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An investigation of temperature and fever burdens in patients with sepsis admitted from the emergency department to the hospital

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Abstract

Aim: We sought to collect granular data on temperature burden to further explore existing conflicting information on the relationship between temperature alterations and outcomes in patients with sepsis requiring hospital admission.

Methods: This was a prospective cohort study that enrolled a convenience sample of patients with sepsis or septic shock admitted to the hospital from the emergency department (ED). A "unit of temperature burden (UTB)" was defined as >1°C (1.8°F) above or below 37°C (98.6°F) for 1 min. Fever burden was defined as the number of UTBs >38°C (100.4°F). The primary objective was to calculate the fever burden in patients with sepsis during their ED stay. This was analyzed for patients who present to triage febrile or hypothermic and also for those who developed temperature abnormalities during their ED stay. The secondary objectives were correlating fever and hypothermia burden with in-hospital mortality, Systemic Inflammatory Response Syndrome (SIRS) criteria, and the quick Sequential (Sepsis-Associated) Organ Failure Assessment (qSOFA) score and identification of patients who may benefit from early implementation of targeted temperature management.

Results: A total of 256 patients met the inclusion criteria. The mean age of patients was 60.1 ± 18.4 years; 46% were female and 29.6% were black. The median (interquartile range [IQR]) fever burden for the fever in triage cohort ($n = 99$) was 364.6 (174.3-716.8) UTB and for the no fever in triage cohort ($n = 157$) was 179.3 (80.9-374.0) UTB ($p = 0.005$). The two groups had similar in-hospital mortality (6.1 vs 8.3%; $p = 0.5$). The median fever burden for the fever anytime cohort was 303.8 (IQR 138.8-607.9) UTB and they had lower mortality than the no fever anytime cohort (4.7% vs 11.2%; $p = 0.052$). Patients with fever at triage had higher mean SIRS criteria than those without (2.8 vs 2.0; $p < 0.001$) while qSOFA points were similar ($p = 0.199$). A total of 27 patients had hypothermia during their ED stay and these patients were older with higher mean SIRS criteria.

Conclusions: Patients with sepsis and septic shock have a significant temperature burden in the ED. When comparing patients who had fever at any time during their ED stay with those who never had a fever, a trend toward an inverse relationship between fever burden and mortality was found.

KEYWORDS
emergency department, fever burden, in-hospital mortality, sepsis, temperature burden

INTRODUCTION

Sepsis, the syndrome of the body's pathophysiologic response to infection, is common and results in significant morbidity, mortality, and health care costs.[1–3] The first international sepsis definitions, created in 1992, included an elevated (>38°C [>100.4°F]) or decreased (<36°C [<96.8°F]) temperature as part of the Systemic Inflammatory Response Syndrome (SIRS) criteria used to screen for patients with possible sepsis.[4] This inclusion was an acknowledgment that body temperature alteration often accompanies infection and can help detect cases of sepsis. The role of fever control in patients with sepsis is unclear.[5] Some physicians have argued that temperature should be normalized for comfort, to control physiological abnormalities including tachycardia and tachypnea produced by fever, and to control insensible fluid losses produced by fever. Others have argued that elevated temperatures should be allowed to persist naturally and that fever is central to the body's innate ability to fight off infections.[6]

When the committee of experts met to create the third international definition of sepsis (Sepsis-3), the SIRS criteria were removed from the definition due to concerns about insufficient sensitivity and specificity.[7,8] The committee proposed the quick Sequential (Sepsis-Associated) Organ Failure Assessment (qSOFA) score as an alternative to SIRS and provided data from large administrative databases supporting improved capture of patients using qSOFA compared with SIRS. Importantly, this change in the Sepsis-3 definition eliminated the role of an elevated or depressed temperature in the screening process for patients with sepsis.[1,9]

For decades, researchers have investigated the relationship between hypothermia, normothermia, and hyperthermia and outcomes in patients with sepsis[10] and there has also been an interest in a possible role for targeted temperature management (TTM) in the treatment of severe sepsis and septic shock.[11–14] A better understanding of the temperature burden in patients with sepsis or septic shock present on admission, from initial intake in the emergency department (ED) through their ED stay until admission to a general ward or the intensive care unit (ICU), will help to define the time course and burden of sepsis-related pyrexia at the proximal point of critical illness. These granular data on temperature burden may provide preliminary insights into the potential role of temperature modulation via early implementation of TTM in the management of patients with sepsis.

