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The pathophysiological basis and consequences of fever

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Abstract

There are numerous causes of a raised core temperature. A fever occurring in sepsis may be associated with a survival benefit. However, this is not the case for non-infective triggers. Where heat generation exceeds heat loss and the core temperature rises above that set by the hypothalamus, a combination of cellular, local, organ-specific, and systemic effects occurs and puts the individual at risk of both short-term and long-term dysfunction which, if severe or sustained, may lead to death. This narrative review is part of a series that will outline the pathophysiology of pyrogenic and non-pyrogenic fever, concentrating primarily on the pathophysiology of non-septic causes.

Keywords: Hyperthermia, Fever, Organ failure, Physiopathology, Heatstroke

Background

"Humanity has but three great enemies: fever, famine, and war, and of these by far the greatest, by far the most terrible, is fever." (William Osler)

The normal human temperature is considered to be 37 °C, but may vary by up to 1 °C in healthy individuals [1]. Elevated core temperature is a common finding in intensive care, affecting up to 70 % of patients [2]. Despite the general usage of the terms 'pyrexia', 'fever', and 'hyperthermia', they are not yet universally defined. The American College of Critical Care Medicine, the International Statistical Classification of Diseases, and the Infectious Diseases Society of America define fever as a core temperature of 38.3 °C or higher, i.e. just above the upper limit of a normal human temperature, irrespective of the cause [1]. Fever has its etymological basis in Latin, meaning simply 'heat', and pyrexia comes from the Greek 'pyr', meaning fire or fever. Some sources use the terms interchangeably, whereas others preserve 'fever' to mean a raised temperature caused by the action of thermoregulatory pyrogens on the hypothalamus; for instance, in sepsis and inflammatory conditions [3].

Hyperthermia also has no agreed definition; it has been defined as a core temperature above 38.2 °C, irrespective of the cause [3]. Others use it for the classification of those conditions that increase the body's temperature above that set by the hypothalamus, and therefore specifically exclude those where fever is caused by pyrogens [4], being due to heat exposure or unregulated heat production in excess of heat loss. Common causes include classical and exertional heatstroke, and drug-related illnesses (for example, malignant hyperthermia and neuroleptic syndrome).

There is, however, increasing evidence that many conditions considered non-pyrogenic may stimulate an inflammatory response, and the division into pyrogenic and non-pyrogenic may therefore be less clear-cut than previously understood.

Generation of fever

Sepsis accounts for up to 74 % of fever in hospitalised patients [5] and, of the remainder, malignancy, tissue ischaemia, and drug reactions account for the majority [6]. Neurogenic fever, and fevers associated with endocrinopathy, are rarer.

Sepsis

Pyrogenic fever is a common response to sepsis in critically ill patients, and the generation of fever occurs through several mechanisms. The interaction of exogenous pyrogens (e.g. micro-organisms) or endogenous pyrogens (e.g. interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α) with the organum vasculosum of the lamina terminalis (OVLT) leads to the production of fever. Exogenous pyrogens may stimulate cytokine production, or may act directly on the OVLT. The OVLT is one of seven predominantly cellular

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structures in the anterior hypothalamus within the lamina terminalis, located in the optic recess at the anteroventral end of the third ventricle. Being a circumventricular organ it is highly vascular and lacks a blood–brain barrier (BBB), permitting it to be stimulated directly by pyrogenic substances. Its stimulation leads to increased synthesis of prostanoids including prostaglandin $(PG)E_2$, which acts in the pre-optic nucleus of the hypothalamus slowing the firing rate of the warm sensitive neurons and resulting in an increase in body temperature. The bioactive lipid derivative, ceramide, which has a proapoptotic as well as a cell signalling role, may act as a second messenger independent of PGE_2, and may be of particular importance in the early stages of fever generation [7]. Lipopolysaccharides (LPS) from gram-negative bacteria may stimulate peripheral production of PGE_2 from hepatic Kupffer cells [8, 9]. LPS-stimulated fever may also be neurally mediated [10]. Neural pathways may account for the rapid onset of fever, with cytokine production responsible for the maintenance, rather than the initiation, of fever [11]. Fever generation is also thought to occur by signalling via the Toll-like receptor cascade, which may be independent of the cytokine cascade [12] (Fig. 1).

The febrile response is well preserved across the animal kingdom, with some experimental evidence suggesting it may be a beneficial response to infection. Retrospective data analysis shows that a raised temperature in patients with infection in the first 24 h following admission to the intensive care unit (ICU) is associated with a better outcome compared with normothermia or hyperthermia above 40 °C [13], and that a temperature between 37.5 °C and 39.4 °C trends towards improved outcome compared with normothermia [14]. In elderly patients with community-acquired pneumonia, the observed mortality rate was significantly higher in patients who lacked fever (29 %) when compared with patients who developed a febrile response (4 %) [15]. A temperature greater than 38.2 °C has also been found to have a protective role against invasive fungal infections in the ICU [16]. The raised temperature may provide protection by several mechanisms. Firstly, human infective pathogens often demonstrate optimal replication at temperatures below 37 °C; thus an elevated host temperature inhibits reproduction [17]. Secondly, increasing the temperature in vitro from 35 °C to 41.5 °C increases the antimicrobial activity of many classes of antibiotics [18]. Thirdly, a rise in temperature may also

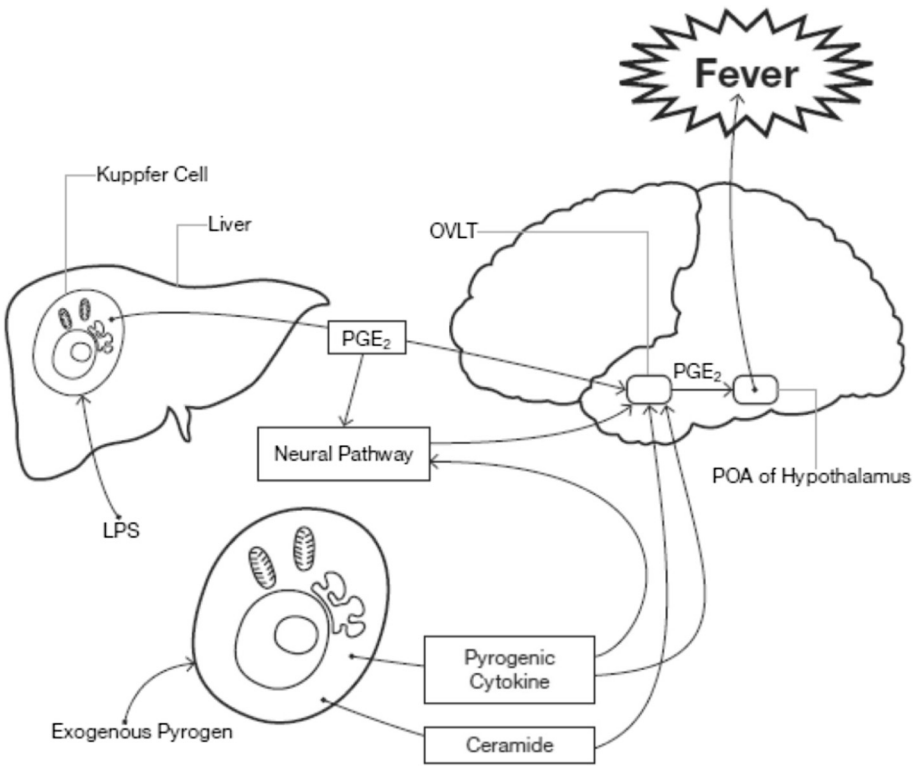

Fig. 1 Proposed mechanisms for the generation of fever in sepsis. Stimulation of sentinel cells by exogenous pyrogens produces endogenous pyrogens which stimulate fever production in the pre-optic area (*POA*) of the hypothalamus by the second messengers prostaglandin E_2 (*PGE_2*), and ceramide. PGE_2 is also produced from Kupffer cells in the liver in response to stimulation from lipopolysaccharide (*LPS*), which additionally stimulates the POA via the vagus nerve. *OVLT* organum vasculosum of the lamina terminalis

be associated with an increase in innate immunity associated with microbial destruction [19]. Interestingly, at temperatures above around 40 °C there is a further mortality increase [13, 14], suggesting that at this stage the deleterious effects of hyperthermia on organ and cellular function outweigh any benefit conferred from hyperpyrexia in acute sepsis. These potential benefits of fever in sepsis may not be well recognised; in one survey of fever monitoring in sepsis from UK ICUs, 76 % of ICU physicians would be concerned about a temperature of 38–39 °C, and 66 % would initiate active cooling at that point [20].

In contrast with a fever in response to sepsis, a non-pyrogenic fever is not of any perceived teleological benefit. A temperature of 37.5 °C or greater at any point during an ICU admission trends towards a worse outcome, and becomes significant at temperatures greater than 38.5 °C [14].

Fever associated with inflammation

In critically ill patients, inflammation is commonly observed to aid repair after traumatic or infective insults. The four cardinal features of pain, heat, redness, and swelling were originally described by Celsus around 2000 years ago and, at about the same time, Hippocrates noted that the fever was of benefit. Fever is a ubiquitous component of inflammation across the animal kingdom, and enhances the host response. A large number of both the cell-derived and plasma-derived inflammatory mediators are pyrogenic; fever associated with inflammation is probably mediated in a similar way to sepsis as described above. Chronic inflammation is deleterious; the recently described compensatory anti-inflammatory response syndrome (CARS) restores homeostasis, and it is likely that the magnitude and relative timings of the inflammatory and anti-inflammatory responses are both important in determining the host outcome.

Fever in patients with malignancy is reported to be sepsis related in around two thirds of cases [21]. The tumour is the direct cause of fever in less than 10 % of febrile episodes; tumour necrosis and production of pyrogenic cytokines is the likely pathogenesis [21].

Regulated autoimmunity is considered to be a natural physiological reaction; however, pathological autoimmunity occurs because of higher titres of more antigen-specific antibodies, often of the IgG isoform, and a reduction in self-tolerance. There are five pathogenic processes associated with autoimmune disease development, and in excess of 80 diseases have been described; fever is considered to be cytokine mediated in the majority of cases [22].

Autoinflammatory conditions differ from autoimmune diseases. In the former, the innate immune system directly causes inflammation without a significant T-cell response, whereas in the latter the innate immune system activates the adaptive immune system, which is in itself responsible for the inflammatory process. The former are also known as periodic fever syndromes, highlighting the intermittent febrile nature of these conditions. Examples include familial Mediterranean fever and some arthopathies, including adult-onset Still's disease. Most autoinflammatory conditions are genetic, and a large number are related to abnormalities in pro-inflammatory cytokine handling, for example IL-1 or interferon (IFN) signalling, or constitutive NF-kB activation, offering therapeutic targets.

Drug-induced fever

The causes of drug-induced fever are shown in Table 1 [23]. Pharmacological agents may cause fever by a number of pathophysiological mechanisms. These include interference with the physiological mechanisms of heat loss from the peripheries, interference with central temperature regulation, direct damage to tissues, stimulation of an immune response, or pyrogenic properties of the drug.

A common mechanism in many of these drugs is considered to be stimulation of non-shivering thermogenesis (NST), primarily in brown adipose tissue and skeletal muscle. Under normal conditions, cellular oxidative phosphorylation allows the synthesis of ATP from ADP for cellular metabolism. NST uncouples the proton movement from this pathway, allowing the energy to be dissipated as heat, under the control of uncoupling proteins, ultimately influenced by thyroid hormones and catecholamines. A number of agents, including sympathomimetics and those which act via the serotonin pathway, are thought to cause fever by modifying the NST pathway at a central, peripheral, or cellular level [24].

