Fever Is Associated with Reduced, Hypothermia with Increased Mortality in Septic Patients: A Meta-Analysis of Clinical Trials

Zoltan Rumbus[1], Robert Matics[1], Peter Hegyi[1,2,3], Csaba Zsiboras[1], Imre Szabo[4], Anita Illes[4], Erika Petervari[1], Marta Balasko[1], Katalin Marta[1,2], Alexandra Miko[1], Andrea Parniczky[1,4], Judit Tenk[1], Ildiko Rostas[1], Margit Solymar[1], Andras Garami[1] *

1 Institute for Translational Medicine, Medical School, University of Pecs, Pecs, Hungary, 2 Department of Translational Medicine, First Department of Medicine, University of Pecs, Pecs, Hungary, 3 Momentum Gastroenterology Multidisciplinary Research Group, Hungarian Academy of Sciences - University of Szeged, Szeged, Hungary, 4 Department of Gastroenterology, First Department of Medicine, University of Pecs, Pecs, Hungary

* andras.garami@aok.pte.hu

Abstract

Background

Sepsis is usually accompanied by changes of body temperature (T_b), but whether fever and hypothermia predict mortality equally or differently is not fully clarified. We aimed to find an association between T_b and mortality in septic patients with meta-analysis of clinical trials.

Methods

We searched the PubMed, EMBASE, and Cochrane Controlled Trials Registry databases (from inception to February 2016). Human studies reporting T_b and mortality of patients with sepsis were included in the analyses. Average T_b with SEM and mortality rate of septic patient groups were extracted by two authors independently.

Results

Forty-two studies reported T_b and mortality ratios in septic patients ($n = 10,834$). Pearson correlation analysis revealed weak negative linear correlation ($R^2 = 0.2794$) between T_b and mortality. With forest plot analysis, we found a 22.2% (CI, 19.2–25.5) mortality rate in septic patients with fever ($T_b > 38.0°C$), which was higher, 31.2% (CI, 25.7–37.3), in normothermic patients, and it was the highest, 47.3% (CI, 38.9–55.7), in hypothermic patients ($T_b < 36.0°C$). Meta-regression analysis showed strong negative linear correlation between T_b and mortality rate (regression coefficient: -0.4318; $P < 0.001$). Mean T_b of the patients was higher in the lowest mortality quartile than in the highest: 38.1°C (CI, 37.9–38.4) vs 37.1°C (CI, 36.7–37.4).

Conclusions

Deep T_b shows negative correlation with the clinical outcome in sepsis. Fever predicts lower, while hypothermia higher mortality rates compared with normal T_b. Septic patients with the lowest (< 25%) chance of mortality have higher T_b than those with the highest chance (> 75%).

Introduction

Sepsis constitutes a global burden for medical care with an estimated 31 million cases per year worldwide [1]. The incidence of sepsis has remained considerable [2–4] and it is associated with high mortality rates even nowadays [3]. It also underlies the importance and actuality of the topic for clinical praxis that the definitions of sepsis and associated illnesses have been updated recently [5].

As a systemic inflammation response, sepsis is often associated with changes of deep body temperature (T_b), which can be manifested as fever or hypothermia in experimental animals [6–8], as well as in human patients [8–10]. Not surprisingly, deep T_b is regularly measured as one of the vital signs in the clinical praxis. In fact, many scoring systems (e.g., APACHE II, PIRO, SAPS II, SIRS), which help in the diagnosis or in the assessment of the progress of sepsis, include an abnormal deviation of T_b from the normal range [5, 11–14]. Usually T_bs below 36.0°C or above 38.0°C are considered equally pathological [15], which values are in accordance with the criteria of the systemic inflammatory response syndrome [5, 11]. Based mainly on experimental data from animal studies Romanovksy and colleagues [6, 8] proposed that fever and hypothermia can both develop as two distinct adaptive mechanisms in sickness syndrome. The former characteristically occurs at the onset of an infection, representing an active fight against the pathogen, while the latter is usually associated with progressed stage or severity of the disease and it aims to secure the vital systems of the host [6, 8]. The two adaptive strategies can develop sequentially (e.g., early phase fever followed by late phase hypothermia) as the severity of the disease progresses [8], but hypothermia can be also one of the earliest developing events in animal models of endotoxin shock [16], moreover, septic patients admitted to ICU develop hypothermia more frequently in the early than in the late stages of their stay [17]. Despite the different pathological background of fever and hypothermia in systemic inflammation, both the increase and the decrease of T_b are evaluated commonly as equally severe signs in the clinical praxis [15]. This can be, at least in part, due to the standpoint that fever and hypothermia both represent an adaptive (though different) biological response to infection [8]. Accordingly, beneficial effects have been shown for elevated T_b on the clinical outcome of sepsis in clinical trials [18, 19], although no association between fever and disease severity was also reported [20]. Therapeutic (i.e., induced) hypothermia has been also shown to improve the outcome of sepsis in human studies [21, 22], but in case of spontaneously occurring hypothermia usually a positive association with mortality rate was found [20, 23, 24]. The definite association of T_b and mortality rate in a large study population has remained unknown.

We hypothesized that the deviation of T_b from the normal range predicts the clinical outcome in sepsis differently, and consequently septic patients with fever have lower chances for mortality than those who develop hypothermia. We performed an extensive literature search for human studies in septic patients and collected data on their T_b and mortality rate. The data were then analyzed with multiple statistical approaches, including Pearson regression, forest

plot, and meta-regression analyses. Based on a high number of patients, we show a strong association between T_b and mortality ratio in sepsis across a wide temperature range.

Materials and Methods

Our meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols [25] (S1 Table). The analysis was based on the Participants, Intervention (prognostic factor), Comparison, Outcome (PICO) model: in septic population, we aimed to assess the predictive role of T_b deviations on the mortality ratio. No review protocol has been registered for the current meta-analysis.

Search strategy

A search of the PubMed, EMBASE, and Cochrane Controlled Trials Registry databases was performed with using the following Medical Subject Headings and search terms (from inception to February 2016): sepsis OR bacteremia OR "septic syndrome" AND ("body temperature" OR fever OR hypothermia OR normothermia OR hyperthermia) AND (mortality OR survival). We restricted our search to original human studies published in English without time period limitations. Publications reporting immunosuppressive conditions (e.g., cancer, transplantation, HIV infection) were not included in the analysis. As a specific example, in the EMBASE database, which identified the highest number of articles, the term "sepsis OR bacteremia OR "septic syndrome" AND ("body temperature" OR fever OR hypothermia OR normothermia OR hyperthermia) AND (mortality OR survival) NOT (cancer OR immunosuppressive OR aids OR hiv OR transplantation)" was entered, and then the following filters were selected: humans, English, article, article in press, conference abstract, conference paper, major clinical study, case control study, clinical trial, cohort analysis, comparative study, controlled clinical trial, controlled study, cross-sectional study, double blind procedure, medical record review, multicenter study, observational study, outcomes research, phase 3 clinical trial, prospective study, randomized controlled trial, retrospective study. The search was conducted separately by two authors (ZR, AG), who also assessed study eligibility and extracted data from the selected studies independently. Disagreements were resolved by consensus with the help of a third party (MR).

Study selection and data extraction

The titles and abstracts of the publications from the literature search were screened and the full text of potentially eligible articles was obtained. We included studies in which both the T_b values and the mortality ratios were reported for the same group(s) of patients with systemic inflammation accompanied by suspected or confirmed blood infection. From all included articles we extracted the sample size, the reported mean T_b value of the patients with its standard error (SEM), and the mortality ratio within the group during 28–30 days in most cases. To analyze the influence of fever, normothermia, and hypothermia on the mortality ratio in sepsis we separated the collected data into three study groups based on the mean T_b of the patients.

Statistical analysis

We have used event rates (mortality rates) as effect size data. Studies were grouped by T_b as low (up to 36.0°C; $n = 890$), medium (36.1 to 38.0°C; $n = 3,904$) and high (above 38.0°C; $n = 6,040$) and forest plots in the three groups were used to describe mortality. Selection of the T_b groups was based on the SIRS criteria [5, 11]. Another grouping was conducted by mortalities, these were split into quartiles and the means of T_bs were compared by investigating the

presence or absence of overlaps in the 95% confidence intervals (CI), just like in case of the grouping by T_b.

