

**Review Article**

An Evolutionary and Clinical Perspective on the Immunological Role of Fever and the Iatrogenic Induction of Cytokine Storms

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Endogenous, as well as behavioural, hyperthermia has been positively selected during phylogenetic evolution, due to a benefit/risk ratio of at least two orders of magnitude. This theoretical paper concerns the pivotal role of supraphysiological temperature in the deployment of innate and adaptive immune reactions during the resolution of infections. The notion of fever as a *pangermicidal* adaptation stems from a vast amount of scientific literature as well as more than two decades of clinical observations on several thousand tumour-bearing patients (one-third of which were immunosuppressed by previous or concomitant chemotherapeutic treatments). The pharmacological blockade of pyrogenic signals ignites an overcompensation reaction of pyrogen-producing first responder cells, which play synchronous roles in both the induction of fever and the mobilization of lymphocytes. In physiological feedback-regulated mechanisms, blocking primary driving signals results in a compensatory increase of such signals. A degree of cytokine overcompensation almost invariably follows a pharmacological suppression of fever and rarely occurs in well-nourished, non-medicated febrile patients. Evidence is presented that mitigating endogenous hyperthermia worsens outcomes within intensive care units and may probably increase mortality at the population level.

Keywords: Fever, Pyrogens, Innate Immunity, Evolutionary Trade-Off, Biological Feedback, Cytokine Supercompensation, SARS CoV 2, COVID-19**Introduction**

The preservation of an endogenous hyperthermic response to pathogens over thousands of generations and its mechanistic similarity in hundreds of organisms indicates that fever must have conferred a high degree of evolutionary advantage, serving as an intermediate adaptation for survival regardless of its transient detrimental effects on the host [1-3]. In a distinct evolutionary trade-off, fever has become a pangermicidal adaptation for survival, analogous to how humans carrying the sickle cell disease β -globin gene are protected against malaria-causing *Plasmodium falciparum*, albeit at the expense of chronic anaemia [4]. Endothermy and homeothermy, characteristic features of mammals, allow for a core body temperature high enough to

prevent microbial infection without exhausting the energy reserves of the host. Tight hypothalamic regulation balances the cost of excess metabolic expenditure required to sustain body temperature with the increased survival benefit gained by creating a *thermally adverse terrain*, which confers a degree of protection against environmental microbes [5-7]. It has been reported that the number of fungal species that can infect a host declines by 6% for every 1°C (1.8 °F) rise in core body temperature [8].

Fever exerts a systemic, *immunoagonic* influence on the organism of the host. This multifaceted action includes the release of heat-shock proteins (Hsps) involved in the protection of cells against a wide variety of biological stressors and the mobilization of lymphocytes, which in turn release antibodies, sending signals to helper T-cells and engaging in the direct destruction of pathogens. Supraphysiological temperature might be an antimicrobial agent in and of itself. One mechanism involves the direct effects of febrile temperature on the infectious potential

of pathogens [9]. The susceptibility of Gram-negative bacteria to serum-induced lysis is greatly enhanced by hyperthermia [10]. In mammalian cells, temperatures in the range of 40–41°C (104–106 °F) generate a 200-fold reduction in the replication rate of poliovirus [11]. Hyperthermia undoubtedly enhances the effectiveness of the antimicrobial response by strengthening both the innate and adaptive arms of the Immune System. The multifaceted interleukin 6 (IL-6) and other endogenous pyrogens such as Tumour Necrosis Factor (TNF), interleukin-1 (IL-1) and interferons induce fever upon the detection of invading pathogens by acting as a modulatory signal to the hypothalamus, upregulating the core temperature set point [12]. Physiological reactions such as shivering and vasoconstriction, also contribute to systemically rising temperature, leading to a stronger primary response. Infection-associated anorexia (which drives down circulating blood sugar, therefore diminishing the availability of fermentable substrates to invading bacteria) does not hinder the hyperthermic response and is also uniformly conserved amongst mammals [13].