Fever after brain injury

Fever after acute brain damage, from trauma or a vascular event, is common, and is independently associated with a worse outcome. The mechanism of fever generation is probably multi-factorial; 41 % of deaths after traumatic brain injury (TBI) in one series displayed hypothalamic lesions, suggesting thermal dysregulation in some cases [25]. Alterations in cellular metabolism, a shift to anaerobic metabolism, and ischaemic–reperfusion injury are all associated with thermogenesis [26]. The cerebral production of a large number of inflammatory and pyrogenic cytokines is increased acutely [27]; IL-6 in particular is associated with fever production after a stroke, and with a worse outcome. After cerebral haemorrhage, both the presence of blood and the presence of its degradation products are associated with heat production [28]. Recent work suggests a protective role for uncoupling of mitochondrial oxidative phosphorylation following neurotrauma under the regulation of uncoupling

Table 1 Causes of drug-induced hyperthermia

Class	Examples of causes
Antimicrobial agents	β-lactam antibiotics (piperacillin, cefotaxime) Sulphonamides
Malignant hyperthermia	Suxamethonium Volatile anaesthetic agents
Neuroleptic malignant syndrome	Dopamine antagonists (chlorpromazine, haloperidol) Atypical agents (serotonin and dopamine antagonists) (olanzapine, risperidone, paliperidone, aripiprazole, quetiapine)
Serotonin syndrome	Antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, bupropion) Opioids (tramadol, pethidine, fentanyl, pentazocine, buprenorphine oxycodone, hydrocodone) Central nervous system stimulants (MDMA, amphetamines, sibutramine, methylphenidate, methamphetamine, cocaine) Psychedelics (5-methoxy-diisopropyltryptamine, lysergide) Herbs (St John's Wort, Syrian rue, Panax ginseng, nutmeg, yohimbine) Others (tryptophan, L-dopa, valproate, buspirone, lithium, linezolid, chlorpheniramine, risperidone, olanzapine, antiemetics (ondansetron, granisetron, metoclopramide), ritonavir, sumatriptan)
Propofol infusion syndrome	Propofol
Anticholinergic agents	Anticholinergics (atropine, glycopyrrolate), Antihistamines (chlorpheniramine), Antipsychotics (olanzapine, quetiapine), Antispasmodics (oxybutynin), Cyclic antidepressants (amitriptyline, doxepin) Mydriatics (tropicamide)
Sympathimometic agents	Prescription drugs (e.g. bronchodilators) Non-prescription drugs (e.g. ephedrine in cold remedies) Illegal street drugs (e.g. cocaine, amphetamines, methamphetamine ('ecstasy'), mephedrone) Dietary supplements (e.g. ephedra alkaloids)
Piperazine compounds	Anti-emetic (cyclizine) Anti-helminths Legal 'club drugs' ('Legal X', 'Legal E', 'Frenzy')
Synthetic cathinones	Street drugs (mephedrone, 'meow-meow') Bupropion (anti-depressant and anti-smoking agent)

Taken from [23] with permission

proteins [29]; the dissipation of the proton gradient produces heat.

Brain injury following a cardiac arrest is well recognised, but the pathology is complex and probably involves multiple mechanisms, including cell death, excitotoxicity, cell signalling changes, ischaemia–reperfusion, and alterations in cellular metabolism [30]; this is very similar to those described following brain injury from other causes, and, as such, the mechanisms of thermogenesis are likely to be similar. The teleological benefit of pyrexia following brain injury is uncertain.

Endocrine fever

Thyroid hormones are essential for regulation of energy metabolism. Hyperthyroidism is associated with hyperthermia; patients with thyroid storm have an average body temperature of 38.0 °C; temperatures above 41 °C have been reported [31]. The mechanism of thermogenesis is not clear; the classical view is that metabolism of peripheral tissues increases through a peripherally mediated pathway. Recent work suggests that thyroid hormones may instead act centrally to increase the hypothalamic 'set-point', and that centrally driven neurogenic activation of uncoupling protein-1 acting on brown adipose tissue may instead be responsible for the thermogenesis [32]. The converse relationship is also present: levels of serum T3, even in non-thyropathic individuals, decrease with increasing body temperature and, above 40 °C, T3 levels would be consistent with severe hypothyroidism. The levels of T4 and thyroid-stimulating hormone (TSH) are unchanged with changes in body temperature [33].

Adrenal insufficiency is rarely associated with fever, but the hyperthermia may be related to the underlying pathology; autoimmunity accounts for the majority of primary insufficiency. A malignant process, or an infectious process, account for a proportion of the remainder; all of the patients in the original description had adrenal tuberculosis [34].

A fever has been reported in 28 % of patients hospitalised with a pheochromocytoma [35]; a large tumour, the presence of necrosis, and higher metabolite excretion increase the likelihood of pyrexia [35].

Mechanisms of damage from fever

There are a number of pathophysiological mechanisms for the deleterious effects of a fever, classified as follows (Fig. 2):

- Direct cellular damage
- Local effects, e.g. stimulation of cytokines and inflammatory response
- Systemic effects, e.g. gut bacterial translocation

Cellular damage

Hyperthermia is directly cytotoxic, affecting membrane stability and transmembrane transport protein function. Consequently, ionic transport is disrupted leading to increased intracellular sodium and calcium with a reduced intracellular potassium concentration. Protein and DNA synthesis is disrupted at various stages in the pathway; while RNA and protein synthesis may recover quickly after cessation of hyperthermia, DNA synthesis remains disrupted for longer [36]. The nuclear matrix shows damage at lower temperatures than other parts of the cell, with significant endothermic changes observed at 40 °C [37]. Direct cell death in humans occurs at temperatures of

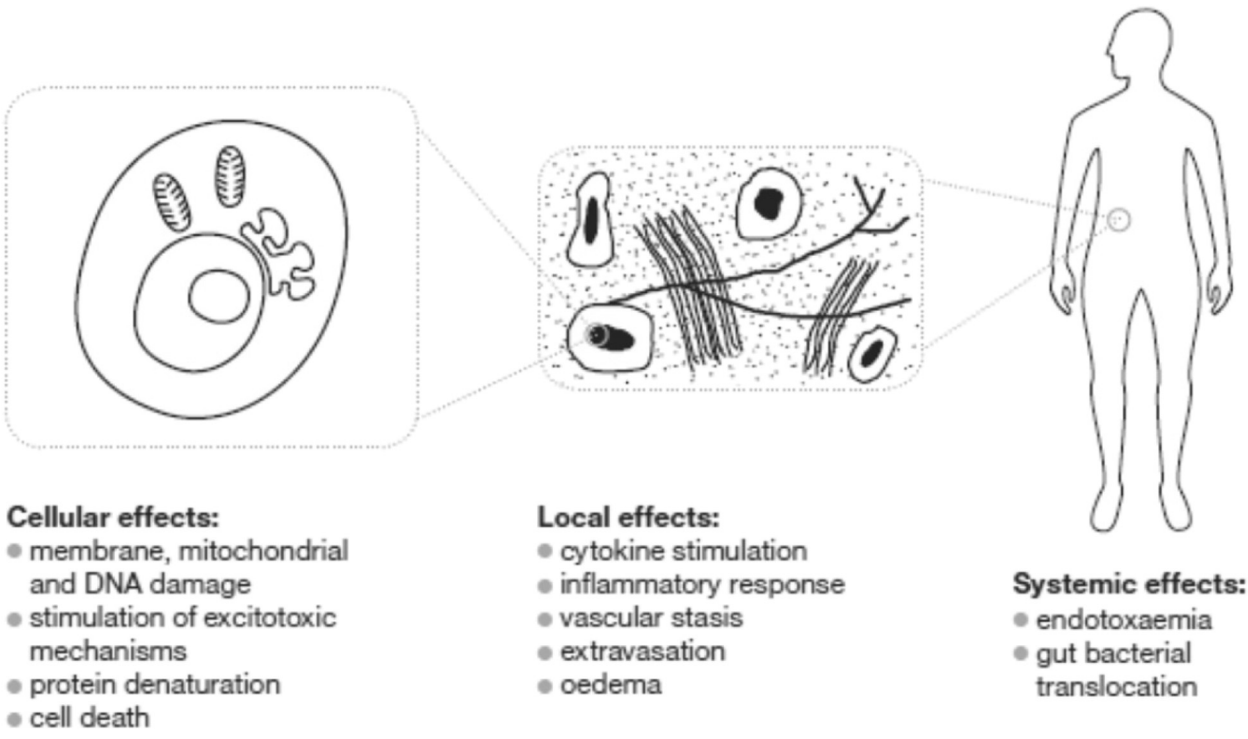

Fig. 2 Diagrammatic representation of the mechanisms of damage from hyperthermia

around 41 °C, with the rate of cell death increasing markedly with even modest further increases in temperature [36, 38]. The thermal energy required for cell death is similar to that required for protein denaturation, suggesting that hyperthermic cell death may occur primarily through its effect on protein structure, although cell death occurs primarily through necrosis or from apoptosis depending on the cell line and the temperature [36]. Cells in mitosis are more thermosensitive than cells in other phases of replication. Given that organ dysfunction occurs at temperatures lower than that required for in-vitro cell death, milder degrees of hyperthermia are also likely to affect cell structure and function with a degree of reversibility.

Local effects

Effect of cytokines and the inflammatory response

The role of cytokines in heat stress is unclear, with an inconsistent response to thermal stress. The levels of a number of pro-inflammatory and anti-inflammatory cytokines are elevated at the time of hyperthermia from heatstroke. Acute phase reactants may also increase. Of these, some (for example, INFγ, IL-1β) are raised in a proportion of patients, whereas IL-6 may be elevated in all patients [39]. Furthermore, there is some correlation with outcome; the rise in IL-6 and the duration of the increased expression is related to mortality, independent of the maximum core temperature obtained [40]. Mice pre-treated with IL-6 before exposure to heat take longer to reach 42.4 °C, showing less organ damage, and attenuation in the increase of other cytokines [41]. Antagonism of IL-1 also improves survival [42].

The cytokine profile of the two forms of heatstroke, classical and exertional, show similarities, and mirrors that produced by exercise [43]. The profile also shows similarities to that produced by endotoxaemia, which is considered to be of importance in the cytokine expression—abolition of endotoxaemia significantly reduces cytokine production [43].

Development of other hyperthermic states may also be associated with inflammatory mediators. Neuroleptic malignant syndrome (NMS) may be at least partly driven by an acute phase response; acute phase response mediators are reported to rise, and peak at 72 h. Conversely, levels of anti-inflammatory agents such as serum iron and albumin initially decline then return to the normal range, coinciding with clinical improvement [44]. It is proposed that the acute phase response may be triggered by the heat stress per se, or by muscle breakdown, or by interaction between a virus and the drug, or the immune system [45]. IL-6 and TNFα levels have also been found to be significantly increased in NMS [46], as has IL-6 in malignant hyperthermia (MH) [47].

Protection by heat shock proteins

Heat shock proteins (HSP) are a family of cell-derived proteins that offer protection against a range of insults,

including heat. They are expressed in response to the insult, and their effect may depend on their location. Intracellularly located HSPs have a protective role, including correcting misfolded proteins, preventing protein aggregation, transport of proteins, and supporting antigen processing and presentation, and limiting apoptosis. In contrast, membrane-bound or extracellular HSPs may be immunostimulatory, and appear to induce cytokine release or provide recognition sites for natural killer cells. HSPs may also have both pro-apoptotic and anti-apoptotic actions [48, 49].

Vascular changes

Animal studies suggest that changes to the vasculature occur rapidly after the onset of hyperthermia and, while some organs are more tolerant to heat stress than others, the majority of organs show similar changes consisting of capillary dilatation, vascular stasis, and extravasation into the interstitium, observed after 30 min at 40.5 °C [50].

Systemic effects

Gastrointestinal bacterial and endotoxin translocation

Non-pyrogenic hyperthermia increases gut bacterial translocation and the gastrointestinal (GI) tract and BBB appear to be more permeable to toxins than during normothermia [51, 52]. Bacterial and endotoxin translocation are also implicated in the development of multi-organ dysfunction in non-pyrogenic hyperthermia. For example, antibiotic administration to dogs with heatstroke appears to improve their survival, suggesting that bacteraemia may have a role even in non-pyrogenic conditions [53]. In a similar study, raising the core temperature in monkeys from 37.5 °C to 39.5 °C and then up to 44.5 °C increased plasma LPS concentration. In the animals pretreated with oral kanamycin, which is very poorly absorbed, and heated to 44.5 °C, no increase in plasma LPS concentrations were seen and there was improved haemodynamic stability, suggesting that the plasma LPS originated from the GI tract [54]. Epidemiological studies after classical heatstroke have demonstrated that over 50 % of heatstroke patients show evidence of concomitant bacterial infections [55]. Furthermore, procalcitonin, which has a high sensitivity and specificity for detecting bacteraemia, was elevated in 58 % of patients with classical heatstroke, which was associated with mortality [56]. However, microbiological and clinical evidence of infection was not significantly higher in this group, and therefore it is unclear whether this represents undiagnosed bacteraemia or procalcitonin elevated in the absence of infection.

Genetics

Genotypic and phenotypic differences may account for how tolerant a particular individual is to heat exposure. Individuals who demonstrate heat-intolerance may show a reduction in HSP levels and, in addition, their vasculature may be less reactive to heat stress [57]. Well-described genotypic differences are seen in particular conditions. MH affects up to 1 in 5000 patients, and is more common in males and in young people, although it can affect all age groups including neonates [58]. It has also been observed in other species, such as dogs, cats, horses and pigs. Mutation in the ryanodine receptor (RYR) accounts for up to 70 % of cases, with more recent genetic abnormalities also having been identified [59]. RYRs in the sarcoplasmic reticulum of skeletal muscle form calcium channels and are the main mediators of calcium-induced calcium release in animal cells. In MH, the RYR functions abnormally such that calcium is released in a greater than normal amount and heat is generated during the processing of this excess calcium. The first documented survivor of MH was in Australia in 1961; a young man required surgery for a fractured tibia. Ten of his family members had previously developed uncontrolled hyperthermia and died during general anaesthesia with ether [60].

