# The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis

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The practice of treating fever predates 2000 BCE, when Shen Nung, a Chinese Emperor, is said to have first described the antipyretic properties of the antimalarial herb ch'ang shan (*Dichroa febrifuga*).[1] Most patients with severe sepsis present with fever,[2] and the use of antipyretic medications in hospitals, including the intensive care unit, is commonplace. However, there is a biological rationale for fever as a protective, adaptive response to infection. Fever is a metabolically expensive process that has been conserved by evolution and is found throughout the animal kingdom.[3] At febrile temperatures, direct inhibition of heat-sensitive microorganisms, such as influenza virus[4] and *Streptococcus pneumoniae*,[5] can occur; as can the induction of protective cellular[6] and immune responses.[7] Increased antibiotic activity at elevated temperatures has also been demonstrated in vitro.[8]

In animal studies, suppression of fever with antipyretic drug therapy has been shown to increase mortality among subjects with viral,[9] bacterial[10] and parasitic infections.[11] Observational studies of humans have shown a positive correlation between febrile temperature during bacteraemia and survival[12,13] and hypothermia as a manifestation of sepsis is a negative predictor of outcome.[2] In other human studies, antipyretic drugs have been shown to increase the duration of chickenpox illness[14] and malarial parasitaemia,[15] augment rhinovirus shedding,[16,17] and inhibit antibody responses.[16,18] Furthermore, a recent randomised controlled trial (RCT) demonstrated a trend towards increased mortality in intensive care patients assigned to the "aggressive" treatment of fever with paracetamol.[19]

Conversely, there may be detrimental effects of fever in promoting energy deficit and hypoxic tissue injury. Fever is an independent predictor of higher mortality in patients in neurological ICUs.[20] Fever suppression among ventilated patients has been shown to reduce oxygen consumption,[21] and the benefits of antipyresis or induced hypothermia have been investigated in the settings of acute respiratory distress syndrome,[22] and after cardiac arrest[23] and neurological injury.[24]

Reflecting this clinical uncertainty, recommendations regarding the use of antipyretics for critically ill patients with sepsis have not been made in international guidelines.[25] Given the common use of pharmacological antipyretics in clinical practice, we undertook a systematic review to identify RCTs of antipyretic drugs among critically ill

## ABSTRACT

**Background:** Antipyretic medications are widely used in critically ill patients with infection despite evidence supporting a protective, adaptive role of fever.

