Intensive Care Med (2004) 30:811–816
DOI 10.1007/s00134-004-2166-z

ORIGINAL

Daliana Peres Bota
Flavio Lopes Ferreira
Christian Mélot
Jean Louis Vincent

Body temperature alterations in the critically ill

Received: 9 July 2003
Accepted: 29 December 2003
Published online: 4 February 2004

D. Peres Bota · F. Lopes Ferreira · C. Mélot · J. L. Vincent (✉)
Department of Intensive Care,
Erasme University Hospital,
Free University of Brussels,
Route de Lennik, 808, 1070 Brussels,
Belgium
e-mail: jlvincen@ulb.ac.be
Tel.: +32-2-5553380
Fax: +32-2-5554555

Abstract *Objective:* To determine the incidence of body temperature (BT) alterations in critically ill patients, and their relationship with infection and outcome. *Design:* Pro-spective, observational study. *Setting:* Thirty-one bed, medico-surgical department of intensive care. *Patients:* Adult patients admitted consecutively to the ICU for at least 24 h, during 6 summer months. *Interventions:* None. *Results:* Fever (BT$\geq$38.3°C) occurred in 139 (28.2%) patients and hypothermia (BT$\leq$36°C) in 45 (9.1%) patients, at some time during the ICU stay. Fever was present in 52 of 100 (52.0%) infected patients without septic shock, and in 24 of 38 (63.2%) patients with septic shock. Hypothermia occurred in 5 of 100 (5.0%) infected patients without septic shock and in 5 of 38 (13.1%) patients with septic shock. Patients with hypothermia and fever had higher Sequential Organ Failure Assessment (SOFA) scores on admission (6.3±3.7 and 6.4±3.3 vs 4.6±3.2; $p<0.01$), maximum SOFA scores during ICU stay (7.6±5.2 and 8.2±4.7 vs 5.4±3.8; $p<0.01$) and mortality rates (33.3 and 35.3% vs 10.3%; $p<0.01$). The length of stay (LOS) was longer in febrile patients than in hypothermic and normothermic (36°C<BT<38.3°C) patients [median 6 (1–57) vs 5 (2–28) and 3 (1–33) days, $p=0.02$ and $p=0.01$, respectively). Among the septic patients hypothermic patients were older than febrile patients (69±9 vs 54±7 years, $p=0.01$). Patients with septic shock had a higher mortality if they were hypothermic than if they were febrile (80 vs 50%, $p<0.01$). *Conclusions:* Both hypothermia and fever are associated with increased morbidity and mortality rates. Patients with hypothermia have a worse prognosis than those with fever.

Keywords Hypothermia · Normothermia · Fever · Infection · Septic shock · Organ failure · Length of stay

Introduction

Fever, defined as a disorder of thermoregulation wherein the hypothalamic set point rises, is a common clinical sign in the intensive care unit (ICU). Although recognized for centuries as an important pathological sign, it is often uncertain whether fever is a friend or a foe. Fever is an important sign of sepsis, but there is also a large spectrum of non-infectious febrile diseases that must be differentiated from infection. Conversely, infection can sometimes be present without fever especially in elderly and debilitated patients [1].

Hypothermia is increasingly recognized as a problem in critical care. Patients presenting with hypothermia, without an obvious cause, should be suspected of having a metabolic disorder such as hypothyroidism, hypopituitarism, or ethanol, barbiturate, or other drug overdose [2]. In the absence of any of these abnormalities, hypothermia can represent a thermoregulatory response to infection.

The proportion of critically ill patients with fever and hypothermia is not well documented. In a group of 100 consecutive ICU admissions, Circiumaru and co-workers [3] recently reported 70 episodes of fever occurring at some time during the ICU stay; however, to our knowledge, no study specifically addresses the question of the prevalence of hypothermia among critically ill patients. Several retrospective studies in patients with Gram-negative bacteremia have shown the mortality rate to be higher among hypothermic patients or patients who failed to produce a febrile response [4, 5, 6]. In a prospective series of 382 septic patients, Clemmer and co-workers [7] reported that 9% were hypothermic, and the mortality rate was significantly higher in these patients than in febrile patients (62 vs 26%). In a clinical trial of ibuprofen in severe sepsis, Arons and co-workers [8] noted a 10% incidence of hypothermia in the study population, with a 90% mortality rate in hypothermic patients in the placebo arm of the study.

The aim of the present study was to determine the frequency of fever and hypothermia in critically ill patients and to analyze their relationships with infection and outcome. Our hypothesis was that fever and hypothermia of infectious origin could be related with a worse outcome than body temperature (BT) alterations of a non-infectious origin.

