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Monocyte function and clinical outcomes in febrile and afebrile patients with severe sepsis

Anne M. Drewry^a, Enyo A. Ablordeppey^{a,b}, Ellen T. Murray^c, Catherine M. Dalton^a, Brian M. Fuller^{a,b}, Marin H. Kollef^d, and Richard S. Hotchkiss^{a,e}

^aDepartment of Anesthesiology, Washington University School of Medicine, St. Louis MO

^bDepartment of Emergency Medicine, Washington University School of Medicine, St. Louis MO

^cUniversity of Missouri-Columbia School of Medicine, Columbia, MO

^dDepartment of Medicine, Washington University School of Medicine, St. Louis, MO

^eDepartment of Surgery, Washington University School of Medicine, St. Louis, MO

Abstract

Introduction—Absence of fever is associated with higher mortality in septic patients, but the reason for this is unknown. Immune dysfunction may be a potential link between failure to mount a fever and poor outcomes. The purpose of this study was to evaluate monocyte function and clinical surrogates of immunity (i.e. mortality and acquisition of secondary infections) in febrile and afebrile septic patients.

Methods—Single-center, prospective cohort study of 92 critically ill septic patients. Patients were categorized into febrile ($\geq 38.0^{\circ}\text{C}$) and afebrile ($< 38.0^{\circ}\text{C}$) groups based on temperature measurements within 24 hours of sepsis diagnosis. HLA-DR expression and LPS-induced TNF- α production were quantified on days 1–2, days 3–4, and days 6–8 after sepsis diagnosis. A repeated measures mixed models analysis was used to compare these markers between the two groups.

Results—Forty-four patients (47.8%) developed a fever within 24 hours of sepsis diagnosis. There were no significant differences in HLA-DR expression or LPS-induced TNF- α production between febrile and afebrile patients at any individual time point. However, HLA-DR expression significantly increased between days 1–2 and days 6–8 (median difference 8118 [IQR 1662, 9878] antibodies/cell, $p = .002$) in febrile patients, but not in afebrile patients (median difference 403 [–3382, 3507] antibodies/cell, $p = .25$). Afebrile patients demonstrated higher 28-day mortality (37.5% vs 18.2%) and increased acquisition of secondary infections (35.4% vs. 15.9%).

Conclusions—Absence of fever is associated with suppressed HLA-DR expression over time, a finding suggestive of monocyte dysfunction in sepsis, as well as worse clinical outcomes.

Corresponding author: Anne M. Drewry, MD, MSCI, Department of Anesthesiology, Washington University School of Medicine, 660 S. Euclid, St. Louis, MO, Phone: 317-747-3581, Fax: 314-747-1710, drewrya@wustl.edu.

Address for reprints: Anne M. Drewry, MD, MSCI, Department of Anesthesiology, Washington University School of Medicine, 660 S. Euclid, St. Louis, MO, Phone: 317-747-3581, Fax: 314-747-1710, drewrya@wustl.edu

Conflicts of Interest:

Anne Drewry, Enyo Ablordeppey, Ellen Murray, Catherine Dalton, Brian Fuller, and Marin Kollef declare they have no competing interests.

Keywords

fever; immunity; mortality; infection; body temperature

Introduction

Fever is considered to be a hallmark of infection, yet over half of critically ill patients with severe sepsis do not exhibit a fever at the time of sepsis diagnosis (1–5). Several studies and a recent meta-analysis have shown that absence of fever is associated with higher morbidity and mortality in septic patients (5–8), but the reason for these worse outcomes is unknown. Failure to mount a fever may be representative of a more severely disrupted thermoregulatory response to infection and thus merely a reflection of increased disease severity. Alternatively, underlying defects in the inflammatory response, due to pathogen- or host-specific factors, may lead to decreased pyrogen production (either systemically or locally in the hypothalamus) and a concomitant increase in susceptibility to infection. Another possibility is that fever directly benefits the host's ability to combat pathogens, by inhibiting pathogen growth or enhancing host immunity. Several *in vitro* and animal studies have demonstrated beneficial effects of elevated body temperature on innate and adaptive immunity (9–11), but there are little data examining the effect of fever on immune function in septic humans.

