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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.[2] However, potential adverse effects exist as well. Proponents of antipyretic therapy contend that fever

raises the metabolic burden, increases oxygen consumption, and potentiates cardiac dysfunction.[3,4] In patients with septic shock, the relative importance of each of these factors on overall outcome is difficult to predict. Certainly, patients in shock are at highest risk for global hypoperfusion, localized tissue injury, and sepsis-induced cardiomyopathy and, therefore, are potentially the most vulnerable to the detrimental effects of fever on metabolism and hemodynamics. On the other hand, these patients are also the most likely to benefit from improved microbial clearance.

Several observational studies clearly demonstrate that hypothermia is a poor prognostic indicator in critically ill septic patients[5,6] and suggest that fever may, in fact, confer protection.[7,8] For example, in a study of 612 patients with gram-negative bacteremia, increased mortality occurred in those who failed to mount a fever within the first 24 h of infection.[7] Likewise, in a prospective study of adult patients in the ICU with invasive candidiasis, a body temperature of $>38.2°C$ at the onset of infection was an independent predictor of survival.[8] Meanwhile, there is little convincing evidence to indicate fever adversely affects outcomes in septic patients. A few observational studies have associated higher temperatures with increased mortality, but most included mixed samples of infected and noninfected critically ill patients.[9,10] Noninfected patients may be disproportionately harmed by fever because they are less apt to benefit from the positive immunomodulating effects of fever but are still able to suffer the negative metabolic and hemodynamic consequences. Therefore, the results from these studies should not be generalized to septic patients.

Based on these observational studies alone, one could argue that the ability to mount a fever indicates a predisposition for survival in septic patients but that fever itself is inherently harmful and should be treated. Antipyretic therapies, however, are not entirely benign. Adverse effects of the two most common pharmacologic treatments for fever—acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs)—include liver dysfunction, nephrotoxicity, and GI bleeding.[2] Also, external cooling lowers skin temperature considerably more than core temperature, leading to cutaneous vasoconstriction, sympathetic stimulation, and increased shivering. Although this has consistently been shown to increase BP in febrile patients, shivering dramatically increases oxygen consumption and resting energy expenditure, thereby counteracting the metabolic benefit derived from fever reduction.[11] Shivering can be prevented with heavy sedation and/or paralysis, but these interventions have their own undesirable consequences and, in accordance with the 2012 Surviving Sepsis Guidelines, should be minimized in septic patients.[12] Most importantly, fever control may hinder recognition of antibiotic failure or secondary infections and could lead to crucial delays in appropriate antimicrobial treatment.

Unfortunately, there are few well-designed clinical trials examining the effects of antipyretic therapy in critically ill patients. Several investigators have conducted small randomized pilot studies in mixed samples of infected and noninfected febrile patients in the ICU.[13-16] Each differed in terms of the specific interventions applied, the thresholds for fever treatment, and the primary end points measured. None was appropriately powered to identify significant changes in clinically relevant outcomes. However, a meta-analysis of five of these randomized controlled trials concluded that antipyretic therapy had no influence on ICU mortality in febrile critically ill adults.[17]

Even fewer trials have specifically addressed the role of antipyretic therapy in septic patients. A large multicenter prospective observational study assessed the effects of acetaminophen, NSAIDs, and physical cooling on 28-day mortality in critically ill patients.[18] Among the 606 patients with sepsis, multivariate analysis demonstrated that fever control with either NSAIDs or acetaminophen was an independent risk factor for death. Physical cooling was neither protective nor harmful. Bernard et al[19] performed a multicenter randomized controlled trial to examine the effects of IV ibuprofen in critically ill patients with severe sepsis. Body temperature, heart rate, minute ventilation, oxygen consumption, and lactate levels were all significantly decreased in the ibuprofen group compared with the placebo group after 48 h. However, degree of organ failure and 30-day mortality were unchanged. When the subset of patients who met the criteria for septic shock was analyzed separately, differences in mortality remained insignificant. All patients randomized to the treatment group were treated with ibuprofen regardless of the presence or absence of fever, so the direct effect of ibuprofen on fever in septic patients is difficult to ascertain. However, it is important to note that although the physiologic goals of fever control were met in the patients treated with ibuprofen (decreased temperature, heart rate, minute ventilation, and oxygen consumption), this had no effect on clinically significant outcomes.

To date, only one large randomized controlled trial has investigated fever control specifically in patients with septic shock. Schortgen et al[20] randomized 200 vasopressor-dependent febrile patients who were mechanically ventilated to external cooling for 48 h or to no fever control. The cooling group demonstrated significantly decreased vasopressor requirements at 12 h (but not at 48 h) and lower mortality at 14 days

(but not at ICU or hospital discharge). Interestingly, the patients included in the study suffered from particularly severe shock and cardiopulmonary compromise: many required inotropic agents (epinephrine or dobutamine), baseline doses of norepinephrine were extremely high, more than one-half received corticosteroids, and the median PaO_2/FIO_2 was well below 200. These patients, therefore, were those most likely to potentially benefit from the favorable metabolic and hemodynamic effects of fever control; yet still, ICU and hospital mortality were unchanged. The authors reported a trend toward increased nosocomial infections in the cooling group and suggested that this may have contributed to the increased number of later deaths seen in those patients. Additionally, the study had several important limitations—lack of blinding, higher baseline doses of vasopressors in the no-cooling group, and failure to control antipyretic use beyond the 48-h study period—that complicate interpretation of the results.