In theory, the immunological importance of fever is recognized by infectologists, however, the practice of vigorously medicating fever is pervasive amongst physicians and demanded by patients due to the symptomatic relief obtained through pharmacological suppression. The widespread professional aversion to allowing fevers to run their course stems from the possibility (but very low probability) of damage to the Central Nervous System (CNS) in the event of uncontrolled fever-induced convulsions. Statistically, though, susceptibility to febrile seizures amongst non-epileptic adults is extremely rare. Comprehensive and quite robust epidemiological studies place the risk of febrile seizures in the *infantile* population around 0,6% -ranging from 3,5/1000 in Arab countries to 17,4/1000 in the rural USA [14-16]. The risk of convulsive episodes gravitates towards children 6 months to 5 years old and is most often triggered by temperatures surpassing the 38.3 °C threshold, making the risk in the adult population extremely low [17].

Evidence for the evolutionary advantages of endogenous and behavioural hyperthermia

Although unable to generate endogenous heat, ectothermic species ranging from annelids and insects to fish and reptiles, engage in behavioural regulation of inner body temperature under microbial infection [18-20]. Heat-seeking behaviour has been conserved across many taxa even though exposure to sunlight -or moving to warmer waters in the case of fish and amphibians- also implies an increased exposure to predators. Experimental models of fungal, viral, and bacterial infections have shown increased survival rates resulting from moderate fever [21]. In an experimental model employing the Gram-negative bacteria *Aeromonas hydrophila* as an invading pathogen to desert reptiles, preventing *Dipsosaurus dorsalis* iguanas to generate exogenous fever through heat-seeking behaviour decreases their survival rate

by 75% [22]. Hyperthermic strategies have even been described in higher plants, mostly associated with pollinating mechanisms, but also in correlation with injured and infected leaves [23]. Through uncoupling oxidative phosphorylation, thus dissipating the H⁺ redox energy and proton electrochemical gradient ($\Delta\mu\text{H}^+$) as heat, the common bean *Phaseolus vulgaris* rises its temperature by 2 °C following fungal infection by *Colletotrichum lindemuthianum* [24]. Manipulative experiments on *Danio rerio* (zebrafish) further support the thesis of behavioural hyperthermia as a synergic immune response to infection in ectotherms. Zebrafish larvae relocate to their preferred temperature level within a vertical gradient tank, displaying behavioural hyperthermia associated with incremental antiviral mRNA expression when subjected to a double-stranded RNA challenge [25-26]. Blocking behavioural hyperthermia -by not allowing larvae to find the optimal environmental temperature- substantially decreases survival under viral infection.

Several elements of the systemic, non-specific host response to infection, including interferon activity, leukocyte mobility, and lymphocyte transformation, are enhanced by increases in somatic temperature [27]. In poikilotherms, generating higher body temperatures requires considerable energy expenditure, which depletes organic reservoirs, lowering energy availability for other physiological processes (including digestion, locomotion, and foraging, as well as social interaction and mental processing in the case of higher primates and humans). Thermogenesis through uncoupling of the respiratory chain at the mitochondrial level is a costly endeavour. Progressive temperature increases above the homeostatic set point require approximately a 12% enhancement in metabolic rate per 1 °C increment, while rising temperature through shivering demands a several-fold increase in metabolic rate [28,29]. Despite its overall cost, fever has been a wildly successful, persistent antimicrobial adaptation in virtually all higher species.

