

# Clinical trial of an air-circulating cooling blanket for fever control in critically ill neurologic patients

S.A. Mayer, MD; C. Commichau, MD; N. Scarmeas, MD; M. Presciutti, RN; J. Bates, BS; and D. Copeland, MPH

**Article abstract**—*Objective:* To evaluate the efficacy of an air-circulating cooling blanket for reducing body temperature in febrile neuro-ICU patients treated with acetaminophen. *Methods:* Two-hundred twenty consecutively admitted neuro-ICU patients whose tympanic membrane temperature reached or exceeded 101 °F (38.3 °C) were randomly assigned to receive acetaminophen (650 mg every 4 hours) alone (n = 107) or acetaminophen plus air blanket therapy (n = 113). After 24 hours of treatment, the authors compared the proportion of subjects who attained treatment success (T ≤ 99 °F) or treatment failure (T ≥ 101 °F for 2 consecutive hours) using the  $\chi^2$  test and the time to reach these endpoints using Kaplan-Meier survival analysis. *Main Results:* Air blanket therapy resulted in a small increase in the proportion of subjects with treatment success (44% versus 36%,  $\chi^2 p = 0.19$ , log rank  $p = 0.10$ ) and a similar small reduction in the proportion of patients with treatment failure (42% versus 53%,  $\chi^2 p = 0.11$ , log-rank  $p = 0.21$ ), compared with treatment with acetaminophen alone. Approximately one third of patients in both groups remained febrile after randomization and “failed” after the first 2 hours of treatment. Twelve percent of patients assigned to air blanket therapy refused or were unable to tolerate treatment, compared with 2% of patients treated with acetaminophen alone ( $p = 0.005$ ). *Conclusions:* Treatment with an air-circulating cooling blanket did not effectively reduce body temperature in febrile neuro-ICU patients treated with acetaminophen. More effective interventions are needed to maintain normothermia in patients at risk for fever-related brain damage.

NEUROLOGY 2001;56:292–298

Fever affects a large proportion of critically ill neurologic patients and may adversely affect outcome.<sup>1</sup> In patients with stroke, temperature elevation on admission is associated with increased morbidity and mortality, an effect that is independent of other established measures of clinical stroke severity.<sup>2–6</sup> This clinical observation is consistent with experimental studies indicating that ischemic neuronal injury may be substantially increased with temperature elevations as small as 1 °C to 2 °C above normal.<sup>7,8</sup> Although the influence of elevated body temperature on outcome after traumatic brain injury (TBI), status epilepticus, or other types of acute brain injury is less clear, experimental evidence for temperature-related brain damage in these conditions exists,<sup>9–12</sup> and it is widely accepted that fever should generally be treated in neurologic patients. As an extension of this philosophy, induced moderate hypothermia has

recently been shown to improve outcome in patients with severe TBI<sup>13</sup> and has been tested as a treatment for massive cerebral infarction.<sup>14</sup>

Despite increasing recognition of the importance of treating fever in patients with stroke<sup>15</sup> or other forms of acute brain injury, little is known about the optimal method for combating fever in critically ill neurologic patients. In most intensive care units, fever is initially treated with acetaminophen, and patients with refractory temperature elevations are treated with water-circulating cooling blankets.<sup>16–18</sup> Although acetaminophen is well-established as an antipyretic in children,<sup>19</sup> its efficacy in critically ill adult patients has never been carefully evaluated. In this study, we compared two first-line approaches for treating fever in critically ill neurologic patients: acetaminophen alone or acetaminophen combined with an air-circulating cooling blanket. We tested

**See also page 286**

From the Division of Critical Care Neurology (Drs. Mayer, Commichau, and Scarmeas, J. Bates, and D. Copeland), Department of Neurology, Columbia University College of Physicians & Surgeons; and the Department of Nursing (M. Presciutti), Columbia–Presbyterian Medical Center, New York Presbyterian Hospital, New York, NY.

Received July 10, 2000. Accepted in final form October 24, 2000.

Address correspondence and reprint requests to Dr. Stephan A. Mayer, Neurological Institute, 710 West 168th Street, Unit 39, New York, NY 10032; e-mail: sam14@columbia.edu

the hypothesis that over a 24-hour observation period, convective air blanket therapy would lead to an absolute increase of at least 20% in the proportion of patients who attained normothermia, avoided persistent fevers, or both.

