# COMMENTARY



# Fever in sepsis: is it cool to be hot?

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See related research by Kushimoto et al., http://ccforum.com/content/17/6/R271

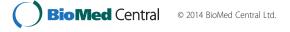
# Abstract

Changes in body temperature are a characteristic feature of sepsis. The study by Kushimoto and colleagues in a recent issue of *Critical Care* demonstrates that hypothermia is a very important manifestation of infection associated with very high mortality. Combined with recent data suggesting that febrile patients with infections have the lowest mortality risk, the study raises the question of whether inducing therapeutic hyperthermia might be beneficial in this patient group. Body temperature is easily measured and manipulated in the ICU, and interventional trials defining the most appropriate temperature targets in ICU patients with infections are urgently needed. One such study is in progress.

### Introduction

The majority of patients with diagnosed sepsis have a fever; however, 10% to 20% of patients are hypothermic [1-4]. The study by Kushimoto and colleagues in a recent issue of *Critical Care* demonstrates that hypothermia is a very important manifestation of infection [1]. In an inception cohort study, the investigators studied 624 patients with severe sepsis and demonstrated that those with a temperature of not more than 36.5°C had higher illness severity scores, more disseminated intravascular coagulation, and higher in-hospital and 28-day mortality rates than those with a temperature of more than 36.5°C [1]. The risk of death at hospital discharge and at 28 days for septic patients with hypothermia was more than double that of patients who were not hypothermic.

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# Time to consider therapeutic hyperthermia

Hypothermia in the context of infection may be a marker of an impaired immune response to infection or a marker of disease severity or both. Moreover, 'cold sepsis' may be more difficult to identify, so that multi-organ failure may be established by the time antibiotics are started. Although it is now clear that sepsis patients who have a low body temperature have an increased risk of death, it is not known whether intervening to warm patients with 'cold sepsis' is beneficial or not. Furthermore, if one were to warm patients with 'cold sepsis', it is not clear whether the appropriate target should be the restoration of normothermia or the induction of mild or moderate hyperthermia.

Our group's previous data involving more than 500,000 patients and more than 300 ICUs in Australia and New Zealand and the UK show that the lowest risk for patients with sepsis occurs at a peak temperature in the first 24 hours in the ICU of somewhere between 38°C and 39.4°C [2]. This observation suggests that moderate therapeutic hyperthermia may be a rational target in the treatment of cold sepsis and warrants investigation.

The use of therapeutic hyperthermia to treat patients with infections is not a new concept. In the early part of the 20th century, therapeutic hyperthermia was used successfully to treat syphilis [5] and gonorrhea [6]. This approach contrasts with the approach investigated in the recently published Sepsiscool Study [7]. In the Sepsiscool Study, 200 febrile patients with septic shock requiring vasopressors, mechanical ventilation, and sedation were allocated to external cooling to achieve normothermia for 48 hours or no external cooling. Fever control using external cooling decreased vasopressor requirements and appeared to delay death. External cooling of febrile patients with septic shock to normothermia and external warming of patients with hypothermia to mild or moderate hyperthermia may seem paradoxical. Yet it is conceivable that warming patients who fail to mount a fever and cooling patients with high fever and significant hypotension might both be useful strategies. A recently published study investigating therapeutic hypothermia for

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the treatment of severe bacterial meningitis was stopped early because of an increased risk of death in the patients assigned to cooling, suggesting that, if cooling of febrile patients with sepsis is undertaken, induced hypothermia should be avoided [8]. However, beyond this, the current evidence base is insufficient to guide practice.

## Conclusions

Given that changes in body temperature are common in patients with infections and that physical and pharmacological interventions are commonly used in the ICU [9,10], clinical trials are overdue. With this in mind, a multicenter randomized double-blind placebo controlled trial called HEAT (permissive HyperthErmia through Avoidance of paraceTamol in known or suspected infection in the ICU) (registration: ACTRN12612000513819) is under way in Australia and New Zealand [11]. The HEAT trial will provide level 1 evidence on the safety and efficacy of using paracetamol to treat elevated body temperature in ICU patients with infections and will help us understand more clearly whether it's hot to be cool or cool to be hot.

#### Abbreviations

HEAT: Permissive HyperthErmia through Avoidance of paraceTamol in known or suspected infection in the intensive care unit.

#### **Competing interests**

The authors declare that they have no competing interests.

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