**Objective:** To assess the mortality risk of antipyretic medications among critically ill patients with infection.
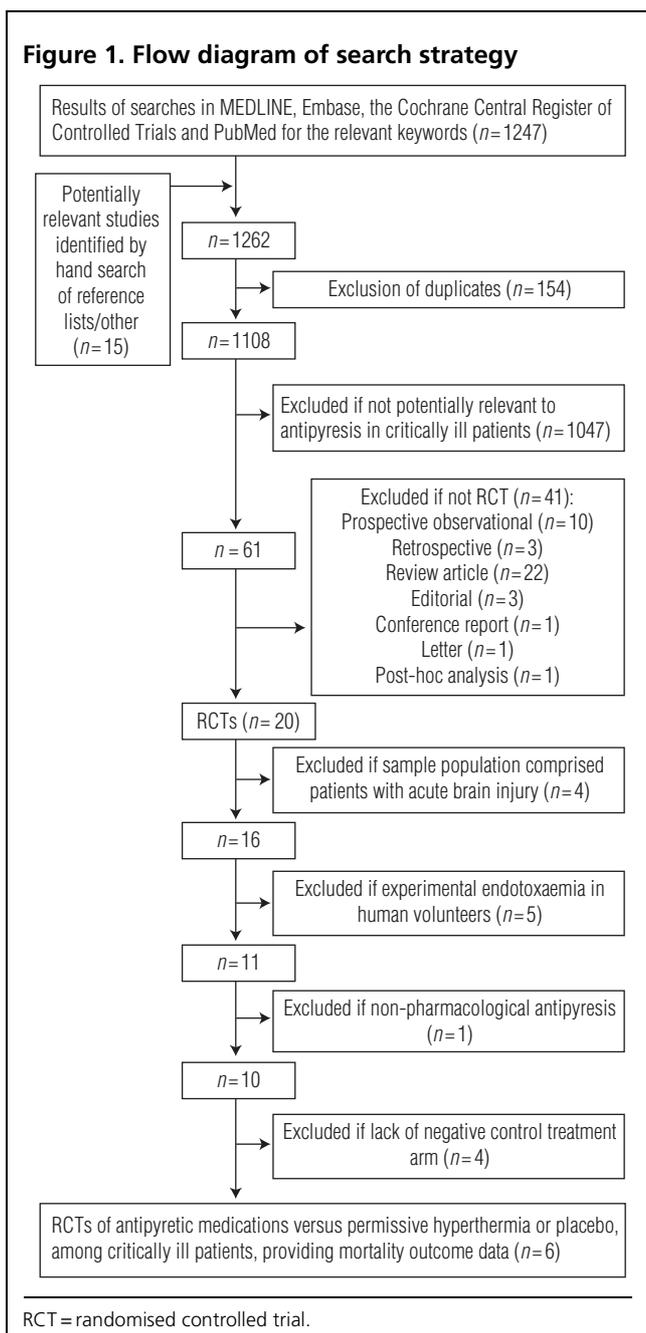
**Methods:** A systematic search of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and PubMed was undertaken to identify randomised controlled trials (RCTs) of antipyretic use among critically ill patients with suspected or confirmed infection that reported mortality. A quantitative meta-analysis of the risk of death was carried out with calculation of the pooled risk of death and standard evaluation of heterogeneity.

**Results:** Six RCTs investigating the use of paracetamol (1) and non-steroidal anti-inflammatory medications (5) met the inclusion criteria for meta-analysis. The trials were heterogeneous in terms of study populations and interventions, were not primarily designed to evaluate antipyretic effect on mortality risk, and significant confounding was present from the use of other concomitant antipyretic strategies. The pooled estimates of odds ratios for mortality with antipyretic treatment were 0.96 (95% CI, 0.68–1.34) and 1.08 (95% CI, 0.60–1.96) for fixed effects and random effects, respectively, and the I-squared value was 34.9 (95% CI, 0.0–73.9).

**Conclusion:** The studies included in this review were insufficient to allow a robust estimate of the effect of pharmacological antipyresis on mortality in critically ill patients with suspected infection. Further RCTs are required to resolve this important area of clinical uncertainty.

patients with infection, excluding trials investigating patients with acute brain injury. By meta-analysis, we aimed to investigate whether antipyretic drug use was associated with an increased risk of mortality. We hypothesised that the use of antipyretic drugs in critically ill patients with infection would be associated with an increased risk of mortality.

## Figure 1. Flow diagram of search strategy

Results of searches in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and PubMed for the relevant keywords (*n*=1247)

Potentially relevant studies identified by hand search of reference lists/other (*n*=15)

*n*=1262

Exclusion of duplicates (*n*=154)

*n*=1108

Excluded if not potentially relevant to antipyresis in critically ill patients (*n*=1047)

*n*=61

Excluded if not RCT (*n*=41):
Prospective observational (*n*=10)
Retrospective (*n*=3)
Review article (*n*=22)
Editorial (*n*=3)
Conference report (*n*=1)
Letter (*n*=1)
Post-hoc analysis (*n*=1)

RCTs (*n*=20)

Excluded if sample population comprised patients with acute brain injury (*n*=4)

*n*=16

Excluded if experimental endotoxaemia in human volunteers (*n*=5)

*n*=11

Excluded if non-pharmacological antipyresis (*n*=1)

*n*=10

Excluded if lack of negative control treatment arm (*n*=4)

RCTs of antipyretic medications versus permissive hyperthermia or placebo, among critically ill patients, providing mortality outcome data (*n*=6)

RCT = randomised controlled trial.

