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To cool or too cool?

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CONTENTS

INTRODUCTION: Why temperature management matters.

The tightly controlled regulatory process of thermoregulation maintains body temperature within a range of 0.2 degrees Celsius [(1)], yet it is not uncommon for the body temperature to fluctuate more than 1.5 degrees Celsius when the process is entrusted to anaesthetists! It is no wonder that more harm is not caused by our sometimes-lackadaisical approach to temperature management. Yet, induced hypothermia and avoidance of pyrexia are key therapeutic goals for patients with a variety of pathologies. Hypothermia can avoid the harmful effects of hyperthermia and exploit the protective effects of lower tissue temperature [(2)].

Our understanding of thermoregulation and anaesthesia has progressed significantly over the last 30 years. Initially research focused on understanding the physiology of thermoregulatory responses, heat balance and thermoregulatory vasoconstriction thresholds to anaesthesia (i.e. core temperatures that trigger a thermoregulatory response). As interest in this topic grew and more research was conducted, in particular by Dr Daniel Sessler [(3, 4)], it became clear that even mild hypothermia had dire consequences that were proportional to the degree of hypothermia. Continued work by Sessler et. al. and later by Frank et. al. showed adverse outcomes relating to surgical wound infection, coagulopathy and cardiac outcomes. Further studies revealed links to prolonged recovery and impaired drug metabolism. The Thermoregulatory Story[(3)], initiated by Dr Sessler ultimately resulted in the establishment of The Department of Outcomes Research at the Cleveland Clinic that co-ordinates the International Outcomes Research Consortium. This group, which is involved in approximately 100 studies at any given time, publishes an average of one full paper a week translating into 10% of the world's clinical anaesthesia research[(5)]! As a result of this work the maintenance of normothermia has become a crucial component of providing anaesthesia and an essential part of a patient's journey through anaesthesia. Many regions in the world demand the maintenance of normothermia as part of their national guidelines and minimum standards, and some regions, notably in the USA, may withhold full payment if normothermia is not maintained during anaesthesia. The United Kingdom has also dedicated NICE guidelines relating to management of a patient's temperature.

Hypothermia is defined as a body temperature reading below 36.0 ºC. It is associated with altered pharmacodynamics and pharmacokinetics, poor wound healing, and patient discomfort with shivering on waking or during awake procedures. Shivering also causes increased oxygen demand and impairs monitoring devices causing artefacts on ECG and NIBP readings. Monitoring for hyperthermia, especially in patients being actively warmed is equally important. It assists in detecting pathologies (e.g. malignant hyperthermia) and prevents the increased metabolic demand and deleterious effects of hyperpyrexia.

Special patient populations demand special and careful attention to temperature management.
The following case vignettes try to illustrate some of the subtleties of temperature management: How would your temperature management differ for the following patients?

- A young man with an isolated head injury, GCS 7/15 who was intubated and is now in your ICU for 48 hours of neuroprotection.
- An elderly previously well granny who had spontaneous return of circulation following an out of hospital cardiac arrest? An airport defibrillator was used to resuscitate her and she is now in your ED.
- One of your ICU patients who is ventilated for sepsis secondary to pneumonia who is pyrexial at 38.9ºC.

