ORIGINAL ARTICLE

Acetaminophen for Fever in Critically Ill Patients with Suspected Infection

Paul Young, M.D., Manoj Saxena, M.D., Rinaldo Bellomo, M.D., Ross Freebairn, M.D., Naomi Hammond, R.N., M.P.H., Frank van Haren, M.D., Ph.D., Mark Holliday, B.Sc., Seton Henderson, M.D., Diane Mackle, M.N., Colin McArthur, M.D., Shay McGuinness, M.D., John Myburgh, M.D., Ph.D., Mark Weatherall, M.D., Steve Webb, M.D., Ph.D., and Richard Beasley, M.D., D.Sc., for the HEAT Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Acetaminophen is a common therapy for fever in patients in the intensive care unit (ICU) who have probable infection, but its effects are unknown.

METHODS

We randomly assigned 700 ICU patients with fever (body temperature, ≥38°C) and known or suspected infection to receive either 1 g of intravenous acetaminophen or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death. The primary outcome was ICU-free days (days alive and free from the need for intensive care) from randomization to day 28.

RESULTS

The number of ICU-free days to day 28 did not differ significantly between the acetaminophen group and the placebo group: 23 days (interquartile range, 13 to 25) among patients assigned to acetaminophen and 22 days (interquartile range, 12 to 25) among patients assigned to placebo (Hodges–Lehmann estimate of absolute difference, 0 days; 96.2% confidence interval [CI], 0 to 1; P=0.07). A total of 55 of 345 patients in the acetaminophen group (15.9%) and 57 of 344 patients in the placebo group (16.6%) had died by day 90 (relative risk, 0.96; 95% CI, 0.66 to 1.39; P=0.84).

CONCLUSIONS

Early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days. (Funded by the Health Research Council of New Zealand and others; HEAT Australian New Zealand Clinical Trials Registry number, ACTRN12612000513819.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Young at the Intensive Care Unit, Wellington Regional Hospital, Private Bag 7902, Wellington South, New Zealand, or at paul.young@ccdhb.org.nz.

*A complete list of investigators in the Permissive Hyperthermia through Avoidance of Acetaminophen in Known or Suspected Infection in the Intensive Care Unit (HEAT) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 5, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1508375

Administration of acetaminophen to lower temperature in patients with fever and probable infection is a frequent intervention in the community and in hospitals. In the intensive care unit (ICU), such treatment is common[1,2] and is based on the rationale that fever places additional physiological stress on patients who are already seriously ill.[3] Treatment of fever in ICU patients with infection is supported by a recent randomized, controlled trial in which physical cooling of mechanically ventilated patients with septic shock to a normal body temperature was associated with a reduction in vasopressor dose and reduced early mortality.[4]

The common practice of treating fever in patients with infection is challenged by studies showing that fever may enhance immune-cell function,[5] inhibit pathogen growth,[6-8] and increase the activity of antimicrobial drugs[9] and by observational studies showing that higher early fever is associated with a lower risk of death among patients with an ICU admission diagnosis of infection.[10,11]

The lack of high-level evidence[12] leaves ICU clinicians uncertain about whether acetaminophen treatment of fever due to probable infection is beneficial, ineffective, or harmful. To address this uncertainty, we conducted a multicenter, blinded, randomized, controlled trial to evaluate the hypothesis that administration of intravenous acetaminophen to treat fever would worsen outcomes. Specifically, we hypothesized that, as compared with placebo, acetaminophen would result in fewer ICU-free days (days alive and free from the need for intensive care) in adult ICU patients with fever and probable infection.

Methods

Study Design

We conducted an investigator-initiated, prospective, parallel-group, blinded, randomized, controlled trial. The management committee (made up of all the authors) designed the trial, which was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group. The George Institute for Global Health (Sydney) and the Medical Research Institute of New Zealand (Wellington) provided subsidized project management and on-site monitoring of data quality for this study. The protocol, which was reported before enrollment commenced[13] and is available with the full text of this article at NEJM.org, was approved by the New Zealand Multi-region Ethics Committee and by each participating institution. Written informed consent before randomization or delayed consent was obtained from each patient or a legal surrogate, unless an institutional ethics committee approved a waiver of consent (e.g., in the event that a patient died before informed consent could be obtained from a surrogate decision maker). The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of this report to the protocol.

