Effect of active temperature management on mortality in intensive care unit patients

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ABSTRACT

Objective: To evaluate the effect of active temperature management on mortality, intensive care unit (ICU) and hospital length of stay, as well as the relative efficacy of antipyretic medications and physical cooling devices for achieving reductions in temperature in critically ill adults.

Design, setting and participants: Systematic review and meta-analysis of randomised controlled trials (RCTs) investigating treatments administered to febrile patients in order to reduce body temperature. Fifteen studies reporting results from 13 RCTs met our eligibility criteria.

Interventions: Treatments administered to reduce body temperature were defined as physical cooling, non-steroidal anti-inflammatory drugs, paracetamol, or any combination of these.

Main outcome measures: The primary outcome variable was all-cause mortality at the longest time point after randomisation. Secondary outcomes were ICU and hospital length of stay, and body temperature 12 hours after randomisation.

Results: Active temperature control had no statistically significant association with mortality (odds ratio, 1.01; 95% confidence interval [CI], 0.81–1.28; $P = 0.95$, for fixed effects). There was no statistically significant association between active temperature management and ICU or hospital length of stay. Active temperature management was associated with a statistically significant reduction in temperature. The fixed effects estimate for the active minus control treatment for pharmaceutical management was –0.62°C (95% CI, –0.72°C to –0.51°C; $P < 0.001$) and for physical cooling was –1.59°C (95% CI, –1.82°C to –1.35°C; $P < 0.001$).

Conclusions: Active temperature management neither increased nor decreased mortality risk in critically ill adults. When the therapeutic goal is to reduce body temperature, physical cooling approaches may be more effective than pharmacological measures in critically ill adults.

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Fever occurs in about half of adult patients in the intensive care unit (ICU)[1] and contributes to increased physiological demand.[2] Moreover, when fever is treated, physiological demand is reduced.[3] Two randomised controlled trials (RCTs) in ICU patients with fever and infection have recently been reported.[4,5] One trial evaluated physical cooling,[4] and the other, the use of paracetamol to treat fever.[5] Both trials reported that treatment of fever delayed death,[4,5] but neither reported a statistically significant reduction of in-hospital or subsequent mortality with fever treatment. In patients with acute brain pathologies, treating fever aggressively may prevent secondary brain injury; however, the effect of this practice on patient-centred outcomes remains uncertain.

To further evaluate the hypothesis that, in critically ill adults, active temperature management with antipyretic drugs or physical cooling methods reduces mortality, we conducted a systematic review and meta-analysis of randomised controlled trials. Our primary aim was to evaluate the effect of active temperature management on landmark mortality. Our secondary aims were to evaluate the effect of active temperature management on ICU and hospital length of stay as well as the relative efficacy of antipyretic medications and physical cooling devices for achieving reductions in body temperature.

Methods

Search strategy, trial eligibility criteria, data extraction and study outcomes

We conducted a systematic review and meta-analysis of randomised controlled trials in accordance with a pre-specified protocol, which we registered on the international prospective registry of systematic reviews, PROSPERO.[6]

We searched MEDLINE, EMBASE, PubMed, CINAHL and the Cochrane Central Register of Controlled Trials in March 2016. We also contacted study authors, as required, to identify further eligible studies and to request additional information. Full details of our search strategy are outlined in the supplementary Appendix (online at cicm.org.au/

Resources/Publications/Journal).

Trials were eligible for inclusion if they were RCTs investigating any treatment or combination of treatments commonly administered to febrile patients in order to reduce body temperature with placebo or standard care, or compared more aggressive temperature control with less aggressive temperature control. Our pre-specified list of treatments was physical cooling, non-steroidal anti-inflammatory drugs, paracetamol, or any combination of these. We included trials investigating all methods of external cooling, as well as those investigating any dose of a non-steroidal anti-inflammatory drug or paracetamol delivered by any route, provided that body temperature was reported as a baseline variable. Non-randomised controlled trials; trials solely conducted in a paediatric ICU, coronary care unit, respiratory care unit or burns unit; and trials of therapeutic hypothermia were excluded.

Two authors (SE, DT) independently reviewed the title and abstract of the full list of articles identified by the search strategy. After initial screening, any articles that met the inclusion criteria were reviewed in full, along with articles where there was doubt regarding eligibility. A shortlist of articles for study inclusion was then agreed between the two reviewing authors; disagreements were resolved by discussion or arbitration by a third author (PY). Two authors (SE, DT) extracted data independently from each eligible study, with disagreements resolved by discussion or arbitration by a third author (PY). Study authors were contacted to address any uncertainties in the data and to attempt to retrieve appropriate data summaries if these were not reported explicitly. Data were managed using reference management software and pre-designed data collection forms.

For eligible studies, we recorded the year of publication, sample size, source of funding, and whether each study was single centre or multicentre. Eligible studies were also analysed using the Cochrane Collaboration tool to assess the risk of bias.[7] Data extracted from each study included patient characteristics (age, sex, number of patients on invasive mechanical ventilation, number of patients on vasopressors, and ICU admission diagnoses), intervention details (number of patients in each study arm, antipyretic therapy or physical cooling technique used, duration of intervention, and details of the control group), and reported outcomes (all-cause mortality at the last time point recorded after randomisation, ICU length of stay, hospital length of stay, and temperature at 12 hours after randomisation). For each analysis, studies meeting inclusion criteria were reviewed by two authors (SE, DT) for clinical and methodological homogeneity. Reviewers resolved disagreements by discussion or arbitration by a third author (PY).