## Methods

### Search strategy

To identify all studies investigating the effect of antipyretics on mortality in sepsis in humans, searches were carried out on 14 October 2010. Four databases were used: MEDLINE (1950 to present); Embase (1947 to present); the Cochrane Central Register of Controlled Trials (1991 to present); and PubMed (1950 to present). Searches were limited to "human" and "clinical trial" and were generated using the following keywords: "sepsis" or "septicaemia" or "bacter-

aemia" or "systemic inflammatory response syndrome" or "SIRS" or "septic shock" or "critical illness"; and "anti-pyre*" or "paracetamol" or "acetaminophen" or "non-steroidal anti-inflammatory" or "cyclo-oxygenase inhibi-tor*" or "COX inhibitor*" or "salicyl*" or "aspirin" or "ibuprofen" or "diclofenac" or "naproxen" or "indometh-acin" or "acemetacin" or "aceclofenac" or "fenoprofen" or "fenbufen" or "dexibuprofen" or "dexketoprofen" or "ketoprofen" or "flurbiprofen" or "oxaprozin" or "sulin-dac" or "etodolac" or "ketorolac" or "nabumetone" or "azapropazone" or "phenylbutazone" or "piroxicam" or "meloxicam" or "tenoxicam" or "droxicam" or "lornoxi-cam" or "isoxicam" or "mefenamic acid" or "meclofenamic acid" or "flufenamic acid" or "tolfenamic acid" or "tiaprofenic acid" or "valdecoxib" or "parecoxib" or "metamizole" or "nimesulide" or "etoricoxib" or "lumiracoxib" or "etori-coxib" or "firocoxib" or "celecoxib" or "rofecoxib". Potentially relevant articles written in foreign languages were translated. Two of us (S J and R W B) examined each article's title and abstract, and the full article if necessary. The reference lists of all relevant articles were also examined and additional hand searching was carried out.

### Inclusion and exclusion criteria

Studies were required to be clinical RCTs that reported clinical outcome measures including mortality, in the investigation of antipyretic medications, administered with a frequency of greater than one dose, among critically ill patients with infection.

Studies were excluded if they:
• Were animal studies;
• Were not RCTs;
• Used experimental models in healthy human volunteers;
• Were studies specifically investigating patients with acute brain injury;
• Did not have a non-active control arm to allow permissive hyperthermia; or
• Examined antipyresis by physical intervention (eg, external cooling by ice packs).

### Data extraction

Extraction of data was based on reported summary statistics (counts, means and standard deviations). The trial quality was assessed using the standard Jadad score based on the adequacy of randomisation, blinding and follow-up, with a maximum score of five points.[26]

### Statistical analysis

The primary outcome variable was mortality. The categorical variables were pooled using the inverse variance weighting method for odds ratios.[27] Homogeneity statistics and the I-squared statistic were calculated for each analysis.[28] Publi-