**Materials and methods.** *Subjects.* All patients admitted to the 12-bed Columbia-Presbyterian Medical Center Neurologic Intensive Care Unit (NICU) between February 1, 1999 and January 31, 2000 were eligible for enrollment. In our NICU, temperature is routinely measured hourly by using an infrared tympanic thermometer (Genius 3000A, Sherwood Medical, St. Louis, MO). Criteria for inclusion in the study was the first recorded temperature equal to or exceeding 101 °F (38.3 °C) during each patient's stay in the NICU. This cutoff was chosen because it conforms with published practice guidelines<sup>20</sup> and is our standard criteria for initiating antipyretic therapy with acetaminophen and for initiating a diagnostic evaluation for infection. Patients could be enrolled only once during a single NICU stay but could be enrolled again if they were readmitted at a later time. To evaluate whether all eligible subjects were enrolled, we reviewed nursing charge reports (which list each patient's maximum temperature per 12-hour shift) on a daily basis and compared it with the study entry log.

The study protocol was approved by the Columbia-Presbyterian Institutional Review Board. The need for written informed consent was waived because the study was thought to pose no significant risk to its participants. Patients were excluded if they or their surrogate declined to participate after the study was explained to them.

*Data collection.* Demographic, clinical, and laboratory data pertaining to each subject was recorded by concurrent chart review. Temperature on enrollment was dichotomized as 101.0 to 101.4 °F and  $\geq 101.5$  °F, and level of consciousness was assessed by using the Glasgow Coma Scale. CT scan reports were reviewed to determine whether intracranial blood was present at the time of enrollment. At the time of NICU discharge, patients were assigned to 1 of the following 12 principle diagnostic categories: 1) intracerebral hemorrhage; 2) subarachnoid hemorrhage; 3) cerebral infarction; 4) traumatic brain or spine injury; 5) CNS neoplasm; 6) seizures; 7) respiratory failure; 8) unruptured aneurysm; 9) carotid endarterectomy; 10) interventional neuro-radiology (INR) procedure; 11) medical complication; and 12) other neurosurgical procedure.

The cause of fever was determined independently by two investigators, who reviewed the medical record and the following diagnostic studies if obtained within 48 hours of enrollment: chest radiography (CXR), sinus CT scans, blood cultures, sputum and nasal cultures, urine analysis and cultures, CSF cultures, stool *Clostridium difficile* toxin assays, and lower extremity Doppler studies. Cause of fever was classified as follows: 1) *explained, infectious*—bacteremia (two positive blood cultures); pneumonia (positive sputum culture with infiltrate on chest radiograph); bronchitis (positive sputum culture without infiltrate on chest radiograph); sinusitis (positive nasal culture with sinus opacification on CT); urinary tract infection (pyuria and positive urine culture with  $>100K$  colonies); cellulitis/wound infection (erythema, tenderness, or purulence with positive cultures); *C difficile* enteritis (positive toxin as-

say), meningitis/ventriculitis (CSF pleocytosis with positive culture); 2) *explained, noninfectious*—deep vein thrombosis (positive lower extremity Doppler), atelectasis (characteristic findings in two or more lung segments on chest radiograph), drug fever (resolution of fever after drug discontinuation); 3) *unexplained* (none of the above criteria identified); 4) *incomplete diagnostic evaluation* (lack of chest radiograph or blood, urine, or sputum culture). When the two reviewers initially disagreed on the diagnostic category, the data were reexamined until a consensus was reached. We also noted whether patients were receiving antibiotics at the time of enrollment.

*Study interventions.* The NICU nursing staff identified eligible study subjects, performed the randomization, administered the study intervention, and recorded the hourly temperature measurements and secondary outcome measures; they were not blinded to treatment assignment. Eligible subjects were assigned a study identification number and randomly assigned to one of two treatment arms, determined by opening a numbered sealed envelope: Group 1 was treated with acetaminophen 650 mg PO/PR (per rectum) every 4 hours; Group 2 was treated continuously with the Polar Air™ Model 600 Air Cooling System (Augustine Medical, Minneapolis, MN) in addition to acetaminophen 650 mg PO/PR every 4 hours. The Polar Air™ system consists of a disposable paper blanket that is circulated with forced cooled air (10 °C; air output 30 CFM, 850 L/m). The blanket is placed over the patient, and the cooled air circulates around the patient through a series of pores on the underside of the blanket.

*Main outcome measures.* After enrollment and randomization, tympanic membrane temperature was recorded hourly, and the study intervention was continued for 24 hours, or until the patient met one of two predefined endpoint criteria. *Treatment success* was defined as the first measured temperature  $\leq 99$  °F (37.2 °C). When this criterion was met, the study protocol was stopped, and further antipyretic therapy was given according to the preferences of the nurse or physician caring for the patient. *Treatment failure* was defined as two consecutive temperatures  $\geq 101$  °F (38.3 °C). When this criterion was met, the study protocol was stopped, and subjects were switched to treatment with a water-circulating cooling blanket in addition to continued therapy with acetaminophen. This is the current standard of care in our NICU for patients who are persistently febrile ( $>2$  hours) after treatment with acetaminophen. A single tympanic membrane thermometer was used to serially record temperature in each subject, and these devices were maintained and calibrated according to the manufacturer's guidelines.

