Things We Do For No Reason™: Treatment of Infection-Related Fever in Hospitalized Patients

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Inspired by the ABIM Foundation's Choosing Wisely® campaign, the "Things We Do for No Reason™" (TWDFNR) series reviews practices that have become common parts of hospital care but may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent "black and white" conclusions or clinical practice standards but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CLINICAL SCENARIO

The hospitalist admitted a 56-year-old man with hypertension and hyperlipidemia to the general medical unit for community-acquired pneumonia and started him on appropriate antimicrobial therapy. On the evening of admission, the nurse woke the patient to take his vital signs and noted a fever of 39.1°C (102.4°F). The patient had a pulse of 90 beats per minute, normal blood pressure, and a stable supplemental oxygen requirement via nasal cannula. The nurse noted an oral acetaminophen "as needed" order for fever. She woke the patient again to administer acetaminophen and notified the hospitalist.

BACKGROUND

Hospitalists frequently encounter febrile patients. According to one large hospital survey, fever occurs in 25% of pediatric and 31% of adult medical patients.[1] Fever in hospitalized patients most commonly results from infection, but autoimmune disease, malignancy, and an array of other inflammatory conditions cause fevers as well.[1]

Defined as an elevated body temperature resulting from a raised hypothalamic set point[2], hospitalists often treat fever with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). These routinely administered medications act centrally to temporarily lower the hypothalamic set point and relieve fever.[2,3] Standard hospital admission order sets commonly include an as-needed antipyretic every 4 to 6 hours for treatment of fever, regardless of the presence of fever-related symptoms.

Fever is differentiated from hyperthermia, where temperature increases because of dysregulated peripheral processes despite a normal hypothalamic set point.[2] Examples of hyperthermia include heat stroke, malignant hyperthermia, and neuroleptic malignant syndrome. Notably, antipyretic medications have no effect on hyperthermia, but physical means, such as cooling blankets, can lead to temperature reduction.[2]

WHY YOU MIGHT THINK TREATMENT OF INFECTION-RELATED FEVER IS HELPFUL IN HOSPITALIZED PATIENTS

Hospitalists prescribe antipyretic medication to alleviate fever-related symptoms, including headache, chills and sweats, and joint and muscle aches.[3] While researchers have sparingly studied this practice, available evidence and experience suggest that fever-related symptoms decline in parallel with defervescence after administration of acetaminophen or NSAIDs in both adult and pediatric populations.[4,5] One randomized, controlled, double-blind study of nearly 400 adult outpatients in Germany with febrile upper respiratory tract infections showed that both aspirin and acetaminophen bested the placebo in reducing fever and associated headache, achiness, and discomfort over a span of 6 hours.[4] In another study, this time with pediatric patients hospitalized with fever and uncomplicated respiratory tract infections, patients who received acetaminophen had statistically significant improvements in activity, alertness, mood, comfort, appetite, and fluid intake 6 hours after receiving that therapy.[5]

Physicians, nurses, and caregivers also commonly believe that fever is inherently noxious and that treatment of infection-related fever contributes to fighting the infection itself.[2,3,6] The pediatric literature describes parents, caretakers, and clinicians who suffer from "fever phobia," the worry that fevers contribute to long-term neurologic complications, recurrent febrile seizures, and death.[6,7]

Finally, healthcare providers administer antipyretic medication to mitigate the demand fever places on the cardiovascular and pulmonary systems.[3] An elevated temperature increases the body's metabolic rate, oxygen consumption, and cardiac output that critically ill patients who have acute and/or chronic compromise to those systems may not tolerate. For example, patients requiring pressor support for hemodynamic shock or mechanical ventilation for respiratory failure may not tolerate an elevated temperature.[8]

WHY THERE IS NO REASON TO TREAT INFECTION-RELATED FEVER IN ASYMPTOMATIC HOSPITALIZED PATIENTS

Fever serves as an adaptive host response to infection, boosting innate and adaptive immunity in a multitude of ways.[8] In

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animal models, fever slows the replication of pathogenic bacteria and enhances the activity of antibiotic agents.[8] In vitro studies demonstrate that fever increases mobility of leukocytes, phagocytic activity, and proliferation of T cells.[8] Retrospective case-control studies of patients hospitalized with severe bacterial illnesses, including gram-negative bacteremia, spontaneous bacterial peritonitis, and community-acquired pneumonia, found that patients with a documented febrile response had increased survival compared with those who remained afebrile during the infection.[9] In addition, a large retrospective cohort study of septic ICU patients found a progressive decline in mortality in association with increasing peak temperature on the day of ICU admission.[10]

