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The association of body temperature with antibiotic therapy and mortality in patients attending the emergency department with suspected infection

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Background and importance **Previous studies found that septic patients with normothermia have higher mortality than patients with fever. We hypothesize that antibiotic therapy is less frequently initiated if infectious patients present with normothermia to the emergency department (ED).**

Objectives **To examine the association of body temperature with the initiation of antibiotic therapy in patients attending the ED with suspected and proven infection. Additionally, the association of temperature with 30-day mortality was assessed.**

Design, settings and participants **We conducted a retrospective cohort study between 2012 and 2016 at a tertiary university hospital. Adult patients attending the ED with a blood culture taken (i.e. suspected infection) and a positive blood culture (i.e. proven bacteremia) were included.**

Exposure **Tympanic temperature at arrival was categorized as hypothermia (<36.1°C), normothermia (36.1–38.0°C) or hyperthermia (>38.0°C).**

Outcome measures and analysis **Primary outcome was the initiation of antibiotic therapy. A secondary outcome was 30-day mortality. Multivariable logistic regression was used to control for covariates.**

Main results **Of 5997 patients with a suspected infection, 45.8% had normothermia, 44.6% hyperthermia and 5.6% hypothermia. Patients with hyperthermia received more often antibiotic therapy (53.5%) compared to normothermic patients (27.6%, adjusted odds ratio [95% confidence interval], 2.59 [2.27–2.95]). Patients with hyperthermia had lower mortality (4.7%) than those with normothermia (7.4%, adjusted odds ratio [95% confidence interval], 0.50 [0.39–0.64]). Sensitivity analyses in patients with proven bacteremia ($n = 934$) showed similar results.**

Conclusion **Normothermia in patients presenting with infection was associated with receiving less antibiotic therapy in the ED compared to presentations with hyperthermia. Moreover, normothermia was associated with a higher mortality risk than hyperthermia.** ***European Journal of Emergency Medicine*** **28: 440–447 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Infections are potential life-threatening conditions with frequent presentations in an acute care setting such as the emergency department (ED) [1]. Body temperature, hereafter temperature, is an important vital sign because fever is known to be a marker of infection [2]. Also, fever is a common reason to visit the ED [3]. Clinical decision support systems [4], such as the Manchester Triage System (MTS) [5] and National Early Warning Score (NEWS) [6], use temperature to assist in quickly identifying patients at high risk of deterioration in a general ED population. These decision support systems assign a higher mortality risk to hyperthermia (>38.0°C) and hypothermia (<36.1°C) compared to normothermia (36.1–38.0°C) [5–7]. However, according to a recent meta-analysis, septic patients with normothermia are at higher risk of dying than patients with hyperthermia [8]. It is unknown whether this is also generalizable to all patients attending the ED with a suspected infection.

We hypothesize that if patients with a suspected infection present to the ED with normothermia, antibiotic

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therapy may not be directly initiated. Instead, these patients are first observed, and antibiotic therapy is started when the temperature becomes deviant or the patient deteriorates [9]. Such treatment delay would be unfavorable if normothermic patients with infection are at higher risk of dying than patients with hyperthermia and can be in contrast to the recommendations of the surviving sepsis campaign regarding timing of antibiotic treatment [10].

