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WHAT'S NEW IN INTENSIVE CARE

Fever control

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Potential risks and benefits of fever

Fever is a commonly encountered phenomenon in the intensive care unit (ICU) which has both potential benefits and potential risks for patients. Among patients with infections who are admitted to the ICU, increasing fever is independently associated with a decreasing risk of in-hospital mortality [1, 2]. From an evolutionary perspective, fever is a broadly conserved biological response to infection, and thus one might expect that for patients with infection, the febrile response could have benefits. Even in the absence of infection, low-grade fever appears to be independently associated with reduced mortality risk compared with normothermia [1].

While such associations might be used to infer that fever should not be treated, they are confounded by genetic differences between patients that may account for variations in the febrile response to critical illness [3]. Moreover, an alternative argument can be made based on the observation that fever increases physiological demand [4]. This is potentially important, because ICU therapies allow patients to be kept alive beyond the limits of usual physiological homeostasis, so that those with acutely life-threatening but reversible illnesses can be supported to recovery. Even for potentially reversible illnesses, however, there are limits to supportive care, and when physiological demand exceeds these limits, patients often die. One rationale for treating fever is that, if shivering is avoided, doing so can reduce physiological demand [4] such that it does not exceed the limits of supportive care. An additional consideration in patients with acute brain pathologies is that treatment of fever may attenuate secondary brain injury.

Potential considerations when deciding whether to treat fever

When deciding whether to treat fever in an individual patient, the balance of potential benefits and risks of fever in the clinical situation should be considered. Additionally, the potential risks associated with treating fever and the risks associated with concomitant therapies that may be required to treat shivering should be considered.

Shivering is the most common side effect of physical cooling. Potential side effects of non-steroidal anti-inflammatory drugs include peptic ulcer disease and renal impairment. While known side effects of paracetamol include hypotension and liver dysfunction, data from randomised placebo-controlled trials suggest that this medicine is generally well tolerated in critical illness [5, 6].

Due to a lack of high-quality evidence, there is often considerable uncertainty about where the balance of risks and benefits lies with respect to treatment decisions. With this in mind, we propose the model outlined in Fig. 1 to be further evaluated through clinical trials. The first consideration in relation to this model is that the risks of fever are likely to increase as the degree of physiological reserve decreases, so that patients with high illness acuity, limited cardiorespiratory reserve due to underlying comorbidities, or frailty might generally be expected to benefit from more aggressive treatment of fever (Fig. 1a). Similarly, the degree of fever may be important (Fig. 1b). For example, the risk associated with a high fever of 41 °C appears to be greater than the risk associated with a fever of 38 °C [1]. The presence or absence of infection [1] (Fig. 1c, d) and the presence or absence of acute brain pathologies [2] such as traumatic brain injury or stroke may also be important considerations when deciding how aggressively to treat fever (Fig. 1e, f).

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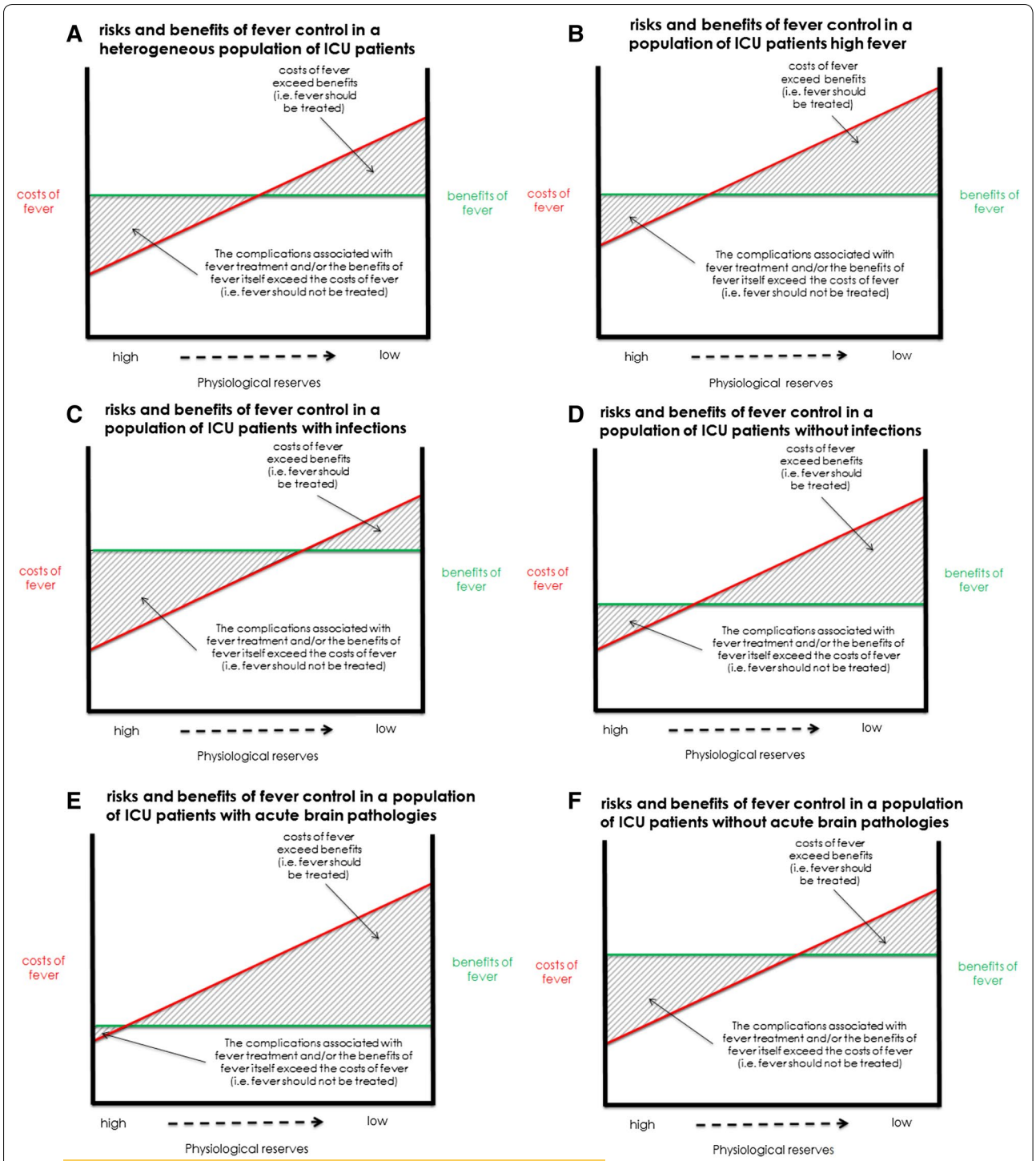