In addition to the above studies supporting the important role of fever in fighting infection, recent evidence definitively demonstrates no mortality or morbidity benefit of using antipyretic medications in infected patients. A 2017 meta-analysis that included eight observational and eight randomized studies, totaling 18,939 adult septic ICU patients, demonstrated no difference in hospital and 28-day mortality in patients treated with antipyretics vs those who were not.[11] The authors again found no mortality benefit with antipyretic use when separately analyzing data from only the randomized controlled trials (1,507 patients) or when stratifying patients based on the type of antipyretic received (acetaminophen, NSAIDs, or physical cooling).[11] They reported no differences in predefined secondary outcomes of shock reversal or nosocomial infections. The authors commented that these robust results likely would not change even with more data from additional trials. In children, a recent meta-analysis of three randomized controlled trials (540 patients) did not find the use of acetaminophen, ibuprofen, or diclofenac effective in preventing febrile seizures.[12] Pediatric practice guidelines consistently recommend using antipyretic medication to alleviate discomfort caused by fever and not solely to reduce temperature.[13,14]

Antipyretic agents interfere with the effectiveness of the body's immune response, as demonstrated in a number of infectious diseases.[2,15-18] Two randomized controlled studies conducted in healthy adult volunteers challenged with rhinovirus reported increased viral shedding and decreased antibody response in those subjects who received aspirin or acetaminophen, compared with those given placebo.[15,16] In another randomized controlled trial conducted in African children with malaria, paracetamol use delayed parasite clearance by 16 hours.[17] A large case-control study correlated the use of NSAIDs with an increased risk of severe skin and soft-tissue complications in children with varicella and in adults with varicella zoster.[18] The international scientific community has raised concerns about worse outcomes with NSAID use in patients with COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); NSAIDs should be avoided in stable patients with COVID-19 until more data are available.[19]

Additional risks and potential harms accompany antipyretic fever therapy. First, NSAIDs or acetaminophen may adversely affect patients with renal or hepatic insufficiency.[2,3] Second, masking fevers may impair the clinician's ability to diagnose or evaluate response to treatment. Third, unnecessarily waking a sleeping patient to check temperature or administer unneeded antipyretics can contribute to hospital-associated problems, including delirium, insomnia, and falls. Treating these iatrogenic problems in turn may require additional medications or interventions. These unintended consequences may potentially prolong hospital stays, increase medication errors and polypharmacy, and detract from a patient's overall healing and recovery.

While the use of antipyretic medications improves fever-related symptoms, it comes at the cost of blunting a protective host response and exposes patients to medication risks without providing a clinical benefit. In sleeping, asymptomatic, or minimally symptomatic hospitalized patients, the risks of administering antipyretic medications clearly outweigh the benefits.

WHEN TREATING FEVER IS INDICATED

Treatment with antipyretic medication can alleviate fever-related symptoms in those patients who have significant headache, body aches, chills, or sweats and in pediatric patients with notable malaise, irritability, or poor oral intake. Debate continues on the use of antipyretics in the ICU setting when managing critically ill patients with severe cardiopulmonary compromise who may not tolerate the additional hemodynamic strain a fever produces (eg, patients with shock requiring vasopressor support or respiratory failure requiring mechanical ventilation). Remember, decrease body temperature in hyperthermia syndromes by physical means.

WHAT WE SHOULD DO INSTEAD

Withhold antipyretic medication (ie, allow permissive fever) in well-appearing general medical patients with asymptomatic infection-related fevers. In patients who tolerate fever with minimal or no symptoms, potential benefits of permissive fever include decreased time to infection resolution and/or decreased risk of hospital-acquired infections. This may result in shorter hospital stays and significant cost savings. If we do not treat patients with asymptomatic fevers, then it follows that we should not check overnight temperatures in hospitalized patients sleeping comfortably.

RECOMMENDATIONS

- Do not order as-needed antipyretic medication for stable patients on general medical units with infection solely to reduce temperature or achieve normothermia.
- Only treat infected febrile patients with antipyretic medications for fever-related symptoms (headache, chills, or body aches or, in pediatric patients, irritability, malaise, or poor oral intake).
- Treat pathologically elevated temperatures (ie, hyperthermia syndromes) with physical measures because antipyretic medications will be ineffective.

CONCLUSIONS

In the clinical scenario, the hospitalist admitted the patient in stable condition for treatment of a community-acquired pneu-

monia. He mounted a febrile response to infection, which suggests that his active immune system may aid in recovery. The nurse noted the fever while the patient slept comfortably without fever-related symptoms.

After discussing these facts with the patient's concerned nurse, the clinician should discontinue the order for as-needed acetaminophen for fever and instead recommend permissive fever without administration of antipyretic medication. This may facilitate recovery, avoid unnecessary polypharmacy, and allow the medical care team to follow his fever curve to ensure that the infection is adequately treated. If the patient develops bothersome fever-related symptoms, the hospitalist can reasonably treat with a single-dose of acetaminophen or NSAID.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason™"? Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason" topics by emailing TWDFNR@hospitalmedicine.org.

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