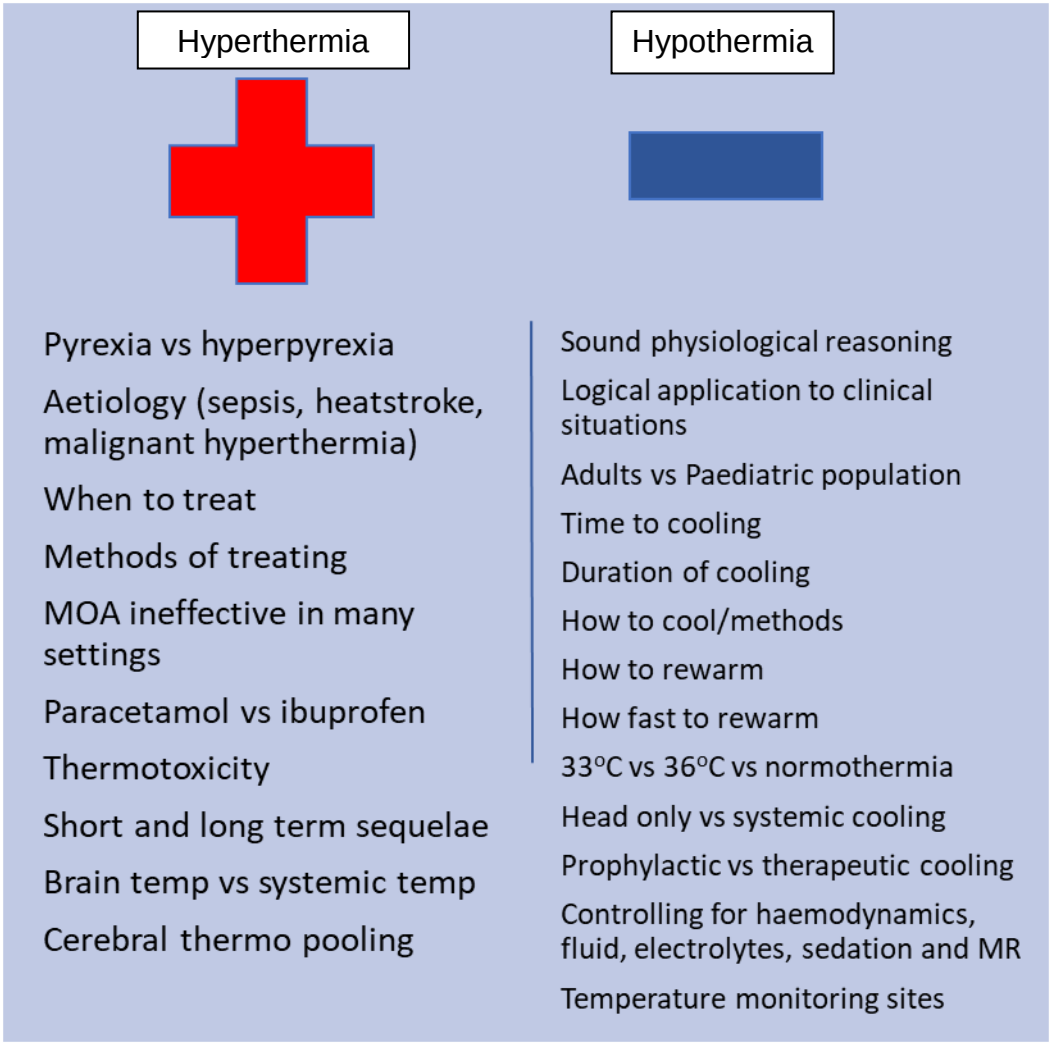
These three distinct patient populations, namely Isolated Traumatic Brain Injury (TBI), Out of hospital cardiac arrest with return of spontaneous circulation (ROSC) and Sepsis induced

pyrexia have been the topic of many research projects and clinical trials. However, there is still controversy in how to best manage these scenarios.

Now if we combine these patient populations into one patient, what is your temperature target for this patient scenario:

- A middle-aged man with delayed presentation of severe TBI, who is septic from a aspiration pneumonia and is now post return of spontaneous circulation following cardiac arrest secondary to an arrhythmia?

Many other controversies also still persist:



And many large clinical trials have tried to answer specific questions:

Title	Year	Area of research
POLAR	2018	TBI
CASS	2018	Sepsis
TTM48	2017	OHCA/ROSCH
Eurotherm3235	2015	TBI
HEAT	2015	Paracetamol and fever
THAPCA-OH	2015	Paediatric OHCA
Niemann	2015	Organ donors and kidney transplant
Suzuki	2015	Paracetamol and fever
Bouwes	2015	TH post cardiac arrest
Lilja	2015	OHCA
CHEER	2015	Cardiac arrest
Saxena	2015	Fever and CNS infection
TTM	2014	OHCA
HACA	2014	OHCA
FACE	2012	Sepsis
Schortgen	2012	Sepsis
The Brain foundation TBI guidelines	2016	TBI
Surviving Sepsis Guidelines	2018	Sepsis
ACA guidelines	2016	
And many more review articles and opinion pieces…		

Yet centre and unit specific protocols still exist, with no clear answer.

This Friday morning meeting booklet aims to illustrate our current understanding of temperature and its relation to patient outcomes in general, and then briefly discuss the implications in specific patient populations which we treat every day.

Understanding temperature in health, sickness and under anaesthesia

In health, as with many other body systems, mammals keep tight control of their thermoregulatory status. Humans have the added advantage of being able to manipulate their environment to maintain their body temperature. We can layer or remove clothes and adjust the aircon to achieve a comfortable environment. Both hypothermia and hyperthermia have deleterious effects.

