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# Should we assume that hypothermia is a dysfunction in sepsis?

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See related research by Wiewel et al., https://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1510-3

Letter

Wiewel et al. [1] clearly showed that development of hypothermia instead of fever in sepsis is not tied to a switch from a pro-inflammatory to an anti-inflammatory state. The authors then suggest that vascular dysfunction could play a role in hypothermia. While this hypothesis deserves attention, we urge researchers to consider that there is no hard evidence indicating that hypothermia is a dysfunction in sepsis.

Not all systems fail simultaneously in sepsis, and those with preserved function are likely to launch evolutionarily conserved compensatory responses. Could thermoregulation be preserved during septic hypothermia? Could hypothermia be adaptive when the costs of fever exceed its benefits? According to evidence from rat models of systemic inflammation, the answers to these questions may be yes. First, hypothermia in endotoxemic rats is an early, transient phenomenon that is not consequential to circulatory shock [2]. Second, hypothermia in endotoxic shock is brought about by downregulation of thermogenesis when thermogenic capacity is unimpaired [2, 3]. Third, rats with endotoxic shock do not attempt to restore normothermia when given the chance to select a warmer environment; on the contrary, they seek a cooler environment [3]. Last, spontaneous hypothermia has been shown to be more advantageous than fever in rats with severe forms of endotoxemia and *Escherichia coli* sepsis [2, 4].

There has been a complete disconnect between these experimental data and clinical studies on this subject. Recently, though, Fonseca et al. [5] published the first effort to reconcile experimental and clinical evidence on septic hypothermia. That study revealed that, similarly to animal models of endotoxemia, hypothermia in human sepsis is usually self-limiting and transient. Perhaps most importantly, hypothermia was rarely observed in the moments that preceded death, when multiple organ failure is presumably at its peak. Hence, it is possible that an early, regulated form of hypothermia exists in human sepsis. By the same token, the reported association between hypothermia and higher mortality should not be taken as evidence that hypothermia is a dysfunction that worsens sepsis. This association could merely reflect the fact that hypothermia replaces fever in the most severe cases of sepsis, both in rats and humans. In our opinion, the impact of septic hypothermia on clinical outcomes can only be adequately addressed by an interventional study in which spontaneous hypothermia is allowed or prevented within the hypothermic subset of septic patients. We are planning such a study and invite those interested to join us.

## Authors' response

Matthew B. Harmon, Maryse A. Wiewel, W. Joost Wiersinga and Nicole P. Juffermans

We are thankful for the letter of Steiner and colleagues in response to our paper on risk factors, host response and outcome of hypothermic sepsis [1]. We fully acknowledge the authors' contributions to the field and their efforts to reconcile experimental and clinical evidence on septic hypothermia [5].

We agree with the authors that hypothermia could be an adaptive response during sepsis. It may be hypothesized that once the metabolic cost of fever outweighs its immune stimulatory benefits, the host may become hypothermic, thereby decreasing metabolism and also potentially decreasing inflammation. We also agree that

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our study was not designed to provide definitive evidence that hypothermia is a dysfunction in sepsis. As mentioned in the limitation section, our study was observational and cause–effect relationships cannot be established due to the nature of the study design. Indeed, findings which have been associated with hypothermia in previous studies, such as increased lymphopenia [6] and increased levels of fractalkine [1], can also be linked to increased disease severity and not to hypothermia per se.

Some of the experimental work may relate to clinical findings. Spontaneous hypothermia in rat endotoxemia may be a pre-emptive strategy to prevent hypoxia [2]. In comparison, patients who are more prone to hypoxia or a metabolic deficit may also develop hypothermia more often, such as those with preexisting circulatory dysfunction (i.e., chronic cardiovascular dysfunction) or those with few metabolic reserves (i.e., low body mass index). That said, however, it is difficult to reconcile an adaptive response in rodents to an evidently increased mortality noted in observational studies in patients [1, 6].

A remark on the interpretation of findings in experimental models is that regulation of body temperature in rodents is profoundly different than in humans due to differences in the ratio of body content to body surface [7]. Therefore, experimental results need to be validated in clinical studies. We look forward to the results of an interventional study in which spontaneous hypothermia is allowed or prevented within the hypothermic subset of patients with sepsis. We would like to participate in this effort and we suggest that this trial includes analyses on the host response, including markers of immune suppression and endothelial dysfunction, to provide further insight into the etiology of hypothermia in sepsis pathogenesis.

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**References**

1. Wiewel MA, Harmon MB, van Vught LA, Scicluna BP, Hoogendijk AJ, Horn J, Zwinderman AH, Cremer OL, Bonten MJ, Schultz MJ, et al. Risk factors, host response and outcome of hypothermic sepsis. Crit Care. 2016;20:328.
2. Corrigan JJ, Fonseca MT, Flatow EA, Lewis K, Steiner AA. Hypometabolism and hypothermia in the rat model of endotoxic shock: independence of circulatory hypoxia. J Physiol. 2014;592:3901–16.
3. Romanovsky AA, Shido O, Sakurada S, Sugimoto N, Nagasaka T. Endotoxin shock: thermoregulatory mechanisms. Am J Physiol. 1996;270:R693–703.
4. Liu E, Lewis K, Al-Saffar H, Krall CM, Singh A, Kulchitsky VA, Corrigan JJ, Simons CT, Petersen SR, Musteata FM, et al. Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide- and *E. coli*-induced systemic inflammation. Am J Physiol Regul Integr Comp Physiol. 2012;302:R1372–83.
5. Fonseca MT, Rodrigues AC, Cezar LC, Fujita A, Soriano FG, Steiner AA. Spontaneous hypothermia in human sepsis is a transient, self-limiting, and nonterminal response. J Appl Physiol (1985). 2016;120:1394–401.
6. Drewry AM, Fuller BM, Skrupky LP, Hotchkiss RS. The presence of hypothermia within 24 hours of sepsis diagnosis predicts persistent lymphopenia. Crit Care Med. 2015;43:1165–9.
7. Wagner F, Asfar P, Calzia E, Radermacher P, Szabo C. Bench-to-bedside review: Hydrogen sulfide–the third gaseous transmitter: applications for critical care. Crit Care. 2009;13(3):213.