Sepsis is associated with numerous immune derangements that can result in profound immunosuppression in previously immunocompetent patients (12). This immune impairment prevents septic patients from eliminating pathogens and increases susceptibility to secondary infections (13). Previous evidence has demonstrated that hypothermia within 24 hours of sepsis diagnosis is associated with a higher incidence of persistent lymphopenia, suggesting that these patients may be at greater risk for developing sepsis-induced immunosuppression (14). Yet to be elucidated, however, is the relationship between body temperature and monocyte function. Functional defects in monocytes also play a key role in the pathophysiology of sepsis-induced immunosuppression (15). Diminished antigen-presenting capacity and decreased production of pro-inflammatory mediators by monocytes is associated with morbidity and mortality in septic patients, and several immunotherapies targeting monocyte function in patients with sepsis are being developed (16). The primary objective of this study was to evaluate monocyte function in febrile and afebrile septic patients to further characterize the relationship between body temperature and immunity. We postulate that patients who are unable to mount a fever in response to infection have altered immune responses that make them more susceptible to developing sepsis-induced immunosuppression and, ultimately, to have worse outcomes.

Several biomarkers have been developed to identify patients with monocytic dysfunction due to sepsis. The two most researched markers include cell surface expression of human leukocyte antigen (HLA)-DR and *ex vivo* lipopolysaccharide (LPS)-induced tumor necrosis factor alpha (TNF- α) production. Decreased levels of HLA-DR expression and TNF- α production are associated with higher mortality and increased acquisition of nosocomial infections in septic patients (17–20). Both of these markers have also successfully been used

in clinical trials to identify potential patients who might benefit from immunostimulatory therapy (21, 22).

Therefore, to achieve the objectives of the study, we evaluated HLA-DR expression and LPS-induced TNF- α production in febrile and afebrile septic patients. We hypothesized that afebrile septic patients, as compared to febrile patients, would exhibit lower levels of both HLA-DR expression and LPS-induced TNF- α production and demonstrate a poorer recovery over time. Secondary aims included an evaluation of the association of fever with clinical surrogates of sepsis-induced immunosuppression including mortality and acquisition of secondary nosocomial infections.

Materials and Methods

Study design

This was a prospective observational study and is reported according to the Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) guidelines (23). It was approved by the institutional Human Research Protections Office, and all patients or their legally authorized representatives provided informed consent prior to participation.

Study setting and population

Patients admitted to the medical or surgical intensive care units (ICUs) of a 1200-bed tertiary care hospital between August 1, 2014 and August 1, 2015 with a new diagnosis of severe sepsis within 48 hours of ICU admission were considered for enrollment. Severe sepsis was defined according to 2012 expert consensus (24). Patients were excluded based on the following criteria: (1) history of immunological disease, (2) treatment with immunosuppressive medications within the previous 3 months, (3) chronic infection with hepatitis B or C virus, (4) admission to the ICU via transfer from another hospital, and (5) treatment with therapeutic hypothermia.

Following enrollment, patients were divided into febrile and afebrile groups based on the presence or absence of a body temperature measurement $\geq 38.0^{\circ}\text{C}$ within 24 hours of sepsis diagnosis. A fever threshold of 38.0°C was chosen based on the definition of fever in Systemic Inflammatory Response Syndrome (SIRS) criteria as well as to be consistent with other published literature in the area of temperature management in septic patients (25). Core body temperatures (esophageal, bladder, or rectal), if recorded, were preferentially assessed to determine group assignment. If only peripheral temperatures were measured during this period, core temperatures were estimated by adding 0.5°C to the documented peripheral temperatures (26, 27).

Data and blood sample collection

Baseline variables included patient demographics, co-morbidities, source of sepsis, culture results, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and body temperature measurements. Blood samples were drawn at three time points following the diagnosis of sepsis, days 1–2 (time point A), days 3–4 (time point B), and days 6–8 (time

point C). The first 24-hour time period following the sepsis diagnosis time was considered to be day 1; the next 24-hour period, day 2; etc.

