



Fever during septic shock, friend or foe?

Palle Toft^{1,2}, Thomas Stroem^{1,2}

¹Department of Intensive Care, Odense University Hospital, 5000 Odense C, Denmark; ²Department of Anaesthesiology, University of Southern Denmark, Winsløwparken 19, 5000 Odense C, Denmark

Correspondence to: Palle Toft. Department of Intensive Care, Odense University Hospital, 5000 Odense C, Denmark. Email: palle.toft@rsyd.dk.

Provenance: This is a Guest Editorial commissioned by the Executive Editor Zhongheng Zhang, MD, MM (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Itenov TS, Johansen ME, Bestle M, *et al.* Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomised, controlled, open-label trial. *Lancet Respir Med* 2018;6:183-92.

Received: 12 April 2018; Accepted: 17 April 2018; Published: 06 May 2018.

doi: 10.21037/jecm.2018.04.06

View this article at: <http://dx.doi.org/10.21037/jecm.2018.04.06>

Fever is a natural response to infection in humans as well as in other mammals. Fever stimulates the effectiveness of the immune system during infection thereby improving the possibilities for combating the infections. Fever is however not without costs. Fever in humans and other mammals is associated with increased metabolic demand. A rise of 1% in body temperature requires around a 10% increase in metabolism. Hypothermia decreases the metabolic demands and has an organ protective function. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection. It might therefore be possible that hypothermia has an organ protective function and the survival benefit in sepsis and septic shock. This has been discussed for years without the existence of a randomized controlled trial until the study by Itenov *et al.* (1).

Hypothermia has been protective in some conditions, but harmful in other circumstances. Following cardiac arrest hypothermia is widely used to protect the brain from hypoxic injury. During cardiac surgery with cardiopulmonary bypass hypothermia is induced to protect the organs. Following major trauma huge efforts have been made to prevent hypothermia which is part of the lethal triad coagulopathy, metabolic acidosis and hypothermia.

There is no perfect animal model for human sepsis. In critically ill patients, the systemic inflammatory response to a severe infection consists of a pro-inflammatory response followed by an anti-inflammatory phase. In most animal studies the animals are exposed to a single intervention? And only the pro-inflammatory response is studied. In addition infusion of endotoxin, not live bacteria is most

often used to produce the pro-inflammatory response with organ dysfunction. In these animal models many anti-inflammatory drugs have improved survival and reduced organ dysfunction. When these immune modulating drugs have been used in septic patients, the results have been disappointing. Since the 1980 immune modulatory drugs have been investigated in large randomized trials without any beneficial effect in septic patients (2).

In the Introduction to the study by Itenov *et al.* (1), they also described how hypothermia protected animals for sepsis in different studies. It would be fair to say that the animals were protected from endotoxemia with organ dysfunction as endotoxin in a single hit model without live bacteria were used.

Fever is produced by the release of endogenous pyrogens such as the cytokines IL-6. In spite of the costs in form of increased metabolism, vasodilatation and tachycardia is the ability to produce fever in response to infection is preserved in all mammals, birds, fish and even in reptiles during millions of years of evolution. Cold blooded animals raise their body temperature in response to infection by seeking a warmer environment. In classical animal studies performed 40 years ago, it was shown that infected lizards, who were allowed to develop fever survived whereas animals prevented from developing fever died (3).

Similarly preventing the development of fever by the use of antipyretic drugs in bacterial infected animals increased mortality dramatically. The use of antipyretic drugs also increased mortality in critically ill patients (3,4).

Fever stimulates the immune system, especially the

cell mediated immunity which is depressed during sepsis. Fever increases the activity of granulocytes, macrophages, T-lymphocytes as well as natural killer cells.

In the study by Itenov *et al.*, 436 patients with septic shock were randomized to 24 hours of hypothermia (32–34 °C) followed by 48 hours of normothermia (36–38 °C) or usual treatment (1).

Although not blinded the authors tried to control for most confounders in the design. The investigators were blinded to the intervention when analyzing data. However, as the authors point out themselves one important aspect was not controlled in both groups: the use of sedation. Recent years focus has been to minimize sedation in critically ill patients undergoing mechanical ventilation (5). In the intervention group receiving hypothermia patients received more sedation compared to the control group receiving standard care with respect to temperature and sedatives. Potentially deeper levels of sedation could have harmed patients and masked a positive effect of hypothermia. Although this seems unlikely the investigators could have controlled the effect of sedation by offering the same level of sedation in both arms of the present trial.

The authors should be praised for performing this important study which was terminated due to futility. The mortality in the hypothermia group was 44.2% as compared to 35.8% in the controlled group ($P=0.07$). The hypothermia group was more often treated with vasoactive drugs and mechanical ventilation. No subgroup benefited from hypothermia, and the authors concluded that patients with septic shock should not be treated with hypothermia. In this way the ability to produce fever in response to an

infection developed in millions of years of evolution proved to be the winner.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Itenov TS, Johansen ME, Bestle M, et al. Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomised, controlled, open-label trial. *Lancet Respir Med* 2018;6:183-92.
2. Toft P, Tonnesen E. Immune-modulating interventions in critically ill septic patients: pharmacological options. *Expert Rev Clin Pharmacol* 2011;4:491-501.
3. Bernheim HA, Bodel PT, Askenase PW, et al. Effects of fever on host defense mechanisms after infection in the lizard *Dipsosaurus dorsalis*. *Br J Exp Pathol* 1978;59:76-84.
4. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat Rev Immunol* 2015;15:335-49.
5. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010;375:475-80.

doi: 10.21037/jeccm.2018.04.06

Cite this article as: Toft P, Stroem T. Fever during septic shock, friend or foe? *J Emerg Crit Care Med* 2018;2:42.