Buzzwords

Therapeutic Hypothermia (TH)
TTM: targeted temperature management
Induced normothermia
Thermotoxicity
Thermosensitivity
Cerebral thermopooling
Cerebral protection

Thermoregulation is the balance between heat production and heat loss. Tight temperature regulation is achieved through complex and integrated systems [(6)]. Heat production is broadly classified into shivering and non-shivering components, and heat loss is predominantly via radiation (60% of heat loss), conduction, convection and evaporation. Skin temperature rises and falls with the environmental temperature, but core temperature is strictly kept constant. The three components of afferent sensing, central control and efferent responses ensure tight thermoregulation. The hypothalamus is responsible for setting a threshold temperature, if temperature inputs from the afferent sensing pathways are above or below this threshold or set point then thermoregulatory mechanisms are initiated. Smooth muscles in arterioles of skin, sweat glands, erector pili muscles in skin, skeletal muscles, adrenal, thyroid, behavioural changes and non-shivering thermogenesis via muscle and brown fat all contribute to this thermoregulatory system.

The Inter-threshold range represents the narrow range of temperature in which the hypothalamus will not initiate thermoregulatory efforts. In well adults the temperature threshold is set at 37 degrees Celsius, with a range of 0.1 below or above this. That is an inter-threshold range of just 0.2 degrees Celsius. Many situations may widen this normally narrow range. Opioids and general anaesthesia both significantly widen this range up to 4 degrees Celsius. This is important to note, as many patients will not report feeling cold and not act as if they are cold but may be up to 4 degrees below their thermoregulatory set point.

However, illness and anaesthesia change all this. When patients find themselves in our care, we take over responsibility for their thermodynamics. They can't keep their clothes on, are unable to run away, or adjust the aircon. It is up to us to monitor and maintain their thermodynamics. A few considerations to keep in mind are that prevention of cooling is easier then re-warming a patient (forced air warmers aren't efficient at rewarming a patient who is vasoconstricted and not redistributing heat to their central compartment) and even mild hypothermia less than 36 degrees Celsius is detrimental.

Equally hyperthermia has systemic and cerebral specific deleterious effects. However, the aetiology of fever may play a more important role in understanding and guiding our management of hyperthermia. Sepsis induces a fever as part of a useful body system, the innate immune system, and provides a means to defend against infection. Given the highly preserved nature of the febrile response to infection, it is reasonable to suggest that fever provides a net survival benefit[(7)]. Pyrexia following head injury may have a central cause and may not be effectively treated by paracetamol as the mechanism of action of paracetamol doesn't address this. Anti-pyrexia agents work by resetting the hypothalamus, this requires intact cerebral pathways, however a central cause of pyrexia implies theses pathways are disrupted [(1)]. Heat stroke has a different mechanism of heating and requires different management goals.

Hypothermia has many deleterious effects; however, we have laboratory and anecdotal evidence to suggest inducing hypothermia may confer cerebral protection. By cooling the brain and reducing its metabolic demand we can protect it from many insults. This evidence is limited in that the laboratory conditions normally induce hypothermia before the injury occurs and anecdotal stories of drowning victims surviving neurologically intact are also probably as a result of cooling and injury happening in a close time proximity.

Cerebral protection with hypothermia: Physiology and applied uses

Cooling the brain by irrigating it directly with ice water was described in 1938, and achieved "extremely gratifying results". [2] Similar gratifying results have been demonstrated in animal and laboratory models. Anecdotal evidence of drowning victims surviving prolonged periods of circulatory arrest are sometimes reported in the media.

The mechanism of tissue protection relies on limiting the primary injury and preventing any secondary injuries. Hypothermia induces protection via a multitude of effects, much more than simply reducing cerebral metabolism. Hypothermia affects excitotoxicity, apoptosis, inflammation, free radial production, reduces blood flow and metabolism, influences neurogenesis, gliogenesis and angiogenesis formation [2]. No single factor accounts for the neuroprotective effects of hypothermia.

Hypothermia has been used successfully in many settings; DHCA, organ transplant, CPB, post ischemia etc. Deep hypothermic circulatory arrest (DHCA) is used for complex cardiac surgery and surgery to major vessels, it has also been used during complex neurosurgical procedures. Importantly, hypothermia is induced prior to any injury, and two objectives are achieved. The first is to optimise and create suitable surgical conditions (circulatory arrest) and the second is organ protection. The cerebral protection may be achieved with a much lesser degree of cooling but circulatory arrest is not.