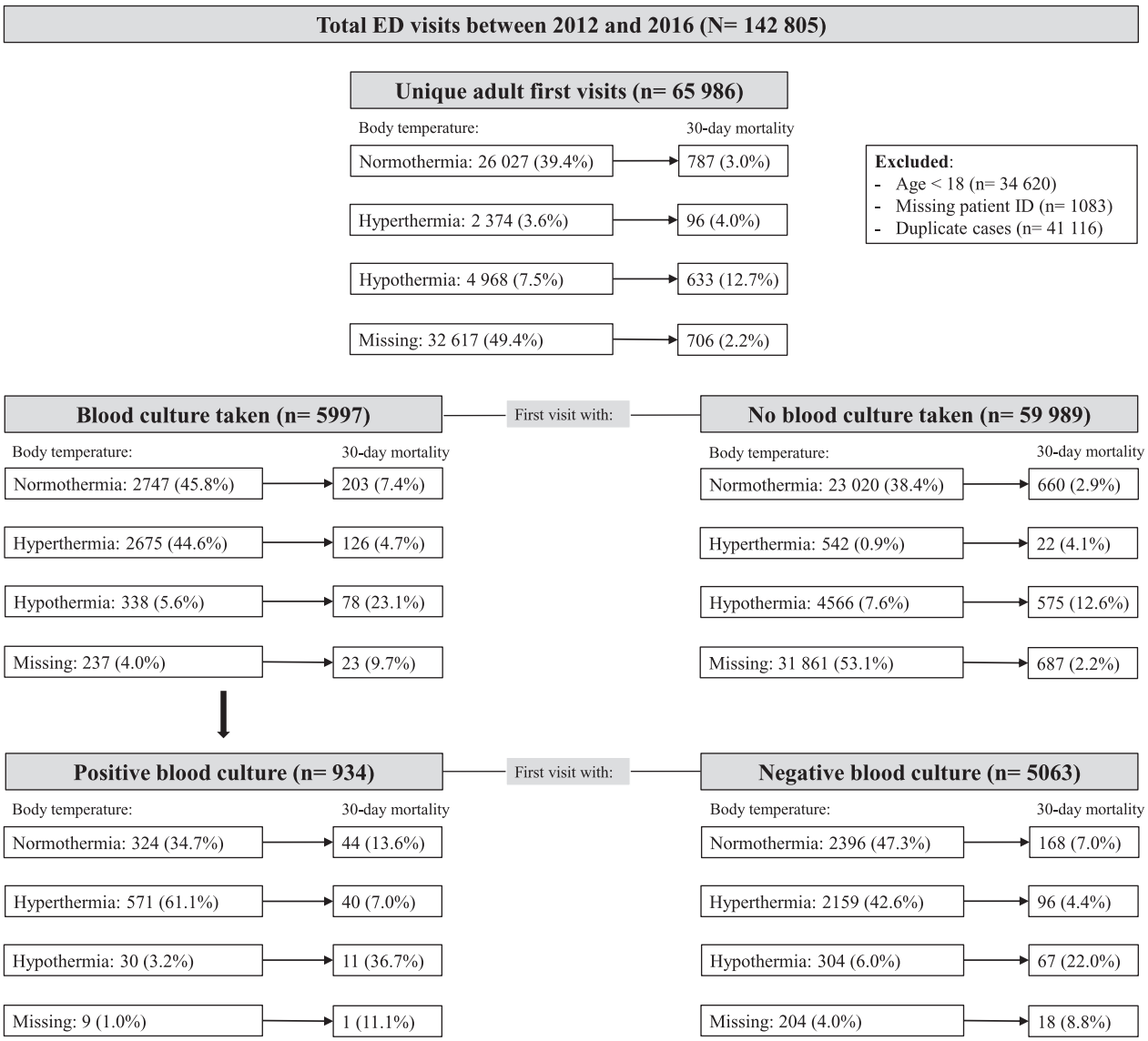
The primary aim of this study was to examine the association of temperature with initiation of antibiotic therapy in patients attending the ED with suspected infection (i.e. with a blood culture taken) and in patients with proven bacteremia (i.e. with a positive blood culture). A secondary endpoint was 30-day mortality.

Method

Study design and setting

We conducted a retrospective cohort study at the Erasmus University Medical Center Rotterdam (Erasmus MC), which is the largest tertiary referral center in the Netherlands. The ED is an open access department with approximately 33 000 annual visits. Our database consists of automatically derived data from all patients admitted

Fig. 1



Flowchart of study selection and mortality (30-day). For all selection steps, first visits were included, and therefore, some patients in the 'blood culture taken'-group and 'positive blood culture'-group are included at a later point in time (e.g. a few patients are included in the 'blood culture taken'-group, but had a positive blood culture in a subsequent ED visit and are therefore in the 'positive blood culture'-group later in time). ED, emergency department.

