Therapeutic Hypothermia and the Risk of Infection: A Systematic Review and Meta-Analysis*

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Objective: Observational studies suggest that infections are a common complication of therapeutic hypothermia. We performed a systematic review and meta-analysis of randomized trials to examine the risk of infections in patients treated with hypothermia.

Data Sources: PubMed, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched for eligible studies up to October 1, 2012.

Study Selection: We included randomized controlled clinical trials of therapeutic hypothermia induced in adults for any indication, which reported the prevalence of infection in each treatment group.

Data Extraction: For each study, we collected information about the baseline characteristics of patients, cooling strategy, and infections.

Data Synthesis: Twenty-three studies were identified, which included 2,820 patients, of whom 1,398 (49.6%) were randomized to hypothermia. Data from another 31 randomized trials, involving 4,004 patients, could not be included because the occurrence of infection was not reported with sufficient detail or not at all. The risk of bias in the included studies was high because information on the method of randomization and definitions of infections lacked in most cases, and assessment of infections was not blinded. In patients treated with hypothermia, the prevalence of all infections was not increased (rate ratio, 1.21 [95% CI, 0.95–1.54]), but there was an increased risk of pneumonia and sepsis (risk ratios, 1.44 [95% CI, 1.10–1.90]; 1.80 [95% CI, 1.04–3.10], respectively).

Conclusion: The available evidence, subject to its limitations, strongly suggests an association between therapeutic hypothermia and the risk of pneumonia and sepsis, whereas no increase in the overall risk of infection was observed. All future randomized trials of hypothermia should report on this important complication. (*Crit Care Med* 2014; 42:231–242)

Key Words: hypothermia; infection; respiratory tract infections; sepsis; temperature; urinary tract infections

Therapeutic hypothermia, the intentional reduction of body temperature, is increasingly used as a treatment for acute brain injury. In randomized trials, hypothermia reduced mortality and improved neurological outcomes in adults with hypoxic-ischemic brain damage after cardiac arrest (1), in newborns with hypoxic ischemic encephalopathy (2), but not in patients with traumatic brain injury (3, 4) or during surgery for intracranial aneurysms (5). Furthermore, hypothermia is a promising treatment for ischemic stroke (6, 7). One large phase III trial of cooling for ischemic stroke is in progress (unique identifier: NCT01123161) and another will start shortly (unique identifier: NCT01833312).

Infections are frequent complications in patients hospitalized for cardiac arrest, traumatic brain injury, or stroke and have been associated with poor outcomes (8–10). Recent observational studies suggest that cooling increases the risk of infection after cardiac arrest (11). In contrast, randomized trials have reported no evidence that therapeutic hypothermia in adults is associated with an increased infection rate (1, 2, 12–14). However, these trials, and meta-analyses of trials limited to a single indication for hypothermia, may be too small to detect a relation between hypothermia and infection. This is important because if infections do occur more often in patients

*See also p. 445.

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treated with hypothermia and if this is associated with a poorer outcome, then the therapeutic benefits of hypothermia might be increased through the use of prophylactic antibiotics.

We therefore performed a systematic review and meta-analysis of all randomized trials of therapeutic hypothermia, irrespective of indication, to assess whether cooling is associated with an increased risk of infections.

MATERIAL AND METHODS

Literature Search

Randomized controlled trials of therapeutic hypothermia were identified from PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to October 1, 2012, with the search terms ("cooling" or "hypothermia" and "randomised" or "randomized" or "randomly"). We searched reference lists of the identified relevant studies for additional citations and compared the results of our search with those of published Cochrane reviews.

Eligibility Criteria

We included all randomized and pseudorandomized clinical trials of therapeutic hypothermia versus control in adult patients. Studies with hypothermia as part of a procedure (e.g., clipping of an intracranial aneurysm) were included, as were studies in which the control group was actively managed to normothermia. We excluded studies with no full text available; in languages other than English, Dutch, or German; using temperature modulation with antipyretics as the active treatment; involving local cooling without lowering of total body temperature; and which did not report the number of infections or the number of patients with an infection. Infections could be reported as "infection" in general or more specifically as pneumonia, urinary tract infection, sepsis, or any other specific infection.

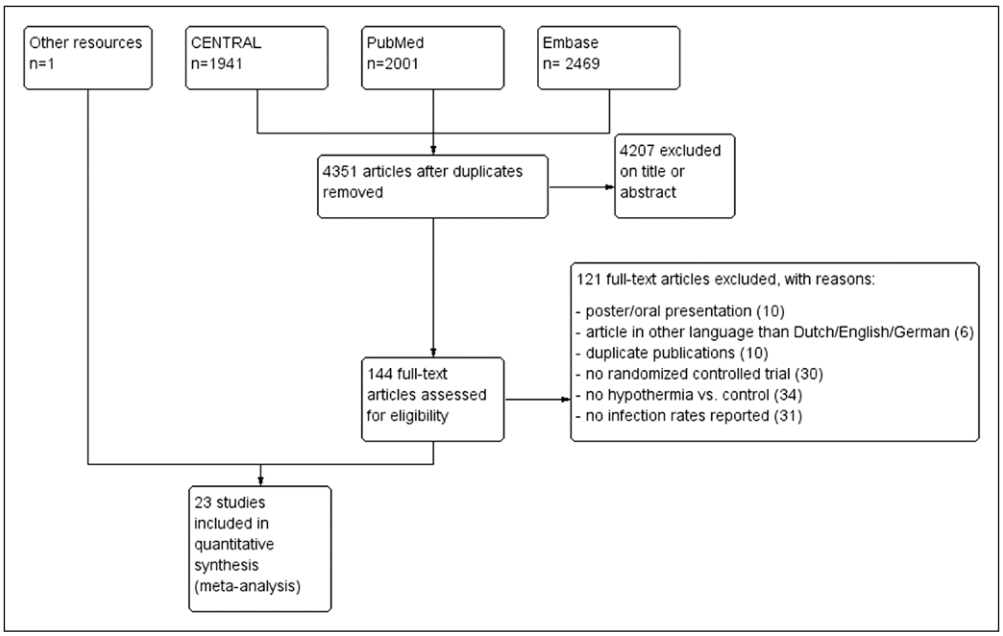

Figure 1. Progression from the literature search to the meta-analysis showing the number of exclusions for the initial literature search.