After completing the study, each subject's hourly temperature record was reviewed by an investigator blinded to treatment status, who assigned one of four main outcome categories: 1) treatment success; 2) treatment failure; 3) neither (patient was treated for 24 hours without meeting criteria for success or failure); and 4) censored (hourly recording of temperature ceased before meeting one of the endpoint criteria). Patients in the latter category were usually transferred out of the NICU to the floor or for a procedure. For patients with treatment success or failure, or who were censored, the time to attain this endpoint was recorded. Secondary outcome measures recorded by the nurse caring for the patient included 1) shivering, 2) re-

fusal of or inability to tolerate the treatment intervention, and 3) dermatologic reactions (i.e., skin breakdown) caused by the study intervention.

**Protocol violations.** Protocol violations were identified based on review of the medical record and the hourly temperature measurements after subjects completed the study. When randomization or treatment did not conform with the study protocol, the reasons were classified as follows: 1) patient had been febrile at some point before enrollment; 2) acetaminophen dose missed or not given on schedule; 3) air blanket therapy interrupted or stopped inappropriately; 4) patient transferred out of NICU before study endpoint; 5) patient improperly enrolled ( $T < 101^\circ\text{F}$ ); 6) air blanket not available; 7) patient refused or was not able to tolerate assigned treatment; 8) air blanket not used properly; 9) temperature not recorded every hour; 10) same thermometer not used consistently; 11) NICU ambient temperature elevated (because of hospital power failure).

**Statistical analysis.** In an intention-to-treat analysis, we compared the relative efficacy of the two study interventions in four ways. Using the  $\chi^2$  test, after 24 hours we compared the proportion of all randomized subjects with treatment success and the proportion with treatment failure. After analyzing a pilot series of 30 patients evaluated before the start of the trial, we estimated a 25% frequency of treatment success and 60% frequency of treatment failure in the control group. Assuming an alpha level of 0.05 (two-tailed) and power of 0.80, we calculated that enrollment of 109 patients in each group would allow us to detect an absolute difference of 20% in these main outcome measures (i.e., a  $>20\%$  increase in the frequency of success, or  $>20\%$  reduction in the frequency of failure in the intervention group). We also compared time to treatment success or treatment failure between the two groups by using Kaplan-Meier survival plots and the Mantel-Cox log-rank test, to account for the possibility that the study intervention might speed the interval to treatment success or delay the interval to treatment failure. Assuming 109 patients in each group, our study had sufficient power to detect a  $\geq 1.49$  increase in the hazard ratio for treatment success, or a  $\leq 0.67$  reduction in the hazard ratio for treatment failure, assuming an alpha level of 0.05 (two-tailed) and power of 0.80.

We compared the proportion of patients with one of the secondary outcome measures using the  $\chi^2$  test or Fisher's exact test, as appropriate.

To assess the impact of other factors that might affect treatment response, we compared treatment response among all patients and within each treatment group according to baseline temperature ( $\geq$  versus  $<101.5^\circ\text{F}$ ), level of consciousness (GCS  $\leq 8$  versus  $>8$ ), antibiotics (yes versus no), age ( $\geq$  versus  $<54$  years), intracranial blood (yes versus no), principle diagnosis (stroke versus other), and cause of fever (infectious versus other; unexplained versus other). These proportions were compared by using the  $\chi^2$  test. For all tests, significance was judged at the  $p < 0.05$  level.

**Results.** The flow of patients through the clinical trial is shown in figure 1. Of 241 potentially eligible patients whose temperature reached or exceeded  $101^\circ\text{F}$ , 220 (91%) were enrolled and randomized. In four instances, the same patient was enrolled twice during two different NICU ad-