Objectives

Primary objective

The primary objective of this study is to calculate the "temperature burden," with a "unit of temperature burden (UTB)" defined as >1°C (1.8°F) above or below 37°C (98.6°F) for 1 min, in patients with sepsis admitted to the hospital. A temperature burden can be positive (fever burden), denoting a period of fever, or negative, denoting a period of hypothermia. In this objective, any variation from the defined "normal body temperature" of 36–38°C will be included in the analysis of temperature burden. This will be analyzed for patients who present to triage febrile or hypothermic and also for those who develop temperature abnormalities during their ED stay.

Secondary objectives

1. To correlate temperature burden with in-hospital mortality (IHM);
2. To assess current efforts (therapeutic interventions) taken to control fever or normalize hyperthermia (antipyretic, yes or no);
3. To examine whether there is a relationship between the increasing number of SIRS criteria and UTB and whether there is a relationship between an increasing number of qSOFA criteria and UTB;
4. Assess for data supporting a cohort of patients who may benefit from early implementation of TTM.

MATERIALS AND METHODS

Setting

This study was a secondary analysis of data collected in the ED of a tertiary referral center and academic hospital with an emergency medicine residency program in Philadelphia, Pennsylvania, USA, as part of a prospective study analyzing SIRS vs qSOFA as ED screening criteria (unpublished). The ED is a level-one trauma center with 54 treatment rooms; the ambient temperature is maintained at 72°F (22.2°C) year-round. The secondary analysis was approved by the Institutional Review Board and granted a waiver of informed consent (IRB Control # 15D.562).

Patient screening

The study used academic associates (AAs) supervised by clinical research coordinators to screen for patients eligible for participation. Inclusion criteria were patients >18 years old; nonpregnant; two or more SIRS criteria during the ED stay or at least two qSOFA criteria during the ED stay; a chief complaint consistent with infection; treatment for infection with antibiotics; classification as either infection, sepsis, or septic shock based on Sepsis-3 criteria; and admission to the wards or the ICU at Thomas Jefferson University Hospital between April 2016 and March 2017.

Data collection

The AAs followed a sequential data collection approach, with prospective screening beginning at intake (modified

triage) and continuing until either discharge from the ED or admission to the hospital. Three data sheets were created: (1) initial ED screening; (2) additional ED information capturing basic clinical interventions recommended in the institution's sepsis protocol; and (3) in-patient information. If a patient aged 18 years or older had a chief complaint consistent with infection and either one or more SIRS criteria or one of the three components of the qSOFA score, the patient was considered "initial screen positive" and additional information was gathered. The AAs then reassessed them every 2 h to see if they subsequently met the SIRS or qSOFA inclusion criteria. Patients who met these inclusion criteria had additional data collected, including demographics (age, sex, race, and comorbidities); serial ED vital signs including temperature (three sets: intake, worst, and discharge from ED); ED length of stay and inpatient admission location (ward vs ICU). Vital signs including temperature were obtained by nurses at intervals that fit into the ED workflow with recommended repeat vital signs occurring at least every 4 h. Acute organ dysfunction attributed to sepsis was defined following the criteria of the 2nd International Sepsis Definitions.

Admitted patients meeting inclusion criteria constituted the final study cohort and had additional data collected including survival to discharge, hospital length of stay, and discharge location. Fever management including acetaminophen, chilled saline, ice bags, and cooling blankets was documented in binary fashion (Yes/No). Screening and data collection sheets were stored in a secured, dedicated research space. Data accuracy was validated by a second AA or clinical coordinator and transcribed from the data collection sheets into a REDCap (Vanderbilt University, Nashville, Tennessee) database, which was constructed exclusively for this clinical investigation. Preliminary classification as infection, sepsis, or septic shock was performed by the AAs, then confirmed or modified by study staff (JP, JLB, and DFG), and reviewed by the senior author (DFG) for accuracy. After data collection, because of limitations in data quality and wide temporal variations in inpatient temperature points, the primary analysis was limited to ED temperature values and ED fever burden analysis.