Between-study heterogeneity was tested with Q homogeneity test (P values of less than 0.05 were considered as indicators of significant heterogeneity) and with I^2 statistical test, where I^2 is the proportion of total variation attributable to between-study variability (an I^2 value of more than 50 was considered as indicating considerable heterogeneity). These two values were used to model selection purposes as well (fixed vs random). The tests revealed considerable heterogeneity in the overall study population ($Q = 809.509$; $I^2 = 89.25$) and also in all three T_b groups, in particular $Q = 270.447$; $I^2 = 85.58$ in the high, $Q = 373.357$; $I^2 = 90.63$ in the medium, and $Q = 36.843$; $I^2 = 70.14$ in the low T_b group. Consequently, we applied the random effect model in our forest plot and meta-regression analyses.

Publication bias was tested by inspecting the funnel plot. Meta-regression was performed to assess the overall effect of T_b to mortality. Except for the Pearson correlation analysis for which Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) was used, all analyses were performed with the Comprehensive Meta-Analysis software (Biostat, Inc., Englewood, MJ, USA).

Results

Study selection

The flow chart of the study selection is presented in Fig 1. Until February 29, 2016 the electronic literature search identified altogether 6,083 studies from the PubMed, EMBASE, and Cochrane databases. After enabling filters for human studies and English language, 762 articles remained, which were screened on title and abstract for inclusion criteria. In 720 studies T_b or mortality rate was not suitably reported in the septic patients, these were also excluded, as a result 42 full-text publications were found eligible for statistical analysis which included data from a total of 10,834 septic patients.

Incidence of mortality in septic patients with fever, normothermia, and hypothermia

As a rude approach, first we performed a common (Pearson) correlation analysis between T_b and mortality rate of all septic patients. A weak negative linear correlation was found ($y = -0.0909x + 3.6902$; $R^2 = 0.2794$), which suggests an association between T_b and mortality in sepsis. This method, however, did not allow us to weight the collected data according to the size of the studied populations, thus a detailed meta-analysis was needed.

First, we investigated the incidence of mortality in fever associated with sepsis. We found 29 studies [18–20, 23, 26–50], in which the authors reported fever (defined as $T_b > 38.0°C$) in sepsis. From these studies, 40 groups of septic patients could be separated and included in the analysis with the random effect model. The meta-analysis of the mortality rates in the septic patients with fever revealed an average event rate of 22.2% (95% CI, 19.2–25.5%; Z = -13.4331) (Fig 2). This percentage was significantly ($P = 0.000$) lower than the 50% chance of mortality, which could be regarded as a random outcome.

Next, we analyzed the mortality ratios of patients who developed neither fever nor hypothermia in association with sepsis, therefore this population could be regarded as normothermic ($T_b = 36.0–38.0°C$). From the 25 studies, in which normal T_b was reported in the septic patients [20, 22, 24, 28, 31, 35–37, 39–41, 43, 44, 47, 50–60], 36 subgroups of patients were separated, which were then analyzed with the random effect model. We found that the average mortality ratio was 31.2% (95% CI, 25.7–37.3%; Z = -5.7089) (Fig 3), which was higher than in

```
┌─────────────────────────────────────────────────────────────────────┐
│ Search term: sepsis OR bacteremia OR "septic syndrome" AND ("body    │
│ temperature" OR fever OR hypothermia OR normothermia OR hyperthermia) │
│ AND (mortality OR survival) NOT (cancer OR immunosuppressive OR aids  │
│ OR hiv OR transplantation)                                            │
└─────────────────────────────────────────────────────────────────────┘
```

| 2061 articles identified using PubMed database | 3755 articles identified using EMBASE database | 267 articles identified using Cochrane database |

6083 articles were filtered for Clinical Study, Observational Study, Comparative Study, Clinical Trial, Controlled Clinical Trial, Humans, Artcile/Article in press/Conference abstract or paper/Only in English

→ 5321 articles were excluded

762 articles were screened on title and abstract for inclusion criteria

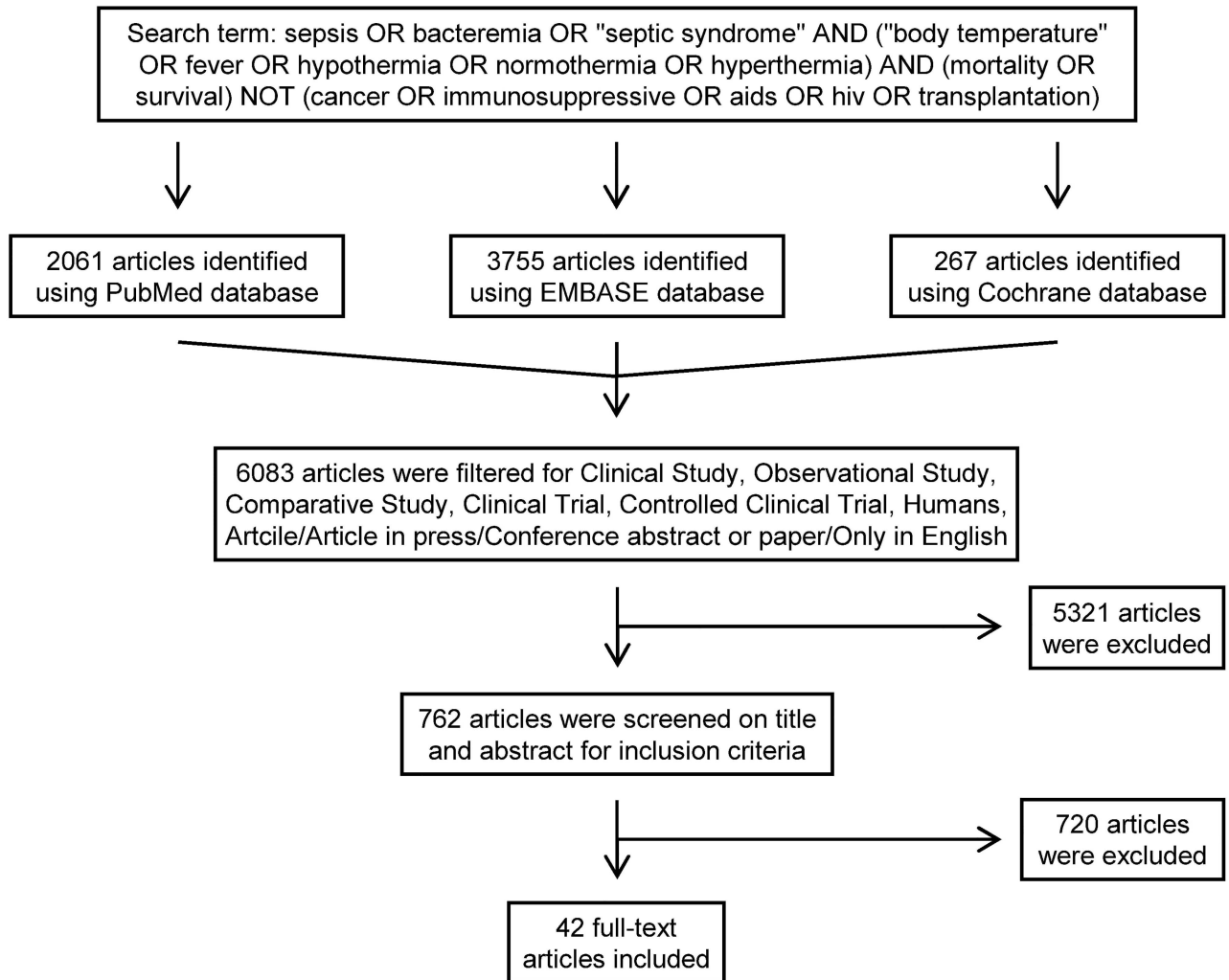→ 720 articles were excluded

42 full-text articles included

Fig 1. Flowchart of study selection and inclusion.

doi:10.1371/journal.pone.0170152.g001

the fever group. The mortality rate was significantly ($P < 0.001$) lower than 50% in this study population.

Then, we examined the incidence of mortality in hypothermic ($T_b < 36.0°C$) septic patients. We identified 11 studies [20, 22–24, 27, 29, 30, 35, 50, 54, 61], which included data on both T_b and mortality in septic patients. From these, the patients could be divided in 12 sub-groups, which served as the basis of the meta-analysis. The random effect model revealed that the average mortality rate was the highest, 47.3% (95% CI, 38.9–55.7; Z = 0.520491) in the hypothermic patients (Fig 4), which did not significantly differ from the 50% random chance ($P = 0.603$).

