at progressively higher core temperatures—that is, skin temperature was an independent trigger of these responses. Skin temperature has also been shown to be as important as core temperature in the determination of subjective thermal comfort [18].

Shivering not only impedes cooling during fever, it imposes an additional metabolic burden. Studies in volunteers have shown that shivering doubles oxygen consumption and respiratory minute volume, increases the percentage of carbon dioxide in expired air during exposure to cold, and increases the respiratory quotient [19, 20]. It also increases sympathetic nervous system activity.

In a recent study of elderly patients undergoing thoracic or abdominal surgery, half were randomized to an experimental group in which forced air warming was used to prevent operative temperature decreases, and half were to randomized to an experimental group receiving routine care [21]. The latter subjects had lower core temperatures, higher serum levels of norepinephrine and epinephrine, and more marked cutaneous vasoconstriction than did the former subjects. In a study of unanesthetized volunteers that compared the effects of infusion of cool versus warm fluids, infusion of cool fluids induced a 7-fold increase in norepinephrine levels, cutaneous vasoconstriction, an increase in mean arterial blood pressure, shivering, and a rise in oxygen consumption [22]. In neither study was there a change in cortisol levels in response to cooling. In another study, fever was induced by IL-2 in human volunteers. Subjects treated with forced cool air had more shivering and greater oxygen consumption, higher levels of plasma epinephrine and norepinephrine, increased mean arterial blood pressure, and more discomfort than did those who were allowed to self-regulate skin temperature [23].

External Cooling of Febrile Children

External cooling in the form of liquids applied to the skin is frequently used to treat fever in young children. The goal of
such treatment is to prevent febrile seizures and to relieve discomfort associated with the fever. Before the 1950s, sponging was often performed with isopropyl alcohol or ethyl alcohol. This practice was discouraged after it became apparent that young children could inhale enough alcohol vapors during treatment to develop hypoglycemia, become comatose, and die [24–27]. Despite recommendations to the contrary, however, the practice is still used in certain communities in the United States, and attendant morbidity continues [28]. Alcohol poisoning has also been documented in an elderly adult who was treated with an isopropyl alcohol sponge bath [29].

Two large, randomized trials comparing the use of tepid-water sponge baths with administration of antipyretics alone for the treatment of young children with temperatures ≥38.9°C have recently been reported (table 1) [30, 31]. Both trials demonstrated the unequivocal superiority of antipyretic drugs for the reduction of temperature within 2–3 h of initiation of treatment. However, antipyretic drugs appeared to work more slowly than did tepid-water sponging. In one study, sponging reduced temperatures more rapidly during the first 30 min; in the other study, the two treatments produced equivalent reductions in temperature during the first 30 min. Differences in patient comfort, in response to the two treatments, were not assessed.

Although the use of sponge baths alone is clearly inferior to administration of antipyretic drugs for the reduction of fever over periods longer than 30 min after initiation of treatment, they might still be of value if they potentiated the activity of antipyretic drugs. Results of randomized trials comparing the combination of antipyretic drugs and sponge bathing with the use of antipyretic drugs alone have provided mixed results (table 2) [32–38]. In 4 of 7 such studies reported to date, the combination treatment has been superior to the use of antipyretic drugs alone for the reduction of temperature in febrile patients overall, as well as for the reduction of temperature during the first 30 min after initiation of therapy. In the remaining 3 studies, the treatments were equally effective in lowering temperature. The preponderance of evidence resulting from examination of the actual temperature plots presented in these publications shows a more rapid reduction in temperature during the first 30 min of treatment when the use of sponging is combined with administration of antipyretic drugs. When one compares the temperature differences at 1 h, the mean difference in the positive studies was 0.41°C (range, 0.27°C to 0.67°C), and that in the negative studies was 0.67°C (range, −0.11°C to 1.4°C), implying that there is, at best, a small difference even during the first 30 min of therapy. Patient discomfort was assessed in 5 of the studies, with patients in the group receiving combined therapy showing greater discomfort in all 5 studies. In the one study in which ice water and isopropyl alcohol in water were used [32], both therapies produced extreme discomfort in 60% of patients, compared with 24%–33% of patients treated with tepid-water sponging and 9% of patients treated with acetaminophen alone.

