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# Hypothermia and cytokines in septic shock

**P. E. Marik**
**G. P. Zaloga**
**and the Norasept II Study Investigators**

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P. E. Marik (✉) · G. P. Zaloga
Department of Internal Medicine,
Division of Critical Care,
Washington Hospital Center,
110 Irving Street, NW, Washington,
DC 20010–2975, USA
e-mail: pem4@mhg.edu
Fax: + 1-202-291 03 86

**Abstract** *Background:* Hypothermic patients with sepsis have been reported to have a higher mortality than febrile septic patients. The failure to mount a febrile response in sepsis is poorly understood. Since the proinflammatory cytokines play a crucial role in the genesis of fever, we postulated that hypothermic patients with sepsis would have lower circulating levels of these cytokines than febrile patients
*Methods:* Patients with septic shock who were enrolled into the placebo limb of the North American study of the safety and efficacy of murine monoclonal antibody to tumor necrosis factor for the treatment of septic shock (NORASEPT II) were analyzed. Body temperature, interleukin-6, tumor necrosis factor α, soluble tumor necrosis factor receptor-55, and soluble tumor necrosis factor receptor-75 concentrations were measured at enrollment. The study population was divided into a hypothermic (temperature ≤ 35.6 °C) and a febrile group (temperature ≥ 38.3 °C) according to the core temperature at enrollment (normothermia was an exclusion criteria). Clinical, demographic, and cytokine data were extracted, allowing for comparisons between these two groups of patients. In addition, the correlation between the core body temperature and cytokine levels at enrollment was determined
*Results:* A complete data set was available for 930 patients; 195 patients (21 %) were hypothermic at enrollment. The 28-day survival of these patients was significantly lower than that of the febrile patients (34 % vs. 59 %, $p < 0.001$). Hypothermia (and enrollment temperature) were independent predictors of mortality. The hypothermic patients had a higher incidence of organ dysfunction at enrollment than the febrile patients. There was no significant difference in the cytokine profile between the two groups of patients. In addition, there was no correlation between the core body temperature at enrollment and the circulating levels of cytokines measured
*Conclusion:* Hypothermic patients with septic shock have a significantly higher mortality with a higher incidence of organ dysfunction than febrile septic shock patients. The hypothermia in these patients cannot be explained by lower levels of circulating proinflammatory cytokines.

**Key words** Fever · Hypothermia · Cytokines · Interleukin-6 · Tumor necrosis factor · Soluble tumor necrosis factor receptors

## Introduction

Although fever is recognized as a cardinal feature of sepsis, some patients with serious infections are hypothermic on presentation to hospital. Although fever has some harmful effects, fever appears to be an adaptive response which has evolved to help rid the host of invading pathogens [1, 2, 3, 4]. Temperature elevation has been shown to enhance several parameters of immune function, including antibody production, T-cell activation, and neutrophil and macrophage function [5, 6, 7, 8]. Thus, inability to mount a febrile response may predispose to a worse outcome. The mortality of hypothermic patients with sepsis has been reported to be twice that of febrile septic patients [9, 10, 11]. However, the etiology of hypothermia during sepsis has not been established [9, 10, 11].

The proinflammatory cytokines tumor necrosis factor (TNF) α and interleukin (IL) 6 as well as IL-1 and δ-interferon play a pivotal role in the generation of the febrile response. These cytokines bind to specific receptors located in close proximity to the preoptic region of the anterior hypothalamus [12, 13]. Here the cytokine receptor interaction activates phospholipase $A_2$, resulting in the liberation of plasma membrane arachidonic acid as substrate for the cyclo-oxygenase pathway. These cytokines also appear to increase cyclo-oxygenase expression directly, leading to liberation of prostaglandin $E_2$. This small lipid mediator diffuses across the blood-brain barrier, where it acts to decrease the rate of firing of preoptic warm-sensitive neurons, leading to activation of responses designed to decrease heat loss and increase heat production [12, 14].

The failure of the septic patient to mount a febrile response may conceivably result from diminished cytokine production (prehypothalamic defect), an abnormality of hypothalamic temperature regulation, or a failure of the peripheral heat generating mechanism (posthypothalamic defect) [11, 13]. We hypothesized that hypothermia in septic patients is due to a defect in proinflammatory cytokine generation (i.e., a prehypothalamic defect). In order to test this hypothesis we utilized data from the placebo limb of the North American study of the safety and efficacy of murine monoclonal antibody to TNF for the treatment of patients with septic shock (NORASEPT II). In this study IL-6, TNF-α, soluble TNF receptors 55 (sTNF-R55) and 75 (sTNF-R75) levels were drawn at randomization. A secondary aim of this study was to determine whether any clinical or laboratory features characterize patients with hypothermia.