There are many mechanisms by which cytoprotection is achieved [6] , early reasoning relied on hypothermia's ability to preserve metabolic stores and achieve a state of suspended animation or hibernation like state. By lowering temperature, the metabolism is slowed but this understanding is incomplete and may be inaccurate. Modern understanding now includes hypothermia's effects on suppression of protein synthesis, inhibiting apoptosis and up-regulation of anti-apoptosis factors. Hypothermia is also understood to up-regulate 'cold shock proteins' which regulate cell survival pathways. Cold inducible RNA binding protein (CIRP) and RNA binding motif protein 3 (RBM3) are just two of these cold shock proteins under investigation [6].

The basic understanding of reducing cerebral oxygen and glucose metabolism by 5% for every degree cooled remains true. Hypothermia thus induces lower blood flow through the coupling of brain energy requirements and blood flow. Glutamate is a potent inducer of brain injury, it binds to ionotropic receptors and allows entry of toxic levels of calcium into the cell. Hypothermia may act to prevent glutamate's actions [6].

Hypothermia needs to be induced prior to, or as close to the time of injury as possible and maintained for 24-48 hours to show improved cerebral outcome. Re-warming must be slow and carefully monitored as rapid re-warming may negate all the protection offered by hypothermia. Hypothermia has been described after cardiac arrest, following brain trauma and neonatal hypoxic encephalopathy as well as after ischaemic and haemorrhagic stroke. Spinal cord protection, hepatic encephalopathy and hypotensive bleeding trauma patients have all been subjected to induced hypothermia [6].

How to cool: **Questions and pitfalls.**

If a patient is to be cooled, there are many questions to answer and practical pitfalls to avoid. Which technique do you use? Invasive via cardio pulmonary bypass machines or surface cooling with automated feedback loops? Which method allows rapid cooling and accurate control of temperature?

How rapid do you cool your patient? And for how long? Are you being vigilant in monitoring for complications of hypothermia and how are you managing them?

If you are aiming to cool the brain, why are you cooling the whole body?

Cost, availability, practicality, familiarity and associated morbidity must be considered.
These questions and pitfalls necessitate unit specific protocols and procedures to ensure appropriate cooling and to minimising adverse effects of hypothermia.

Establishment of hypothermia can be divided into three phases; induction, maintenance and re-warming.

<table>
<tr><td colspan="4">To cool? If yes:</td></tr>
<tr><td colspan="2">Pharmacological

Consider in:
Non-sedated patients
Concomitant need for analgesia</td><td colspan="2">Physical
(internal vs external*)

Consider in:
Hypothalamic dysfunction
Need for rapid cooling
Need for strict temperature control
Failure or contra-indications of pharmacological techniques
Haemodynamically unstable patients</td></tr>
<tr><td>Paracetamol</td><td>Ibuprofen</td><td>Surface cooling (FAWD, Ice packs, Artic Sun)</td><td>Intravenous cooling (Fluids, Bypass, automated systems)</td></tr>
</table>

*data doesn't seem to favour one technique over another [7].

Multiple therapeutic options are available for managing pyrexia, however pharmacotherapy versus surface cooling has not been shown to be advantageous [1].

Monitoring sites

Pulmonary artery catheter thermistor

- Gold standard but invasive.

Oesophageal temperature

- Ease of placement and minimal risk, can be affected by cold gases and proximity to trachea

Nasopharyngeal temperature

- Approximates brain temperature, often used as a surrogate for core temperature [8]. (NB. Brain temperature is not homogenous and often higher than core temperature [9])
-

Tympanic membrane temperature

- Eardrum is close to carotid artery and hypothalamus, often used as a measure of core temperature. Requires special monitor [10].

Bladder temperature

- Often quoted as an accurate core temperature monitoring site, may be influenced by urine output and abdominal procedures [10].

Rectal temperature

- Often quoted as an accurate core temperature monitoring site, depth of insertion, presence of faeces and heat generating bacteria may influence readings [10].

Skin temperature

- Many confounding factors, balance of vasomotor tone can significantly influence readings, many be affected by ambient temperatures [10].

Axillary temperature

- May be reliable if placed deep in the apex of axilla/over axillary artery with the patients arms at their sides [10].

Complications

- Infection and immune dysfunction (NB. Pneumonia, surgical site sepsis)
- Myocardial injury (cold induced hypertension, elevated noradrenaline concentrations, arrythmias)
- Electrolyte abnormalities (Hypokalemia)
- Coagulopathies (platelet dysfunction, clotting factor inhibition, increased fibrinolysis)
- Thermal discomfort and shivering
- Altered pharmacokinetics and pharmacodynamics
- Increased cardiotoxicity of local anaesthetics
- Impaired monitoring (artefact on ECG, NIBP, obliteration of oximetry reading)
- Rapid re-warming (adverse consequences may seriously limit the protective effects of hypothermia, may lead to raised ICP, rewarming hypoglycaemia and hypotension and may worsen cognitive dysfunction [2, 7])

Hypothermia and induced hypothermia in TBI: **To cool or too cool?**

TBI is a leading cause of death and disability. In Europe more than a third of all injury-related mortality is caused by or associated with TBI. Of those who have a severe TBI (GCS < 8), almost half will have an unfavourable outcome of death, vegetative state or severe disability. Hypothermia has been touted as a treatment to reduce secondary injury following TBI as there is scientific rationale and experimental evidence that neuronal damage at the cellular and molecular level is highly temperature sensitive and that hypothermia is neuroprotective.