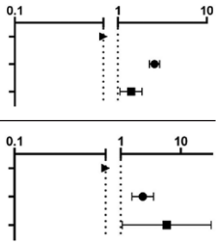
Table 1 Patient characteristics in normothermia, hyperthermia and hypothermia for patients with a blood culture taken in the emergency department – that is, suspected infection ($n = 5997$)

Characteristic	Missing	Normothermia, $n = 2747$ (45.8)	Hyperthermia, $n = 2675$ (44.6)	*P* value hyper versus normothermia	Hypothermia, $n = 338$ (5.6)	*P* value hypo versus normothermia
Sex, men	0	1528 (55.6)	1509 (56.4)	0.56	225 (66.6)	<0.001
Age, mean (SD)	0	56 (17.2)	55 (17.8)	0.11	63 (15.6)	<0.001
Arrival, by ambulance	0	324 (11.8)	396 (14.8)	0.001	135 (39.9)	<0.001
Triage by MTS, acute/highly urgent	271 (4.5)	302 (11.4)	450 (17.5)	<0.001	145 (46.2)	<0.001
Vital signs, mean (SD)						
Temperature, °C	237 (4.0)	37.2 (0.5)	38.8 (0.6)	<0.001	35.1 (1.3)	<0.001
Heart rate, per min	294 (4.9)	95 (20.0)	107 (19.2)	<0.001	89 (26.7)	<0.001
Respiratory rate, per min	2435 (40.6)	21 (7.2)	22 (7.7)	<0.001	21 (8.2)	0.15
Systolic blood pressure, mmHg	388 (6.5)	131 (23.4)	134 (24.0)	<0.001	127 (34.0)	0.08
Oxygen saturation, %	424 (7.1)	96 (3.7)	96 (3.3)	0.002	95 (5.1)	0.04
Any supplemental oxygen	0	764 (27.8)	952 (35.6)	<0.001	177 (52.4)	<0.001
Consciousness, not alert	1251 (20.9)	286 (13.0)	338 (15.5)	0.02	111 (39.8)	<0.001
NEWS, mean (SD)[a]	0	4 (3.3)	6 (3.4)	<0.001	7 (4.4)	<0.001
NEWS without temperature, mean (SD)[a]	0	4 (3.3)	5 (3.3)	<0.001	6 (4.1)	<0.001
NEWS without temperature and heart rate, mean (SD)[a]	0	3 (2.9)	3 (2.9)	<0.001	5 (3.7)	<0.001
Inflammation parameters, median (IQR)						
CRP, mg/L	998 (16.6)	58 (120.4)	58 (91.7)	0.93	19 (88.9)	<0.001
Leukocyte count, $\times 10^3/\mu L$	1024 (17.1)	7.7 (11.5)	5.0 (9.6)	0.90	13.2 (15.1)	0.07

Normothermia (36.1–38.0°C) is compared to hyperthermia (>38.0°C) and hypothermia (<36.1°C). Data are presented as number (percentage) of patients unless otherwise indicated. Data in this table are unimputed.CRP, C-reactive protein; MTS, Manchester Triage System; NEWS, national early warning score.
[a]NEWS imputed as normal.

Table 2 Temperature and initiation of antibiotic therapy

Temperature	*N*	Antibiotics (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Blood culture taken[b]	5997			
Normothermia (36.1–38.0°C)	2747	758 (27.6)	1.0 (reference)	1.0 (reference)
Hyperthermia (>38.0°C)	2675	1430 (53.5)	2.96 (2.65–3.31)	2.59 (2.27–2.95)
Hypothermia (<36.1°C)	338	161 (47.6)	2.21 (1.77–2.75)	1.42 (1.08–1.87)
Positive blood culture[c]	934			
Normothermia (36.1–38.0°C)	324	234 (72.2)	1.0 (reference)	1.0 (reference)
Hyperthermia (> 38.0°C)	571	496 (86.9)	2.64 (1.88–3.73)	2.40 (1.59–3.61)
Hypothermia (<36.1°C)	30	28 (93.3)	5.54 (1.29–23.84)	5.91 (1.00–32.86)



Hyperthermia (> 38.0°C) and hypothermia (< 36.1°C) are compared to normothermia (36.1–38.0°C). Data on number and percentages are unimputed; odds ratios are obtained from imputed data.
CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.
[a]Adjusted for: sex, age, arrival, triage category, heart rate, respiratory rate, systolic blood pressure, oxygen saturation, any supplemental oxygen, consciousness, CRP and leukocyte count.
[b]Data on temperature were missing for 237 (4.0%) patients in which antibiotic were administered in 31 (13.1%). Excluding these patients did not affect the results.
[c]Data on temperature were missing for 9 (1.0%) patients in which antibiotics were administered in 6 (66.7%). Excluding these patients did not affect the results.

to the ED between 1 July 2012 and 31 December 2016. The Medical Ethics Committee of the Erasmus MC reviewed the study and concluded that our study did not fall under the scope of the Medical Research Involving Human Subjects Act, and therefore, no informed consent needed to be obtained. Our study is registered under MEC-2018-1744 and MEC-205-106.

