PROTCOL

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Study objectives

Primary:
(1) To determine the impact of antipyretic therapy on 28-day and hospital mortality in critically ill septic patients
Secondary:
(1) To determine the impact of antipyretic therapy on 28-day and hospital mortality in febrile critically ill septic patients
(2) To determine the impact of antipyretic therapy on 28-day and hospital mortality in patients with septic shock
(3) To determine the effect of antipyretic therapy on secondary outcomes including early mortality (defined as occurring ≤ 14 days or in ICU), acquisition of nosocomial infections, and changes in body temperature, heart rate, and minute ventilation.

PICOT

Population: Critically ill adult patients with a diagnosis of sepsis
Intervention: Antipyretic therapy (acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), physical cooling) at any dose or duration
Comparator: No antipyretic therapy or permissive hyperthermia
Outcome: 28-day/hospital mortality
Type of studies: Randomized controlled trials, prospective non-randomized studies, observational cohort studies, case-control studies, cross-sectional studies

Primary hypothesis

Antipyretic therapy will improve physiologic status (temperature, heart rate, respiratory rate), but will not impact 28-day/hospital morality.

Search strategy

Literature will be searched using strategies designed by a medical librarian for the concepts of sepsis, fever, antipyretics, and physical cooling in adults. These strategies will be established using a combination of standardized terms and key words implemented in Ovid Medline, Embase, Scopus, Cumulative Index of Nursing and Allied Health Literature, Cochrane Database of Systematic Reviews, Cochran Central Register of Controlled Trials, NHS Economic Evaluation Database, and ClinicalTrials.gov. Non-English articles will be removed. All results will be exported into EndNote, and the automatic duplicate finder in Endnote will be used to remove duplicates. Non-English articles will also be removed.

Two study team members will independently review titles and abstracts of the search results with application of inclusion and exclusion criteria. The full article of any study identified as potentially eligible by either reviewer will be reviewed.

Meeting abstracts from the American Society of Anesthesiology, International Anesthesia Research Society, Society of Critical Care Medicine, European Society of Intensive Care Medicine, Shock, Chest,

and Society of Academic Emergency Medicine from 2008 to 2015 will be hand searched for relevant studies.

Study team members will also review bibliographies from review articles and the included studies to identify other potentially eligible studies.

Inclusion/exclusion criteria

Inclusion criteria:
Observational or randomized studies
Inclusion of patients with sepsis or infection
Evaluation of antipyretic treatment (pharmacological or physical cooling)
Mortality (at any time point) reported
English-language version available

Exclusion criteria:
Editorials and reviews
Non-human studies
Pediatric studies
Healthy volunteer studies
Inclusion of patients with neurological injury
Lack of a control or permissive hyperthermia group
Insufficient data reported for analysis

Selection of studies

Two study team members will review full reports of all potentially relevant studies with application of inclusion and exclusion criteria to identify eligible studies. Disagreements regarding study inclusion will be resolved by discussion, or if needed, input from a third study team member.

Studies involving both septic and non-septic patients will be included if mortality results are provided for the subgroup of septic patients. If this information is not provided, and the study would otherwise be eligible, the study authors will be contacted to determine whether this information is available prior to excluding the study.

Data extraction

An electronic data collection form will be created in RedCap, an electronic data management system. Two study team members will independently extract data, and the data comparison tool in RedCap will be used to compare extracted data. Discrepancies will be resolved via discussion, or if needed, a third study team member. Data that is reported solely in figure form (rather than in the article text or tables) will be extracted using an online data extraction tool (http://arohatgi.info/WebPlotDigitzer/) (1). Study authors will be contacted as needed to provide missing data.

Variables collected

The following variables will be extracted from each study:

Study characteristics: Study title, authors, publication year, study design, number of centers enrolling patients, location of study centers, beginning and ending dates of enrollment (month/year), and sources of

funding. The study design will be determined as outlined in Table 13.2.a and Box 13.4a in the *Cochrane Handbook for Systematic Reviews of Interventions* (2).

Study setting and participants: Study setting (e.g. intensive care unit (ICU), emergency department, etc), types of ICUs from which patients were recruited, inclusion criteria for study, definition of fever (°C), total study sample size, number of males, number of patients requiring vasopressors, number of patients requiring mechanical ventilation, number of patients with fever, patient age, measures of disease severity, baseline body temperature, baseline heart rate, baseline minute ventilation. Binary variables will be extracted in terms of absolute numbers of patients with or without the variable present. Continuous variables will be extracted using mean or median and, if available, measures of dispersion such as standard deviation (SD), standard error (SE), or interquartile ranges (IQR).

Intervention details: Antipyretic modalities being evaluated, description of intervention (including dosing intervals, duration of intervention, and/or targeted body temperature), description of placebo or control.

