Long-term Health Effects of Antipyretic Drug Use in the Ageing Population: A Systematic Review

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Abstract

Background: It is unclear whether fever suppression is beneficial or harmful in the long term in the elderly, due to different immune profile and body temperature compared to the young. Our objective was to determine the long-term health effects of antipyretic treatment in the elderly during infections.

Methods: A systematic review was carried out using PubMed, Embase and Cochrane CENTRAL databases. Studies with a sample age ≥60 years investigating any antipyretic drug during infections, comparing with any other drug/therapy/placebo/none were included. Studies in which these drugs were used in roles other than antipyresis were excluded. Databases were searched from their inception until the date of last analysis (27/03/2021). Primary outcome was the onset or worsening of chronic inflammatory diseases. Secondary outcomes were fever reduction, length of hospital stay, patient satisfaction, mortality, laboratory parameters indicative of morbidity, and progress to complications.

The Risk of Bias (ROB) was assessed for each study type with the respective ROB formats– Cochrane's ROB tool for RCTs, ROBINS-I tool for observational studies, Joanna Brigg's critical appraisal tool for case series and the Cochrane handbook prescribed domains for case reports. Narrative synthesis was performed because high heterogeneity rendered meta-analysis impossible.

Results: Of 11481, 17 studies (2 RCTs, 7 observational, 1 case series and 7 case reports) were included.

No studies investigated the primary outcome and patient-reported outcomes.

The Risk-of-bias of the studies was unclear to high.

Fever reduction was significant in the RCTs, in the antipyretic group. BP drop was significant in five studies, in the antipyretic group. Morbidity indicators and length of stay were available only in studies that reported adverse events. Mortality was significant for these drugs in one observational study.

The certainty of evidence (GRADE) was low to very low for all outcomes, including fever reduction and mortality.

Discussion/Conclusions: There is insufficient evidence regarding the long-term benefit or harm from fever suppression with antipyretics during infections in the elderly.

Systematic review registration: This study was funded by the Taylor's University Ageing Flagship Program and the protocol was registered on PROSPERO (registration number: CRD42020160854)

Background

An undercurrent of chronic inflammation alters the immune responses as one ages (1, 2), making infections more difficult to identify and more damaging than in the younger population (3–7). Elderly individuals (> 60 years old) are known to have a lower baseline body temperature than the younger population, an adaptive phenomenon for longevity (8–11). It has been reported that the immune responses of elderly people are comparatively less effective than those of younger people, and this may be detrimental to their outcomes in terms of acute and severe illnesses (6, 12, 13). On the other hand, there is evidence demonstrating adverse effects of "over-reaction" of immune system and the protective effects of hypothermia in survival, for example, during infections (14–16). Until now, no conclusive answer exists on whether fever is beneficial or harmful (17–21). However, fever is routinely suppressed, to curb the extra metabolic and cardiorespiratory demand that it levies on the patient, as well as to reduce fever-associated discomfort (22–25), and most of the time, involves over the counter drugs without medical advice (23, 26–28). Some studies have connected the onset and progression of chronic inflammatory diseases to the suppression of acute inflammation, including fever (29–34), stating it to be one of the factors contributing to the growing global burden of chronic inflammatory diseases (29, 35). However, there is no comprehensive review of the current evidence regarding the overall benefit and harm of treating fever in the elderly during infections. Based on the existing literature, we hypothesised that reducing fever during infections in the elderly may be detrimental in the long term, leading to the onset or worsening of chronic inflammatory diseases.

Objectives

In this review, we attempted to synthesise available evidence to determine the long-term effects of fever suppression during infection in the elderly with antipyretic drugs. Our secondary objectives were to determine the effect of such treatment on fever reduction, length of hospital or ICU stay, patient satisfaction, mortality, changes in morbidity indicators and progress to complications (including adverse events).

Methods

The study protocol was registered on PROSPERO (reg. no. CRD42020160854) and published on a Scopus indexed publishing platform (36, 37).

Literature search

Three databases were searched from their inception, PubMed, Embase and Cochrane CENTRAL, using personalised search terms for each of them. Medical subject headings (MeSH) terms were used for PubMed, Emtree terms for Embase and title/abstract terms for Cochrane CENTRAL. The terms "elderly" and its variants, "antipyretics" and its variants were used (Supplementary material). The databases were searched from their inception until the last date of analysis (27/03/2021). The process of screening and inclusion is depicted in the PRISMA flow chart (Fig. 1)

Two researchers independently screened and included relevant studies.

Inclusion/ Exclusion criteria:

- The elderly population receiving any antipyretic drug, given for fever reduction during an episode of infection were included
- Compared, to placebo/other drug/therapy, or not compared to anything, were considered.
- Studies that included exclusively or predominantly, the elderly population were included, along with studies that provided separate data for the elderly.
- No restriction was laid on study design or language.
- Only studies on humans and peer reviewed published literature were included.
- Studies where antipyretics were administered for purposes other than antipyresis, such as analgesia were not included.

Outcomes:

Primary outcome:

The onset or worsening of chronic inflammatory disease post fever intervention, as variously defined by the study authors (Long-term implying an effect lasting more than three months from fever suppression).

Secondary outcomes:

The secondary outcomes were fever reduction, all-cause mortality, progress to complications, adverse events, length of stay in ICU/hospital, changes in the laboratory or radiological findings indicative of morbidity and patient satisfaction from the use of these interventions.

Data collected

The data from the included studies were extracted via personalised data extraction forms (38) of the Cochrane Effective Practice and Organisation of Care (EPOC) (supplementary material).

The following information from each paper were extracted from the search:

- Journal name; title; authors; year of publication; funding sources.
- Type of study; study setting; sampling size; control and intervention arms; blinding information; type of infection; type of intervention; details of intervention delivery - dose, combination etc
- Mean age; age range; gender distribution; inclusion and exclusion criteria; health status
- Outcomes assessed; follow up period; participant attrition; statistical analysis population (Intention to treat/per protocol); statistical analysis; conclusions.

Relevant statistical comparisons and measures were extracted from these studies for each outcome. Any missing data were recorded as such and the whole sample (intention to treat) was considered for analysis. A meta-analysis was planned if the data could be pooled and in case the pooling was not possible, a narrative synthesis was planned.

Risk of bias (ROB) was evaluated in each study using the Cochrane ROB and ROBINS-I tools for RCTs and observational studies respectively (39, 40). Joanna Brigg's ROB tool (41, 42) was used for case series and the ROB according to domains suggested by the Cochrane handbook was used for case reports (40) (supplementary material).

The certainty of evidence from these studies was assessed using the GRADE guidelines, adapted to narrative synthesis (43). The outcomes were assessed for risk of bias due to study design, inconsistency, imprecision, publication bias, existence of residual confounding, large effect and dose response gradient (supplementary material).