Outcome Definition

The primary outcome measure of this meta-analysis is "any infection." Pancreatitis was not considered an infection, because the etiology of pancreatitis is not necessarily infectious. The occurrence of fever alone, without other evidence of an infection, was not considered an infection. Secondary outcomes of this meta-analysis are the occurrence of pneumonia, urinary tract infection, or sepsis.

Study Selection and Data Extraction

Two reviewers (M.G., P.H.C.K.) independently applied the eligibility criteria to all titles and abstracts, and if necessary full-text articles, extracted the data using a standardized form, and resolved discrepancies by discussion. For each study, we collected information about the baseline characteristics of patients (type of injury), cooling strategy (whether hypothermia was used as procedural treatment, mode and duration of hypothermia, target temperature, whether the patient was mechanically ventilated, and time until start of treatment), and infections (prevalence, definition as reported in the original article).

Assessment of Risk of Bias

The risk of bias was estimated independently by two reviewers (M.G., P.H.C.K.) using the Cochrane Risk of Bias Methods (15). Publication bias was assessed by constructing a funnel plot based on the primary outcome and with Egger's regression test (16).

Data Analysis

We used RevMan 5.1 (Copenhagen: The Nordic Cochrane Collaboration, 2011) for data analysis. We calculated rate ratios (the ratio of the prevalence rate of infections in the hypothermia groups to that in the control groups) and 95% CIs for the primary outcome, unadjusted for baseline variables, with a random effects model. We calculated rate ratios rather than risk ratios because most articles just reported the total number of infections and did not mention whether some patients had more than a single infection (**Table 1**). We therefore interpreted the data as count data, with number of infections as numerators and patient years (defined as the total duration of follow-up for all patients combined, unless it was stated that the occurrence of infections was assessed during a different measurable time period) (Table 1) as denominators. Forest plots are based on total number of infectious

events. For the secondary outcomes (pneumonia, urinary tract infection, or sepsis), we considered it most likely that the majority of patients had only a single infectious event. We therefore calculated risk ratios (the ratio of the risk of infections in the hypothermia groups to that in the control groups) and 95% CIs for the secondary outcomes with a random effects model. We assessed statistical heterogeneity with the *I*-squared (I^2) index both in overall analyses and in subgroup analyses (17).

Subgroup Analysis

We analyzed the risk of infections in subgroups of studies, based on the type of injury, duration of cooling, whether hypothermia was applied as part of a procedure, the mode of hypothermia, and the use of mechanical ventilation. These subgroup analyses were prespecified in the protocol. A prespecified subgroup analysis based on the target temperature could not be performed because most studies used a range of target temperatures instead of a single one. We therefore performed a post hoc analysis based on the temperature achieved. Because some studies have suggested that even active management to normothermia increases the risk of infection, a post hoc subgroup analysis exploring the impact of prophylactic normothermia in the control group was undertaken after the results had been compiled. Subgroup differences were analyzed with the I^2 index.

RESULTS

We identified 4,351 unique articles of which 144 were read in full. One additional article was identified from a published Cochrane meta-analysis. Twenty-three articles were included

TABLE 1. Overview of Characteristics of Patients, Cooling Strategy, and Infections in Included Studies

Reference	*n* (Cooled Patients)	No. of Infectious Events (Cooled Patients)	No. of Infectious Events (Controls)	No. of Events vs. No. of Patients With Events	Duration of Follow-Up for Infections	Total Duration of Follow-Up (Mo)
Clifton et al (21)	46 (24)	18	11	Unclear	During hospitalization	3
Shiozaki et al (35)	22 (9)	9	14	Events	Unclear	6
Hindman et al (36)	109 (53)	1	3	Patients	During hospitalization	3
Grimm et al (37)	144 (72)	2	1	Patients	Unclear	4
Shiozaki et al (38)	16 (8)	11	5	Events	Unclear	6
Jiang et al (39)	87 (43)	32	39	Events	14 d	12
Shiozaki et al (22)	83 (43)	33	12	Events	14 d	3
Hypothermia after Cardiac Arrest Study Group (40)	273 (135)	67	49	Unclear	7 d	6
Hashiguchi et al (23)	17 (9)	11	2	Events	1 wk	6
Nathan et al (41)	144 (71)	1	2	Patients	1 mo	1
De Georgia et al (42)	39 (18)	4	5	Events	1 mo	1
Todd et al (43)	1,001 (499)	35	34	Unclear	3 mo	3
Els et al (44)	25 (12)	0	0	Unclear	Unclear	6
Liu et al (45)	44 (21)	8	8	Patients	Unclear	24
Chouhan et al (46)	47 (24)	3	2	Patients	Death or discharge	0.5
Boodhwani et al (47)	267 (133)	4	8	Patients	Unclear	3
Qiu et al (48)	80 (40)	23	13	Patients	Unclear	12
Weber et al (49)	44 (22)	2	8	Events	7 d	3
Hemmen et al (50)	58 (28)	14	3	Patients	Unclear	3
Lee et al (51)	31 (15)	8	9	Unclear	Unclear	6
Gotberg et al (52)	18 (9)	3	0	Patients	Unclear	1
Stone et al (53)	128 (58)	1	4	Unclear	30 d	1
Clifton et al (3)	97 (52)	29	31	Events	Death or discharge	6

TABLE 2. Number of Infectious Events and Duration of Follow-Up in Included Studies