Interference of antipyretic medications in the interleukin/hypothalamus thermoregulatory feedback loop

The shedding of toxins by invading pathogens -most notably lipopolysaccharides- that act as pyrogenic triggers within the host organism, has been described at length. Sensed primarily by macrophages acting as first responders, white blood cells synthesise and secrete endogenous pyrogens (interleukin-1, interleukin-6, interferon), with multiordinal roles in the biological machinery of vertebrates that are fundamental to the immune response [29]. Endogenous pyrogenic molecules are carried by the blood into the hypothalamic thermoregulatory centre, specifically the *organum vasculosum* within the *lamina terminalis* (OVLT), inducing the synthesis of prostaglandins, with PGE2 as the prominent isoform [30]. Subsequently, prostaglandins raise the thermostatic set point to initiate the febrile response. Besides acting as an endopyrogen, IL-1 induces T-lymphocytes to secrete INF and IL-2, a truly pleiotropic cytokine, which also

helps orchestrate the immune response [31]. The synchronous induction of hyperthermia and lymphocytic activation by the same molecular effectors is strong evidence of an *immunoagonic* role of fever. In a well-understood analogy, the secretion of prolactin in the anterior hypophysis simultaneously increases lactation and depresses ovulation. In this manner, blocking fertilization for the length of the neonatal period -therefore preserving nutrients-enhances the probability of survival of the lactating offspring. Finally, hyperthermia exerts a degree of inhibition over bacterial growth while enhancing the germicidal capabilities of neutrophils, increasing the synthesis of acute-phase reaction molecules, and, more broadly, redirecting physiology towards the alarm phase of the General Adaptation Syndrome [32].

On the iatrogenic induction of cytokine “storms”

In the last decade, due to our involvement with hyperthermic and metabolic interventions in the adjuvant treatment of solid tumours, our group has developed an awareness that, in the case of viral infections, inflammatory overreactions manifest almost exclusively as a consequence of sustained antipyretic treatment in poorly nourished patients [33]. Understandably, fear of damage to the CNS has blindfolded modern physicians from the many benefits of fever. In addition to suppressing a powerful, evolutionary-designed immune response, the problem with mitigating fever is that a pharmacological blockade of the pyrogenic signals ascending towards the hypothalamus intensifies the release of pyrogenic/inflammatory cytokines in an escalating attempt to raise the core temperature to an optimal germicidal range [34-35]. It has been our experience, based on a large number of observations, that cytokine supercompensation almost invariably follows a pharmacological suppression of fever and rarely, if ever, occurs in non-medicated febrile patients. In physiological feedback-regulated mechanisms, blocking primary driving signals results in a compensatory increase of such signals [36]. A preclinical model using rabbits infected with rinderpest virus showed that suppression of fever with acetylsalicylic acid (ASA) had a markedly deleterious effect on the course of infection, increasing mortality, rising viral load in the mesenteric lymph nodes, and retarding recovery amongst the experimental animals that did manage to survive the induced infection [37]. At the same time, the antipyretic treatment resulted in *higher serum interferon levels* in the early phase of infection, also pointing at a supercompensatory release of pyrogenic messengers. A randomized control trial on the use of acetaminophen (paracetamol) in the treatment of PCR-confirmed influenza in humans, found no effect on viral shedding or clinical outcomes [38]. Incidentally, improper use and/or self-medicating with acetaminophen -a notoriously hepatotoxic drug-is responsible for around 50% of acute liver failures every year in developed countries [39-40].

At the population level, the use of antipyretic drugs to curb fever correlates to a 5% increase in mortality in large human groups infected with the influenza virus while negatively affecting patient outcomes in the intensive care unit [41]. Several randomized controlled clinical trials have shown that aggressively medicating fever in critically ill patients may lead to a higher mortality rate, especially in cases of sepsis [42-44]. In a particularly large study involving 8,711 ICU patients requiring mechanical ventilation, the authors concluded that the use of antipyretic therapy is associated with an increased risk of mortality (OR: 1.41, 95% CI: 1.20-1.66, $p < 0.001$) and that external cooling may even be deleterious [45]. Clinicians should bear in mind that, within the febrile range of 37.5 °C to 40 °C, hyperthermia becomes a biological response modifier phylogenetically selected towards an enhancement of the innate immune response.