Selection of participants

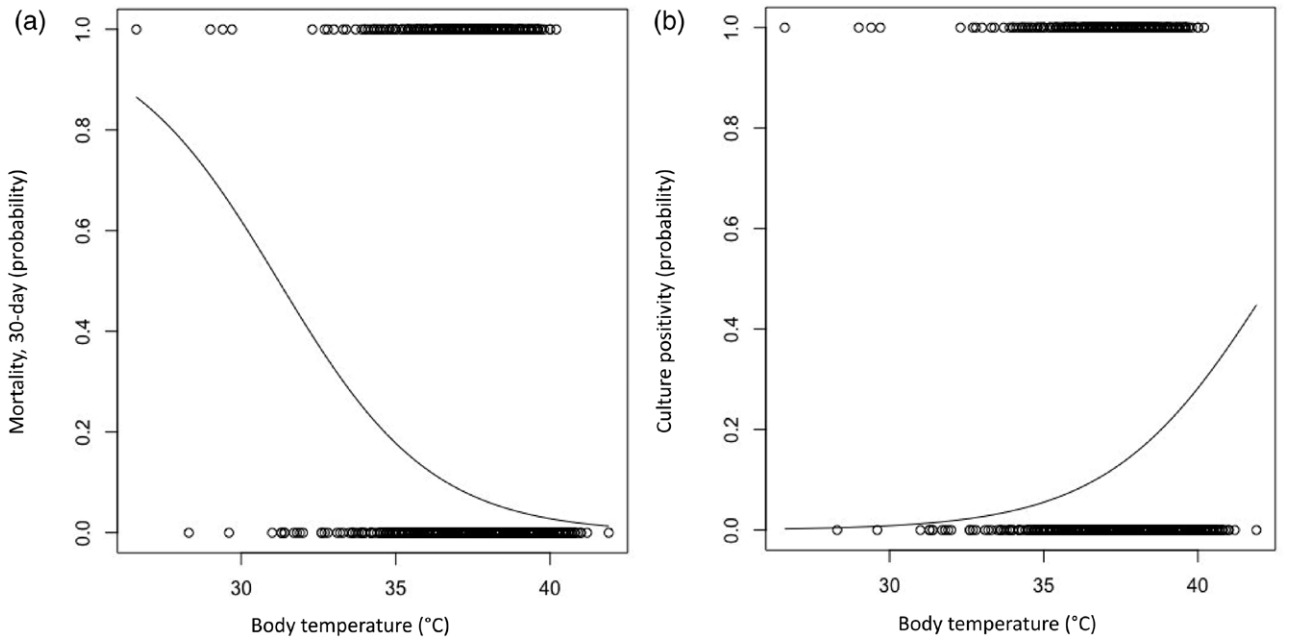
Patients were eligible for inclusion if they were at least 18 years of age and had a blood culture taken in the ED (i.e. a suspected infection). Blood cultures were obtained prior to administering antibiotic therapy (in line with the surviving sepsis campaign [10]) in patients with presentations suggestive of infection (i.e. based on history, vital signs, inflammation parameters [11]) requiring intravenous antibiotics in patients that were prone for a severe course of infection (e.g. patients with immunodeficiency), or in severely ill patients with undifferentiated presentations.

Subsequently, we selected a subgroup of patients in which blood cultures were positive (i.e. proven bacteremia). Only the first ED visit of both the 'blood culture taken'-group and the 'positive blood culture'-group was included to prevent the domination of results by a small group of individuals that frequently visited the ED.

Data collection

Data were derived from the ED and were combined with a database from Medical Microbiology, containing all collected blood cultures [12]. The ED database was collected automatically with text mining from patient charts and consists of first recorded tympanic temperature, antibiotic therapy initiated in the ED and mortality, which

Fig. 2



(a) Unadjusted probability of mortality (30-day) and (b) culture positivity for temperature in patients with a blood culture taken. (a) There was an inverse association between temperature and mortality rather than a U-shaped association. Modeling temperature as a restricted cubic spline (three knots) did not improve the model. The lower temperature was associated with a higher risk of mortality. (b) Among patients with a blood culture taken, the probability of a positive blood culture increased with an increasing temperature.