## Methods

The placebo limb of the NORASEPT II database was analyzed. The details of the NORASEPT II study have been previously published [15]. In summary, adults older than 18 years of age admitted to hospital with septic shock and who met all the following criteria were eligible for enrollment: (a) duration of shock less than 12 h, (b) clinical evidence of acute infection, (c) a core temperature of 38.3 °C/101 °F or higher (febrile group) or one of 35.6 °C/96 °F or lower (hypothermic group), (d) tachycardia, (e) need for mechanical ventilation or tachypnea, and (f) evidence of organ dysfunction within 12 h prior to enrollment. Shock was defined as hypotension (a systolic blood pressure less than 90 mmHg for longer than 30 min, a decrease in systolic blood pressure of greater than 40 mmHg from previously established values for longer than 30 min or vasopressor use to maintain systolic pressure greater than 90 mmHg) present at enrollment and refractory to an intravascular volume challenge of at least 500 ml organ dysfunction included: (a) oliguria ( < 30 ml/h not resolved by ≥ 500 ml fluid challenge), (b) coagulopathy (decrease in platelet count > 25 % from the patients baseline or from the lower end of the normal range and prothrombin time > 20 % normal or partial thromboplastin time > 20 % normal or fibrin split products > 20 % normal or D-dimer > 500 ng), (c) unexplained metabolic acidosis (pH < 7.3) or elevated plasma lactate level, (d) acute change in mental status not due to exogenous drugs or localized central nervous system (CNS) infection, and (e) hypoxemia ($PaO_2/FiO_2 \leq 280$). Patients who met the inclusion criteria, and in whom informed consent was obtained were randomized to receive either TNF-α monoclonal antibody or placebo. The patients were followed for 28 days. A complete data set was available for 930 patients. There were 563 (61 %) male patients; 527 (64 %) patients were white, 197 (22 %) black, and 77 (8 %) Hispanic. The patients' mean age was 59 ± 17 years (range 18–102).

The investigators identified the primary infection leading to shock, causative organisms, and therapy received. IL-6, TNF-α, sTNF-R55, and sTNF-R75 concentrations were measured by enzyme-linked immunosorbent assay at enrollment (Cistron Biotechnology, Pine Brook, N. Y., and Bayer, Berkeley, Calif., USA). The enrollment serum cytokine samples were obtained at the time that the enrollment clinical data (including temperature) was recorded. The minimum detectable concentration for TNF-α was 15 pg/ml, 75 pg/ml for IL-6, and 0.4 ng/ml for the sTNF-R55 and sTNF-R75 assays. The intra and interassay coefficients of variation were less than 9 %.

The placebo NORASEPT II data were provided by the sponsor (Bayer, West Haven, Conn., USA) as 30 comma delimited text files. These files were imported into Access 97 (Microsoft, Redmond, Wash., USA) and linked to form a relational database. The study population was divided into a hypothermic and febrile group according to the core temperature at enrollment (normothermia was an exclusion criteria). The following data were extracted to describe each group: patient demographics, acute physiology and laboratory variables including cytokine levels at enrollment, Acute Physiology and Chronic Health Evaluation II (APACHE II) score (day 1), primary pathogens, and 28-day outcome.

Summary statistics were computed to describe the two groups of patients. A $\chi^2$ analysis was used to compare categorical data. Student's $t$ test and the Mann-Whitney $U$ test were used to compare continuous variables. The correlation between the enrollment core body temperature and enrollment cytokine levels were determined using Pearson's product moment correlation coefficient. Logistic regression analysis with forward variable selection was performed to determine those variables independently predictive