Patients

Patients 16 years of age or older with a temperature of 38°C or higher within 12 hours before enrollment and who were receiving antimicrobial therapy for a known or suspected infection were eligible for inclusion. Among the exclusion criteria were acute brain disorders and liver dysfunction that contraindicated the use of acetaminophen. A full list of exclusion criteria is provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

Randomization and Study Drugs

Eligible patients were randomly assigned, in a 1:1 ratio, to receive either an infusion containing 1 g of intravenous acetaminophen (Perfalgan, Bristol-Myers Squibb) or an infusion of 5% dextrose in water, every 6 hours. The study medications were packaged in indistinguishable 100-ml glass bottles. Randomization was performed with the use of an encrypted Web-based system involving block randomization with a block size of six and was stratified according to participating center. Investigators were unaware of the randomization block size.

Patients continued to receive the study drug until 28 days after enrollment or until the occurrence of one of the prespecified cessation criteria: discharge from the ICU, resolution of fever as defined by a prespecified algorithm (Fig. S1 in the Supplementary Appendix), cessation of antimicrobial therapy, death, or the development of a contraindication to the study drug.

Rescue physical cooling was permitted if the body temperature rose to 39.5°C or higher. The use of open-label acetaminophen was permitted after the course of study medication was completed. The use of other treatments to reduce body

temperature was restricted by the protocol (see the Supplementary Appendix).

OUTCOME MEASURES

The primary outcome measure was ICU-free days to day 28.[14] ICU-free days is a composite outcome combining mortality and ICU length of stay. The number of ICU-free days was calculated as 28 minus the number of days or part-days spent in the ICU during the first 28 days after randomization (excluding any days of ICU readmission); patients who died were assigned the worst possible outcome of zero ICU-free days.[14]

Secondary outcomes, within a 90-day follow-up period, were all-cause mortality at day 28 and day 90; survival time (number of days alive) from randomization until day 90; ICU and hospital length of stay; and hospital-free days, days free from mechanical ventilation, days free from inotropes or vasopressors, days free from renal-replacement therapy, and days in the ICU that were free from support. To be deemed free from support in the ICU, a patient was required to be free from mechanical ventilation, inotropes or vasopressors, and renal-replacement therapy for an entire calendar day and had to remain free from such supports until discharge from the ICU. Patients who died were assigned zero days for all outcome measures involving freedom from support or hospital-free days.

Physiological- and laboratory-related outcome variables were mean and maximum axillary temperature; the proportion of patients who stopped the study drug owing to the development of liver dysfunction; mean serum C-reactive protein (CRP) levels measured in the ICU on days 1, 3, 5, and 7; the proportion of patients in the ICU with a serum creatine kinase level of more than 5000 units on days 1, 3, 5, or 7; and highest serum creatinine level in the ICU during the first 7 days after randomization.

The primary outcome was examined in four prespecified subgroups defined according to the following prerandomization criteria: the presence or absence of septic shock (defined as sepsis-induced hypotension despite adequate fluid resuscitation), the use or nonuse of aspirin, the presence or absence of high fever (defined as a temperature of ≥39°C in the 12 hours before enrollment), and the location of infection acquisition (community, hospital, or ICU). Full details of the study design can be found in the protocol.

STATISTICAL ANALYSIS

The statistical analysis plan was reported before the interim analysis was conducted.[15] On the basis of an inception cohort study[16], we assumed a mean control value of 16.0±9.2 ICU-free days. With this assumption and allowing for a 15% inflation in sample size to account for the use of a rank-based test[15] and an additional 5% inflation to account for loss to follow-up, we calculated that a sample size of 700 patients would provide 80% power to detect an absolute difference of 2.2 ICU-free days at 28 days after randomization, at an alpha level of 0.05.

All analyses were conducted on an intention-to-treat basis with masking to study-group assignments. We defined the intention-to-treat population as all enrolled patients except those who withdrew consent for use of data. We made no imputation for missing values. For the primary analysis comparing ICU-free days between study groups, we used a Wilcoxon rank-sum test and present results as point estimates of absolute difference, using 96.2% confidence intervals to account for the interim efficacy analysis conducted after enrollment of 233 patients. Point estimates of absolute difference that are provided are the median of all paired differences between observations in the two groups, calculated with the use of the Hodges–Lehmann method.[17]

The risk of death at day 28 and day 90 was estimated by means of Poisson regression and is presented as a relative risk with 95% confidence intervals. For mortality at day 28 and day 90, adjusted analyses were performed with the use of multivariate Poisson regression. Prespecified covariates were age, ICU admission source, and Acute Physiology and Chronic Health Evaluation (APACHE) II score.[18] We compared survival times to day 90 using log-rank tests and present these as Kaplan–Meier curves and used a Cox proportional-hazards model to calculate hazard ratios for death. ICU and hospital length of stay were compared in the overall study groups and, as prespecified, among survivors and nonsurvivors separately.