Data synthesis and analysis

The effect measures for all outcomes were provided in diverse forms. We attempted to extract similar data to common effect sizes such as the risk ratio (RR) or Odds ratio (OR) with their respective 95% confidence intervals for meta-analysis, but this was impossible, for reasons detailed below in the results. We transformed all measures to mean and standard deviations using standard conversion techniques, and combined drugs into the same group where two were separately given. In the absence of poolable data, we planned to conduct a narrative synthesis based on framework provided by Cochrane Consumers and Communications Group (44) (Supplementary material) and the ESRC methods programme (45)

The results are presented as tables and figures for the outcomes assessed.

Results

Results of search

The initial search yielded 11481 studies of which on removing duplicates amounted to 10812 studies. Furthermore, we found 12 studies by searching the references in the included studies. We extracted studies using a reference manager system (46). Finally, 17 studies were included in the analysis:

2 RCTs (47, 48),

5 prospective observational studies (49–53),

2 retrospective observational studies (54, 55),

1 case series (56) and

7 case reports (57–63).

The data from these studies was extracted to personalised data extraction forms (38) of the Cochrane Effective Practice and Organisation of Care (EPOC) (supplementary material). Full-text screened studies, when excluded, were done so with explanation in these forms. Table 1 provides the characteristics of included studies including the study design, number of participants, interventions, outcomes assessed, and the risk of bias.

Totally, there were 25,722 participants from 17 studies.

The interventions in these studies were acetaminophen and its derivatives, and NSAIDs, compared between themselves, external cooling, with placebo or not compared at all.

A meta-analysis was not possible as the data could not be pooled. This was because, i) the study designs were heterogenous ii) the outcomes were measured at different time points, using various techniques and were reported in heterogenous ways and iii) some studies used comparison between interventions, and others did not.

Therefore, a narrative synthesis was conducted, following the guidelines of the Cochrane Consumers and Communications Group (44) (Supplementary material) and the ESRC methods programme (45). The results were synthesised accordingly, and the review reported, in keeping with the PRISMA (64) and the SWiM protocol extension for narrative synthesis (65) (Supplementary material). To assess the certainty of evidence, the guidelines adapting the GRADE assessment for narrative synthesis (43) was followed. The final findings were represented in a summary of findings table.

Grouping by study types

The studies were grouped according to the study design as their natural similarities rendered well for comparing effects. Below is a summary of all included studies according to the study type.

RCTs

Both the RCTs compared the antipyretic drugs among themselves and with placebo for efficacy of fever reduction. They also reported the adverse events. Cunietti's study included participants with simple self-limiting upper respiratory tract bacterial/viral infections.

Observational studies

Four of the five prospective observational studies focused on the cardiovascular effects along fever reduction from intravenous antipyretics. Furthermore, Krajcova's study investigated the mechanism of hypotension by observing cardiac output related measurements. Cantais' and Lee's studies investigated mortality from antipyretics. Lee further sought to compare the effect of antipyretic therapy between sepsis and non-sepsis groups. They also incorporated fever temperature ranges and investigated for association of mortality and antipyretic therapy.

Both the included retrospective observational studies investigated mortality from antipyretics and external cooling, comparing those who developed sepsis with those who did not.

All the included observational studies were conducted on ICU patients.

Case series and reports

The case series reported Steven Johnson syndrome and toxic epidermal necrolysis from antipyretics during viral infections. The case reports reported on adverse events from antipyretics taken for common conditions such as flu and upper respiratory tract infections. The adverse evets reported were pneumonitis, hypotension, eosinophilia, fixed drug eruption, SJS/TEN and aseptic meningitis.

Risk of bias (ROB)

The two RCTs had unclear ROB, due to unavailability of the full text and original publication and all the other studies had high ROB due to their study designs and some due to confounding and missing data. (Table 1)

Table 1

Characteristics of included studies

Study ID	Country	Design	Setting	Population	Intervention	Comparator	Outcomes	Observation period	N	ROB
Cunietti 1993	Not mentioned	RCT	Not mentioned	≥ 65 Y viral/ bacterial infections URTI/LRTI Fever > 38oC informed consent	Nimesulide	Paracetamol	1. Fever reduction 2. Progress to complications, hemodynamic 3. Laboratory markers of morbidity	3 days	39	U
Reiner 1985	Not mentioned	RCT	Not mentioned	18–90 Y with fever	Nimesulide	Diclofenac, Placebo	Fever reduction	6 hours	81	U
Cantais 2016	France	Obs - P	ICU	Adult patients requiring IV acetaminophen infusion according to the attending physician's judgment and having arterial pressure monitored via an arterial catheter	Paracetamol	Nil	1. Fever reduction 2. Progress to complications, hemodynamic 3. Mortality	3 hours	160	H
Hersch 2008	Israel	Obs – P	ICU	critically ill patients in the ICU who were febrile (body temperature ≥ 38°C), ventilated, sedated, and experiencing sepsis	Propacetamol	Nil	1. Fever reduction 2. Progress to complications, hemodynamic	2 hours	14	H
Krajcova 2012	Czech Republic	Obs - P	ICU	> 18Y, artificially ventilated and administered paracetamol, monitored by PiCCO, with sinus rhythm	Paracetamol	Ranitidine	1. Fever reduction 2. Progress to complications, hemodynamic	Till resolution of fever occurred	6	H
Lee 2012	Korea and Japan	Obs - P	ICU	All adult patients requiring ICU > 48 hours	NSAIDs, paracetamol	External cooling	1. Fever reduction 2. Mortality	28 days	1425	H
Poblete 1997	Switzerland	Obs - P	ICU	Patients undergoing mechanical ventilation in ICU with rectal temperature > 38.5C and in whom the attending physician wished to reduce fever (Patients did not have inspired O2 fraction of > 0.6; did not consume caloric intake exceeding energy expenditure calculated at baseline)	Propacetamol, metamizole	External cooling	1. Fever reduction 2. Progress to complications, hemodynamic 3. Mortality	Till metabolically stable state was acheived	20	H

(RCT: randomised controlled trials; Obs P: prospective observational; Obs R: retrospective observational; CS: case series; CR: Case reports; U: unclear; H: steroidal anti-inflammatory drugs; LOS: length of stay; AdEv: adverse events; TEN: toxic epidermal necrolysis)