The primary outcome variable of interest was all-cause mortality at the longest time point after randomisation reported in each study. Secondary outcomes of interest included ICU length of stay, hospital length of stay, and body temperature 12 hours after randomisation.

Statistical analyses

Aggregate data were used for all analyses. For all-cause mortality, we recorded numerators and denominators by treatment group from which estimates of risks of death were derived. All outcome variables were pooled using the inverse variance weighting method, with the odds ratio (OR) and its variance used for dichotomous variables, and the mean difference and pooled variance used for continuous variables. Data are reported as Forest plots showing the individual trial estimates as well as pooled estimates.

Groups of studies that were judged to be sufficiently similar on a clinical and methodological basis were evaluated for statistical heterogeneity using the Cochran Q test and the I^2 statistic. A threshold of $P < 0.1$ was defined as indicating evidence of statistical heterogeneity. In one analysis (12 hours post-randomisation temperature), the homogeneity statistic was statistically significant and, in accordance with our pre-specified plan, we used fixed effects for study level covariates to partition the χ^2 statistic for homogeneity for meta-regression. Publication bias was examined through funnel plots and a correlation test. SAS version 9.4 (SAS Institute) was used for analyses.

Results

Fifteen publications[4,5,8-20] reporting results from 13 clinical trials met our eligibility criteria (Figure 1 and Table 1). A total of 1780 participants were included in the trials identified by our systematic review: 907 participants received active temperature management and 873 received placebo or standard care (Table 1). A number of trials were identified to have a high risk of bias (Figure 2).

All 13 trials reported mortality. Active temperature control had no statistically significant association with mortality at the last reported time point after randomisation (OR, 1.01; 95% confidence interval [CI], 0.81–1.28; $P = 0.95$, for fixed effects) (Figure 3). There was no statistically significant heterogeneity (χ^2, 17.1; 12 degrees of freedom [df]; $P = 0.14$; $I^2 = 30.2\%$; 95% CI, 0–63.9) (Figure 2) and there was no evidence of publication bias (Figure 4).

Six studies reported mean and standard deviation for ICU length of stay as an outcome, and three reported hospital length of stay. There was no statistically significant effect of association between active temperature management and ICU length of stay (absolute difference in length of stay: active minus control, –0.24; 95% CI, –1.65 to 1.18 days for

Figure 1. Search results and screening to identify eligible trials*

Total identified by database search	4056
CINAHL	29
Medline	225
Embase	396
PubMed	1354
Cochrane Database	2052

Total excluded after title/abstract review†	4038
Duplicates	1561
Non-Human	11
Non-English	126
Non-RCT	732
Paediatric population	289
Adult Non-ICU population	1173
Therapeutic hypothermia	32
Intervention not on pre-specified list	95
Comparator not on pre-specified list	19

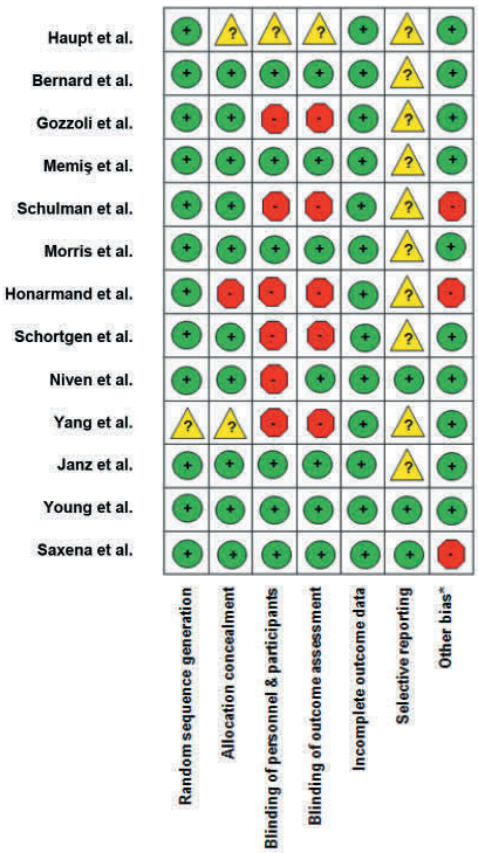
18 Full-text articles assessed for eligibility

Total excluded after full text review	4
Non-RCT	3
No baseline temperature recorded	1

14 Full-text articles
(reporting results from 12 studies)
included in systematic review

ICU = intensive care unit. RCT = randomised controlled trial. * One additional trial[20] was identified subsequently. † Full text reviewed as required to clarify exclusion subgroup.