Statistical analysis

For descriptive analysis, continuous data were expressed as means (± standard deviations) and differences were tested using the Student *t* test. Categorical variables were presented as proportions and analyzed using the chi-square test. SIRS are reported as median and interquartile range (IQR). Temperature burden was calculated using a sensitivity analysis where temperature was analyzed over time using multiple temperature points during the ED stay and presented as medians with hypothesis testing by the Kruskal–Wallis test. Time zero was defined as the first temperature, usually obtained at ED intake. The temperature at time zero was assigned to the entire time frame until the next temperature measurement and so on after each subsequent temperature value was obtained. To further assess the implications of temperature variation, this was calculated as follows: (1) A unit of "temperature burden," UTB, was defined as >1°C (1.8°F) above or below 37°C (98.6°F) for 1 min and analyzed over the length of the ED stay; in other words, any temperature value between 36°C and 38°C contributed zero UTB to the patient's total UTB; (2) patients were then classified as having fever at triage or fever anytime during their ED stay (fever burden); (3) patients were further subgrouped into those with hypothermia, normothermia, or fever at triage.

RESULTS

Numbers screened and enrolled

During the study period (April 1, 2016, to March 25, 2017), approximately 61,000 patients presented to the ED; 1003 patients were initially screened positive; 303 patients met the SIRS and/or qSOFA inclusion criteria; and 256 patients were classified as having sepsis or septic shock, complete data collection for analysis, and comprised the final study cohort (Figure 1).

Demographics and clinical data

The average age of the patients in the final study cohort was 60.1 ± 18.4 years; 54% were male; 58.4% were white; 29.6% were black; and 11.6% were nursing home residents. IHM was 7.5% (Table 1). The median number of SIRS criteria (median [IQR]) for the cohort was 2 (2-3); the median number of qSOFA points was 1 (0-1). The mean lactate level was 2.7 ± 2.1 mmol/L (Table 2); 190 patients (74.2%) were classified as having sepsis and 66 (25.8%) as having septic shock. A total of 99 patients (38.7%) were febrile in triage; 148 patients (57.8%) had a temperature over 38°C (100.4°F) at some point during their ED stay. All 148 patients with fever in the ED (100%) received antipyretic medication; no other means of temperature control were used in the ED (Table 3).

Fever burden data

Fever in triage

The median (IQR) units of fever burden (UTB) for the fever in triage cohort ($n = 99$) was 365 (174-717) and for the no fever in triage cohort ($n = 157$) was 179 (81-374; $p = 0.005$). Compared with patients with no fever in triage, the fever in triage cohort was younger (56.4 vs 62.9 years; $p = 0.005$) and had similar IHM (6.1% vs 8.3%; $p = 0.5$). Patients with fever in triage had a higher median number of SIRS criteria than those in the no fever in triage cohort: 3 (2-3) vs 2 (2-2);

