# Is sepsis treatment heating up?

Paul J Young

Low body temperature is strongly independently associated with increased mortality risk in intensive care unit (ICU) patients with infections.[1] While failure to mount a febrile response to an infection is potentially a marker of a suboptimal host immune response, low body temperature itself might also be harmful in a more direct sense. High body temperature inhibits the growth of a range of pathogenic parasites, bacteria and viruses; it also decreases the minimum inhibitory concentration of a number of antibiotics in vitro.[2] Accordingly, it logically follows that the growth of pathogenic organisms might be more rapid and antibiotics might be less effective when the body temperature is abnormally low. While active warming has been suggested as a potential therapeutic modality for patients with infections,[3] it has not been evaluated in randomised controlled trials in the critically ill.

The study from Gouldthorpe and colleagues[4] in this issue of *Critical Care and Resuscitation* provides an important step towards a long term goal of evaluating therapeutic warming in "cold" sepsis. In this single centre retrospective study of patients who required admission to the ICU from the emergency department (ED) with community-acquired sepsis, 34 of 151 patients (22.5%) had a body temperature of 36.4°C or less at ED presentation.[4] A total of 90 of 117 remaining patients (76.9%) had a documented body temperature of 36.4°C or less either during their ED stay or during the first 24 hours in the ICU. The median time spent with a body temperature of 36.4°C or less up until the end of the first 24 hours in the ICU was 11.0 hours (interquartile range, 5.0–16.8). Only one patient received active warming. These findings suggest that active warming could be used in the early phase of care in a substantial proportion of critically ill adults with infections. This may result in increased body temperature compared with standard care. Certainly, this hypothesis appears readily testable in a feasibility study. However, there are a number of important caveats to consider and many questions remain unanswered.

First, what should the temperature threshold to consider active warming be? The rationale for choosing a threshold temperature of 36.4°C or less used in the current study is not clear. Previous data suggest that among those with an infection-related ICU admission diagnosis, a peak body temperature of 36–36.4°C in the first 24 hours in the ICU is associated with an increased risk of in-hospital mortality compared with a peak body temperature of 36.5–36.9°C.[1] However, in this prior study, with the exception of the highest body temperature category (peak temperature in the first 24 hours in the ICU ≥ 40°C), mortality risk declined as body temperature increased.[1] Such data suggest that active warming might be useful in normothermic or even in mildly febrile patients. If the threshold used for warming is 36.4°C or less, the relatively high proportion of patients with a low temperature seen in the current study might reflect the fact that peripheral measures of body temperature are commonly used in the ED. Such temperature measurements are typically lower than the core measures used more commonly in the ICU.[5] If a threshold of 36.4°C or less is used to initiate warming in ICU patients, the potential patient population of interest may be somewhat smaller than it appears to be in the Gouldthorpe study.[4]

Second, will critically ill patients tolerate active warming? As increasing body temperature increases both metabolic demand and physiological demand it may result in demand that exceeds critically ill patients' ability to compensate.[6] The timing of warming might be important. Warming patients with established multi-organ failure and limited reserves makes less intuitive sense than early initiation of warming to try and kill pathogens before organ dysfunction is established. However, such early intervention would be logistically challenging in a randomised controlled trial.

Third, as heating represents a physiological stressor and will lead to a compensatory physiological response that includes sweating and vasodilation, will these compensatory responses result in unanticipated harm? Fourth, will such physiological responses prevent active warming achieving desired temperature effects?

Fifth, does the question of whether active warming of cool sepsis improves outcomes resonate with clinicians? Framing a research program evaluating warming that is acceptable to clinicians may prove challenging when recent data indicate that further research evaluating cooling to normothermia of ICU patients who have fever and infection is warranted[7] and current research in this area is underway.[8] Nevertheless, the current study is a timely reminder that the degree of uncertainty about temperature management in critically ill adults with infections is such that testing both cooling and warming are reasonable.

## Competing interests

Paul Young reports receiving speaker's fees from Bard Medical and is the Chief Investigator for the Randomised Evaluation of Active Control of Temperature *v* Ordinary Temperature Management (REACTOR) research program.

## Author details

Paul J Young[1,2]

1 Intensive Care Unit, Wellington Hospital, Wellington, New Zealand.

2 Medical Research Institute of New Zealand, Wellington, New Zealand.

***Correspondence*:** Paul.Young@ccdhb.org.nz

## References

1 Young PJ, Saxena M, Beasley R, et al. Early peak temperature and mortality in critically ill patients with or without infection. *Intensive Care Med* 2012; 38: 437-44.

2 Young PJ, Saxena M. Fever management in intensive care patients with infections. *Crit Care* 2014; 18: 206.

3 Young PJ, Bellomo R. Fever in sepsis: is it cool to be hot? *Crit Care* 2014; 18: 109.

4 Gouldthorpe OT, Pilcher DV, Bellomo R, Udy AA. Prevalence of low–normal body temperatures and use of active warming in emergency department patients presenting with severe infection. *Crit Care Resusc* 2019; 21: 96-101.

5 Saxena MK, Taylor C, Billot L, et al. The effect of paracetamol on core body temperature in acute traumatic brain injury: a randomised, controlled clinical trial. *PLoS One* 2015; 10: e0144740.

6 Young PJ, Nielsen N, Saxena M. Fever control. *Intensive Care Med* 2018; 44: 227-30.

7 Young PJ, Bellomo R, Bernard GR, et al. Fever control in critically ill adults. An individual patient data meta-analysis of randomised controlled trials. *Intensive Care Med* 2019; 45: 468-76.

8 Young PJ, Bailey MJ, Beasley RW, et al. Protocol and statistical analysis plan for the Randomised Evaluation of Active Control of Temperature versus Ordinary Temperature Management (REACTOR) trial. *Crit Care Resusc* 2017; 19: 81-7.

---

## Erratum

Al-Bassam W, Dade F, Bailey M, et al. "Likely overassistance" during invasive pressure support ventilation in patients in the intensive care unit: a multicentre prospective observational study. *Crit Care Resusc* 2019; 21: 18-24.

In the Research article above, the label of the y axis in Figure 1 was incorrect; the correct label is "Number of observations". The change has been made online.