For the prespecified subgroups, we performed a proportional-odds analysis with the number of ICU-free days categorized as 0 to 7 days, 8 to 14

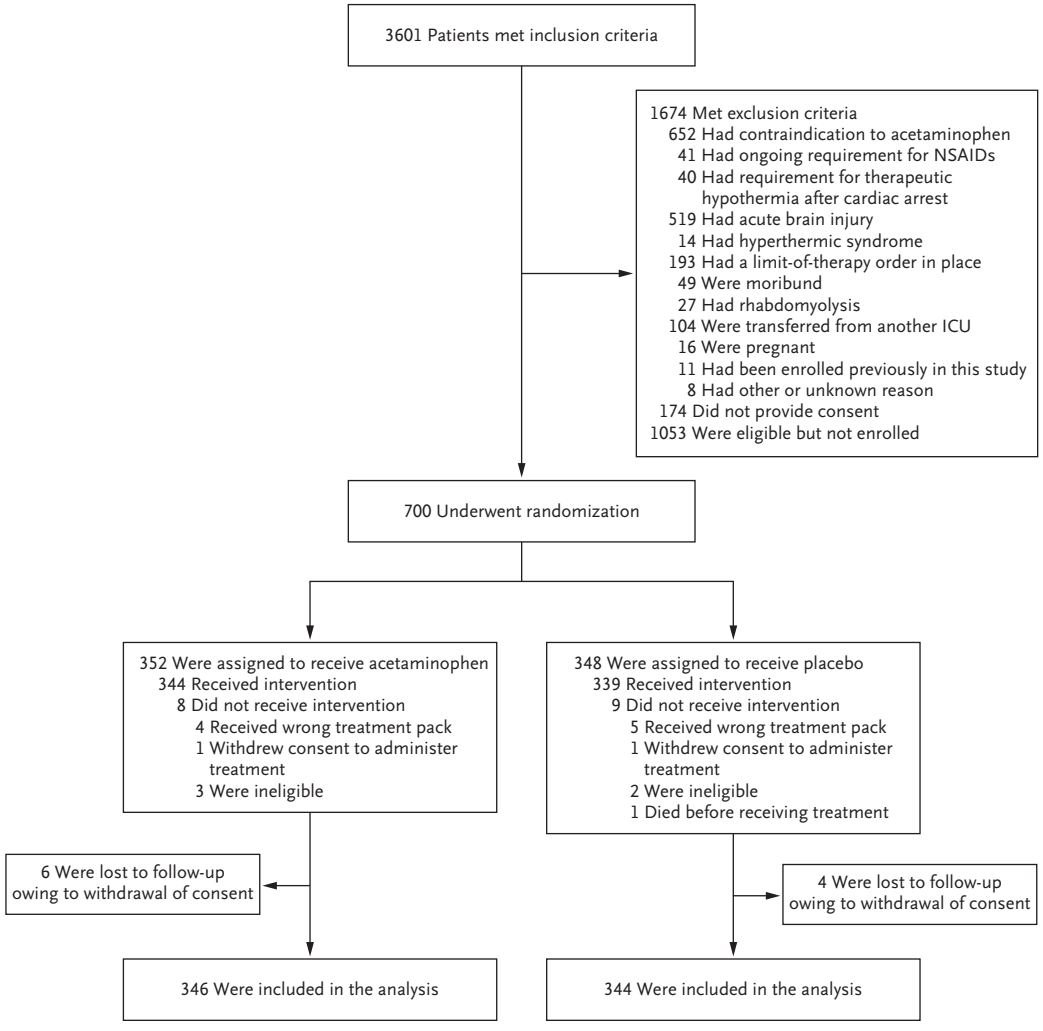

Figure 1. Screening, Randomization, and Follow-up.

ICU denotes intensive care unit, and NSAIDs nonsteroidal antiinflammatory drugs.

days, 15 to 21 days, or 22 to 27 days. This facilitated a formal test for subgroup heterogeneity with an interaction term. All analyses were conducted with the use of SAS statistical software, version 9.3 (SAS Institute). Two-sided P values of less than 0.05 were considered to indicate statistical significance, except in the case of the primary outcome, for which a P value of 0.0379 or less was used.[19]

Study results were initially reviewed by the management committee, whose members were unaware of the study-group assignments. Post hoc analyses were performed to further evaluate the effects of the study drugs on temperature and the use of cointerventions that might have affected body temperature before the study-group assignments were unmasked. Additional details of statistical analyses and post hoc analyses are available in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

From February 2013 through July 2014, we enrolled 700 patients in 23 adult medical–surgical ICUs in Australia and New Zealand, with 352 patients assigned to receive acetaminophen and 348 to receive placebo (Fig. 1). Ten participants withdrew

consent, resulting in an intention-to-treat population of 690, of whom 346 were assigned to receive acetaminophen and 344 were assigned to receive placebo. Data on the primary outcome were available for the entire intention-to-treat population.