In 2001 the NEJM published work by Cifton et al.[11] Their randomised control trial including 392 patients with severe TBI where they were cooled to 33 degrees Celsius within eight hours of injury, showed no improvement in outcomes. In the same NEJM edition an editorial called, "Hypothermia for Traumatic Brain Injury — A Good Idea Proved Ineffective" by Narayan[12] seems to put the issue to bed. However, many were concerned that the induction of hypothermia was delayed and not rapid enough to be neuroprotective in this study.

The National Acute Brain Injury Study: Hypothermia 2 (NABISH 2)[13] trial was terminated after enrolling 232 patients, it showed no benefit of induced hypothermia. However, when the data was re-analysed, there were suggestions that cooling to 35 degrees Celsius soon or during craniotomy and maintained for 48 hours may be beneficial in severe TBI or when large haematomas were present.

A meta-analysis of the highest quality clinical trials of hypothermia in severe TBI was conducted by the Brain Trauma Foundation (BTF) which reported a significant increase in long term favourable neurological outcomes. However, this failed to translate into their current guidelines. The current guidelines state that prophylactic hypothermia may improve outcomes if maintained for 48hours but lack any clear evidence for mortality benefit. The 4th edition of the BTF guidelines for the management of severe traumatic brain injury (September 2016) include a chapter on prophylactic hypothermia. This chapter presents a summary of relevant literature and studies related to TBI and explores the current evidence in the following areas, hypothermia vs. normothermia, length of cooling, and head vs systemic cooling.

The current recommendations are

Level 1 and 2A	Insufficient evidence
Level 2B	Early (within 2.5hours), short-term (48hours post injury) prophylactic hypothermia is <u>not</u> recommended to improve outcomes in patients with diffuse injury

EUROtherm 3235 [14] was designed to assess TBI patients with elevated ICP and targeting a temperature of 32 or 35 degrees Celsius. EUROtherm3235 demonstrated a greater risk of death and worse neurological outcomes in survivors managed with therapeutic hypothermia compared to standard therapy. Mixed results at best from the body of knowledge we currently have.

In 2018 the POLAR trial [15] provided us with the answer to the clinical question of, "In patients with severe blunt traumatic brain injury (TBI) does early and sustained cooling compared with standard care improve neurological outcomes at 6 months?" In short, No.

The POLAR RCT [15] was designed to rapidly induce hypothermia at the pre-hospital/early hospital stage with the idea that early and sustained cooling may offer benefit. The POLAR study was designed to address the concerns with previous studies where cooling was thought to have been initiated too late to show benefit. The author had some strong opinions and conclusions, "There is absolutely no sign in this trial that early and sustained prophylactic

hypothermia improves neurological outcome and this trial puts hypothermia to bed!". There was no benefit demonstrated, with an increase in complications.

An review by Shazad [16] in Surgical Neurology International concluded that the growing body of knowledge has discredited the use of hypothermia in the management of severe TBI. In general, empiric hypothermia for severe TBI should be avoided. However, based on the results of recent trials, there may be some patients, such as those in Asian centers (some of the data sets from Asian countries show better outcomes) or with focal neurologic injury, who may benefit from hypothermia.

In the editorial by Dr Polderman titled 'An injured brain needs cooling down: YES" [9] the concerns surrounding fever and acute brain injury are explored. The causes are often variable. Central (non-infective) causes are common and relate to direct brain injury. The brain injury patient is susceptible to infections and so many causes may also be sepsis related. It must also be noted that brain temperature is not the same as body temperature [9]. Temperature within the brain itself is often higher than systemic temperature and more so is not uniform within the brain. Cerebral thermopooling is the trapping of heat in injured areas of the brain due to local oedema and vascular blockage [9]. This results in the most vulnerable areas of the brain being exposed to the highest temperatures!

Hypothermia and induced hypothermia in OHCA: To cool or too cool?