**Table 1. Characteristics of studies included in the meta-analysis**

| Study | Participants | Antipyretic treatment arm | Control treatment | Control for other antipyretics | Primary Outcome variable | Antipyretic effect with treatment |
|---|---|---|---|---|---|---|
| Schulman et al[19] | > 72 h in trauma ICU; temp > 38.5°C; patients with brain injuries excluded | Paracetamol po/pr 650 mg 6-hourly at temp > 38.5°C for duration of febrile episode(s) | Paracetamol po/pr 650 mg 6-hourly plus cooling blanket at temp > 40.0°C for duration of febrile episode(s) | Not stated | Positive culture | Yes |
| Memis et al[33] | Severe sepsis | Lornoxicam IV 8 mg 12-hourly for six doses | Placebo | Recent COX inhibitors or aspirin use exclusion criteria. Others not stated. | Not stated | Yes |
| Bernard et al, 1997[30] | Severe sepsis | Ibuprofen IV 10 mg/kg (max 800 mg) 6-hourly for six doses | Placebo | Paracetamol use not controlled. Other NSAID use avoided. Steroid use not stated. | 30-day mortality | Yes |
| Haupt et al[32] | Severe sepsis | Ibuprofen IV loading dose (600/800 mg) then 800 mg pr 6-hourly for three doses | Placebo | Other NSAIDs and corticosteroids use avoided. Control of paracetamol not stated. | Not stated | Yes |
| Bernard et al, 1991[31] | Severe sepsis | Ibuprofen 800 mg pr 4-hourly for three doses | Placebo | Other NSAID use avoided. Paracetamol and corticosteroid use not controlled. | Prostacyclin and thromboxane A2 levels | Yes |
| Morris et al[34] | Critically ill (requiring mechanical ventilation ± vasopressor support); temp ≥ 38.3°C for ≥ 15 min before first dose of study drug; brain injury excluded | IV ibuprofen (100mg, 200mg, 400mg) 4-hourly for six doses | Placebo | Rescue treatment if temp ≥ 39.4°C ≥ 2 hours after study drug — paracetamol, cold packs, cooling blankets, alcohol baths or other physician-designated treatment (aspirin/other NSAID use excluded). Corticosteroid use excluded. | Reduction in temp at 4 h in 400 mg group v placebo | Yes |

ICU = intensive care unit. Temp = temperature. po = by mouth. pr = per rectum. IV = intravenous. COX = cyclo-oxygenase. NSAID = non-steroidal anti-inflammatory drug.

cation bias was examined through funnel plots and formal tests of publication bias described by Macaskill and colleagues.[29] We had intended to perform meta-regression based on study-level covariates; for example, use of paracetamol compared with other antipyretics, different mortality end points, and severe sepsis versus other; but there was insufficient heterogeneity to allow meta-regression, and for some of these covariates only single studies.

## Results

Figure 1 illustrates the results of the search strategy. Following identification of 1247 articles, there were 61 potentially relevant to the subject of antipyresis among critically ill adults. Of these, 20 were RCTs, of which 14 were excluded: four investigated the use of paracetamol in patients with acute brain injury; five used antipyretics in previously healthy human volunteers with experimental endotoxaemia; one examined the use of external cooling but not antipyretic drugs; and four compared the antipyretic and haemodyamic effects of either paracetamol or external cooling or combination, propacetamol or metamizol, and propacetamol or metamizol or external cooling, but did not include a non-active control arm.

Six studies met the inclusion criteria[19,30-34] (Table 1). In total, 689 critically ill patients were studied, with 358 receiving antipyretic drugs and 329 receiving placebo or permissive hyperthermia. The antipyretic intervention was paracetamol in one study and a non-steroidal anti-inflammatory drug (NSAID) in five (ibuprofen, 4; lornoxicam, 1). There was no significant association between antipyretic drug use among critically ill patients and mortality (Figure 2). The pooled estimates of odds ratios for mortality with antipyretic treatment were 0.96 (95% CI, 0.68–1.34) and 1.08 (95% CI, 0.60–1.96) for fixed effects and random effects, respectively, and the I-squared value was 34.9 (95% CI, 0.0–73.9) (Table 2). There was no evidence of publication bias in formal tests or funnel plots (Figure 3).

## Methodological issues with included studies

The primary methodological issue was that most of the included studies were not designed to assess mortality risk due to the antipyretic effects of the study medication. This introduced the significant potential for confounding with the undocumented or uncontrolled use of other antipyretic

**Table 2.**

**A. The risk of mortality associated with antipyretic treatment for individual studies**

| Study | Mortality (%) | | Odds ratio (95% CI) |
|---|---|---|---|
| | Antipyretic | Control | |
| Bernard et al, 1991[31] | 3/16 (18.8%) | 6/14 (42.9%) | 0.3 (0.06–1.6) |
| Bernard et al, 1997[30]* | 83/224 (37.1%) | 92/231 (39.8%) | 0.9 (0.6–1.3) |
| Haupt et al[32] | 9/16 (56.3%) | 4/13 (30.8%) | 2.9 (0.6–13.5) |
| Memis et al[33]* | 7/20 (35%) | 8/20 (40%) | 0.8 (0.2–2.9) |
| Morris et al[34] | 5/40 (12.5%) | 1/13 (7.7%) | 1.9 (0.2–17.4) |
| Schulman et al[19] | 7/44 (15.9%) | 1/38 (2.6%) | 7.0 (0.8–59.8) |