Evidence points towards a complex reciprocal regulation connecting the inflammatory and heat shock response pathways [46]. The hyperthermic state provides a most needed -and relied upon- activation to the heat shock response pathway, altering cytokine gene expression, cellular signalling, and immune cell mobilisation to infected/injured loci. Pointing in the same direction, it has been found that the proinflammatory agonist Toll-like receptor (TLRs) alters the transcriptional programme induced by thermal stress along with HSPs gene expression following co-exposure to infection and heat shock [47].

Closely related to the phenomenon of fever and acute-phase reactions, there has been increasing interest in the clinical observation that viral infections can, on occasion, generate an intense uncontrolled inflammatory response, dubbed cytokine “storm” [48]. The popular moniker, divulged in connection with the 2005 H5N1 influenza virus, resonated with health professionals and the public alike, cementing the perception of inflammatory overreactions as an unavoidable component of microbial infections [49]. This is not the case, however, in properly nourished, unencumbered hyperthermic patients. In fact, a high percentage of individuals that have experienced “silent” SARS-CoV 2 infections, with roughly the same viral load as acutely ill patients, developed either mild or no signs of inflammation [50-51]. A review of the prevalence of asymptomatic infections recorded in 16 separate studies, found silent cases ranging from 43% in Iceland residents (n=13,080) to as high as 96% in several state prison inmates from the USA (n=4,693), confirming this concept [52]. Transcriptomic profiling of SARS-CoV 2 infected patients presenting with either fever, no fever, or requiring supplemental oxygen, showed a strong inverse correlation between hyperthermia and inflammatory signalling, including expression of TLR [53]. As the illness progressed, the researchers found that the expression of most of the proinflammatory genes actually lagged behind the nadir of respiratory function (on day 5), reaching its

peak around the sixth day. Interleukins, tumour necrosis factor, and interferon alfa-1 were either expressed within the range of healthy controls or were induced only *after* O₂ saturation nadir. Unsurprisingly, it has also been reported that afebrile patients with severe acute respiratory syndrome coronavirus infection have a longer viral positivity duration [54].

The nexus between micronutritional status and immunocompetence is well established, and several recent studies on Covid-19 have demonstrated that both time-of-diagnosis vitamin D levels and post-diagnostic supplementation are highly correlated with the severity of illness and mortality [55-59]. Adequate levels of 25-OH-D, ascorbate, and zinc are now unequivocally proven to decrease infectious morbidity and mortality regarding viral/bacterial pathogens, including SARS-CoV 2 [60-62]. In close connection with cytokine supercompensation in Covid-19, vitamin D levels are increasingly seen as a decisive factor in mortality [63]. More than 40 studies have reported a strong inverse correlation between 25-OH-vitamin D and Covid-19 morbidity and fatality rates, with over 90% of critically ill/diseased patients found to be grossly deficient in it (< 10ng/ml) [64]. Inflammatory reactions are a natural and indispensable part of the immune response against microbial pathogens and, provided no pharmacological suppression of hyperthermia is enforced and an adequate nutritional status is preserved, no cytokine overcompensation is to be expected.

Discussion

Aggressively treating fever in critically ill patients seems to lead to a higher mortality rate. Mitigating the concomitant symptoms of an active infection -which in itself doesn't improve clinical outcomes and might indeed worsen the case- allows for higher circulation of asymptomatic but nonetheless infectious hosts within their community [41]. Pharmacological disruption of fever may increase the transmission rate (R_0) of the incumbent pathogens. A higher R_0 implies that larger segments of the susceptible population will contract the pathogen, meaning that these pervasive, protocol-driven antipyretic interventions are likely to lead to increased morbidity and mortality relative to untreated populations [65].

