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FRONT MATTER: DISCOVERY

Fever, hypothermia, and mortality in sepsis*

Comment on: Rumbus Z, Matics R, Hegyi P, Zsiboras C, Szabo I, Illes A, Petervari E, Balasko M, Marta K, Miko A, Parniczky A, Tenk J, Rostas I, Solymar M, Garami A. Fever is associated with reduced, hypothermia with increased mortality in septic patients: a meta-analysis of clinical trials. PLoS One. 2017;12(1):e0170152. DOI: 10.1371/journal.pone.0170152

Sepsis presents a major challenge for critical care and the society worldwide. Despite the ample research interest in understanding the underlying mechanisms, mortality rate remains considerably high in sepsis even nowadays. In order to assess the prognosis and the severity of the disease, thus to initiate the most optimal treatment, it is necessary to identify vital signs and biomarkers, which can predict the outcome. As a manifestation of systemic inflammation, sepsis is often accompanied by changes in body temperature (T_b): fever or hypothermia. Our understanding of the thermoregulatory manifestations of systemic inflammation has advanced in the past decades, but it has remained unanswered whether fever and hypothermia can serve as predictors of the outcome in sepsis. In the highlighted study, we investigated the association between the alterations of T_b and the rate of mortality in septic patients [1].

By conducting a meta-analysis of clinical trials, we studied the association between changes in T_b and mortality in a big number (> 10,000) of septic patients [1]. We found that in septic patients with fever the estimated mortality rate was ~ 22%, which was higher (~ 31%) in normothermic patients, while it was the highest (~ 47%) in hypothermic patients [1]. When we compared the T_b data of all septic patients divided into mortality quartiles, we found that T_b was by 1°C higher in patients with the lowest (< 25%) mortality than in patients with the highest rate of death (> 75%). The results of our meta-analyses clearly demonstrate a negative correlation between T_b and mortality in sepsis: fever is associated with decreased, whereas hypothermia with increased rate of death. However, this association does not automatically imply that fever is always beneficial and hypothermia is harmful in sepsis (Table 1). The causative relationship between the thermoregulatory manifestations and the outcome in systemic inflammation could not be assessed in our study and it deserves discussion.

The beneficial versus harmful effect of fever has been debated since the time of Hippocrates. Despite the advancements in our understanding of the molecular, cellular, and physiological mechanisms of the fever response, the question of whether it is a friend or foe is asked even in recent days. The controversies between the findings on beneficial versus harmful effects of fever can be mitigated by focusing on the question of when instead of whether fever is a friend or a foe as suggested by Romanovsky and Szekely [2]. It was proposed that the thermoregulatory manifestations of systemic inflammation can be regarded as adaptations in constellation of the sickness syndrome. Two sickness patterns can be distinguished as part of the syndrome, which represent sequential stages of the body's response to systemic inflammation and constitute two different adaptive strategies to infection [2]. The two distinguished patterns of the syndrome, the early and the late phase syndrome, correspond to mild and severe forms of systemic inflammation. Romanovsky and Szekely [2] proposed that fever, as part of the early phase syndrome, should be regarded as an adaptive strategy of the organism, which occurs at the onset of the infection and constitutes a response of the healthy organism to the forthcoming disease. In this regard, the biological purpose of the early phase syndrome is to engage active defense mechanisms (fever), notify the host about the pathogenic insult (hyperalgesia), and secure the means (vigilance, hyperactivity, hypertension, and anorexia), which can empower the active search for optimal environment (warmth seeking, adequate water supply, protection from external stressors) for fighting the disease. This type of adaptation to

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Table 1. Disease coping strategies in different premorbid conditions, thermoregulatory manifestations, and potential outcomes in different severities of sepsis.

Infection severity	Premorbid condition	Coping strategy	Deep body temperature	Predicted outcome	Effect on mortality
Mild	Healthy	Disease fighting	Fever	Pathogen clearance	Not applicable
Moderate	Healthy	Disease fighting	Fever	Pathogen clearance	↓
			Extreme fever	Organ failure, energy depletion	↑
	Comorbidities* or exhaustion†	Disease fighting	Fever	Organ failure, energy depletion	↑
		Energy saving	Hypothermia	Disease tolerance††	↓
Severe (e.g., septic shock)	Healthy	Energy saving	Hypothermia	Disease tolerance	↓
	Comorbidities or exhaustion		Extreme hypothermia	Organ failure	↑

Effects on mortality are marked as: ↓, decrease; ↑, increase. *E.g., pre-existing cardiovascular, pulmonary, neurological disease. †E.g., because of old age, starvation, prolonged systemic inflammation. ††The host's ability to tolerate the presence of the pathogen; for details, see Garami et al. [3].

infections develops at a high energy cost. A short-lasting, mild infectious challenge (common cold or influenza) is often characterized by the early phase syndrome only. In a previously fit and healthy patient, fever will be likely beneficial (Table 1). On the contrary, the beneficial value of fever can be compromised by an already existing or forthcoming energy deficiency, for example, in moderate-to-severe infections of patients with different (e.g., nutritional, cardiovascular, and respiratory) comorbidities, who lack adequate protection from external stressors. The energy resources are depleted more rapidly in extremely high fevers, resulting in the worsening of the outcome of the disease. In such situations, the beneficial value of fever diminishes and its harmful consequences emerge (Table 1). It has to be noted that because of data unavailability, extreme fever responses (T_b above 39.9°C), which could have detrimental consequences, were not included in the meta-analysis in focus [1].