**B. Pooled odds ratios for risk of mortality with antipyretic treatment and homogeneity statistics**

**Pooled estimates**

| | |
|---|---|
| Fixed effect | 0.96 (95% CI, 0.68–1.34); $P = 0.80$ |
| Random effects | 1.08 (95% CI, 0.60–1.96); $P = 0.79$ |
| Homogeneity test | $\chi^2$, 7.67; 5 df, $P = 0.17$ |
| I-squared value | 34.9 (95% CI, 0.0–73.9) |
| Macaskill bias test | $P = 0.60$ |

\* Numbers calculated from percentages given in table, which were rounded to zero decimal places

agents during the trial periods. Bernard and colleagues allowed administration of paracetamol during the study period, documenting an increase in the proportion of patients using paracetamol in the placebo group (29% of patients at baseline and 44% at 24 hours) and a decrease in paracetamol use in the ibuprofen group (33% at baseline and 22% at 24 hours).[30] In an earlier study, Bernard and colleagues allowed the use of cooling blankets, paracetamol and corticosteroids during the trial.[31] The use of antipyretic medications, other than paracetamol, was not described by Schulman and colleagues,[19] and Haupt and colleagues did not control for paracetamol use.[32] The study protocol by Morris and colleagues permitted "rescue" antipyresis by a variety of methods (see Table 1) for fever $\geq 103°$F ($\geq 39.4°$C) present a minimum of 2 hours after study drug administration.[34] Therefore, although all trials demonstrated a significant reduction in temperature in their treatment groups versus placebo/permissive arms, the significance of the independent variables cannot be reliably determined from the available data.

Individually, the quality of the methodology described in the six included studies was variable, as assessed by the Jadad score.[26] All trials using NSAIDs as their active intervention had a Jadad score of 4/5[31,33] or 5/5.[30,32,34] The design of the study by Schulman and colleagues did not use a placebo control and required the variable treatment of temperature thresholds between groups;[19] it therefore did not enable blinding of treatment and, with a



**Figure 2. Forest plot of odds ratio for death by antipyretic versus placebo treatment**
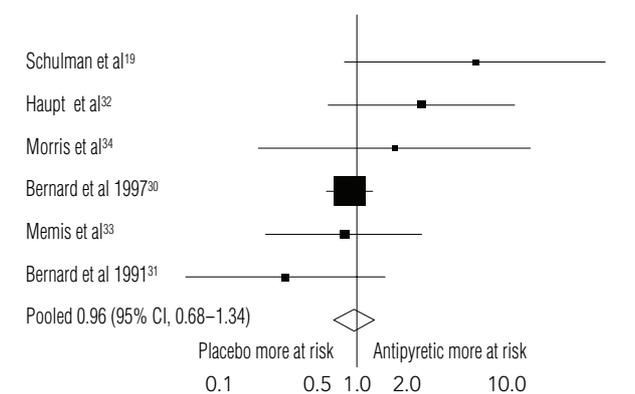
The individual trial estimates are shown as well as pooled estimates, with the size of the boxes on the forest plot inversely proportional to the size of the variance of the study estimates, so that more precise studies have larger boxes.