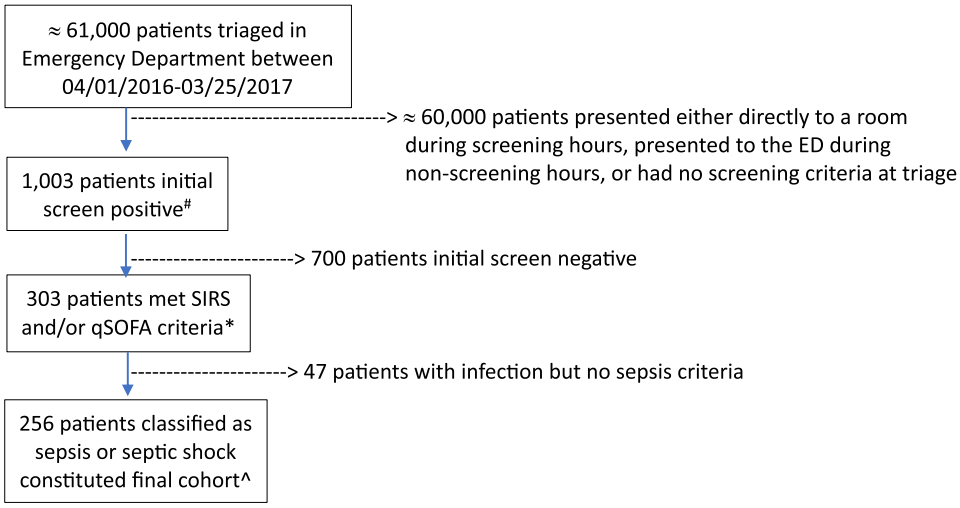

FIGURE 1 Patient recruitment flowchart. qSOFA, quick Sequential (Sepsis-Associated) Organ Failure Assessment; SIRS, Systemic Inflammatory Response System Criteria.

TABLE 1 Demographics and outcomes.

Variable	Values (N=256)
Age (years), mean ± SD	60.1 ± 18.4
Sex, n (%)	
Female	118 (46)
Male	138 (54)
Race, n (%)	
White	149 (58)
Black	76 (30)
Asian	18 (7)
Hispanic	17 (7)
No PCP	87 (34)
NH resident	30 (12)
Emergency Severity Index (ESI), n (%)	
ESI-1	6 (2)
ESI-2	107 (42)
ESI-3	143 (56)
Hospital variables	
Ever admitted to ICU, n (%)	72 (28)
Ever intubated, n (%)	27 (11)
In-hospital mortality, n (%)	19 (7)
LOS at the hospital (n = 240)	8.1 ± 7.7

Abbreviations: ICU, intensive care unit; LOS, length of stay; NH, nursing home; PCP, primary care physician; SD, standard deviation.

$p < 0.001$. There was no significant difference in median triage qSOFA points in the fever in triage group vs the no fever in triage group ($p = 0.199$; Table 3).

Fever anytime in the ED

The median fever burden for the fever anytime in the ED cohort was 304 (139-608) UTB. Compared with no fever anytime in the ED, the fever anytime cohort was younger (56.1 vs 66.4 years; $p < 0.001$) and trended toward lower IHM (4.7 vs 11.2%; $p = 0.052$). Similar to those with fever in triage, patients with fever anytime in the ED had a higher median number of SIRS criteria than those who never developed a fever during their ED stay: 2 (2-3) vs 2 (2); $p < 0.001$. There was a significant difference in median qSOFA points in the fever anytime cohort vs the no fever anytime cohort ($p = 0.035$; Table 4).

Hypothermia, normothermia, and fever data

Twenty patients in the no fever in triage cohort (20/157; 12.7%) had hypothermia (<36°C [96.8°F]) as their first temperature reading. These patients were older, had higher median triage SIRS criteria, and a trend toward higher median triage qSOFA scores when compared with the normothermia and febrile groups at triage. Forty-nine (35.8%) patients in the normothermia at triage cohort became febrile at some point during their ED stay, while seven (5.1%) became hypothermic (Table 5). In comparison, no patients moved from the fever at triage to the hypothermia category or vice versa.

The median ED fever deviation was statistically significantly higher for patients who were febrile in triage vs those who developed a fever during their ED stay (365 vs 179; $p = 0.005$) and the median ED hypothermia deviation was higher for those who were hypothermic in triage vs

those who developed hypothermia during their ED stay, 281 (153-391) vs 114 (26-561; p = 0.086), but this did not reach statistical significance (Table 5).

TABLE 2 Clinical variables.