Outcomes

The primary outcome was assessment of monocyte function, as measured by monocyte HLA-DR expression and LPS-induced TNF- α production at 3–4 days and 6–8 days after sepsis diagnosis. Serial measurements were analyzed based on evidence that changes in these markers over time may more reliably predict clinical outcomes than levels at any individual time point (28).

Quantification of HLA-DR expression and LPS-induced TNF- α production were performed by research assistants blinded to all clinical variables, as previously described (29). Briefly, to determine HLA-DR expression, whole blood was incubated with BD Quantibrite Anti-HLA-DR/Anti-Monocyte Stain (Becton-Dickinson, San Jose, CA), lysed, and fixed in 2% paraformaldehyde. Samples were acquired on a FACScan (Becton-Dickinson, San Jose, CA) and flow files were acquired and analyzed in CellQuest Pro (Becton-Dickinson, San Jose, CA). Forward and side scatter properties were used to identify the region roughly associated with circulating monocytes. Following this, we gated on the cell population positive for the BD anti-monocyte pool. Antibodies bound per cell (ABC) were calculated by standardizing HLA-DR geomean fluorescent intensity (GMFI) of monocytes to BD Quantibrite-phycoerythrin (PE) beads (Becton-Dickinson, San Jose, CA). To quantify LPS-stimulated whole TNF- α production, 50 microliters of whole blood was added to microcentrifuge tubes containing 0.5 mL RPMI-1640 fortified with 10% fetal bovine serum, penicillin-streptomycin, non-essential amino acids, and either plus or minus 0.5 ng/mL LPS, and the tubes were incubated at 37°C for 4 hours. Supernatants were then removed and stored at –80°C until enzyme-linked immunosorbent assays (ELISA) were performed for TNF- α production.

Secondary outcomes included ICU-, hospital-, and 28-day mortality as well as the incidence of secondary infections. For patients discharged from the hospital prior to 28 days, 28-day mortality was determined via phone calls with the patients or their legally authorized representatives. Secondary infections were defined as new infections, diagnosed by the treating physicians at least 48 hours after the primary diagnosis of sepsis, which required a new course of antibiotics. Patients were followed for the development of secondary infections for thirty days or until hospital discharge or death, whichever occurred first. ICU- and hospital lengths of stay were also recorded for patients surviving to ICU or hospital discharge.

Statistical Analysis

Descriptive statistics, including mean (SD) and median (IQR), were used to describe each group. Normality of the baseline variables was assessed using histograms and the Kolmogorov-Smirnov test, and these variables were compared using independent samples t-tests, Mann-Whitney U tests, or chi-square tests, as appropriate.

Monocyte HLA-DR expression and LPS-induced TNF- α production were reported as median (IQR) values at each time point in febrile and afebrile patients. Median (IQR)

changes between time points A and B and time points A and C were calculated based on values from patients who had blood drawn at both time points. Monocyte HLA-DR expression and LPS-induced TNF- α production were compared between the febrile and afebrile groups using a repeated measures mixed model analysis implemented in SAS (SAS Institute Inc., Cary, NC, USA). The appropriate statistical contrasts were used to test the null hypotheses that: (a) values at time points A, B, and C were equal between the groups; (b) change in values between time point A and time point B were equal between the groups; and (c) change in values between time point A and time point C were equal between the groups. These contrasts were not adjusted for multiple comparisons.

Dichotomous clinical outcomes were compared among the febrile and afebrile groups using chi square tests. Kaplan-Meier curves for 28-day mortality and secondary infections were also created and the febrile and afebrile groups were compared using the log-rank test. To determine the independent effect of fever on mortality and acquisition of secondary infections, multivariable logistic regression with a forced entry method was used to model the odds of death at 28 days and the odds of developing a secondary infection. A priori, the decision was made to include age and APACHE II score in the model. All other baseline variables that varied between those with and without the outcome of interest with a p value less than 0.05 during univariable comparison were also included. Collinearity diagnostics were evaluated to ensure variable independence.