Table 3 Temperature and mortality (30-day)

Temperature	N	30-day mortality (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	
Blood culture taken	5997				
Normothermia[b] (36.1–38.0°C)	2747	203 (7.4)	1.0 (reference)	1.0 (reference)	
Hyperthermia (>38.0°C)	2675	126 (4.7)	0.57 (0.46–0.72]	0.50 (0.39–0.64]	
Hypothermia (<36.1°C)	338	78 (23.1)	3.56 (2.69–4.71]	1.52 (1.07–2.15]	
Temperature, °C (continuous)[c]	5760	407 (7.1)	0.66 (0.62–0.71]	0.74 (0.69–0.81]	
Positive blood culture	934				
Normothermia (36.1–38.0°C)[d]	324	44 (13.6)	1.0 (reference)	1.0 (reference)	
Hyperthermia (>38.0°C)	571	40 (7.0)	0.47 (0.30–0.74)	0.54 (0.31–0.94)	
Hypothermia (<36.1°C)	30	11 (36.7)	3.64 (1.62–8.18)	2.35 (0.79–7.00)	
Temperature, °C (continuous)[e]	925	95 (10.3)	0.62 (0.52–0.74)	0.72 (0.58–0.89)	

Hyperthermia (>38.0°C) and hypothermia (<36.1°C) are compared to normothermia (36.1–38.0°C). Data on number and percentages are unimputed; odds ratios are obtained from imputed data. Modeling temperature as a restricted cubic spline (3 knots) did not improve the crude and adjusted models for both patients with a blood culture taken [c] and patients with a positive blood culture [e].CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

[a]Adjusted for: sex, age, arrival, triage category, heart rate, respiratory rate, systolic blood pressure, oxygen saturation, any supplemental oxygen, consciousness, CRP, leukocyte count and antibiotic therapy.

[c]Data on temperature were missing for 237 (4.0%) patients in which 30-day mortality was 23 (9.7%). Excluding these patients did not affect the results.

[e]Data on temperature were missing for 9 (1.0%) patients in which 30-day mortality was 1 (11.1%). Excluding these patients did not affect the results.

was updated from municipal death registration records. Collected patients characteristics were demographics (age, sex), arrival mode (by ambulance), triage category (according to the MTS) [5], other first recorded vital signs (i.e. systolic blood pressure, respiratory rate, peripheral oxygen saturation, consciousness [13]), whether there was a need for any supplemental oxygen and hospital admittance. Additionally, we collected the inflammation parameters: C-reactive protein (CRP) and leukocyte count. We had no data on the exact time to antibiotic administration in the ED. However, if antibiotics were prescribed for patients that were hospitalized the first dose was always given in the ED.

The Medical Microbiology database contains data about the type of pathogen for all positive blood cultures in the ED. Positive blood culture was defined as a presence of a known pathogen (e.g. *Escherichia coli*) in one blood

culture or a less pathogenic bacteria (e.g. *Staphylococcus epidermidis*) [14] in at least two blood cultures collected on separate occasions within two days from ED admission [14, 15]. For all patients with positive blood culture, we manually reviewed patient charts and additionally collected: disposition to the ICU directly from the ED, chills [16], vomiting [16], need for vasopressors and the age-adjusted Charlson comorbidity index (CCI) [17].

Data processing

We handled missing data with multiple imputations using the chained equations method with five datasets [18]. To provide constant temperature groups, the temperature was single imputed. The temperature at arrival was categorized as hypothermia (<36.1°C), normothermia (36.1–38.0°C) or hyperthermia (>38.0°C). This categorization corresponds to previous studies and the cutoff values of NEWS [6, 8]. Additionally, we calculated the NEWS because this is proposed as an accurate early warning system in patients with suspected infection in the ED [7]. The initiated intravenous antibiotic therapy in the ED was recorded while accounting for potential typing errors, abbreviations and brand names (e.g. Cefuroxime was scored if either 'cefur' or 'zinacef' was documented).