**Table 1** Clinical and laboratory findings at enrollment in hypothermic compared to febrile patients

| | Hypothermic (n = 195) | Febrile (n = 735) | p value |
|---|---|---|---|
| Temperature (°C) | 34.4 ± 1.2 | 39.3 ± 0.8 | – |
| Temp. Maximum (°C)* | 36.7 ± 1.4 | 39.4 ± 0.8 | – |
| Survival (%) | 66 (34 %) | 427 (59 %) | < 0.001 |
| Age | 59 ± 15 | 59 ± 17 | NS |
| Systolic BP (mm Hg) | 99 ± 20 | 100 ± 20 | NS |
| Lowest MAP (mmHg)* | 41 ± 15 | 44 ± 14 | 0.006 |
| Arterial pH | 7.13 | 7.28 | < 0.001 |
| Organ failure: | | | |
| Oliguria | 88 (45 %) | 384 (52 %) | NS |
| Altered mental status | 92 (47 %) | 257 (35 %) | 0.003 |
| Coagulopathy | 70 (36 %) | 198 (27 %) | 0.02 |
| Hypoxemia | 72 (37 %) | 250 (34 %) | NS |
| APACHE II | 32 ± 9 | 28 ± 8 | < 0.001 |
| WBC ($\times 10^9$/l) | 19.2 ± 14.9 | 17.8 ± 15.5 | NS |
| s-creatinine (mg/dl) | 3.0 ± 2.5 | 2.3 ± 1.9 | < 0.001 |
| BUN (mg/dl) | 44 ± 34 | 37 ± 28 | 0.01 |
| Albumin g/dl | 2.1 ± 0.8 | 2.3 ± 0.8 | 0.001 |
| LDH (U/L) | 1038 ± 1875 | 733 ± 1588 | NS |
| AST (U/L) | 839 ± 3249 | 248 ± 1175 | 0.003 |
| ALT (U/L) | 352 ± 1340 | 115 ± 470 | 0.002 |
| T. bilirubin (mg/dl) | 2.4 ± 4.6 | 2.0 ± 2.9 | NS |
| Alkaline phosphatase (U/L) | 172 ± 212 | 135 ± 138 | 0.02 |
| Amylase (U/L) | 137 ± 193 | 132 ± 310 | NS |

* first 24 hours

of mortality. Unless otherwise stated, all data are expressed as mean ± SD, with statistical significance declared for probability values of 0.05 or less.

## Results

The 28-day survival was 57 %. The core body temperature at enrollment was 38.7 ± 1.8 °C in the survivors and 37.6 ± 2.4 °C in non-survivors ($p < 0.001$). One hundred and ninety-five patients (21 %) were hypothermic at enrollment. The 28-day survival was significantly lower in the hypothermic patients compared to the febrile patients (34 % vs. 59 %, $p < 0.001$). The was no gender difference in survival (men 56 %, women 59 %).

The clinical and laboratory data of the hypothermic and febrile patients at enrollment are listed in Table 1. The hypothermic patients had significantly higher APACHE II scores, more organ dysfunction at enrollment (renal, CNS, and coagulopathy), with significantly greater hepatocellular dysfunction than the febrile patients. Logistic regression analysis identified the APACHE II score, followed by enrollment temperature (or hypothermia), IL-6 level, serum creatinine, and sTNF-R55 level as independent predictors of mortality. There was no correlation between the APACHE II score and enrollment temperature ($R^2 = 0.03$).

The cytokine levels of the hypothermic and febrile patients are listed in Table 2. There was no significant difference in the cytokine profile between the two groups of patients. Furthermore, there was no correlation between core temperature and the circulating levels of IL-6 and TNF-α or the levels of the circulating soluble TNF receptors (IL-6, $R^2 = 0.0005$, $p = 0.6$; TNF-α, $R^2 = 0.006$, $p = 0.12$; sTNF-R55, $R^2 = 0.002$, $p = 0.2$; sTNF-R75, $R^2 = 0.0$, $p = 0.97$). Scatter plots of the enrollment temperature and IL-6 and TNF-α levels are depicted in Figs. 1 and 2. The was no gender difference in cytokines levels (IL-6, 45.5 ± 142.4 μg/ml in men and 42.9 ± 111.0 μg/ml in women; TNF-α, 411.7 ± 497.9 pg/ml in men and 394.4 ± 441.8 pg/ml in women; sTNF-R75, 21.7 ± 20.6 ng/ml in men and 22.7 ± 21.6 ng/ml in men; and sTNF-R55, 23.8 ± 18.6 ng/ml in men and 24.2 ± 20.1 ng/ml in women. The bacterial isolates are provided in Table 3. There was no significant difference in the spectrum of infecting pathogens between the hypothermic and febrile patients.

## Discussion

We found that hypothermic patients with septic shock had a mortality almost twice that of febrile patients with septic shock. In addition, hypothermic patients