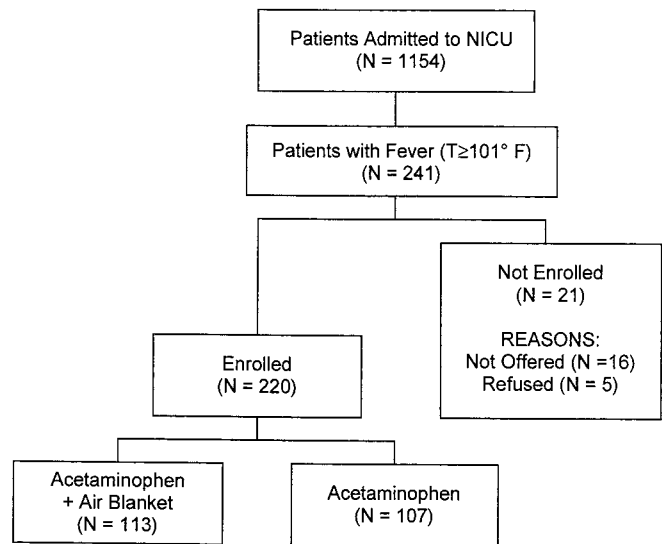


Figure 1. Flow of patients screened for the trial.

missions. One hundred seven subjects were assigned to acetaminophen, and 113 were assigned to acetaminophen plus air blanket therapy.

Baseline characteristics of the study patients are shown in table 1. The two groups were well matched with regard to age, gender, race/ethnicity, medical history, Glasgow Coma Scale (GCS) score, principle diagnosis, and cause of fever; however, patients assigned to acetaminophen plus air blanket therapy were more often postoperative (65% versus 49%). Among all patients, mean temperature at randomization was  $101.5^\circ\text{F}$  (range,  $100.0^\circ$  to  $104.4^\circ\text{F}$ ). The most common causes of infectious fever were pneumonia ( $n = 74$ ), bronchitis ( $n = 23$ ), bacteremia ( $n = 14$ ), urinary tract infection ( $n = 11$ ), and *C difficile* colitis ( $n = 5$ ).

In an intention-to-treat analysis (table 2), treatment with the air blanket in addition to acetaminophen resulted in a modest increase in the proportion of patients with treatment success, and a similar reduction in the proportion of patients with treatment failure. At the end of the 24-hour study period, treatment success had occurred in 35.5% (38 of 107) of the patients treated with acetaminophen, compared with 44.2% (50/113) of patients treated with acetaminophen plus the air blanket ( $p = 0.19$ ), an 8.7% increase in the absolute proportion of patients with a favorable outcome (95% CI +21.6% to -4.0%). Survival curves comparing time with treatment success are shown in figure 2, panel A ( $p = 0.096$ , log-rank test).

Treatment failure occurred in 53.3% (56/107) of the patients treated with acetaminophen, compared to 41.6% (47/113) of patients treated with acetaminophen plus the air blanket ( $p = 0.11$ ). Blanket therapy resulted in an 11.7% reduction in the absolute proportion of patients with an unfavorable outcome (95% CI -23.9% to +2.4). A large proportion of patients in both groups "failed" treatment after the first two hours of the study: 37.4% (40/107) in the acetaminophen group, and 32.7% (37/113) in the acetaminophen plus air blanket group. Survival curves comparing the proportion of subjects free of treatment failure are shown in figure 2B ( $p = 0.208$ , log-rank test).

Protocol violations occurred in 33% of the patients treated with acetaminophen, and 39% of those treated with acetaminophen plus air blanket, but most were minor

**Table 1** Baseline characteristics of the study patients

Characteristic	Acetaminophen, n = 107	Acetaminophen + air blanket, n = 113
Age, y	53.1 ± 16.6	55.0 ± 15.8
Female	55 (51)	58 (51)
Race/ethnicity		
White	53 (50)	52 (46)
African	18 (17)	20 (18)
Hispanic	27 (25)	29 (26)
Other	9 (8)	12 (11)
Past medical history		
Hypertension	46 (43)	47 (42)
Coronary artery disease	21 (20)	13 (12)
Diabetes mellitus	13 (12)	13 (12)
Diagnostic category		
Subarachnoid hemorrhage	39 (36)	33 (29)
Intracerebral hemorrhage	16 (15)	20 (18)
Traumatic brain injury	14 (13)	13 (12)
CNS neoplasm	9 (8)	16 (14)
Cerebral infarction	9 (8)	6 (5)
Seizures	6 (6)	8 (7)
Temperature at enrollment, °F	101.5 ± 0.5	101.6 ± 0.6
Antibiotic therapy	56/98 (57)	60/97 (62)
Leukocyte count	13.0 ± 5.0	13.3 ± 4.9
Postoperative	49/100 (49)	68/105 (65)
Cause of fever		
Infectious	60 (56)	61 (54)
Unexplained	25 (23)	29 (26)
Incomplete diagnostic evaluation	22 (21)	21 (19)
Deep vein thrombosis	0 (0)	2 (2)
Median GCS score	10	10
Intracranial hemorrhage	69/101 (68)	72/110 (65)

Values are mean ± SD or n (%) unless otherwise noted.

