Review

Clinical review: Fever in intensive care unit patients

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Abstract

Fever is a common response to sepsis in critically ill patients. Fever occurs when either exogenous or endogenous pyrogens affect the synthesis of prostaglandin E_2 in the pre-optic nucleus. Prostaglandin E_2 slows the rate of firing of warm sensitive neurons and results in increased body temperature. The febrile response is well preserved across the animal kingdom, and experimental evidence suggests it may be a beneficial response to infection. Fever, however, is commonly treated in critically ill patients, usually with antipyretics, without good data to support such a practice. Fever induces the production of heat shock proteins (HSPs), a class of proteins critical for cellular survival during stress. HSPs act as molecular chaperones, and new data suggest they may also have an anti-inflammatory role. HSPs and the heat shock response appear to inhibit the activation of NF-κβ, thus decreasing the levels of proinflammatory cytokines. The anti-inflammatory effects of HSPs, coupled with improved survival of animal models with fever and infection, call into question the routine practice of treating fever in critically ill patients.

Keywords fever, heat shock proteins, intensive care unit, nuclear factor-κB, sepsis

Fever occurs commonly in hospitalized patients. It is estimated that nosocomial fevers occur in approximately one-third of all medical patients at some time during their hospital stay [1]. In patients admitted to the intensive care unit (ICU) with severe sepsis, the incidence of fever is more than 90% [2]. As there is variation in the incidence of reported fevers, the etiology of fever in critically ill patients is similarly diverse–both infectious and noninfectious etiologies are common [1,3,4].

The definition of fever is arbitrary. The mean body temperature (oral) in healthy individuals is approximately 36.8°C (98.2°F), with a range of 35.6°C (96°F) to 38.2°C (100.8°F) and a slight diurnal variation [5]. The Society of Critical Care Medicine and the Infectious Disease Society of America, in a recent consensus statement, suggested that a temperature of above 38.3°C (101°F) should be considered a fever and should prompt a clinical assessment [4].

Physician and staff response to fever varies institutionally. Besides evaluating the patient and initiating a workup based on the clinical evaluation, it is common for the patient to receive either pharmacologic or mechanical antipyretic therapy. However, there is little evidence that would support such routine practice. The traditional view, at least in pediatrics, is that an exuberant febrile response is inherently dangerous and can, in the worse case, lead to seizures and brain damage [6]. Adult nonhealthcare workers (i.e. patient family members) also have significant misconceptions regarding the perceived detrimental effects of fever [7]. In this complicated psychosocial setting, it is easy for the physician to merely treat the fever. However, there are costs associated with such therapies. It is estimated that when either paracetamol, icepacks or cooling blankets are used, it can cost one 18-bed ICU between $10,000 and $29,000 per year [8]. Pharmacological means to reduce fever cause renal and hepatic dysfunction in patients who are volume depleted or who have underlying kidney or liver disease [9]. Additionally, there is evidence, at least in animal models, that fever is a beneficial host response to infection [10–12].

COX-2 = cyclooxygenase-2; HSF = heat shock factor; HSP = heat shock protein; ICU = intensive care unit; IL = interleukin; NF = nuclear factor; OVLT = organum vasculosum of the laminae terminalis; TNF-α = tumor necrosis factor alpha.

The goal of the present review is to question, by critically evaluating the literature, the practice of routinely treating fever in the ICU patient. The pathophysiology of fever will be reviewed, the animal and human data that have evaluated the role and the potential beneficial effects of fever in disease states will be examined, and the hemodynamic and metabolic costs of fever will be summarized.

The physiology of fever

Fever is extremely well preserved throughout evolution. It has been found in numerous phyla and is estimated to be more than four million years old [13]. Fever is seen in mammals, reptiles, amphibians, and fish as well as in some invertebrates. Not only is it found in endothermic (warm-blooded) animals, it is also seen in ectothermic (cold-blooded) animals [11]. In response to infection, lizards will elevate their body temperature by selecting a warmer microclimate [14]. The febrile response, defined by Plaisance and Mackowiak, is a "complex physiologic reaction to disease involving a cytokine mediated rise in core temperature, generation of acute-phase reactants, and activation of numerous physiologic endocrinologic and immunologic systems" [15].