Reference	*n*	Type of Injury	Mechanical Ventilation	Mode of Cooling	Target Body Temperature (°C)	Achieved Body Temperature (°C)
Clifton et al (21)	46	TBI	Yes	Surface	33	33
Shiozaki et al (35)[a]	22	TBI	Yes	Surface	33.5–34.5	Unknown
Hindman et al (36)[a]	109	IA surgery	Yes	Surface	33.5	33.7
Grimm et al (37)	144	CPB	Yes	Unclear	32	Unknown
Shiozaki et al (38)	16	TBI	Yes	Surface	34	Unknown
Jiang et al (39)	87	TBI	Yes	Surface	33–35	Unknown
Shiozaki et al (22)[a]	83	TBI	Yes	Surface	34.5–35.5	34.0
Hypothermia after Cardiac Arrest Study Group (40)[a]	273	Cardiac arrest	Yes	Surface	32–34	33
Hashiguchi et al (23)	17	TBI	Yes	Surface	34	Unknown
Nathan et al (41)	144	CPB	Yes	Surface	34	34.1
De Georgia et al (42)[a]	39	Ischemic stroke	No	Endovascular	33	Unknown
Todd et al (43)	1,001	IA surgery	Yes	Surface	33	33.3
Els et al (44)	25	Ischemic stroke and hemicraniectomy	Yes	Endovascular	35	Unknown
Liu et al (45)[a]	44	TBI	Yes	Surface	33–35	37
Chouhan et al (46)	47	IA surgery	Yes	Surface	33–34.5	33.7
Boodhwani et al (47)	267	CPB	Yes	Surface	34	34
Qiu et al (48)	80	TBI	Yes	Surface	33–35	34.5–36
Weber et al (49)	44	Ischemic stroke	No	Surface	35	35.4
Hemmen et al (50)[a]	58	Ischemic stroke	No	Endovascular	33	33.4
Lee et al (51)[a]	31	TBI	Yes	Surface	33–35	Unknown
Gotberg et al (52)[a]	18	Percutaneous coronary intervention	No	Endovascular	< 35	34.7
Stone et al (53)	128	Contrast nephropathy	No	Endovascular	33–34	33.6
Clifton et al (3)	97	TBI	Yes	Surface	33	33

n = total number of patients assessed for infections, TBI = traumatic brain injury, IA = intracranial aneurysm, NA = not applicable, CPB = cardiopulmonary bypass, UTI = urinary tract infection.

[a]Not all included patients could be assessed for infections.

Duration of Cooling	Time Until Start of Hypothermia	Types of Infection Reported	Definition of Infection
48 hr	< 6 hr	Pneumonia, sepsis	Unclear
24–48 hr	Unclear	Pneumonia, CNS infection	Unclear
Procedural: duration unclear	NA	Pneumonia	Unclear
Procedural: duration unclear	NA	Wound infection	Unclear
48 hr	Unclear	Pneumonia, meningitis	Unclear
3–14 d	Mean, 15 hr	Pneumonia, UTI	Unclear
48 hr	Unclear	Pneumonia, meningitis	Unclear
24 hr	Median, 105 min	Pneumonia, sepsis	Unclear
48 hr	Unclear	Pneumonia, meningitis	Pneumonia: at least three of the following criteria: new infiltrates on chest radiograph, purulent tracheobronchial secretions, positive pathogenic bacterial culture from tracheobronchial secretions, and impaired pulmonary gas exchange; meningitis: WBC counts in cerebrospinal fluid > 100 cells/L
Procedural: duration unclear	NA	Chest and leg wound infections	Wound infection: documented by using established definitions
24 hr	< 12 hr	Pneumonia, UTI, sepsis	Unclear
Procedural: duration unclear	NA	Pneumonia, incision or bone-flap infection, meningitis or ventriculitis, bacteremia, UTI	Unclear
48 hr	NA	Sepsis	Sepsis criteria of the American College of Chest Physicians
3 d	Mean, 8.6 hr	Pneumonia	Unclear
Procedural: duration unclear	NA	Meningitis	Unclear
Procedural: duration unclear	NA	Wound infection	Unclear
72 hr	NA	Pneumonia	Unclear
9 hr	< 6 hr	Pneumonia, UTI	Unclear
24 hr	< 6 hr	Pneumonia	Unclear
Procedural: duration unclear	Unclear	Pulmonary infection, UTI, sepsis	Unclear
Procedural: duration 3 hr	NA	Fever and C-reactive protein ≥ 100 mg/L	Pneumonia: fever, cough, focal crepitations on auscultation
Procedural: duration 3 hr	NA	UTI, sepsis	Unclear
48 hr	Mean, 1.6 hr	Pneumonia, UTI, bloodstream infections, sinusitis, surgical site infections, ventriculitis, meningitis, asymptomatic bacteriuria, positive culture of catheter tip, fever of unknown origin, and soft-tissue infections together	Unclear

TABLE 3. Methodologic Quality Summary: Review Authors' Judgment About Each Methodologic Quality Item for Each Included Study

Reference	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Clifton et al (21)	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low risk
Shiozaki et al (35)	Unclear	Unclear	High	Unclear	Low	Low	Low
Hindman et al (36)	Low	Low	High	High	Unclear	Low	Low
Grimm et al (37)	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low
Shiozaki et al (38)	Unclear	Unclear	High	Unclear	Low	Low	Low
Jiang et al (39)	Unclear	Unclear	High	High	Low	Unclear	Low
Shiozaki et al (22)	Unclear	Unclear	Unclear	Unclear	High	Low	Low
Hypothermia after Cardiac Arrest Study Group (40)	Low	Low	High	Low	Low	Low	Low
Hashiguchi et al (23)	Unclear	Unclear	High	Unclear	Low	Low	Low
Nathan et al (41)	Low	Low	High	Unclear	Unclear	Low	Low
De Georgia et al (42)	Low	Low	High	Unclear	Low	Low	Low
Todd et al (43)	Low	Low	High	Low	Low	Low	Low
Els et al (44)	Unclear	Unclear	High	Low	Low	Low	Low
Liu et al (45)	Low	High	High	Unclear	Low	Unclear	Low
Chouhan et al (46)	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
Boodhwani et al (47)	Low	Low	High	Unclear	Low	Low	Low
Qiu et al (48)	Low	Low	High	Low	Low	Low	Low
Weber et al (49)	Low	Low	Unclear	Unclear	Unclear	Low	Low
Hemmen et al (50)	Low	Unclear	High	Unclear	Low	Unclear	Low
Lee et al (51)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Gotberg et al (52)	Low	Low	Unclear	Unclear	Low	Unclear	Low
Stone et al (53)	Unclear	Unclear	High	Unclear	High	High	Low
Clifton et al (3)	Low	Low	High	Low	Low	Low	Low

