Antipyretic Therapy in Patients with Sepsis

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Sepsis is a clinical syndrome characterized by a systemic inflammatory response to infection. Mortality rates in sepsis have remained high, despite recent advances in our understanding of the immunological mechanisms that cause sepsis. Fever, a nonspecific acute-phase response, has been associated with improved survival and shortened disease duration in some infections. This article reviews the biological effects of fever and the influence of antipyretic therapy on the outcome in sepsis in experimental models and in humans and offers clinical recommendations for antipyretic therapy in early and late stages of the disorder.

Sepsis is a syndrome characterized by a systemic inflammatory response to infection. Mortality rates in human sepsis have remained high (30%–50%), despite heroic efforts to pharmacologically block its suspected mediators. As a result, it remains the leading cause of death in noncoronary intensive care units [1].

In 1991, sepsis and related syndromes were rigorously defined in a consensus conference of the Society of Critical Care Medicine and the American College of Chest Physicians [2], a development signaling an important advance in the study of these disease processes, because it permitted more valid interpretation of the effects of various interventions. The term "systemic inflammatory response syndrome" (SIRS) was introduced to describe a systemic inflammatory state manifested by ≥2 of the following criteria: (1) core temperature >38°C or <36°C; (2) heart rate >90 beats/min; (3) respiratory rate >20 breaths/min or $PaCO_2$ >32 mm Hg; and (4) WBC count >12,000 or <4000 cells/mm³ blood or >10% immature forms. Sepsis was defined as SIRS in the setting of a documented infection. When accompanied by dysfunction of ≥2 organ systems, sepsis was classified as severe. Septic shock was defined as sepsis accompanied by hypotension refractory to fluid resuscitation.

In an effort to provide a framework to better understand and treat sepsis syndromes, Bone [3] has proposed 3 stages in the development of SIRS. In stage I, there is local release of cytokines that regulate the local inflammatory responses and promote wound healing. In stage II, small quantities of these same cytokines are released into the circulation and elicit a systemic response that enhances local resistance to infection. In stage III, normal regulation of the systemic response is replaced by a massive systemic reaction with the activation of a number of potentially destructive humoral cascades, activation of cytolytic effector cells, and diffuse host tissue injury.

Approximately 90% of patients with severe sepsis are febrile [4–6], whereas many of the remainder are hypothermic (core temperature ≤35.5°C). Considerable data suggest that fever is an adaptive response [7]. However, its role in the pathophysiology of sepsis is uncertain. Although antipyretic therapy is commonly administered to septic patients, there are few data to support this practice. In 1 large prospective, blinded, placebo-controlled study, ibuprofen therapy did not improve survival in patients with sepsis, although it caused reductions in both body temperature and metabolic rate [6]. Ibuprofen, however, has many biological effects other than antipyresis that might also modify the course of sepsis (principally the inhibition of prostaglandin and thromboxane synthesis). Consequently, the results of this study must be interpreted with caution. It was the anti-inflammatory properties of ibuprofen, rather than its antipyretic actions, that formed the theoretical basis for the study. Moreover, because 44% of the patients in the placebo group and 22% of those in the ibuprofen group received acetaminophen, the role of ibuprofen as an antipyretic agent in the outcome of sepsis cannot be determined from this investigation.

To our knowledge, there have been no other prospective controlled studies of antipyretic therapy in human sepsis. Only 2 retrospective, chart reviews have been published. In these surveys, administration of acetaminophen, an antipyretic with weak anti-inflammatory activity, was an independent predictor of survival in patients with *Escherichia coli* bacteremia [8] and *Pseudomonas aeruginosa* sepsis [9]; however, in these studies, use of acetaminophen and improvement in survival were not correlated with reductions in core temperature.