Statistical tests were performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA), except where otherwise stated. All tests were two-tailed, and p values less than 0.05 were considered to be statistically significant.

Results

A total of 92 patients were included in the study; 48 were afebrile and 44 were febrile within 24 hours of sepsis diagnosis (Figure 1). Baseline characteristics of the afebrile and febrile patients are shown in Table 1. More patients in the afebrile group required surgery (29.2% vs 13.6%), and more patients in the febrile group had a pulmonary source of infection (47.7% vs 29.2%), though neither reached statistical significance.

Boxplots demonstrating the distribution of monocyte HLA-DR expression and LPS-induced TNF- α production in the afebrile and febrile patients are shown in Figure 2. Table 2 reports the results of the mixed models analysis. There were no significant differences in HLA-DR expression or LPS-induced TNF- α production between the afebrile and febrile patients at any individual time point. However, in febrile patients, HLA-DR expression significantly increased between time point A (days 1–2) and time point C (days 6–8) (median difference 8118 [IQR 1662, 9878] antibodies/cell, $p = .002$) whereas it did not significantly increase during this time period in the afebrile patients (median difference 403 [–3382, 3507] antibodies/cell, $p = .25$). Though there was a large difference in change between the afebrile (403 [–3382, 3507] antibodies/cell) and febrile group (8118 [1662, 9878] antibodies/cell) group, this did not reach statistical significance ($p = .08$). A line plot showing HLA-DR values at time point A and time point C for all individuals with measurements at both time points is shown in Supplemental Digital Content 1.

Univariable comparisons of the clinical outcomes are shown in Table 3. Compared to the afebrile group, febrile patients had significantly shorter hospital lengths of stay (median 8.3 days [IQR 4.9, 12.7] vs median 12.6 days [IQR 7.4, 19.2], $p = .02$), lower ICU mortality (11.4% vs 29.2%, $p = .04$), lower 28-day mortality (18.2% vs 37.5%, $p = .04$), and fewer secondary infections (15.9% vs 35.4%, $p = .03$). The Kaplan-Meier curves for 28-day mortality and secondary infections are shown in Figure 3. Supplemental Digital Content 2 lists the site and types of organisms responsible for secondary infections in the febrile and afebrile patients.

Comparisons of baseline variables among 28-day survivors and non-survivors and patients who did and did not develop secondary infections are shown in Supplemental Digital Content 3 and 4. After adjusting for age, APACHE II score, and other significant baseline differences, fever was associated with a lower incidence of secondary infections (adjusted odds ratio (OR) 0.34 [95% CI 0.12, 0.94], $p = .04$) (Table 4). Fever was associated with an 19.3% absolute risk reduction in 28-day mortality (adjusted OR 0.40 [95% CI 0.14, 1.13]), which did not reach statistical significance after controlling for potential confounders ($p = 0.08$) (Table 4).

Discussion

Multiple studies have demonstrated that absence of fever is associated with higher morbidity and mortality in septic patients (4–8). Given the role of inflammation and immunity in the physiology of fever generation, immune dysfunction has been proposed as a potential link between failure to mount a fever and worse clinical outcome. Little data exist, however, characterizing immunity in afebrile septic patients. To date, most studies evaluating immune function in afebrile patients with sepsis have focused on quantifying circulating pro- and anti-inflammatory cytokines in hypothermic and non-hypothermic patients (30–32). These studies found either no differences in cytokine levels (31, 32) or higher levels of pro-inflammatory cytokines in hypothermic compared to non-hypothermic patients (30). Measurement of circulating cytokines, however, is a poor marker of overall immune status (33). Plasma cytokine concentrations fluctuate rapidly, and circulating cytokine levels may not reflect the concentration of cytokines at local sites of infection. Furthermore, plasma concentrations of some cytokines do not become elevated until after saturation of abundant cellular cytokine receptors and thus may not be an accurate indicator of the extent of cytokine involvement in the host response. A sole focus on plasma cytokine levels also overlooks the potential role of other immunosuppressive mechanisms in disruption of the normal thermoregulatory response in septic patients.

