CRITICAL CARE

COMMENTARY

Fever in sepsis: is it cool to be hot?

Paul J Young[1,2*] and Rinaldo Bellomo[3]

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.

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

* Correspondence: paul.young@ccdhb.org.nz
[1]Intensive Care Unit, Wellington Regional Hospital, Capital and Coast District Health Board, Riddiford Street, Newtown, Wellington 6021, New Zealand
[2]Medical Research Institute of New Zealand, Wellington, New Zealand
Full list of author information is available at the end of the article

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.

Author details

[1]Intensive Care Unit, Wellington Regional Hospital, Capital and Coast District Health Board, Riddiford Street, Newtown, Wellington 6021, New Zealand. [2]Medical Research Institute of New Zealand, Wellington, New Zealand. [3]Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Centre, Level 6, 99 Commercial Road, Melbourne, Victoria 3004, Australia.

Published: 13 February 2014

References

1. Kushimoto S, Gando S, Saitoh D, Mayumi T, Ogura H, Fujishima S, Araki T, Ikeda H, Kotani J, Miki Y, Shiraishi SI, Suzuki K, Suzuki Y, Takeyama N, Takuma K, Tsuruta R, Yamaguchi Y, Yamashita N, Aikawa N: **The impact of body temperature abnormalities on the disease severity and outcome in patients with severe sepsis: an analysis from a multicentre, prospective survey of severe sepsis.** *Crit Care* 2013, **17:**R271.
2. Young PJ, Saxena M, Beasley R, Bellomo R, Bailey M, Pilcher D, Finfer S, Harrison D, Myburgh J, Rowan K: **Early peak temperature and mortality in critically ill patients with or without infection.** *Intensive Care Med* 2012, **38:**347–444.
3. Clemmer TP, Fisher CJ Jr, Bone RC, Slotman GJ, Metz CA, Thomas FO: **Hypothermia in the sepsis syndrome and clinical outcome, The Methylprednisolone Severe Sepsis Study Group.** *Crit Care Med* 1992, **20:**1395–1401.
4. Peres Bota D, Lopes Ferreira F, Melot C, Vincent JL: **Body temperature alterations in the critically ill.** *Intensive Care Med* 2004, **30:**811–816.
5. Wagner-Jauregg J: **The treatment of dementia paralytica by malaria innoculation**. In *Nobel Lectures: Physiology or Medicine 1922–1941.* New York: Elsevier; 1927:159–169.
6. Owens C: **The value of fever therapy for gonorrhea.** *JAMA* 1936, **107:**1942–1946.
7. Schortgen F, Clabault K, Katsahian S, Devaquet J, Mercat A, Deye N, Dellamonica J, Bouadma L, Cook F, Beji O, Brun-Buisson C, Lemaire F, Brochard L: **Fever control using external cooling in septic shock: a randomized controlled trial.** *Am J Respir Crit Care Med* 2012, **185:**1088–1095.
8. Mourvillier B, Tubach F, van de Beek D, Garot D, Pichon N, Georges H, Lefevre LM, Bollaert PE, Boulain T, Luis D, Cariou A, Girardie P, Chelha R, Megarbane B, Delahaye A, Chalumeau-Lemoine L, Legriel S, Beuret P, Brivet F, Bruel C, Camou F, Chatellier D, Chillet P, Clair B, Constantin JM, Duguet A, Galliot R, Bayle F, Hyvernat H, Ouchenir K, *et al*: **Induced hypothermia in severe bacterial meningitis: a randomized clinical trial.** *JAMA* 2013, **310:**2174–2183.
9. Hammond NE, Saxena MK, Taylor C, Young P, Seppelt I, Glass P, Myburgh J: **Temperature management of non-elective intensive care patients without neurological abnormalities: a point prevalence study of practice in Australia and New Zealand.** *Crit Care Resusc* 2013, **15:**228–233.
10. Lee BH, Inui D, Suh GY, Kim JY, Kwon JY, Park J, Tada K, Tanaka K, Ietsugu K, Uehara K, Dote K, Tajimi K, Morita K, Matsuo K, Hoshino K, Hosokawa K, Lee KH, Lee KM, Takatori M, Nishimura M, Sanui M, Ito M, Egi M, Honda N, Okayama N, Shime N, Tsuruta R, Nogami S, Yoon SH, Fujitani S, *et al*: **Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study.** *Crit Care* 2012, **16:**R33.
11. Young PJ, Saxena MK, Bellomo R, Freebairn RC, Hammond NE, van Haren FM, Henderson SJ, McArthur CJ, McGuinness SP, Mackle D, Myburgh JA, Weatherall M, Webb SA, Beasley RW, ANZICS Clinical Trials Group: **The HEAT trial: a protocol for a multicentre randomised placebo-controlled trial of IV paracetamol in ICU patients with fever and infection.** *Crit Care Resusc* 2012, **14:**290–296.

doi:10.1186/cc13726
Cite this article as: Young and Bellomo: **Fever in sepsis: is it cool to be hot?.** *Critical Care* 2014 **18**:109.