Exogenous stimuli, such as endotoxin, staphylococcal erythotoxin and viruses, induce white blood cells to produce endogenous pyrogens. The most potent of these endogenous pyrogens are IL-1 and tumor necrosis factor alpha (TNF-α) [16]. Other endogenous pyrogens that are integral in the febrile response include IL-6 and the interferons [17]. These endogenous pyrogens act on the central nervous system at the level of the organum vasculosum of the laminae terminalis (OVLT). The OVLT is surrounded by the medial and lateral portions of the pre-optic nucleus, the anterior hypothalamus and the septum pallusolum [18].

The exact mechanism of how circulating cytokines in the systemic circulation effect neural tissue remains unclear. It has been hypothesized that a leak in the blood–brain barrier at the level of the OVLT allows the central nervous system to sense the presence of endogenous pyrogens. Additional proposed mechanisms include active transport of cytokines into the OVLT or activation of cytokine receptors in endothelial cells of the neural vasculature, which than transduce signals to the brain [19].

The OVLT synthesizes prostaglandin, especially prostaglandin E_2, in response to endogenous pyrogens. Prostaglandin E_2 acts directly on the cells of the pre-optic nucleus to reduce the rate of firing of warm sensitive neurons, and it is one of the downstream products of the arachidonic acid pathway [20,21]. There is ample evidence that cyclooxygenase-2 (COX-2) in neural vasculature is important in the formation of fever. Induction of the febrile response by lipopolysaccharide, TNF-α, and IL-1β resulted in increased COX-2 mRNA in the cerebral vasculature of numerous experimental models of fever [22]. In a murine model COX-2 knockout mice were unable to mount a febrile response to endotoxin, and in humans COX-2 selective inhibitors were shown to reduce fever [23,24]. In fact, over 30 years ago, the NSAIDS were shown to inhibit the action of COX-2 [25]. Shortly afterwards, a similar mechanism was discovered for acetaminophen, but this effect was only found in neural COX-2 enzymes; thus explaining why acetaminophen is a strong anti-pyretic but devoid of anti-inflammatory effects [26].

Fever and clinical outcomes

Although the febrile response has existed for millions of years, controlled studies evaluating the benefits of fever do not exist. Most of the studies in humans evaluating clinical outcomes, fever and infection have been case–control series. For example, in the pre-antibiotic era, artificial fever was used, with limited success and without controlled trials, to treat neurosyphilis [27,28]. Evaluation of fever in animal models is confounded by the fact that stressed animals often increase their body temperature several degrees with handling and is confounded by questions about the appropriate pyrogenic stimulus in a particular species [11]. It has been postulated that a behavior so widely preserved, yet metabolically expensive, must convey some net benefit to the host or it would not have been retained during evolution [11].

In vitro and animal data evaluating the effect of temperature on survival during infection suggest that fever may be beneficial to the host. Increased survival with fever has been demonstrated in animal studies [29,30]. In fact, the majority of studies (14 out of 21 studies) evaluated in one review demonstrated a deleterious effect of lowering body temperature [11]. Additionally, increasing temperature has effects on the minimum inhibitory concentration of antibiotics to bacteria. As the experimental temperature increased past 38.5°C, the authors of one study found reductions in the minimum inhibitory concentrations, representing a progressive increase in the antimicrobial activity of antibiotics [31].

While *in vitro* data and animal data seems to suggest that treatment of fever does not favorably impact morbidity and mortality, human studies in this area are lacking. In a study with 218 patients who had gram-negative bacteremia, fever correlated positively with survival [32]. However, this data is confounded by the fact that the majority of afebrile septic patients who died did not receive appropriate antibiotic therapy. Additionally, another retrospective case series showed that failure to mount a febrile response within the first 24 hours was associated with increased mortality [33]. When patient comfort was evaluated as a primary outcome variable, there was no difference in the comfort level of patient who had fever treated versus control [8].