Variable	Values
Sepsis screening variables	
Temperature (°F) (n = 255), mean ± SD	99.9 ± 2.2
Heart rate (beats/min) (n = 255), mean ± SD	109 ± 21
Respiratory rate (breaths/min) (n = 256), mean ± SD	20 ± 5
White blood cell count (1000/μL) (n = 254), mean ± SD	14.4 ± 8.9
Band count (%) (n = 56), mean ± SD	18 ± 15
Systolic blood pressure (mmHg) (n = 255), mean ± SD	120 ± 24
GCS (n = 255), mean ± SD	14 ± 2
Total SIRS, triage (n = 256), median (IQR)	2 (2-3)
Total qSOFA, triage (n = 256), median (IQR)	1 (0-1)
Sepsis care metrics, n (%)	
Blood cultures, two or more sets, in ED before ABx	250 (97.6)
ABx in ED	236 (92)
Lactate checked	242 (94.4)
Lactate (mmol/L) (n = 240), mean ± SD	2.7 ± 2.1
Fluid in ED, n (%)	250 (97.6)
Amount fluid, 6 h (mL) (n = 250), mean ± SD	1998 ± 1069
Number of acute organ dysfunctions, n (%)	
1	105 (41.2)
2	88 (34.4)
3	44 (17.2)
≥4	19 (7.3)
Final sepsis classification, 3rd international definitions, n (%)	
Sepsis	190 (74.2)
Septic shock	66 (25.8)

Abbreviations: ABx, antibiotics; ED, emergency department; GCS, Glasgow Coma Score; IQR, interquartile range; qSOFA, quick Sequential (Sepsis-Associated) Organ Failure Assessment; SD, standard deviation; SIRS, Systemic Inflammatory Response System Criteria.

DISCUSSION

This study demonstrates a significant early temperature burden in patients with sepsis admitted from the ED to the hospital wards or ICU. This temperature burden can be a fever burden or a hypothermia burden. An inverse relationship existed between fever burden and mortality. When classified into those who were febrile at any time during their ED stay and those who were never febrile, the inverse relationship between fever burden and mortality reached statistical significance. This research presents very granular data about temperature and fever in patients with sepsis, providing quantifiable insight into the amount and duration of temperature deviation during the ED stay for patients with sepsis admitted to the hospital.

The findings that there was a significant inverse relationship between overall fever burden and IHM in patients with sepsis suggest that elevated temperatures in the ED may not require modulation by temperature management strategies other than antipyretics, which is administered for patient comfort only and not impact outcomes. These results are consistent with those of Arons et al15 who explored the effect of ibuprofen on patients with sepsis in the ICU. In patients with fever, treatment with ibuprofen did not have any mortality benefit but did significantly decrease body temperature. Similarly, in the HEAT trial, Young and colleagues[16] randomized ICU patients with fever (temperature ≥38°C) and known or suspected infection to receive either 1000 mg of acetaminophen or placebo every 6 h until ICU discharge, resolution of fever, antimicrobial termination, or death. There was no difference in ICU-free days or mortality in the two groups. Regardless of these results, antipyretics are consistently administered to patients for their comfort and to manage physiological abnormalities. Our findings, which show that 100% of patients with a fever during their ED stay received antipyretic medication and that this group had lower IHM, support the continued use of this comfort strategy. However, these results do not allow us to draw any conclusions about the role of antipyretics in reducing mortality within our specific patient cohort.

TABLE 3 Fever burden in the fever at triage vs fever at triage cohorts.

	No fever in triage (≤38°C) (n = 157)	Fever in triage (>38°C) (n = 99)	p value
Age (years), mean ± SD	62.9 ± 17.2	56.4 ± 18.7	0.005
Sex (male), n (%)	82 (52.9)	54 (54.6)	0.8
SIRS (triage), median (IQR)	2 (2-3)	3 (2-3)	<0.001
qSOFA (triage), n (%)			
0	71 (45.2)	50 (50.5)	0.199
1	73 (46.5)	36 (36.4)	
2	13 (8.3)	13 (13.1)	
IHM, n (%)	13 (8.3)	6 (6.1)	0.5
ED fever burden (UTB × min, median (IQR)	179 (81-374)	365 (174-717)	0.005

Abbreviations: ED, emergency department; IHM, in-hospital mortality; IQR, interquartile range; qSOFA, quick Sequential (Sepsis-Associated) Organ Failure Assessment; SD, standard deviation; SIRS, Systemic Inflammatory Response System Criteria; UTB, unit of temperature burden.

TABLE 4 Fever burden at any time during ED stay vs no fever burden.