Figure 2. Risk of bias in identified trials



* The trial by Honarmand et al appeared to have no pre-specified sample size; the trial by Schulman et al was stopped early without use of conventional stopping rules; the study by Saxena et al modified the sample size during the conduct of the trial.

the fixed effects estimate and no evidence of heterogeneity [χ^2, 1.4; 5 df; P = 0.74; I^2 = 0%; 95% CI, 0–10.8]) (Figure 3). There was no statistically significant association between active temperature management and hospital length of stay (absolute difference in length of stay: active minus control, –0.87; 95% CI, –3.87 to 2.13 days for fixed effects estimate and no evidence of heterogeneity [χ^2, 3.4; 2 df; P = 0.18; I^2 = 41.2%; 95% CI, 0–82.1]) (Figure 3). There was no evidence of publication bias for these two variables (Figure 3).

Eight studies reported mean and standard deviation for temperature 12 hours after randomisation (Figure 5). There was very strong evidence of heterogeneity for all eight studies combined (χ^2, 65.1; 7 df; P < 0.001). Seven studies had a point estimate consistent with a lower temperature in the active treatment arm, and for all but three of these studies this difference was statistically significant. Heterogeneity in the overall analysis was predominately explained by whether temperature management was pharmaceutical (n = 6) or physical (n = 2) (χ^2, 55.1; 1 df; P < 0.001). The fixed effects estimate for the active minus control treatment for pharmaceutical management was –0.62°C (95% CI, –0.72°C to –0.51°C; P < 0.001), and the estimate for physical cooling was –1.59°C (95% CI, –1.82°C to –1.35°C; P < 0.001).

Discussion

Key findings

In this systematic review and meta-analysis of RCTs, we found that active temperature management neither increased nor decreased mortality in critically ill adults compared with controls. Moreover, we found that active temperature management was associated with a statistically significantly reduction in body temperature compared with controls. Finally, we found that the use of physical cooling led to a 2.5-fold greater reduction in temperature than the use of pharmaceutical temperature management.

Table 1. Details of included studies

Schortgen et al, 2012[4]
Multicentre investigator-initiated trial in sedated, mechanically ventilated adults in ICU with septic shock conducted in France and Switzerland
(*n* = 200)

Participant characteristics	Intervention (*n* = 101)	Control (*n* = 99)
Variable		
Age (years), median (IQR)	62 (51–70)	61 (49–70)
Male sex	75/101 (74.3%)	67/99 (67.8%)
Invasively ventilated	101/101 (100%)	99/99 (100%)
On vasopressors	101/101 (100%)	99/99 (100%)
Proven infection	78/101 (77.2%)	72/99 (72.7%)
Diagnosis of acute brain pathology	Not reported	Not reported
Intervention details		
Nature of intervention	External cooling to normothermia (36.5–37°C)	No external cooling
Duration of study treatment (days)	2	2
Outcomes		
Mortality at last reported time point (hospital discharge)	43/101 (42.6%)	48/99 (48.5%)
ICU length of stay (days)	17 ± 14	16 ± 17
Hospital length of stay (days)	36 ± 40	28 ± 31
Body temperature at 12 hours (°C)	36.8 ± 0.7	38.4 ± 1.1

Young et al, 2015[5]
Multicentre investigator-initiated trial in ICU patients with fever and suspected in infection conducted in Australia and New Zealand
(*n* = 690)

Participant characteristics	Intervention (*n* = 347)	Control (*n* = 344)
Variable		
Age (years)	59.1 ± 16.9	57.9 ± 17.4
Male sex	224/347 (64.6%)	225/344 (65.4%)
Invasively ventilated	176/347 (50.7%)	182/344 (52.0%)
On vasopressors	174/347 (50.1%)	181/344 (52.6%)
Proven infection	217/347 (62.5%)	214/344 (62.2%)
Diagnosis of acute brain pathology	0/347 (0.0%)	0/344 (0.0%)
Intervention details		
Nature of intervention	Paracetamol	Placebo
Duration of study treatment (days)	Up to 28	Up to 28
Outcomes		
Mortality at last reported time point (90-day mortality)	55/345 (16.0%)	57/344 (16.6%)
ICU length of stay (days)	7.2 ± 9.3	7.9 ± 12.2
Hospital length of stay (days)	19.3 ± 19.1	21.0 ± 23.8
Body temperature at 12 hours (°C)	37.1 ± 0.9	37.7 ± 0.9

Table 1. Details of included studies (continued)

Memiş et al, 2004[8]
Single centre trial* in ICU patients with severe sepsis conducted in Turkey
(*n* = 40)

Participant characteristics	Intervention (*n* = 20)	Control (*n* = 20)
Variable		
Age (years)	49 (SD not reported)	51 (SD not reported)
Male sex	13/20 (65.0%)	9/20 (45.0%)
Invasively ventilated	20/20 (100%)	20/20 (100%)
On vasopressors	Not reported	Not reported
Proven infection	20/20 (100%)	20/20 (100%)
Diagnosis of acute brain pathology	Not reported	Not reported
Intervention details		
Nature of intervention	Lornoxicam	Placebo
Duration of study treatment (days)	3	3
Outcomes		
Mortality at last reported time point (ICU mortality)	7/20 (35.0%)	8/20 (40.0%)
ICU length of stay (days)	10.2 ± 7.1 (survivors only; *n* = 13)	9.2 ± 8.4 (survivors only; *n* = 12)
Hospital length of stay (days)	Not reported	Not reported
Body temperature at 12 hours (°C)	Not reported	Not reported