In contrast to fever, the biological significance of hypothermia has been almost completely ignored in systemic inflammation. The possible reasons for this inattention include the lower incidence rate of hypothermia compared to fever, improper T_b-measuring techniques that result in cases that go undetected, and the low priority of decreased T_b in critically ill patients who are often in extremely poor conditions when presented to the physician. From a physiological perspective, hypothermia can be regarded as a part of the late phase syndrome, which represents the systemic response to infection when the disease has already progressed, thus damaged and weakened the organism [2]. The pain has lost its warning function, resulting in hypoalgesia. High energy-consuming responses are not affordable; consequently, somnolence, motor depression, and normo- or hypotension are characteristic. In severe clinical cases (e.g., septic shock), the late phase syndrome becomes predominant and it can completely replace the early phase syndrome. As a general rule, hypothermia is a beneficial response when the damage is severe enough to cause or facilitate energy depletion (Table 1). In severe forms of inflammation, the energy resources can be reduced by the overwhelming inflammatory response, involving pathological energy expenditure and increased oxygen demand of damaged tissues. At the same time, the energy supply is commonly decreased or completely absent due to the compromised ability to get food and the development of adaptive anorexia. Because of the dependence of biochemical rates on temperature (van't Hoff's rule), tissue metabolic requirements decrease by more than 10% for every 1°C drop in T_b. Direct experiments have shown that spontaneous hypothermia is more advantageous than fever in rats with severe forms of aseptic (lipopolysaccharide-induced) or septic (Escherichia coli-induced) systemic inflammation [reviewed in ref. 3]. In these studies, the development of hypothermia (vs fever) exerted a pronounced influence on survival rates of the rats with systemic inflammation: the survival rate of hypothermic rats was markedly higher than that of the febrile rats in both aseptic and

septic models of severe systemic inflammation. Further advantages of hypothermia over fever included the suppression of endotoxemia and reduced lung infiltration by neutrophil leukocytes. The more severe the pathogenic challenge, premorbid pathology, and actual conditions, the more likely that hypothermia and its energy-saving actions will be advantageous for the host (Table 1). If the patient is sleepy, depressed, hypoactive, hypotensive, and hypoalgesia occurs, the energy-saving strategy of hypothermia is likely to be protective [2]. It should be also noted that in severe cases of sepsis, particularly in patients with pre-existing energy exhaustion or comorbidities, T_b may fall to critical levels and the adverse consequences of the extreme hypothermia (e.g., cardiac arrhythmias, neurological dysfunctions) can overcome its adaptive value (Table 1).

Despite the growing body of evidence for the adaptive value of hypothermia in systemic inflammation, hypothermia is generally perceived in clinical settings as something dysregulated and accidental, and prompt rewarming is regularly considered for those septic patients who display a fall in T_b. The first effort to reconcile experimental and clinical evidence in septic hypothermia was made only recently; it was revealed that hypothermia is predominantly transient, self-limiting, and nonterminal response, which naturally occurs in human sepsis [4]. Consequently, it can be questioned whether rewarming is at all necessary in the subset of septic patients who naturally develop hypothermia. To answer the question, well-designed, interventional clinical studies are warranted, in which spontaneous hypothermia is allowed or prevented within the hypothermic subset of septic patients.

As a perspectival approach, the utilization of controlled, targeted modulation of T_b by pharmacological tools could also be studied in systemic inflammation; new hypo- and hyperthermia-inducing drugs may be used one day, like the antagonists of the transient receptor potential vanilloid-1 channel [5]. Such and similar studies with targeted modulation of T_b in systemic inflammation could unequivocally determine the cause-effect relationship between the thermoregulatory manifestations and the outcome in sepsis, thus further advance our understanding of the association between T_b and mortality observed in the highlighted article [1].

References

[1] Rumbus Z, Matics R, Hegyi P, et al. Fever is associated with reduced, hypothermia with increased mortality in septic patients: a meta-analysis of clinical trials. PLoS One. 2017;12(1):e0170152.
[2] Romanovsky AA, Szekely M. Fever and hypothermia: two adaptive thermoregulatory responses to systemic inflammation. Med Hypothesis. 1998;50(3):219–226.
[3] Garami A, Steiner AA, Romanovsky AA. Fever and hypothermia in systemic inflammation. In: Thermoregulation, Part II: from basic neuroscience to clinical neurology. Romanovsky AA, editor. Handb Clin Neurol. Aminoff MJ, Boller F, Swaab DF, Series editors. Oxford, UK: Elsevier, 2018:157: in press.
[4] Fonseca MT, Rodrigues AC, Cezar LC, et al. Spontaneous hypothermia in human sepsis is a transient, self-limiting, and nonterminal response. J Appl Physiol. 2016;120(12):1394–1401.
[5] Garami A, Pakai E, McDonald HA, et al. TRPV1 antagonists that cause hypothermia, instead of hyperthermia, in rodents: compounds' pharmacological profiles, in vivo targets, thermoeffectors recruited, and implications for drug development. Acta Physiol (Oxf). 2018;223(3):e13038.

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