Exertional heatstroke (EHS) is increasingly observed in endurance athletes [61]. EHS has clinical and biochemical similarities to MH, and there are case reports of patients with both conditions. While some patients with EHS display mutations in the RYR1 gene, the genetics probably differ from MH, although some authorities advise that heatstroke patients should go on to be tested for MH as they may be susceptible to its development [62]. Recently, there has been some interest in another similar sarcoplasmic skeletal muscle protein, calsequestrin (CASQ1), which appears to modulate the function of RYR1. Ablation of CASQ1 in mice increases the risk of MH-like episodes when exposed to both heat and halothane, supporting the possibility that there is a genetic basis to EHS similar to that of MH [63].

Other hyperthermic states may also have a genetic basis. Genetic mutations or polymorphisms in the dopamine D2 receptor, serotonin receptor, and cytochrome P450 2D6 have been studied in cases of NMS [64]. Such cases may run in families, suggesting a genetic mechanism for predisposition to the syndrome. In a study of patients who had developed NMS, the frequency of the A1 allele of the DA2 receptor was significantly higher in the patients who developed NMS (56.8 %) than in the control group of patients with schizophrenia who had not (35.1 %). The proportion of patients who were A1 carriers was significantly higher in the patients with NMS compared with those without (93.3 % vs 57.2 %) [65]. However, the relationship between NMS and serotonin receptor mutations remains currently undetermined. Early work in patients who are genetically deficient in the cytochrome P450 2D6 enzyme suggests that they may be more susceptible to the effects of serotonin-containing drugs [66].

EHS is more common in men than women; whether this is the protective effect of oestrogen, or the reduced

muscled muscle bulk in women compared with men, or genetic differences is not clear.

Deleterious consequences of pyrexia

Most patients fully recover after a period of hyperthermia, but patients exposed to higher temperatures and for longer periods of time are more at risk of complications, which may lead to multi-organ failure and death in extreme cases. The similarities between the different hyperthermic aetiologies suggest that the pathological features are at least partly a result of hyperthermia, irrespective of the cause.

The risk from hyperthermia may be significant; heatstroke is the most severe form of heat illness with a mortality rate of up to 58 % [67] to 64 % [68]. Classical heatstroke, often seen in meteorological heat waves, is responsible for thousands of excess deaths each year. Most survivors appear to recover fully, but there is increasing concern over long-term organ dysfunction, susceptibility to further injury, and delayed mortality.

Immediate cooling remains the mainstay of treatment, a delay in a reduction in the temperature being associated with increased mortality [68]. In classical heatstroke, cooling to below 38.9 °C within 60 min is associated with a trend towards improved survival [69]. Hyperthermia is associated with the inflammatory cascade [43]; heatstroke in particular is considered a pro-inflammatory and procoagulant condition. Given this, steroids [70], mannitol [70], and recombinant activated protein C [71, 72] have all been studied as putative treatments, and have shown benefit in trials; however, none are currently recommended for clinical practice. Anti-pyretic drugs would not be expected to have a significant effect in non-pyrogenic hyperthermia and, although non-steroidal anti-inflammatory drugs (NSAIDs) have not been extensively studied, aspirin may have beneficial effects on survival in animal studies [73]. Neither aspirin nor paracetamol have been shown to be of any proven benefit in humans and are therefore not recommended in temperature control in heatstroke.

Specific organ dysfunction

Hyperthermia has many systemic effects, which may present as specific organ dysfunction.

Gastrointestinal tract

Systemic hyperthermia increases the permeability of the GI tract, and increases the rate of gut bacterial translocation. Blood flow to the GI tract is reduced at temperatures above 40 °C [74] and hyperthermia damages cell membranes, denatures proteins, and may increase oxidative stress. This leads to loss of the GI barrier integrity and increases the potential for endotoxaemia, which initiates release of pro-inflammatory cytokines leading to a systemic inflammatory cascade [51]. GI oedema and petechial haemorrhage are also described [75].

A theoretical mechanism following hyperthermia to the GI tract appears to be increased free radical production from the splanchnic viscera, which may stimulate oxidative stress and contribute to cellular dysfunction [74]. Free radical production can be increased in the presence of heavy metals and this may exacerbate cytotoxicity. Heavy metals themselves may also translocate across a dysfunctional BBB, and are implicated in the development of hyperthermia-induced neurocognitive dysfunction [76].

Renal

The glomerular filtration rate reduces after an increase of 2 °C, and worsens further with increasing temperature. Plasma concentrations of creatinine and urea consequently increase [77]. Morphological studies demonstrate glomerular capillary dilatation, haemorrhage into the interstitium, and vascular stasis, in small and large vessels [50]. Stimulation of the renin–angiotensin system in hyperthermia reduces renal blood flow [78]. Direct thermal injury, renal hypoperfusion, and rhabdomyolysis also probably contribute to acute kidney injury (AKI).

The development of EHS (>40 °C) in endurance athletes significantly increases the risk of AKI compared with those without EHS. Military data suggest that one in six hospitalised EHS victims will develop AKI [79] in comparison with marathon runners generally; the Comrades marathon have reported an average of only one runner each year admitted with renal failure [80].

Classical heatstroke is also associated with the development of AKI; for example, of 22 patients admitted to an ICU after heatstroke during a heatwave, serum creatinine levels were significantly higher 24 h after admission, and 18 % required renal replacement therapy (RRT). The degree of renal impairment was worse in non-survivors than in those who survived [68]. Of 58 patients hospitalised with classical heatstroke during the 1995 Chicago heat wave, 53 % had at least moderate renal impairment [55].

AKI has been reported in one series of patients with neuroleptic malignant syndrome to occur in 7 out of 24 (30 %) patients, of whom 2 (8 %) required RRT [81]. Renal failure sufficient to require RRT has also been described after hyperthermia due to NMS [82], MH [83] and recreational drug use [84].

Cardiovascular system

In the acute phase, patients tend to be hypotensive, with a hyperdynamic circulation and a high cardiac output. The hypotension is probably a combination of redistribution of blood, and nitric oxide-induced vasodilatation. The electrocardiogram in heatstroke and MH may show a variety of abnormalities, including conduction defects, QT and ST changes, T-wave abnormalities, and malignant

arrhythmias [85]. In addition, cardiac dysfunction and associated pulmonary oedema have also been described [86].

In common with other organs, myocardial vessels are dilated, and extravasation occurs into the myofibril structure. Fragmentation of the myocardial fibres occurs [50]. Serum troponin I levels are significantly raised and, interestingly, more so in non-survivors [68]. Whether this represents myocardial cytotoxicity, myocardial disruption, or another problem is not currently clear.

Brain

Neurological and cognitive dysfunction may occur acutely after an episode of hyperthermia and may lead to chronic damage, reported to occur in 50 % of survivors discharged from an ICU after heatstroke [87]. The pathophysiological mechanisms are presumed to be similar to those described above, but, in addition, the integrity of the BBB is disrupted allowing translocation of systemic toxins to enter the cerebral circulation. If neurological symptoms fail to improve after the acute episode, cerebellar dysfunction predominates. This is thought to be a result of the sensitivity of the Purkinje cells to thermal damage.

Liver failure

Liver dysfunction is common. At temperatures above 40 °C, elevations in plasma aspartate transaminase (AST) and alanine transaminase (ALT) are observed [88] and the hepatocellular damage has been sufficient to require transplant in some cases; however, results from transplantation are disappointing, with only a minority surviving long-term [89]. Hence, conservative management has been advocated in patients who would otherwise meet the criteria for transplantation [89].

Similar to histological changes in other organs, small and large vessel dilatation is seen, with stasis and haemorrhage [50]. A reduction in liver blood flow is also implicated [90]. Liver dysfunction may continue to deteriorate even after cessation of the hyperthermia [68].

Haemostatic system

Coagulopathy is common, with a reported incidence of 45 % in classical heatstroke [55], and probably contributes to the multi-organ dysfunction in hyperthermia. Thrombocytopenia, increased plasma fibrin degradation products, prolonged clotting times, and spontaneous bleeding are often seen. This probably reflects hepatic dysfunction, as coagulopathy is rare without liver derangement and is temporally related to alterations in liver function [91]. Hyperthermia inhibits platelet aggregation, which becomes increasingly marked at higher temperatures, and may begin to happen at 38 °C [92]. Disseminated intravascular coagulation (DIC) may also be driven by release of pro-coagulant cellular components from damaged muscle.

Long-term follow-up

Even in survivors of the acute episode, hyperthermia reduces life expectancy and worsens functional outcome. In one epidemiological study of patients with classical heatstroke, the 28-day mortality was 58 %, increasing to 71 % at 2 years [67]. An episode of exertional heatstroke is associated with an increased risk of mortality of 40 % after recovery from the initial episode [93].

Heatstroke is reported to cause moderate to severe functional impairment in 33 % of survivors at 1 year [55], with 41 % of survivors requiring institutional care at 1 year [66]. There may be little or no improvement after discharge from hospital [55].

Conclusions

A mild elevation in core temperature is of benefit in sepsis. Non-pyrogenic hyperthermia is associated with short-term, medium-term, and long-term effects in a variety of organs. The damage occurs via a number of local and systemic mechanisms. Additionally, there appears to be emerging evidence of an overlap in the mechanisms of heat generation in different conditions. The evidence is that in sepsis the beneficial effects of pyrexia may balance these deleterious factors. However, in non-sepsis, the accumulation of the deleterious consequences of hyperthermia occurs early, at even mild degrees of fever. Hyperthermia above 40 °C appears to carry a high mortality by whatever cause. Early recognition, immediate cooling, and organ support are the mainstays of treatment, and to this end an improved understanding of the pathophysiology will continue to develop.

Abbreviations

AKI, acute kidney injury; BBB, blood–brain barrier; CASQ1, calsequestrin; EHS, exertional heatstroke; GI, gastrointestinal; HSP, heat shock proteins; ICU, intensive care unit; IFN, interferon; IL, interleukin; LPS, lipopolysaccharides; MH, malignant hyperthermia; NMS, neuroleptic malignant syndrome; NSAID, non-steroidal anti-inflammatory drug; NST, non-shivering thermogenesis; OVLT, organum vasculosum of the lamina terminalis; PG, prostaglandin; RRT, renal replacement therapy; RYR, ryanodine receptor; TNF, tumour necrosis factor

Authors' contributions

EJW, SH-J, MC and LF contributed to the literature review and the drafting of the manuscript. All authors read and approved the final manuscript.

Authors' information

EJW has an interest in pre-hospital and ICU hyperthermia, and has provided medical cover for major sporting and public events. He is lead author of the FSEM UK heatstroke consensus guidelines, and has also published and spoken internationally in this area.

Competing interests

The authors declare that they have no competing interests.

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REVIEW Open Access

Pyrexia: aetiology in the ICU

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Abstract

Elevation in core body temperature is one of the most frequently detected abnormal signs in patients admitted to adult ICUs, and is associated with increased mortality in select populations of critically ill patients. The definition of an elevated body temperature varies considerably by population and thermometer, and is commonly defined by a temperature of 38.0 °C or greater. Terms such as hyperthermia, pyrexia, and fever are often used interchangeably. However, strictly speaking hyperthermia refers to the elevation in body temperature that occurs without an increase in the hypothalamic set point, such as in response to specific environmental (e.g., heat stroke), pharmacologic (e.g., neuroleptic malignant syndrome), or endocrine (e.g., thyrotoxicosis) stimuli. On the other hand, pyrexia and fever refer to the classical increase in body temperature that occurs in response to a vast list of infectious and noninfectious aetiologies in association with an increase in the hypothalamic set point. In this review, we examine the contemporary literature investigating the incidence and aetiology of pyrexia and hyperthermia among medical and surgical patients admitted to adult ICUs with or without an acute neurological condition. A temperature greater than 41.0 °C, although occasionally observed among patients with infectious or noninfectious pyrexia, is more commonly observed in patients with hyperthermia. Most episodes of pyrexia are due to infections, but incidence estimates of infectious and noninfectious aetiologies are limited by studies with small sample size and inconsistent reporting of noninfectious aetiologies. Pyrexia commonly triggers a full septic work-up, but on its own is a poor predictor of culture-positivity. In order to improve culturing practices, and better guide the diagnostic approach to critically ill patients with pyrexia, additional research is required to provide more robust estimates of the incidence of infectious and noninfectious aetiologies, and their relationship to other clinical features (e.g., leukocytosis). In the meantime, using existing literature, we propose an approach to identifying the aetiology of pyrexia in critically ill adults.

Keywords: Pyrexia, Fever, Hyperthermia, Temperature, ICU, Etiology, Aetiology, Cause, Incidence

Background

Temperature is commonly measured as part of the routine assessment of patients admitted to adult ICUs. Normal body temperature is between 36.0 and 37.5 °C [1]. Elevated body temperature is detected in approximately 50 % of patients admitted to adult ICUs [2–6]. In addition to being common, elevated body temperature is associated with increased mortality in subpopulations of critically ill patients including those with acute neurological conditions [7–9], noninfectious aetiologies of pyrexia [10], and medical patients that develop pyrexia in the ICU [3]. Although the optimal approach to managing elevated body temperature in critically ill patients remains controversial [11–15], it is widely accepted that elevated body temperature is an evolutionarily conserved sign of an underlying physiologic stressor and its presence should trigger a systematic search for the aetiology.