The primary aim of this exploratory study was to evaluate monocyte dysfunction in afebrile and febrile patients by comparing serial measurements of HLA-DR expression and LPS-induced TNF- α production. While there were no significant differences in either of these markers at any individual time point, there was an increase in HLA-DR expression between days 1–2 and days 6–8 in the febrile patients which was not observed in the afebrile patients. Wu and colleagues previously demonstrated that changes in HLA-DR expression over time, rather than at individual time points, discriminates more accurately between survivors and non-survivors and may be a better indication of sepsis-induced immunosuppression (28).

Compared to febrile patients, afebrile patients were more likely to develop secondary infections, which could possibly be related to a greater incidence of sepsis-induced immunosuppression in these patients. As an observational study, however, it is impossible to determine whether secondary infections were a result of monocyte dysfunction or whether the increased rate of secondary infections contributed to a reduction in HLA-DR expression at later time points in the afebrile patients. While the majority of secondary infections occurred after the third blood draw (the median time to secondary infection was 10–11 days in both the groups), some of these infections occurred prior to days 6–8 and may have influenced the immune results. Therefore, while the results of this study do not point to a definitive association between monocyte function and fever, as a hypothesis-generating study, they do provide sufficient evidence to warrant additional research in this area.

There were no significant differences in LPS-induced TNF- α production over time between the febrile and afebrile groups, a finding similar to that previously seen in hypothermic and non-hypothermic patients (32). This may be further evidence that TNF- α production may be a less reliable indicator of sepsis-induced immunosuppression as compared to HLA-DR expression (29). This could be due, in part, to the lack of standardization and the greater degree of inter-laboratory methodological variation of the TNF- α production assay as compared to HLA-DR expression assay. Also, in the current study, median values of LPS-induced TNF- α production in both the febrile and afebrile patients were lower than those reported in other studies (19, 20), which could have been due to differences in patient characteristics (e.g. pediatric vs adult) or assay technique. The narrower response range of TNF- α production in this study may have impacted the ability to detect differences between groups, especially given the smaller sample sizes during the later time points.

Another important finding in this study was that septic patients without fever within 24 hours of their sepsis diagnosis are at higher risk for death and acquisition of secondary infections as compared to febrile patients. While fever was not a statistically significant independent predictor of 28-day survival ($p = .08$) in this study, the effect size (%) is large and suggests that the small sample size limited statistical power. Results from previous cohort studies, which included much larger sample sizes, support the premise that fever predicts survival irrespective of disease severity (4, 5). The results of the current study do point to absence of fever as an independent risk factor for the development of secondary infections, a finding which has not previously been reported. Most previous data have focused on the association between hypothermia and outcomes in septic patients and have shown the presence of hypothermia to be predictive of mortality (2, 5, 32), ICU-acquired infections (34), and persistent lymphopenia (14). The current results demonstrate that in addition to hypothermia being a negative prognostic factor in septic patients, as reported in prior studies, fever may be a positive one. Going forward, larger prospective studies should focus on the mechanisms by which body temperature affects immune function and clinical outcomes.

This study has important limitations. Body temperature measurement was not standardized, and both core and peripheral measurements were recorded. While this may have added a small amount of heterogeneity in temperature measurement, it reflects real world practice. Furthermore, external factors, such as differences in ambient temperature, which could

potentially mask a physiological fever were not evaluated in this study. To minimize possible misclassification and study group crossover, core temperature measurements were preferentially assessed and a correction factor was added to peripheral measurements in cases where core measurements were not available. Additionally, the number of patients included in the analysis of monocyte function at the later time points was limited due to death or discharge from the ICU. Both HLA-DR expression and LPS-induced TNF- α production trended upward in the febrile patients as compared to the afebrile patients by days 6–8. Perhaps, with greater statistical power, statistically significant differences would have been observed at this later time point.

