Point: Should Antipyretic Therapy Be Given Routinely to Febrile Patients in Septic Shock? Yes

Abbreviations: NSAID = nonsteroidal antiinflammatory drug

Fever is a highly conserved response to infection in animal species. The presence of fever implies immune competence, and although some postulate the ability to mount fever portends survival advantages, the magnitude of fever has been associated with higher mortality in sepsis. Unfortunately, the pathophysiologic derangements accompanying septic shock overcome the protective value of fever, and in some cases fever contributes to a cycle of vasodilatory shock, myocardial dysfunction, and organ failure that precedes death. Critical care physicians should strongly consider external cooling to minimize the harmful effects of fever, especially among the most seriously ill patients. We base this position upon the following arguments:

1. A physiologic rationale exists to support fever therapy;
2. Contradictory conclusions in the literature result primarily from heterogeneity of studies (eg, severity of illness, methods of cooling, and timing of interventions); and
3. The strongest clinical trial supports fever treatment.

Benefits of Fever

Fever intuitively seems like it should have value. For a mechanism that comprises 23% of the metabolic requirement in a critically ill human, it is amazingly prevalent among nonhuman species. Cold-blooded lizards, rabbits, mice, and sheep mount fever, and fever seems important in these animals’ ability to fight infection. The conservation of this response across species suggests a great importance of fever, so impairing natural immune function through antipyretic therapy seems counterintuitive. Several human series have demonstrated faster viral clearance and improved vaccine response in the presence of fever. Febrile-range hyperthermia has been associated with several protective mechanisms, including decreased bacterial replication, increased antimicrobial effects, enhanced immune function, leukocyte activation, negative feedback on proinflammatory cytokines, and increased expression of heat shock protein chaperones.

Risks of Fever

Unfortunately, fever also imparts deleterious physiology. First, fever places an incredibly expensive metabolic load on patients in whom oxygen delivery is already compromised. In a series of 12 critically ill patients, treating fever decreased oxygen consumption, CO₂ production, and energy expenditure. Second, fever has been shown to be a direct depressant of myocardial function, and it contributes to vasodilatory shock. Third, hyperthermia may worsen oxygen exchange in patients with lung injury. Among 27 septic patients with ARDS, PaO₂/FiO₂ was inversely associated with temperature. A subsequent study of mild therapeutic hypothermia in 19 patients with sepsis and ARDS demonstrated that those assigned to hypothermia had improved oxygenation (PaO₂/PaO₂, 0.27 vs 0.15; P < .01) and mortality (67% vs 100%; P < .05) compared with those assigned to normothermia.

Despite decades of looking for a universal survival advantage from withholding antipyretic therapy, convincing evidence has been elusive. Multiple animal studies, observational studies, and seven randomized clinical trials have been performed to evaluate the safety and effectiveness of fever control, with conflicting results. Although most have been underpowered to evaluate clinical outcomes, few have shown clear harm from antipyretic therapy. Yet heterogeneity persists regarding the benefits of fever control. Why do studies disagree on the value of fever control?

Sources of Conflicting Evidence in the Literature

Severity of Illness

The heterogeneous effects of antipyretic therapy are partially a result of variations in severity of illness.
across studies. In a rat model of intraabdominal sepsis, therapeutic hypothermia resulted in an increased survival time and decreased organ injury in those animals with severe septic shock (cecal incision with peritoneal spillage, control group mortality 100%), whereas no such benefit existed for moderately severe septic shock (cecal puncture only with no spillage, control group mortality 67%). Thus, it is quite relevant that of all the clinical trials of fever control, the one that most strongly supports fever control also enrolled the most seriously ill cohort.

External Cooling vs Drug Therapy

The existing literature reports different methods of antipyretic therapy, largely categorized as studies of external cooling or of pharmacologic therapy. The strongest evidence supporting fever control uses external cooling; drug therapy is not as well supported. Many studies used antipyretic medication, but physical cooling allows for temperature control without the potential inhibition of protective inflammatory responses inherent in pharmacologic antipyractics. For example, in febrile rabbits infected with Pasteurella multocida, a sodium salicylate infusion for fever control increased mortality from 29% to 100% (P < .005), whereas physical cooling in a separate model decreased mortality from 90% to 46% (P < .03). The largest human trial examining the use of ibuprofen therapy in sepsis (n = 455) showed no significant difference in mortality (37% vs 40%, P = .56) despite a significant decrease in oxygen consumption and lactate. This study enrolled a cohort that were not as sick (only 64% of patients required vasopressor therapy at study enrollment; mean APACHE II score, 15), but ibuprofen therapy did not show an improvement in survival.