Fever and the immune response

Increased temperature is known to induce changes in many of the effector cells of the immune response. In addition to these changes, fever induces the heat shock response. The

heat shock response is a complex reaction to fever, to cytokines, or to numerous other stimuli. The end result of this reaction is production of heat shock proteins (HSPs), a class of proteins crucial to cellular survival [34]. Ritossa first reported the heat shock response in 1962 when he noticed changes in the *Drosphilia* chromosome in response to increased temperature [35]. The protein products of these chromosomal changes were subsequently isolated and called HSPs [36].

The heat shock response provides a cell or organism with thermotolerance. When a cell is subjected to a sublethal heat stress, this sublethal stress protects the organism from a subsequent potentially lethal heat stress [37]. This response seems to not only function to provide protection from heat, but can, by a mechanism called cross-tolerance, be induced by a particular stressor (e.g. heat) and can protect against cell death from an entirely different lethal stress (e.g. endotoxin) [34].

HSPs have subsequently been found in numerous organisms, and the DNA sequencing and subsequent protein structure is highly preserved between organisms [38]. Because they are so well preserved throughout nature, it is postulated that HSPs are critical for cell survival. They are molecular chaperones that escort proteins marked for translocation throughout the organelles of a cell, they participate in refolding proteins that have become denatured during cellular stress, and they transport severely damaged proteins to proteolytic organelles for destruction [39]. Additionally, HSPs also are important in the apoptotic response, modulating the immune response, and in regulating steroid hormone receptors.

Inducible HSPs exist in the cytosol, bound to proteins called heat shock factors (HSFs) [34]. A stress causes HSPs to dissociate from HSFs, and the HSFs are then phosphorylated . These phosphorylated HSFs form a trimer that enters the nucleus of the cell and, after further phosphorylation, bind to the cellular DNA on a sequence called a heat shock element. The heat shock element is a promoter sequence for the HSP. Binding of the HSF to the heat shock element causes transcription of HSP mRNA. Translation of the mRNA occurs, and further HSPs are produced [39].

This system is regulated on several levels. HSPs bind to dissociated HSFs in the cytosol, preventing the formation of further HSF trimers to act as DNA promoters. Additionally, there is evidence of post-transcriptional regulation of HSP production [34]. *In vitro* experiments show that while HSP mRNA is increased secondary to a stressor, the amount of HSPs produced is variable and is dependent on the magnitude of the stressor [40].

Heat shock response: clinical implications in sepsis

The importance of the heat shock response *in vivo* has been demonstrated in numerous experiments. Ryan and colleagues heated rats from 39°C to 42.5°C and then, 24 hours later, administered a lethal dose of endotoxin to the animals [10]. The mortality in the control group at 48 hours was 71.4%, while no rats died in the heat-treated group. Villar and colleagues showed that, during intra-abdominal sepsis, previous heat treatment significantly impacted mortality and reduced organ injury [12]. In this study, rats underwent heat treatment 18 hours before cecal ligation and puncture. Survival at 7 days was noted, and rats were sacrificed at various times after the cecal ligation and puncture to examine the organ histology. The HSP-72 levels increased in the lungs and the heart of heat-treated animals shortly after heat treatment. Animals that underwent cecal ligation and puncture without previous heat treatment had no detectable expression of HSP-72 at any time in the course of their illness. The heat-treated rats had improved mortality, had less organ damage, and had less evidence of acute lung injury.

Interestingly, severe sepsis may be associated with a diminished heat shock response. Lymphocytes obtained from a group of patients with severe sepsis were compared with lymphocytes obtained from critically ill postoperative patients and healthy volunteers [41]. At baseline, all three groups had similar percentages of lymphocytes expressing HSP-70. When the lymphocytes were given an endotoxin challenge, however, the percentage of lymphocytes that expressed HSP-70 was significantly less in the septic group. If patients recovered from severe sepsis, there was an increase in the percentage of their lymphocytes that produced HSP-70 to endotoxin challenge. This may suggest that HSPs modulate the septic response.

