Perspective

Fever: suppress or let it ride?

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Abstract: While our ability to detect and manage fever has evolved since its conceptualization in the 5th century BC, controversy remains over the best evidence-based practices regarding if and when to treat this physiologic derangement in the critically ill. There are two basic fields of thought: (I) fever should be suppressed because its metabolic costs outweigh its potential physiologic benefit in an already stressed host; *vs.* (II) fever is a protective adaptive response that should be allowed to run its course under most circumstances. The latter approach, sometime referred to as the "let it ride" philosophy, has been supported by several recent randomized controlled trials like that of Young *et al.* [2015], which are challenging earlier observational studies and may be pushing the pendulum away from the Pavlovian treatment response.

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Historical perspectives and progress

The concept of "fever" has been a major focus of medicine for centuries, and while our ability to detect and manage fever has evolved, controversy remains over the best practices with respect to the treatment of this physiologic derangement. Hippocrates, in the 5th century BC, was perhaps one of the first to understand and characterize fever as part of the immune response (1). Sydenham described fever as "*nature's engine which she brings into the field to remove her enemy*" (2). Several giants in medicine continued attempts to characterize the role of fever in infection over the next twenty centuries such as Galen of Pergamon and Girolamo Fracastoro, but were limited in that their understanding considered fever as a disease in itself rather than a sign of other disease (3). Further impeding the understanding and study of fever was the lack of a reliable and valid measurement tool, which was not widely applied until the 19th century when Karl Wunderlich instituted the use of thermometers and temperature cards to monitor changes in patients over time, therefore incorporating this vital sign into the standard diagnostic algorithm (3).

The next challenge in the characterization of fever was the creation of a uniform definition. Currently, this delineation is still arbitrary and dependent on the purpose for which it is defined. In general, fever is defined as an elevated body temperature above normal variation due to an altered hypothalamic set point. A joint task force from the American College of Critical Care Medicine and the Infectious Diseases Society of America defines fever as a body temperature of 38.3 ℃ (101 ℉) or higher, which is generally accepted as fever for patients in the ICU setting (4).

While it took centuries to reach somewhat of a consensus regarding the characterization and definition of fever, unanimity concerning when and if to treat it in critical care patients is still in its infancy. Complicating this matter is both the heterogeneous etiology of fever as well as practice dogma. While 70% of ICU patients manifest fever, only about 53% are of infectious etiology (5). Despite its source, practitioners often seem to possess an ingrained philosophic opposition towards fever, prompting a knee-jerk response to treat that is not supported by high-level evidence in the ICU population.

Suppress it

In general, two critical assumptions form the basis of the

argument for treating fevers, neither of which have been experimentally validated: (I) fever is noxious, and (II) suppression of fever will reduce its noxious effect (6,7). One condition justifying treatment consideration is when a fever's metabolic cost exceeds its physiologic benefit, but this again, is challenging to quantify (6,8). The only clinical condition with abundant evidence to support aggressive antipyretic treatment is in acute brain injury (9-11). Even the management of febrile seizures in the pediatric population has moved away from antipyretic use as prophylaxis since fever reducing drugs do not reduce seizure recurrence (12,13). Fever reduction via cooling in the ICU setting has been documented in a randomized controlled trial to be of benefit in patients with septic shock leading to a reduction in vasopressor use and mortality (14). Most of the other studies supporting the association of fever with poorer outcomes have been observational in nature (15). In theory, these critically ill patients and those faced with additional physiologic stress may benefit from fever reduction (8), but the evidence on both sides of the argument appears to be mostly equivocal.

Let it ride

Those in the "let it ride" camp advocate that fever is a protective mechanism with benefits ranging from enhancing immune-cell function to promoting antimicrobial activity (16,17). In the past decade several studies have supported this hypothesis. A randomized control trial published by our institution in 2005 sought to evaluate the impact of antipyretic therapy on outcomes in critically ill patients (18). Patients were randomized to an aggressive treatment group, consisting of acetaminophen 650 mg every 6 hours for fever >38.5 ℃ with addition of a cooling blanket for temperature of >39.5 ℃, or a permissive group where treatment was initiated at a temperature of >40 ℃ with acetaminophen and cooling blankets. The study had to be terminated at the interim analysis as there were seven deaths in the aggressive group and only one death in the permissive group. Another randomized controlled trial in critically ill patients without neurotrauma or severe hypoxia also failed to support the treatment of fever showing no significant differences in fever recurrence, infection, antibiotic therapy, ICU and hospital length of stay, or mortality between those receiving external cooling for temperature ≥38.5 ℃ *vs.* no antipyretic treatment (19).

New evidence

Despite this evidence, treatment of fever is common in the ICU setting and likely related to standard dogma rather than evidence-based practice. In this prospective controlled trial by Young *et al.* published in the *NEJM* on December 3, 2015, 700 ICU patients with fever of known or suspected infectious etiology were randomized to receive either 1 g of intravenous acetaminophen or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death (20). The patients in the treatment group did have a statistically, but likely not clinically, relevant lower mean daily average temperature (absolute difference −0.28 ℃, P<0.001). Sustained resolution of fever was also significantly higher in the treatment versus placebo group (22.8% *vs.* 16.9%, P=0.05). The main outcome was ICU-free days until day 28, which was not shown to be decreased in the treatment arm. Secondary outcomes, including 28 and 90-day mortality and ICU and hospital length of stay, were also not significantly different between groups. However, acetaminophen was associated with a shorter ICU stay than placebo among survivors and a longer stay in non-survivors. In terms of adverse events, there was no difference between groups in discontinuation of the drug due to liver dysfunction, and one patient in the placebo group suffered from markedly elevated temperature associated with death. It should be noted that the study population was predominantly non-surgical and that the treatment period was relatively short. More and more high-level randomized controlled trials are supporting the "let it ride" philosophy compared to the original prospective observational studies, which seem to support the opposite.

To treat or not to treat?

Is fever good or bad? Scientifically, we just do not know. However, if we take the evolutionary perspective, then blunting of the adaptive febrile response must be maladaptive. Fever is estimated to be more than 4 million years old and has been documented in the phyla Vertebrata, Arthropoda, and Annelida (7). Despite its long history of study, the exact mechanism of fever and its potentially protective effect is not fully delineated. One could hypothesize that treatment of fever compromises immune competence and renders patients more susceptible

to infection. Take, for example, the classic experiment by Kluger *et al*. in 1981 (21,22). Here, Kluger *et al*. infected cold-blooded iguanas with bacteria. He gave them the opportunity to seek heat via sunlamps and all but one sought the warmth to raise their temperature. The one who did not was the only one who died. Next, he injected the iguanas with bacteria and gave them antipyretics. The iguanas that were able to mount a fever despite the antipyretic were the only ones that survived. This simplistic experiment, in addition to the biologic plausibility for the beneficial effects of fever, now supported by several key randomized controlled trials, suggests maybe the pendulum is due to swing back to a more permissive approach to fever.

While clinicians will likely continue to argue the validity of the proposed adaptive or maladaptive mechanisms of fever, recent studies such as the one by Young *et al*. should support reconsideration of the Pavlovian treatment response to elevated temperature in the critical care setting.

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Footnote

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