As a further statistical approach, we also performed a meta-regression analysis on the collected data. We found a significant ($P < 0.001$) negative linear correlation between T_b and mortality rate (regression coefficient: -0.4318; 95% CI, -0.6699 - -0.1938) based on 51 studies included in the analysis (Fig 5).

Last, we divided the patients into quartiles (Q1-Q4) of mortality ratios (Q1: 0–25, Q2: 26–50, Q3: 51–75, and Q4: 76–100%) and calculated the average T_b for each mortality quartile.
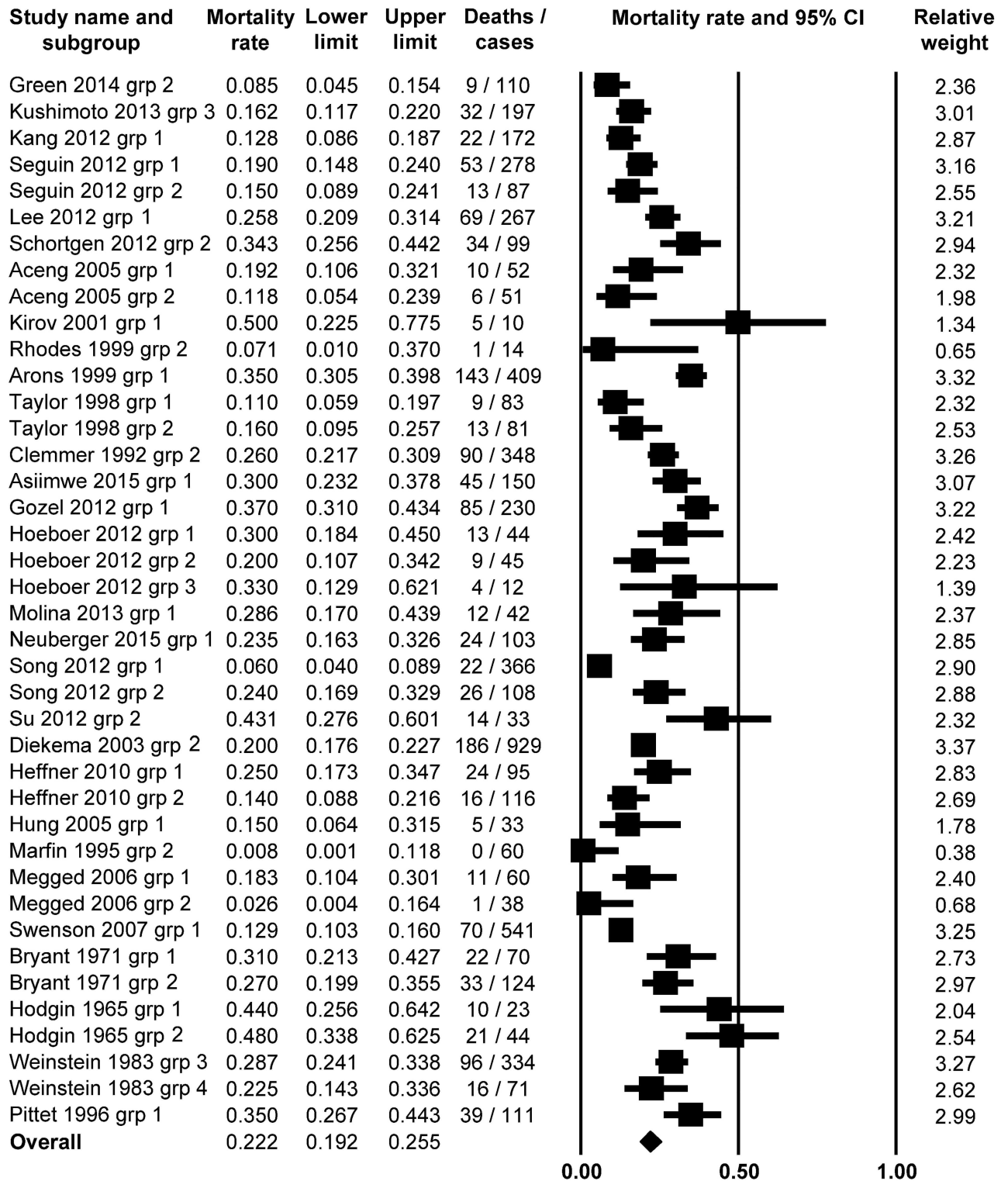
Study name and subgroup	Mortality rate	Lower limit	Upper limit	Deaths / cases	Mortality rate and 95% CI	Relative weight
Green 2014 grp 2	0.085	0.045	0.154	9 / 110		2.36
Kushimoto 2013 grp 3	0.162	0.117	0.220	32 / 197		3.01
Kang 2012 grp 1	0.128	0.086	0.187	22 / 172		2.87
Seguin 2012 grp 1	0.190	0.148	0.240	53 / 278		3.16
Seguin 2012 grp 2	0.150	0.089	0.241	13 / 87		2.55
Lee 2012 grp 1	0.258	0.209	0.314	69 / 267		3.21
Schortgen 2012 grp 2	0.343	0.256	0.442	34 / 99		2.94
Aceng 2005 grp 1	0.192	0.106	0.321	10 / 52		2.32
Aceng 2005 grp 2	0.118	0.054	0.239	6 / 51		1.98
Kirov 2001 grp 1	0.500	0.225	0.775	5 / 10		1.34
Rhodes 1999 grp 2	0.071	0.010	0.370	1 / 14		0.65
Arons 1999 grp 1	0.350	0.305	0.398	143 / 409		3.32
Taylor 1998 grp 1	0.110	0.059	0.197	9 / 83		2.32
Taylor 1998 grp 2	0.160	0.095	0.257	13 / 81		2.53
Clemmer 1992 grp 2	0.260	0.217	0.309	90 / 348		3.26
Asiimwe 2015 grp 1	0.300	0.232	0.378	45 / 150		3.07
Gozel 2012 grp 1	0.370	0.310	0.434	85 / 230		3.22
Hoeboer 2012 grp 1	0.300	0.184	0.450	13 / 44		2.42
Hoeboer 2012 grp 2	0.200	0.107	0.342	9 / 45		2.23
Hoeboer 2012 grp 3	0.330	0.129	0.621	4 / 12		1.39
Molina 2013 grp 1	0.286	0.170	0.439	12 / 42		2.37
Neuberger 2015 grp 1	0.235	0.163	0.326	24 / 103		2.85
Song 2012 grp 1	0.060	0.040	0.089	22 / 366		2.90
Song 2012 grp 2	0.240	0.169	0.329	26 / 108		2.88
Su 2012 grp 2	0.431	0.276	0.601	14 / 33		2.32
Diekema 2003 grp 2	0.200	0.176	0.227	186 / 929		3.37
Heffner 2010 grp 1	0.250	0.173	0.347	24 / 95		2.83
Heffner 2010 grp 2	0.140	0.088	0.216	16 / 116		2.69
Hung 2005 grp 1	0.150	0.064	0.315	5 / 33		1.78
Marfin 1995 grp 2	0.008	0.001	0.118	0 / 60		0.38
Megged 2006 grp 1	0.183	0.104	0.301	11 / 60		2.40
Megged 2006 grp 2	0.026	0.004	0.164	1 / 38		0.68
Swenson 2007 grp 1	0.129	0.103	0.160	70 / 541		3.25
Bryant 1971 grp 1	0.310	0.213	0.427	22 / 70		2.73
Bryant 1971 grp 2	0.270	0.199	0.355	33 / 124		2.97
Hodgin 1965 grp 1	0.440	0.256	0.642	10 / 23		2.04
Hodgin 1965 grp 2	0.480	0.338	0.625	21 / 44		2.54
Weinstein 1983 grp 3	0.287	0.241	0.338	96 / 334		3.27
Weinstein 1983 grp 4	0.225	0.143	0.336	16 / 71		2.62
Pittet 1996 grp 1	0.350	0.267	0.443	39 / 111		2.99
Overall	0.222	0.192	0.255			