Considering the vast expanse of the evolution of vertebrates, the appearance of antipyretic medication is negligibly recent, having no bearing on the survival of our species. Given the fact that hominids have survived (and succumbed to) innumerable infections -undergoing a strong selection towards fever and inflammation over the last 60 million years-, it is highly improbable that many humans exist today who do not benefit from hyperthermia. However, host susceptibility does vary within the human population and may indeed increase mortality in undernourished individuals suffering from advanced infections [66]. It has been elucidated that a small percentage of the population exhibit single nucleotide polymorphisms (SNPs) that render them prone

to inflammatory overreactions. In particular, polymorphisms affecting TLR-mediated responses seem to predispose their carriers to inflammatory overreactions in the event of microbial infections, worsening clinical outcomes. In two control studies, hospitalized septic patients carrying a *TLRI-7202G* polymorphism had worse organ dysfunction and death outcomes (OR: 1.82 and 3.84, respectively) than matching controls [67]. These outcomes indicate that the existence of hypermorphic variation in the *TLRI* gene is associated with increased susceptibility to organ dysfunction and mortality in hospitalized septic patients, *i.e.*, subjected by protocol to vigorous antipyretic interventions, potentially disruptive to the immune response.

All the potential risks associated with uncontrolled high fever are well understood, as are the benefits of its non-pharmaceutical management, such as cooling the head, which in fact has been the way humans have dealt with high temperatures for at least five thousand years. Although the negative effect of fever suppression has been observed both in individual clinical outcomes and at the population level, fever is not universally beneficial. Individuals with a recent history of cardiac arrest, traumatic brain injury, or cerebrovascular accidents are prone to be negatively affected by uncontrolled high temperatures. Uncontrolled hyperthermia has been linked to worse outcomes in patients with CNS injury or advanced sepsis [68], while an adaptation consisting of endogenously depressing core temperature has evolved in higher species to deal with extreme inflammation [69-71]. After a major brain injury, CNS temperature is often higher than -and can vary independently of- systemic temperature. Following traumatic brain injury, subarachnoid haemorrhage, or stroke, the CNS becomes acutely sensitive to temperature variations and, to a certain extent, even thermolabile [72-73]. The many benefits of endogenous hyperthermia are therefore not applicable in the above-described instances.

In the case of susceptible children, febrigenic seizures tend to occur within the first 24 hours since the onset of the infection, with a core temperature of 38.3 °C being regarded as a threshold [74]. Lower fevers represent a much lesser risk. Upper airway viral infections, otitis, and bacterial comorbidities are considered the main triggering factors. Frequently, infantile febrile seizures have a spontaneous resolution and quickly respond to physical interventions such as placing ice packs on the head and armpits, not requiring any drug treatment [75-77]. Discerning physicians may easily take preventing and/or corrective measures in such cases while allowing the adult population to benefit from their immune-boosting fevers.

Conclusions

The scientific literature shows overwhelming evidence of the pivotal role of fever -a *pangermicidal* adaptive tool conserved across virtually all species- in the deployment of both the innate and

adaptive immune response. The fact that endogenous/behavioural hyperthermia has been selected throughout vertebrate evolution along 6×10^8 years, strongly argues that febrile temperatures confer a survival advantage that far outweighs its metabolic costs. The use of antipyretic drugs intensely interferes with the immune response in all reported experimental models as well as *in Homo*. The pharmacological blockade of pyrogenic signals ascending towards the hypothalamus intensifies the compensatory release of even more pyrogenic/inflammatory cytokines in an attempt to raise the core temperature to the optimal germicidal range. The potential risk of febrile seizures and neuronal damage in the non-epileptic adult population is negligible, while infantile fever-induced convulsions can easily be defused through non-pharmacological interventions.

Funding

All funds required for the research, writing and publication of this paper have been provided entirely by the author.

Conflicts of Interests

As of this writing, the author has no competing interests (directly or indirectly, by ownership or by affiliation) with any brand, company, or institution. No outside contributors had any role in the design, implementation, or analysis of the study or the write-up of this paper.

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