Study ID	Country	Design	Setting	Population	Intervention	Comparator	Outcomes	Observation period	N	ROB
Ye 2017	USA	Obs - R	ICU	All patients meeting criteria for sepsis, receiving mechanical ventilation; with fever and hypothermia	NSAIDs, paracetamol	External cooling	Mortality	Not specified	8711	H
Zhang 2015	USA	Obs - R	ICU	All patients meeting criteria for sepsis	NSAIDs, paracetamol	External cooling	Mortality	Not specified	15268	H
Ban 2016	Korea	CS	Allergy clinic	Patients presenting with fever and blistering lesions with a history of acetaminophen exposure preceding onset of symptoms	Paracetamol	Nil	1. AdEv 2. LOS 3. Laboratory marker of morbidity	Case 1: 67 days Case 2: 36 days	2	H
Akashi 1997	Japan	CR	Hospital	64- and 70-year-old with Acetaminophen induced pneumonitis	Paracetamol	Nil	1. AdEv 2. Laboratory marker of morbidity	Case 1: 4 months Case 2: 3 days	2	H
Ayonrinde 2000	Australia	CR	Hospital	65-year-old with anaphylactoid reaction	Paracetamol	Nil	1. AdEv 2. Laboratory marker of morbidity	3 days	1	H
Danguy 2010	France	CR	Hospital	71-year-old with Acetaminophen induced hypotension	Paracetamol	Nil	Progress to complications, hemodynamic	5 days	1	H
Gonzalo - Garijo 2006	Spain	CR	Hospital	68-year-old with Ibuprofen induced fever	Ibuprofen	Nil	1. AdEv 2. LOS 3. Laboratory marker of morbidity	3 months	1	H
Kim 2014	Korea	CR	Hospital	60-year-old with TEN	Paracetamol	Nil	1. AdEv 2. LOS 3. Laboratory marker of morbidity	30 days	1	H
Kondo 1993	Japan	CR	Hospital	63-year-old with Acetaminophen induced eosinophilia	Paracetamol	Nil	1. AdEv 2. Laboratory marker of morbidity	7 days	1	H
Prabhu 2005	Nepal	CR	Hospital	65-year-old with fixed drug eruption	Paracetamol	Nil	1. AdEv 2. Laboratory marker of morbidity	48 hours	1	H

(RCT: randomised controlled trials; Obs P: prospective observational; Obs R: retrospective observational; CS: case series; CR: Case reports; U: unclear; H: high; ICU: intensive care unit; NSAIDs: non-steroidal anti-inflammatory drugs; LOS: length of stay; AdEv: adverse events; TEN: toxic epidermal necrolysis)

Narrative Synthesis

No study investigated the primary outcome, onset/worsening of chronic inflammatory disease from antipyretic use. We could find no study that investigated patient satisfaction from use of these drugs either.

Fever reduction:

Antipyretics were beneficial in reducing fever as seen in the included RCTs [Mean 1.6 ± 0.42^{o}C] (47, 48). This did not, however, appear to extend to the sepsis scenario or where the patients were critically ill from infections [fever reduction ranged from 0.21±1.15 to 0.69±0.4^{o}C], as seen in observational studies (50–53). The effect of external cooling was similar [fever reduction ranged from 0.2±0.1 to 2±1.44^{o}C] in all the studies investigating this therapy (50, 53). The case

d only one case report mentioned that “fever reduced” after paracetamol (60).

Table 2
Outcomes – Fever reduction

Study ID	Temperature reduction Intervention	Temperature reduction Comparator	Time points reported
Cunietti 1993	**1.6 ± 0.42**	**1.6 ± 0.42**	6, 7, 8, 9 and 10 am and at 2, 6 and 10 pm on the first day and at 6 and 10 am and at 2, 6 and 10 pm on the second and third days
Reiner 1985	**Significant**		Before, 30, 60, 90, 120, 240 and 360 minutes after drug administration
Cantais 2016	0.69 ± 0.4 **p < 0.0001**	Nil	Mean drop at 30 mins post infusion
Hersch 2008	0.3 ± 0.75	Nil	At 30 mins post infusion. Measures reported at before and 15, 30, 45, 60, 90, 120 minutes after propacetamol administration;
Krajcova 2012	0.35 ± 0.13 **p = 0.02**	Nil	69th minute
Lee 2012 Antipyretic drugs and external cooling in sepsis patients	0.39 ± 0.14	0.2 ± 0.1	From application of antipyretic to next temperature monitoring
Lee 2012 Antipyretic drugs and external cooling in non-sepsis patients	0.38 ± 0.16	0.1 ± 0.05	From application of antipyretic to next temperature monitoring
Poblete 1997 Antipyretic drugs and external cooling	0.21 ± 1.15	2 ± 1.44 **p < 0.0001**	On achievement of metabolically stable state
Prabhu 2005	**Fever reduced**	Nil	Not mentioned
Temperature changes in ^{o}C			

Progress to haemodynamic complications:

Seven of the 17 studies reported development of hypotension, although the magnitude differed from study to study [SBP drop of 3 to 4% in one RCT (47); MAP drop ranging from 4.8 ± 12.28 to 12.59 ± 8.1 mmHg in prospective observational studies, (49, 51, 52) except in one study, that showed no change in MAP (50) and drop of varying degrees in BP in the case reports (58, 61)].

Heart rate was also measured in four studies and showed a trend towards reduction after the administration of antipyretics, although the degree of reduction did not reach statistical significance (47, 49, 50, 58). One study found a non-statistical significant trend towards reduction in peripheral resistance and cardiac output from antipyretic drugs (49).

Table 3
Outcomes - Progress to hemodynamic complications

Study ID	Mean blood pressure drop Intervention	Mean blood pressure drop Comparator	Time points reported
Cunietti 1993	0 events	0 events	6, 7, 8, 9 and 10 am and at 2, 6 and 10 pm on the first day and at 6 and 10 am and at 2, 6 and 10 pm on the second and third days
Cantais 2016 (≥ 15% MAP drop group)	11.5 ± 25.44 **p < 0.0001** **(83/160 events)**	overall MAP drop: 5.96 ± 4.91 **p < 0.0001**	30 minutes after infusion of acetaminophen
Hersch 2008	13.48 ± 11 **p < 0.05** (24/72 events)	Nil	At 30 mins; measures also reported at before and 15, 30, 45, 60, 90, and 120 minutes after propacetamol administration
Krajcova 2012 Febrile cycles	12.59 ± 8.1	Mean rise 3.28 ± 37.69 **p = 0.001**	19th minute and post intervention
Krajcova 2012 afebrile cycles	6.59 ± 9	Mean rise 1.36 ± 18.72	19th minute and post intervention
Poblete 1997 Antipyretic drugs and external cooling	0 ± 22.27	Mean rise 2 ± 25.5	End of intervention
Ayonrinde 2000	SBP: 85 DBP: 50	Nil	30 mins after ingestion of drug
Danguy 2010	SBP: 72 DBP: 40	Nil	Day 4 post intervention
blood pressure changes in mmHg			

Mortality: (Fig 2, 3 & 4)

There were no events of mortality in studies involving common self-limiting viral/bacterial disease, as reported in the RCTs and case reports. However, in sepsis and ICU patients (reported in observational studies), mortality was positively associated with antipyretic therapy in the highest fever temperature range [OR (95%CI): 2.61 (1.11, 6.11) and 2.05 (1.19, 3.55) for NSAIDs and acetaminophen respectively] (Table 3), when compared to external cooling [OR (95%CI): 1.2 (0.70, 2.05)] (55). Mortality was not affected by antipyretic drugs in other temperature ranges and did not differ from non-sepsis group (54, 55).