	No fever anytime (≤38°C) [*n* = 108]	Fever anytime (>38°C) [*n* = 148]	p value
Age (years), mean ± SD	66.4 ± 16.8	56.1 ± 17.6	<0.001
Sex (male), n (%)	56 (52.8)	80 (54.1)	0.847
SIRS (triage), median (IQR)	2 (2-2)	2 (2-3)	<0.001
qSOFA (triage), n (%)			
0	42 (38.9)	79 (53.4)	0.035
1	56 (51.9)	53 (35.8)	
2	10 (9.3)	16 (10.8)	
IHM, n (%)	12 (11.2)	7 (4.7)	0.052
ED fever burden (UTB × min), median (IQR)	N/A	304 (139-608)	N/A

Abbreviations: ED, emergency department; IHM, in-hospital mortality; N/A, not applicable; IQR, interquartile range; qSOFA, quick Sequential (Sepsis-Associated) Organ Failure Assessment; SD, standard deviation; SIRS, Systemic Inflammatory Response System Criteria; UTB, unit of temperature burden.

TABLE 5 Fever and hypothermia burdens when classified as hypothermia, normothermia, or fever at triage.

	Hypothermia in triage (<36°C) (n = 20)	Normothermia in triage (36°C–38°C) (n = 137)	Fever in triage (>38°C) (n = 99)	p value
Age (years), mean ± SD	67.2 ± 19.6	62.3 ± 16.8	56.4 ± 18.7	0.009
Sex (male) (*n* = 254), n (%)	7 (35.0)	75 (55.6)	54 (54.6)	0.220
SIRS (triage), median (IQR)	3 (2-4)	2 (2-2)	3 (2-3)	<0.001
qSOFA (triage), n (%)				
0	4 (20)	67 (48.9)	50 (50.5)	0.057
1	13 (65)	60 (43.8)	36 (36.4)	
2	3 (15)	10 (7.3)	13 (13.1)	
IHM, n (%)	3 (15.8)	10 (7.3)	6 (6.1)	0.333
ED fever burden (UTB × min), median (IQR)	N/A	179 (81-374) [a]	365 (174-717)	0.005
ED hypothermia burden (UTB × min), median (IQR)	281 (153-391)	114 (26-565)[b]	N/A	0.086

Abbreviations: ED, emergency department; IHM, in-hospital mortality; IQR, interquartile range; qSOFA, quick Sequential (Sepsis-Associated) Organ Failure Assessment; SD, standard deviation; SIRS, Systemic Inflammatory Response System Criteria; UTB, unit of temperature burden.

[a]49 (35.8%) patients with normothermia in the triage cohort became febrile during their ED stay.

[b]7 (5.1%) patients with normothermia in the triage cohort became hypothermic during their ED stay.

Our findings of an inverse relationship between fever burden and IHM suggest that increased temperature in patients with sepsis may be adaptive and protective, or that patients who are healthier at baseline more frequently mount a fever in response to pathogen stimulation. Several recent studies have revealed similar results. Yamamoto et al[17] demonstrated an inverse relationship between body temperature and 30-day IHM in patients with bacterial infection, with the greatest benefit at temperatures >40°C (odds ratio [OR] 0.1, 95% CI [0.04–0.4]; p < 0.001) compared with normothermia of 36–36.9°C (OR 0.3, 95% CI [0.2–0.8]; p < 0.001). In addition, in patients with sepsis or septic shock admitted to ICUs in Sweden, there was a linear inverse association between body temperature and mortality, with body temperature as the best predictor of survival among all clinical signs.[18] By contrast, an analysis from a multicenter prospective survey of sepsis, performed by Kushimoto et al,[19] did not find any significant relationship between mortality and body temperature in patients with body temperatures in the following categories: 37.6°C–38.5°C, 38.6°C–39.5°C, and ≥39.6°C, when compared with patients with normothermia (36.6°C–37.5°C). However, they did find significantly increased mortality in patients with the lowest body temperatures (≤35.5°C) when compared with patients with normothermia (36.6°C–37.5°C) (40.4% vs 20.5%; OR 3.096; p = 0.001) and for patients with a body temperature of 35.6°C–36.5°C when compared with normothermia (34.4% vs 20.5% mortality; OR 2.032; p = 0.047). Further investigations have combined temperature variation with other vital sign trajectories to create subphenotypes of patients with sepsis[20] and have examined the longitudinal temperature trajectories, classifying patients into slow and fast resolvers.[21] These more granular approaches allow the identification of subgroups with variations in mortality and potential benefits from temperature-modulation strategies.

