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WHEN LESS IS MORE IN THE ACTIVE MANAGEMENT OF ELEVATED BODY TEMPERATURE OF ICU PATIENTS.

Paul J. Young[1,2], **Hallie C. Prescott**[3,4]

[1]Intensive Care Unit, Wellington Regional Hospital, Wellington, New Zealand [2]Medical Research Institute of New Zealand, Wellington, New Zealand [3]Division of Pulmonary & Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA [4]VA Center for Clinical Management Research, Ann Arbor, MI, USA

Fever is a pathophysiological response in which the body's normal thermoregulatory set-point is adjusted upwards leading to an increase in body temperature. In contrast, hyperthermia occurs from excessive heat production or insufficient thermoregulation (*e.g.* heat stroke or drug reactions). Although temperature elevation is common in Intensive Care Unit (ICU) patients, a newly elevated body temperature should prompt consideration of a diagnostic evaluation. It is always prudent to consider the possibility of infection; however, for critically patients with acute brain pathologies in particular, elevated body temperature is common, even in the absence of infection. Body temperature may be elevated due to drugs, particularly antipsychotic, serotonergic, sympathomimetic, anaesthetic, and anticholinergics drugs[1]. Thyrotoxicosis and phaeochromocytoma should also be considered in the differential diagnosis. Often elevated temperature is multifactorial and, in many patients, particularly after major surgery, a specific cause is not found.

Although body temperature is recorded assiduously in the ICU[2], it is often unclear when or how to intervene when a patient's body temperature is elevated. A recent individual patient data meta-analysis reported that *more* active fever management did not increase survival compared with *less* active fever management in an all-comers population of critically ill adults[3]. Survival by treatment group was similar in a range of subgroups defined by age, illness severity, receipt of specific organ supports, and presence versus absence of high fever at baseline. These data suggest that, in general, when it comes to active management of fever in ICU patients, although less may not be more, doing less to treat fever results in similar outcomes to doing more.

FEVER IN PATIENTS WITH INFECTIONS

Fever is a broadly conserved biological response to infection across many animal species including insects, reptiles, fish, and mammals[4]. It is logical that a response that occurs in such diverse species has an evolutionary advantage, particularly given that fever is metabolically costly[5]. Fever therapies have even been used in humans to treat infections

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including gonorrhoea and syphilis[4]. However, for patients with fever and suspected infection, the common practice of administering paracetamol to treat fever does not appear to either improve or worsen patient outcomes[6]. Moreover, in a phase two study evaluating active cooling to target normothermia in patients with sepsis who were sedated and mechanically ventilated, active temperature management reduced early mortality compared with usual care[7]. Routine cooling of septic patients to normothermia is the subject of ongoing research and is best considered an experimental therapy[8]. However, it important to note that cooling critically ill patients with infections to below a normal body temperature may be harmful[9, 10] and, if cooling is employed, particular care should be taken to avoid hypothermia.

TEMPERATURE MANAGEMENT IN PATIENTS WITH HYPOXIC BRAIN INJURIES

One group of patients where more stringent temperature management is recommended is those with hypoxic brain injuries. Therapeutic hypothermia improves survival and neurodevelopmental outcomes in neonates with moderate to severe hypoxic ischaemic encephalopathy[11]. In adults, two phase two trials comparing therapeutic hypothermia at 32 to 34°C with a permissive approach to temperature management suggested that therapeutic hypothermia increased survival and improved neurological outcomes following out of hospital cardiac arrest[12, 13]. A subsequent trial comparing two hypothermia regimens (33°C and 36°C) showed that these resulted in similar outcomes[14]. Following this trial, there was widespread de-adoption of a 33°C target in Australian and New Zealand ICUs, which was associated with an increase frequency of fever, and a trend towards decreased survival[15]. Although further research evaluating temperature management in out-of-hospital cardiac arrest patients is underway, current guidelines recommend avoidance of fever in this group of patients[16].

TEMPERATURE MANAGEMENT IN PATIENTS WITH TRAUMATIC BRAIN INJURIES

Thermoregulatory disturbances often complicate acute brain pathologies. Aggressive management of elevated body temperature is typically considered desirable in patients with brain pathologies such as traumatic brain injury (TBI), and stroke. Although a body temperature of over 39°C in the first 24 hours in ICU is associated with increased mortality risk in such patients[17], it is possible that fever is a marker of brain damage rather than a modifiable risk factor for adverse outcomes. Although strict maintenance of normothermia in patients with TBI might improve outcomes compared to a reactive approach of treating fever when it occurs, this is largely untested. Systematic evaluation of prophylactic normothermia in patients with TBI in a randomised trial is needed. However, in such patients, hypothermia reduces intracranial hypertension but appears to worsen outcomes compared with alternative approaches to reducing intracranial pressure[18].

SEVERE TEMPERATURE ELEVATION AND HYPERTHEMIA

Active control of temperature is clearly preferred in some situations. Very high body temperature is associated with increased mortality risk in most ICU patient groups[17, 19]. As peripheral thermometry can substantially underestimate core body temperature[20] and temperature can rise rapidly[1], it is prudent to monitor core body temperature continuously in critically ill patients with fever. Although uncommon, there are certainly instances where patients develop extremely high body temperature (>42°C) and die soon after[6]. In such patients, it is plausible that death is a direct consequence of elevated temperature. If a patient is critically ill, we submit that it is nearly always best to prevent core body temperature from exceeding 41°C.