GCS = Glasgow Coma Scale.

(table 3). The most common violation was a delay in enrolling patients with fever, which affected 13% of subjects (28 of 220). Twelve percent (13 of 113) of patients assigned to acetaminophen plus air blanket therapy refused or were unable to tolerate the treatment, compared with only 2% (2 of 107) of patients assigned to acetaminophen alone ( $p = 0.005$ ,  $\chi^2$  test). Shivering was observed in no patients treated with acetaminophen, compared with 7% (8 of 113) of patients assigned to acetaminophen plus air blanket therapy ( $p = 0.007$ , Fisher's exact test). However, shivering was generally mild and well tolerated; in only one instance was treatment stopped. There were no cases of rash or skin breakdown related to air blanket therapy.

To identify factors other than treatment assignment that might affect response to antipyretic therapy, we compared a variety of factors among all subjects and within

each treatment group. We found no effect of age, baseline temperature, level of consciousness, intracranial blood, diagnosis, antibiotic use, or cause of fever on the proportion of patients who attained treatment success or failure at the end of 24 hours (data not shown).

**Discussion.** Although it is generally accepted that aggressive measures should be taken to combat fever in patients with acute brain injury, the most effective method for doing so is unclear. In this study, we found that treatment with an air-circulating cooling blanket and acetaminophen provided no additional benefit when compared with acetaminophen alone. In our view, however, the most important and surprising finding of this study was the large extent to which both treatment arms were inadequate for controlling fever. More than one third of patients in each group remained febrile after randomization and exited the study as a "treatment failure" after the first 2 hours of treatment. This finding suggests that more robust interventions are needed to maintain normothermia in neurologic patients at risk for fever-related secondary brain damage.

Two types of interventions can be used to reduce elevated body temperature: antipyretic agents, and external cooling. *Antipyretic agents*, including acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAID), work by lowering the hypothalamic setpoint, which is increased in fever.<sup>16,19,21</sup> Endogenous pyrogens such as interleukin-1 and interleukin-6, released by leukocytes in response to infection, drugs, blood products, or other stimuli, cause fever by stimulating cerebral prostaglandin-E synthesis.<sup>19,21</sup> Antipyretic agents block this process by inhibiting cyclooxygenase-mediated prostaglandin synthesis in the brain. The result is a lowering of the hypothalamic setpoint, which activates the body's two principle mechanisms for heat dissipation: vasodilation and sweating.<sup>19,21</sup>

Antipyretic drugs lower body temperature in pyrogen-induced fever, which implies intact thermoregulation, but may be ineffective in brain-injured patients with impaired thermoregulatory mechanisms.<sup>22</sup> There appear to be only minor differences in efficacy between different nonsteroidal antipyretic agents.<sup>19,23</sup> Corticosteroids also have antipyretic

**Table 2** Twenty-four-hour treatment outcomes

Characteristic	Acetaminophen, n = 107	Acetaminophen + air blanket, n = 113	<i>p</i> Value*
Success (T ≤ 99.0 °F)	38 (36)	50 (44)	0.186
Failure (T ≥ 101.0 °F for 2 consecutive h)	56 (53)	47 (42)	0.111
Neither	3 (4)	1 (1)	
Censored	10 (9)	15 (13)	

\* *p* Values refer to chi-square test, comparing the proportion of patients with treatment success or failure versus all other outcomes.