Therefore, for febrile children, the combination of sponging and administration of antipyretic drugs appears to lower temperature slightly more rapidly during the first 30 min while causing significantly more discomfort. As a result, combined therapy cannot be justified on the basis of enhancing patient comfort. It might be justified, nevertheless, if it reduced the incidence of febrile seizures. Unfortunately, this effect has never been demonstrated. Studies have shown that acetaminophen is not effective in this regard [39, 40]. Therefore, it is unlikely that the modest and transient improvements in temperature brought about by combining sponging and administration of antipyretic drugs are effective prophylaxis against febrile seizures. Nevertheless, a survey of 41 Internet sites advising parents on home management of childhood fever found that 54% of sites recommended tepid-water sponging for the treatment of fever, whereas only 2% discouraged such therapy [41].

**Physical Cooling of Seriously Ill Febrile Patients**

Data documenting the capacity of fever to increase morbidity in patients with severe underlying conditions are sparse. Fever has been reported to potentiate neurologic injury and brain edema [42–44], cardiac ischemia, and tissue hypoxia [45], and to accelerate the terminal stages of fulminant infections (through cytokine-induced tissue injury [46]). Fever also appears to increase the risk of fetal malformation and spontaneous abortion in pregnant women [45]. External cooling is frequently administered in the hope that it will reduce the burden of these complications.

There are several reasons why antipyretic drugs might be combined with external cooling to alleviate fever in seriously ill patients. Many patients with cardiac conditions are obese,

**Table 1. Results of randomized studies of antipyresis in children: use of tepid-water sponging versus antipyretic drug therapy.**

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>n</th>
<th>Age, y</th>
<th>Initial temp., °C</th>
<th>Antipyretic drug</th>
<th>Cooling</th>
<th>Increased discomfort with physical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>[30] 1997</td>
<td>224</td>
<td>0.5–5</td>
<td>≥39 (rectal)</td>
<td>Aspirin, paracetamol, ibuprofen</td>
<td>Best with sponging</td>
<td>Best with antipyretic drug (3°C difference at 3 h)</td>
</tr>
<tr>
<td>[31] 1997</td>
<td>80</td>
<td>0.5–4.5</td>
<td>39.5–40 (axillary)</td>
<td>Paracetamol</td>
<td>Sponging equivalent</td>
<td>Best with antipyretic drug (1.5°C difference at 2 h)</td>
</tr>
</tbody>
</table>
and the insulating effects of obesity impair heat dissipation [47]. Similarly, patients with diminished cardiac output or hypertension have reduced peripheral blood flow that might compromise heat exchange at body surfaces [48]. There is conflicting evidence that individuals >65 years of age have a higher temperature threshold for sweating than do younger individuals [48]. Finally, many such patients are treated with medications that decrease sweating (e.g., anticholinergics), increase heat production (e.g., CNS stimulants or lithium), or both [48].

In a recent comparison of the methods of antipyresis used for neurologic patients [49], 21 febrile patients were randomized to 1 of the following 3 treatment groups: acetaminophen only, acetaminophen accompanied by tepid-water sponging, and acetaminophen accompanied by use of hypothermia blankets [49]. The mean time required for rectal temperature to decrease to 37.8°C was 100 min for patients in the group using hypothermia blankets and 144 min for the patients in the group using sponging. The difference was not statistically significant. The study design did not allow for comparison with the group treated with acetaminophen only. Blanket use produced shivering significantly more frequently than did the other two treatments. In a separate study comparing the temperatures of 4 patients treated with hypothermia blankets, higher blanket temperatures cooled patients as well as lower blanket temperatures did, and such treatment produced less discomfort and shivering [50].