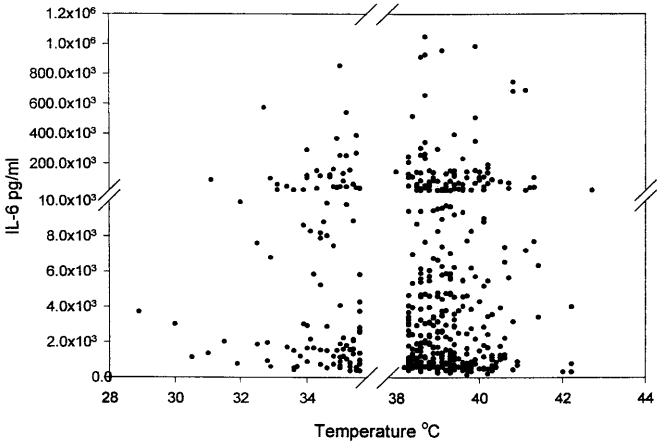


**Fig. 1** Scatter plot of the enrollment temperature and IL-6 level

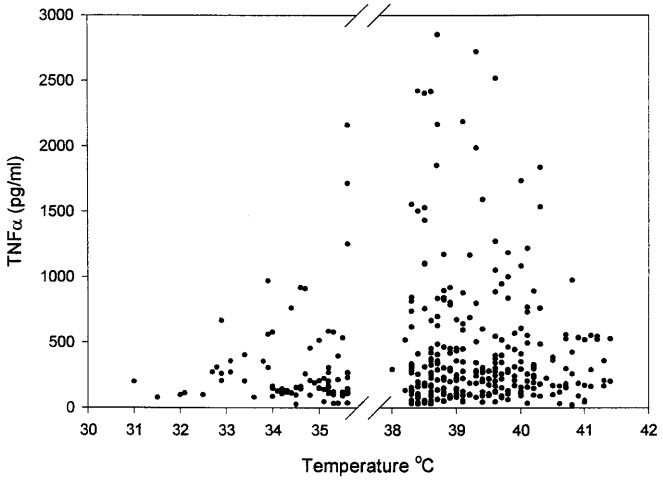


**Fig. 2** Scatter plots of the enrollment temperature and TNF-α level

were more likely to have organ dysfunction at presentation. Surprisingly, there was no difference between the circulating levels of IL-6, TNF-α, sTNF-R55, and sTNF-R75 between these two groups of patients at enrollment, and no correlation between the core body temperature at enrollment and the circulating levels of these cytokines. In addition, there was no difference in the spectrum of infecting pathogens between the hypothermic and febrile patients.

The incidence of hypothermia at enrollment was 9% in the Methylprednisolone Severe Sepsis Study [9], 9.7% in the Veteran Administration Systemic Sepsis Cooperative Study of Glucocorticoid Therapy [10], and 10% in the Ibuprofen Sepsis Study Group [11]. The higher incidence of hypothermia in our study may be related to the stringent inclusion and exclusion criteria of the NORASEPT II study and the exclusion of normothermic septic patients. Furthermore, the higher incidence

**Table 2** Cytokine levels in the hypothermic and febrile patients

| | Hypothermic (n = 195) | Febrile (n = 735)* |
|---|---|---|
| IL-6 † | 123 (63%) | 443 (60%) |
| IL-6 (ug/ml) | 50.2 ± 122.4 | 42.9 ± 133.2 |
| TNF † | 80 (41%) | 287 (39%) |
| TNF (pg/ml) | 385 ± 355 | 413 ± 502 |
| sTNF-R75 † | 174 (89%) | 632 (86%) |
| sTNF-R75 (ng/ml) | 22.6 ± 17.9 | 22.0 ± 21.1 |
| sTNF-R55 † | 166 (85%) | 608 (83%) |
| sTNF-R55 (ng/ml) | 26.4 ± 21.4 | 23.3 ± 18.5 |

* no significant difference between groups
† number of patients (%) in whom cytokine/cytokine receptor levels were detected in serum

**Table 3** Implicated pathogens in the hypothermic and febrile patients

| | Hypothermic (n = 195) | Febrile (n = 735)* |
|---|---|---|
| Escherichia coli | 47 (24%) | 181 (25%) |
| Staphylococcus aureus (MSSA) | 24 (12%) | 133 (18%) |
| Pseudomonas aeruginosa | 26 (13%) | 125 (17%) |
| Klebsiella pneumoniae | 39 (20%) | 110 (15%) |
| Streptococcus pneumoniae | 28 (14%) | 87 (12%) |
| Enterobacter cloacae | 13 (6%) | 48 (7%) |
| Proteus mirabilis | 8 (4%) | 43 (6%) |
| Candida albicans | 15 (8%) | 39 (5%) |
| MRSA | 4 (4%) | 32 (4%) |

* no significant difference between groups

of hypothermia in our study may be related to the fact that the previous studies enrolled a wide spectrum of septic patients, whereas this study included only patients with septic shock [9, 10, 11]. However, in agreement with these other studies the mortality was significantly higher in the hypothermic patients. In the Methylprednisolone Severe Sepsis Study the mortality was 62% in the hypothermic patients compared to 26% in the febrile group [9]. In addition, these authors reported that the hypothermic patients had a higher incidence of altered mental status and elevated serum bilirubin levels when compared with the febrile patients. In the Veteran Administration Systemic Sepsis Cooperative Study the mortality of the hypothermic patients was 57% compared to 28% in the febrile patients. Similarly, in the Ibuprofen Sepsis Study Group the mortality rate was 70% in the hypothermic patients as compared to 35% for the febrile patients [11].