Outcomes: Primary and secondary outcomes of study, duration of mortality reported (e.g. 28-day, hospital, ICU, etc.), number of patients who died and survived in the intervention and control groups, number of patients who did or did not acquire a nosocomial infection in the intervention and control groups, number of patients who did or did not meet criteria for shock reversal in the intervention and control groups, change in body temperature pre- to post-intervention, change in heart rate pre- to post-intervention, change in minute ventilation pre- to post-intervention. For interventions continuing throughout the ICU length of stay, post-intervention physiological values will be measured at 48 hours after the start of the intervention, if available. For observational studies, both adjusted and unadjusted odds ratios (ORs) for mortality and acquisition of nosocomial infections and the variables on which the ORs were adjusted will also be collected. Binary outcomes will be extracted in terms of absolute numbers of patients with or without the variable present. Continuous outcomes will be extracted using mean or median and, if available, measures of dispersion such as standard deviation (SD), standard error (SE), or interquartile ranges (IQR).

Risk of bias assessment

Randomized studies: Study methodological quality will be assessed via the "component approach" using the Cochrane Collaboration Risk of Bias Tool (3). Each study will be evaluated as having a low risk, high risk, or unclear risk of bias in the following areas: (1) sequence generation, (2) allocation concealment, (3) blinding of participants/personnel/outcome assessors, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other sources of bias.

Observational studies: Quality will be assessed using the Newcastle-Ottawa Tool (2). Each study will be evaluated on a 9-point scale in the domains of patient selection, comparability, exposure and outcome.

Two study team members will independently assess quality of each study. Areas of discrepancy will be resolved by a third study team member. Results will be reported for each domain, rather than with an overall score. However, for the purposes of a stratified analysis by study quality, studies with an unclear or high risk of bias in two or more categories on the Cochrane Collaboration Risk of Bias tool or an overall score lower than 8 on the Newcastle-Ottawa tool will be considered low quality/high risk of bias.

Data management

For each study, 5 data collection forms (study characteristics, study setting and participants, intervention details, outcomes, and risk of bias) will be created in RedCap. Three versions of each form will be generated, one for each of the two independent data extractors and a third to record the consensus data.

For analysis, consensus data will be downloaded into Microsoft Excel spreadsheets to be uploaded into statistical software.

The dataset and metadata associated with this meta-analysis will be made widely available and archived for at least 10 years with the Washington University Digital Research Materials Repository.
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Statistical analysis

Randomized and observational studies will be analyzed separately. STATA/IC 14.1 will be used to analyze all data. Pooling of data will occur for any outcome reported by at least two studies. Heterogeneity will be assessed with the Higgens I^2 test, and significant heterogeneity will be assumed to be present if the I^2 is greater than 30%. Data will be combined using the DerSimonian and Laird random effects model (4) regardless of measured heterogeneity due to the limitations of statistical tests for heterogeneity and because the random effects model collapses to a fixed model in the absence of heterogeneity. A two-tailed *P* value less than .05 will be considered statistically significant.

For continuous outcome data reported in the form of median (IQR), mean (SD) will be estimated using published methods (5). For continuous data that is not reported with a measure of dispersion (i.e. SE, SD, or IQR), a SD will be imputed based on the mean of SDs as reported in the other studies (6). If none of the studies reports a measure of dispersion for any continuous outcome, that outcome will not be pooled in the meta-analysis.

Randomized studies: For categorical outcomes in randomize studies, a relative risk (RR) with 95% confidence interval (CI) will be calculated for each study and combined. For continuous outcomes, weighted mean differences will be calculated for each study and combined using a random effects model for continuous outcomes. For the primary outcome, if the meta-analysis results are not statistically significant, an extended funnel plot will be created to graphically display the effect size and standard error combinations needed for an additional randomized study to change the results of the meta-analysis (7, 8). Simulation will be used to create a graph showing the power attained by studies of increasing sample size to change the results of the meta-analysis to a significant result (9, 10).

Observational studies: For categorical outcomes of observational studies, an OR with 95% confidence interval will be extracted from each study and combined. If the unadjusted OR is not provided in the text or table, it will be calculated using the number of patients with and without the outcome in the exposed and non-exposed groups. For studies that report multiple adjusted ORs, the OR adjusted for the greatest number of variables will be used in the meta-analysis. For studies that evaluate more than one antipyretic modality, an OR will be extracted and preferentially used in the meta-analysis for the overall effect of antipyresis. ORs for the effect of specific antipyretic modalities will be used in stratified or subgroup analyses. If an overall OR for overall antipyresis is not reported, the individual ORs for each modality will be entered into the meta-analysis. For continuous outcomes, weighted mean differences will be calculated for each study and combined using a random effects model for continuous outcomes.

Publication bias for the primary outcome will be assessed separately in the randomized studies and observational studies using funnel plots and Egger's test.

Subgroup and stratified analyses

The primary outcome will be evaluated in two subgroups of patients, those with fever and those with shock. Also, stratified analyses will be done based on type of intervention, study quality, goal of intervention (treatment of fever vs. anti-inflammatory effect of medication). Additional subgroup and stratified analyses will be considered based on study variability.

Reporting of results

Results will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (11) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (12).

Study registration

This meta-analysis will be registered on PROSPERO prior to completion of data extraction.

References

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