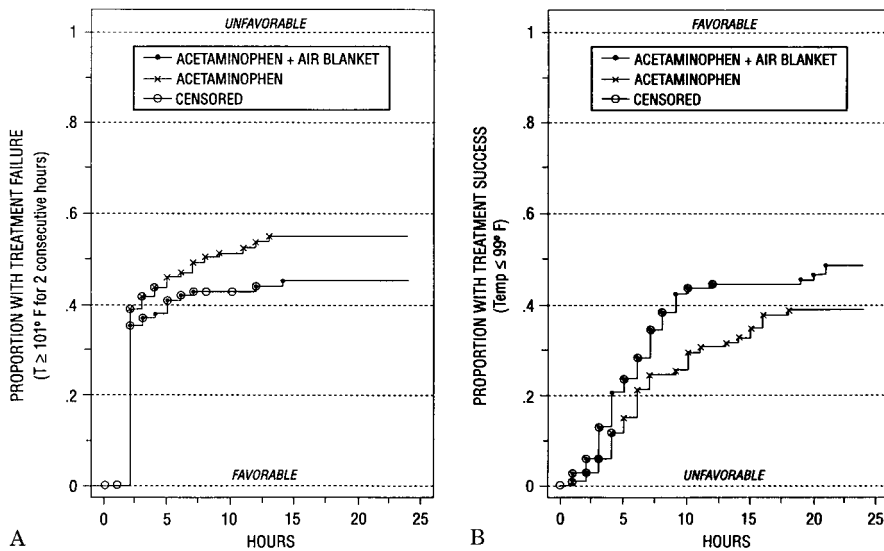


Figure 2. Kaplan-Meier survival curves comparing the proportion of patients during the 24-hour study period with treatment failure (panel A), defined as  $T \geq 101^\circ\text{F}$  for two consecutive hours, or treatment success (B), defined as  $T \leq 99^\circ\text{F}$ . Although fewer patients treated with air blanket therapy “failed” after 24 hours (A), the difference was small ( $p = 0.208$ , log-rank test). Patients treated with air blanket therapy were more likely to attain treatment success, but again, the difference was small ( $p = 0.096$ , log-rank test).

properties but are not used clinically to treat fever because of their side effects.<sup>16,21</sup>

Whether acetaminophen alone is more effective than placebo for treating fever in adult ICU patients is unknown. Our study did not address this question, and controlled studies of acetaminophen use in febrile adult ICU patients are lacking; almost all studies comparing acetaminophen with placebo or other NSAID have involved children.<sup>19</sup> Regardless, our results indicate that acetaminophen at the dose we gave (650 mg every 4 hours) is unsatisfactory for controlling fever in critically ill neurologic patients. This relative lack of efficacy may be explained by inadequate dosing (doses of up to 15 mg/kg are used in children),<sup>19</sup> by the fact that acetaminophen may take as long as 3 hours to reach its peak effect, or because many of our patients may have had central fever with impaired thermoregulation (the cause of fever could not be explained by infection in approximately 25% of subjects).

External cooling reduces body temperature by promoting heat loss, without affecting the hypothalamic set point. Four modes of heat transfer constitute the basis of interventions to promote heat loss: 1) *evaporation* (e.g., water sprays or sponge baths); 2) *conduction* (e.g., ice packs, water-circulating cooling blankets, immersion); 3) *convection* (e.g., fans, air-circulating cooling blankets); and 4) *radiation* (i.e., exposure of skin).<sup>21,22</sup> In patients with temperature elevations caused by impaired thermoregulation, such as heat stroke and central fever, antipyretic agents are ineffective, and temperature reduction can only be promoted by external cooling.<sup>21</sup> By contrast, in febrile patients with an elevated set point, external cooling can result in reflex shivering and vasoconstriction, as the body attempts to generate heat and “fight” the cooling process. Shivering, which increases body temperature and energy expenditure and is uncomfortable, has been shown to be less prominent with external cooling when the extremities are wrapped.<sup>21</sup>

Few controlled studies have evaluated the efficacy of external cooling interventions for lowering body temperature in humans. Three experimental studies have shown that the combination of evaporative and

Table 3 Protocol violations

Violation	Acetaminophen, n = 107	Acetaminophen + air blanket, n = 113
Improper enrollment		
Previous temperature $\geq 101^\circ\text{F}$	12 (11)	16 (14)
Index temperature $< 101^\circ\text{F}$	2 (2)	2 (2)
Incomplete data		
Temperature not recorded every hour	10 (9)	5 (4)
Transferred out of NICU	5 (5)	7 (6)
Treatment disruption		
Patient refused or was unable to tolerate treatment	2 (2)	13 (12)
Acetaminophen stopped or interrupted	9 (8)	5 (4)
Air blanket stopped or interrupted	0 (0)	6 (5)
Air blanket not available	0 (0)	5 (4)
Air blanket not used properly	0 (0)	1 (1)
Miscellaneous		
Different thermometer device used	1 (1)	0 (0)
Extremely elevated ambient temperature	0 (0)	1 (1)
Total	35 (33)	44 (39)

Values are n (%). Sum of individual items exceeds the total number of subjects because patients may have had more than one violation.

NICU = neurologic intensive care unit.

convection cooling, with water sprays or sponging and forced airflow, is more effective than conduction cooling or either method alone for reducing temperature in patients with hyperthermia induced by exercise and heat exposure.<sup>24-26</sup> Two clinical studies evaluated the effect of evaporative cooling with water sponging in children treated with acetaminophen; one found a benefit,<sup>27</sup> and the other did not.<sup>28</sup>