0.00   0.50   1.00

Fig 2. Forest plot analysis of mortality rate using random-effects model in septic patients with fever (body temperature above 38.0°C; *n* = 6,040).
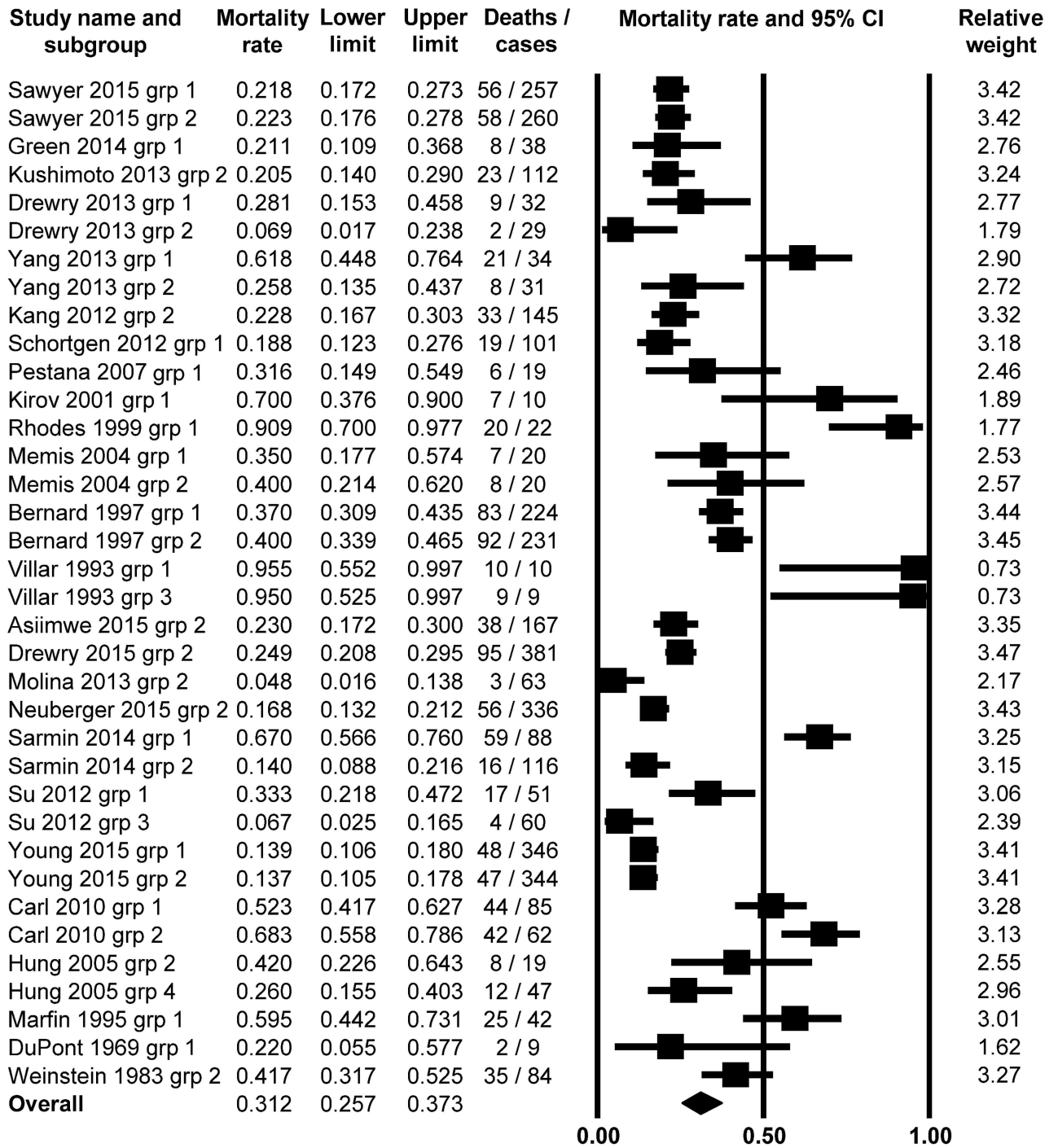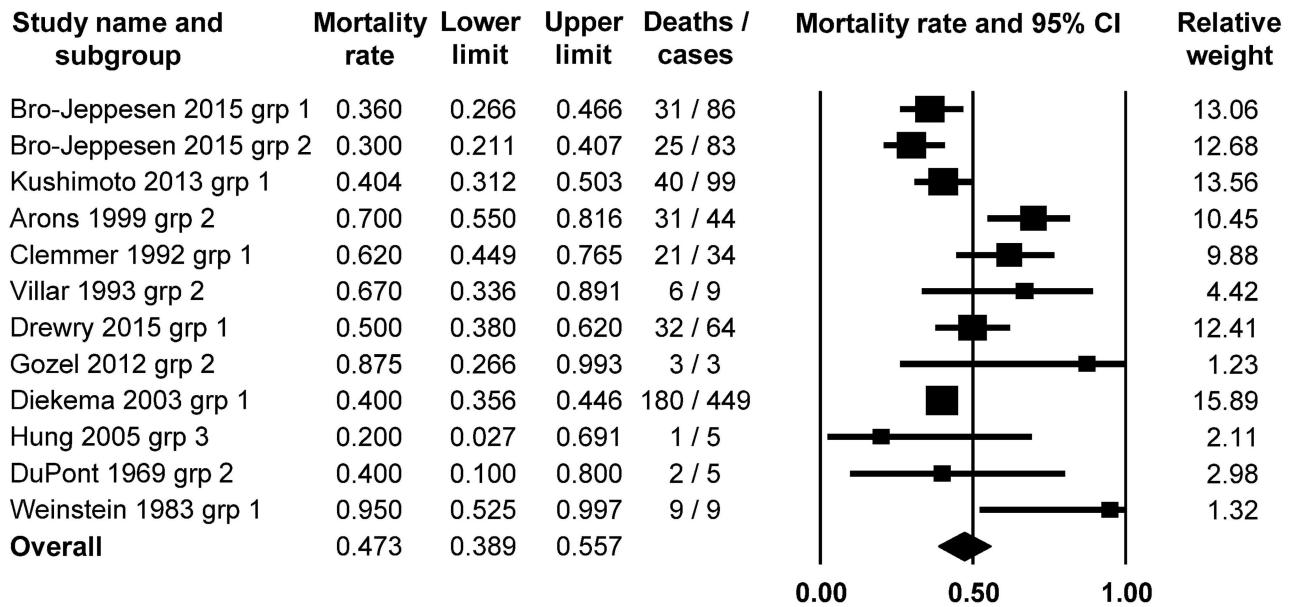
doi:10.1371/journal.pone.0170152.g002

Study name and subgroup	Mortality rate	Lower limit	Upper limit	Deaths / cases	Mortality rate and 95% CI	Relative weight
Sawyer 2015 grp 1	0.218	0.172	0.273	56 / 257		3.42
Sawyer 2015 grp 2	0.223	0.176	0.278	58 / 260		3.42
Green 2014 grp 1	0.211	0.109	0.368	8 / 38		2.76
Kushimoto 2013 grp 2	0.205	0.140	0.290	23 / 112		3.24
Drewry 2013 grp 1	0.281	0.153	0.458	9 / 32		2.77
Drewry 2013 grp 2	0.069	0.017	0.238	2 / 29		1.79
Yang 2013 grp 1	0.618	0.448	0.764	21 / 34		2.90
Yang 2013 grp 2	0.258	0.135	0.437	8 / 31		2.72
Kang 2012 grp 2	0.228	0.167	0.303	33 / 145		3.32
Schortgen 2012 grp 1	0.188	0.123	0.276	19 / 101		3.18
Pestana 2007 grp 1	0.316	0.149	0.549	6 / 19		2.46
Kirov 2001 grp 1	0.700	0.376	0.900	7 / 10		1.89
Rhodes 1999 grp 1	0.909	0.700	0.977	20 / 22		1.77
Memis 2004 grp 1	0.350	0.177	0.574	7 / 20		2.53
Memis 2004 grp 2	0.400	0.214	0.620	8 / 20		2.57
Bernard 1997 grp 1	0.370	0.309	0.435	83 / 224		3.44
Bernard 1997 grp 2	0.400	0.339	0.465	92 / 231		3.45
Villar 1993 grp 1	0.955	0.552	0.997	10 / 10		0.73
Villar 1993 grp 3	0.950	0.525	0.997	9 / 9		0.73
Asiimwe 2015 grp 2	0.230	0.172	0.300	38 / 167		3.35
Drewry 2015 grp 2	0.249	0.208	0.295	95 / 381		3.47
Molina 2013 grp 2	0.048	0.016	0.138	3 / 63		2.17
Neuberger 2015 grp 2	0.168	0.132	0.212	56 / 336		3.43
Sarmin 2014 grp 1	0.670	0.566	0.760	59 / 88		3.25
Sarmin 2014 grp 2	0.140	0.088	0.216	16 / 116		3.15
Su 2012 grp 1	0.333	0.218	0.472	17 / 51		3.06
Su 2012 grp 3	0.067	0.025	0.165	4 / 60		2.39
Young 2015 grp 1	0.139	0.106	0.180	48 / 346		3.41
Young 2015 grp 2	0.137	0.105	0.178	47 / 344		3.41
Carl 2010 grp 1	0.523	0.417	0.627	44 / 85		3.28
Carl 2010 grp 2	0.683	0.558	0.786	42 / 62		3.13
Hung 2005 grp 2	0.420	0.226	0.643	8 / 19		2.55
Hung 2005 grp 4	0.260	0.155	0.403	12 / 47		2.96
Marfin 1995 grp 1	0.595	0.442	0.731	25 / 42		3.01
DuPont 1969 grp 1	0.220	0.055	0.577	2 / 9		1.62
Weinstein 1983 grp 2	0.417	0.317	0.525	35 / 84		3.27
Overall	0.312	0.257	0.373			