The terms "low," "unclear," and "high" refer to the risk of bias according to the Cochrane Risk of Bias Methods (15).

in this meta-analysis (**Fig. 1**). Thirty-one articles on randomized controlled trials of hypothermia, involving 4,004 patients, were excluded because they did not report the rate of infections with sufficient detail ($n = 8$) or not at all ($n = 23$). There were no significant differences in the effects of hypothermia on mortality or functional outcomes between studies included and excluded from our meta-analysis.

The 23 included studies involved 2,820 patients, of whom 1,398 (49.6%) had been randomized to hypothermia. Of these 23 studies, eight used hypothermia during a procedure only. Of the other 15 studies, 10 involved patients with traumatic brain injury, four with ischemic stroke, and one with cardiac arrest. Surface cooling was used in 17 studies, endovascular cooling in five, and one article did not specify the mode of cooling. The duration of cooling ranged from several hours for procedural hypothermia to several days for traumatic brain injury. One nonprocedural hypothermia study did not specify the duration of cooling. In 18 studies, patients were intubated and mechanically ventilated. All articles reported at least one type of infection. Sixteen articles reported on the occurrence of pneumonia, six on urinary tract infection, and six on sepsis. One article reported only on all infectious complications together, not specified per type of infection. A definition of infections was given in four articles (**Table 2**). None of the articles mentioned that the occurrence of infections was assessed blinded to treatment allocation, and the exact mode of randomization was reported in 11 articles.

An evaluation of the risk of bias is presented in **Table 3**. Given the lack of uniform and explicit definitions of infections, the open assessment of infections, and the lack of information

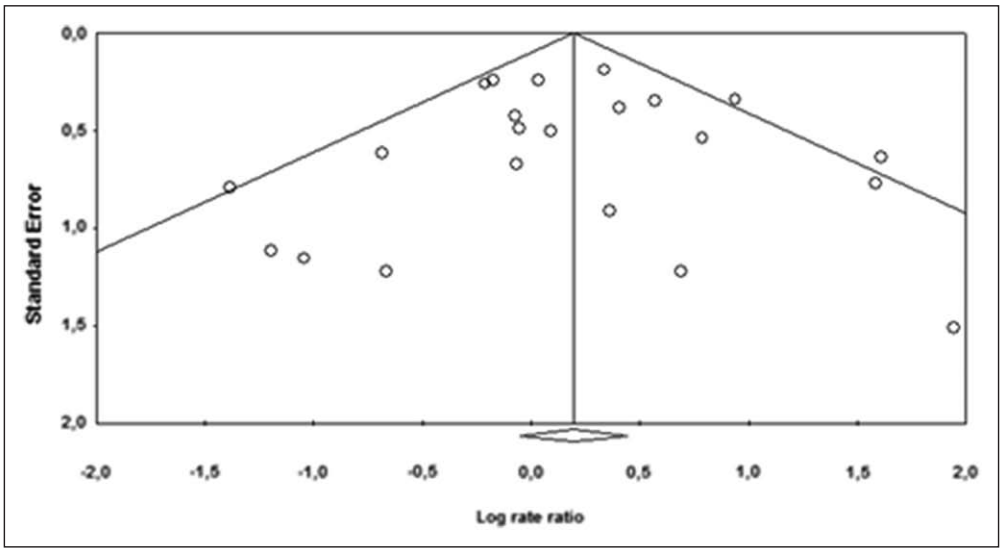

Figure 2. Funnel plot of study precision against the log rate ratio of infections. In the absence of publication bias, the pattern of points should resemble an inverted funnel.

on the methods of randomization in the large majority of studies, there was a high risk of bias. The funnel plot did not show major asymmetry, suggesting no major effect of bias on the results (**Fig. 2**). In addition, no statistically significant effect of publication bias was found with Egger's regression ($p = 0.47$).

A total of 579 infectious events were reported, of which 316 occurred in patients treated with hypothermia and 263 in controls (rate ratio, 1.21 [95% CI, 0.95–1.54]). The degree of heterogeneity (I^2) was 33% in the overall analysis (**Fig. 3**), suggesting moderate heterogeneity between studies in the prevalence of infection, perhaps reflecting the different clinical settings (17).

Pneumonia comprised 295 of 579 infections identified (51%) and occurred more frequently in patients treated with hypothermia than in controls (risk ratio, 1.44 [95% CI, 1.10–1.90]). Hypothermia was also associated with an almost two-fold increase in the risk of sepsis (risk ratio, 1.80 [95% CI, 1.04–3.10]). Urinary tract infection occurred 36 times in patients treated with hypothermia and 48 times in controls (risk ratio, 0.86 [95% CI, 0.58–1.28]) (**Fig. 4**).