Lacking definitive clinical studies of the effect of antipyretic therapy on the outcome of sepsis, one must turn to studies of the effect of fever itself on sepsis. Many studies suggest that fever's effect is beneficial and, by extrapolation, that suppression of fever might be detrimental in infected patients. For example, a survey of elderly patients with community-acquired pneumonia documented a mortality rate of 29% in patients with neither fever nor leukocytosis, compared with only 4% in

those exhibiting temperatures >37.8°C and circulating leukocyte counts >10,000 cells/mm^3 [10]. Fever has also been reported to be associated with improved survival in patients with spontaneous bacterial peritonitis [11, 12], polymicrobial sepsis [13], *E. coli* bacteremia [8], and *P. aeruginosa* sepsis [9].

By contrast, several retrospective studies have shown that human survival during serious infections is reduced in the face of hypothermia (core temperature <35.5°C) [4–6, 14] or a failure to generate a fever, which is defined as a core temperature >38.3°C. In 3 recent prospective studies of sepsis, hypothermia was present in ∼10% of patients surveyed and was associated with ⩾2-fold higher mortality than that of febrile patients [4–6]. In a large prospective study of ibuprofen treatment in sepsis, mortality in the patients receiving placebo was 90% when hypothermia was present, compared with only 35% in the febrile patients [6].

Unfortunately, these observational studies are of limited value in assessing the role of elevations of core temperature, because the underlying illnesses themselves might dictate both a weak febrile response and a low survival rate. Studies that use experimental fever models are also fraught with confounding variables that complicate interpretation of their results. In most of these studies, core temperatures were manipulated by externally warming or cooling the animals, thereby bypassing the normal mechanisms responsible for generating fever. Therefore, one should exercise caution in applying the results of these studies to the febrile patient. One such study found that housing herpesvirus-infected mice at 38°C for 6 days increased their core temperature (by ∼2°C) and survival rate (0%–85%), compared with that of mice maintained at 23°C–26°C [15]. Bell and Moore [16] reported a similar survival benefit of warming mice infected with rabies virus. Increasing core temperature to the febrile range has also been associated with increased survival rates in experimental bacterial infections. In an experimental model using the ectothermic lizard *Diposaurus dorsalis,* Kluger et al. [16–22] showed a direct correlation between the animal's ability to resist infection after subdermal inoculation with *Aeromonas hydrophilia* and increases in body temperature within its physiological range. The improved survival in the warmer animals was associated with a greater neutrophil infiltration at the inoculation site [23]. A similar relationship has been observed in a mouse bacterial peritonitis model [24]. In this study, mice infected intraperitoneally with *Klebsiela pneumoniae,* the survival rate improved from 0% to 50%, and the ip bacterial load decreased 100,000-fold when core temperatures increased from basal (36.5°C–37°C) to febrile (39°C–39.5°C) levels by housing mice at 35.5°C. In rabbits infected with pneumococcus, bacteremia has been shown to clear more rapidly in the presence of hyperthermia but was also associated with a modestly higher mortality [25].

In several other animal models, administration of antipyretic agents have been associated with reduce survival [26–29] during bacterial infections. Interestingly, when sodium salicylate was administered to infected lizards, heat-seeking behavior was abolished, and survival was reduced [17]. Such data raise further questions about the validity of retrospective studies that suggest a beneficial effect of antipyretic agents on the outcome of sepsis in humans [8, 9].

Published investigations of the influence of body temperature on host immunological responses are difficult to interpret for several reasons. The temperature ranges studied in experimental models have varied. Moreover, many models have used external heat to raise the body temperature of experimental animals. In some studies, the temperatures reached have been more typical of heat shock than of fever. Although the study of classic heat-shock temperatures may be relevant to heatstroke, the core temperatures attained in these experimental models have frequently exceeded the febrile range observed during infections. Some models have used high doses of bacterial endotoxin or proinflammatory cytokines that induce responses more closely modeling late (stage III) sepsis, whereas models that use challenges with small inocula of viable pathogens have more closely resembled earlier stages (stages I–II) of sepsis. These parameters must be considered when extrapolating from the results of such experimental studies to clinical disease. For example, our own laboratory found that increasing murine core temperature from 37°C to 40°C by external warming for 6 h increased peak plasma TNF-α levels by 13-fold (figure 1*A*), failed to improve survival rate, and tended to shorten survival time (figure 1*B*) in mice challenged with an LD$_{75}$ dose of lipopolysaccharide (LPS) [30, 31], but increasing core temperature to 39.5°C reduced plasma TNF-α levels (figure 1*C*) and significantly improved survival rate (figure 1*D*) in mice with experimental *Klebsiella pneumoniae* peritonitis [24].