The study groups had similar characteristics at baseline (Table 1, and Tables S2 and S3 in the Supplementary Appendix). The most common sites of infection were the lungs and the abdomen. A causative organism was identified in 217 of 347 patients (62.5%) assigned to acetaminophen and in 214 of 344 patients (62.2%) assigned to placebo (Tables S4 and S5 in the Supplementary Appendix).

The median number of doses of study drug was 8 (interquartile range, 5 to 14) in the acetaminophen group and 9 (interquartile range, 6 to 15) in the placebo group (absolute difference, −1 dose; 95% confidence interval [CI], −2 to 0; P=0.15) (Fig. S2A in the Supplementary Appendix). The study drug was administered in accordance with the protocol in 281 of 347 patients (81.0%) assigned to acetaminophen and in 289 of 344 patients (84.0%) assigned to placebo. All protocol deviations are listed in Table S6 in the Supplementary Appendix. The most common reasons for discontinuation of the study drug were discharge from the ICU and resolution of fever (Table S7 in the Supplementary Appendix).

Open-label acetaminophen was administered in the ICU in 104 of 347 patients (30.0%) assigned to acetaminophen and in 101 of 344 patients (29.4%) assigned to placebo (odds ratio, 1.01; 95% CI, 0.86 to 1.19; P=0.86) and was used predominantly in the latter phases of ICU treatment (Fig. S2B and S2C in the Supplementary Appendix). There were no significant differences between study groups in the use of physical cooling or nonsteroidal antiinflammatory drugs (Fig. S3 and S4 in the Supplementary Appendix).

PHYSIOLOGICAL EFFECTS

Patients assigned to receive acetaminophen had a lower mean daily peak body temperature than those assigned to placebo (38.4±1.0°C vs. 38.6±0.8°C; absolute difference, −0.25°C; 95% CI, −0.38 to −0.11; P<0.001) and a lower mean daily average body temperature (37.0±0.6°C vs. 37.3±0.6°C; absolute difference, −0.28°C; 95% CI, −0.37 to −0.19; P<0.001) (Fig. S5 and S6 and Table S8 in the Supplementary Appendix). The study drug was discontinued because of sustained resolution of fever in 79 of 347 patients (22.8%) assigned to acetaminophen and in 58 of 344 patients (16.9%) assigned to placebo (odds ratio, 1.45; 95% CI, 0.99 to 2.12; P=0.05). Among patients in whom the study drug was discontinued owing to discharge from the ICU, 19 of 154 patients (12.3%) assigned to acetaminophen and 37 of 161 patients (23.0%) assigned to placebo had a temperature of 38°C or higher on their last day in the ICU (odds ratio, 0.47; 95% CI, 0.26 to 0.86; P=0.01). CRP, creatinine, and creatine kinase values were similar in the two groups (Table S9 in the Supplementary Appendix).

PRIMARY OUTCOME

The number of ICU-free days to day 28 did not differ significantly between the acetaminophen group and the placebo group: 23 days (interquartile range, 13 to 25) among patients assigned to acetaminophen and 22 days (interquartile range, 12 to 25) among patients assigned to placebo (absolute difference, 0 days; 96.2% CI, 0 to 1; P=0.07) (Table 2). The distribution of ICU-free days according to study group is shown in Figure S7 in the Supplementary Appendix.

SECONDARY OUTCOMES

There were no significant differences between the acetaminophen group and the placebo group with respect to mortality at day 28 or at day 90 (Table 2, and Table S10 in the Supplementary Appendix) or with respect to survival time to day 90 (Fig. 2). A total of 55 of 345 patients (15.9%) assigned to acetaminophen and 57 of 344 patients (16.6%) assigned to placebo had died by 90 days (relative risk, 0.96; 95% CI, 0.66 to 1.39; P=0.84).