Bernard et al, 1997[10]
Multicentre investigator-initiated trial in ICU patients with sepsis conducted in the USA and Canada
(*n* = 455)

Participant characteristics	Intervention (*n* = 224)	Control (*n* = 231)
Variable		
Age (years)	54 ± 18	56 ± 16
Male sex	93/224 (41.5%)	79/231 (34.2%)
Invasively ventilated	175/224 (78.1%)	176/231 (76.2%)
On vasopressors	Not reported	Not reported
Proven infection	168/224 (75.0%)	176/231 (76.2%)
Diagnosis of acute brain pathology	Not reported	Not reported
Intervention details		
Nature of intervention	Ibuprofen	Placebo
Duration of study treatment (days)	2	2
Outcomes		
Mortality at last reported time point (Day 30 mortality)	83/224 (37.1%)	92/231 (39.8%)
ICU length of stay (days)	Not reported	Not reported
Hospital length of stay (days)	Not reported	Not reported
Body temperature at 12 hours (°C)	36.9 ± 1.1 (*n* = 224)	37.6 ± 1.2 (*n* = 231)

Table 1. Details of included studies (continued)

Gozzoli et al, 2001[11]
Single centre trial* in surgical ICU patients with fever and SIRS conducted in Switzerland
(*n* = 38)

Participant characteristics	Intervention (*n* = 18)	Control (*n* = 20)
Variable		
Age (years)	54 ± 13	53 ± 19
Male sex	14/18 (77.8%)	16/20 (80.0%)
Invasively ventilated	Not reported	Not reported
On vasopressors	Not reported	Not reported
Proven infection	9/18 (50.0%)	10/20 (50.0%)
Diagnosis of acute brain pathology	Not reported	Not reported
Intervention details		
Nature of intervention	External cooling started if temperature > 38.5°C, and stopped if temperature < 37.5°C	No antipyretic treatment
Duration of study treatment (days)	Until ICU discharge	Until ICU discharge
Outcomes		
Mortality at last reported time point (ICU mortality)	2/18 (11.1%)	3/20 (15.0%)
ICU length of stay (days)	11 ± 13	9 ± 10
Hospital length of stay (days)	28 ± 22	31 ± 24
Body temperature at 12 hours (°C)	Not reported	Not reported

Haupt el al, 1991[12]
Multicentre pharmaceutical company trial in ICU patients with severe sepsis conducted in the USA
(*n* = 29)

Participant characteristics	Intervention (*n* = 16)	Control (*n* = 13)
Variable		
Age (years)	48 ± 16	55 ± 14
Male sex	10/16 (62.5%)	6/13 (46.2%)
Invasively ventilated	13/16 (81.3%)	11/13 (84.6%)
On vasopressors	Not reported	Not reported
Proven infection	6/16 (37.5%)	6/13 (46.2%)
Diagnosis of acute brain pathology	Not reported	Not reported
Intervention details		
Nature of intervention	Ibuprofen	Placebo
Duration of study treatment (days)	1	1
Outcomes		
Mortality at last reported time point (in-hospital mortality)	9/16 (56.3%)	4/13 (30.8%)
ICU length of stay (days)	Not reported	Not reported
Hospital length of stay (days)	Not reported	Not reported
Body temperature at 12 hours (°C)	37.1 ± 0.9 (*n* = 16)	38.1 ± 0.7 (*n* = 12)

Table 1. Details of included studies (continued)

Honarmand et al, 2012[13]
Single centre pharmaceutical company trial in ICU patients with fever and SIRS conducted in Iran
(*n* = 20)

Participant characteristics	Intervention (*n* = 10)	Control (*n* = 10)
Variable		
Age (years)	49.5 ± 17.0	45.4 ± 21.1
Male sex	8/10 (80.0%)	6/10 (60.0%)
Invasively ventilated	10/10 (100%)	10/10 (100%)
On vasopressors	Not reported	Not reported
Proven infection	4/10 (40.0%)	5/10 (50.0%)
Diagnosis of acute brain pathology	0/10 (0.0%)	0/10(0.0%)
Intervention details		
Nature of intervention	Paracetamol if temperature > 38.3°C	Antipyretic only if temperature > 40°C (treatment not explicitly described)
Duration of study treatment (days)	10	10
Outcomes		
Mortality at last reported time point (ICU mortality)	2/10 (20.0%)	3/10 (30.0%)
ICU length of stay (days)	23.6 ± 13.7	22.1 ± 10.9
Hospital length of stay (days)	Not reported	Not reported
Body temperature at 12 hours (°C)	37.7 ± 0.9	37.4 ± 0.6

Janz et al, 2015[14]
Single centre investigator-initiated trial in ICU patients with severe sepsis conducted in the USA
(*n* = 40)