Water-circulating cooling blankets, a form of conductive cooling, are the most commonly used treatment for acetaminophen-refractory fever in critically ill adults. Antipyretics<sup>17</sup> and cooling blankets<sup>18</sup> are used particularly frequently in neurologic patients, which is not surprising given the concern that fever may exacerbate brain injury. However, there are few data regarding their efficacy. Two small controlled studies have evaluated external cooling in adult ICU patients. One study compared the use of acetaminophen alone with tepid water sponging, or with a water-circulating cooling blanket in 21 febrile neurologic patients, and found no difference between the three treatments; however, this study had important methodologic problems and inadequate power to detect differences between the three groups.<sup>29</sup> Another study of 20 febrile patients under sedation, analgesia, and mechanical ventilation found that ice-water sponging was superior to two IV NSAID (paracetamol and metamazol) in a nonrandomized crossover study.<sup>30</sup> A large observational study found no difference in the mean cooling rate in febrile ICU patients treated with or without water-circulating cooling blankets.<sup>18</sup>

In our study of febrile neuro-ICU patients treated with acetaminophen, air-blanket cooling had a small benefit that did not reach statistical significance in an intention-to-treat analysis. The relative ineffectiveness of convection cooling in our patients may have several explanations. Protocol violations occurred in a large proportion of both groups: 39% in the air blanket plus acetaminophen group, and 33% percent in the acetaminophen only group. This might be explained in part by the fact that nurses were responsible for enrolling patients and giving the study intervention, while juggling clinical demands in the ICU. Air blanket therapy was stopped or interrupted because the patient refused or was unable to tolerate treatment in 12%, because of a nursing error in 5%, and because the device was not available in 4%. Though it is possible that a significant treatment effect might have been found had these interruptions not occurred, they reflect the vagaries of clinical practice, which are inevitable in the hectic setting of an ICU.

Shivering occurred in 8 of 113 (7%) patients treated with an air blanket. Though it led to discontinuation of therapy in only one case, by increasing heat production, shivering also may have hindered the efficacy of air blanket therapy in some patients. Concurrent treatment with an opioid agent such as meperidine, which suppresses shivering,<sup>22</sup> may have improved the efficacy of air blanket therapy. This notion is supported by the observation that air blan-

ket cooling can effectively lower body temperature in stroke patients to less than 33 °C when paralysis and sedation are used.<sup>14</sup>

Although we treated patients who failed therapy in either group with a water-circulating cooling blanket, we did not record temperatures after they reached this study endpoint. Therefore, we have no data regarding the relative efficacy of water-blanket cooling in patients with refractory fever.

Other limitations of our study also deserve mention. We measured tympanic membrane temperature by using an infrared device. Although these devices may be less accurate than other devices for measuring core body temperature,<sup>31,32</sup> they are the standard of care in our NICU, primarily because of their ease-of-use. To minimize variability due to differences in calibration between devices, we took care to ensure that the same device was used to trend temperature in each subject. Of note, tympanic membrane temperature, as well as core temperature (e.g., rectal, bladder), may underestimate brain temperature in brain-injured patients.<sup>33</sup> Our study was unblinded, which may have led to bias on the part of nurses who treated patients and recorded hourly temperatures. However, the final designation of treatment outcome was based on review of the temperature records by an investigator blinded to treatment assignment. Finally, we enrolled patients with relatively mild new-onset fever (mean, 101.5 °F). Air blanket therapy might be more effective in patients with higher temperatures, a group that might include a higher proportion of patients with central fever.

Given the presumed importance of treating fever in patients with acute brain injury, it seems clear that further research is needed to improve on current methods for lowering body temperature in neurologic patients. If normothermia can be effectively maintained in patients with stroke or other types of acute brain injury, whether this can improve functional outcome remains to be seen.

### Acknowledgment

The authors thank Dr. Robert Vosskuhler and Augustine Medical, Inc., for donating the air blanket used for this trial. They also thank Evelyn Du, PhD, for reviewing the statistical analysis, and the nursing staff of the Columbia-Presbyterian Neuro-ICU for their efforts in executing this clinical trial.

### References

1. Albrecht RF, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. *Mayo Clin Proc* 1998;73:629-635.
2. Hajat C, Hajat S, Sharma P. Effects of post-stroke pyrexia on stroke outcome: a meta-analysis of studies on patients. *Stroke* 2000;31:410-414.
3. Wang Y, Lim L L-Y, Levi C, Heller RF, Fisher J, Maths B. Influence of admission body temperature on stroke mortality. *Stroke* 2000;31:404-409.
4. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality and outcome. *Lancet*. 1996;347:422-425.
5. Castillo J, Davalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. *Stroke* 1998; 29:2455-2460.

6. Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L. Fever in acute stroke worsens prognosis: a prospective study. *Stroke* 1995;26:2040–2043.
7. Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intracerebral brain temperature critically determine the extent of ischemic injury. *J Cereb Blood Flow Metab* 1987;7:129–138.
8. Kim Y, Busto R, Dietrich WD, Kraydich S, Ginsberg MD. Delayed postischemic hyperthermia in awake rats worsens the histopathologic outcome of transient forebrain ischemia. *Stroke* 1996;27:2274–2281.
9. Clifton GL, Jiang JY, Lyeth BG, Jenkins LW, Hamm RJ, Hayes RL. Marked protection by moderate hypothermia after experimental traumatic brain injury. *J Cereb Blood Flow Metab* 1991;11:114–121.
10. Dietrich WD. The importance of brain temperature in cerebral injury. *J Neurotrauma* 1992;9(suppl 2):S475–S485.
11. Clasen RA, Pandolfi S, Laing I, Casey D Jr. Experimental study of relation of fever to cerebral edema. *J Neurosurg* 1974;41:576–581.
12. Lebovitz RM. Effects of temperature on interictal discharge in penicillin epileptogenic foci. *Epilepsia* 1975;16:215–22.
13. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997;336:540–546.
14. Schwab S, Schwarz S, Spranger M, et al. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke* 1998;29:2461–2466.
15. Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. *Stroke* 1998;29:529–534.
16. Klein NC, Cunha BA. Treatment of fever. *Infect Dis Clin North Am* 1996;10:211–216.
17. Isaacs SN, Axelrod PI, Lorber B. Antipyretic orders in a university hospital. *Am J Med* 1990;88:31–35.
18. O'Donnell J, Axelrod P, Fisher C, Lorber B. Use and effectiveness of hypothermia blankets for febrile patients in the intensive care unit. *Clin Infect Dis* 1997;24:1208–1213.
19. Ameer B, Greenblatt DJ. Acetaminophen. *Ann Intern Med* 1977;87:202–209.
20. O'Grady NP, Barie PS, Bartlett J, et al. Practice parameters for evaluating new fever in critically ill adult patients. *Crit Care Med* 1998;26:392–408.
21. Holtzclaw BJ. The febrile response in critical care: state of the science. *Heart Lung* 1992;21:482–501.
22. Guyton AG. Body temperature, temperature regulation and fever. In: Guyton AG, ed. *Textbook of Medical Physiology*, 8<sup>th</sup> ed. Philadelphia: WB Saunders, 1991:797–808.
23. Done AK. Treatment of fever in 1982: a review. *Am J Med* 1983;74:27.
24. Wyndham CH, Strydom NB, Cooke HM, et al. Methods of cooling subjects with hyperpyrexia. *J Appl Physiol* 1959;14:771–776.
25. Weiner JS, Khogali M. A physiologic body-cooling unit for treatment of heat stroke. *Lancet* 1980;1:507–509.
26. Kielblock AJ, Van Rensberg JP, Franz RM. Body cooling as a method for reducing hyperthermia. *S Afr Med J* 1986;69:378–380.
27. Steele RW, Tanaka PT, Lara RP, Bass JW. Evaluation of sponging and of oral antipyretic therapy to reduce fever. *J Pediatr* 1970;77:824–829.
28. Newman J. Evaluation of sponging to reduce body temperature in febrile children. *Can Med Assoc J* 1985;132:641–642.
29. Morgan SP. A comparison of three methods of managing fever in the neurologic patient. *J Neurosci Nurs* 1990;22:19–24.
30. Poblette B, Romand J-A, Pichard C, Konig P, Suter PM. Metabolic effects of i.v. propacetamol, metamizol or external cooling in critically ill febrile sedated patients. *Br J Anaesth* 1997;78:123–127.
31. Erickson RS, Kirklin SK. Comparison of ear-based, bladder, oral and axillary methods for core temperature measurement. *Crit Care Med* 1993;21:1528–1534.
32. Schmitz T, Bair N, Falk M, Levine C. A comparison of five methods of temperature measurement in febrile intensive care patients. *Am J Crit Care* 1995;54:286–292.
33. Crowder CM, Tempelhoff R, Theard MA, Cheng MA, Torodov A, Dacey RG. Jugular bulb temperature: comparison with brain surface and core temperatures in neurosurgical patients during mild hypothermia. *J Neurosurg* 1996;85:98–103.

## Access *www.neurology.org* now for full-text articles

*Neurology* online is now available to all subscribers. Our online version features extensive search capability by title key words, article key words, and author names. Subscribers can search full-text article *Neurology* archives to 1995 and can access link

references with PubMed. The one-time activation requires only your subscriber number, which appears on your mailing label. If this label is not available to you, call 1-800-638-3030 (United States) or 1-301-714-2300 (outside United States) to obtain this number.