There was no significant difference between the two groups with respect to ICU length of stay (4.1 days [interquartile range, 2.1 to 8.3] among patients assigned to acetaminophen and 4.2 days [interquartile range, 2.0 to 9.0] among patients assigned to placebo; absolute difference, −0.1 days; 95% CI, −0.7 to 0.4; P=0.65) or with respect to hospital length of stay (13.7 days [interquartile range, 7.6 to 22.9] among patients assigned to acetaminophen and 13.8 days [interquartile range, 7.1 to 24.3] among patients assigned to placebo; absolute difference, −0.01 days; 95% CI, −1.6 to 1.6; P=0.98). There was heterogeneity of response, with acetaminophen associated with a shorter me-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Acetaminophen (N=347)	Placebo (N=344)
Age — yr	59.1±16.9	57.9±17.4
Male sex — no. (%)	224 (64.6)	225 (65.4)
Weight — kg	86.2±26.0	85.4±24.8
Ethnic group — no. (%)†		
New Zealand European	137 (39.5)	123 (35.8)
Australian European	108 (31.1)	113 (32.8)
Maori	26 (7.5)	32 (9.3)
Pacific Islander	19 (5.5)	21 (6.1)
Aboriginal or Torres Strait Islander	8 (2.3)	4 (1.2)
Other	49 (14.1)	51 (14.8)
Coexisting conditions — no. (%)		
Cancer	74 (21.3)	67 (19.5)
Chronic pulmonary disease	41 (11.8)	47 (13.7)
Congestive heart failure	13 (3.7)	19 (5.5)
Diabetes	91 (26.2)	86 (25.0)
End-stage renal failure	10 (2.9)	5 (1.5)
HIV infection	7 (2.0)	3 (0.9)
Ischemic heart disease	52 (15.0)	52 (15.1)
Severe neurologic dysfunction	15 (4.3)	26 (7.6)
Source of admission to ICU — no. (%)		
Emergency department	115 (33.1)	116 (33.7)
Hospital ward	128 (36.9)	96 (27.9)
Transfer from another ICU	14 (4.0)	18 (5.2)
Transfer from another hospital, except from another ICU	22 (6.3)	24 (7.0)
Operating room after elective surgery	15 (4.3)	23 (6.7)
Operating room after emergency surgery	53 (15.3)	67 (19.5)
Time from admission to randomization — days	1.3±1.8	1.4±2.3
Physiological characteristics‡		
Peak temperature in the 12 hr before randomization — °C	38.8±0.6	38.7±0.6
Mean arterial pressure — mm Hg	76.7±12.8	76.9±12.2
Heart rate — beats/min	100.2±20.6	99.8±20.7
Minute ventilation — liters/min	10.3±4.0	9.8±3.3
Sepsis status — no. (%)§		
Sepsis	346 (99.7)	344 (100)
Severe sepsis	289 (83.3)	285 (82.8)
Septic shock	65 (18.7)	73 (21.2)
APACHE II score¶	19.1±6.7	18.7±7.5
Physiological support — no. (%)		
Inotropic or vasopressor support	174 (50.1)	181 (52.6)
Mechanical ventilation		
Invasive	176 (50.7)	182 (52.9)
Noninvasive	21 (6.1)	23 (6.7)

Table 1. (Continued.)

Characteristic	Acetaminophen (N=347)	Placebo (N=344)
Renal-replacement therapy	12 (3.5)	12 (3.5)
Other extracorporeal therapy	0	1 (0.3)
Receiving glucocorticoid therapy — no./total no. (%)	49/320 (15.3)	62/327 (19.0)
Receiving aspirin therapy — no. (%)	53 (15.3)	54 (15.7)

* Plus–minus values are means ±SD. There were no significant differences between study groups in any of the measured baseline characteristics except for peak temperature in the 12 hours before randomization (P=0.049). Data were available for 347 patients assigned to acetaminophen because 1 patient who withdrew consent for study follow-up approved the use of study data that were collected before withdrawal of consent. HIV denotes human immunodeficiency virus, and ICU intensive care unit.

† We determined the ethnic group by reviewing patients' demographic data at hospital admission or by asking patients or their next of kin.

‡ Data on baseline physiological characteristics were not available for all patients. Details on missing data are provided in the Supplementary Appendix.

§ Sepsis was defined as suspected or confirmed infection, with at least two out of four signs of a systemic inflammatory response. Severe sepsis was defined as sepsis with evidence of organ dysfunction. Septic shock was defined as sepsis-induced hypotension despite fluid resuscitation of at least 30 ml per kilogram of intravenous fluid administered within the period spanning the 4 hours before and 4 hours after initiation of vasopressor therapy.[20]

¶ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

dian ICU length of stay than placebo among survivors (3.5 days [interquartile range, 1.9 to 6.9] vs. 4.3 days [interquartile range, 2.1 to 8.9], P=0.01) and with a longer median ICU length of stay among nonsurvivors (10.4 days [interquartile range, 4.1 to 16.9] vs. 4.0 days [interquartile range, 1.7 to 9.4], P<0.001) (P<0.001 for interaction) (Table 3).

There were no significant differences between the study groups with respect to any other secondary outcome variables (Table 2). There was no significant heterogeneity in study-drug effect on ICU-free days in any of the prespecified subgroups (Table S11 in the Supplementary Appendix).