This patient population is probably the least controversial group to treat. The evidence is clear that rapidly induced hypothermia for ROSC following a cardiac arrest (due to ventricular fibrillation) will improve neurological outcome at 6 months. The controversies centre on whether this can be extrapolated to all cardiac arrest patients.

In 2002 the NEJM [17, 18] showcased two trails demonstrating therapeutic hypothermia in cardiac arrest secondary to ventricular fibrillation improves mortality and neurological outcomes. These results were demonstrated with early cooling to 33 degrees Celsius. More recently in 2013 Nielsen et al. [19] showed targeted temperature management of 33 degrees Celsius did not confer any further cerebral benefit over 36 degrees Celsius.

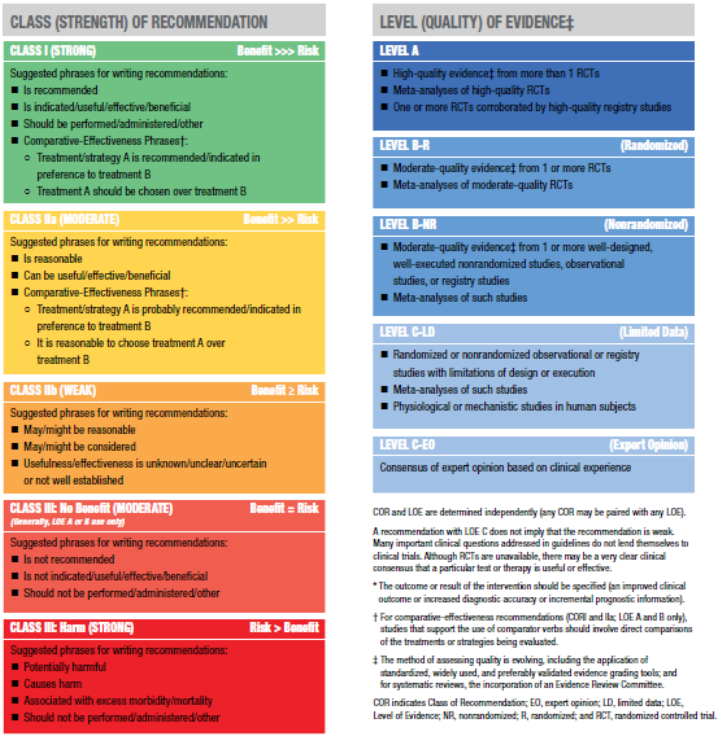
It is interesting to note that the change in terminology, therapeutic hypothermia (TH) transitions to targeted temperature management (TTM) and many recent texts refer to 'induced normothermia'.

Within the TTM trails, it was noted that the avoidance or induced normothermia was of particular importance in terms of outcome and survival. [7]

The 2015 AHA resuscitation guidelines recommendation is targeted temperature management for all adult patients with ROSC and decreased level of consciousness. The suggested range is 32°C to 36°C, with a single temperature to be selected and maintained for at least 24 hours. In making this recommendation, they also commented that no difference in outcome between 33°C and 36°C, but a higher neurologic morbidity and mortality with no temperature management protocol. The initiation of hypothermia in the out-of-hospital setting is advised against. Again, hyperthermia should be actively avoided – fever is associated with a poorer neurological result. Although weak evidence supports this, expert opinion recommends it on the basis that it is a relatively benign intervention and has potential to improve neurological outcome.

The AHA recommendations are

We recommend that comatose (ie, lack of meaningful response to verbal commands) adult patients with ROSC after cardiac arrest have TTM (Class I, LOE B-R for VF/pVT OHCA; for non-VF/pVT (ie, "nonshockable") and in-hospital cardiac arrest). (Class I, LOE C-EO)
We recommend selecting and maintaining a constant temperature between 32ºC and 36ºC during TTM. (Class I, LOE B-R)



Pyrexia of sepsis: **too hot or to heat?**

The definition of pyrexia varies according to the multitude of causes of fever. Pyrexia or fever secondary to infection is defined as a core temperature of 38.3^0C or more. [(1)] Fever can be highly destructive to the vulnerable brain, but all fever is not a purely harmful phenomenon. It is a highly preserved evolutionary feature of our innate immune system and must confer a net survival basis. It can be protective and helpful in certain situations.

Thermotoxicity is complex interaction of cellular, local and systemic mechanism resulting from increased temperature [(20)]. A temperature of greater than 37.5 degrees Celsius tends towards worse outcomes and becomes significant above 38.5 degrees Celsius. The central nervous system, and especially the cerebellum, is particularly vulnerable to hyperpyrexia. The proposed benefit of pyrexia seen in sepsis is outweighed when the temperature rises beyond 40 degrees Celsius. And harm has been reported in TBI when temperature is above 38 degrees Celsius.