Timing of Treatment

Antipyretic studies start antipyretic therapy at various times in the development of sepsis, with some initiating therapy prior to infection. This also contributes to the heterogeneity of results. Some fever studies prevent fever in patients who are not infected, oftentimes before experimental models of septic shock are induced. These models are likely different from patients with septic shock, who often have had significant fever prior to receiving medical care. Several animal studies illustrate that applying heat stress prior to the experimental induction of life-threatening infection can improve survival. A small trial (N = 82) of febrile trauma patients that randomized primarily noninfected patients to aggressive fever control vs permissive temperature management (using mostly pharmacologic therapy) was stopped at an interim safety analysis because of a significantly higher mortality in the group being aggressively cooled. A randomized trial of preoperative local warming (N = 421) also showed significant protection at preventing wound infections when the operative site was warmed prior to clean surgery. Although these models can teach us about the role of fever in conditioning a host for infection, they do not inform us about patients presenting with septic shock.

Clinical Evidence

The largest clinical trial using external cooling in patients with septic shock supports induced normothermia in septic shock. A recently published French trial randomized 200 febrile patients with septic shock to external cooling (36.5°C to 37°C) vs no cooling for 48 h. The patients studied all had septic shock (median norepinephrine dose in placebo group was 0.65 μg/kg/min), with a placebo group ICU mortality of 43%. External cooling was effective at reducing temperature (P < .01), decreasing vasopressor dose by >50% at 12 h (54% vs 20%, P < .01), and avoiding dialysis (10% vs 21%, P = .03). Most importantly, ICU mortality showed a trend toward benefit with external cooling (35% vs 43%, P = .26). Febrile patients with septic shock should be cooled using external cooling to normothermia to optimize clinical outcome.

Summary

In summary, fever is clearly an important adaptive response to infection. Similar native responses to septic shock include capillary leak, hypotension, myocardial dysfunction, overwhelming inflammatory response, organ failure, and death. For patients with the highest mortality, the benefit of controlling fever outweighs the harm from impairing fever-dependent immune function. Data opposing fever control are drawn primarily from patient populations having lower severity of illness, using drug therapy for antipyresis, or controlling temperature prior to infection. The only quality clinical trial that tests external cooling in patients with septic shock supports fever control for improving resolution from shock and for decreasing mortality. Hyperthermia therapy was popular in the early 20th century as a pre-antibiotic treatment of infection. Is interest in the therapeutic value of fever in critical illness based on clinical data, or do we think that fever is important only because “it must be”? Emerging data are clear—our most seriously ill patients do not tolerate fever well, and we should use temperature management as an additional therapy to optimize sepsis physiology.

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**REFERENCES**


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**Point/Counterpoint Editorials**

**Counterpoint: Should Antipyretic Therapy Be Given Routinely to Febrile Patients in Septic Shock? No**

Fever is a classic symptom of sepsis in critically ill patients and commonly prompts ICU physicians to evaluate for infection. Despite the frequency with which fevers occur in patients in the ICU, there is surprisingly little consistency among intensivists regarding whether fevers should be treated.1 Certainly, there are subsets of critically ill patients—those with neurologic injury or active myocardial ischemia, for example—who are particularly susceptible to the deleterious effects of fever and should undoubtedly receive antipyretic therapy.2 Sepsis, however, is a complex and heterogeneous disease. Although some patients may benefit from the protective effects of fever control, others may not, depending on the severity of their disease and their degree of end-organ dysfunction. Unfortunately, there are few randomized controlled trials to guide clinical practice. Based on the available evidence, though, our opinion is that fever should not routinely be treated in patients with septic shock.

Fever potentially benefits infected patients via multiple mechanisms. In vitro and animal studies have shown that elevated temperatures augment immune function, increase production of protective heat shock proteins, directly inhibit microorganism growth, reduce viral replication, and enhance antibiotic effectiveness.3 However, potential adverse effects exist as well. Proponents of antipyretic therapy contend that fever...