Patients and methods

The study, performed during a 6-month period (April to July and October to November 1999) included all adult patients consecutively admitted for more than 24 h to a 31-bed medico-surgical department of intensive care of an academic hospital. This unit accepts trauma patients only if they require a neurosurgical intervention. The hospital ethics committee approved this study and, in view of its observational nature, felt that informed consent was not necessary.

Demographic (age, gender), clinical [BT, respiratory rate (RR), heart rate (HR), mean arterial pressure (MAP), Glasgow Coma Scale (GCS)], laboratory, and microbiological data were collected throughout the ICU stay. No additional investigations or procedures were carried out on the patients for the benefit of the study. Antipyretic agents and cooling maneuvers are routinely used in the ICU and this practice was continued during the study. Warming blankets are sometimes used for postoperative patients.

The Acute Physiology and Chronic Health Evaluation (APACHE) II score [9] was calculated for the first 24 h and the SOFA score [10] every 2 days.

Core temperature was considered as the temperature measured rectally, or in the pulmonary artery when a pulmonary artery catheter was in place. In the absence of these measurements the core temperature was approximated by adding 0.5°C to measured axillary or inguinal temperature. In patients after cardiac surgery, the first temperature taken into consideration was measured at least after 8 h following ICU admission.

Patients were divided into three groups according to their core temperature: hypothermia (BT$\leq$36°C) at any time; normothermia (36°C<BT<38.3°C) at all times; and fever (BT$\geq$38.3°C) at any time. Fever after a minimum 48-h period of being afebrile was considered as a new episode of fever. Postoperative fever was defined as fever occurring in the first 4 days after surgery without proven infection [11]. Prolonged fever was defined as fever lasting for more than 5 days.

The Centers for Disease Control (CDC) definitions were used to define the presence of infection [11]. Septic shock was defined according to the ACCP/SCCM consensus guidelines [12].

Statistical methods

Differences between groups for continuous variables were determined using a one-way analysis of variance (ANOVA) with unpaired *t* tests for pairwise comparisons if the variable was normally distributed, or Kruskal-Wallis non-parametric with Mann-Whitney tests if the variable was not Gaussian. Categorical variables were analyzed using chi-square tests. Univariate logistic regression evaluated the potential predictors for BT alteration (i.e., T$\leq$36°C or T$\geq$38.3°C among the following: days on antibiotics; age; days on hemofiltration; days on mechanical ventilation; infection; and SOFA admission. Due to correlation between SOFA day, SOFA admission, and SOFA max, we retained SOFA admission as a predictor. This was followed by a multivariable logistic regression, using backward elimination, to find independent predictors of body temperature alteration. A p value <0.05 was considered statistically significant.

Results

Of the 493 patients (319 men, 174 women) included in the study, 139 (28.2%) had fever and 45 (9.1%) had hypothermia at some point during their ICU stay. Body temperature was measured in the pulmonary artery in 123 patients (25%) for as long as the pulmonary artery catheter was in situ and, thereafter, inguinal or axillary temperature was recorded. Rectal temperatures were measured in 26 patients (5%). Eight patients received renal replacement therapy for 3–7 days. No patients were cooled as a treatment option.

Of the patients with febrile episodes, fever was present on admission in 106 patients (76.3%) and developed during the ICU stay in 33 patients (23.7%). Hypothermia was present on admission in 32 patients (71.1%) and developed during the ICU stay in 13 patients (28.9%). None of the hypothermic patients were receiving drugs that could have influenced their body temperature. The most common causes of fever were infection, cerebral hemorrhage, and post-surgery (Table 1). The main causes of hypothermia were infection, ethanol abuse, sedative overdose, and post-cardiopulmonary resuscitation (CPR; Table 2).

The principal characteristics of the patients are presented in Table 3. Hypothermic and febrile patients were younger than normothermic patients (p=0.02). There were no differences in APACHE II score on admission among hypothermic, normothermic, and hyperthermic patients. The SOFA score on admission was higher in patients with hypothermia and fever than in patients with normothermia (p<0.01). The maximum SOFA score (SOFA max), defined as the highest score for a 24-h period during the ICU stay, and mortality, were higher in hypothermic and

Table 1 Causes of fever (16 patients had two episodes of fever, 6 had three episodes). *ARDS* acute respiratory distress syndrome, *AMI*-acute myocardial infarction, *GI* gastrointestinal

Cause of fever	On admission (*n*=106)	During ICU stay (*n*=33)	Total (*n*=139)
Infection	63	13	76
Cerebral hemorrhage	18	2	20
Postoperative	10	17	27
Trauma	5	0	5
ARDS	2	1	3
AMI	2	0	2
Pancreatitis	3	0	3
GI bleeding	3	0	3

Table 2 Causes of hypothermia

Cause of hypothermia	On admission (*n*=32)	During ICU stay (*n*=13)	Total (*n*=45)
Infection	3	7	10
Ethanol abuse	8	0	8
Sedative overdose	8	0	8
Hypoglycemia	1	1	2
Hypothyroidism	2	1	3
Acute renal failure	2	2	4
Acute hepatic failure	1	2	3
Status post CPR	7	0	7

Table 3 Principal characteristics of the three groups of patients. *SOFA* Sequential Organ Failure Assessment

Characteristic	Hypothermia (*n*=45)	Normothermia (*n*=309)	Fever (*n*=139)
Age (years)	54±18*	61±17	56±17*
Gender (M/F)	29/16	191/118	92/47
Type of admission Medical/surgical	29/16	157/152	88/51*
SOFA admission	6.3±3.7*	4.6±3.2	6.4±3.3*
SOFA day	5.4±3.5	4.5±3.3	5.8±3.0*
SOFA max	7.6±5.2***	5.4±3.8	8.2±4.7***
Duration of mechanical ventilation (days)	1.7±3.1	1.6±3.7	5.2±8.3***
Length of ICU stay (days)**	5 (2–28)	3 (1–33)	6 (1–57)***
APACHE II score	15.4±6.2	13.6±7.0	14.9±7.8
Mortality	33.3***	10.3	35.3***

*$p<0.05$ vs normothermia values expressed as mean±SD
**Values expressed as median (range)
***$p<0.01$ vs normothermia

Table 4 Sources of infection in the 138 infected patients

Source of infection	Hypothermia (*n*=29)	Normothermia (*n*=33)	Fever (*n*=76)
Blood stream[a]	12	3	15
Lungs	8	23	32
Abdomen	9	2	16
Urinary tract	0	4	1
Cardiovascular system	0	0	3
CNS	0	0	7
Skin and soft tissue	0	1	2

[a] Including catheter-related infections

febrile than in normothermic patients (both $p<0.01$). The SOFA score on the day the temperature was considered (SOFA day) was higher in hypothermic than in normothermic and febrile patients ($p=0.01$). In survivors, the length of stay (LOS) and the duration of mechanical ventilation were longer in febrile patients than in hypothermic and normothermic patients (both $p<0.01$).

Patients who developed hypothermia during their ICU stay had a higher SOFA score (6.9±2.6 vs 4.2±1.6) and a higher mortality (67 vs 33%) than those who were admitted with hypothermia.

Infection was identified in 138 patients, including 29 hypothermic, 33 normothermic, and 76 febrile patients (Table 4). ICU-acquired infection was present in 79

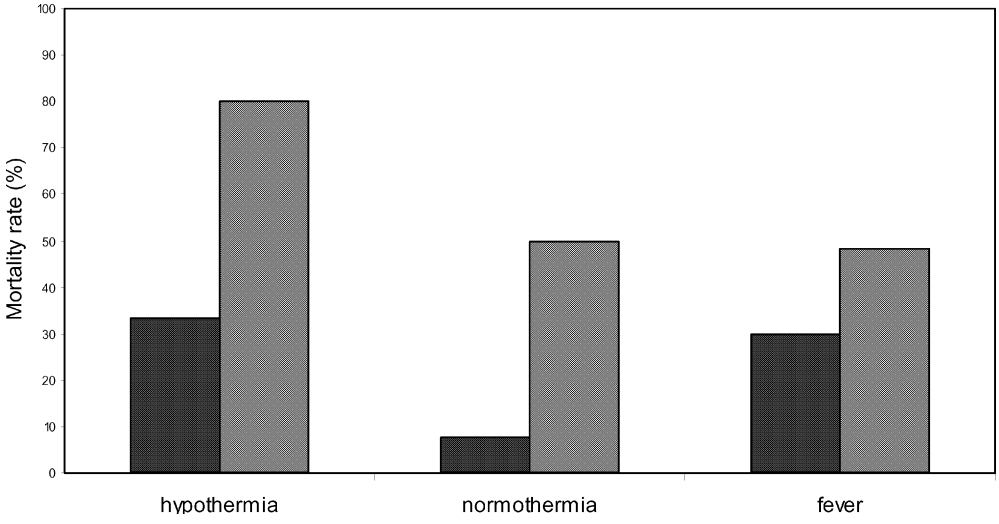

Fig. 1 Overall mortality rates (*black bars*) and mortality rates in patients with septic shock (*gray bars*), in the three groups of patients

patients (7 hypothermic, 23 normothermic, and 49 febrile). Septic shock was diagnosed in 38 patients, including 5 hypothermic (13.2%), 2 normothermic (5.2%), and 31 febrile (81.6%) patients. In these patients, the SOFA score was higher in hypothermic (10.2±4.9) than in febrile (7.2±3.0) patients (p=0.02), and the mortality was higher in patients with hypothermia (80%) than in normothermic (50%) and febrile patients (48.3%; p=0.01; Fig. 1). Infected patients had a higher mortality when BT alterations occurred during the ICU stay than when these alterations were present at admission (p=0.03). Among the non-infected patients, hypothermia that occurred during the ICU stay was associated with a higher mortality rate than fever occurring during the ICU stay (p=0.03).

Sixteen patients had a second episode of fever, 14 of infectious and 2 of non-infectious (cerebral hemorrhage) origin. Six patients developed a third episode of fever that was of infectious origin in all cases.

The mean duration of a febrile episode was 3.2±1.1 days. Forty-one patients had a prolonged fever (>5 days). In 32 of these patients, fever was due to infection and in 9 to a non-infectious process (6 cerebral hemorrhage and 3 trauma). Mortality in patients with prolonged fever was higher than in patients with fever lasting less than 5 days (67.2 vs 22.4%; p<0.01).

The mean duration of postoperative fever was 1.6±1.2 days. An infection was documented in all 10 patients who developed postoperative fever that lasted more than 4 days.

The duration of fever in patients with cerebral hemorrhage was 4.2±1.1 days, and a persistent fever for more than 5 days was attributed to infection in 14 of 19 (73.6%) of these patients.

Multiple logistic regression revealed infection (OR: 10.5; 95% CI: 6.5–17.1; p=0.0001), SOFA admission (OR: 1.16; 95% CI: 1.09–1.24; p=0.0001), and age (OR: 0.97; 95% CI 0.96–0.98; p=0.0001) as independent factors for BT alterations. BT alteration was an independent predictor for mortality (OR: 3.07; 95% CI: 1.65–5.74; p=0.0005).

Discussion

Our study emphasizes that BT alterations are common in ICU settings with fever occurring in 28% of patients and hypothermia in 9% of patients at some rime during their ICU stay. The onset of hypothermia or fever during the ICU stay was generally related to infection and was associated with a worse outcome. In addition, mortality was higher in patients with fever of infectious than of non-infectious origin.

Despite the frequency of BT alterations in ICU patients, there are few data on the epidemiology of fever and hypothermia in critically ill patients. Importantly, BT alterations may have more than one potential cause in ICU patients, and this may represent a limitation of the study as no specific allowance was made for this possibility. Another possible limitation is that the study was conducted predominantly during the summer months, and it is possible that the results may have been different if the study had been conducted during the winter, although the seasonal variations in Belgium's temperate climate are not so large.

The commonest causes of fever in our patients were infection, post-surgery, and cerebral hemorrhage. Others have also shown infection to be a common cause of fever in hospitalized patients [13, 14], although there are few data specifically among ICU patients. Circiumaru and coworkers [3] found, in a prospective study of 93 ICU patients (100 consecutive ICU admissions), that 70% had fever (BT≥38.4°C) at some point during their admission, and this was associated with infection in 53% of cases,

with post-operative fever responsible for the majority of other cases (49%). In our patients, postoperative fever was the primary cause of non-infectious fever, followed by cerebral hemorrhage. In a neurological ICU, 87 of 387 patients developed fever, and 52% of fevers were explained by infection [15]. In 330 patients with acute stroke, Georgilis et al. [16] observed that fever (BT$\geq$37.5°C) was present in 37.6% (22.7% had a documented infection and 14.8% had fever without documented infection). The onset of fever was associated more often with intracerebral hemorrhage than with ischemic infarct and it occurred earlier in patients without recognized infection [16].

An interesting finding in our study was that infection was present in the majority of patients with a fever lasting more than 5 days, and that prolonged fever was associated with a higher mortality; others have reported similar findings [3].