Cellular	Local	Systemic
Membrane, mitochondrial and DNA damage Stimulation of excitotoxic mechanisms Protein denaturation	Ischemia Haemorrhage Infarction Inflammatory changes Oedema	Changes in cerebral blood flow Endotoxaemia Bacterial translocation

Beneficial effects of pyrexia are presumed because of its preservation by evolution and net species survival benefit. Heat shock proteins are a group of proteins that are produced by cells when exposed to stressful conditions and act as protection against a wide variety of noxious stimuli. There is increased production of these proteins when the CNS is exposed to hyperthermia. However this is a large family of proteins, where much is still not fully understood and research is ongoing. [(20)] Fever slows bacterial replication, enhances activity of antibiotics, increases motility of leucocytes and enhances phagocytosis, mitigates endotoxin effects, increases T-cell proliferation, amplifies the immune response and increases the transcription of heat shock proteins.

On the other hand, cooling of pyrexial patients have shown a 10% reduction in oxygen consumption per degree Celsius, and increased lactate clearance has been observed in septic shock patients treated with ibuprofen. [(1)]

The concern is how to effectively manage the balance of beneficial and harmful effects of pyrexia. Like the so called “Goldilocks” dilemma, too hot or too cold, we need to know where the middle is. Both hypothermia and hyperpyrexia are shown to be markers of increased morbidity and mortality [(21)]. Perhaps the question should rather be in which patients to treat fever. As previously discussed, hyperthermia in the setting of TBI is a poor prognostic indicator but pyrexia in the setting of CNS infections does not carry the same poor prognosis. Saxena concluded in 2015, the relationship between peak temperature (>39^{o}C) in the first 24 h after ICU admission and in-hospital mortality differs for TBI/stroke compared to CNS infection. For CNS infection, increased temperature is not associated with increased risk of death [(22)]. Similarly, an observational study revealed differing associations between mortality and peak temperature based on the presence of infection or not in non-neurological ICU patients. [(12)]

A special article published in 2016 by Golding and colleges explores this question. “Targeted temperature management in intensive care – Do we let nature take its course?” The answer is not straightforward and there is no universal agreement! Potential harm from targeted temperature management include altered metabolic pathways, and methods to cool depend on cost and availability of equipment. Internal as compared to external cooling have different

beneficial and harmful connotations. (E.g. Internal cooling may be more rapid and easier to control but require invasive lines.) Overcooling, rebound hyperthermia, hypoglycaemia and hypotension may complicate all cooling methods.

Shortgen conducted an RCT with patients in septic shock. The patients were randomised to non-cooling or TTM (aiming for normothermia) arms. Shortgen was able to demonstrate reduced early vasopressor use and reduced early mortality in the TTM group, however there was no survival benefit at 28days or at discharge. Critics of this study bemoaned the relatively small volume of fluids used to resuscitate patients and postulated the insensible losses from the pyrexia patients may have meant they were hypovolemic [1, 23].

The "HEAT" study was a landmark randomised control trial comparing fever treated by intravenous paracetamol use compared to placebo. 691 ICU patients with temperature >38°C and suspected infection were included. ICU free days and mortality at 28 and 90-days were similar. [13]

The current body of knowledge seems to indicate that treating fever in septic shock patients is safe, effective and beneficial, but these effects were not seen when treating less severe forms of sepsis therefor treatment of fever in sepsis only remains controversial. Avoidance of hypothermia in any strategy is of great importance [1].

The beneficial effects of fever seem to be limited when adequate source control and appropriate anti-microbial therapy is initiated. A balance between the severe metabolic stress of pyrexia and its possible contribution to immune function and host defences must always be sought and it is not yet clear at what temperature level the scales are tipped.