This was a preliminary observational study, and the results primarily serve to aid additional hypothesis generation and planning for future studies evaluating relationships between fever and immune outcomes. As an observational study, causality between fever and outcome cannot be inferred. Furthermore, this study did not take into consideration the duration or magnitude of fever nor any techniques to lower body temperature in febrile patients or actively rewarm hypothermic patients. Also, body temperatures were not recorded beyond 24 hours after sepsis diagnosis, so the impact of later fevers on outcomes was not assessed.

Randomized trials of antipyretic therapy in septic patients have failed to show differences in 28-day or hospital mortality (25, 35). This fact, together with the results of the current study, suggests that any potential benefit conferred by fever may occur early in the septic course, prior to the initiation of antipyretic therapy. Another possibility is that the ability to generate fever, regardless of maximum temperature achieved, may be an indication of underlying physiology, such as robust immunity, that enables survival. Alternatively, absence of fever may also simply be an indication of greater disease severity or lead to delayed or less aggressive therapy (8). Determination of whether fever-range hyperthermia benefits septic patients independent of underlying physiology requires a randomized study in which afebrile patients are randomized to treatment with or without external warming. Such a trial is currently in progress ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02706275) NCT02706275) and will help inform future management of these patients.

In conclusion, absence of fever is associated with suppressed HLA-DR expression over time, a finding suggestive of monocyte dysfunction in early sepsis, as well as worse clinical outcomes. Additional research is needed to refine the role of monocyte dysfunction and temperature manipulation in septic patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluate
CI	confidence interval
COPD	chronic obstructive pulmonary disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HLA	human leukocyte antigen
ICU	intensive care unit
IQR	interquartile range
LPS	lipopolysaccharide
OR	odds ratio
SD	standard deviation
SIRS	Systemic Inflammatory Response Syndrome
STROBE	Strengthening and Reporting of Observational Studies in Epidemiology
TNF-α	tumor necrosis factor alpha

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Figure 1.

Flow diagram of included patients and reasons for patient exclusion. HBV, hepatitis B virus; HCV, hepatitis C virus.

Figure 2. Median and interquartile range of (a) HLA-DR expression and (b) LPS-induced TNF- α production in febrile and afebrile patients.

Figure 3.
Kaplan-Meier curves for 28-day survival and secondary infections in febrile and afebrile septic patients.

Table 1

Baseline characteristics of febrile and afebrile patients

	Afebrile n = 48	Febrile n = 44	p
Age (years), mean (SD)	61.4 (16.7)	60.3 (17.2)	.75
Sex (male), n (%)	26 (54.2)	31 (70.5)	.11
APACHE II ^a , median (IQR)	20 (14, 24)	20 (17, 21)	.33
ICU type, n (%)			.32
Medical	29 (60.4)	22 (50.0)	
Surgical	19 (39.6)	22 (50.0)	
Surgical procedure, n (%)	14 (29.2)	6 (13.6)	.08
Source of infection, n (%)			.09
Lung	14 (29.2)	21 (47.7)	
Abdomen	13 (27.1)	5 (11.4)	
Urinary tract	5 (10.4)	9 (20.5)	
Bone or soft tissue	7 (14.6)	3 (6.8)	
Other/unknown	9 (18.8)	6 (13.6)	
Culture positive, n (%)	30 (62.5)	25 (56.8)	.58
Organism, n (%)			.43
Gram-negative	11 (22.9)	14 (31.8)	
Gram-positive	8 (16.7)	6 (13.6)	
Mixed	8 (16.7)	2 (4.5)	
Fungal	1 (2.1)	1 (2.3)	
Viral	2 (4.2)	2 (4.5)	
Site of temperature measurement, n (%)			.53
Core	25 (52.1)	20 (45.5)	
Peripheral	23 (47.9)	24 (54.5)	
Co-morbidities, n (%)			
Coronary artery disease	12 (25.0)	12 (27.3)	.80
Cerebrovascular disease	5 (10.4)	6 (13.6)	.63
Congestive heart failure	12 (25.0)	14 (31.8)	.47
Diabetes	15 (31.3)	14 (31.8)	.95
Chronic renal insufficiency	9 (18.8)	11 (25.0)	.47
Liver disease	5 (10.4)	3 (6.8)	.54
COPD	9 (18.8)	9 (20.5)	.84

^aExcluding neurological component.