ADVERSE EVENTS

Liver dysfunction led to discontinuation of the study drug in 28 of 347 patients (8.1%) assigned to acetaminophen and in 34 of 344 patients (9.9%) assigned to placebo (odds ratio, 0.89; 95% CI, 0.69 to 1.16; P=0.40). There was a serious adverse event of markedly elevated body temperature associated with death in 1 patient assigned to placebo (see the Supplementary Appendix).

DISCUSSION

In this binational, blinded, randomized, controlled trial, we observed that the early administration of acetaminophen for treatment of fever in adult ICU patients with probable infection resulted in neither more ICU-free days nor fewer ICU-free days than those observed with administration of placebo. Although acetaminophen was associated with a shorter ICU stay than placebo among survivors and a longer stay among nonsurvivors, there was no significant difference between the acetaminophen group and the placebo group with respect to 28-day mortality, 90-day mortality, or survival time to day 90. Patients who received intravenous acetaminophen had a lower body temperature than those who received placebo and did not have significantly more adverse events.

Data are lacking from previous blinded, randomized, controlled trials to evaluate the use of intravenous acetaminophen to treat fever in ICU patients with suspected infection. The magnitude of the temperature reduction observed in our study is consistent with that in studies involving patients with acute ischemic stroke[21] and critically ill adults with fever and the systemic inflammatory response syndrome.[22]

Our observation that ICU and hospital length of stay were longer with acetaminophen than with placebo among patients who died is consistent with the finding of a study in which physical cooling to normothermia delayed death in mechanically ventilated patients with septic shock.[4]

Table 2. Study Outcomes.*

Outcome	Acetaminophen (N=346)	Placebo (N=344)	Absolute Difference†	P Value
			days (95% CI)	
Primary outcome: ICU-free days — median (IQR)	23 (13–25)	22 (12–25)	0 (0–1)‡	0.07
Key secondary outcomes				
Hospital-free days — median (IQR)	12 (0–19)	10 (0–18)	0 (0–0)	0.27
Days free from mechanical ventilation — median (IQR)	27 (19–28)	26 (17–28)	0 (0–0)	0.14
Days free from inotropes or vasopressors — median (IQR)	27 (25–28)	27 (24–28)	0 (0–0)	0.36
Days free from renal-replacement therapy — median (IQR)	28 (28–28)	28 (28–28)	0 (0–0)	0.53
Days free from ICU support — median (IQR)	26 (16–27)	25 (15–27)	0 (0–1)	0.14
			Relative Risk (95% CI)	**P Value**
			Unadjusted / Adjusted§	Unadjusted / Adjusted§
Death by day 28 — no. (%)	48 (13.9)	47 (13.7)	1.02 (0.68–1.52) / 1.00 (0.67–1.50)	0.94 / 0.99
Death by day 90 — no. (%)¶	55 (15.9)	57 (16.6)	0.96 (0.66–1.39) / 0.94 (0.65–1.35)	0.84 / 0.73

* CI denotes confidence interval, and IQR interquartile range.
† Shown is the Hodges–Lehmann estimate of absolute difference between acetaminophen and placebo. The Hodges–Lehmann estimate is the median of all paired differences between observations in the two samples.
‡ A 96.2% confidence interval was used for the primary outcome to account for the interim analysis.
§ The relative risk was adjusted for the source of admission, age, and APACHE II score.
¶ Vital status at day 90 was not available for one patient assigned to acetaminophen.

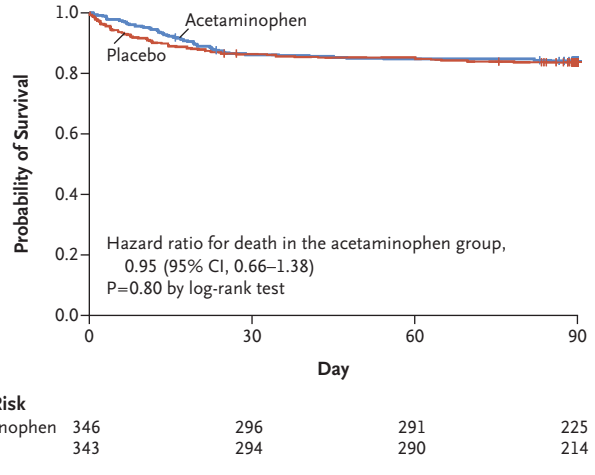

Figure 2. Kaplan–Meier Estimates of the Probability of Survival to Day 90.
Tick marks indicate censored observations.

These observations are also consistent with a recent retrospective cohort study in which a Cox proportional-hazards analysis showed that ICU patients who received acetaminophen had a significantly longer time to death than those who did not.[23]

We sought to minimize ascertainment bias through centralized randomization, concealment of allocation to study groups, and masking of the study drugs. We used a primary outcome that is not subject to observer bias. To further minimize bias, we published the statistical analysis plan[15] and conducted all analyses, including post hoc analyses, before unmasking the study-group assignments. Although our predominantly nonsurgical patient population had low mortality, illness-severity scores were higher than those observed in a recent trial involving patients with septic shock.[24] Moreover, our re-

Table 3. Logarithmic Transformation Analysis of ICU and Hospital Length of Stay among Survivors versus Nonsurvivors.*

Variable	Acetaminophen	Placebo	Difference in Logarithms (95% CI)	Exponent of Difference (95% CI)	P Value	P Value for Interaction
	median no. of days (IQR)					
Hospital length of stay						<0.001
Nonsurvivors	13.9 (7.1 to 22.2)	7.7 (2.9 to 17.0)	0.64 (0.30 to 0.99)	1.90 (1.35 to 2.69)	<0.001	
Survivors	13.2 (7.7 to 25.0)	14.1 (8.1 to 27.1)	–0.12 (–0.27 to 0.04)	0.89 (0.76 to 1.04)	0.13	
ICU length of stay						<0.001
Nonsurvivors	10.4 (4.1 to 16.9)	4.0 (1.7 to 9.4)	0.75 (0.36 to 1.14)	2.12 (1.43 to 3.13)	<0.001	
Survivors	3.5 (1.9 to 6.9)	4.3 (2.1 to 8.9)	–0.18 (–0.35 to 0.01)	0.84 (0.70 to 0.99)	0.01	

* The exponent of the difference in natural logarithms can be interpreted as the ratio of mean values. An exponent of more than 1 implies a longer stay with acetaminophen than with placebo and an exponent of less than 1 a shorter stay.

sults are generalizable because we studied the broad population of ICU patients with infections who receive acetaminophen to treat fever in routine practice. We used the intravenous formulation of acetaminophen to eliminate any confounding that might be attributable to impaired and unpredictable enteral absorption.

Our study has certain limitations. The median duration of study-drug administration was short, and approximately one third of the patients in each study group were exposed to acetaminophen in the ICU after the course of study-drug administration had been completed. Consequently, our study findings are relevant primarily to the early use of acetaminophen to treat fever in the ICU. We did not collect information about the use of acetaminophen before randomization or after ICU discharge. Protocol deviations were minor and were unlikely to have materially affected our findings.

Our findings suggest that acetaminophen has a modest clinical effect as an antipyretic in ICU patients with fever and probable infection but does not reduce ICU-free days in these patients. Our observation that early administration of acetaminophen to treat fever is associated with a longer ICU stay than placebo among nonsurvivors and a shorter stay among survivors must be regarded as hypothesis-generating, thereby requiring caution in interpretation. Such findings may relate to the physiological effects of reducing fever[3] and the way that these effects may influence clinicians' perception of the patient's illness severity, prognosis, or both. This perception may induce clinicians to discharge improving patients from the ICU faster and to support for a longer period of time patients who will ultimately succumb. An alternative or additional interpretation is that acetaminophen exerts biologically important effects on the natural history of sepsis.

We evaluated the administration of acetaminophen to treat fever and administered it for a relatively short period of time. Thus, our results do not preclude the possibility that a more prolonged course of acetaminophen may have a greater influence on patient-centered outcomes. Further studies are required to evaluate this possibility.

In conclusion, early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days. There was no significant between-group difference in 28-day mortality, 90-day mortality, or survival time to day 90.

Supported by research grants from the Health Research Council of New Zealand, the Australian and New Zealand Intensive Care Foundation, and the Waikato Medical Research Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Intensive Care Unit, Wellington Regional Hospital (P.Y., D.M.), Medical Research Institute of New Zealand (P.Y., R.F., M.H., S.H., D.M., C.M., S.M., R. Beasley), and Wellington School of Medicine, University of Otago (M.W.), Wellington, Intensive Care Unit, Hawke's Bay Hospital, Hastings (R.F.), Intensive Care Unit, Christchurch Hospital, Christchurch (S.H.), and the Department of Critical Care Medicine (C.M.) and Cardiothoracic and Vascular Intensive Care Unit (S.M.), Auckland City Hospital, Auckland — all in New Zealand; and the Critical Care and Trauma Division, George Institute for Global Health, Sydney (M.S., N.H., J.M.), Intensive Care Unit, St. George Hospital, Kogarah (M.S., J.M.), Malcolm Fisher Department of Intensive Care Medicine, Royal North Shore Hospital, St. Leonards (N.H.), and Faculty of Medicine, St. George Clinical School, University of New South Wales, Kensington (J.M.), NSW, Intensive Care Unit, Austin Hospital (R. Bellomo), the Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University (R. Bellomo), and Faculty of Medicine, University of Melbourne (R. Bellomo), Melbourne, VIC, the Intensive Care Unit, Canberra Hospital, Canberra, ACT (F.H.), and the Intensive Care Unit, Royal Perth Hospital, Perth (S.W.), and the School of Medicine and Pharmacology, University of Western Australia, Crawley (S.W.), WA — all in Australia.

REFERENCES

1. Hammond NE, Saxena MK, Taylor C, et al. Temperature management of non-elective intensive care patients without neurological abnormalities: a point prevalence study of practice in Australia and New Zealand. Crit Care Resusc 2013;15:228-33.
2. Saxena MK, Taylor CB, Hammond NE, et al. Temperature management in patients with acute neurological lesions: an Australian and New Zealand point prevalence study. Crit Care Resusc 2013;15:110-8.
3. Manthous CA, Hall JB, Olson D, et al. Effect of cooling on oxygen consumption in febrile critically ill patients. Am J Respir Crit Care Med 1995;151:10-4.
4. Schortgen F, Clabault K, Katsahian S, et al. Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med 2012;185:1088-95.
5. Berman JD, Neva FA. Effect of temperature on multiplication of Leishmania amastigotes within human monocyte-derived macrophages in vitro. Am J Trop Med Hyg 1981;30:318-21.
6. Chu CM, Tian SF, Ren GF, Zhang YM, Zhang LX, Liu GQ. Occurrence of temperature-sensitive influenza A viruses in nature. J Virol 1982;41:353-9.
7. Moench M. A study of the heat sensitivity of the meningococcus in vitro within the range of therapeutic temperatures. J Lab Clin Med 1926;57:665-76.
8. Small PM, Täuber MG, Hackbarth CJ, Sande MA. Influence of body temperature on bacterial growth rates in experimental pneumococcal meningitis in rabbits. Infect Immun 1986;52:484-7.
9. Mackowiak PA, Ruderman AE, Martin RM, Many WJ, Smith JW, Luby JP. Effects of physiologic variations in temperature on the rate of antibiotic-induced bacterial killing. Am J Clin Pathol 1981;76:57-62.
10. Saxena M, Young P, Pilcher D, et al. Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. Intensive Care Med 2015;41:823-32.
11. Young PJ, Saxena M, Beasley R, et al. Early peak temperature and mortality in critically ill patients with or without infection. Intensive Care Med 2012;38:437-44.
12. Zhang Z. Antipyretic therapy in critically ill patients with established sepsis: a trial sequential analysis. PLoS One 2015;10(2):e0117279.
13. Young PJ, Saxena MK, Bellomo R, et al. The HEAT trial: a protocol for a multicentre randomised placebo-controlled trial of IV paracetamol in ICU patients with fever and infection. Crit Care Resusc 2012;14:290-6.
14. Young P, Hodgson C, Dulhunty J, et al. End points for phase II trials in intensive care: recommendations from the Australian and New Zealand Clinical Trials Group consensus panel meeting. Crit Care Resusc 2012;14:211-5.
15. Young PJ, Weatherall M, Saxena MK, et al. Statistical analysis plan for the HEAT trial: a multicentre randomised placebo-controlled trial of intravenous paracetamol in intensive care unit patients with fever and infection. Crit Care Resusc 2013;15:279-86.
16. Young P, Saxena M, Eastwood GM, Bellomo R, Beasley R. Fever and fever management among intensive care patients with known or suspected infection: a multicentre prospective cohort study. Crit Care Resusc 2011;13:97-102.
17. Lehmann EL. Nonparametric confidence intervals for a shift parameter. Ann Math Stat 1963;34:1507-12.
18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
19. Emerson SS, Fleming TR. Symmetric group sequential test designs. Biometrics 1989;45:905-23.
20. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29:530-8.
21. Dippel DW, van Breda EJ, van der Worp HB, et al. Timing of the effect of acetaminophen on body temperature in patients with acute ischemic stroke. Neurology 2003;61:677-9.
22. Greenberg RS, Chen H, Hasday JD. Acetaminophen has limited antipyretic activity in critically ill patients. J Crit Care 2010;25(2):363.e1-363.e7.
23. Suzuki S, Eastwood GM, Bailey M, et al. Paracetamol therapy and outcome of critically ill patients: a multicenter retrospective observational study. Crit Care 2015;19:162.
24. Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496-506.