Both potentially beneficial and detrimental effects of fever on components of the immune response have been reported [reviewed in 7, 32]. Human polymorphonuclear cell (PMN) motility [33, 34] and phagocytosis [35, 36] are potentiated at febrile temperatures in several models, although PMN chemotaxis is not enhanced, and bactericidal capacity is only weakly and inconsistently enhanced by exposure to febrile temperature [37, 38]. In contrast with the potentiation of antimicrobial functions at febrile temperatures, exposure to temperatures above the usual human febrile range (41°C–45°C) has been shown to reduce bacterial phagocytosis and killing [35, 38–41], which suggests that any enhancement of relevant PMN functions during fever might be lost if body temperature exceeds the usual febrile range.

Several macrophage functions have also been reported to be enhanced at febrile range temperatures, including expression of Fc receptors, phagocytosis, pinocytosis, reduction of nitro blue tetrazolium [42, 43], and killing of intracellular bacteria [44]. Like PMNs, macrophages, however, have markedly reduced function at temperatures >41°C [42, 43, 45]. By contrast, the cytotoxic activity of human natural killer (NK) cells has been shown to be reduced at temperatures within the usual febrile
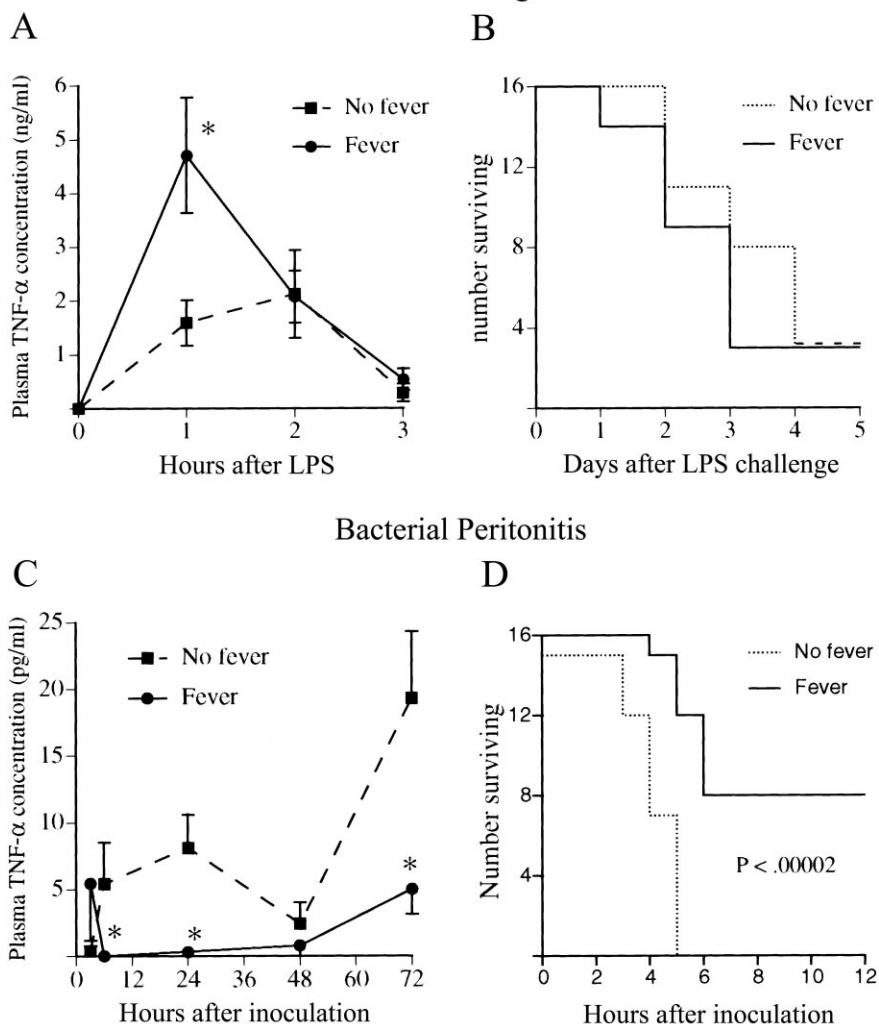
LPS challenge