In this article, we will review the contemporary literature investigating the aetiology and incidence of elevated body temperature among patients admitted to adult ICUs. We will begin by examining literature pertaining to the measurement of body temperature and definitions for what constitutes an elevated temperature. We will then focus on the aetiology of pyrexia in medical and surgical patients with and without acute neurological conditions, including a brief discussion on hyperthermia syndromes. Because immunocompromised patients present

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a distinct set of aetiologic considerations, they will not be reviewed.

Literature review

Relevant articles were identified through three sources. First, a semistructured literature review was conducted using MEDLINE from 1966 to 15 January 2016. The objective of the search was to identify English-language articles that reported on the aetiology or incidence of pyrexia among medical and surgical patients admitted to adult ICUs. The search used a combination of exploded Medical Subject Heading terms and text words that included synonyms for pyrexia and ICU, and a validated search filter for identifying studies investigating aetiology [16]. Titles and abstracts were screened for relevance, and appropriate full-length articles were retrieved for appraisal. Second, additional articles were identified using the "related articles" feature in PubMed and by handsearching bibliographies of included studies, previously published reviews [17, 18], and relevant societal guidelines [19]. Finally, the authors' personal files were screened for other articles of relevance.

Body temperature measurement and definitions

Normal body temperature is between 36.0 and 37.5 °C, with intraindividual variability of 0.5–1.0 °C depending on the time of day (low in early morning, peak in early afternoon/late evening) [1, 20]. Elevated body temperature is classified as pyrexia or hyperthermia. Although these two terms are often used interchangeably, their biological mechanisms and response to therapy are different—thus their distinction is important and will be maintained in this article. Pyrexia, also referred to as fever, is an adaptive response to a physiologic stress that is tightly regulated through endogenous pyrogenic and anti-pyretic pathways, and is associated with an increase in the hypothalamic set point [18]. As such, the elevated body temperature in patients with pyrexia responds to pharmacologic anti-pyretic therapies such as acetaminophen. On the contrary, the elevated body temperature that occurs in hyperthermia syndromes often exceeds 41.0 °C, and reflects a pathologic increase in body temperature that is not associated with an increased hypothalamic set point [21]. This elevated temperature in hyperthermia is therefore not responsive to pharmacologic anti-pyretic therapy. For this article, pyrexia and fever will be used interchangeably, but hyperthermia will refer to the syndrome that accompanies specific environmental, pharmacologic, or endocrine stimuli (Fig. 1).

There is considerable heterogeneity among clinicians in the temperature threshold used to define an episode of pyrexia or hyperthermia [22]. This heterogeneity includes not only temperature variability related to the normal diurnal variability in body temperature, but also differences in the thermometer used to measure temperature. Guidelines in critically ill adults recommend measuring temperature using a central thermometer that provides a direct measure of the core temperature [19]. Examples of such central thermometers include the pulmonary artery catheter, and urinary bladder, esophageal, and rectal thermistors. Although these thermometers provide the most accurate assessment of core body temperature, they are not commonly employed as the primary method of temperature measurement in critically ill patients. Rather, temperature is commonly measured using thermometers that measure temperature from a peripheral site (e.g., tympanic membrane, temporal artery, axilla, mouth) and use proprietary algorithms to convert the measured temperature into a core temperature [22, 23]. Unfortunately, peripheral thermometers are among the least accurate, especially in patients with fever or hypothermia. A recent systematic review and meta-analysis found that, compared with central thermometers, the sensitivity and specificity of peripheral thermometers for the detection of fever was 64 % (95 % CI 55–72 %) and 96 % (95 % CI 93–97 %), respectively [23]. Therefore, for patients where exact temperature measurement is critical or when measured temperature is not congruent with the clinical picture, confirmation with a central device is a key step in determining the underlying aetiology.

A systematic review of observational studies in febrile critically ill adults reported five different definitions of pyrexia among the nine included studies, with 38.3 °C being the most frequently cited threshold [4]. A meta-analysis examining thermometer accuracy found seven distinct definitions of pyrexia, with 37.8 °C being the most frequently cited temperature threshold [23]. A multinational survey of 139 ICUs in 23 countries found 14 discreet temperature thresholds used to define pyrexia with a range of 37–40 °C and a median (interquartile range) of 38.2 °C (38.0–38.5 °C) [22]. Guidelines in critically ill adults define pyrexia as a temperature of 38.3 °C or greater, with the caveat that a lower threshold should be used in immunocompromised patients who are more likely to harbor a severe illness without significant elevation in body temperature [19]. Although not a well-established inherited or acquired state of immunodeficiency, being critically ill presents multiple factors that may impair immune system function and the likelihood of responding to physiologic stress through an elevation in body temperature. These factors include but are not limited to the presence of invasive catheters, decreased mobility and ability to communicate, frequent use of anti-pyretic analgesic drugs and/or broad-spectrum antimicrobials, and extracorporeal forms of organ system support. Therefore, in this article a core body temperature of 38.0 °C or greater will represent pyrexia or hyperthermia.

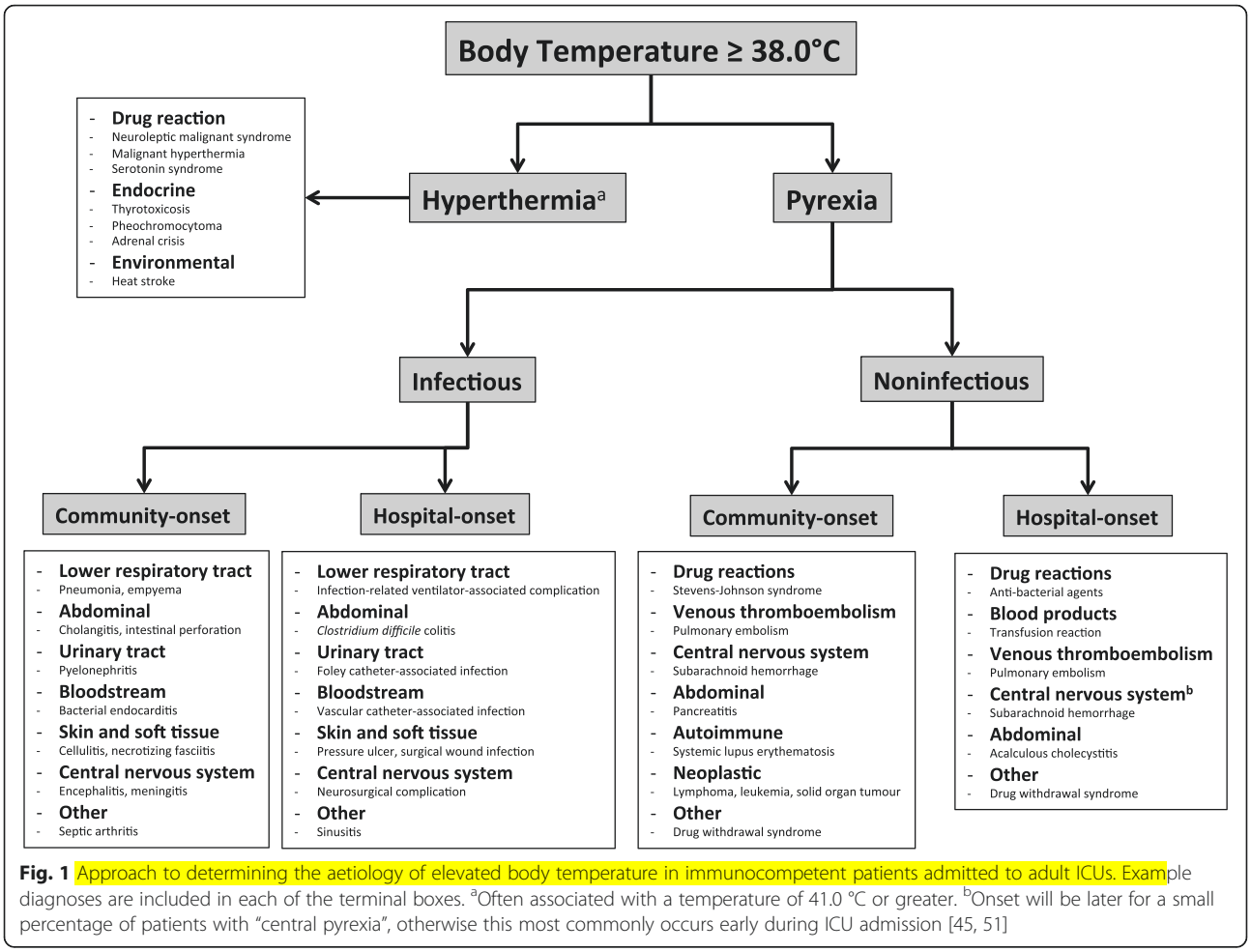

Fig. 1 Approach to determining the aetiology of elevated body temperature in immunocompetent patients admitted to adult ICUs. Example diagnoses are included in each of the terminal boxes. [a]Often associated with a temperature of 41.0 °C or greater. [b]Onset will be later for a small percentage of patients with "central pyrexia", otherwise this most commonly occurs early during ICU admission [45, 51]

High pyrexia will be defined as a temperature of 39.5 °C or greater [18].

Aetiology and incidence of hyperthermia and pyrexia

The absolute body temperature and the response to pharmacological anti-pyretic therapy are often useful in distinguishing between hyperthermia and pyrexia. A temperature that exceeds 41.0 °C and is not responsive to pharmacologic anti-pyretic therapy is more commonly observed in patients with hyperthermia. Therefore, patients with milder elevations in body temperature and/or those whose temperature decreases when administered pharmacologic anti-pyretic drugs are unlikely to be suffering from a hyperthermia syndrome. On the contrary, the absolute temperature is not as helpful in differentiating between infectious and noninfectious pyrexia. Rather, this requires careful examination and investigation for a broad number of infectious and noninfectious diagnoses (Fig. 1). The following sections will provide an overview of several common aetiologies of hyperthermia and pyrexia, followed by presentation of data supporting their incidence in medical, surgical, and neurologically impaired patients.

Hyperthermia syndromes

The hyperthermia syndromes, generally characterized by severely elevated body temperature, include: environmental hyperthermia including heatstroke [24]; drug-induced hyperthermia, including malignant hyperthermia [21], neuroleptic malignant syndrome [25], and serotonin syndrome [26]; and endocrine causes including thyrotoxicosis, pheochromocytoma, and adrenal crisis [27]. Heatstroke is defined clinically as a core temperature greater than 40 °C associated with central nervous system impairment and multisystem organ failure [24]. Classic heat stroke occurs among older, chronically ill, and debilitated individuals during heat waves, wherein a high external temperature overwhelms the body's thermoregulatory capacity to dissipate the heat [28]. Exertional heat stroke typically occurs in young, otherwise healthy individuals undergoing strenuous physical activity, wherein the excessive heat production disrupts usual thermal homeostasis [28]. Complications

of heat stroke include rhabdomyolysis, disseminated intravascular coagulation, renal and liver failure, and severe metabolic derangements including hypoglycemia, lactic acidosis, and hyperkalemia [24]. Malignant hyperthermia occurs among patients with inherited mutations in the ryanodine receptor and is characterized by the acute onset of muscle rigidity, hyperthermia, and acidosis in response to exposure to inhalational anesthetics or depolarizing paralytic medications [21]. Neuroleptic malignant syndrome is characterized by the insidious onset of muscle rigidity, hyperthermia, and mental status changes that occur because of the administration of centrally-acting dopamine antagonists, usually typical or atypical antipsychotics, but may also include antinauseant medications such as metoclopramide [25]. Serotonin syndrome presents with the rapid onset of hyperthermia and other signs of autonomic instability including tachycardia, mydriasis, and diaphoresis, as well as cognitive and neuromuscular changes that may include tremor, hyperreflexia, and clonus in patients with excess central and peripheral serotonergic agonism [26]. Typically, serotonin syndrome occurs following intentional self-poisoning with prescription or illicit serotonergic agents, but may also occur in the context of therapeutic drug use, including antibiotic therapy with linezolid, or inadvertent drug interactions [26]. Endocrine emergencies occasionally present with hyperthermia. While less commonly the case for pheochromocytoma and adrenal crisis, hyperthermia is a common feature of severe thyrotoxicosis, and is one of the diagnostic features of thyroid storm [27].

Pyrexia due to infectious aetiologies

Many episodes of pyrexia are due to infections, and can be broadly divided according to whether they are community onset or hospital onset, with hospital-onset infections manifesting 48 hours or more after admission to hospital [29]. Whether community onset or hospital onset, the most common source of infection in immunocompetent critically ill patients is the lower respiratory tract [12, 30]. For patients admitted from the community this typically represents an infectious bronchitis, or community-acquired pneumonia with or without its associated complications such as abscess or empyema. Most lower respiratory tract infections that take origin in the community are due to a viral pathogen such as human rhinovirus or influenza A/B, with a smaller portion being bacterial, such as *Streptococcus pneumoniae*, less commonly mycobacterial, or rarely fungal [31]. For mechanically ventilated patients, hospital-onset lower respiratory tract infection is typically an infectious tracheobronchitis or ventilator-associated pneumonia. These events are usually due to bacteria such as *Staphylococcus aureus*, Gram-negative bacilli, and less frequently fungal aetiologies.