In meta-analyses limited to studies of ischemic stroke or traumatic brain injury, no differences were found in the risk of infections between both groups (**Fig. 5**). In the only study of cardiac arrest providing sufficient data, the risk of infections was not significantly higher in patients treated with hypothermia than in controls (Fig. 5). A trend toward a higher overall infection rate was observed only in patients cooled for more than 12 hours (**Fig. 6**). Where hypothermia was induced as part of a procedure and only for the duration of that procedure, there was no increased prevalence of infection (rate ratio, 1.02 [95% CI, 0.69–1.50] in patients

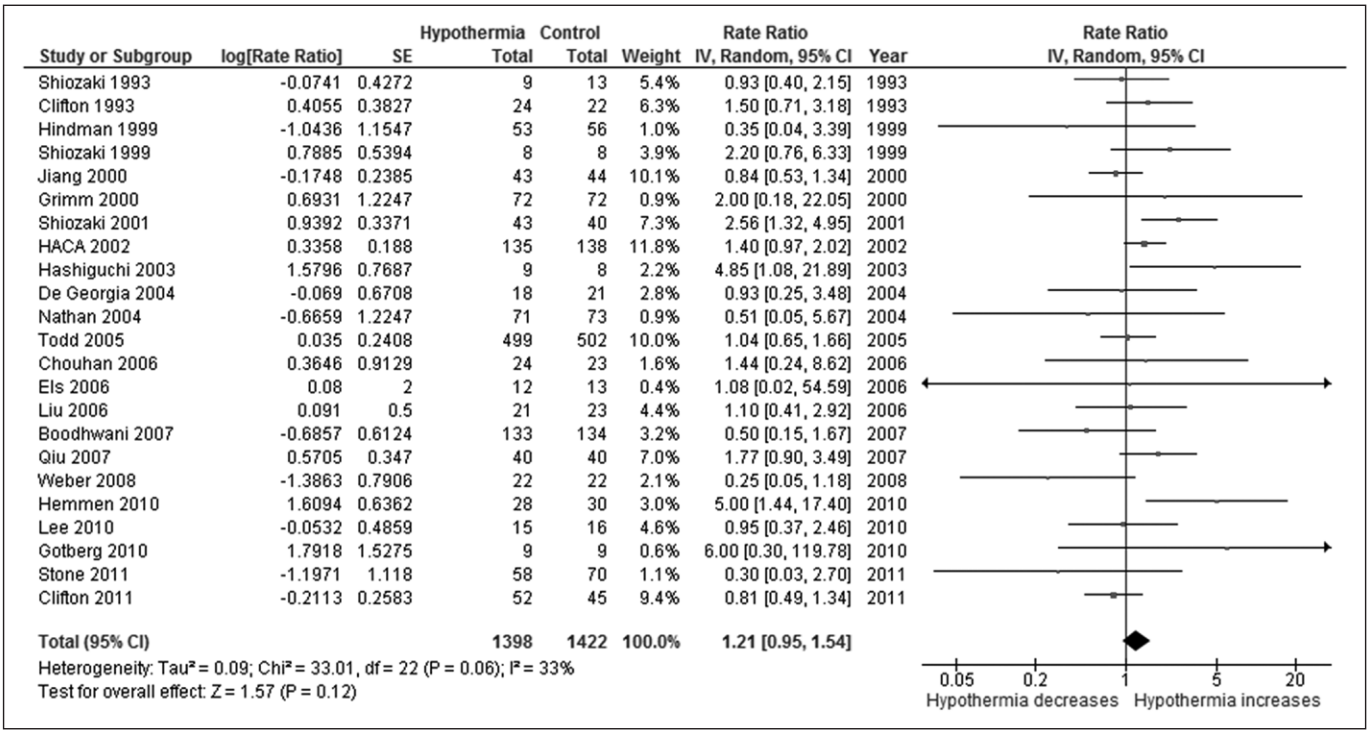

Figure 3. Effect of hypothermia on the occurrence of any infection (rate ratio). HACA = Hypothermia after Cardiac Arrest Study Group. *Closed diamonds* indicates polled result for all studies. *Squares* indicates risk or rate ratio for each study. *Horizontal lines* indicate CI.