**Figure 3. Funnel plot for publication bias**
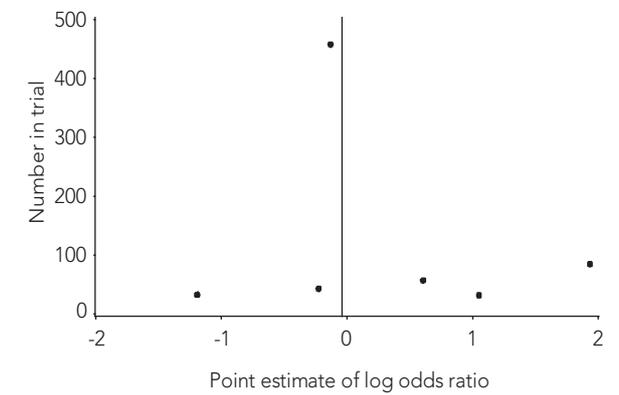
The reference line represents the fixed effect point estimate. There is one large study that dominates the estimate (Bernard et al 1997[30]) and the remaining five small studies are evenly distributed on either side of the pooled point estimate, so there is no visual evidence of publication bias. The formal statistical test for publication bias was also not statistically significant ($P = 0.60$).

### Table 3. Outcomes other than temperature and mortality, according to statistically significant differences between antipyretic treatment and control groups

| Study | Significant effect with antipyretic treatment | No significant effect with antipyretic treatment |
|---|---|---|
| Schulman et al[19] | ↑ daily SIRS score<br>↑ days of antibiotic use | Number of culture-positive infections; presence of SIRS or MODS; days of mechanical ventilation; duration of ICU stay. |
| Memis et al[33] | Nil | All haemodynamic and biochemical parameters; cytokine levels; inspired fractional oxygen – arterial oxygen tension ratio; duration of mechanical ventilation; duration of ICU stay. |
| Bernard et al, 1997[30] | ↓oxygen consumption<br>↓heart rate<br>↓blood lactate levels<br>↓urinary prostacyclin and thromboxane levels<br>Subgroup analysis: ↓mortality in hypothermic group | Incidence and duration of shock, ARDS or AEs. |
| Haupt et al[32] | Nil | All haemodynamic, respiratory and biochemical variables, including levels of COX metabolites; development and reversal of shock or ARDS. |
| Bernard et al, 1991[31] | ↓heart rate<br>↓peak airways pressure<br>↓COX metabolites | Shock reversal; mean systolic BP; pulmonary dysfunction; AEs. |
| Morris et al[34] | 100 mg and 200 mg ibuprofen groups ↑ postenrolment bacteraemia | All laboratory parameters; days of mechanical ventilation; duration of ICU or hospital stay; SAEs or AEs. |

SIRS = systemic inflammatory response syndrome. MODS = multiple organ dysfunction syndrome. ICU = intensive care unit. ARDS = acute respiratory distress syndrome. AE = adverse event. COX = cyclo-oxygenase. BP = blood pressure. SAE = serious adverse event.

Jadad score of 3/5, this trial was at greatest risk of bias. However, two studies did not provide a specified primary outcome variable[32,33] and there were other additional issues of internal validity among the articles.

The other methodological features of the trials are summarised in Table 1 and further described below. Routes and schedules of randomised treatments varied among trials; for example, Schulman et al randomised patients after an initial 3 days in the ICU and ran their protocol for the duration of the ICU stay,[19] whereas other trials administered their treatment arms for no longer than 72 hours; administration was per rectum in two studies, producing low serum ibuprofen levels;[30,32] and the dosing schedule for ibuprofen altered during the trial by Haupt et al to match changing national guidelines.[32]

Five of the six trials were not designed to assess mortality as a primary outcome and were inadequately powered.[19,31-34] Bernard and colleagues' ibuprofen trial contributed about two-thirds of included participants, so their study findings dominated the meta-analysis.[30] Schulman et al's study was designed to be a large multicentre trial, but it was stopped at its first interim analysis having demonstrated a trend towards increased mortality with the "aggressive" treatment of fever versus the permissive hyperthermia group (7/44 v 1/38 deaths, respectively; $P = 0.06$).[19] The included studies measured different mortality end points: inhospital,[32] ICU,[19,33] at 28 days[34] or at 30 days.[30,31] Findings for other outcomes studied are presented in Table 3.