In patients with hyperthermia, rather than fever, careful monitoring of body temperature and early intervention using physical cooling measures with or without neuromuscular paralysis is prudent. In this situation, impaired heat loss and/or excessive heat production can result in life-threatening complications such as rhabdomyolysis and secondary hyperkalaemia, metabolic acidosis, multi-organ failure and disseminated intravascular coagulation[1].

In patients with muscle rigidity and agitation, benzodiazepines can be used to reduce the generation of heat[1]. Although use of bromocriptine and dantrolene have been reported in patients with neuroleptic malignant syndrome, and chlorpromazine and cyproheptadine can be used in serotonin syndrome, most patients with hyperthermia can be managed with supportive care and conventional cooling methods rather than requiring specific drug therapies[1]. One notable exception to this is in patients with malignant hyperthermia where dantrolene should be administered promptly[1].

A suggested approach to management of elevated body temperature is shown in Figure 1. Prompt temperature reduction makes sense in patients with severely elevated body temperature due to hyperthermia because in these patients the primary problem may be failed thermoregulation. However, in many patient groups with elevated temperature we simply do not know whether less intervention is better when it comes to active temperature control in the critically ill.

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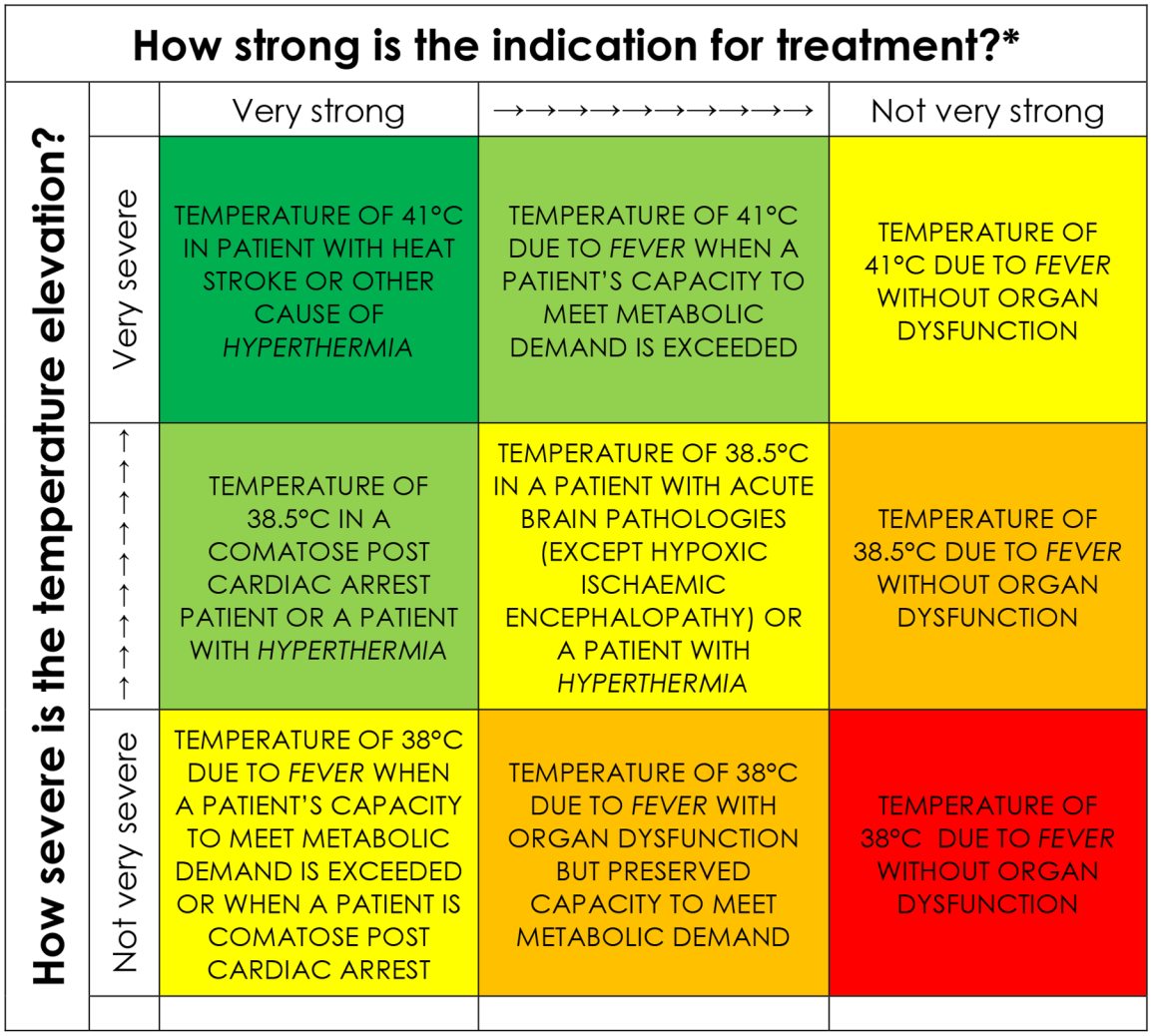

Figure 1. When to Initiate Active Management of Elevated Body Temperature in the Critically Ill*

* A strong indication for treatment combined with a severely elevated temperature is reflected by dark green shading, which corresponds to a situation where active management elevated body temperature very reasonable; red shading indicates situations where active temperature management may be less desirable; other shades indicate different degrees of certainty about the appropriateness of treatment.