0.00   0.50   1.00

Fig 3. Forest plot analysis of mortality rate using random-effects model in septic patients with normothermia (body temperature between 36.1 and 38.0°C; *n* = 3,904).

doi:10.1371/journal.pone.0170152.g003

The weighted average T_bs were 38.1 (95% CI, 37.9–38.4°C), 37.8 (95% CI, 37.5–38.2°C), 37.6 (95% CI, 36.5–38.7°C), and 37.1°C (95% CI, 36.7–37.4°C) in the Q1, Q2, Q3, and Q4 groups, respectively. These results also indicate that in sepsis a higher T_b is associated with better outcome, while a lower T_b is related with higher risk of mortality. Of note, the T_bs in Q1 and Q4

Study name and subgroup	Mortality rate	Lower limit	Upper limit	Deaths / cases	Mortality rate and 95% CI	Relative weight
Bro-Jeppesen 2015 grp 1	0.360	0.266	0.466	31 / 86		13.06
Bro-Jeppesen 2015 grp 2	0.300	0.211	0.407	25 / 83		12.68
Kushimoto 2013 grp 1	0.404	0.312	0.503	40 / 99		13.56
Arons 1999 grp 2	0.700	0.550	0.816	31 / 44		10.45
Clemmer 1992 grp 1	0.620	0.449	0.765	21 / 34		9.88
Villar 1993 grp 2	0.670	0.336	0.891	6 / 9		4.42
Drewry 2015 grp 1	0.500	0.380	0.620	32 / 64		12.41
Gozel 2012 grp 2	0.875	0.266	0.993	3 / 3		1.23
Diekema 2003 grp 1	0.400	0.356	0.446	180 / 449		15.89
Hung 2005 grp 3	0.200	0.027	0.691	1 / 5		2.11
DuPont 1969 grp 2	0.400	0.100	0.800	2 / 5		2.98
Weinstein 1983 grp 1	0.950	0.525	0.997	9 / 9		1.32
Overall	0.473	0.389	0.557			

Fig 4. Forest plot analysis of mortality rate using random-effects model in septic patients with hypothermia (body temperature up to 36.0˚C; _n_ = 890).

(i.e., in the groups with lowest and highest mortality, respectively) are clearly distinct from each other, as the 95% CIs do not overlap.

Discussion

In the current analysis we revealed a clear association between T_b and mortality in septic patients by using a detailed statistical approach which was based on an extensive literature search of previous human studies. We found that the presence of fever reduces, while that of hypothermia promotes mortality in septic patients as compared to normothermic subjects.

From previous studies of septic patients only limited information is available to show an association between T_b and mortality in a wide temperature range. While a worse outcome was consistently found to be related to hypothermia [20, 23, 24, 27], those studies compared hypothermia with fever [23, 27] or with nonhypothermic (i.e., by merging febrile and normothermic) patients [20, 24]. In one study, no association was found between hypothermia and the clinical outcome of sepsis [19]. Regarding the role of fever, different clinical trials came to controversial results in sepsis. Several authors showed that a higher T_b was beneficial [18, 19, 50, 62], others that it was disadvantageous [44, 63], and a few found no association between fever and mortality [20, 60]. The discrepancy among the studies may result from the limited sample size used in the trials. Another explanation for not detecting significant association could be the insensitivity of the used statistical method. Indeed, when we first performed a commonly used regression analysis, the Pearson correlation, which did not allow us to weight the collected data for example for sample size, we found only a very weak negative correlation ($P = 0.047$) between T_b and mortality ratio in sepsis. Thus, we applied more precise statistical tools (forest plot and meta-regression analyses).

In our analyses, we used a sizeable, heterogeneous population of septic patients ($n = 10,834$) with a wide range of T_b (33.0–39.9˚C). We showed that in sepsis mortality rates are lower if fever is present and higher in cases of hypothermia as compared to the normothermic group. In addition, we demonstrated a strong negative correlation ($P = 0.0004$) between T_b and
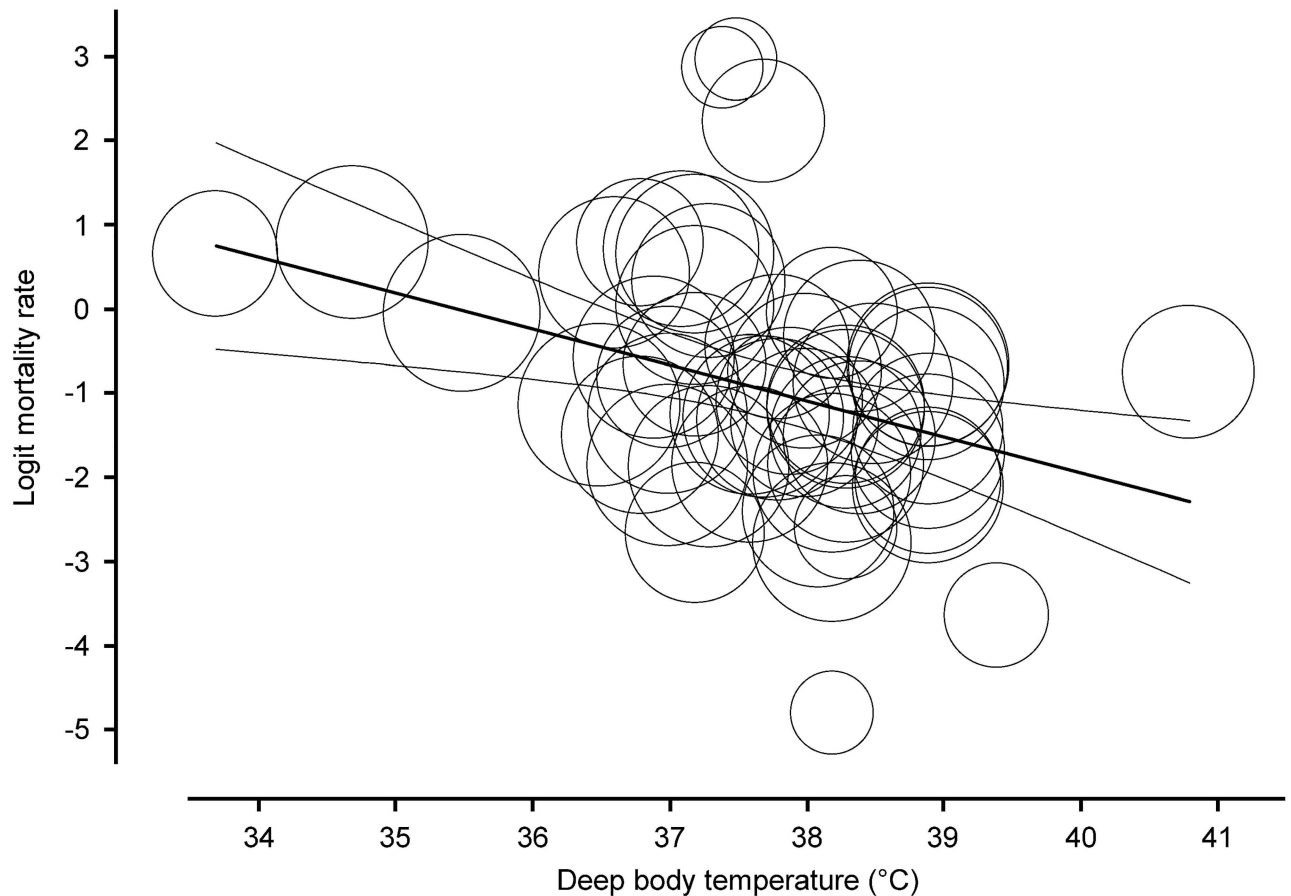
Fig 5. Meta-regression analysis of the association between body temperature and mortality ratio in septic patients ($n = 10, 834$).

doi:10.1371/journal.pone.0170152.g005

mortality ratio with the help of meta-regression analysis. In our statistical approach, we also included a substantial number of septic patient groups with average T_bs within the normal range ($n = 3,904$). Furthermore, when we calculated the mean T_bs of septic patients in the mortality quartiles, we found that it gradually decreased from the lowest to the highest quartile and it was significantly higher in the lowest (0–25%) than in the highest quartile (75–100%) of mortality (38.1 ± 0.1 vs 37.1 ± 0.2°C for mean ± SEM, respectively). Taken together the results from all of our statistical approaches, our data strongly suggest a predictive role of T_b for the outcome of sepsis.