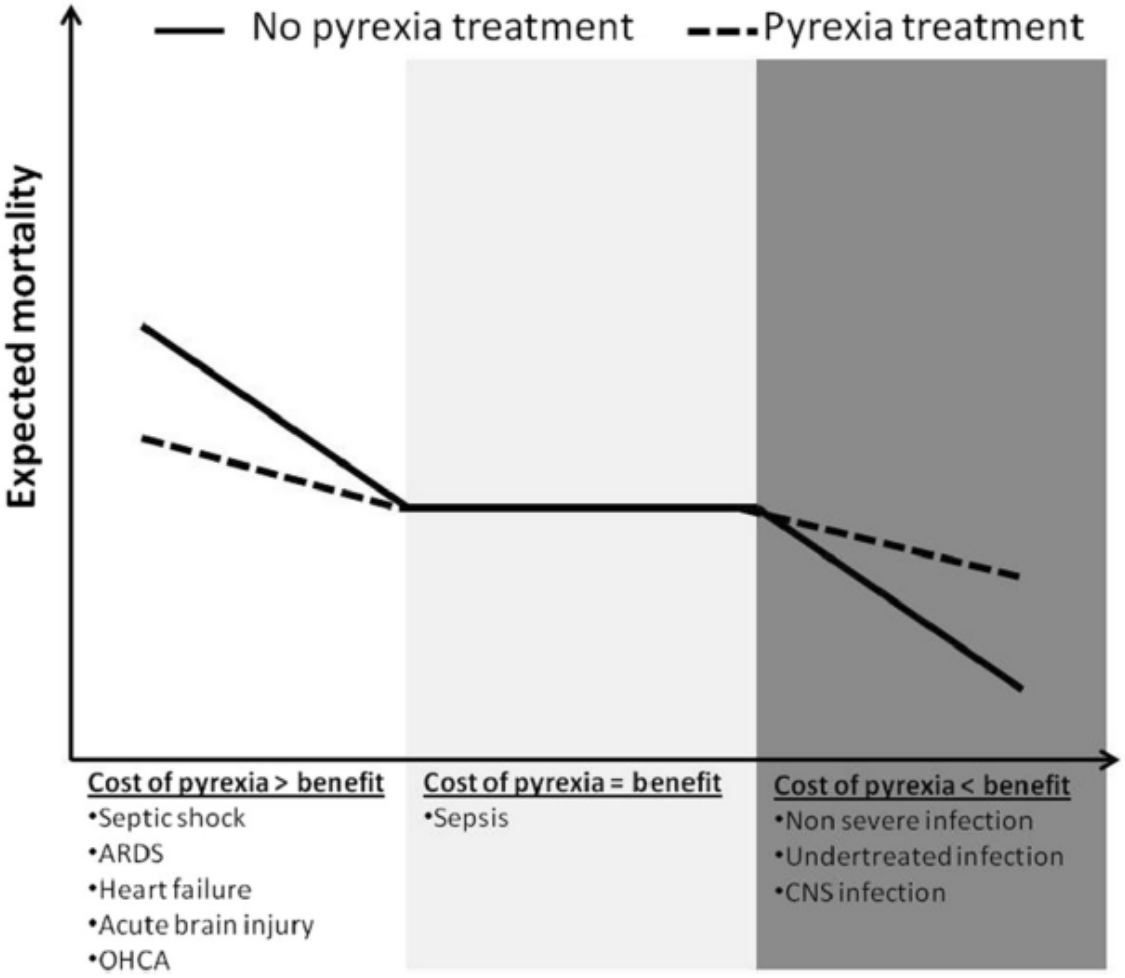


Figure 1: *impact of pyrexia treatment on outcome according to clinical context.* [1]

CONCLUSION

1. Hyperpyrexia is bad, many clinical trials may have shown benefit from cooling by simply preventing hyperthermia. (“Induced normothermia”)

2. Rapid re-warming is harmful, if done inappropriately will negate any benefit gained from hypothermia.

3. Cooling patients is difficult.

4. TBI: Cooling unlikely to offer benefit and hyperthermia is harmful.

5. Polytrauma: Cooling is harmful.

6. Sepsis: Benefit of pyrexia is likely outweighed by potential harm.

7. OHCA and paediatrics: Cooling may provide benefit. TTM between 32 and 36^{o}C advocated with emphasis on avoidance of pyrexia (>37,6^{o}C)[(1)].

8. If cooling is to be implemented, it must be done as soon as possible after the injury and be maintained for 24-48 hours. Rewarming must be slow and carefully controlled.

As general guidelines I would recommend:

Develop unit/centre protocol on temperature measuring. (e.g. All procedures >30min or high-risk patients for abnormal thermoregulation required Oesophageal temperature monitoring if receiving a GA or correctly placed axillary monitoring if regional technique is to be used)

Aim for ‘Induced normothermia” (Target 36.5-37 degrees Celsius)

Avoid iatrogenic hyperthermia and prevent hypothermia.

Try reset hypothalamic set point with paracetamol or ibuprofen (if not contra-indicated) in patients who will not be intubated post operatively (i.e. to prevent thermoregulatory mechanisms resulting shivering on waking).

Physical modalities when pharmacology has failed, or rapid reduction required. This will likely necessitate deep sedation and possible ventilation to achieve.

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