Peritonitis due to intra-abdominal infection is a common community-onset infectious syndrome [30]. Frequently encountered diagnoses include intestinal perforation, intestinal ischemia with consequential perforation or secondary bacterial invasion of the bloodstream, cholecystitis, appendicitis, perforated diverticular abscess, or hepatic abscess. For patients recovering from abdominal surgery, especially those with intestinal perforation who may have had contamination of the peritoneal space with intestinal contents, intra-abdominal abscess should be sought as a source of pyrexia; otherwise this is generally an uncommon source of new hospital-onset infection. However, colitis due to *Clostridium difficile* infection should not be overlooked in the hospitalized patient with fever and diarrhea, especially in patients who have been treated with broad-spectrum antibiotics [32].

Urinary tract infection is another common aetiology of pyrexia [12]. While the majority of community-onset lower urinary tract infections are not associated with fever and systemic symptoms, patients admitted to hospital and especially the ICU owing to a urinary tract infection typically have infection of the upper urinary tract wherein high fever and other signs of sepsis are common. In patients whose urinary tract infection develops while in the ICU, this is usually the result of an accumulated biofilm on the urinary bladder catheter. In these patients, not only is the bladder catheter the source of the infection, it may also mask the development of symptoms classically ascribed to infection of the urinary tract, and pyrexia may be the only presenting sign [33]. For community-onset infections, the organisms most frequently detected include *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus* species [34], whereas *Pseudomonas aeruginosa* is frequently isolated among patients with a urinary tract infection acquired in the ICU [35].

Any infection, but especially those in the lower respiratory tract, abdomen, or urinary tract, can invade the bloodstream. Given that bloodstream infection can also be primary or catheter related, the bloodstream is a common site of infection in critically ill patients with pyrexia [3, 5, 19, 36]. Among patients admitted to the ICU owing to a severe bloodstream infection that is community onset, the most common pathogens are *E. coli*, *S. aureus*, and *S. pneumoniae* [37]. For those infections that are hospital onset, *S. aureus* and *E. coli* are also the two most common pathogens, followed by Gram-negative Enterobacteriaceae and *Enterococcus faecalis* [37]. Risk factors for developing a severe bloodstream infection (community or hospital onset) include older age and the presence of underlying medical comorbidities especially diabetes mellitus, dialysis-dependent renal failure, cancer, lung disease,

and alcoholism [37]. Fungemia with *Candida albicans* and non-albicans *Candida* species is important to consider as a cause of pyrexia that develops in hospital, especially in patients with risk factors such as recent surgical operation, sepsis, treatment with parenteral nutrition, and/or broad-spectrum antibacterial agents. Although rates of catheter-related bloodstream infection have decreased considerably owing to use of infection prevention bundles and early removal of unnecessary catheters [38, 39], this remains an important source of pyrexia in patients admitted to ICUs. While classically thought to present negligible risk, the infectious risk associated with arterial catheters is similar to central venous catheters [40, 41]. Coagulase-negative staphylococci are the most common pathogen isolated in patients with catheter-related bloodstream infection, with other common organisms including *S. aureus*, enterococcal species, and Gram-negative Enterobacteriaceae [42, 43].

Other sources of infection include the skin and soft tissue, bone/joints, central nervous system, and ethmoid and maxillary sinuses [30]. Diagnoses such as cellulitis and necrotizing fasciitis commonly take origin in the community, although they may rarely be hospital onset. Skin breakdown particularly in the sacral area is a common problem in patients with long ICU or hospital lengths of stay, and these areas may become infected. In addition, any operative wound can become colonized and ultimately infected. Hospital-onset infections of the central nervous system are uncommon outside the neurosurgical setting; however, among patients with persistent bacteremia and prolonged pyrexia, consideration should be given to potential seeding of the paraspinal and/or epidural spaces. Finally, for patients with prolonged insertion of nasogastric and/or nasotracheal tubes, sinusitis commonly develops, and may be responsible for pyrexia that is not accompanied by other systemic signs of infection [44].

Pyrexia due to noninfectious aetiologies

Noninfectious diagnoses are also common causes of pyrexia in adult ICUs, especially among patients with an acute neurological condition [45]. Unless there are obvious signs and symptoms of the particular noninfectious problem, such as an exanthem in the context of a drug reaction or asymmetric leg edema in the context of deep vein thrombosis, these diagnoses are often not made until infectious aetiologies have been ruled out by detailed examination and an appropriate set of investigations. Similar to infectious aetiologies, noninfectious aetiologies can be grouped according to community or hospital onset. Although there may be a fair bit of overlap between the types of noninfectious community and hospital-onset problems responsible for pyrexia, this distinction is important because autoimmune and neoplastic aetiologies rarely develop in hospital. On the contrary, blood products and medications are commonly prescribed to hospitalized patients, and thus transfusion reactions and drug hypersensitivity, in particular to antimicrobial or antiepileptic agents, are frequent causes of noninfectious fever that develops in hospital. In addition, despite meticulous attention to appropriate prescription of venous thromboembolism prophylaxis, deep vein thrombosis and pulmonary embolism can be the source of a new episode of pyrexia, especially if complicated by septic thrombophlebitis. Abdominal sources may also be responsible for a noninfectious fever. Patients admitted to the ICU with pancreatitis may be febrile at ICU admission; however, fever may recur in hospital if pancreatitis is severe and complicated by necrosis and/or pseudocyst formation. While acalculous cholecystitis is not a typical diagnosis at ICU admission, it commonly develops in patients recovering from nonbiliary surgery and/or in those with significant periods of hypotension [46]. Although the mechanism behind the development of early postoperative fever remains unclear, and may or may not involve lung atelectasis [47], early-onset fever is commonly noninfectious in origin for patients admitted to the ICU following elective surgery [2]. For patients admitted to the ICU with a neurological condition such as subarachnoid hemorrhage, traumatic brain injury, or intracerebral hemorrhage, pyrexia that occurs within the first couple days of ICU admission is most likely central fever due to the temperature dysregulation associated with the neurological injury rather than another infectious or noninfectious process.

Incidence of pyrexia and aetiologies

The incidence of pyrexia among critically ill adults depends on the defining temperature threshold and the population studied (Table 1). A systematic review of nine observational studies in patients admitted to the ICU without an acute neurological condition found that the fever incidence varied between 26 and 88 % [4]. The largest studies were from Barie et al. [2] and Laupland et al. [3]. Defined as a temperature of 38.2 °C or greater, Barie and colleagues found that fever was present in 26 % of 2419 patients admitted to their surgical ICU over a 14-month period [2]. Infections were responsible for 46 % of febrile episodes, and were more likely in patients whose fever occurred at the time of admission following emergency surgery. On the contrary, among patients admitted to the ICU following elective surgery, early fever within 72 hours of admission was more likely to be noninfectious, and infectious aetiologies did not emerge until after 72 hours in the ICU. Defined as a temperature 38.3 °C or greater, Laupland and colleagues found that the cumulative incidence of fever was 44 %

Table 1 Studies reporting the aetiology of pyrexia in immunocompetent patients admitted to adult ICUs with or without an acute neurological condition

Study	Setting	Design	Total patients (*n*)	Episodes of pyrexia (*n*)	Pyrexia definition (°C)	Aetiology	
						Infectious diagnosis (*n*, %)[a]	Noninfectious diagnosis (*n*, %)[a]
No acute neurological condition							
Circiumaru et al., 1999 [56]	Medical–surgical ICU	Prospective observational study	93	70	≥38.4	Total (37, 53) Respiratory (15, 21) BSI (9, 13) Abdominal (5, 7) Other (8, 11)	Total (33, 47) ARDS (4, 6) MI (3, 4) Vasculitides (2, 3) Pancreatitis (1, 1) Atelectasis (1, 1) GVHD (1, 1) ICH (1, 1) Unclear (20, 29)[b]
Peres Bota et al., 2004 [57]	Medical–surgical ICU	Prospective observational study	493	139	≥38.3	Total (76, 55)	Total (63, 45) Postoperative (27, 19) Cerebral hemorrhage (20, 14) Trauma (5, 4) ARDS (3, 2) MI (2, 1) Pancreatitis (3, 2) GI bleed (3, 2)
Barie et al., 2004 [2]	Surgical ICU	Prospective observational study	2419	626	≥38.2	Total (286, 46)[c]	Total (330, 53)[c]
Laupland et al., 2008 [3]	3 medical–surgical ICUs, 1 CVICU	Retrospective observational study	20,466[d]	10,730	≥38.3	Culture-positive (1847, 17) BSI (1004, 9)	Culture-negative (8883, 83)
Niven et al., 2011 [36]	3 medical–surgical ICUs, 1 CVICU	Retrospective observational study	7535	100[e]	≥38.3	Total (73, 73) Pneumonia (51, 51) BSI (6, 6) Other (15, 15)	Total (27, 27)
Gozzoli et al., 2001 [58]	Surgical ICU	RCT	38	38	≥38.5	Total (18, 47)	Total (20, 53)
Niven et al., 2013 [59]	2 medical–surgical ICUs	RCT	26	26	≥38.3	Total (23, 88) Respiratory (15, 58) UTI (2, 8) BSI (1, 4) Other (5, 19)	Total (3, 12)
Schortgen et al., 2012 [11]	7 medical–surgical ICUs	RCT	200	200	>38.3	Total (200, 100)[f] Lungs (138, 69) Abdomen (13, 7) Genitourinary (12, 6) Other (28, 14) Unknown (9, 5)	Not applicable
Young et al., 2015 [12]	23 medical–surgical ICUs	RCT	700	700	>38.0	Total (700, 100)[f] Respiratory (237, 34) Abdominal (92, 13) UTI (68, 10) BSI (42, 6) Skin/soft tissue (54, 8) Other (207, 30)	Not applicable
Acute neurological condition							
Commichau et al., 2003 [49]	Neurological ICU	Prospective observational study	387	87	≥38.3	Total (45, 52)[g] Respiratory (37, 42) *Clostridium difficile* (4, 4) UTI (3, 3) Sinusitis (1, 1)	Total (2, 2) DVT (2, 2)
Rabinstein et al., 2007 [45]	Neurological ICU	Prospective observational study	93	93	≥38.3	Total (62, 67) Respiratory (46, 49) Other (16, 17)	Total (31, 33) Central fever (27, 29) Alcohol withdrawal (3, 3) Phenytoin toxicity (1, 1)
Hocker et al., 2013 [51]	Neurological ICU	Retrospective observational study	526	526	>38.3	Total (280, 53)	Total (246, 47)

[a]Proportion refers to percentage of total number of pyrexia episodes
[b]Inconsistencies in reporting of pyrexia aetiologies; total number infectious and noninfectious aetiologies did not total the number of pyrexia episodes
[c]Detailed data for infectious and noninfectious aetiologies presented in graphical format only
[d]A total of 24,204 ICU admissions among 20,466 patients
[e]Convenience sample of 100 randomly selected patients. Total number of patients with fever during study period was 2216
[f]Both Schortgen et al. [11] and Young et al. [12] preferentially enrolled patients with suspected or confirmed infection
[g]Forty-two pyrexia episodes did not have a clear aetiology
ARDS acute respiratory distress syndrome, *BSI* bloodstream infection, *CVICU* cardiovascular intensive care unit, *DVT* deep vein thrombosis, *GI* gastrointestinal, *GVHD* graft versus host disease, *ICH* intracerebral hemorrhage, *MI* myocardial infarction, *RCT* randomized controlled trial, *UTI* urinary tract infection

among 20,466 critically ill adults with a broad range of admission diagnoses, with the highest incidence among trauma/neurologic patients [3]. Cultures from blood, urine, sputum, cerebrospinal fluid, and/or other sterile fluid were positive in 17 % and 31 % of fever and high fever episodes, respectively [3]. Bloodstream infection occurred in 9 % and 19 % of fever and high fever episodes, respectively. Culture-positivity was most likely among medical patients. However, this study probably underestimated the incidence of infectious fever because the authors did not systematically evaluate the results of diagnostic tests other than cultures for identifying infection [3]. Another study in the same health region that undertook a detailed chart review to investigate pyrexia management practices in 100 medical and surgical critically ill patients without an acute neurological condition found that infections were responsible for 73 % of pyrexia episodes, with pneumonia the most common infection, occurring in 70 % of infectious fevers [36]. This is consistent with a large, prospective study of infection occurrence in 71 ICUs in Italy, wherein the most common source of infection was pneumonia [30].

Unfortunately, the current literature does not consistently document the incidence of noninfectious aetiologies of pyrexia. Similarly, the incidence of the hyperthermia syndromes among ICU patients with an elevated body temperature is not clear.