Data analysis

We described arrival temperature (i.e. normothermia, hyperthermia, hypothermia or missing) and proportions of 30-day mortality for our total ED population, for patients with and without a blood culture taken, and for patients with- and without a positive blood culture. All subsequent analyses were performed in patients with a blood culture taken and for sensitivity analysis repeated in the subgroup of patients with a positive blood culture.

We examined presenting patient characteristics among patients with normothermia, hyperthermia and hypothermia. Based on distribution, data were compared using unpaired *t* tests, chi-square tests, Mann–Whitney *U* test or Fisher's exact tests.

We investigated the association between temperature (i.e. hyperthermia compared to normothermia and hypothermia compared to normothermia) and (1) initiation of antibiotic therapy in the ED, (2) 30-day mortality, (3) hospital admittance and (4) blood culture positivity. Thus, our reference category was normothermia. For the association between temperature and 30-day mortality, we analyzed temperature as a continuous variable as well and investigated whether there was a U-shaped association (as proposed by MTS and NEWS [4,6,7]) or an inverse association (as proposed by a recent meta-analysis [8]) with use of restricted cubic splines (with three knots). For all associations, we used multivariable logistic regression to control for covariates (i.e. sex, age, triage category, vital signs, inflammation parameters, for detailed information, see Supplementary Appendix A, Supplemental digital content 1, *http://links.lww.com/EJEM/A306*).

Results were presented as odds ratios (OR) with 95% confidence intervals (CI). All hypothesis tests were two-sided, with a significance level of $P < 0.05$. Statistical analyses were performed using R version 4.0.1.

Results

Of 65 986 unique adult patients that visited our ED between 1 July 2012 and 31 December 2016 we included 5997 patients with a blood culture taken (i.e. suspected infection) in the ED (Fig. 1). For the sensitivity analysis, 934 patients with a positive blood culture (i.e. proven bacteremia) were selected (Fig. 1).

Patient characteristics

In all 5997 patients with suspected infection: 45.8% had normothermia, 44.6% hyperthermia and 5.6% hypothermia. Temperature was missing in 4.0% (Fig. 1). Normothermic patients were less frequently categorized as urgent (11.4%) than patients with hyperthermia (17.5%) or hypothermia (46.2%). The average NEWS was higher for patients with hyperthermia (6 ± 3.4) compared to patients with normothermia (4 ± 3.3), but comparable if temperature and heart rate were not incorporated (3 ± 2.9 for hyperthermia versus 3 ± 2.9 for normothermia). Patients with hypothermia had a higher NEWS than patients with normothermia, also without incorporating temperature and heart rate (5 ± 3.7 for hypothermia versus 3 ± 2.9 for normothermia). CRP and leukocyte count did not differ between normothermic patients and patients with hyperthermia. Hypothermic patients had more deviating inflammation parameters (Table 1).

In the sensitivity analysis limited to 934 patients with positive blood culture, 34.7% had normothermia, 61.1% hyperthermia and 3.2% hypothermia. Temperature was missing in 1.0% (Fig. 1). Most patient characteristics were comparably distributed to patients with a blood culture taken (Supplementary Appendix B, Supplemental digital content 1, *http://links.lww.com/EJEM/A306*). However, compared to patients with hyperthermia, normothermic patients needed vasopressors more frequently (2.5 versus 5.2%). CRP and leukocyte count were higher for normothermic patients (resp. median 207 mg/L and 7.8×10^3/μL) than for patients with hyperthermia (resp. median 85 mg/L and 3.7×10^3/μL). Thus, normothermic patients with a positive blood culture appeared more seriously ill than patients with hyperthermia. Comorbidity, expressed as the CCI, was equal for each temperature group (Supplementary Appendix B, Supplemental digital content 1, *http://links.lww.com/EJEM/A306*).

Temperature and initiation of antibiotic therapy

In all 5997 patients with suspected infection, antibiotic therapy was more often initiated in the ED if patients had hyperthermia or hypothermia (resp. 53.5 and 47.6%) compared to normothermic patients (27.6%, crude OR [95% CI] for hyperthermia: 2.96 [2.65–3.31] and for

hypothermia 2.21 [1.77–2.75], Table 2). These associations were independent of covariates (adjusted OR [95% CI] for hyperthermia: 2.59 [2.27–2.95] and for hypothermia 1.42 [1.08–1.87], Table 2).

In the sensitivity analysis limited to 934 patients with positive blood culture, antibiotic therapy was also more often administered in patients with hyperthermia or hypothermia (resp. 86.9 and 93.3%) compared to patients with normothermia (72.2, crude OR [95% CI] for hyperthermia: 2.64 [1.88–3.73] and for hypothermia 5.54 [1.29–23.84], Table 2). After adjustment, these associations subsisted (adjusted OR [95% CI] for hyperthermia: 2.40 [1.59–3.61] and for hypothermia 5.91 [1.00–32.86], Table 2).

Temperature and mortality (30-day)

In all 5997 patients with suspected infection, the mortality rate was higher for normothermic patients (7.4%) than for patients with hyperthermia (4.7%, Fig. 1). There was an inverse association between temperature and mortality rather than a U-shaped association (Fig. 2a). An increasing temperature was associated with lower 30-day mortality, both crude (OR per degree increase [95% CI], 0.66 [0.62–0.71]) and after adjustment for covariates (OR per degree increase [95%CI], 0.74 [0.69–0.81], Table 3).

In the sensitivity analysis limited to 934 patients with a positive blood culture (n = 934), normothermic patients had a higher mortality rate (13.6%) compared to those with hyperthermia (7.0%). An increasing temperature was associated with lower mortality both crude (OR per degree increase [95% CI], 0.62 [0.52–0.74]) and after adjustment for covariates (OR per degree increase [95%CI], 0.72 [0.58–0.89], Table 3).

For both the total of ED visits (N = 65 986) and for patients without a blood culture taken (n = 59 989), mortality rates were higher for patients with hyperthermia (4.0–4.1%) than for patients with normothermia (2.9–3.0%), which corresponds to scoring by MTS and NEWS (Fig. 1).

Temperature and hospital admittance

In all patients with suspected infection, hyperthermia resulted more often in hospital admittance (83.8%) than normothermia (73.5%, Supplementary Appendix C, Supplemental digital content 1, *http://links.lww.com/EJEM/A306*).

In the sensitivity analysis limited to patients with positive blood culture, there were no statistically significant differences in hospital admittance between temperature groups, Supplementary Appendix C, Supplemental digital content 1, *http://links.lww.com/EJEM/A306*).

Temperature and blood culture positivity

Blood cultures were positive in 11.9% of patients with normothermia and in 20.9% of patients with hyperthermia. An increasing temperature was associated with blood culture positivity both crude (OR [95% CI], 1.46 [1.36–1.40], Fig. 2b) and after adjustment for covariates (OR [95% CI], 1.48 [1.37–1.60], Supplementary Appendix D, Supplemental digital content 1, *http://links.lww.com/EJEM/A306*).

Negative blood cultures

In patients with negative blood cultures (n = 5063), comparable rates of antibiotic administration, 30-day mortality, and hospital admittance for normothermia, hyperthermia and hypothermia were found as for patients with a (positive) blood culture taken (Supplementary Appendix Table E, Supplemental digital content 1, *http://links.lww.com/EJEM/A306*).

Discussion

In this study, the association of temperature with the initiation of antibiotic therapy and additionally 30-day mortality was addressed in patients attending the ED with suspected infection (i.e. blood culture taken). Normothermic infections were common, and antibiotic therapy was significantly less frequently initiated if patients presented with normothermia, compared to presentations with hyperthermia or hypothermia. However, normothermia was associated with higher 30-day mortality than hyperthermia, as has been described by others [8, 21, 22]. Patients with hypothermia had the highest mortality risk. Moreover, in patients with proven bacteremia (i.e. positive blood cultures), normothermia implied higher disease severity, and yet these patients received less antibiotic therapy.

Higher mortality among normothermic patients with infection has multiple explanations. One explanation is that normothermic patients are potentially incorrectly assessed as lower acuity because fever is lacking. Which can result in a delay in diagnosis and initiation of antibiotic therapy if these patients are first observed (i.e. 'watchful waiting'), and antibiotic therapy is started only when the temperature becomes deviant or the patient deteriorates. These delays are understandable because hyperthermia is considered a marker of infection [23]. However, hyperthermia is a poor predictor of mortality among infectious patients as an increasing temperature was associated with lower 30-day mortality (i.e. an inverse association). Clinical decision support systems such as NEWS [6] and MTS [5] assign a higher mortality risk to hyperthermia than to normothermia. This seems appropriate for a general ED population but not for patients with infection.