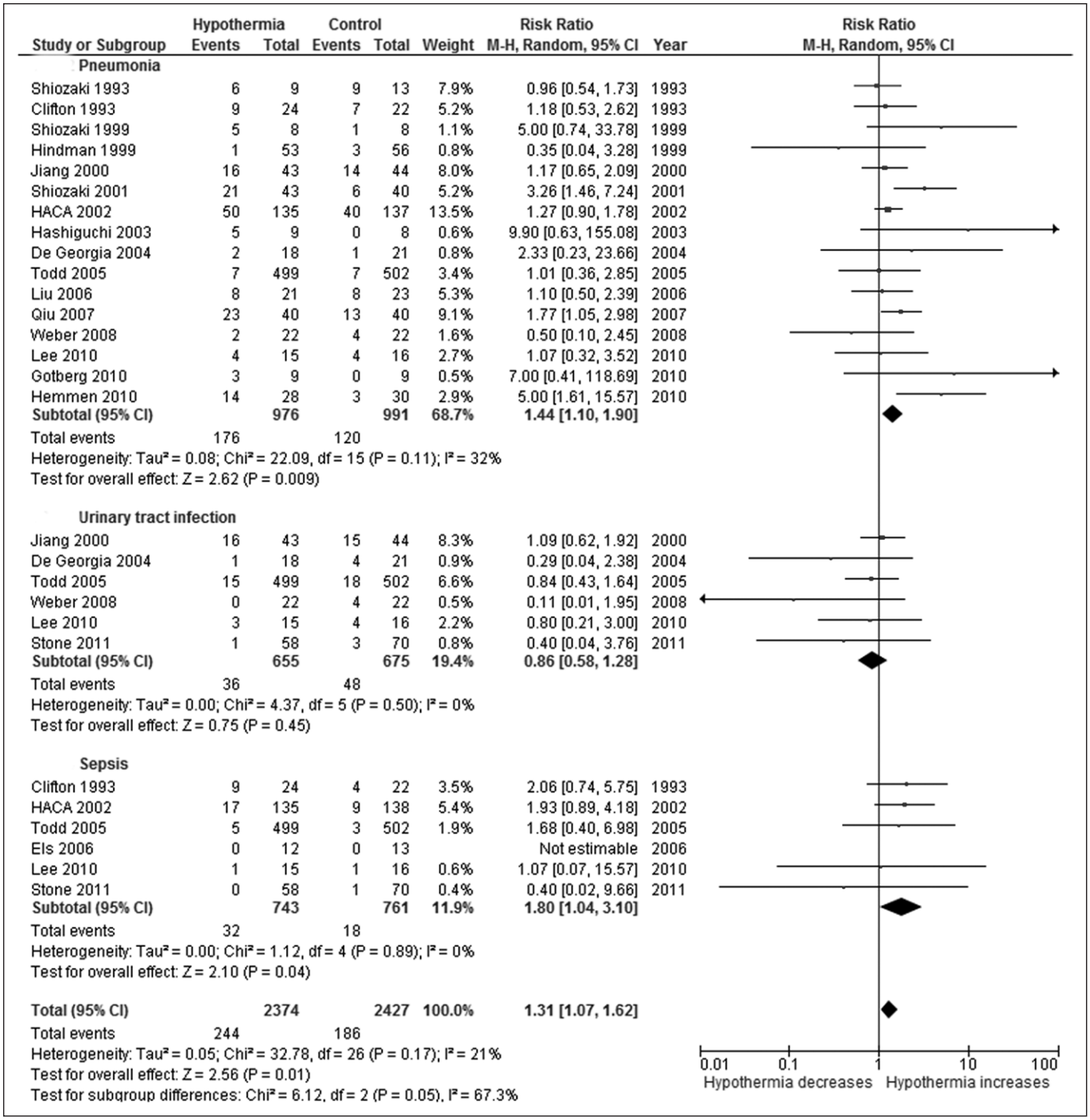

Figure 4. Effect of hypothermia on the occurrence of pneumonia, urinary tract infection, and sepsis (risk ratio). M-H = Mantel-Haenszel, HACA = Hypothermia after Cardiac Arrest Study Group. *Closed diamonds* indicates polled result for all studies. *Squares* indicates risk or rate ratio for each study. *Horizontal lines* indicate CI.

cooled during a procedure; rate ratio, 1.28 [95% CI, 0.94–1.75] in patients cooled for other indications) (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A724, which describes the effect of hypothermia on the occurrence of infections by context: procedural versus nonprocedural hypothermia [rate ratio]).

Both surface cooling and endovascular cooling were associated with a trend toward more infections (rate ratio, 1.17 [95% CI, 0.92–1.49]; rate ratio, 1.64 [95% CI, 0.52–5.16], respectively) (**Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A724, which describes the effect of hypothermia on the occurrence of infections by context: mode of cooling [rate ratio]). There was a statistically significant increase in the risk of pneumonia in surface-cooled patients (risk ratio, 1.32 [95% CI, 1.04–1.69]) and in patients treated with endovascular cooling (risk ratio, 4.56 [95% CI,

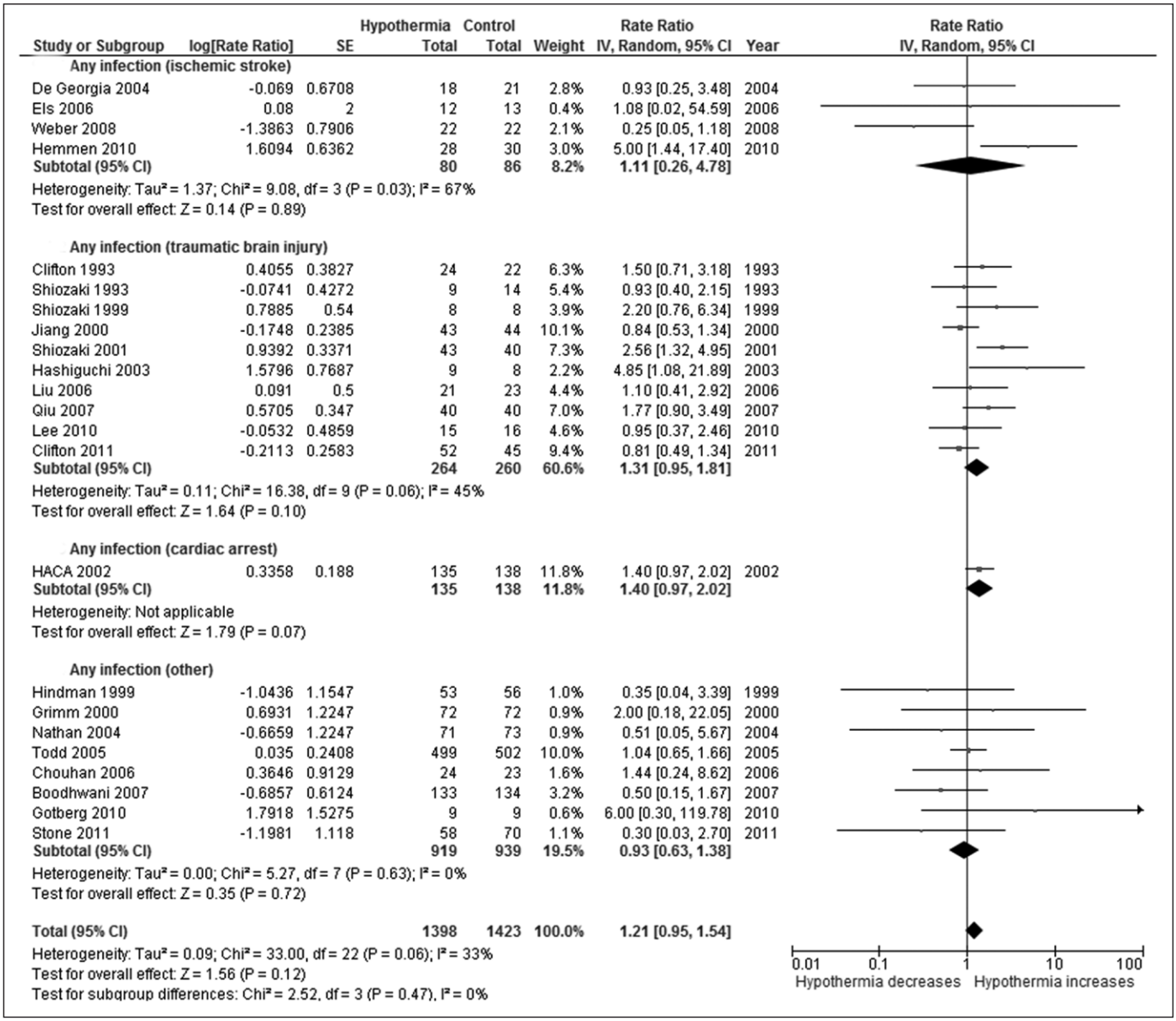

Figure 5. Effect of hypothermia on the occurrence of infections by type of disease or procedure (rate ratio). HACA = Hypothermia after Cardiac Arrest Study Group. *Closed diamonds* indicates polled result for all studies. *Squares* indicates risk or rate ratio for each study. *Horizontal lines* indicate CI.

1.75–11.90]) (**Supplemental Fig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A724, which describes the effect of hypothermia on the occurrence of pneumonia by context: endovascular versus surface cooling [rate ratio]). Mechanical ventilation did just not significantly affect the rate ratio of infections (rate ratio, 1.21 [95% CI, 0.97–1.49] in mechanically ventilated patients and rate ratio, 1.09 [95% CI, 0.30–4.03] in patients who are not mechanically ventilated) (**Supplemental Fig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A724, which describes the effect of hypothermia on the occurrence of infections by context: mechanical ventilation versus no mechanical ventilation [rate ratio]).

The achieved temperature did not significantly affect the rate ratio of infections, but nine studies had to be excluded from this analysis as the achieved temperature was not reported (**Supplemental Fig. 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/A724, which describes the effect of hypothermia on the occurrence of infections by context: achieved temperature [rate ratio]).

Excluding the three studies using prophylactic normothermia in the control group did not change the overall results (rate ratio, 1.08 [95% CI, 0.86–1.35]; forest plot not shown).

DISCUSSION

In this systematic review and meta-analysis, we found an increased risk of both pneumonia and sepsis in patients treated with hypothermia, although the prevalence of sepsis was low. No convincing evidence of an increased risk of all infections in patients treated with hypothermia compared with controls was found. Cooling limited to the duration of an invasive procedure, for example, the clipping of an intracranial aneurysm, did not increase the rate ratio of all infections.

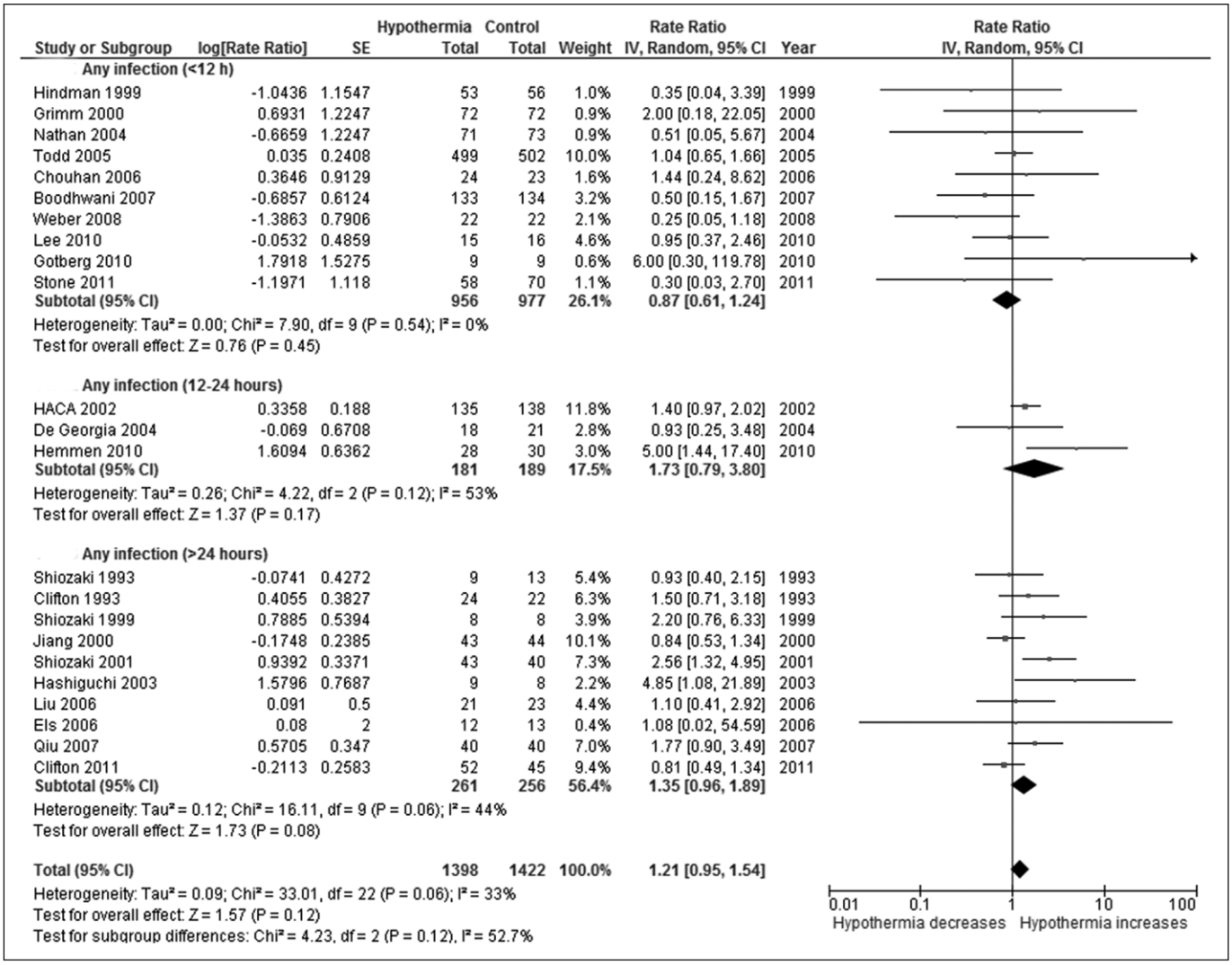

Figure 6. Effect of hypothermia on the occurrence of infections by duration of cooling (rate ratio). HACA = Hypothermia after Cardiac Arrest Study Group. *Closed diamonds* indicates polled result for all studies. *Squares* indicates risk or rate ratio for each study. *Horizontal lines* indicate CI.