When all the studies comparing overall mortality between antipyretic drugs and external cooling in sepsis patients were considered, the OR and 95%CI was 0.75 (0.64, 0.87) (p = 0.0003)(26, 53, 55). Mortality in antipyretic drugs group compared to external cooling in the non-sepsis group, however, was not different and yielded an OR and 95%CI of 0.30 (0.07, 1.30) p = 0.11. Mortality in antipyretic drugs group compared to non-treatment in sepsis patients was higher but statistically non-significant OR and 95%CI: 1.11 (0.96, 1.28) p = 0.15

Table 4
Outcomes – Mortality

Study ID	No of events	Mortality Intervention OR and 95%CI	Time points reported
Cantais 2016 (For development of ≥ 15% MAP drop) N = 160	42/83	1.6 (0.86, 3) P = 0.14	In hospital and ICU
Lee 2012 Antipyretic drugs and external cooling in sepsis patients	53/147:64/307	2.14 (1.38, 3.43) **P = 0.0006**	28 days from admission
Lee 2012 Antipyretic drugs and external cooling in non-sepsis patients	2/131:18/364	0.3 (0.68, 1.32) P = 0.11	28 days from admission
Poblete 1997	1/8	Cannot calculate as not associated with antipyretic	In hospital/ICU
Ye 2017 Antipyretic drugs and external cooling (all sepsis patients)	121/652:206/892	0.22 (0.18, 0.27) **P < 0.0001**	In ICU
Ye 2017 Antipyretic drugs and non-therapy (all sepsis patients)	121/652:1196/7167	1.14 (0.93, 1,5) P = 0.22	In ICU
Zhang 2015 Antipyretic drugs and external cooling (all sepsis patients)	129/1027:212/1006	0.54 (0.42, 0.68) **P < 0.0001**	In ICU
Zhang2015 Antipyretic drugs and non-therapy (all sepsis patients)	129/1027:1389/12208	0.54 (0.42, 0.68) **P < 0.0001**	In ICU

Length of stay (ICU/hospital):

A mean 51.5 days resulted from the antipyretic treatment adverse effects in the case series (56). Case reports yielded a mean 4 days from the adverse effect of these drugs (57–63). The observational study that reported the length of stay did not assess the effect of treatment on it (53).

Table 5
Outcomes - Length of stay

Study ID	length of stay Intervention	Length of stay Comparator	Time point measured
Lee 2012 (No assessment of antipyretic drugs on LOS)	With sepsis: Mean: 8 days (5, 14) Without sepsis: Mean: 5 days (4, 7)	Nil	At discharge
Ban 2016	Case 2: 67 days Case 6: 36 days	Nil	At discharge
Gonzalo - Garijo 2006	2.5 days	Nil	At discharge
Kim 2014	17 days	Nil	At discharge

Morbidity indicators (laboratory and radiological findings) (supplementary material)

The details of laboratory markers influenced by antipyretic drugs was provided in the case reports of adverse events (56–63). Detailed laboratory readings from these studies are provided in the supplementary material

Adverse events

Adverse events were reported in the RCTs, the case series and all the case reports. Altogether, 18 episodes of adverse effects were reported in 10 studies (47, 48, 56–63), including mild transitory effects, hypotension, Steven Johnson syndrome/toxic epidermal necrolysis, aseptic meningitis, pneumonia, and fixed drug eruption. All the case reports confirmed causality of the adverse events.

Table 6
Outcomes - Adverse events

Study ID	Adverse events Intervention	Adverse events Comparator	Time point reported
Cunietti 1993	1/39 (skin rashes)	Nil	End of trial
Reiner 1985 (Both were antipyretics)	3/30 (Transient adverse effects)	4/24 (transient adverse effects)	End of trial
Ban 2016	SJS/TEN	Nil	7days after acetaminophen
Akashi 1997	Acetaminophen induced pneumonitis	Nil	18 and 5 days after ingestion of acetaminophen
Ayonrinde 2000	Anaphylactoid reaction	Nil	30 mins after ingestion of acetaminophen
Gonzalo - Garijo 2006	Aseptic meningitis (clinically suspected)	Nil	15 minutes after ibuprofen
Kim 2014	SJS/TEN	Nil	14 days after administration of paracetamol
Kondo 1993	Acetaminophen induced eosinophilia	Nil	5 days after ingestion of Kinuya-chinetsu
Prabhu 2005	Fixed drug eruption	Nil	After paracetamol

Certainty of evidence

The certainty of evidence from included studies turned out to be low for fever reduction and mortality and very low for other outcomes.

Table 7
GRADE Summary of Findings table

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Fever reduction (assessed with: temperature)									
8	observational studies	serious [a]	serious [b]	not serious	not serious	publication bias strongly suspected strong association [c]	Quality of evidence does not generate confidence in the effect	⨁⨁◯◯ LOW	CRITICAL
Mortality (assessed with: death or alive)									
5	observational studies	serious [a]	serious [b]	not serious	not serious	none	Quality of evidence generates moderate level of confidence in the effect	⨁⨁◯◯ LOW	CRITICAL
Hemodynamic changes (assessed with: BP)									
6	observational studies	serious [a]	not serious [b]	not serious	serious [d]	publication bias strongly suspected [c]	Quality of evidence does not generate confidence in the effect	⨁◯◯◯ VERY LOW	CRITICAL
Morbidity indicators (assessed with: laboratory values)									
7	observational studies	serious [a]	not serious	not serious	serious [d]	publication bias strongly suspected [c]	Quality of evidence does not generate confidence in the effect	⨁◯◯◯ VERY LOW	IMPORTANT
Length of stay (assessed with: days)									
8	observational studies	serious [a]	not serious	not serious	serious [d]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [c]	Quality of evidence does not generate confidence in the effect	⨁◯◯◯ VERY LOW	NOT IMPORTANT
Adverse events (assessed with: development of adverse events)									
8	observational studies	not serious	serious [b]	not serious	serious [d]	publication bias strongly suspected [c]	Quality of evidence does not generate confidence in the effect	⨁◯◯◯ VERY LOW	IMPORTANT

(a. observational studies; wide variance of point estimates/minimal or no overlap of CIs/all studies show low p values; c. small studies with significant changes; d. small sample size)