Although fever is the most frequent thermoregulatory response to infection, hypothermia can occur in severe cases of sepsis, usually associated with septic shock. Doherty and co-workers [17] found that 7 of 26 patients with severe infections and shock were hypothermic and had a higher mortality rate (71%) than normothermic patients (37%). Advanced age and decreased mental status appeared to be risk factors for the development of hypothermia in their patients [17]. In a series of 54 elderly patients with hypothermia, Kramer et al. [1] found that the most common cause of hypothermia was sepsis and even proposed that hypothermia in these patients should be treated as sepsis unless proven otherwise, in light of the poor prognosis of this condition. In our study, slightly less than 10% of patients had hypothermia. In 82 critically ill hypothermic patients divided according to where the hypothermia occurred (indoors or outdoors), Megarbane et al. [18] found that principal co-morbidities in outdoor patients were alcohol and drug intoxication, and in indoor patients sepsis and neuropsychiatric disorders. We also found that when hypothermia was present at admission, it was due mainly to ethanol abuse and intoxication, whereas nosocomial hypothermia was of infectious origin in the majority of cases. An interesting finding was that in non-infected patients with hypothermia those who developed the hypothermia in the ICU had a worse outcome than those who had hypothermia on admission. The main underlying disease in these non-infected patients who developed hypothermia during the ICU stay was acute renal and/or hepatic failure. Thermoregulation in these patients thus seems to be impaired, even if the alterations in immune response are not clinically evident.

Clemmer and co-workers [7] reported hypothermia in 9% of 382 patients with the sepsis syndrome. When compared with febrile patients, the hypothermic patients more commonly had central nervous system dysfunction, increased serum bilirubin concentrations, prolonged prothrombin times, and higher mortality rates. In our study, the degree of morbidity (as assessed by the SOFA day score) and mortality were higher in patients with septic shock who developed hypothermia than in those who developed fever.

Conclusion

In conclusion, our observations indicate that fever and hypothermia are often encountered in critically ill patients, affecting approximately one-third of patients. In this mixed ICU, temperature alterations occurring during the ICU stay are related to infection in the majority of cases. Patients with fever or hypothermia have mortality rates three to four times higher than normothermic patients, highlighting the importance of temperature alterations on ICU prognostication.

References

1. Kramer MR, Vandijk J, Rosin AJ (1989) Mortality in elderly patients with thermoregulatory failure. Arch Intern Med 149:1521–1523
2. Reuler JB (1978) Hypothermia: pathophysiology, clinical settings, and management. Ann Intern Med 89:519–527
3. Circiumaru B, Baldock G, Cohen J (1999) A prospective study of fever in the intensive care unit. Intensive Care Med 25:668–673
4. Bryant RE, Hood AF, Hood CE, Koenig MG (1971) Factors affecting mortality of gram-negative rod bacteremia. Arch Intern Med 127:120–128
5. Hodgin UG, Sanford JP (1965) Gram-negative rod bacteremia. An analysis of 100 patients. Am J Med 39:952–960
6. Kreger BE, Craven DE, McCabe WR (1980) Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med 68:344–355
7. Clemmer TP, Fisher CJ, Bone RC, Slotman GJ, Metz GA, Thomas FO (1992) Hypothermia in the sepsis syndrome and clinical outcome. Crit Care Med 20:1395–1401
8. Arons MM, Wheeler AP, Bernard GR, Christman BW, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson W, Wright P, Dupont WD, Swindell BB (1999) Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in Sepsis Study Group. Crit Care Med 27:699–707
9. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
10. Vincent JL, Moreno R, Takala J, Willatts S, de Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 22:707–710
11. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections, 1988. Am J Infect Control 16:128–140

12. ACCP-SCCM Consensus Conference (1992) Definitions of sepsis and multiple organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864–874
13. McGowan JE, Jr., Rose RC, Jacobs NF, Schaberg DR, Haley RW (1987) Fever in hospitalized patients. With special reference to the medical service. Am J Med 82:580–586
14. Filice GA, Weiler MD, Hughes RA, Gerding DN (1989) Nosocomial febrile illnesses in patients on an internal medicine service. Arch Intern Med 149:319–324
15. Commichau C, Scarmeas N, Mayer SA (2003) Risk factors for fever in the neurologic intensive care unit. Neurology 60:837–841
16. Georgilis K, Plomaritoglou A, Dafni U, Bassiakos Y, Vemmos K (1999) Aetiology of fever in patients with acute stroke. J Intern Med 246:203–209
17. Doherty NE, Fung P, Lefkowitz M, Ellrodt AG (1985) Hypothermia and sepsis. Ann Intern Med 103:308
18. Megarbane B, Axler O, Chary I, Pompier R, Brivet FG (2000) Hypothermia with indoor occurrence is associated with a worse outcome. Intensive Care Med 26:1843–1849