Participant characteristics	Intervention (*n* = 18)	Control (*n* = 22)
Variable		
Age (years), median (IQR)	50 (41–64)	58 (47–63)
Male sex	9/18 (50.0%)	12/22 (54.5%)
Invasively ventilated	8/18 (44.4%)	6/22 (27.3%)
On vasopressors	8/18 (44.4%)	10/22 (45.5%)
Proven infection	Not reported	Not reported
Diagnosis of acute brain pathology	Not reported	Not reported
Intervention details		
Nature of intervention	Paracetamol	Placebo
Duration of study treatment (days)	3	3
Outcomes		
Mortality at last reported time point (ICU mortality)	1/18 (5.6%)	4/22 (18.2%)
ICU length of stay (days)	Not reported	Not reported
Hospital length of stay	Not reported	Not reported
Body temperature at 12 hours (°C)	Not reported	Not reported

Table 1. Details of included studies (continued)

Morris et al, 2010[15]
Multicentre pharmaceutical company trial in hospitalised patients with fever (some of whom were critically ill) conducted in USA, Thailand and Australia
(*n* = 53 critically ill patients)

Participant characteristics	Intervention (*n* = 40)	Control (*n* = 13)
Variable		
Age (years)	Not reported for the critically ill patients specifically	Not reported for the critically ill patients specifically
Male sex	Not reported for the critically ill patients specifically	Not reported for the critically ill patients specifically
Invasively ventilated	40/40 (100%)	13/13 (100%)
On vasopressors	4/40 (10.0%)	0/13 (0.0%)
Proven infection	Not reported for the critically ill patients specifically	Not reported for the critically ill patients specifically
Diagnosis of acute brain pathology	Not reported	Not reported
Intervention details		
Nature of intervention	Ibuprofen	Placebo
Duration of study treatment (days)	1	1
Outcomes		
Mortality at last reported time point (ICU mortality)	5/40 (12.5%)	1/13 (7.7%)
ICU length of stay (days)	Not reported for the critically ill patients specifically	Not reported for the critically ill patients specifically
Hospital length of stay (days)	Not reported for the critically ill patients specifically	Not reported for the critically ill patients specifically
Body temperature at 12 hours (°C)	38.0[†]	38.5 ± 0.8

Niven et al, 2013[16]
Multicentre investigator-initiated trial ICU patients with fever conducted in Canada
(*n* = 26)

Participant characteristics	Intervention (*n* = 14)	Control (*n* = 12)
Variable		
Age (years), median (IQR)	53 (43–67)	58 (49–69)
Male sex	8/14 (57.1%)	8/12 (66.7%)
Invasively ventilated	14/14 (100%)	12/12 (100%)
On vasopressors	3/14 (21.4%)	7/12 (58.3)
Proven infection	14/14 (100%)	9/12 (75.0%)
Diagnosis of acute brain pathology	0/14 (0.0%)	0/12 (0.0%)
Intervention details		
Nature of intervention	Paracetamol if temp ≥ 38.3°C; physical cooling if temp ≥ 39.5°C	Paracetamol if temp ≥ 40.0°C; physical cooling if temp ≥ 40.5°C
Duration of study treatment (days)	Until ICU discharge	Until ICU discharge
Outcomes		
Mortality at last reported time point (28-day mortality)	3/14 (21.4%)	2/12 (16.7%)
ICU length of stay (days)	Not reported	Not reported
Hospital length of stay (days)	Not reported	Not reported
Body temperature at 12 hours (°C)	Not reported	Not reported

Table 1. Details of included studies (continued)

Schulman et al, 2005[18]
Single centre trial* in trauma ICU patients with fever conducted in the USA
(*n* = 82)

Participant characteristics	Intervention (*n* = 44)	Control (*n* = 38)
Variable		
Age (years)	47 ± 20	47 ± 20
Male sex	30/44 (68.2%)	29/38 (76.3%)
Invasively ventilated	Not reported	Not reported
On vasopressors	Not reported	Not reported
Proven infection	Not reported	Not reported
Diagnosis of acute brain pathology	0/44 (0.0%)	0/38 (0.0%)
Intervention details		
Nature of intervention	Paracetamol if temperature > 38.5°C, with addition of a cooling blanket if temperature > 39.5°C	Paracetamol and a cooling blanket if temperature > 40°C
Duration of study treatment	Until ICU discharge	Until ICU discharge
Outcomes		
Mortality at last reported time point (ICU mortality)	7/44 (15.9%)	1/38 (2.6%)
ICU length of stay (days)	22 ± 30	20 ± 14
Hospital length of stay (days)	Not reported	Not reported
Body temperature at 12 hours (°C)	Not reported	Not reported

Yang et al, 2013[19]
Single centre trial* in ICU patients with refractory septic shock conducted in China
(*n* = 65)

Participant characteristics	Intervention (*n* = 34)	Control (*n* = 31)
Variable		
Age (years)	68.8 ± 18.0	66.6 ± 13.0
Male sex	18/34 (53.0%)	16/31 (52.0%)
Invasively ventilated	34/34 (100%)	31/31 (100%)
On vasopressors	34/34 (100%)	31/31 (100%)
Proven infection	29/34 (85.0%)	28/31 (90.0%)
Diagnosis of acute brain pathology	0/34 (0.0%)	0/31(0.0%)
Intervention details		
Nature of intervention	Physical cooling to maintain temperature at 36.0–37.5°C	Physical cooling to maintain temperature at 37.5–38.3°C
Duration of study treatment (days)	3	3
Outcomes		
Mortality at last reported time point (28-day mortality)	21/34 (61.8%)	8/31 (25.8%)
ICU length of stay (days)	Not reported	Not reported
Hospital length of stay (days)	Not reported	Not reported
Body temperature at 12 hours (°C)	36.4 ± 1.2	37.8 ± 1.6