SD, standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; IQR, 25%, 75% interquartile range; ICU, intensive care unit, COPD, chronic obstructive pulmonary disease

Table 2

Mixed models analysis of HLA-DR expression and LPS-induced TNF- α production in afebrile and febrile patients

		Afebrile, n = 48	Febrile, n = 44	<i>p</i>
HLA-DR expression (antibodies/cell), median (IQR)	Sample A (days 1–2) ^a	7178 (4546, 13129) n = 44	6681 (3737, 15824) n = 37	.88
	Sample B (days 3–4) ^a	8235 (4222, 14658) n = 36	6953 (3476, 16303) n = 29	.23
	Sample C (days 6–8) ^a	9722 (4280, 15324) n = 19	11639 (7009, 23942) n = 10	.10
	Sample A to B	–630 (–1926, 918) <i>p</i> = .48 ^b	1116 (71, 4464) <i>p</i> = .11 ^b	.09
	Sample A to C	403 (–3382, 3507) <i>p</i> = .25 ^c	8118 (1662, 9878) <i>p</i> = .002 ^c	.08
LPS-induced TNF- α production (pg/ml), median (IQR)	Sample A (days 1–2) ^a	167 (73, 330) n = 45	171 (65, 486) n = 37	.44
	Sample B (days 3–4) ^a	186 (94, 237) n = 37	275 (71, 452) n = 26	.09
	Sample C (days 6–8) ^a	233 (88, 368) n = 21	320 (162, 603) n = 9	.41
	Sample A to B	–5 (–75, 59) <i>p</i> = .34 ^b	14 (–24, 71) <i>p</i> = .32 ^b	.17
	Sample A to C	12 (–43, 122) <i>p</i> = .30 ^c	16 (–57, 79) <i>p</i> = .30 ^c	.78

^aDays after sepsis diagnosis.

^b*p*-value for within-group comparison of HLA-DR expression or TNF- α production at time points A and B.

^c*p*-value for within-group comparison of HLA-DR expression or TNF- α production at time points A and C.

HLA-DR, human leukocyte antigen-DR; IQR, 25%, 75% interquartile range; LPS, lipopolysaccharide; TNF- α , tumor necrosis factor-alpha

Table 3

Clinical outcomes in afebrile and febrile septic patients

	Afebrile n = 48	Febrile n = 44	<i>p</i>
ICU length of stay ^a (days), median (IQR)	6.2 (2.9, 10.5)	4.4 (3.0, 7.4)	.17
Hospital length of stay ^b (days), median (IQR)	12.6 (7.4, 19.2)	8.3 (4.9, 12.7)	.02
ICU mortality, n (%)	14 (29.2)	5 (11.4)	.04
Hospital mortality, n (%)	15 (31.3)	7 (15.9)	.09
28-day mortality, n (%)	18 (37.5)	8 (18.2)	.04
Secondary infections, n (%)	17 (35.4)	7 (15.9)	.03

^aIncludes only patients who survived to ICU discharge.^bIncludes only patients who survived to hospital discharge. ICU, intensive care unit; IQR, interquartile range.

Table 4

Multivariable logistic regression analyses for 28-day mortality and secondary infections

	Adjusted OR ^a (95% CI)	<i>P</i>
28-day mortality		
Fever ^b	0.40 (0.14, 1.13)	.08
Age	1.01 (0.98, 1.05)	.36
APACHE II score ^c	1.17 (1.04, 1.31)	.007
Diabetes	0.29 (0.08, 1.04)	.07
Secondary infections		
Fever ^b	0.34 (0.12, 0.94)	.04
Age	0.98 (0.95, 1.01)	.23
APACHE II score ^c	1.03 (0.94, 1.13)	.52

^aFor continuous variables, odds ratios reflect the increased odds of 28-day mortality for a one unit increase in the variable. For categorical variables, the reference category is absence of the condition.

^bBody temperature ≥ 38.0°C within 24 hours of sepsis diagnosis.

^cAge component removed. OR, odds ratio; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation.