Should We Treat Fever in Septic Patients?

Key Articles

- *Young P, et al. Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med 2015; 373:2215-24.*
- *Sunden-Cullberg J, et al. Fever in the emergency department predicts survival of patients with severe sepsis and septic shock admitted to the ICU. Crit Care Med 2017 [epub ahead of print]*
- *Drewry AM, et al. Antipyretic therapy in critically ill septic patients: A systematic review and meta-analysis. Crit Care Med 2017; 45:806-813.*

Background

- Occurs in approximately 40% of critically ill septic patients at some point during their ICU stay
- Treating fever is very common in the ED and ICU
    - Recent survey reported that over 80% of clinicians provide antipyretic therapy most or all of the time

Is Fever Beneficial?

- Negative feedback on the release of pyogenic cytokines
- Improved immune cell function
- Inhibit pathogen growth; slows viral replication
- Improved antibiotic activity during fever

Is Fever Harmful?

- Raises the metabolic rate
- Increases oxygen consumption
- May adversely affect cardiac function
- Belief that fever places additional physiologic stress on critically ill patients

Current Literature

- *Young P, et al. Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med 2015; 373:2215-24.*
    - Objective
        - Evaluate the hypothesis that administration of intravenous acetaminophen to treat fever would worsen outcomes
    - Study
        - Prospective, parallel-group, blinded, randomized, controlled trial

        - 23 ICUs in Australia and New Zealand
        - Patients
            - 16 years or older
            - Temperature of 38 C or higher within 12 hours of enrollment
            - Receiving antimicrobial therapy for known or suspected infection
        - Randomized in 1:1 ratio
            - 1 g of intravenous acetaminophen every 6 hours OR
            - Placebo of D5 water
        - Study drug continued until
            - 28 days after enrollment OR
            - Discharge from the ICU
            - Resolution of fever
            - Cessation of antibiotics
            - Death
            - Development of contraindication to study drug
    - Outcomes
        - Primary
            - ICU-free days to 28 days [composite outcome of mortality and ICU LOS]
        - Secondary
            - 28-day and 90-day mortality
            - ICU and hospital LOS
            - Days free from mechanical ventilation, inotropes, vasopressors, RRT
    - Results
        - 700 patients
        - Primary outcome
            - <u>No difference in ICU-free days</u>
                - 23 days in acetaminophen group
                - 22 days in placebo group
        - Secondary outcomes
            - No difference in 28-day and 90-day mortality
            - No difference in ICU or hospital LOS
                - However, acetaminophen associated with longer ICU and hospital LOS in non-survivors
            - No difference in mechanical ventilation, inotropes/vasopressors, or RRT
    - Limitations
        - Composite outcome used
        - Used IV formulation of acetaminophen
        - 1/3rd of patients in each group received acetaminophen after course of study drug

        - Did not collect information about acetaminophen use before randomization or after ICU discharge
        - Findings relevant to early use of acetaminophen to treat fever in ICU
    - **Take Home Point**
        - **Early use of acetaminophen to treat fever in ICU patients with suspected infection does not affect 28-day or 90-day mortality.**

- *Sunden-Cullberg J, et al. Fever in the emergency department predicts survival of patients with severe sepsis and septic shock admitted to the ICU. Crit Care Med 2017 [epub ahead of print]*
    - Objective
        - Assess the prognostic significant of body temperature, measured in the ED, in patients with severe sepsis or septic shock admitted to the ICU within 24 hours of arrival.
    - Study
        - Cohort study of a prospectively complied Swedish national quality sepsis register
            - Adult patients > 17 years
            - Admitted to any of 30 ICUs in Sweden
            - Diagnosis of severe sepsis or septic shock
    - Results
        - 2,225 patients in analysis
            - 750 from 7 tertiary (university) ICUs
            - 1,475 from 23 secondary (county) hospitals
            - In-hospital mortality 24.7% with median LOS of 13 days
        - Admission temperature and mortality
            - 55% of patients had a temp of < 38.3 C
            - 23% had a temp < 37 C
            - On average, crude in-hospital mortality decreased more than 5% per increase of C from 35 C to more than 41 C
            - Mortality fell significantly with increasing temperature
            - LOS of survivors fell with increasing temperature
            - Quality of care (as measured by optimal bundle compliance) improved markedly with rising temperatures – patients with higher temperature received more timely care but this did not affect temperature-mortality association
        - Subgroup analyses
            - Relationship between body temperature and mortality remained unchanged by age, lactate level, bacterial etiology, or bundle achievement
            - No difference in temperature-mortality association between secondary and tertiary hospitals
    - Limitations

        - Temperature measured during variable circumstances – could cause measurement errors
        - Only 58% of patients in registry had complete information on all variables and could be included in final analysis
        - Did not include severity of illness scores
        - Did not contain information on the use of antipyretics or immune-modifying drugs prior to body temperature measurement
    - **Take Home Point**
        - **In this large, multicenter study of patients with severe sepsis and septic shock, there was a strong inverse relationship between increased body temperature and mortality**

- *Drewry AM, et al. Antipyretic therapy in critically ill septic patients: A systematic review and meta-analysis. Crit Care Med 2017; 45:806-813.*
    - Objective
        - Evaluate the effect of antipyretic therapy on mortality in critically ill septic patients.
    - Study
        - Systematic review and meta-analysis
            - Ovid Medline
            - Embase
            - Scopus
            - Cumulative Index of Nursing and Allied Health Literature
            - Cochrane Database
            - Cochrane Central Register of Controlled Trials
            - ClinicalTrials.gov
        - Randomized and observational trials were included
    - Primary outcome
        - 28-day mortality
    - Secondary outcomes
        - "Early" mortality – mortality prior to day 14
        - frequency of nosocomial infections
        - frequency of shock reversal
        - mean changes in heart rate and minute ventilation
    - Results
        - 16 trials included: 8 RCTs, 8 observational
        - RCTs
            - 4 studies (1,198 patients) reported 28-day mortality
                - No difference in mortality
            - 4 studies (1,507 patients) reported hospital mortality
                - No difference in mortality
            - Physical cooling and NSAIDs lowered temp more effectively than acetaminophen

        - Heart rate and minute ventilation were not significantly different between the groups
        - No difference in nosocomial infections or shock reversal
        - No publication bias
    - Observational trials
        - Six trials of high quality; 2 of low quality
        - 6 studies (2,058 patients) reported 28-day mortality
            - No difference in mortality
        - No specific antipyretic method was significantly associated with mortality benefit
        - Publication bias not present
- Limitations
    - Most of studies in this meta-analysis were not designed primarily to evaluate effectiveness of fever treatment
    - Administration of antipyretics was not controlled
    - Studies also varied in terms of specific antipyretic used and duration of treatment
- **Take Home Point**
    - **While associated with lowering body temperature, antipyretic therapy does not confer a 28-day or hospital mortality benefit in septic patients**
    - **Shock reversal and acquisition of nosocomial infections were also unchanged**