Thus, no evidence supports routinely treating fever in patients with septic shock. Studies of pharmacologic antipyretics have failed to show any clinical benefit and have even suggested harm.[18] And although external cooling was found to decrease vasopressor requirements and 14-day mortality in one randomized study, it had no effect on long-term mortality.[20] Further studies are needed to determine whether there are certain subsets of septic patients who may derive long-term benefit from the metabolic effects of fever control. Currently, though, we cannot recommend routine antipyretic treatment in all patients with septic shock.

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Rebuttal From Drs Mohr and Doerschug

In their counterpoint editorial, Drs Drewry and Hotchkiss[1] present a well-reasoned argument of why fever may benefit those with life-threatening infections. We agree with several of their points that likely merit little further discussion:

1. Fever is an adaptive response and affords some host protection;
2. Little evidence-based support exists for use of antipyretic medications to improve fever-associated morbidity and/or mortality; and
3. Fever control in life-threatening infection merits further high-quality study.

With respect to the interpretation of existing data on external cooling, however, we must respectfully disagree. Severity of illness and cooling modality are two very important covariates that complicate the association between fever control and outcome. Unfortunately, much of the raw data continue to suffer from significant heterogeneity and insufficient power. Drs Drewry and Hotchkiss appropriately referenced a recent meta-analysis that pooled clinical trials in this area.[2] Although the analysis boasts low statistical heterogeneity, the clinical heterogeneity is significant—the studies use different methods of cooling, durations of therapy, infection status, and follow-up. Interestingly, studies of external cooling showed a trend toward benefit, and studies of pharmacologic cooling showed a trend toward harm.[2] We believe that applying standard pooling procedures to studies with this degree of clinical heterogeneity makes a pooled risk ratio difficult to interpret, and we advocate for considering stratified analysis (Fig 1).[3] Dividing studies by cooling method nearly eliminates the statistical heterogeneity ($I^2 = 0\%$ for each stratum). Additionally, among trials that used antipyretic drug therapy, the pooled relative risk (2.11, 95% CI 0.72-6.20) closely approximates the observational association from a recent multicenter cohort study (acetaminophen OR, 2.05; $P = .028$) that Drs Drewry and Hotchkiss referenced.[4]

Schortgen et al[5] reported significant improvements in hemodynamics and early mortality with cooling. Drs Drewry and Hotchkiss highlight that the effect size was greatest on early mortality and falls with later outcome measures. Because the intervention was time limited (48 h), we find it expected that early outcomes would show the greatest impact. In addition to early survival, however, cooling seemed to attenuate worsening of the Sequential Organ Failure Assessment

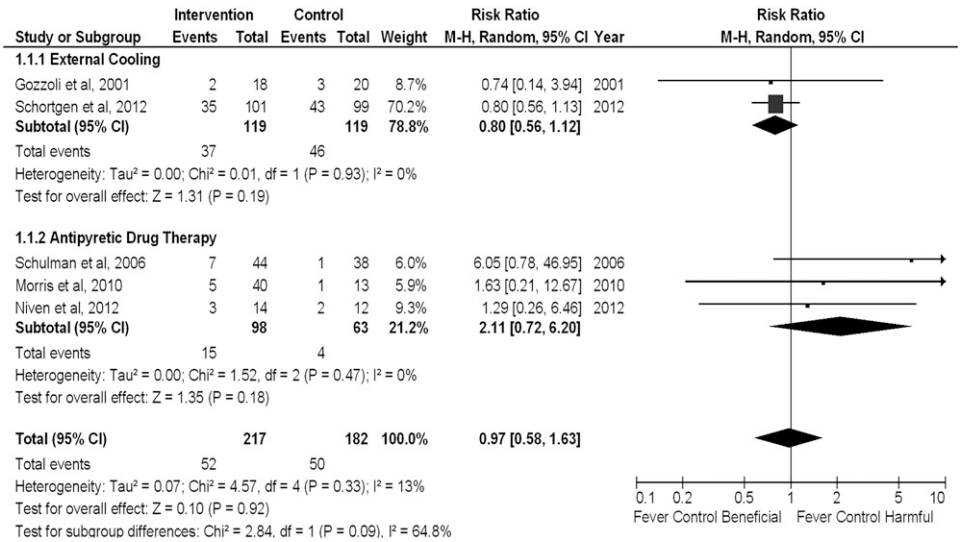

FIGURE 1. Forest plot of risk ratio for ICU mortality among five included randomized controlled trials from a recent meta-analysis, stratified by method of antipyretic therapy.[3] Because the included studies had significant clinical heterogeneity, incorporating a stratified analysis explains most of the statistical heterogeneity. df = degrees of freedom. (Adapted from data published by Niven et al.[2])