Among critically ill patients with an acute neurological condition, the reported incidence of fever varies between 23 and 51 % [6, 48–50]. The largest study investigating the epidemiology of fever among patients admitted to the ICU with an acute neurological condition is that of Rincon et al. [6]. Of 13,587 patients admitted to 94 ICUs in the United States, 6965 (51 %) had fever defined as a temperature of 37.5 °C or greater. The incidence of fever was highest among patients with traumatic brain injury (60 %) or aneurysmal subarachnoid hemorrhage (54 %), and lowest among patients with acute ischemic stroke (37 %) [6]. Unfortunately, Rincon and colleagues did not report on the aetiologies of pyrexia, and therefore estimates of the occurrence of infectious and noninfectious fever in neurological patients derive from smaller studies (Table 1). Among 93 patients admitted to a neurological ICU in the United States who developed pyrexia, infection was the cause in 62 patients (67 %) with noninfectious causes accounting for the other 31 (33 %) patients [45]. Infections were more common in patients with traumatic brain injury, whereas a noninfectious cause, most probably central fever, was more likely in patients with subarachnoid hemorrhage. Admission diagnosis of subarachnoid hemorrhage (odds ratio (OR) 11.79, 95 % CI 3.0–59.4) and fever onset within 72 hours of ICU admission (OR 2.21, 95 % CI 1.22–4.34) were statistically significant predictors of noninfectious fever [45]. Hocker and colleagues examined the occurrence of infectious and noninfectious aetiologies of fever in 526 patients admitted to a neurological ICU in the United States [51]. Because their objective was to develop a model predictive of the probability of central fever, they unfortunately excluded patients with other noninfectious causes of pyrexia. Nonetheless, they found that fever was infectious in 53 % and central in 47 %. The combination of negative cultures (urine, blood, respiratory secretions, cerebrospinal fluid, peritoneal fluid, stool, sinus aspirates, and *C. difficile* PCR), an absence of infiltrate on chest radiograph, the diagnosis of subarachnoid hemorrhage, intraventricular hemorrhage, or tumor, and the onset of fever within 72 hours of admission predicted central fever with a probability of 0.90 [51].

Investigations in patients with hyperthermia or pyrexia

There is a relative lack of data pertaining to the approach to determining the aetiology of pyrexia. In a multinational survey of temperature management practices in 139 general medical–surgical ICUs, 59 % of respondents indicated that new pyrexia triggers a full septic work-up, mostly via specific physician order, not a standardized protocol [22]. In a study examining management practices among febrile critically ill adults without an acute neurological condition, Niven et al. [36] found that 89 % of the population had at least one culture sent to the laboratory for analysis within the first 48 hours of fever onset. The most common culture was a blood culture (73 %), followed by urine culture (62 %) and respiratory secretion culture (61 %). A chest radiograph was ordered in nearly all study participants (95 %) within 48 hours of fever onset [36].

Not surprisingly, given the paucity of studies describing the approach to determining the aetiology of pyrexia in patients admitted to ICUs, there is a similar lack of data describing the yield of such investigations in febrile patients. A series of three retrospective cohort studies in trauma patients admitted to one surgical/trauma ICU in the United States examined the relationship between the presence of fever and/or leukocytosis and: the ordering of urine [52], blood [53], and respiratory secretion [54] cultures; or the occurrence of urinary tract, bloodstream, and lower respiratory tract infections, respectively. For each fluid cultured, the results were generally the same; namely, a strong relationship between the presence of pyrexia and the ordering of urine [52], blood [53], and respiratory secretion [54] cultures, but no significant relationship between the presence of pyrexia and positive culture from the urine, blood, or lower respiratory tract. In a meta-analysis, Coburn et al. [55] examined clinical and laboratory features predictive of bacteremia in immunocompetent adults. The majority of the 35 included

studies did not include critically ill patients; however, according to their meta-analysis, irrespective of the severity of pyrexia, elevated body temperature was not independently associated with the presence of bacteremia [55]. In addition, the absence of pyrexia was not sufficient to rule out bacteremia (temperature ≥ 38.3 °C, negative likelihood ratio (LR) 0.80, 95 % CI 0.61–1.0). The presence of shaking chills or rigors was modestly predictive of bacteremia (positive LR 4.7, 95 % CI 3.0–7.2), whereas the absence of the systemic inflammatory response syndrome (SIRS) was the strongest predictor of negative blood cultures (negative LR 0.09, 95 % CI 0.03–0.26).

Guidelines recommend a clinically driven, cost-conscious approach, rather than a protocolized, dogmatic approach, to obtaining cultures and imaging studies in critically ill patients with pyrexia [19]. Based on existing literature that suggests a poor association between pyrexia and the likelihood of a positive culture, yet a high likelihood that pyrexia heralds the presence of an infection, most infections are likely diagnosed based on clinical and radiographic findings. Therefore, we suggest for immunocompetent patients with an elevated body temperature that investigations should be guided by the clinical probability of the aetiologies outlined in Fig. 1. Blood cultures should be obtained in any patient with rigors, and may be avoided in febrile patients without concomitant SIRS.

Conclusions

Whether due to pyrexia or a hyperthermia syndrome, elevated body temperature is commonly encountered in patients admitted to adult ICUs. Although estimates of the incidence of infectious and noninfectious aetiologies are derived from studies with small sample size and inconsistent reporting of noninfectious aetiologies, current literature suggests that pyrexia is most frequently the sign of an infection. Among patients admitted to the ICU following surgery and/or an acute neurological condition, early fever may indicate a noninfectious process. Pyrexia commonly triggers a full septic work-up, but on its own is a poor predictor of culture-positivity. In order to improve culturing practices, and better guide the diagnostic approach to critically ill patients with pyrexia, additional research is required to provide more robust estimates of the incidence of infectious and noninfectious aetiologies, and their relationship to other clinical features. In the meantime, we suggest that investigations in patients with an elevated body temperature should be guided by the clinical probability of the aetiologies outlined in our proposed diagnostic approach.

Abbreviations

LR, likelihood ratio; OR, odds ratio; SIRS, systemic inflammatory response syndrome

Authors' contributions

Both authors contributed equally to the conception and design of the article. DJN drafted the full manuscript, and KBL contributed key revisions to the intellectual content. Both authors gave final approval of the version to be published.

Competing interests

The authors declare that they have no competing interests.

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REVIEW Open Access

Should we treat pyrexia? And how do we do it?

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Abstract

The concept of pyrexia as a protective physiological response to aid in host defence has been challenged with the awareness of the severe metabolic stress induced by pyrexia. The host response to pyrexia varies, however, according to the disease profile and severity and, as such, the management of pyrexia should differ; for example, temperature control is safe and effective in septic shock but remains controversial in sepsis. From the reported findings discussed in this review, treating pyrexia appears to be beneficial in septic shock, out of hospital cardiac arrest and acute brain injury.

Multiple therapeutic options are available for managing pyrexia, with precise targeted temperature management now possible. Notably, the use of pharmacotherapy versus surface cooling has not been shown to be advantageous. The importance of avoiding hypothermia in any treatment strategy is not to be understated.

Whilst a great deal of progress has been made regarding optimal temperature management in recent years, further studies will be needed to determine which patients would benefit the most from control of pyrexia and by which means this should be implemented. This narrative review is part of a series on the pathophysiology and management of pyrexia.

Background

Around 35 % of in-hospital patients will develop pyrexia [1], increasing up to 70 % amongst the critically unwell [2]. Pyrexia has long been thought of as a protective physiological response to help host defences, although this is now being challenged. Despite recent advances, it remains unclear whether pyrexia or the physiological response to pyrexia causes morbidity and mortality and whether management of pyrexia with pharmacological agents or physical cooling actually confers benefit. We review some of the recent evidence for and against treating pyrexia with reference to varying disease severity. Finally, we discuss treatment strategies and methods.

This narrative review of pyrexia and associated treatment options is based on the latest available published evidence. We searched MEDLINE, EMBASE and CINAHL for articles published in English before 12 Feb 2016. We used the search terms "fever", "pyrexia", "hyperthermia" in combination with "ICU" or "sepsis" or "brain injury" or "cardiac arrest" and with "cooling" or "antipyretics" or "acetaminophen" or "NSAIDS". We largely selected publication from the past 15 years. Further evidence was selected from these articles' reference lists and from our previous knowledge of the subject. Review articles are cited to provide further information on aspects that are not within the remit of this article.

What is pyrexia?

Pathophysiology

The process of tightly regulating body temperature within a specified range (±0.2 °C), or thermoregulation, is an essential homeostatic mechanism. Thermoregulation consists of afferent signalling via warm and cold thermoreceptors, central processing within the hypothalamus and efferent response. These responses include regulation of peripheral blood flow, diaphoresis and shivering. Whilst there is strict control there is also rhythmic temperature variability over a 24-h period [3]. This circadian rhythm is altered in critically ill patients with both temporal shifts and a larger magnitude of variation, both increasing with disease severity [4].

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Pyrexia (also named fever) is the altering upward of the thermoregulatory set point, often secondary to the systemic inflammatory response to a stimulus such as infection. The molecular basis is summarized in Fig. 1 [5, 6]. Fever has been defined by The American College of Critical Care Medicine, the International Statistical Classification of Diseases and the Infectious Diseases Society of America as a core temperature of 38.3 °C or higher [7]. Pyrexia secondary to the systemic inflammatory response should be distinguished from hyperthermia resulting from excessive heat production, as observed in heatstroke and malignant syndromes, or from ineffective heat loss. Temperature levels encountered during hyperthermia are usually higher than during pyrexia because thermoregulation is abolished; indication of rapid temperature control is, therefore, indisputable to avoid irreversible tissue damage.

Grading and measurement

The definition of pyrexia in itself is complex as there is no agreed consensus. This is further complicated by peripheral thermometers not accurately estimating body core temperature [8]. The causes of pyrexia are multiple and contribute to different definitions. During infection, fever is usually defined as a temperature greater that 38.3 °C [7, 9]; in the post-resuscitation care of cardiac arrest, a threshold of 37.6 °C is used [10]; and in stroke, thresholds of 37.2, 37.5 and 38 °C are all applied [11]. Whatever the clinical situation, hypothermia is usually defined by a core temperature lower than 36 °C [7, 10, 12].

Should we treat pyrexia?

The cost of pyrexia

The cost of pyrexia should be considered in several ways. Pyrexia has a metabolic cost such that cooling febrile ICU patients will reduce oxygen consumption by 10 % per °C [6]. Small studies in sedated patients demonstrated a significant reduction in VO_2 (the rate of oxygen consumption) and VCO_2 (the rate of carbon dioxide elimination) during cooling [13, 14]. In septic shock, temperature lowering by ibuprofen was associated with increased lactate clearance [15]. In patients with acute brain injury, pyrexia may increase intracranial pressure and worsen secondary ischemic damage [16]. These suggest the possibility of therapeutically offloading the cardiorespiratory system and preserving brain function at times of stress. Whether the cost of pyrexia translates to unfavourable outcomes remains unknown. The incidence of pyrexia is decreasing over time with an absolute reduction of 35 % found in Canadian ICUs [17]. This did not coincide with an appreciable decrease in mortality, suggesting that important outcomes may not be affected by the incidence of pyrexia.

Perhaps the question should not be "should we treat pyrexia?" but "in what conditions is it beneficial to treat pyrexia?" (Fig 2). This is highlighted in a large

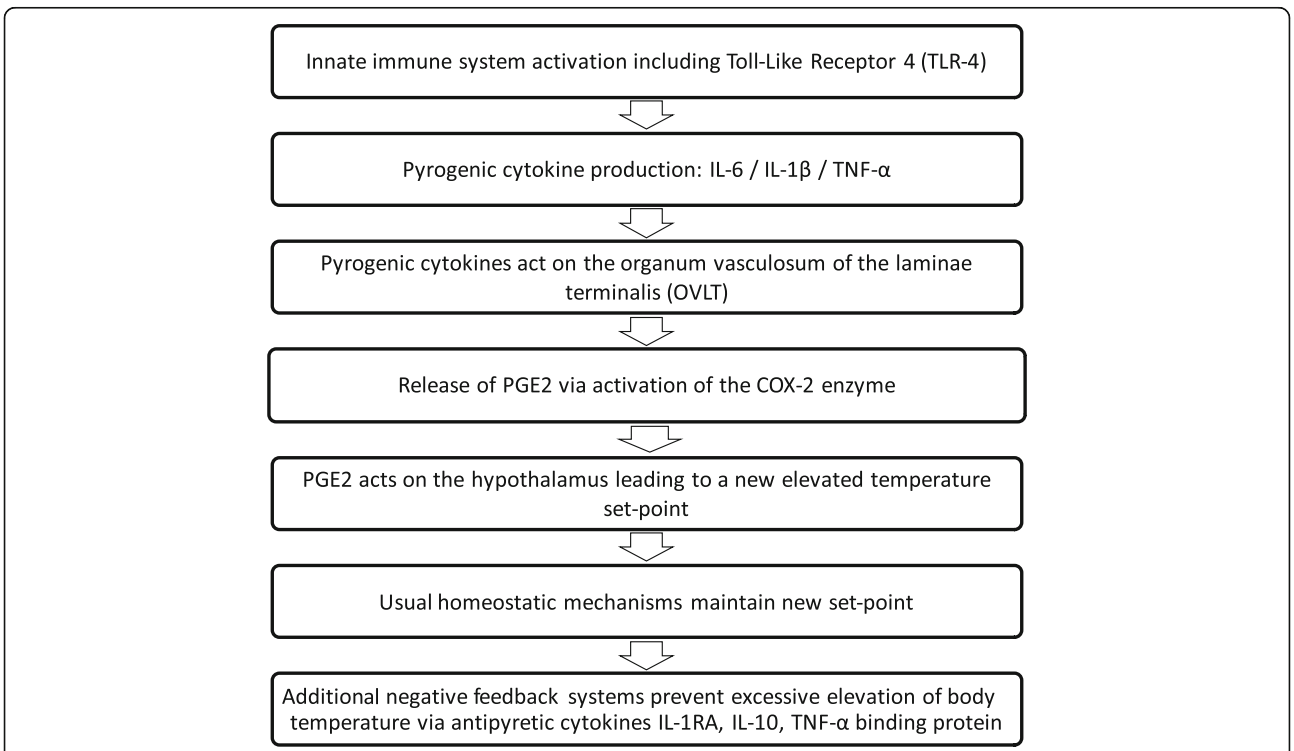

Fig. 1 The main stages of the molecular basis of pyrexia. *IL* interleukin, *PGE2* prostaglandin E2, *TNF* tumour necrosis factor