An increased risk of infection in patients treated with hypothermia might be expected because hypothermia decreases the secretion of proinflammatory cytokines and also inhibits leukocyte migration and phagocytosis. Suppression of neuroinflammation is one of the presumed neuroprotective mechanisms of therapeutic hypothermia, but this may come at the cost of an increased risk of infection (18). This is supported by the observation that unintentional hypothermia during surgery has convincingly been associated with an increased risk of wound infections (19).

In a previous meta-analysis (20) of therapeutic hypothermia in traumatic brain injury, a two-fold increased risk of pneumonia in patients treated with hypothermia was reported. However, in a later Cochrane review on the same topic, this finding was not confirmed (4). One reason for this discrepancy may be underreporting of infections in randomized trials, but differences between studies in patient selection and in the definition of infections may also play a role. A recent meta-analysis on complications of hypothermia after cardiac arrest showed a trend toward an increased pneumonia rate, which was just not statistically significant, possibly because of the relatively small number of trials (8) and patients (795) included (12).

It has been suggested that a longer duration of cooling increases the risk of infection (18). In our meta-analysis, we indeed found a trend toward a higher risk of infections when cooling was maintained for more than 12 hours than for shorter periods. However, cooling durations of more than 24 hours all involved patients with traumatic brain injury, and cooling durations of 12 hours involved procedural cooling in all but one of the studies. We therefore cannot rule out that the association between the risk of infection and the duration of cooling is caused by confounding factors.

The present systematic review and meta-analysis is the first to specifically evaluate the risk of infection in a large number of patients treated with hypothermia for different indications. Because the review was limited to randomized and pseudorandomized trials, the risk of bias was reduced.

Our review draws attention to important limitations of published reports of randomized trials of hypothermia and therefore may support the design and reporting of future studies.

Subject to these limitations, the available evidence summarized in this review strongly suggests an association between therapeutic hypothermia and the risk of pneumonia and sepsis, whereas no increase in the overall risk of infection was observed.

Certain limitations of our study have to be considered. First, there was a moderate heterogeneity in effect size across the studies. We included studies of various types of injury and thus various patient populations. Furthermore, there was a large variation in the mode, duration, and depth of cooling. This should be considered when interpreting the results of the overall analysis. Therefore, we analyzed subgroups in which there was more homogeneity and analyzed our data with a random effects model rather than with a fixed effects model.

Second, we included three studies in our meta-analysis in which the patients in the control group received prophylactic normothermia. These patients were actively managed to a body temperature of less than 37.5°C (21–23). Some studies suggest that even with active normothermia, the risk of infections is increased (24, 25). Excluding these studies from our meta-analysis did however not change the results.

Third, we did not assess the effects of therapeutic hypothermia on mortality and neurological outcomes. These have already been reported in earlier systematic reviews and meta-analyses (1, 2, 4–6), and repeating these analyses would not have added to the existing literature on hypothermia.

Our results are limited by the quality and availability of the existing literature. We had to exclude 31 articles involving 4,004 patients. Eight of these 31 articles (26–33) described "no significant differences in infection rate between both groups," but because no numbers were reported, we could not add these to the meta-analysis. The other 23 articles just did not report on the occurrence of infections. According to the CONSORT statement, all adverse events occurring in a trial should be reported (34). We consider the occurrence of an infection as important, also because this has been related to increased mortality and poorer neurological outcomes (8–10). Although we can only speculate on the reasons for not reporting numbers of infections in a very substantial part of the trials, we think that the main reason is poor reporting. Theoretically, infections could not have been reported because they simply did not occur, but this appears highly unlikely in the relevant patient populations.

The definition of infection was not clear in most articles. In many cases, this is likely to have been a clinical diagnosis, based on clinical symptoms such as fever and elevated infection variables in the blood. However, it has been suggested that infection variables such as C-reactive protein and leukocytes have a limited predictive value in hypothermic patients (25). In the presence of infection, these variables can be normal or only slightly elevated in cooled patients. However, because of the short duration of hypothermia, any infection left untreated will have been detected shortly after termination of active cooling. We therefore think that there is no reason to assume underreporting of infections in patients treated with hypothermia.

The open assessment of infections may have resulted in detection bias, but even in ongoing and future trials of hypothermia, this limitation is almost unavoidable.

In the majority of articles, it was not clear whether infections occurred more than once in a single patient. For this reason, we used the rate ratio for the primary outcome of all infections combined. Because we considered it most likely that in the large majority of patients with a specific infection such as pneumonia this did not recur, we used the more common risk ratio for the analyses of the secondary outcomes.

The follow-up period varied considerably between studies, but given the fact that infections related to hypothermia are likely to occur during or early after the termination of cooling, we do not think this will have had an important effect on the results of our study.

A separate analysis based on target temperature was not possible, because most studies used a range of target temperatures instead of a single one. The analysis based on the achieved temperature was limited by the fact that the achieved temperature was not reported in all studies.

Future randomized trials of hypothermia should prospectively assess and report the occurrence of infections, also based on established definitions. Further research should focus on identifying high-risk patients and on the effect of prophylactic treatment with antibiotics.

CONCLUSIONS

Cooling increased the risk of pneumonia and sepsis, but no convincing evidence of an increased overall rate of infections was observed. Clinicians treating patients with hypothermia should be aware of this common side effect so that treatment can start early.

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