There were important differences in the defined sample populations in the studies, which influence the external validity of this meta-analysis. Three of the trials[30-32] commenced before publication of the 1991 joint American College of Chest Physicians and Society of Critical Care Medicine sepsis definitions.[35,36] These trials used variations of the systemic inflammatory response syndrome (SIRS) criteria with presumed or confirmed infection, plus markers of organ dysfunction, to define their populations of severe sepsis patients. Memis et al used contemporary definitions of severe sepsis with the specific requirement for "bacteriologically documented infections" at study entry.[33] By defining their patient populations by sepsis criteria, these trials also included patients with normothermic and hypothermic sepsis (actual numbers only provided by one study[30]). This contrasts to the selected study populations in the remaining two trials.

Morris et al stratified patients into febrile critically ill (mechanical ventilation or vasopressor requirement) and febrile non-critically ill (acutely ill hospitalised) groups at randomisation.[34] There was sufficient data for the inclusion of the critically ill group alone in our meta-analysis. Although rates of SIRS were not given, the average baseline temperatures and heart rates for each group met two of the four SIRS criteria, and 95% of the trial's total study population had a documented probable site of infection at baseline. Schulman et al investigated patients who developed fever after 72 hours of admission in a trauma ICU for

the purpose of addressing their primary outcome variable: the rate of development of culture-positive infection by varying degrees of antipyresis.[19] Around 90% of participants had documented SIRS and most patients from both groups developed culture positive infection. Of the eight deaths in this study, sepsis was cited as a cause in all cases. This study was distinct as the only trial to specifically exclude patients with acute brain injury,[19] although no other study specified recruitment from neurological ICUs or specifically included patients with acute brain injury.

## Discussion

The studies meeting the criteria for this review were insufficient to allow a robust estimate of effect of pharmacological antipyresis on mortality in critically ill patients with suspected infection. Therefore, this important research question is not answerable with currently available evidence.

### Strengths and limitations

There are several issues relevant to the interpretation of the findings of our meta-analysis. The first is whether all relevant studies were identified. We are confident that our extensive search strategy of four major databases, and the reference lists of relevant articles, identified all eligible studies published since 1947, including those not written in English. Furthermore, there was no evidence of publication bias in formal tests or funnel plots (Table 2 and online supplement).

Second, the major limitation is that many of the included trials were not designed for the primary purpose of evaluating antipyretic effects on clinical outcomes such as mortality.[30-34] As such, there is a significant potential for confounding with the use of adjuvant antipyretics.

Third, the outcome of this meta-analysis is limited by the heterogeneity of the studies included. Although the homogeneity statistic was not statistically significant, the I-squared was large with a wide confidence interval, and the pooled estimate was heavily dominated by the largest study.[30] In addition to the different antipyretics used according to differing dosing schedules, there were other important differences in mortality end points and the populations studied. Study inclusion criteria varied and infection was not confirmed in all study patients; it is therefore possible that some of the patients had non-infective illnesses, for example, trauma-induced SIRS. Many of the studies included patients with sepsis who were not necessarily febrile.

### Recommendations for future study

Given the biological rationale for fever being part of a protective, adaptive response to infection and the widespread use of antipyretic interventions, it is important that further RCTs of antipyretics in critically ill patients with infection are undertaken to assess their efficacy and safety on patient-centred outcomes. Fever is potentially both harmful and beneficial in different clinical situations and the challenge will be to determine in which circumstances antipyretics have a favourable or detrimental risk–benefit profile.

We propose that investigating the effect of paracetamol among critically ill septic patients with fever would have the greatest clinical relevance. Paracetamol is the drug of choice for antipyresis and is commonly used in hospital-based care, including the ICU, due to its otherwise more favourable safety profile than NSAIDs. Possible designs for future studies investigating the effect of paracetamol in critically ill patients with sepsis include a double-blind placebo-controlled trial, or an aggressive versus permissive treatment regime based on temperature thresholds.

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