Sepsis continues to constitute a major challenge in critical care medicine [1–4]. As a systemic inflammation process, sepsis is frequently accompanied by abnormalities of T_b, like fever and hypothermia. In animal experiments, lower doses of endotoxin usually cause fever, whilst higher doses lead to the development of hypothermia [64, 65], indicating that the severity of the disease determines the change in T_b and not the way around. Based on our statistical analyses of human studies fever seems beneficial, but hypothermia rather disadvantageous for the organism regarding the outcome. However, it has to be noted that the current analysis does not allow us to conclude that the change of T_b per se is responsible for the lower and higher mortality rates in fever and hypothermia, respectively. Instead of a cause-effect relationship, the abnormal T_b should be rather regarded as a prognostic vital parameter of the severity and progress of the inflammation, and as such, as a warning sign, which can help doctors to asses the outcome of to the infection.

With regard to the adaptive biological value of T_b alterations in mammals, the development of fever in systemic inflammation is considered to indicate the activation of defense mechanisms of the body to fight the intruding agent [6–8]. By enhancing immune functions and accelerating the elimination of the microorganism from the body, at the onset of the inflammation fever is an adaptive, beneficial thermoregulatory response, although it involves a higher energy cost [6–8]. Therefore, fever itself is assumed to have a direct, advantageous effect on the mortality ratio in systemic inflammation (e.g., sepsis), when it is affordable for the host. However, T_b regulation should be considered in the framework of complex energy balance [66], therefore, the beneficial value of fever as an energetically expensive defense response is doubtable when there is a risk of energy deficiency, which often develops as the severity of the disease further progresses. In support of that, the administration of antipyretics resulted in an increase of mortality rate of critically ill patients in prospective clinical trials [38, 67]. However, in severe sepsis or septic shock, the use of pharmacological antipyretics did not influence mortality [51, 68], while fever control with external cooling decreased early mortality in human studies [44].

Spontaneous hypothermia represents a distinct, adaptive mechanism to systemic inflammation in experimental animals [69] and in septic patients [17]. It characteristically develops in severe cases of already progressed diseases, when—instead of actively coping with the microorganism—the organism attempts to increase survival by saving its energy resources [6, 8]. A recent study by Fonseca et al. [17] revealed that spontaneous hypothermia is a transient, self-limiting, and nonterminal event in human sepsis, which underlies its biological value as an adaptive mechanism in the critically ill patients.

Although the results of our analysis showed that hypothermia is associated with higher mortality, it should be noted that we can not be sure how mortality ratio of the patients would have changed if hypothermia had not developed or if the patients were rewarmed. As of today, to our knowledge, the effect of rewarming vs non-rewarming on the mortality of septic patients with spontaneous hypothermia has not been compared in randomized controlled trials. Therefore, hypothermia in itself should not be regarded harmful for the body as the associated higher mortality rate of the septic patients is presumably due to their more severe clinical condition. We suggest that the difference between the mortality rates of febrile and hypothermic patients with sepsis is due to the different severity and progression of the inflammation and not due to T_b itself. As a consequence, T_b itself serves not as a detrimental factor, but instead, as an indicative predictor for the severity of the disease and as such for mortality in sepsis.

From a clinical perspective, our results highlight the importance of precise and regular measurements of deep T_b, since its abnormalities can help physicians—especially in critical care medicine—not only in the diagnosis, but also in the follow up of the progression, and in the prognosis of sepsis. Based on our findings, it would be worth to consider that hypothermia should be weighted differently than fever and not equally as currently used in many scoring systems (e.g., SIRS, APACHE, PIRO), since hypothermia indicates a more severe stage of sepsis, and, therefore it is associated with worse clinical outcome. Regarding therapeutic interventions, the T_b management of septic patients should be always carefully evaluated and perhaps guidelines could be established (e.g., for the initiation of antipyretic treatment) to improve the clinical outcome in sepsis.

Conclusions

The abnormalities of deep T_b are strongly associated with the clinical outcome in sepsis. The mortality ratio of febrile patients is lower, while in patients with hypothermia it is markedly

higher than that of patients with normal T_b. In cases of sepsis, there is a strong negative correlation between the mortality ratio and deep T_b in a wide temperature range. Septic patients with the lowest ($< 25\%$) chance of mortality have significantly higher deep T_b than those who belong to the highest mortality quartile ($> 75\%$).

Strengths and Limitations

Our meta-analysis included data from a total of 10,834 septic patients with overall 2,724 mortality events. We believe that our search strategy was adequately broad and included the three main databases of human studies. As result, 42 full-text articles could be indentified and used in our analyses. Although the sample size and the overall event rate can be considered large enough to draw solid conclusions about the association of T_b and mortality rate in sepsis, our study has certain limitations.

First, due to the nature of the meta-analysis method, we have studied the reported mean T_bs in populations of patients, rather than the association between T_b and the outcome of sepsis in individual patients. The latter approach would certainly allow one to draw firmer conclusions about the association between T_b and mortality, but it would also necessitate access to the original data of the analyzed articles, which is not feasible. Alternatively, a well-designed clinical trial with a big sample size could also provide high-quality individual data and based on our results it can be warranted to conduct such trials.

Second, the studied population of patients is quite diverse, which diversity could also have its own impact on the results. For example, T_b measurements were performed in different ways and not at the same time points in the analyzed studies. Despite such differences, we believe that the size of the analyzed sample was big enough to mitigate the methodological differences among the studies and to allow for drawing conclusions about the association of T_b and mortality in the septic patients.

Supporting Information

S1 Table. PRISMA 2009 checklist.
(DOC)

Author Contributions

Conceptualization: ZR AG.

Data curation: RM.

Formal analysis: ZR RM AG.

Funding acquisition: PH AG.

Investigation: ZR RM CZ EP MB KM AM JT IR MS.

Methodology: ZR RM AG.

Project administration: ZR PH AG.

Resources: PH AG.

Software: RM PH.

Supervision: PH EP MB AG.

Visualization: ZR RM CZ KM AM AP JT IR AG.

Writing – original draft: ZR AG.

Writing – review & editing: ZR RM PH CZ IS AI EP MB KM AM AP JT IR MS AG.

References

1. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016; 193(3):259–72. Epub 2015/09/29. doi: 10.1164/rccm.201504-0781OC PMID: 26414292

2. Esteban A, Frutos-Vivar F, Ferguson ND, Penuelas O, Lorente JA, Gordo F, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. Crit Care Med. 2007; 35(5):1284–9. Epub 2007/04/07. doi: 10.1097/01.CCM.0000260960.94300.DE PMID: 17414725

3. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med. 2014; 2(5):380–6. Epub 2014/04/18. doi: 10.1016/S2213-2600(14)70061-X PMID: 24740011

4. Walkey AJ, Lagu T, Lindenauer PK. Trends in sepsis and infection sources in the United States. A population-based study. Ann Am Thorac Soc. 2015; 12(2):216–20. Epub 2015/01/09. doi: 10.1513/AnnalsATS.201411-498BC PMID: 25569845

5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8):801–10. Epub 2016/02/24. doi: 10.1001/jama.2016.0287 PMID: 26903338

6. Romanovsky AA, Almeida MC, Aronoff DM, Ivanov AI, Konsman JP, Steiner AA, et al. Fever and hypothermia in systemic inflammation: recent discoveries and revisions. Front Biosci. 2005; 10:2193–216. Epub 2005/06/23. PMID: 15970487

7. Saper CB, Romanovsky AA, Scammell TE. Neural circuitry engaged by prostaglandins during the sickness syndrome. Nat Neurosci. 2012; 15(8):1088–95. Epub 2012/07/28. doi: 10.1038/nn.3159 PMID: 22837039

8. Romanovsky AA, Szekely M. Fever and hypothermia: two adaptive thermoregulatory responses to systemic inflammation. Med Hypotheses. 1998; 50(3):219–26. Epub 1998/05/13. PMID: 9578327

9. Cunha BA. With sepsis: If fever is good, then hypothermia is bad! Crit Care Med. 2012; 40(10):2926. Epub 2012/09/19. doi: 10.1097/CCM.0b013e31825f78aa PMID: 22986674

10. Kushimoto S, Yamanouchi S, Endo T, Sato T, Nomura R, Fujita M, et al. Body temperature abnormalities in non-neurological critically ill patients: a review of the literature. J Intensive Care. 2014; 2(1):14. Epub 2014/12/19. doi: 10.1186/2052-0492-2-14 PMID: 25520830

11. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992; 101(6):1644–55. Epub 1992/06/01. PMID: 1303622

12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985; 13(10):818–29. Epub 1985/10/01. PMID: 3928249

13. Opal SM. Concept of PIRO as a new conceptual framework to understand sepsis. Pediatr Crit Care Med. 2005; 6(3 Suppl):S55–60. Epub 2005/04/29. doi: 10.1097/01.PCC.0000161580.79526.4C PMID: 15857560

14. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993; 270(24):2957–63. Epub 1993/12/22. PMID: 8254858

15. Beverly A, Walter E, Carraretto M. Management of hyperthermia and hypothermia in sepsis: A recent survey of current practice across UK intensive care units. J Intensive Care Soc. 2016; 17(1):88–9.

16. Corrigan JJ, Fonseca MT, Flatow EA, Lewis K, Steiner AA. Hypometabolism and hypothermia in the rat model of endotoxic shock: independence of circulatory hypoxia. J Physiol. 2014; 592(17):3901–16. Epub 2014/06/22. doi: 10.1113/jphysiol.2014.277277 PMID: 24951620

17. 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. J Appl Physiol (1985). 2016; 120 (12):1394–401. Epub 2016/03/19.

18. Bryant RE, Hood AF, Hood CE, Koenig MG. Factors affecting mortality of gram-negative rod bacteremia. Arch Intern Med. 1971; 127(1):120–8. Epub 1971/01/01. PMID: 4923385

19. Megged O, Yinnon AM, Raveh D, Rudensky B, Schlesinger Y. Group A streptococcus bacteraemia: comparison of adults and children in a single medical centre. Clin Microbiol Infect. 2006; 12(2):156–62. Epub 2006/01/31. doi: 10.1111/j.1469-0691.2005.01311.x PMID: 16441454

20. Kushimoto S, Gando S, Saitoh D, Mayumi T, Ogura H, Fujishima S, et al. The impact of body temperature abnormalities on the disease severity and outcome in patients with severe sepsis: an analysis from a multicenter, prospective survey of severe sepsis. Crit Care. 2013; 17(6):R271. Epub 2013/11/14. doi: 10.1186/cc13106 PMID: 24220071

21. Blair E, Henning G, Hornick R, Cowley RA. Hypothermia in Bacteremic Shock. Arch Surg. 1964; 89:619–29. Epub 1964/10/01. PMID: 14186792

22. Villar J, Slutsky AS. Effects of induced hypothermia in patients with septic adult respiratory distress syndrome. Resuscitation. 1993; 26(2):183–92. Epub 1993/10/01. PMID: 8290813

23. Clemmer TP, Fisher CJ Jr., Bone RC, Slotman GJ, Metz CA, Thomas FO. Hypothermia in the sepsis syndrome and clinical outcome. The Methylprednisolone Severe Sepsis Study Group. Crit Care Med. 1992; 20(10):1395–401. Epub 1992/10/11. PMID: 1395659

24. Drewry AM, Fuller BM, Skrupky LP, Hotchkiss RS. The presence of hypothermia within 24 hours of sepsis diagnosis predicts persistent lymphopenia. Crit Care Med. 2015; 43(6):1165–9. Epub 2015/03/21. doi: 10.1097/CCM.0000000000000940 PMID: 25793436

25. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015; 349:g7647. Epub 2015/01/04. doi: 10.1136/bmj.g7647 PMID: 25555855

26. Aceng JR, Byarugaba JS, Tumwine JK. Rectal artemether versus intravenous quinine for the treatment of cerebral malaria in children in Uganda: randomised clinical trial. BMJ. 2005; 330(7487):334. Epub 2005/02/12. doi: 10.1136/bmj.330.7487.334 PMID: 15705690

27. Arons MM, Wheeler AP, Bernard GR, Christman BW, Russell JA, Schein R, et al. Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in Sepsis Study Group. Crit Care Med. 1999; 27(4):699–707. Epub 1999/05/13. PMID: 10321658

28. Asiimwe SB, Abdallah A, Ssekitoleko R. A simple prognostic index based on admission vital signs data among patients with sepsis in a resource-limited setting. Crit Care. 2015; 19:86. Epub 2015/04/19. doi: 10.1186/s13054-015-0826-8 PMID: 25888322

29. Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. J Clin Microbiol. 2003; 41(8):3655–60. Epub 2003/08/09. doi: 10.1128/JCM.41.8.3655-3660.2003 PMID: 12904371

30. Gozel MG, Erbay A, Bodur H, Eren SS. Risk factors for mortality in patients with nosocomial gram-negative bacteremia. Turkiye Klinikleri J Med Sci. 2012; 32(6):1641–7.

31. Green JE, Ariathianto Y, Wong SM, Aboltins C, Lim K. Clinical and inflammatory response to bloodstream infections in octogenarians. BMC Geriatr. 2014; 14:55. Epub 2014/04/24. doi: 10.1186/1471-2318-14-55 PMID: 24754903

32. Heffner AC, Horton JM, Marchick MR, Jones AE. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. Clin Infect Dis. 2010; 50(6):814–20. Epub 2010/02/11. doi: 10.1086/650580 PMID: 20144044

33. Hodgin UG, Sanford JP. Gram-negative rod bacteremia. An analysis of 100 patients. Am J Med. 1965; 39(6):952–60. Epub 1965/12/01. PMID: 5853047

34. Hoeboer SH, Alberts E, van den Hul I, Tacx AN, Debets-Ossenkopp YJ, Groeneveld AB. Old and new biomarkers for predicting high and low risk microbial infection in critically ill patients with new onset fever: a case for procalcitonin. J Infect. 2012; 64(5):484–93. Epub 2012/01/18. doi: 10.1016/j.jinf.2012.01.002 PMID: 22248983

35. Hung MN, Chen SY, Wang JL, Chang SC, Hsueh PR, Liao CH, et al. Community-acquired anaerobic bacteremia in adults: one-year experience in a medical center. J Microbiol Immunol Infect. 2005; 38 (6):436–43. Epub 2005/12/13. PMID: 16341345

36. Kang MJ, Shin TG, Jo IJ, Jeon K, Suh GY, Sim MS, et al. Factors influencing compliance with early resuscitation bundle in the management of severe sepsis and septic shock. Shock. 2012; 38(5):474–9. Epub 2012/10/09. doi: 10.1097/SHK.0b013e31826eea2b PMID: 23042195

37. Kirov MY, Evgenov OV, Evgenov NV, Egorina EM, Sovershaev MA, Sveinbjornsson B, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Crit Care Med. 2001; 29 (10):1860–7. Epub 2001/10/06. PMID: 11588440

38. 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. Epub 2012/03/01. doi: 10.1186/cc11211 PMID: 22373120

39. Marfin AA, Sporrer J, Moore PS, Siefkin AD. Risk factors for adverse outcome in persons with pneumo-coccal pneumonia. Chest. 1995; 107(2):457–62. Epub 1995/02/01. PMID: 7842778

40. Molina J, Penuela I, Lepe JA, Gutierrez-Pizarraya A, Gomez MJ, Garcia-Cabrera E, et al. Mortality and hospital stay related to coagulase-negative Staphylococci bacteremia in non-critical patients. J Infect. 2013; 66(2):155–62. Epub 2012/10/30. doi: 10.1016/j.jinf.2012.10.021 PMID: 23103291

41. Neuberger A, Yahav D, Daitch V, Akayzen Y, Farbman L, Avni T, et al. The significance of persistent fever in the treatment of suspected bacterial infections among inpatients: a prospective cohort study. Eur J Clin Microbiol Infect Dis. 2015; 34(4):805–10. Epub 2014/12/17. doi: 10.1007/s10096-014-2288-3 PMID: 25502509

42. Pittet D, Thievent B, Wenzel RP, Li N, Auckenthaler R, Suter PM. Bedside prediction of mortality from bacteremic sepsis. A dynamic analysis of ICU patients. Am J Respir Crit Care Med. 1996; 153(2):684–93. Epub 1996/02/01. doi: 10.1164/ajrccm.153.2.8564118 PMID: 8564118

43. Rhodes A, Lamb FJ, Malagon I, Newman PJ, Grounds RM, Bennett ED. A prospective study of the use of a dobutamine stress test to identify outcome in patients with sepsis, severe sepsis, or septic shock. Crit Care Med. 1999; 27(11):2361–6. Epub 1999/12/01. PMID: 10579249

44. Schortgen F, Clabault K, Katsahian S, Devaquet J, Mercat A, Deye N, et al. Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med. 2012; 185(10):1088–95. Epub 2012/03/01. doi: 10.1164/rccm.201110-1820OC PMID: 22366046

45. Seguin P, Roquilly A, Mimoz O, Le Maguet P, Asehnoune K, Biederman S, et al. Risk factors and out-comes for prolonged versus brief fever: a prospective cohort study. Crit Care. 2012; 16(4):R150. Epub 2012/08/15. doi: 10.1186/cc11465 PMID: 22889136

46. Song YH, Shin TG, Kang MJ, Sim MS, Jo IJ, Song KJ, et al. Predicting factors associated with clinical deterioration of sepsis patients with intermediate levels of serum lactate. Shock. 2012; 38(3):249–54. Epub 2012/06/12. doi: 10.1097/SHK.0b013e3182613e33 PMID: 22683735

47. Su L, Han B, Liu C, Liang L, Jiang Z, Deng J, et al. Value of soluble TREM-1, procalcitonin, and C-reac-tive protein serum levels as biomarkers for detecting bacteremia among sepsis patients with new fever in intensive care units: a prospective cohort study. BMC Infect Dis. 2012; 12:157. Epub 2012/07/20. doi: 10.1186/1471-2334-12-157 PMID: 22809118

48. Swenson BR, Hedrick TL, Popovsky K, Pruett TL, Sawyer RG. Is fever protective in surgical patients with bloodstream infection? J Am Coll Surg. 2007; 204(5):815–21; discussion 22–3. Epub 2007/05/08. doi: 10.1016/j.jamcollsurg.2007.01.033 PMID: 17481490

49. Taylor TE, Wills BA, Courval JM, Molyneux ME. Intramuscular artemether vs intravenous quinine: an open, randomized trial in Malawian children with cerebral malaria. Trop Med Int Health. 1998; 3(1):3–8. Epub 1998/03/04. PMID: 9484961

50. Weinstein MP, Murphy JR, Reller LB, Lichtenstein KA. The clinical significance of positive blood cul-tures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference to factors influencing prognosis. Rev Infect Dis. 1983; 5(1):54–70. Epub 1983/01/01. PMID: 6828812

51. Bernard GR, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, et al. The effects of ibu-profen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. N Engl J Med. 1997; 336(13):912–8. Epub 1997/03/27. doi: 10.1056/NEJM199703273361303 PMID: 9070471

52. Carl DE, Grossman C, Behnke M, Sessler CN, Gehr TW. Effect of timing of dialysis on mortality in criti-cally ill, septic patients with acute renal failure. Hemodial Int. 2010; 14(1):11–7. Epub 2010/04/10. doi: 10.1111/j.1542-4758.2009.00407.x PMID: 20377649

53. Drewry AM, Fuller BM, Bailey TC, Hotchkiss RS. Body temperature patterns as a predictor of hospital-acquired sepsis in afebrile adult intensive care unit patients: a case-control study. Crit Care. 2013; 17 (5):R200. Epub 2013/09/14. doi: 10.1186/cc12894 PMID: 24028682

54. DuPont HL, Spink WW. Infections due to gram-negative organisms: an analysis of 860 patients with bacteremia at the University of Minnesota Medical Center, 1958–1966. Medicine (Baltimore). 1969; 48 (4):307–32. Epub 1969/07/01.

55. Memis D, Karamanlioglu B, Turan A, Koyuncu O, Pamukcu Z. Effects of lornoxicam on the physiology of severe sepsis. Crit Care. 2004; 8(6):R474–82. Epub 2004/11/30. doi: 10.1186/cc2969 PMID: 15566594

56. Pestana D, Casanova E, Villagran MJ, Tormo C, Perez-Chrzanowska H, Redondo J, et al. Continuous hemofiltration in hyperthermic septic shock patients. J Trauma. 2007; 63(4):751–6. Epub 2007/12/20. doi: 10.1097/TA.0b013e31802b9575 PMID: 18090001

57. Sarmin M, Ahmed T, Bardhan PK, Chisti MJ. Specialist hospital study shows that septic shock and drowsiness predict mortality in children under five with diarrhoea. Acta Paediatr. 2014; 103(7):e306–11. Epub 2014/03/26. doi: 10.1111/apa.12640 PMID: 24661049

58. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015; 372(21):1996–2005. Epub 2015/05/21. doi: 10.1056/NEJMoa1411162 PMID: 25992746

59. Yang YL, Liu DW, Wang XT, Long Y, Zhou X, Chai WZ. Body temperature control in patients with refractory septic shock: too much may be harmful. Chin Med J (Engl). 2013; 126(10):1809–13. Epub 2013/05/16.

60. Young P, Saxena M, Bellomo R, Freebairn R, Hammond N, van Haren F, et al. Acetaminophen for Fever in Critically Ill Patients with Suspected Infection. N Engl J Med. 2015; 373(23):2215–24. Epub 2015/10/06. doi: 10.1056/NEJMoa1508375 PMID: 26436473

61. Bro-Jeppesen J, Kjaergaard J, Wanscher M, Nielsen N, Friberg H, Bjerre M, et al. Systemic Inflammatory Response and Potential Prognostic Implications After Out-of-Hospital Cardiac Arrest: A Substudy of the Target Temperature Management Trial. Crit Care Med. 2015; 43(6):1223–32. Epub 2015/03/11. doi: 10.1097/CCM.0000000000000937 PMID: 25756419

62. Mackowiak PA, Browne RH, Southern PM Jr., Smith JW. Polymicrobial sepsis: an analysis of 184 cases using log linear models. Am J Med Sci. 1980; 280(2):73–80. Epub 1980/09/01. PMID: 7435520

63. Manthous CA, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, et al. Effect of cooling on oxygen consumption in febrile critically ill patients. Am J Respir Crit Care Med. 1995; 151(1):10–4. Epub 1995/01/01. doi: 10.1164/ajrccm.151.1.7812538 PMID: 7812538

64. Pakai E, Garami A, Nucci TB, Ivanov AI, Romanovsky AA. Hyperbilirubinemia exaggerates endotoxin-induced hypothermia. Cell Cycle. 2015; 14(8):1260–7. Epub 2015/03/17. doi: 10.1080/15384101.2015.1014150 PMID: 25774749

65. Rudaya AY, Steiner AA, Robbins JR, Dragic AS, Romanovsky AA. Thermoregulatory responses to lipopolysaccharide in the mouse: dependence on the dose and ambient temperature. Am J Physiol Regul Integr Comp Physiol. 2005; 289(5):R1244–52. Epub 2005/08/06. doi: 10.1152/ajpregu.00370.2005 PMID: 16081879

66. Garami A, Szekely M. Body temperature: Its regulation in framework of energy balance. Temperature (Austin). 2014; 1(1):28–9. Epub 2014/04/01. [pii].

67. Schulman CI, Namias N, Doherty J, Manning RJ, Li P, Elhaddad A, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. Surg Infect (Larchmt). 2005; 6(4):369–75. Epub 2006/01/26.

68. Mohr N, Skrupky L, Fuller B, Moy H, Alunday R, Wallendorf M, et al. Early antipyretic exposure does not increase mortality in patients with gram-negative severe sepsis: a retrospective cohort study. Intern Emerg Med. 2012; 7(5):463–70. Epub 2012/08/29. doi: 10.1007/s11739-012-0848-z PMID: 22926744

69. 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. Am J Physiol Regul Integr Comp Physiol. 2012; 302(12):R1372–83. Epub 2012/04/20. doi: 10.1152/ajpregu.00023.2012 PMID: 22513748