To examine to what extent higher mortality among normothermic patients with infection is attributable to the lack of antibiotic treatment can only fairly be studied in research with prospective designs. Retrospective data does not allow to study the effects of antibiotic therapy on mortality because there is a high risk of bias due to confounding by indication (i.e. patients that are already at high risk of dying are more likely to receive antibiotic therapy than lower acuity patients) [19, 20]. Nonetheless, it is likely to assume that mortality among patients with infection could at least, for some extent, have been

reduced, would these patients have had early initiation of antibiotic therapy in the ED [10].

Aside from inadequate recognition of disease severity and subsequent lack of antibiotic treatment, there are other potential explanations for higher mortality among normothermic patients with infection. Normothermic patients may have an impaired febrile response to infection due to older age, comorbidity, use of antipyretic drugs or because of more critical acute illness [23]. As a result, normothermic patients might represent a patient group that is older and has higher disease severity than patients with hyperthermia. There were no differences in age or comorbidity; however, among normothermic patients with bacteremia, CRP and leukocyte levels were higher compared to patients with hyperthermia. Also, these normothermic patients needed vasopressors more frequently in the ED. Consequently, physicians should be aware that in patients with infection, normothermia is not a sign of minor disease but may even imply a more serious course of illness. If the only drawback of initiation of antibiotic therapy is the absence of fever, physicians should more often reconsider starting.

Limitations

This study has some limitations. Retrospectively collected data was used, which makes it prone to bias [19]. However, the quality of available data was high as all data used was essential for daily clinical practice. To preserve generalizability, patients with a blood culture taken in the ED were selected because this is the point in time in which antibiotic therapy should be initiated if indicated according to the surviving sepsis campaign [10]. However, patients with a blood culture taken may also resemble noninfectious pathology. Therefore, analyses were repeated in the subgroup of patients with proven bacteremia, which is a group that retrospectively had a true bacterial infection. Also, blood cultures were taken in case of a certain suspicion of infection (e.g. sepsis), which potentially ruled out patients with localized infections, and therefore, our results are not generalizable to this group. Another limitation of this study is that only admission temperature was accessible, and there were no data on the use of antipyretic drugs prior to the ED visit. Additionally, in our research setting (the ED), it was not possible to obtain all SOFA criteria, and therefore, our population could not formerly be defined as being septic or not according to the sepsis-3 definitions. We were unable to study the association between temperature and delays in antibiotic administration because there was no data on the exact time to antibiotic administration in the ED. However, if antibiotics are prescribed for patients that are hospitalized, the first dose is always given in the ED independent from ED length of stay. Moreover, it would be interesting to study the effects of antibiotic therapy on mortality among normothermic patients with infection. However, we were unable to examine this with our retrospective study design because of the high risk of bias due to confounding by indication (i.e. patients that are already at high risk of dying are more likely to receive antibiotic therapy than lower acuity patients) [19,20]. Additionally, the possibility of missing cases receiving antibiotic therapy in patients with suspected infection cannot be excluded due to data collection with automatic text mining. However, for patients with proven bacteremia, patient charts were manually reviewed, and comparing both ways of data collection did not affect the results.

Conclusion

In this retrospective cohort study in patients presenting with infection, normothermia was associated with receiving less antibiotic therapy in the ED compared to presentations with hyperthermia. Moreover, normothermia was associated with a higher mortality risk than hyperthermia. Physicians should be aware that normothermia does not exclude infection and may even imply a more serious course of illness.

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R.S., A.B., J.A., J.D.S. and H.L. conceptualized the article. R.S and H.L. prepared the methodology. R.S., A.B., J.A. and J.D.S. formally analyzed and investigated the article. R.S. and A.B. wrote and prepared the original draft. J.A., J.D.S., A.V., S.S. and H.L. wrote, reviewed and edited the article. H.L., A.V. and S.K.N. supervised the study.

The Medical Ethics Committee of the Erasmus MC reviewed the study and concluded that our study did not fall under the scope of the Medical Research Involving Human Subjects Act, and therefore, no informed consent needed to be obtained. Our study is registered under MEC-2018-1744 and MEC-205-106.

Conflicts of interest

There are no conflicts of interest.

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