In a nonrandomized study, Poblete et al. [51] examined the metabolic effects of external cooling by use of cloths soaked in ice water on febrile mechanically ventilated, critically ill patients [51]. This treatment was compared with treatment with iv antipyretic drugs. Externally cooled patients exhibited significantly lower core temperatures and lower daily energy expenditures than did those who were not subjected to external cooling (1791 kilocalories/day vs. 2409 kilocalories/day). Mantous et al. [52] also observed a significant decrease in core temperature and daily energy expenditure among critically ill febrile patients after application of cooling blankets. In both studies, patients received large doses of drugs (morphine plus midazolam, and pancuronium/atracurium plus “sedation,” respectively) directed at inhibition of shivering. In a small pilot study of 14 critically ill febrile patients, those receiving antipyretic drugs plus physical cooling were found to have lower core temperatures—and systemic vascular resistance indexes that were closer to normal—than those receiving antipyretic drugs alone [53]. In this study, the use of drugs to stop patients from shivering was not described.

In 1997, O'Donnell et al. [54] reported the results of a survey of hypothermia blanket use among 83 febrile, varyingly sedated, intensive care unit patients [54]. In their subjects, the mean cooling rates were identical for patients treated with hypothermia blankets and those treated with antipyretic drugs alone (0.016°C/h). The similar rates of cooling persisted even after the authors controlled for potentially confounding clinical variables. Patients treated with blankets had significantly

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**Table 2. Results of randomized studies of antipyresis in children: comparison of the use of sponging plus administration of antipyretic drugs with administration of antipyretic drugs alone.**

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>n</th>
<th>Age, y</th>
<th>Initial temp., °C</th>
<th>Antipyretic drug</th>
<th>Cooling</th>
<th>Increased discomfort with physical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>[32] 1970</td>
<td>115</td>
<td>0.5–5</td>
<td>≥39.4</td>
<td>Acetaminophen</td>
<td>Combination superior</td>
<td>No difference</td>
</tr>
<tr>
<td>[33] 1973</td>
<td>37</td>
<td>0.5–5</td>
<td>&gt;39.5</td>
<td>Aspirin, paracetamol</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>[34] 1985</td>
<td>130</td>
<td>0.25–2</td>
<td>≥39.0</td>
<td>Aspirin, acetaminophen</td>
<td>No difference at 50 min</td>
<td>No difference</td>
</tr>
<tr>
<td>[35] 1990</td>
<td>54</td>
<td>0.33–4</td>
<td>≥38.9</td>
<td>Acetaminophen</td>
<td>No difference</td>
<td>Combination superior at 60 min</td>
</tr>
<tr>
<td>[36] 1992</td>
<td>26</td>
<td>0.25–5</td>
<td>37.8–39.9</td>
<td>Paracetamol</td>
<td>Combination superior</td>
<td>Combination superior over 4 h, but difference small</td>
</tr>
<tr>
<td>[37] 1994</td>
<td>75</td>
<td>0.5–5</td>
<td>≥38.5</td>
<td>Paracetamol</td>
<td>Combination superior</td>
<td>Combination superior for time to reach temp. &lt;38°C; 10% have fever rebound (temp. &gt;38°C) in combination group 0% in antipyretic group</td>
</tr>
<tr>
<td>[38] 1997</td>
<td>20</td>
<td>0.5–6</td>
<td>≥38.9</td>
<td>Acetaminophen</td>
<td>Combination superior, first hour</td>
<td>No difference</td>
</tr>
</tbody>
</table>

**NOTE.** Temp., temperature. Sponging is with tepid water, unless otherwise indicated. Subjects in groups receiving placebo or sponging alone are excluded. Temperatures are rectal unless otherwise indicated.

* Axillary.
greater to-and-fro temperature fluctuations and a greater risk of overshoot hypothermia. Although frostbite had been reported previously as a potential complication of cooling blankets [55], this complication was not observed by O'Donnell et al. [54].

Summary

Physical cooling methods are clearly indicated for the treatment of hyperthermia, but their use for the treatment of fever remains controversial because of their propensity to induce cutaneous vasoconstriction, shivering, sympathetic activation, and, perhaps most importantly, discomfort. The ultimate value of external corporeal cooling for the treatment of fever will require randomized trials that use clinically meaningful "illness outcome" end points, rather than mere comparisons of rates of core temperature cooling.

References