Since IL-6 and TNF-α play a pivotal role in the generation of the febrile response, we were surprised that their was no significant difference in the levels of these cytokines between the two groups of patients. Furthermore, the circulating levels of the soluble TNF receptors were similar between the two groups of patients. As

TNF-α is released early in the inflammatory cascade and has a short half-life, and because TNF-α is the major factor responsible for the release of its receptors, the circulating levels of sTNF-R55 and sTNF-R75 have been suggested to reflect the earlier TNF-α peak [16, 17, 18, 18, 20, 21, 22]. The fact that the levels of the soluble TNF receptors were similar between the two groups of patients provides further evidence that there was no significant difference in the cytokine profile between the hypothermic and febrile patients. In the Ibuprofen Sepsis Study Group ($n = 455$), TNF-α and IL-6 levels were measured in 30 hypothermic patients and 44 randomly selected febrile patients at enrollment [11]. Contrary to our findings, both the TNF-α and IL-6 were significantly higher in the hypothermic patients. We have no explanation for these differing results, except for the fact that our study sample was much larger than that of the Ibuprofen Sepsis Study Group. Although the TNF-α levels in both these studies were measured using an enzyme-linked immunosorbent assay (which measures total circulating levels of TNF-α), it is possible that differences in the sensitivity and specificity of the assays could account for these disparate results. Potential limitations of our study include the fact that IL-1 levels were not available at enrollment and that the total circulating levels of TNF-α were measured rather than the free biologically active molecule. While the TNF-α level as measured in this study reflects both free biologically active and receptor-bound TNF, it does provide an index of the total amount of circulating TNF-α and total TNF-α production.

The exact etiology of hypothermia in sepsis remains unknown; however, the results of our study suggest that it may not be due to decreased circulating levels of pyrogenic cytokines (i.e., prehypothalamic causes). We suggest that the hypothermia of sepsis may be due to hypothalamic dysfunction with alteration in the thermal set-point. In hypothalamic hypothermia, with lowering of the thermal set-point, there is a loss of reactive peripheral vasoconstriction and shivering. In our study, as in the Methylprednisolone Severe Sepsis Study, there was a higher incidence of mental status changes in the hypothermic patients [9]. We suggest that hypothermia may be a manifestation of CNS dysfunction induced by altered brain neurotransmitter activity in patients with sepsis. Depressed levels of norepinephrine, dopamine, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid have been demonstrated in the brains of septic animals, while the levels of phenylacetic acid are markedly increased [23, 24, 25]. Hypothalamic-pituitary dysfunction is common in sepsis and results in altered levels of thyroid hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and other pituitary hormones [26, 27, 28]. Neuromedin C, a peptide found in high concentrations in the hypothalamus, as well as thyrotropin-releasing hormone, have been demonstrated to produce dose-dependent decreases in body temperature [29, 30]. Altered levels of these and other neurotransmitters and hormones may therefore be responsible for the hypothermia of sepsis. It is, however, also plausible that a circulating "mediator" or cryogen produced by the inflammatory cascade may act directly to lower the thermal set-point [31].

Although men predominate (60–65 % of patients) in the sepsis studies which have been performed to date, the role of gender on the outcome in sepsis and on the circulating levels of cytokines has not been well studied [32]. Female sex hormones have been demonstrated to have immunostimulating properties while androgenic hormones are immunosuppressive [33, 34, 35, 36]. Furthermore, in a cecal ligation model, Zellweger and colleagues [37] demonstrated an improved cell-mediated immune response and higher survival in female than in male mice. In our study there was no difference in survival or the levels of circulating proinflammatory cytokines between men and women.

In conclusion, the findings of our study support the notion that hypothermic septic patients are clinically distinct from febrile septic patients [11]. These patients frequently have evidence of marked cellular and organ dysfunction and have a higher mortality than febrile septic patients. We report that hypothermia in septic shock patients does not result from decreased levels of circulating proinflammatory cytokines. We suggest that hypothermia of sepsis is a consequence of hypothalamic dysfunction in these patients. However, it is unclear from our study whether hypothermia is merely a marker of patients who have sustained a more severe physiological insult than febrile patients, or whether hypothermia is a pathophysiological factor in itself. Further, studies are required to better define the etiology of hypothermia during sepsis. The studies should focus on hypothalamic and posthypothalamic causes of hypothermia.

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