Figure 1. Influence of the experimental model on effects of febrile-range core temperature on survival and expression of TNF-α. Effect of increasing core temperature to febrile levels on plasma TNF-α levels *(A and C)* and survival *(B and D)* in mice challenged with an LD_{75} dose (50 μg) of lipopolysaccharide (LPS) *(A and B)* or infected intraperitoneally with an LD_{100} inoculum of *Klebsiela pneumoniae*. Data are mean $\pm$ SE of 6 *(A)* or 8 *(C)* mice. LPS-challenged mice *(A and B)* were warmed to 40°C core temperature by anesthetizing with tribroimoethanol and by immersing in water baths for $\leq$6 h. *K. pneumoniae*–infected mice were warmed to 39.5°C core temperature by housing at 39.5°C for 3 days. *$P < .05$ vs. mice without fever. *A* and *B* modified from Jiang et al. [32]; *C* and *D* reprinted from Jiang et al. [26] with permission.

range [46–48], which demonstrates that the effects of fever on immune function might be cell specific.

Exposing human lymphocytes to febrile-range temperatures (38°C–41°C) in vitro enhances their L-selectin–mediated binding to lymphatic endothelium [49], an important early step in lymphocyte recruitment. Several groups have shown that exposing T lymphocytes to febrile temperatures also enhances their proliferative response to nonspecific mitogens [37, 50–52], allogeneic lymphocytes [53] , IL–1, and IL-2 [54, 55]. However, like PMNs and macrophages, T lymphocytes exhibit a reduced proliferative response when exposed to temperatures $\geq$41°C [55, 56]. In mice, T helper cell potentiation of the B cell antibody response [57–59] and the generation of cytotoxic T lymphocytes to allogeneic cells [53] and virus-infected cells [60, 61] are also enhanced by early exposure to febrile temperatures. Together,

these studies indicate that T lymphocyte recruitment, activation, and expression of helper and cytotoxic functions might be enhanced by the increases in temperature that occur during fever.

Antimicrobial defenses are orchestrated, at least in part, by a structurally and functionally diverse group of proteins called cytokines. Such cytokines have complex biological activities, sometimes overlapping and sometimes antagonistic, which influence immune cell functions. Some cytokines, notably IL-1, TNF-α, and IFNs, are required for optimal host defense [62–64] and yet, when dysregulated, appear to participate in the pathogenesis of sepsis [65]. The net effect of these cytokines on survival during sepsis is determined by the magnitude, timing, and pattern of their collective expression. For example, coadministration of IL-1β [66] or IFN-γ [67] enhances the lethal

the magnitude of the increase in temperature, and the stimulus used to induce IFN production. Incubating human peripheral blood mononuclear cells (PBMC) at febrile-range temperatures reduces IFN-γ in LPS-stimulated cells [74] but not in mitogen-stimulated cells [75]. Exposing PBMC to temperatures in the upper end of the febrile range reduces generation of IFN-γ in mitogen-stimulated, but not in influenza virus-infected, cells [76]. By contrast, increasing core temperature of humans and monkeys to febrile levels before collecting PBMC increased
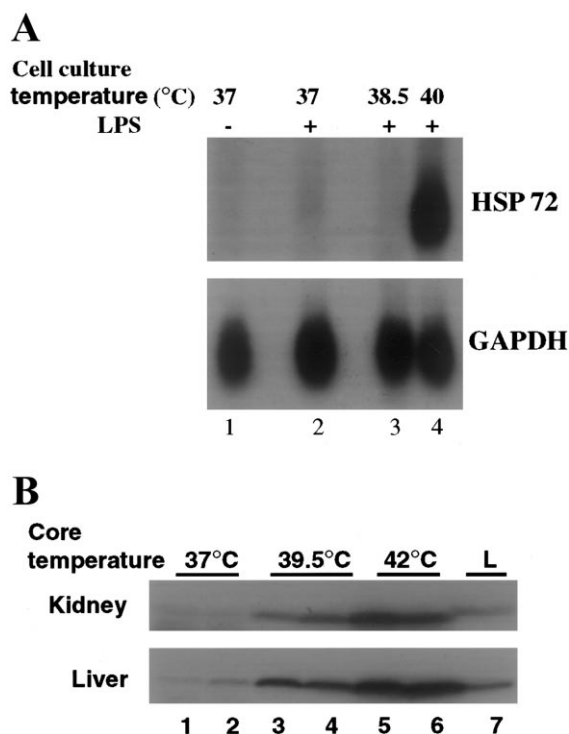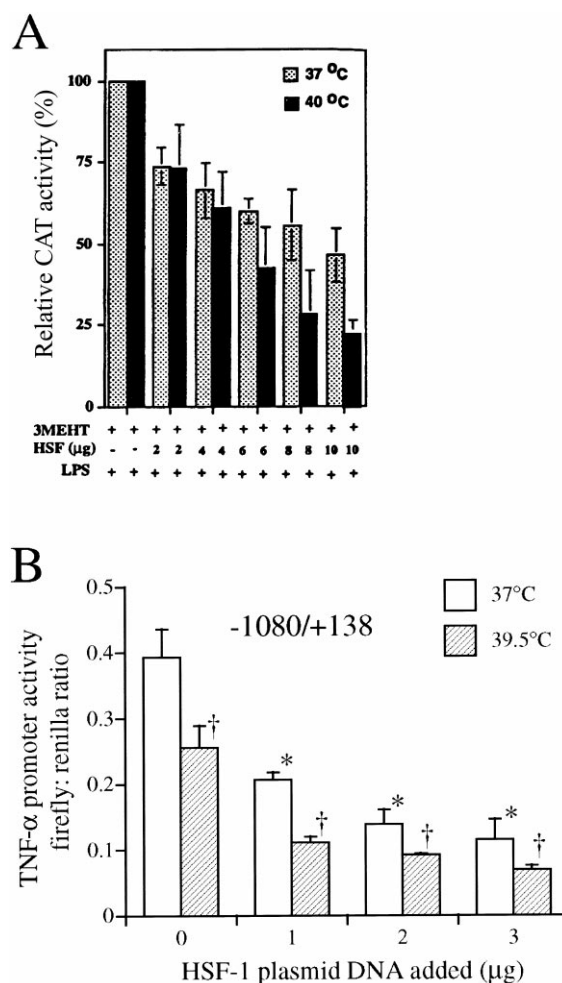

Figure 2. Heat shock protein (HSP) 72 expression in human macrophages and mouse tissues after exposure to febrile temperatures. *A,* Human monocyte–derived macrophages, which were preincubated at the indicated temperature for 30 min and then were stimulated with *Esherichia coli* lipopolysaccharide (LPS; 0.5 μg/mL) for 4 h. Total RNA was isolated, and levels of HSP72 mRNA were analyzed by Northern blotting and were compared with expression of the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA. *B,* Pairs of mice, which were maintained at 37°C *(lanes 1* and *2)* or 40°C core temperature by anesthetizing with tribromoethanol and by immersing in 37°C or 40°C water baths for 3 h *(lanes 3* and *4)*. Mice were allowed to recover for 3 h, were killed, and liver and kidneys were collected, homogenized, and analyzed for HSP72 protein levels by Western blotting. Heat-shocked control mice were exposed to 42°C for 20 min and were killed 6 h later *(lanes 5* and *6)*. "L" *(lane 7)* denotes a positive control prepared from heat-shocked murine L929 cells (42°C for 90 min and then 37°C for 18 h). *A* modified from Ensor et al. [71]; *B* reprinted from Jiang et al. [33] with permission.

effects of TNF-α in experimental animals. A growing body of literature has shown that expression of these cytokines is influenced by body temperature, but these effects are complex and are influenced by the magnitude and timing of changes in temperature and by the cytokine-producing cells studied. Early exposure to temperatures within, as well as above, the usual febrile range attenuates TNF-α and IL-1ß expression by human and murine macrophages [30, 68–72], whereas delayed exposure to supraphysiologic temperatures (42°C–43°C) enhances TNF-α release [68, 73].