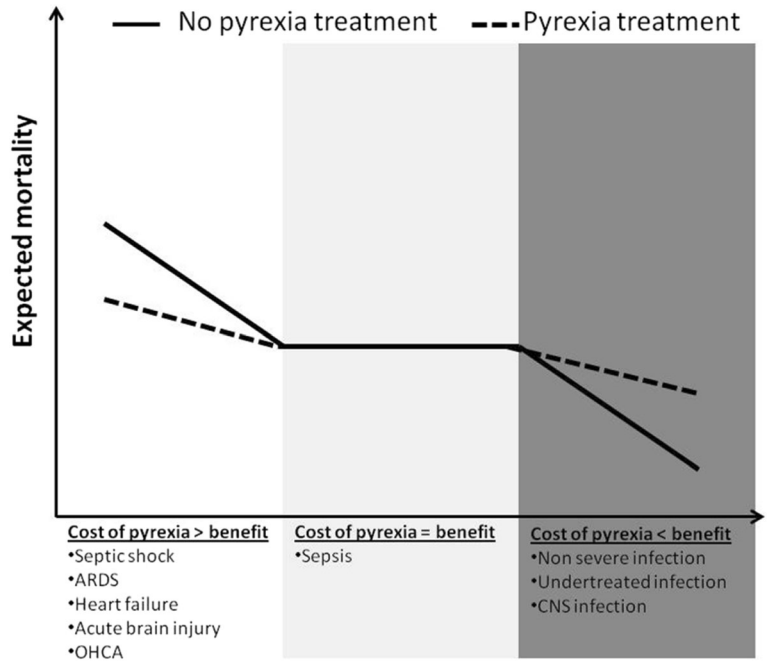

Fig. 2 Suggested impact of pyrexia treatment on outcome according to clinical context. *ARDS* acute respiratory distress syndrome, *CNS* central nervous system, *OHCA* Out-of-hospital cardiac arrest

observational study where fever within the first 24 h of ICU admission was significantly associated with decreased mortality in patients with infection while peak fever ≥40 °C was associated with increased mortality in patients without infection [18]. An observational study on 1400 non-neurological critically ill patients also revealed different associations between the maximal peak temperature and mortality according to the presence of sepsis or not [19]. Fever ≥39.5 °C was associated with increased mortality in non-septic patients while moderate fever (37.5–38.4 °C) was associated with decrease mortality in septic patients. Moreover, this study highlights different impacts of fever treatment. Physical cooling did not alter the mortality risk and the use of antipyretic agents did not alter mortality in the non-septic group but did increase 28-day mortality in the septic group (adjusted odds ratio 2.61 ($P = 0.028$) for non-steroidal anti-inflammatory drugs (NSAIDs) and 2.05 ($P = 0.01$) for paracetamol [19].

In patients with acute brain injury, pyrexia has been identified as an independent risk factor for increased mortality and poorer neurological outcome [16, 20–22]. Results are, however, inconsistent as fever could be a marker of brain injury severity [23]. The presence or not of infection may also alter the relationship between body temperature and outcome [24, 25]. In more than 100,000 patients, a negative association between early peak fever above 39 °C and hospital mortality was found in patients with traumatic brain injury and stroke but not in patients with central nervous system infection [25].

Pyrexia related to whole body ischemia-reperfusion syndrome is frequent after cardiac arrest and studies found a negative impact of pyrexia on mortality [10]. Patients with successful return of spontaneous circulation are considered as good candidates for targeted temperature management (TTM) with the minimal goal of not exposing patients to pyrexia [10].

Besides the context of fever and disease severity, individual patient's characteristics may determine the ability to cope with the cost of pyrexia, costs that may be detrimental in those patients with low cardiac and/or respiratory reserve, typically seen in elderly patients and those with significant comorbidities. Evidence to quantify this in terms of the ability to cope with the cost of pyrexia is not available, so consideration of the clinical context is required.

Pyrexia treatment in specific situations

Sepsis

For many years pyrexia has been considered a physiological host defence which may confer benefit. The development of antipyretics was justified in terms of patient comfort and the physiological reduction of cardiorespiratory stress. During sepsis, fever is not consistently reported as deleterious and may be protective [18, 19]. The opposite impacts of pyrexia on inflammation and microbiological control may explain discrepant results. Pyrexia enhances inflammation but decrease bacterial and viral load. This dual effect has been highlighted in animals with

pneumonia, showing that pyrexia treatment is beneficial for survival only when antibiotics allow effective control of bacterial load [26].

Whilst the advantages of cooling in sepsis remain a controversial topic, there is now good evidence that cooling is safe and effective in septic shock. One study allocated 200 sedated and ventilated patients with severe sepsis on vasopressors to external cooling or none [27]. The findings demonstrated a significant decrease in vasopressor requirement and in 14-day mortality (19 versus 34 %; absolute difference −16 %; 95 % confidence interval (CI) −28 to −4) with cooling. The mortality outcome was similar. In a post hoc analysis, it was confirmed that temperature control was a main mediator of early mortality [28]. The benefits of cooling could be explained by specific patients' profiles and the cooling strategy used. Patients with severe sepsis benefit the most from the prevention of pyrexia. In this trial the main source of infection was pneumonia with a large majority of patients under adequate antimicrobial therapy at the time of cooling initiation. None were exposed to hypothermia and only two experienced shivering, all being sedated.

The "HEAT" study compared pyrexia control by intravenous paracetamol with placebo in 691 randomized ICU patients with suspected infection and temperature >38 °C [29]. Only 20 % of patients experienced septic shock. Paracetamol was well tolerated. The outcomes for ICU free days and 28-day and 90-day mortalities were similar between the groups.

These two randomised controlled trials (RCTs) in sepsis show that fever control is safe. Interestingly, both noted that patients who received pyrexia treatment had a longer time to death. The avoidance of pyrexia costs at the early stage of severe infection may be balanced by delayed adverse effects. Of these, an acquired hypo-immune state may lead to increased late mortality.

Out of hospital cardiac arrest

Out of hospital cardiac arrest (OHCA) is one of the most studied areas for the practical application of temperature control in adults. The physiological basis of cooling management strategies is relevant [10]. Hypothermia reduces cerebral metabolism, inflammation and cell death. These favourable effects resulted in improved neurological outcome of comatose patients with shockable rhythm managed with 32–34 °C TTM [30]. Of note, pyrexia was not treated in the control group; thus, the TTM benefit may have been merely related to the avoidance of pyrexia rather than to hypothermia itself. The latest evidence from this field comes from a large RCT comparing TTM at 33 °C and 36 °C. The benefit seen previously from hypothermia disappeared, with no significant difference in mortality or neurological outcome [31]. This has led to European guidelines changing to indicate a target between 32 and 36 °C for OHCA patients in whom temperature control is used [10]. Whether simple prevention of pyrexia or strict modest hypothermia (36 °C) is required remains to be tested. In children, TTM at 33 °C was compared with normothermia (target 36.8 °C) [32]. Survival and neurobehavioral outcomes were similar, suggesting that a strict avoidance of pyrexia may help minimise secondary brain injury.

Acute brain injury

For decades, experts advocated for aggressive treatment of pyrexia in neurological critical care and the pathophysiological basis of secondary brain injury caused by hyperthermia is supported by strong evidence. Pyrexia control is, however, not supported by evidence from clinical comparative studies.

Traumatic brain injury Hyperthermia is common in traumatic brain injury (TBI) and has been shown to worsen neurological outcome. In a comparative cohort study the implementation of strict normothermia via means of intravascular cooling demonstrated a significant reduction of intracranial pressure [33]. Clinical studies have also examined therapeutic hypothermia but failed to demonstrate better outcome, with more frequent favourable neurological outcomes in the normothermia group [34]

Cerebrovascular diseases Treatment of pyrexia is advocated by guidelines for acute stroke management [11]. The largest RCT did not find better neurological outcome with paracetamol therapy initiated within the first 12 h in patients with admission temperatures of 36–39 °C [35]. A post hoc analysis showed a beneficial effect in the group of patients with higher baseline temperature (37–39 °C). A new trial focusing on these patients is on-going [36].

Seizure control Pyrexia decreases the seizure threshold and temperature control is thus advocated in the control of status epilepticus. Although viewed as a good clinical practice, it is not supported by clinical studies.

Organ donation

Brain death results in the loss of temperature control. Hyperpyrexia can be encountered initially but hypothermia usually occurs thereafter. Guidelines for organ donor management recommend that physiological parameters, including body core temperature, should be maintained in normal ranges without scientific evidence [37]. Hypothermia could, however, prevent or reduce ischemia-reperfusion injury in several organs. Hypothermia of 34–35 °C compared with normothermia (36.5–37.5 °C) in organ donors has been recently found to significantly

reduce the incidence of delayed graft function in kidney recipients [38]. If hypothermia can improve kidney graft functions, it would be justified to, at the least, treat fever. This trial raises the question of the impact of temperature control on acute kidney injury prevention in general, which remains unclear [39].

General ICU patients

Many other clinical situations with systemic inflammation or endocrine disorders can promote fever. Since the cause of fever may determine a patient's outcome by itself, no conclusion can be drawn from observational studies on the impact of fever in general ICU patients. A systematic approach to controlling pyrexia in general ICU patients is not supported by evidence.

Overall guidance

Several attempts have been made in the literature to discern best practice for pyrexia management in critically ill patients (Table 1). Given the above conflicting data, the association between pyrexia, aetiology, antipyretic management, morbidity, and mortality is particularly complex, with more unanswered questions than answered. As illustrated in Fig. 2, some critically ill patients may benefit from fever control while others may benefit from pyrexia. It is important, however, to put into context the severity of disease; for example, whilst pyrexia may be of benefit in non-severe infection, in a condition with low morbidity and mortality the issue of patient comfort may override any benefit from permissive pyrexia.

A meta-analysis limited to RCTs of antipyretic therapy in the ICU included five trials totalling 399 patients and did not find a difference in mortality [40]. The inclusion of the more recent "HEAT" study would not change this result [29].

Management of pyrexia

Temperature target

Different approaches to fever treatment have been proposed:

- Control of pyrexia when it occurs: treatment administered when temperature exceeds a predefined threshold
- Strict avoidance of pyrexia: temperature maintained below fever threshold
- Strict maintenance of normothermia: TTM with a predefined normothermia range, e.g., 36–37 °C.

The absence of consensus over a definition of fever, the multitude of clinical situations and the scarcity of trials hinder setting goals for clinical practice in terms of treatment timing, rapidity of normothermia induction, temperature target and duration of treatment.

For patients with OHCA, some data can be drawn from the TTM 33 versus 36 °C study [31]. After the 4-h period to achieve the targeted temperature, 95 % of the patients in the 36 °C group had a core body temperature below 37.5 °C for the first 24 h. Treatment of pyrexia in this population may, therefore, correspond to a strict maintenance of body temperature below 37.5 °C. Whether strict normothermia is superior to a strategy that aims to control pyrexia at >37.5 °C once it occurs remains to be tested.

In the "Eurotherm" study, the evolution of body core temperature shows that, in the control group, patients were strictly maintained at 37 °C, which could correspond to "standard" normothermia in TBI [34].

In septic shock, fever control with a TTM of 36.5–37 °C over a 48-h period was found to be advantageous [27]. In a post hoc analysis, the association between different thresholds of temperature and mortality were tested [28]. The time spent with a core body temperature below 38.4 °C within the first 48 h was the most discriminatory. This raises the question of whether a strict avoidance of pyrexia could be sufficient to induce similar benefits.

Efficacy and risks of antipyretic methods

Antipyretic agents, mainly paracetamol and NSAIDs, and physical cooling methods can be used to control pyrexia. Cooling with surface devices is usually preferred for fever control while endovascular methods are more commonly restricted to therapeutic hypothermia. Infusions of cold fluids are easy to administer and inexpensive but this strategy exposes patients to unnecessary volume expansion and does not allow precise temperature control.

