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Fever in Sepsis: Still a Hot Topic

To the Editor:

With great interest, we read the paper by Bhavani and colleagues (1), who report a novel method to distinguish between sepsis phenotypes based on body temperature. Using trajectory modeling, the authors identify four phenotypes, each displaying distinct demographic characteristics, physiological parameters, and prognosis. The data presented reveal that the so-called hyperthermic, fast resolving patients, who presented with a high temperature that decreased rapidly afterward, had the lowest in-hospital mortality. In addition, a more swift increase in temperature was also positively related to survival. The authors plausibly argue that hyperthermic, fast resolvers may be able to mount a strong, but nevertheless well-balanced, inflammatory response, resulting in a better clinical outcome.

What is currently missing is more solid evidence for whether or not there is an immunological basis for the proposed temperature-based phenotypes. Insight into the release of so-called endogenous pyrogens (2), mainly represented by cytokines such as TNFα (tumor necrosis factor α) and IL-6, could provide the missing link between the underlying immune status and the body temperature trajectories observed.

In the experimental human endotoxemia model, *Escherichia coli* endotoxin is administrated intravenously to healthy volunteers, inducing a standardized short-lasting systemic inflammatory response, which captures relevant hallmarks of the immune response observed in patients with sepsis (3). Serial measurements of cytokines and body temperature during endotoxemia allow for determination of their relationship. Using data from 20 male subjects allocated to the control group (no intervention other than bolus administration of 1 ng/kg endotoxin followed by continuous infusion of 1 ng/kg/h endotoxin over the course of 3 h) of a recent interventional study performed by our group (4), we analyzed the relationship between peak plasma cytokine concentrations and body temperature changes over time. We divided the subjects according to the median cytokine levels, resulting in 10 low and 10 high cytokine producers, and calculated the slope of the endotoxin-induced temperature increase ($Temp_{slope}$ = Δ temperature increase/time to peak temperature).

On average, plasma concentrations of TNFα, IL-6, and IL-10 reached their maximum at 2.5, 3, and 3.5 hours after endotoxin administration, respectively, whereas peak temperatures were observed 4 hours after endotoxin. $Temp_{slope}$ strongly correlated with peak temperature (Spearman $r = 0.92$; $P < 0.0001$). In subjects who produced high levels of the proinflammatory cytokines IL-6 and TNFα, $Temp_{slope}$ was significantly higher than in low proinflammatory cytokine producers, whereas $Temp_{slope}$ did not differ between low and high producers of antiinflammatory IL-10 (Figure 1). Spearman correlation coefficients for the relationship between cytokines and $Temp_{slope}$ were $r = 0.75$ for IL-6 ($P < 0.0001$) and $r = 0.52$ for TNFα ($P = 0.02$). Furthermore, peak temperatures were reached earlier by high IL-6 and TNFα producers (high responders: 3.6 ± 0.1 vs. low responders: 4.5 ± 0.2 h [$P = 0.002$] and high responders: 3.7 ± 0.2 vs. low responders: 4.4 ± 0.2 h [$P = 0.02$], respectively). After the peak, temperatures gradually normalized, but the slope of the temperature decrease did not correlate with levels of any of the measured cytokines.

Taken together, these findings indicate that indeed higher levels of proinflammatory, but not antiinflammatory, cytokines precede a more potent and swift temperature increase. These data provide

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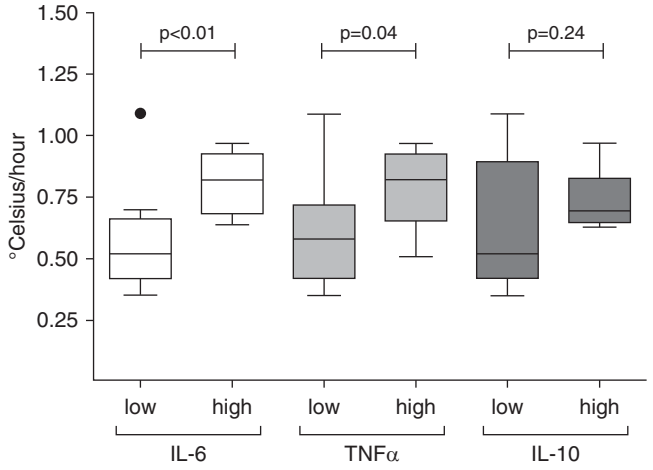

Figure 1. Slope of the temperature increase ($Temp_{slope}$) after endotoxin administration for subjects with low and high peak levels of IL-6, TNFα (tumor necrosis factor α), and IL-10. Data are presented as box-and-whisker plots (Tukey).

an immunological basis for the hypothesis of Bhavani and colleagues, who state that hyperthermia may be the result of a more proinflammatory phenotype, whereas a less pronounced immune response might relate to a lower (or absent) temperature increase. In view of the more favorable prognosis of hyperthermic patients in whom temperature swiftly increases and quickly resolves, a more pronounced but adequately balanced proinflammatory response is of apparent benefit to the host. This further elucidates why dozens of trials using immunosuppressive agents failed to improve sepsis outcome and stresses the need for therapies aimed at maintaining or restoring a well-functioning immune system. ■

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Reply to Leijte *et al.*

From the Authors:

We thank Dr. Leijte, Dr. Kox, and Dr. Pickkers for their comments on our recent article on using temperature trajectories to identify sepsis subphenotypes (1). Using group-based trajectory modeling, we identified four subphenotypes with different demographics, physiological characteristics, and levels of inflammatory markers, and we hypothesized an immunological basis for these subphenotypes. Supporting our hypothesis of a connection between temperature and immunological markers, Leijte and colleagues present a human endotoxemia model revealing correlation between temperature slopes and levels of endogenous pyrogens (IL-6 and TNFα [tumor necrosis factor α]) in healthy volunteers after administration of *Escherichia coli* endotoxin (2). This data provide evidence for the relationship between body temperature and cytokine responses. In addition, the data use dynamic temperature measurement (i.e., temperature slopes) to study associations with cytokine levels. This finding aligns with our work indicating that dynamic measures of temperature (i.e., temperature trajectory, variability, and slopes) may have more significance than static measures.

Although the cytokine responses in this study provide an immunological basis for our hypothesis, the systemic inflammatory response is intentionally self-limited in these healthy volunteers. We believe that measurement of cytokine levels in naturally occurring sepsis would add further information to the relationship between the thermoregulatory and immunological systems. Sepsis is defined as a dysregulated immunological response to infection. After the initial endotoxin-driven cytokine storm in sepsis, there is a protracted dysregulated immunological process that follows. We propose that temperature trajectories may elucidate not only the initial cytokine response but also the sustained immunological process in patients with sepsis. For instance, hyperthermic, slow resolvers may have sustained high levels of proinflammatory cytokines, whereas hyperthermic, fast resolvers may have the same initial proinflammatory cytokine storm followed by a defervescence process. We look forward to studies such as those of Dr. Leijte, Dr. Kox, and Dr. Pickkers to illuminate the relationship between temperature and the immunological system. ■

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