Table 1. Details of included studies (continued)

Saxena et al, 2015[20]
Multicentre investigator-initiated trial in ICU patients with acute traumatic brain injury in Australia
(*n* = 41)

Participant characteristics	Intervention (*n* = 21)	Control (*n* = 20)
Variable		
Age (years)	33 ± 16	33 ± 18
Male sex	18/21 (85.7%)	15/20 (75.0%)
Invasively ventilated	21/21 (100%)	20/20 (100%)
On vasopressors	5/21 (24.0%)	6/20 (30%)
Proven infection	Not reported	Not reported
Diagnosis of acute brain pathology	21/21 (100%)	20/20 (100%)
Intervention details		
Nature of intervention	Paracetamol	Placebo
Duration of study treatment (days)	3	3
Outcomes		
Mortality at last reported time point (hospital mortality)	3/21 (14.3%)	1/20 (5.0%)
ICU length of stay (days), median (IQR)	13.0 (7.0–15.0)	12.0 (6.0–15.0)
Hospital length of stay (days), median (IQR)	36.5 (23.0–48.0)	29.0 (20.0–41.0)
Body temperature at 12 hours (°C)	37.2 ± 0.6	37.6 ± 0.8

ICU = intensive care unit. IQR = interquartile range. SD = standard deviation. SIRS = systemic inflammatory response syndrome. USA = United States of America.

Relationship to previous studies

No previous study has compared the effectiveness of physical cooling with pharmaceutical strategies of active temperature management in achieving temperature reduction in the critically ill.[21] Our findings suggest that physical cooling results in a substantially greater reduction in temperature at 12 hours than pharmaceutical measures; however, the best method of temperature control with respect to time to achieve normothermia, and durability, tolerability and stability of temperature control achieved is unknown.

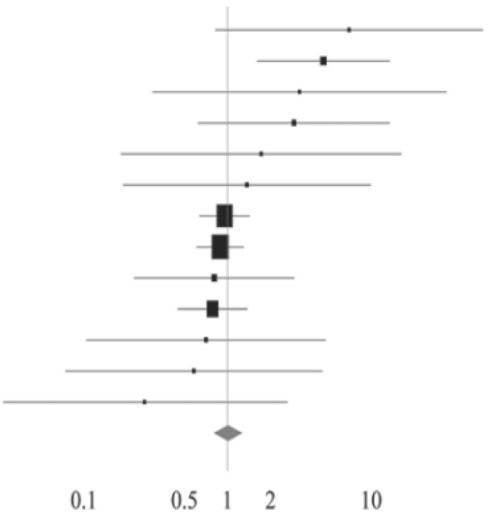
With respect to the effect of active temperature control on mortality, our findings are generally in accord with a recent similar systematic review and meta-analysis of RCTs and observational studies which found that antipyretic therapy had no effect on 28-day mortality in critically ill adults with sepsis.[22] The authors of this previous study concluded that antipyretic treatment does not significantly alter 28-day in-hospital mortality and that additional studies would likely be underpowered to alter this conclusion. We identified a number of RCTs that were not included in this recent meta-analysis and showed a high risk of bias in many of the included RCTs. Moreover, mortality estimates had wide CIs that do not preclude the possibility of clinical significant benefit or harm with active temperature control. Thus, given the overall poor quality of the existing data,[22] our study suggests that the effect of active temperature management, a commonly used strategy in critically ill adults, requires further evaluation in high quality clinical trials.

Strengths and weaknesses

We used a comprehensive search strategy to identify relevant RCTs and chose not to include observational studies in our analysis because such studies do not provide data from which causal inferences about the effectiveness of treatments can be reliably drawn.[23] We did not demonstrate any evidence of publication bias. Although we attempted to identify trials in a broad cohort of critically ill patients both with and without sepsis, all of the RCTs we identified except one[20] included at least some patients with proven infection, and most aimed to include patients with sepsis exclusively. As a result, there remains a particularly high degree of uncertainty about the role of active temperature management in critically ill patients without sepsis. In particular, it is notable that only one of the studies identified in our systematic review included

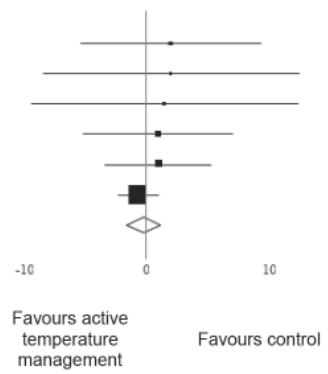
Figure 3. Forest plots: effect of temperature control on mortality, ICU length of stay, and hospital length of stay

	Active temperature management		Control		Odds ratio	Odds ratio,* 95% CI
Mortality at last reported time point						
Study	**Events**	**Total**	**Events**	**Total**	**Fixed, 95%CI**	
Schulman	7	44	1	38	7.00, 0.82–59.8	
Yang	21	34	8	31	4.64, 1.61–13.4	
Saxena	3	21	1	20	3.17, 0.30–33.1	
Haupt	9	16	4	13	2.89, 0.62–13.5	
Morris	5	40	1	13	1.71, 0.18–16.2	
Niven	3	14	2	12	1.36, 0.19–9.91	
Young	55	345	57	344	0.95, 0.64–1.43	
Bernard	83	224	92	231	0.89, 0.61–1.30	
Memiş	7	20	8	20	0.81, 0.22–2.91	
Schortgen	43	101	48	99	0.79, 0.45–1.38	
Gozzoli	2	18	3	20	0.71, 0.10–4.81	
Honarmand	2	10	3	10	0.58, 0.07–4.56	
Janz	1	18	4	22	0.26, 0.03–2.61	
Total	**241**	**905**	**232**	**873**	**1.01, 0.81–1.26**	



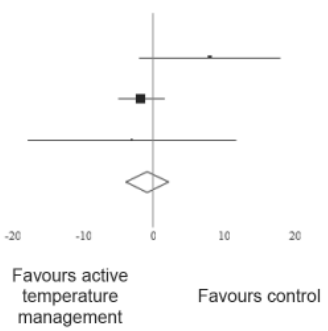
Heterogeneity: $\chi^2 = 17.1$, df = 12 ($P = 0.14$); $I^2 = 30.2\%$ (95% CI, 0–63.9)
Publication bias: 0.10; $P = 0.63$
Statistical significance of overall effect: $P = 0.95$ (fixed effect)

	Active temperature management		Control		Absolute difference	Absolute difference,* 95% CI
ICU length of stay (days)						
Study	**Mean ± SD**	***n***	**Mean ± SD**	***n***	**Intervention minus control, 95% CI**	
Gozzoli	11 ± 13	18	9 ± 10	20	2, –5.33 to 9.33	
Schulman	22 ± 30	44	20 ± 14	38	2, –8.4 to 12.4	
Honarmand	23.6 ± 13.7	10	22.1 ± 10.9	10	1.5, –9.35 to 12.35	
Memiş	10.2 ± 7.1	13	9.2 ± 8.4	12	1, –5.08 to 7.08	
Schortgen	17 ± 14	101	16 ± 17	99	1, –3.31 to 5.31	
Young	7.2 ± 9.3	346	7.9 ± 12.2	343	–0.7, –2.32 to 0.92	
Pooled effect (fixed)					**–0.24, –1.65 to 1.18**	



Heterogeneity: $\chi^2 = 1.4$, df = 5 ($P = 0.13$); $I^2 = 0\%$ (95% CI, 0–10.8)
Publication bias: correlation coefficient 0.07; $P = 0.85$
Statistical significance of overall effect: $P = 0.74$ (fixed effect)

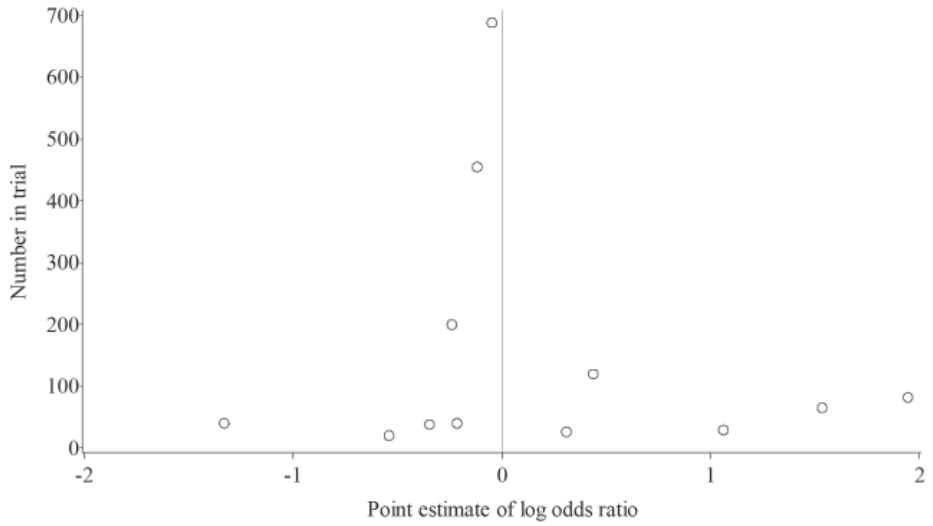
	Active temperature management		Control		Absolute difference	Absolute difference,* 95% CI
Hospital length of stay (days)						
Study	**Mean ± SD**	***n***	**Mean ± SD**	***n***	**Intervention minus control, 95% CI**	
Shortgen	36 ± 40	101	28 ± 31	99	8, –1.93 to 17.93	
Young	19.3 ± 19.1	346	21 ± 23.8	343	–1.7, –4.92 to 1.52	
Gozzoli	28 ± 22	18	31 ± 24	20	–3, –17.7 to 11.7	
Pooled effect (fixed)					**–0.87 (–3.87 to 2.13)**	



Heterogeneity: $\chi^2 = 3.4$, df = 2 ($P = 0.18$); $I^2 = 41.2\%$ (95% CI, 0–82.1)
Publication bias: correlation coefficient 0.33; $P = 0.60$
Statistical significance of overall effect: $P = 0.74$ (fixed effect)

CI = confidence interval. df = degrees of freedom. SD = standard deviation. * The weight of individual trials is proportional to the box size.

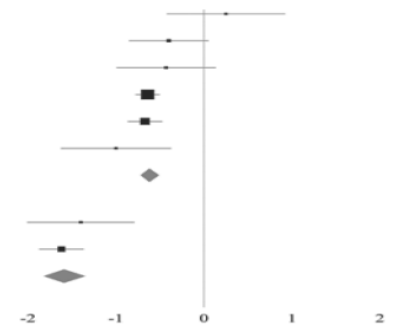
Figure 4. Funnel plot to evaluate publication bias in relation to mortality effects*



* Correlation coefficient, 0.03; $P = 0.89$.

Figure 5. Forest plot: effect of active temperature management on body temperature

Study	Active temperature management: Temperature (°C)	Total	Control: Temperature (°C)	Total	Absolute difference (°C): Intervention minus control
Intervention: pharmaceuticals†					
Study	**Mean ± SD**	***n***	**Mean ± SD**	***n***	**Fixed, 95% CI**
Honarmand	37.3 ± 0.9	10	37.4 ± 0.6	10	0.25, –0.42 to 0.92
Saxena	37.2 ± 0.6	21	37.6 ± 0.8	20	–0.40, 0.85 to 0.05
Morris	38 no SD	40	38.5 ± 0.8	13	–0.43, –0.99 to –0.13
Young	37.1 ± 0.9	338	37.7 ± 0.9	333	–0.64, –0.78 to –0.50
Bernard	36.9 ± 1.1	224	37.6 ± 1.2	231	–0.67, –0.87 to –0.47
Haupt	37.1 ± 0.9	16	38.1 ± 0.7	12	–1.0, –1.63 to –0.37
Pooled effect (fixed)					–0.62, –0.72 to –0.51
Intervention: physical cooling					
Yang	36.4 ± 1.18	34	37.8±1.57	31	–1.40, –2.01 to –0.79
Schortgen	36.8 ± 0.71	101	38.4±1.12	99	–1.62, –1.87 to –1.37
Pooled effect (fixed)					**–1.59, –1.82 to –1.35**



Heterogeneity:‡ $\chi^2 = 65.1$, df = 7 ($P < 0.001$); $I^2 = 89.2\%$ (95% CI, 81.2–93.9)
Publication bias: correlation coffiicent –0.07; $P = 0.81$
Statistical significance of overall effect: $P < 0.001$ for overall comparison of active temperature management *v* control, and also for both pharmaceutics and physical cooling interventions individually

CI = confidence interval. df = degrees of freedom. SD = standard deviation. * The weight of individual trials is proportional to the box size. † All studies evaluated ibuprofen except for Young et al and Saxena et al, which evaluated paracetamol. ‡ Heterogeneity in the overall analysis was almost completely explained by whether temperature management was pharmaceutical or physical (χ^2, 55.1; 1 df; $P < 0.001$); within-groups were heterogeneous for pharmaceuticals ($P = 0.09$) and homogeneous for physical cooling (P = 0.51).

patients with acute brain pathologies.[20] ICU and hospital length of stay variables should be interpreted in light of the fact that these variables are not normally distributed. This means that our findings in relation to these variables may be biased by outlier values in individual studies, particularly, given that many of the studies included in our analysis are small. An additional consideration, which further confounds the interpretation of this variable, is that length of stay may be reduced by either increase in early deaths or by discharge due to recovery.

Study implications

While our findings do not indicate benefit or harm with more aggressive active temperature management, most trials included in our meta-analysis allowed for some form of active temperature management in the control arm. As a consequence, our results should not be used to infer the safety of more permissive temperature management strategies than were used in the control arm of the respective trials.

In addition to the uncertainty about overall estimates of the effect of active temperature management on mortality, the possibility of benefit or harm from active temperature management in particular subgroups of patients cannot be excluded. It has been suggested that patients with higher illness acuity may be more likely to benefit from active temperature management than patients who are less severely unwell.[24] Because trials in our meta-analysis generally included heterogeneous patient populations with a range of illness severities, our data do not preclude this possibility. Observational data show that the association between peak body temperature in the first 24 hours in the ICU and in-hospital mortality differs for patients with and without infection, with increasing temperature associated with increased mortality risk in the absence of infection but with reduced mortality risk in the presence of infection.[25] These findings raise the possibility that active management of temperature might be of benefit in the absence of infection. The role of active temperature management in particular subgroups of patients, including those with infections and high illness acuity, could be evaluated through an individual patient data meta-analysis of RCTs identified in this systematic review.

Conclusions

Active temperature management appears to neither increase nor decrease mortality risk in heterogeneous populations of critically ill adults. However, CIs around pooled treatment estimates are wide, and many RCTs have methodological weaknesses that potentially undermine the accuracy of these estimates. Finally, our findings suggest that when the therapeutic goal is to reduce body temperature, physical cooling approaches may be more effective than pharmacological measures in critically ill adults.

Competing interests

None declared.

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