The direct effects of elevated temperature on IFN generation are variable and appear to depend on the type of IFN studied,

Figure 3. Inhibition of in vitro IL-1β and TNF-α promoter activity during overexpression of heat shock factor (HSF)–1. *A,* THP-1 promonocyte cell line, which was transiently transfected with a chloramphenicol acetyltransferase (CAT) reporter construct driven by the human IL-1β promoter (3MEHT) and increasing concentrations of an HSF-1 expression plasmid. Transfectants were stimulated with lipopolysaccharide (LPS) for 24 h at either 37°C or 40°C, and CAT activity was measured. *B,* Raw 264.7 mouse macrophages, which were transiently transfected with a luciferase reporter construct driven by the mouse TNF-α promoter and increasing concentrations of an HSF-1 expression plasmid. Transfectants were stimulated with LPS for 5 h at either 37°C or 40°C, and luciferase activity was measured. *A* reprinted from Cahill et al. [96]; *B* modified from Singh et al. [95].
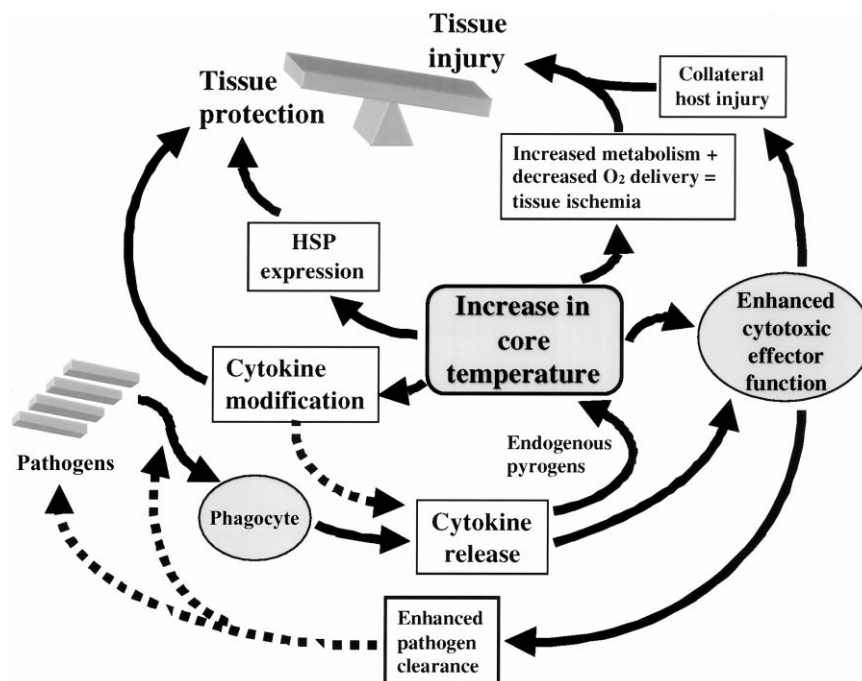
Figure 4. Proposed mechanism for protective and detrimental effects of fever in sepsis. Dashed line indicates inhibitory effect. HSP, heat shock protein.

their capacity for generating IFN-γ after stimulation with phytohemagglutinin in vitro [77, 78].

In mice, warming to core temperatures within the febrile range has a beneficial effect on experimental *Klebsiella pneumiae* peritonitis, which is associated with suppressed systemic expression of TNF-α and delayed appearance of circulating IFN-γ [24]. Meanwhile, coexpressioin of TNF-α and IFN-γ is enhanced within the infected peritoneal compartment in the same animals. The former effect might contribute to the enhanced survival of febrile animals by reducing systemic toxicity [67] whereas the latter effect might contribute by enhancing antimicrobial defenses in the infected peritoneal compartment [79].