Discussion

Though the primary objective of this study was to assess the long-term effects of fever suppression, we did not restrict the follow-up period of the study for inclusion as we were also interested in the immediate effects, which were our secondary outcomes of interest. The period of observation in included studies ranged from 2 hours to 4 months. Only two studies had follow-ups long enough to assess long term effects but neither made any comment nor observation of such effects. The reviewed literature offers some insight into the widely variable role of fever during infections in humans. In this study, we could not find any evidence regarding the chronic inflammatory disease onset or worsening from fever suppression but identify it as a knowledge gap considering many immunological studies addressing this phenomenon (30, 32, 66). While in common infections, which are self-limiting, pharmacological antipyresis use is beneficial in reducing the temperature and alleviating the symptoms (47, 48, 60), the same benefit was not appreciated in sepsis or critical illness (49–54, 67). Physical cooling appeared not to have benefit, except in those who were sedated and were suffering severe sepsis (50, 53, 54, 67), where some benefits like decrease of energy expenditure, reduction of fever and heart rate were observed (50). There was a strong association of mortality with antipyretic therapy at high fever range in sepsis (67). The reason behind the findings was postulated by some authors as possibly resulting from the difference in the role fever plays in different subjects during different infection episodes with varying severity. Fever is protective in some and harmful in others (53). The available meta analyses regarding active fever management compared to less active intervention yielded no supporting evidence for such intervention even in physiologically

mmendation so far seems to be that each case must be regarded for immune compromise and organ damage

before recommending or refuting antipyresis (69). They also recommend watching out for organ dysfunction and presence of acute brain pathologies/coma/cardiac arrest before deciding the regimen. The recommendation is permissive fever management in the absence of such pathologies or organ compromise, where the temperature is below 41^{o}C. However, this recommendation is not based on high quality evidence and is generalised to all cases with fever in the ICU and needs further investigation.

Hypotension appeared to be an adverse effect of note following the administration of antipyresis, as it was reported in seven of the included studies (47, 49–52, 61). The mechanism of development of hypotension was postulated by the study authors as probably resulting from loss of peripheral resistance and decreased cardiac output (49). Other adverse events, like pneumonitis, anaphylactoid reaction, SJS/TEN, fixed drug eruption and aseptic meningitis were rare but adequately reported in seven studies (56–60, 62, 63). The length of stay and morbidity indicators were available but were of little consequence.

Earlier systematic reviews investigating the effect of antipyretic treatment on sepsis either found insufficient evidence for any robust estimate to be made regarding mortality from such treatment, or favourable evidence for fever reduction (67, 70–73). However, they did not consider the elderly specifically and did not include non-randomised studies.

This review focussed on elderly people and included all study types. The reviewers decided early on to include case series and reports. While it is desirable to conduct a systematic review and meta-analysis of RCTs for their methodological superiority, a study aiming to assess the adverse effects of a drug may not find much evidence in them. The ethical/practical issues associated with conducting such studies make it necessary to include observational studies. The evidence is more likely to be better represented in anecdotal reports such as case series and case reports where the real-world situation is depicted better. The inclusion population for RCTs is usually very restricted, making the inclusion of case series, case reports and observational studies imperative, to be able to get more generalisable evidence. However, the inherent limitations of these reports mandate a cautious approach in their assessment and incorporation into the body of evidence.

In the end, with the scarce findings on elderly population were similar to those in previous systematic reviews on general population.

Assessment of large studies

There were three large studies in this review (53–55) which incidentally compared antipyretic drug with external cooling. Lee et. al. compared these in septic and non-septic patients whereas Ye's and Zhang's study compared them only in septic patients. All three studies investigated mortality only. Forest plots of these studies (Figs. 2, 3 and 4) show that there may be slightly more mortality in the antipyretic drug group when compared to non-treatment in the septic patients, although, this was not statistically significant. All three studies, however, show a significant increase in mortality from antipyretic therapy in general (combining external cooling and drugs) against non-treatment in the septic patients. However, this effect seems to result mostly from the external cooling than drugs. The certainty of evidence on mortality from these three studies is low as they are observational studies and have a glaring confounding factor that cannot be ruled out – that the sicker patients may have been given antipyretic therapy compared to those who were less sick, automatically increasing the mortality. Thus, even considering the large studies included in this review, it is not possible to recommend or deter treatment of fever with antipyretic drugs in the elderly during infections.

Thus, while in the individual studies, we found significant effect of the antipyretic drugs on fever reduction, mortality, and development of hypotension, when the findings were synthesised systematically, their certainty turned out to be low or very low.

Strengths and Limitations

The strength of this study is that it considered a wide range of study designs, including case reports and case series, allowing for the review to be close to real-world clinical situations and cover a broad base with regard to aetiology. The review faced challenges in procurement of full text from Reiner's study and original publication of Cunietti's. Poblete's study was also lacking in explicit information separately for the elderly. We had to work with partial data that was available. Furthermore, the primary outcome of interest was not evaluated and reported in any study. We emphasise this as a research gap and advise a study assessing the long-term effect of antipyretic drugs in the elderly. As a review looking at the harmful effects from an intervention, narrative synthesis creates limitation in our ability to quantitatively compare the effect. This could not be avoided due to the heterogeneity of measures and study types. However, narrative synthesis when conducted systematically as done here, adhering meticulously to the framework followed by rigorous quality assessment of the evidence, provides an overall picture about the outcomes, which is reliable to a great extent.

Future research

With this review, the question of long-term effect of antipyretic treatment in the elderly during infections was identified as a research gap and considering the proclivity of such practice in general population, we need to investigate this in the future. We identified issues in the conduct of investigations that may be responsible for such confusion on the subject. The population of aging adults has not been the focus of any quality study. This is essential as the immunological phenomena changes with age and what applies to the younger population may not be applicable in the aged. Furthermore, none of the studies conducted a long enough follow up to observe long-term effect of the acute disease with fever or the effect of antipyretics. This again, is an important factor to consider, as the elderly tend to suffer from chronic inflammation as already demonstrated, and drugs can be major modulators of the immune system. Such studies with long enough follow up period and of sufficient sample size need to be conducted. There are a few confounders that the studies need to take care of. For example, most studies did not differentiate between pharmacological antipyresis and external cooling. This is a flaw as the mechanism of temperature reduction by these two methods and the body's response to them are entirely different. Similarly, it would be better to separate the population based on seriousness and aetiology of their illness for the study. The adverse events that develop from such drugs are amply available in case reports and series and such data need to be used for immunological research to identify the exact mechanism behind them to guide in whom such treatment must be avoided.

Immunological studies also need to investigate the connection between fever and chronic inflammation as the latest pandemic has given rise to interesting observations such as absence of fever and presence of chronic comorbidities leading to increased mortality from the infection (74, 75). We need to examine these factors through extensive observational studies and use the results to plan RCTs to evaluate the exact relevance of antipyretic treatment in the elderly. Furthermore, we also require physiological and immunological studies to identify the role of fever is sepsis in the elderly and what exactly happens during an antipyretic treatment.

Conclusions

In summary, this systematic review and narrative synthesis of long-term health effects of fever treatment with antipyretic drugs during infections in the elderly could not find sufficient evidence for any firm conclusion. Specifically, no evidence was available for the association between fever suppression and chronic inflammatory disease. The evidence regarding fever reduction and mortality were of low quality and those regarding hemodynamic alterations, length of stay and adverse events of very low certainty. Future high-quality studies with sufficient follow up period, addressing this question are warranted, considering how common the use of antipyretics is in the elderly and how easily this population suffers from the effects of acute inflammatory diseases.