Fig. 1 Hypothetical framework for evaluation of the risks and benefits of fever control in critically ill patients. On each graph the green line represents the potential benefits of fever, while the red line represents the potential harms; shaded areas above each green line represent circumstances in which treatment of fever may be beneficial, and shaded areas below each green line represent circumstances in which treatment of fever may be harmful. The physiological reserves represented on the horizontal axis will depend on both the physiological demands and the patients' capacity to meet those demands. Demands will typically increase with increasing illness acuity, and a patient's capacity to meet demand will fall with increasing age and in the presence of comorbidities

Fever management in patients with traumatic brain injury, ischaemic stroke, and haemorrhagic stroke

Although early fever of over 39 °C is associated with an increased risk of in-hospital mortality in ICU patients with traumatic brain injury (TBI), stroke, and subarachnoid haemorrhage [2], there are no data demonstrating that fever causes brain damage in humans, and it is possible that fever is simply an epiphenomenon associated with more severe brain damage.

In patients with TBI, therapeutic hypothermia does not appear to improve outcomes either when initiated early [7] or when used as a treatment for intracranial hypertension [8]. While it is plausible that strict maintenance of normothermia in patients with TBI might improve outcomes compared to a reactive approach of treating fever when it occurs, this hypothesis remains largely untested. One small trial evaluating the use of paracetamol in TBI patients has shown that paracetamol has, at best, a modest effect on core temperature and is insufficient to prevent fever from occurring [5].

Data in relation to fever management in ICU patients with ischaemic stroke or intracerebral haemorrhage are limited [9]. In a ward setting, the Paracetamol (Acetaminophen) In Stroke trial showed no overall benefit with paracetamol compared to placebo [10]. However, in a post hoc analysis, paracetamol use was associated with improved functional outcomes in patients admitted with a body temperature of 37–39 °C [10].

Fever management in hypoxic ischaemic encephalopathy

Two randomised clinical trials (RCTs) demonstrating improved outcomes with hypothermia versus no temperature control after cardiac arrest led to the widespread use of targeted temperature management (TTM) down to 32 °C in these patients [11]. However, when the TTM-trial found no difference in outcome between TTM at 33 °C and TTM at 36 °C [12], the international guideline-recommended temperature target for post-cardiac arrest patients was modified from 32–34 to 32–36 °C. While TTM is currently the accepted paradigm, we consider that it is possible that simply treating fever promptly and aggressively would result in outcomes similar to those with TTM.

Fever management in patients with infections

One group of patients with brain pathologies where aggressive treatment of fever may not be appropriate is those with central nervous system (CNS) infections. In such patients, the presence of fever in the first 24 h in ICU is associated with a reduced risk of in-hospital mortality [2]. Moreover, a trial investigating the use of 48 h of moderate hypothermia in adults with severe bacterial meningitis was stopped early because of excess mortality in the hypothermia group [13].

Two RCTs in ICU patients with fever and infections outside the CNS have recently been reported [6, 14]. One trial evaluated physical cooling [14] and the other the use of paracetamol to treat fever [6]. Both trials suggested that treatment of fever may delay death [6, 14]; however, neither reported a statistically significant reduction in hospital or subsequent mortality with fever treatment.

Ongoing research

The hypothesis that aggressive treatment of fever improves the outcomes of ICU patients without acute brain pathologies who have high illness acuity is being investigated in the Randomised Evaluation of Active Control of Temperature vs. ORdinary temperature management (REACTOR) research programme [15]. The Cooling And Surviving Septic (CASS) shock trial is investigating external cooling to 32–34 °C in patients with septic shock and acute respiratory failure (ClinicalTrials.gov Identifier: NCT01455116). For patients with cardiac arrest and global ischaemia, the TTM2-trial (ClinicalTrials.gov Identifier: NCT02908308) will compare hypothermia to 33 °C with a control group, which will receive fever treatment if and when fever occurs. For patients with TBI, the TTM-TBI research programme (ACTRN12615001119583p) is investigating the use of prophylactic TTM to 36 °C for 72 h in patients with severe TBI.

Conclusions

While a number of factors may be important in relation to treatment decisions about fever control, because the current evidence base is so limited, there is often uncertainty regarding how and when to treat fever. Further research is a high priority.

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Compliance with ethical standards

Conflicts of interest

All authors report receiving speaker's fees from Bard Medical. PY is the chief investigator for the REACTOR research programme, NN is chief investigator for TTM-2 trial, and MS is the chief investigator for the TTM-TBI research programme.

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