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**Journal Club Synopsis**  
**Wright State University Emergency Medicine Residency**  
**5 October 2016**

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Faculty Host: James Brown, MD

Resident Discussion Leaders: Robert Nichols, DO and Benjamin Holland, DO

Assisted by: Thomas Dailey, MD and Son Pham, MD

Topic: Treatment of fever in Sepsis, does it help?

Rational for consideration: Sepsis is a frequent syndrome encountered in the emergency department. While most vital sign abnormalities associated with sepsis are aggressively treated using supportive measures or going for the cause of sepsis, there is a common practice of directly lowering the fever using antipyretics. The available medical literature was therefore examined to see if this practice is evidence based, beneficial, and worth continuing.

Clinical Vignette: It's time for the Sunday morning E"C"F patients to begin arriving. Your first such patient is a 58 year old, trach & PEG dependent patient, Mr. Johnson. He's nonverbal and does not really move secondary to a poor neurologic outcome from prolonged cardiac arrest 5 years ago. The ECF sent him in for "fatigue". His usual nurse last saw him well on Thursday, but she's been off and when she came in today, she said he was "different" and sent him to you. His initial vitals are 98/50, 125, 98% on FiO<sub>2</sub> of 0.30 (baseline), RR is at 24, and temp is 39.8/103.6. On exam, he has rhonchorous breath sounds, a small stage 2 clean sacral ulcer, and is otherwise at previously documented baseline for mental status and physical exam. Labs show a white count of 19,000 with bandemia and a lactate of 4.9. He is subsequently diagnosed with a RLL pneumonia. You follow standard sepsis care, and he is fairly fluid responsive: now 116/65 and 110. You page the intensivist. The RN comes you and says "You forgot to give Mr. Johnson Tylenol. I put a verbal order in under your name and I gave 650 mg PR." You then wonder, are antipyretics truly helpful or could they be harmful? What's the evidence to show that we need to treat the fever in sepsis? Could the fever in fact be a physiologic response that we should allow?

Background article: (Gardner J. Is fever after infection part of the illness or the cure? Emerg Nurse. 2012;19:20-5)

This article from 2012 was a decent review of the physiology of fever formation and the pharmacology of antipyretics. It is primarily geared towards inpatient/critical nurses; however, it does still provide a decent overview of the history of treating fever. It concludes that in general fever (38 to 41°C) does not necessarily benefit the patient and that the fever is a normal physiologic response to a bacterial sepsis.

Discussion article one: (Suzuki S, Eastwood GM, Bailey M, et al. Paracetamol therapy and outcome of critically ill patients: a multicenter retrospective observational study. Crit Care. 2015;19:162)

This multicenter retrospective observational study looked at 4 ICUs in Australia and gathered data over about 10 years. Data was only collected on patients that had recorded temperature that received at least 1000mg of paracetamol. These patients were then compared to the patients that did not receive paracetamol with the outcomes of hospital mortality, ICU mortality, and both surgical and medical patients were compared. Overall, the data showed that there was *improved* mortality in patients that *did* receive paracetamol (10% mortality in those receiving and 20% in those who did not). Because the study was not always able to tell who received paracetamol for fever vs for pain, it is possible that some patients may have been well enough (ie awake and off the ventilator) to endorse pain, and therefore received paracetamol for pain instead of fever. This of course would lead to a survivor bias. As with all observational studies, there are other confounding variables (such as therapeutic hypothermia) that may have also played a role in the results. The authors conclude, as did the discussion at the journal club, that while they did demonstrate a strong correlation between antipyretics and decreased survival, an RCT needs to be done to better evaluate this.

Discussion article two: (Young P, Saxena M, Bellomo R, et al. Acetaminophen for Fever in critically Ill Patients with Suspected Infection. N Engl J Med. 2015;373:2215-24)

This very large (23 ICU), multicenter double blinded RCT performed in 2 countries performed over about 17 months. There as a large number of patients involved: 700. All of these adult patients had a temp of >38°C that was assumed to be due to infection that were receiving antibiotics. The intervention group received paracetamol (1000mg every 6 hours) while the control group received normal saline of the same volume. Researchers found that the primary outcome of ICU free days as well as secondary outcomes of mortality, days on the vent, days with pressors, day with dialysis all had no significant difference between the control and intervention group. While the design and the implementation of this study is strong, it is possible that some patients received paracetamol prior to being randomized or after being moved out of the ICU. The discussion at the journal club was that this study certainly did not tip the scale in favor for or against the use of paracetamol.

Discussion article three: (Zhang Z, Chen L, Ni H. Antipyretic therapy in critically ill patients with sepsis: an interaction with body temperature. PLoS One. 2015;10:e0121919)

This retrospective database review was published in March of 2015. The researchers analyzed a database and identified about 15,000 febrile, septic patients. These patients were then analyzed for receiving a treatment meant to decrease body temperature—either external cooling or by an NSAID. The patients were then compared with the primary outcome of ICU discharge of alive or dead. The researchers used a multivariable regression model using body temp and the maximum temp recorded as the continuous variable. The study found that those patients with the highest temps did have an overall higher mortality, but that those that had high temps and received an antipyretic still had a worse outcome than those that did not receive an antipyretic. The researchers did find that use of external cooling had an OR of 1.51 for mortality. At the journal club discussion, the general consensus was that this article was difficult to understand with how the data was provided. As with any retrospective review there is potential for confounding to be given for a reason other than fever and affect the data. While the researchers used this statistical analysis to show that simply treating a fever correlated with worse outcomes, it did not appear to strongly sway the group to stop treating fevers.

Final conclusions from the journal club:

Antipyretics are commonly given in patients who present with a febrile illness. Our journal club attempted to answer the question of whether treating fever in an ill patient actually improved patient outcomes, or should fever be allowed because the elevated body temperature actually improves the function of the immune system.

The only article that we found that recommended allowing fever to go untreated was the Zhang article. This article found there was no difference in mortality between the antipyretic group and the untreated fever group with temperatures < 39 C. However, there did appear to be a higher mortality with treating fever with antipyretics in patients with a temp > 39 C. This would suggest that fever is a natural protective phenomenon, and allowing fever in the critically ill patient actually improves patient outcomes. Our consensus was that further investigation needs to be done, and until these findings are replicated in a peer-reviewed journal, antipyretics can still be given to febrile patients.

As far as affect on practice, the main take away is that aggressively treating the fever with antipyretics has not been definitely shown to help or hurt a patient, although external cooling may be something to reconsider. Therefore, do what appears to be most comfortable and appropriate for the patient; if he or she appears to be uncomfortable or expending excessive energy to mount a fever, consider an antipyretic. If he or she is stable, comfortable, and waiting in the ED for admission, it certainly is not malpractice or abuse to not give an antipyretic.