Declarations

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Conflicts of interest:

The authors declare no conflict of interest

Data availability and Supplementary material: (76)

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Authors' contributions:

SM conceived and designed the study, performed the research, analyzed the data and wrote the paper

EvdW designed the study, analyzed the data and contributed to paper writing

MM conceived the study and performed the research

GV conceived the study and analyzed the data

LNM designed the study, analyzed the data and contributed to paper writing

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not applicable

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not applicable

References

1. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69 Suppl 1:S4-9.
2. Bajaj V, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, Immunity, and COVID-19: How Age Influences the Host Immune Response to Coronavirus Infections? Front Physiol. 2020;11:571416.
3. Norman DC. Fever in the Elderly. Clinical Infectious Diseases. 2000;31(1):148-51.
4. Kiekkas P, Velissaris D, Karanikolas M, Aretha D, Samios A, Skartsani C, et al. Peak body temperature predicts mortality in critically ill patients without cerebral damage. Heart Lung. 2010;39(3):208-16.
5. Lin RJ, Lee TH, Leo YS. Dengue in the elderly: a review. Expert Rev Anti Infect Ther. 2017;15(8):729-35.
6. Abbara A, Collin SM, Kon OM, Buell K, Sullivan A, Barrett J, et al. Time to diagnosis of tuberculosis is greater in older patients: a retrospective cohort review. ERJ Open Res. 2019;5(4).
7. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging (Albany NY). 2020;12(10):9959-81.

8. Waalen J, Buxbaum JN. Is older colder or colder older? The association of age with body temperature in 18,630 individuals. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2011;66(5):487-92.
9. Lu SH, Leasure AR, Dai YT. A systematic review of body temperature variations in older people. J Clin Nurs. 2010;19(1-2):4-16.
10. Székely M, Garai J. Thermoregulation and age. Handb Clin Neurol. 2018;156:377-95.
11. Flouris AD, Piantoni C. Links between thermoregulation and aging in endotherms and ectotherms. Temperature (Austin, Tex). 2014;2(1):73-85.
12. Florez-Duquet M, Peloso E, Satinoff E. Fever and behavioral thermoregulation in young and old rats. Am J Physiol Regul Integr Comp Physiol. 2001;280(5):R1457-61.
13. Cunha LL, Perazzio SF, Azzi J, Cravedi P, Riella LV. Remodeling of the Immune Response With Aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response. Front Immunol. 2020;11:1748.
14. Liu E, Lewis K, Al-Saffar H, Krall CM, Singh A, Kulchitsky VA, et al. Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide-and Escherichia coli-induced systemic inflammation. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2012;302(12):R1372-R83.
15. Fonseca MT, Rodrigues AC, Cezar LC, Fujita A, Soriano FG, Steiner AA. Spontaneous hypothermia in human sepsis is a transient, self-limiting, and nonterminal response. Journal of applied physiology. 2016;120(12):1394-401.
16. Wrotek S, Sobocińska J, Kozłowski HM, Pawlikowska M, Jędrzejewski T, Dzialuk A. New insights into the role of glutathione in the mechanism of fever. International Journal of Molecular Sciences2020.
17. Blatteis CM. Fever: pathological or physiological, injurious or beneficial? Journal of thermal biology. 2003;28(1):1-13.
18. Belon L, Skidmore P, Mehra R, Walter E. Effect of a fever in viral infections—the 'Goldilocks' phenomenon? World Journal of Clinical Cases. 2021;9(2):296.
19. Druml W. [Fever in the critically ill : To treat or not to treat]. Med Klin Intensivmed Notfmed. 2019;114(2):173-84.
20. Donoso A, Arriagada D. Fever and antipyretic therapy in the septic patient in the intensive care unit: An update. Boletin Medico del Hospital Infantil de Mexico2018. p. 171-83.
21. Gul MH, Htun ZM, Inayat A. Role of fever and ambient temperature in COVID-19. Expert Rev Respir Med. 2021;15(2):171-3.
22. Dorks M, Allers K, Hoffmann F. Pro Re Nata Drug Use in Nursing Home Residents: A Systematic Review. J Am Med Dir Assoc. 2019;20(3):287-93 e7.
23. Hew YH, Blebil AQ, Dujaili JA, Khan TM. Assessment of knowledge and practices of parents regarding childhood fever management in Kuala Lumpur, Malaysia. Drugs & Therapy Perspectives. 2018;35(1):29-35.
24. Clericetti CM, Milani GP, Bianchetti MG, Simonetti GD, Fossali EF, Balestra AM, et al. Systematic review finds that fever phobia is a worldwide issue among caregivers and healthcare providers. Acta Paediatrica, International Journal of Paediatrics2019. p. 1393-7.
25. Hiller MG, Caffery MS, Bégué RE. A Survey About Fever Knowledge, Attitudes, and Practices Among Parents. Clinical pediatrics. 2019;58(6):677-80.
26. Castellano VE, Talamona N, Giglio ND, Sabbaj L, Gentile Á. Knowledge and management of fever in parents of children under 5 years of age at a children's hospital. Arch Argent Pediatr. 2020;118(2):89-94.
27. Chong CP, Tan SF, Chooi WT. An Evaluation on Consumers' Usage Pattern of Acetaminophen (Paracetamol): A Multicenter Study from Penang, Malaysia. Archives of Pharmacy Practice. 2017;8(1).
28. Dawood OT, Hassali MA, Saleem F, Ibrahim IR, Abdulameer AH, Jasim HH. Assessment of health seeking behaviour and self-medication among general public in the state of Penang, Malaysia. Pharm Pract (Granada). 2017;15(3):991.
29. Vithoulkas G, Carlino S. The "continuum" of a unified theory of diseases. Med Sci Monit. 2010;16(2):15.
30. Rajakariar R, Yaqoob MM, Gilroy DW. COX-2 in inflammation and resolution. Molecular interventions. 2006;6(4):199.
31. Panigrahy D, Gilligan MM, Huang S, Gartung A, Cortés-Puch I, Sime PJ, et al. Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? Cancer Metastasis Rev. 2020;39(2):337-40.
32. Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2017;31(4):1273-88.
33. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol. 2005;6(12):1191-7.
34. Chan MM-Y, Moore AR. Resolution of inflammation in murine autoimmune arthritis is disrupted by cyclooxygenase-2 inhibition and restored by prostaglandin E2-mediated lipoxin A4 production. The Journal of Immunology. 2010;184(11):6418-26.
35. Mahesh S, Mallappa M, Habchi O, Konstanta V, Chise C, Sykiotou P, et al. Appearance of Acute Inflammatory State Indicates Improvement in Atopic Dermatitis Cases Under Classical Homeopathic Treatment: A Case Series. Clinical Medicine Insights: Case Reports. 2021;14:1179547621994103.
36. Long-term health effects of antipyretic drug use in the ageing population [Internet]. National Institute of Health Research. 2019.
37. Mahesh S, van der Werf E, Mallappa M, Vithoulkas G, Lai N. Long-term health effects of antipyretic drug use in the ageing population: protocol for a systematic review [version 1; peer review: awaiting peer review]. F1000Research. 2020;9(1288).
38. Cochrane Effective Practice and Organisation of Care (EPOC). Data collection form, Intervention review – Randomised trials and non-randomised trials. Cochrane Collaboration, EPOC resources for review authors; 2017.
39. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
40. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1. 0 [updated March 2011]. 2011. The Cochrane Collaboration. 2011.

41. The Joanna Briggs Institute. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews. Checklist for Case Series 2017. Available from: https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Case_Series2017_0.pdf.
42. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, et al. Methodological quality of case series studies: An introduction to the JBI critical appraisal tool. JBI evidence synthesis. 2020;18(10):2127-33.
43. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. BMJ Evidence-Based Medicine. 2017;22(3):85-7.
44. Ryan R. 'Cochrane Consumers and Communication Review Group: data synthesis and analysis. Cochrane Consumers and Communication Review Group. 2013.
45. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version. 2006;1:b92.
46. Clarivate analytics. Endnote X9.3.3. 2020. p. reference management software.
47. Cunietti E, Monti M, Vigano A, D'Aprile E, Saligari A, Scafuro E, et al. A comparison of nimesulide vs paracetamol in the treatment of pyrexia in the elderly. Drugs. 1993;46 Suppl 1:124-6.
48. Reiner M, Cereghetti S, Haeusermann M, Monti T. Antipyretic activity of nimesulide suppositories: double blind versus diclofenac and placebo. Int J Clin Pharmacol Ther Toxicol. 1985;23(12):673-7.
49. Krajčová A, Matoušek V, Duška F. Mechanism of paracetamol-induced hypotension in critically ill patients: A prospective observational cross-over study. Australian Critical Care. 2013;26(3):136-41.
50. Poblete B, Romand JA, Pichard C, König P, Suter PM. Metabolic effects of i.v. propacetamol, metamizol or external cooling in critically ill febrile sedated patients. British Journal of Anaesthesia. 1997;78(2):123-7.
51. Cantais A, Schnell D, Vincent F, Hammouda Z, Perinel S, Balichard S, et al. Acetaminophen-Induced Changes in Systemic Blood Pressure in Critically Ill Patients: Results of a Multicenter Cohort Study. Crit Care Med. 2016;44(12):2192-8.
52. Hersch M, Raveh D, Izbicki G. Effect of intravenous propacetamol on blood pressure in febrile critically ill patients. Pharmacotherapy. 2008;28(10):1205-10.
53. Lee BH, Inui D, Suh GY, Kim JY, Kwon JY, Park J, et al. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. Crit Care. 2012;16(1):R33.
54. Ye S, Xu D, Zhang C, Li M, Zhang Y. Effect of Antipyretic Therapy on Mortality in Critically Ill Patients with Sepsis Receiving Mechanical Ventilation Treatment. Can Respir J. 2017;2017:3087505.
55. Zhang Z, Chen L, Ni H. Antipyretic therapy in critically ill patients with sepsis: an interaction with body temperature. PLoS One. 2015;10(3):e0121919.
56. Ban G-Y, Ahn S-J, Yoo H-S, Park H-S, Ye Y-M. Stevens–johnson syndrome and toxic epidermal necrolysis associated with acetaminophen use during viral infections. Immune Network. 2016;16(4):256-60.
57. Akashi S, Tominaga M, Naitou K, Fujisawa N, Nakahara Y, Hiura K, et al. [Two cases of acetaminophen-induced pneumonitis]. Nihon Kyobu Shikkan Gakkai Zasshi. 1997;35(9):974-9.
58. Ayonrinde OT, Saker BM. Anaphylactoid reactions to paracetamol. Postgrad Med J. 2000;76(898):501-2.
59. Gonzalo-Garijo MA, Bobadilla P. Ibuprofen-induced fever in Sjogren's syndrome. J Investig Allergol Clin Immunol. 2006;16(4):266-7.
60. Prabhu MM, Prabhu S, Mishra P, Palaian S. Cellulitis-like fixed drug eruption attributed to paracetamol (acetaminophen). Dermatol Online J. 2005;11(3):24.
61. Danguy des Deserts M, Nguyen BV, Giacardi C, Commandeur D, Paleiron N. [Acetaminophen-induced hypotension after intravenous and oral administration]. Ann Fr Anesth Reanim. 2010;29(4):313-4.
62. Kim E-J, Lim H, Park SY, Kim S, Yoon S-Y, Bae Y-J, et al. Rapid onset of Stevens-Johnson syndrome and toxic epidermal necrolysis after ingestion of acetaminophen. Asia Pac Allergy. 2014;4(1):68-72.
63. Kondo K, Inoue Y, Hamada H, Yokoyama A, Kohno N, Hiwada K. Acetaminophen-induced Eosinophilic Pneumonia. Chest. 1993;104(1):291-2.
64. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009;6(7):e1000097.
65. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020;368:l6890.
66. Wrotek S, LeGrand EK, Dzialuk A, Alcock J. Let fever do its job: the meaning of fever in the pandemic era. Evolution, Medicine, and Public Health. 2020.
67. Zhang Z. Antipyretic therapy in critically ill patients with established sepsis: a trial sequential analysis. PLoS One. 2015;10(2):e0117279.
68. Young PJ, Bellomo R, Bernard GR, Niven DJ, Schortgen F, Saxena M, et al. Fever control in critically ill adults. An individual patient data meta-analysis of randomised controlled trials. Intensive Care Medicine: Springer Berlin Heidelberg; 2019. p. 468-76.
69. Young PJ, Prescott HC. When less is more in the active management of elevated body temperature of ICU patients. Intensive Care Medicine: Springer Berlin Heidelberg; 2019. p. 1275-8.
70. Hammond NE, Boyle M. Pharmacological versus non-pharmacological antipyretic treatments in febrile critically ill adult patients: a systematic review and meta-analysis. Aust Crit Care. 2011;24(1):4-17.
71. Jefferies S, Weatherall M, Young P, Eyers S, Perrin KG, Beasley CR. The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis. Crit Care Resusc. 2011;13(2):125-31.