Antipyretic agents act on the hypothalamic set point. To be effective, the integrity of the thermoregulatory system should be intact. This explains why antipyretic agents are usually ineffective in the control of pyrexia in acute brain injury [16]. Cooling reduces temperature by removing heat without decreasing the set point, which exposes patients to reflex shivering. These different mechanisms have opposite consequences on vasotonicity. The fall in temperature set point promotes vasodilation to enhance heat loss whilst cooling induces vasoconstriction. In patients with sepsis, this results in different mean arterial pressure evolution [41].

Methods of temperature management have mostly been studied in the context of hypothermia induction and have been extensively reviewed elsewhere [16, 42, 43]. For pyrexia treatment, choices between methods have not yet been determined on the basis of robust evidence but rather according to clinical criteria (listed in Table 2).

Pharmacological methods

Paracetamol Paracetamol is the most commonly administered antipyretic in clinical practice [44]. Compared

Table 1 Main RCTs comparing antipyretics with no treatment in adult critically ill patients

	Study	Patients	Number	Temperature criteria at inclusion	Baseline temperature in the treatment group	Antipyretic method	Duration of treatment	Primary end point	Main results
SIRS and Sepsis	Gozolli et al. [41]	SIRS	38	≥38.5 °C	39 (SD 0.3)	Surface cooling	Up to fever resolution (≤37.5 °C)	Temperature difference	Similar temperature and comfort evolution
	Bernard et al. [15]	Severe sepsis	455	None[a]	37.9 (SE 0.2)	NSAID: IV ibuprofen 10 mg/kg/6 h	48 h	30-day mortality	Lower temperature in the treatment group
									No difference in mortality
	Memis et al. [50]	Severe sepsis	40	None[a]	37.8 (SD 0.75)	NSAID: IV lornoxicam 8 mg/12 h	72 h	Anti-inflammatory effects	Similar temperature evolution
	Schortgen et al. [27]	Septic shock	200	≥38.3 °C	38.8 (IQR 38.6–39.2)	TTM 36.5–37 °C with surface cooling	48 h	Dose of vasopressor	Less vasopressor requirement and 14-day mortality in the treatment group
	Janz [48]	Severe sepsis	40	None[a]	37.7 (IQR 37–38.5)	IV paracetamol 1 g/6 h	3 days	Antioxidant effect	Lower maximal temperature in the treatment group
	Young et al. [29]	Suspected infection	700	≥38 °C	38.5 (SD 0.5)	IV paracetamol 1 g/ 6 h	Up to fever resolution (<37.5 °C, 24 h) or day 28	ICU-free days up to day 28.	Lower temperature in the treatment group
									No difference in ICU-free days
Acute brain injury	den Hertog et al. [35]	Stroke	1400	Between 36 and 39 °C	36.9 (SD 0.6)	Enteral paracetamol 1 g/4 h	72 h	Modified Rankin scale at 3 months	Lower temperature in the treatment group
									No difference in neurological outcome
	Saxena et al. [46]	TBI	41	Between 36 and 39 °C	37.3 (SD 0.8)	IV paracetamol 1 g/4 h	72 h	Temperature difference	No difference in temperature

[a]Antipyretics were given with the aim of testing the anti-inflammatory effects of NSAIDs

IQR 25th–75th interquartile range, *IV* intravenous, *NSAID* non-steroidal anti-inflammatory drug, *SD* standard deviation, *SE* standard error, *SIRS* systemic inflammatory response syndrome, *TBI* traumatic brain injury

Table 2 Proposed criteria for choosing between pharmacological and non-pharmacological antipyretic methods

Antipyretic agents	Physical cooling
• Non sedated patients • Concomitant need for analgesia	• Hypothalamic dysfunction • Need for rapid induction • Need for strict temperature control • Patients with hemodynamic instability • Failure of antipyretic agents

with placebo or no treatment, the difference in body temperature usually reaches statistical significance, although this is modest with uncertain clinical significance. In patients with brain injury, a standard dose (3 g/day) of paracetamol is often reported as ineffective [16]. This justified increasing the dose to 6 g/day, i.e., above the recommended maximal daily dose of 4 g. This higher dose was shown to reduce body temperature by 0.3 °C within 4 h compared with placebo [45]. In the "PAIS" trial, 6 g/day paracetamol administered by the enteral route in patients with stroke resulted in a mean body temperature significantly lower than with placebo [35]. This difference was limited to 0.26 °C (95 % CI 0.18–0.31) at 24 h. Of note, this study did not find any improved outcome with paracetamol. Recently, a pilot study in TBI failed to show a significant reduction in core body temperature despite the use of 6 g/day intravenous paracetamol [46]. The combination of 1 g paracetamol and 800 mg ibuprofen was tested for its ability to control fever in 79 neurological ICU patients [47]. Temperature lowering was enhanced by the combined treatment compared with patients who received paracetamol alone.

In the "HEAT" trial performed in sepsis, the efficacy of 4 g/day intravenous paracetamol was disappointing compared with placebo [29]. Whilst statistically significant within the first three days of treatment, the maximum difference between mean daily temperatures was recorded on day 1, with a between group difference of 0.48 °C (95 % CI −0.59 to −0.36), only. This modest difference may be related to the lack of paracetamol's efficacy or the rapid spontaneous normalisation of temperature in the placebo group. The negative result of this study could be explained by insufficient difference in temperatures. In addition to its antipyretic properties, paracetamol is an antioxidant. In a placebo-controlled phase II trial including 40 patients with severe sepsis, a reduction in oxidative stress related to cell-free haemoglobin was found with paracetamol [48]. All these recent trials show that paracetamol is well tolerated when patients with liver dysfunction are excluded. The safety of paracetamol remains to be evaluated in patients at higher risk of ischemic liver failure and with hypotension.

Non-steroidal anti-inflammatory agents (NSAIDs) NSAIDs are regularly used in the ICU despite the lack of adequate safety evaluation. NSAIDs have a well known side effect profile including hypotension, impaired hepatic and renal function, sodium and water retention, gastrointestinal bleeding and platelet dysfunction. In an attempt to avoid some of these effects, low dose continuous infusion of diclofenac has been proposed. In a small RCT, a low dose infusion was sufficient to control fever in patients with brain injury with fewer episodes of pyrexia compared with the standard bolus dosing group [49]. In a RCT including 79 neurological ICU patients, a similar temperature profile was found after a single dose of ibuprofen compared with paracetamol [47]. In sepsis, NSAIDs have been tested for their ability to modulate the inflammatory response [15, 50]. Although fever was not an inclusion criterion, an antipyretic effect was observed compared with placebo. In 40 patients treated with loraxicam, the maximum between-group difference in temperature was ≈0.6 °C after 24 h of treatment [50]. In the landmark study on ibuprofen, a NSAID allowed a more rapid decrease in temperature with a maximal between-group difference of ≈0.9 °C [15]. Similar outcomes and adverse effects were observed with NSAIDs and placebo. Nevertheless, NSAID use should be discouraged in sepsis until further safety evaluations have been performed. NSAIDs are clearly a risk for worsening the evolution of severe infections [51, 52].

Non-pharmacological methods

Various surface and endovascular automatic cooling devices allowing tight temperature control are now available [42]. When used with the aim of normothermia induction and maintenance, the main advantage of automatic devices is the avoidance of hypothermia. Automatic devices are more expensive but reduce the nursing workload.

Surface cooling devices Three main types of surface cooling devices are available: air-circulating blankets, water circulating blankets and hydrogel-coated water-circulating pads [42]. There is no evidence to support the use of fans for temperature control. Fans are usually considered to help with patient comfort but they can induce shivering [42].

In febrile ICU patients, air-circulating blankets seem less effective for the induction of normothermia compared with the other surface cooling devices [53]. For the maintenance of normothermia, all surface cooling devices were equivalent [53]. Opposite results showing better control using air-circulating blankets were found in two smaller studies [1, 54]. In a RCT including 53 neurological ICU patients, water-circulating pads showed a significantly more rapid induction of normothermia with better control compared with conventional water-cooling blankets

[55]. Shivering occurred more frequently with pads (39 versus 8 %). The tolerance of all surface cooling devices appears to be acceptable with very few skin injury complications reported.

Endovascular cooling devices Several intravenous heat exchange catheter devices are available for temperature management [42]. Endovascular cooling was initially evaluated for therapeutic hypothermia. Some controlled studies are now available in patients with acute brain injury managed with controlled normothermia. The obvious disadvantage is their associated risks, which are likely similar to those associated with invasive central vascular access.

In 296 neurological ICU patients randomized to receive fever treatment either by heat exchange catheter or by paracetamol plus cooling blanket, the burden of fever was significantly reduced with the use of endovascular cooling with no more adverse events [56]. The occurrence of shivering was rare (3.7 %) but of note all patients were ventilated and sedated. A RCT including 102 patients with cerebrovascular disease also demonstrated a significant reduction in fever burden with endovascular cooling compared with a NSAID plus water-circulating blanket [21]. The overall incidence of infection was significantly higher with endovascular cooling compared with an antipyretic and surface cooling. Whether this was related to the invasive device or, finally, to better control of pyrexia with decreased host defences needs to be studied further.

Renal replacement therapies are not typically indicated for temperature control but, in patients requiring renal support, they contribute to heat loss and participate in pyrexia control. Negative heat balance may improve hemodynamic tolerance through better vascular tone [57]. Renal replacement therapies may represent a confounding factor in comparative trials on temperature control.

Thermal tolerance of cooling Any decrease in core and/or peripheral temperature will result in vasoconstriction followed by shivering. In normal and febrile conditions, shivering commences at a body core temperature of ≈1.5 °C under the hypothalamic set point [58]. Skin temperature accounts for around 20 % of thermoregulation and cold stress can promote shivering while the core temperature remains constant [59]. Some studies report less shivering with endovascular cooling but the results are inconsistent [42].

Cooling patients with an elevated temperature set point will promote the shivering reflex to produce heat and counter core temperature lowering. Shivering not only impedes thermal control but its metabolic cost is substantial [60, 61]. Cooling awake septic patients increases VO_2 by up to 60 % [61]. Shivering also promotes the cardiovascular and respiratory stress response and increases cerebral metabolic stress. Avoidance of shivering is, therefore, a crucial component of the cooling procedure. The administration of an antipyretic agent to reduce the temperature set point before commencement of cooling is a common practice but appears to be ineffective [60, 61].

Pharmacological and non-pharmacological management of shivering has been proposed [16, 43]. Given the indication for cooling, many of these disease processes occur in patients who are already receiving some form of sedation. Slight anaesthesia decreases the shivering threshold and represents the most efficient way to prevent it and achieve the goal of VO_2 and cardiovascular stress reduction [13, 14, 27]. In awake patients, the benefit of pyrexia treatment using cooling should be clearly evaluated against the risk of metabolic and cerebral stress induced by shivering, especially given that shivering can occur without any clinical manifestation and may only be detected by VO_2 monitoring [60].

Pharmacological versus non-pharmacological methods

A meta-analysis of 11 trials considered pharmacological versus non-pharmacological antipyretic treatments with outcome measures being targeted temperature and haemodynamic effects [62]. It found that intravascular as opposed to surface cooling had better target temperature results, although there was a non-significant trend towards higher mortality. Only three small studies consisted of a head-to-head comparison of pharmacologic and non-pharmacologic methods, for which the analysis was inconclusive [62].

In sepsis, the three largest RCTs compared ibuprofen [15], paracetamol [29] and surface cooling [27] against placebo or no treatment. The maximal between-group differences in temperatures reported were 0.6 °C on day 1, 0.9 °C at 10 h and 1.6 °C at 12 h, respectively. Although inconclusive, these data may suggest that controlling fever by surface cooling is more efficient than by antipyretic agents.

Conclusions

There is now awareness that a balance is required between the severe metabolic stress induced by pyrexia and its possible contribution to host defences. On what side the balance is can strongly vary between patient groups. The precise, safe and efficient control of temperature is now well within our ability, although analysis of the literature does not provide recommendations for preferred methods of treatment in clinical practice. Several studies have found certain techniques have some superiority over others but none have demonstrated a beneficial clinical impact of a more rapid induction or a better control of normothermia on patient outcome. Further studies are needed to determine which patients

would benefit the most from control of pyrexia and by which means this should be implemented.

Abbreviations

CI: Confidence interval; ICU: Intensive care unit; OHCA: Out-of-hospital cardiac arrest; NSAID: Non-steroidal anti-inflammatory drug; RCT: Randomised controlled trial; TBI: traumatic brain injury; TTM: Targeted temperature management; VCO_2: Rate of elimination of carbon dioxide; VO_2: Rate of oxygen consumption

Authors' contributions

JD performed the initial literature search and wrote the first draft and was subsequently involved with manuscript revision and approval of the final submission. FS performed an extensive revision of the first draft and contributed to the literature search and subsequently approved revisions and the final submission.

Competing interests

The authors declare that they have no competing interests.

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