Although there is still debate about the benefit of fever in patients with sepsis, it is generally accepted that patients with sepsis who present with hypothermia have higher rates

of morbidity and mortality.[15–23] Patients with sepsis with hypothermia have been shown to have significantly higher rates of altered mental status, central nervous system dysfunction, increased serum bilirubin concentrations, prolonged prothrombin time, and circulatory shock[22]; higher lactate levels, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and lower mean arterial pressures[15]; and increased organ failure, disseminated intravascular coagulopathy, and SOFA scores.[23] Consistent with these studies, we found that patients with no fever and patients with hypothermia, defined as a duration of time with a temperature <36°C (96.8°F), had statistically higher IHM when compared with patients with a fever at some point during their ED stay. Our data support these findings regarding patients with sepsis with hypothermia, although our small sample size of patients with hypothermia precluded statistical significance. These findings raise the hypothesis that controlled normothermia may have a role in patients with initially hypothermic sepsis.

Temperature burden, obtained by systematic iterative temperature measurements at specified time intervals, should be used for a more precise depiction of thermoregulatory deviations, both toward hypothermia and toward fever, in the critically ill. Current studies stratify patients into categories with various temperature cutoff points, which complicates comparison and analysis. Using temperature and fever burden could standardize differences in body temperature reported in studies. Future studies could investigate whether continuous vital sign monitoring can quantify the temperature burden and serial SIRS criteria, if these can be correlated with outcomes in patients with sepsis, and whether specific interventions can be targeted to temperature abnormalities associated with poor clinical outcomes.

Limitations

This study has a number of important limitations. First, it is a single-center study and the results may not be generalizable to other EDs and hospitals in different settings or patient populations. Second, although all patients enrolled in the study were admitted to the hospital and met Sepsis-3 criteria for either sepsis or septic shock, the overall mortality was only 7.5%. This low mortality may have underpowered our statistical analyses. Third, we observed less frequent and irregular temperature recordings for inpatients, which prevented us from calculating the ongoing temperature burden after their departure from the ED. Fourth, vital sign readings including temperature were obtained by nurses at intervals that fit into their overall ED workflow not at specific, fixed intervals. However, the ED's recommended timing of vital signs (at least every 4 h) was followed in all patients. More systematic data and more accurate calculations of UTB could be obtained if hourly temperature readings were recorded. Fifth, this is a retrospective observational study, not an interventional study, so it was not possible to judge the pros and cons of temperature control in patients with sepsis. Sixth, it is possible that the fever burden is underestimated when severely ill patients are admitted more quickly (e.g., to the ICU), or overestimated when febrile, stable patients wait an extended period for initial evaluation, delaying their second temperature measurement and inflating their temperature burden. Future studies need to collect patient temperatures at fixed times to more accurately assess the true temperature burden. Finally, we did not document the amount of antipyretic use, which may have outcome implications in this patient cohort, although the typical ED dose and medication were most commonly 650 or 1000 mg of acetaminophen.

CONCLUSIONS

This preliminary study of fever and temperature burdens in a cohort of patients with sepsis admitted to the hospital suggested an inverse relationship between fever at any time during ED stay and IHM. Further studies are needed to assess whether this relationship exists in larger more heterogeneous cohorts of patients with sepsis.

The data used in this study are available from the corresponding author for additional analyses given reasonable notice.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to disclose in relation to this work.

DATA AVAILABILITY STATEMENT

The data used in this study are available from the corresponding author for additional analyses given reasonable notice.

ETHICS STATEMENT

Approval of the research protocol: This research was approved by the Thomas Jefferson University Institutional Review Board.
Informed consent: The research protocol was granted a waiver of informed consent (IRB Control # 15D.562).
Registry and registration no. of the study/trial: N/A.
Animal studies: N/A.

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