72. Serpa Neto A, Pereira VG, Colombo G, Scarin FC, Pessoa CM, Rocha LL. Should we treat fever in critically ill patients? A summary of the current evidence from three randomized controlled trials. Einstein (Sao Paulo). 2014;12(4):518-23.
73. Drewry AM, Ablordeppey EA, Murray ET, Stoll CRT, Izadi SR, Dalton CM, et al. Antipyretic therapy in critically ill septic patients: A systematic review and meta-Analysis. Critical Care Medicine2017. p. 806-13.
74. Nabors C, Sridhar A, Hooda U, Lobo SA, Levine A, Frishman WH, et al. Characteristics and Outcomes of Patients 80 Years and Older Hospitalized With Coronavirus Disease 2019 (COVID-19). Cardiol Rev. 2021;29(1):39-42.
75. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
76. Mahesh S, van der Werf E, Mallappa M, Vithoulkas G, Lai NM. data_SR_antipyretics_elderly2021.

Supplementary Materials

Supplementary Materials are not available with this version.

Figures

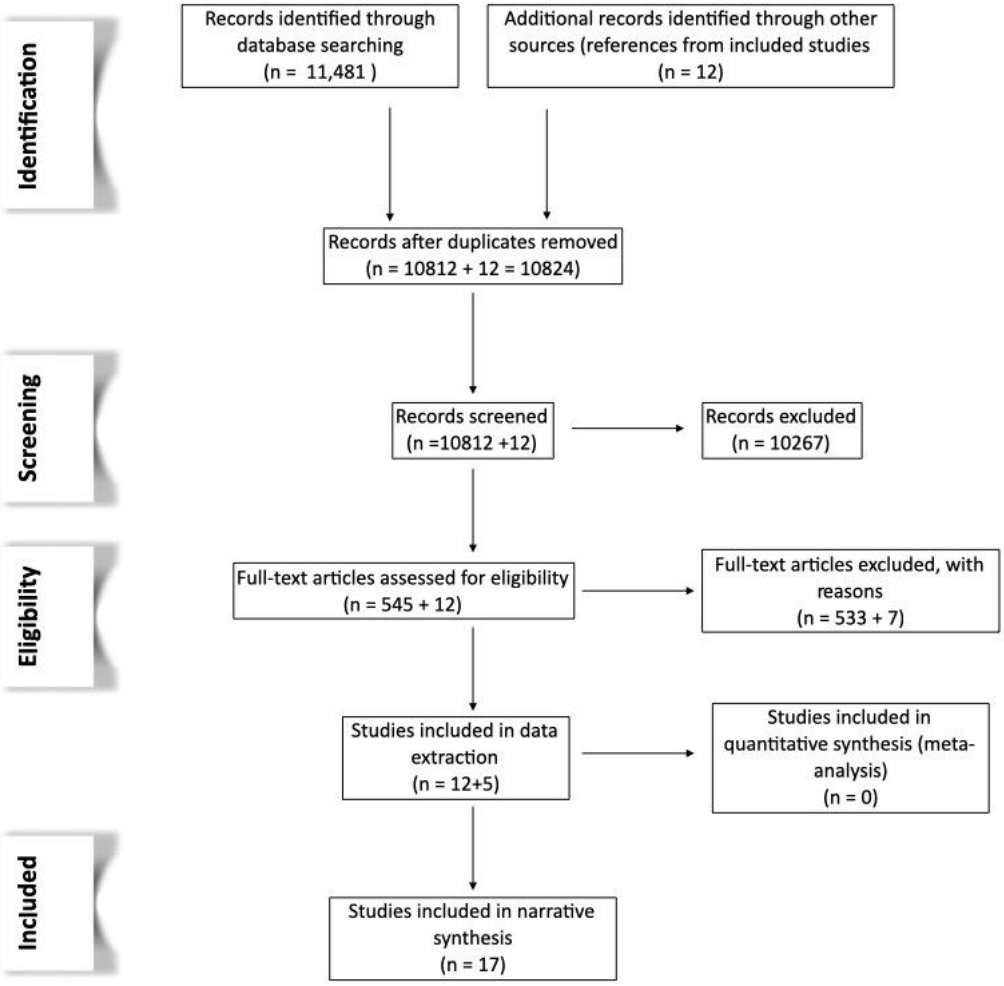

Figure 1

PRISMA chart depicting the inclusion-exclusion process of the review

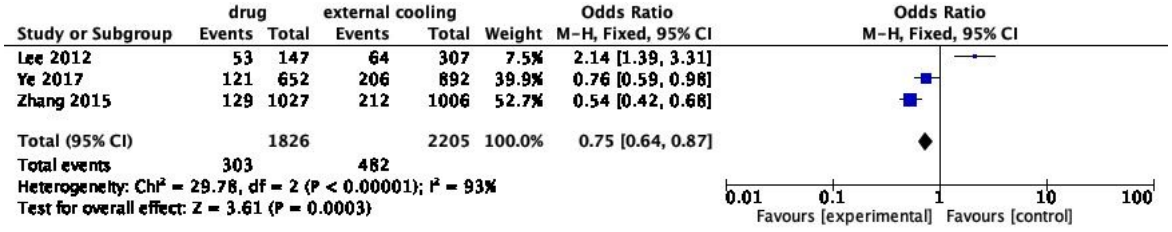

Figure 2

Forest plot showing mortality odds ratio of antipyretic drugs against external cooling in sepsis patients.

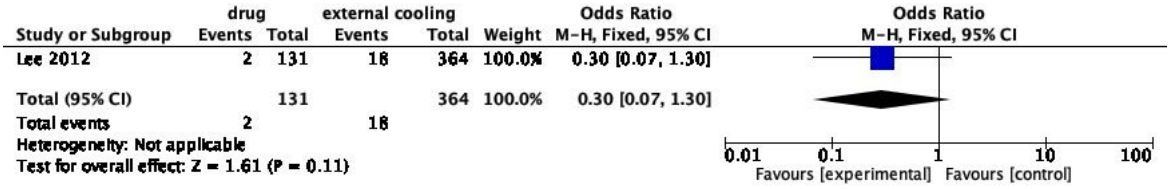

Figure 3

Forest plot showing mortality odds ratio of antipyretic drugs against external cooling in non-sepsis patients.

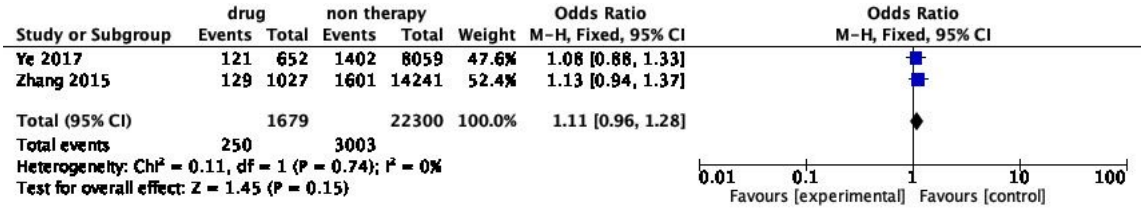

Figure 4

Forest plot showing mortality odds ratio of antipyretic drugs against non-therapy in sepsis patients.

Supplementary Files

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