Febrile temperatures appear to influence the biological activities of cytokines, as well as their expression. Increases in temperature within the febrile range have been shown to enhance the cytotoxity of human TNF-α [80–82], increase the thymocyte comitogen activity of murine and rabbit IL-1 [83, 84], increase the antiviral, antiproliferative, and NK cell–stimulating activities of human and murine IFNs [48, 85, 86], and potentiate IFN-induced generation of anergy in mice [87].

A common rationale for reducing fever is to prevent tissue injury caused by elevated core temperatures. This rationale not withstanding, we know of no published reports showing that exposure to temperatures within the usual febrile range is cytotoxic. On the contrary, exposing animals or isolated cells or tissues to supraphysiologic temperatures (42°C–45°C) is pro-

tective in a number of injury models [reviewed in 88, 89], including sepsis [90]. Cytoprotection during heat shock is mediated by 4 families of heat shock proteins (HSPs). The reader is referred to 2 recent reviews for a description of the biological activities of these proteins [91, 92]. Although the human heat shock response is generally thought to be activated by temperatures above the usual human febrile range (42°C–45°C), incubating LPS-stimulated human macrophages at 40°C for 18 h [70] (figure 2*A,* lane 4) or raising core temperature by externally warming LPS-challenged mice from 37° to 39.5°C core temperature for 3 h [31] (figure 2*B,* compare lanes 3 and 4 with heat-shocked controls in lanes 5 and 6) has been shown to induce HSP72 expression. Exposing rat myoblast cultures to 39°C for 24–48 h increases expression of HSP-73 and confers protection against subsequent oxidative injury [93]. Heat shock factor (HSF)–1, the major stress-induced transcription factor for HSP genes, is at least partially activated when Raw 264.7–transformed murine macrophages are exposed to 39.5°C for only 60 min in both the presence and absence of LPS [94]. Interestingly, when overexpressed in macrophages, HSF-1 is a negative regulator of the proinflammatory cytokines IL-1β[95] (figure 3*A*) and TNF-α [94] (figure 3*B*). Although it is clear that HSF activation and HSP expression may modify the host inflammatory response during febrile illnesses, the role of HSPs in infections and sepsis is not yet clear.

Another rationale for blocking fever in the septic patient is

to reduce the metabolic demands of the febrile response. Oxygen consumption increases 20% when core temperature is increased from 38°C to 41°C by externally warming anesthetized, paralyzed dogs [96]. In 12 critically ill patients with fever refractory to acetaminophen, reduction of core temperature from 39.4°C to 37°C by therapeutic paralysis and external cooling has been shown to decrease oxygen consumption by 18% and to reduce carbon dioxide production by 20% and cardiac output by 23% [97]. The host's ability to meet the increased metabolic demands of fever may be limited in sepsis because of disturbances in normal cardiac and pulmonary function. Increases in core temperature also cause a progressive reduction in affinity of hemoglobin for oxygen, which impairs oxygen loading in the lungs and thus may reduce oxygen delivery to tissues. This may, however, be balanced by the enhanced tissue oxygen extraction.

Possible contributions of fever to the outcome of sepsis are summarized in figure 4. The increase in core temperature in response to acute phase cytokines enhances cytotoxic activity of effector cells (e.g., neutrophils and macrophages), leading to more rapid pathogen clearance, but may also increase the risk of collateral host tissue injury. Tissue injury may be further enhanced if the high metabolic demand and limited oxygen delivery leads to tissue ischemia. The collateral tissue injury may be mitigated as a result of expression of HSPs, optimization of proinflammatory cytokine expression, and accelerated elimination of the immunostimulatory pathogens.

It is clear that prospective, placebo-controlled studies of antipyretic therapy in sepsis are needed to develop rational protocols for treating fever in septic patients. On the basis of the available data, we recommend that antipyretic therapy be withheld during the early stages of sepsis and SIRS, unless body temperature exceeds the usual febrile range (>41°C), or the metabolic demands of fever pose a specific risk, such as in patients with severe cardiac or pulmonary dysfunction. Unfortunately, the available data do not allow us to make recommendations regarding antipyretic therapy in severe sepsis at this time.

Acknowledgments

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