There is strong evidence that HSPs have anti-inflammatory roles. *In vitro* studies have shown that the heat shock response reduces levels of TNF-α, IL-1, IL-6, and IL-10 [42]. This effect is not isolated to cell cultures, as it has also been demonstrated in murine models of sepsis [43,44]. The ability of the heat shock response to inhibit a wide array of inflammatory mediators implies that it must modulate the septic response at one or more key regulatory steps. Indeed, recent data has demonstrated that induction of the heat shock response downregulates the activity of NF-κB.

Heat shock response and NF-κB

NF-κB is a nuclear transcription factor that, when activated, binds to DNA promoter regions that encode for the mRNA of numerous inflammatory molecules. The effect of this binding is to enhance the expression of these inflammatory mediators [45]. NF-κB, therefore, is a potent upstream modulator of the proinflammatory response. NF-κB is a dimer composed of two proteins from the ReL family. It is contained in the cytosol of the cell, bound to an inhibitory protein called I-κB. During the process of NF-κB activation, I-κB is phosphorylated by a kinase called IKK [38]. This causes the I-κB to dissociate from NF-κB, uncovering the nuclear translocation signal on the NF-κB dimer. Unbound NF-κB is than able to serve its role as a DNA promoter to enhance the transcription of mRNA, which codes for the inflammatory molecules.

NF-κB activity has been reported to correlate with mortality in septic shock patients. Borher and colleagues followed daily NF-κB activity obtained from nuclear extracts of peripheral blood monocytes. They found that survivors of septic shock, when compared with patients who died, had significantly less increases in their daily NF-κB activity. In fact, all five patients who died had a doubling of their baseline NF-κB activity [46]. In a similar study, Paterson and colleagues showed that there was increased nuclear activity of NF-κB in both monocytes and neutrophils of septic patients when compared with healthy controls [47]. The patients who died from sepsis had increased levels of NF-κB activity in the nucleus of monocytes, as compared with patients who survived sepsis.

The exact mechanism by which hyperthermia, via induction of the heat shock response, appears to modulate the immune response to sepsis is thought to be through inhibition of IKK proteins [45]. As mentioned earlier, IKK has been shown to be an important regulator of NF-κB activity. This protein phosphorylates I-κB and allows the regulatory protein to disassociate from NF-κB, thus allowing NF-κB to migrate into the nucleus of the cell [38,45]. Inhibition of IKK will therefore lead to decreased NF-κB activation and, ultimately, to less downstream proinflammatory cytokine gene expression.

After induction of the heat shock response with TNF-α, human respiratory and alveolar cells had less production of inflammatory cytokines, had less phosphorylated I-κB, had higher total levels of I-κB, and had less IKK activity [48]. Additionally, recent *in vitro* experiments in human endothelial cells have duplicated this work, showing that the heat shock response reduces the activation of IKK, thereby reducing the phosphorylation of the inhibitory protein I-κB and preventing activation of NF-κB [49].

These data, which link fever and heat shock response to inhibition of NF-κB, and thus decreased downstream cytokine production, raise an important question about the wisdom of treating hypothermia in septic patients.

Summary

Fever in the ICU, and especially in patients with sepsis, is extremely common. It occurs from activity of endogenous pyrogens that enhance prostaglandin E_2 production in the pre-optic region of the hypothalamus. Drugs that inhibit COX-2, as well as measures that promote active cooling, are effective at suppressing fever and are frequently used during critically illness. Despite their widespread use, there is data that suggest fever is beneficial to animals with infection, and there is no evidence that treating fever changes mortality. There is theoretical benefit that, through the heat shock response and subsequent reduction of NF-κB, fever may play a protective role in the survival of patients with severe sepsis. In the absence of meaningful evidence for the beneficial effects of fever reduction, the commonplace reduction of fever in critically ill patients must be called into question.

Competing interests

None declared.

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