

Acetaminophen for febrile patients with suspected infection: potential benefit and further directions

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Fever, increased body temperature, is a physiological expression of the host's response to an infective (1) or non-infective pathology (2-6). Non-infective fever is common in critically ill patients, which includes ones related with post-surgical reaction, acute myocardial infarction, cerebral infarction, cerebral hemorrhage, acute pancreatitis, malignant tumor, post-transfusion reaction, transplant rejection and drug fever. Fever is also common in infective patients. In multicenter observational study, among the patients who developed body temperature equal or more than 38.5 °C, approximately 63% of patients were diagnosed as sepsis (7).

Fever may have detrimental effects such as increasing the oxygen consumption and worsen the neurological outcomes (8-10). Thus, antipyretic treatments are frequently administered in critically ill patients. Among septic patients, at least one antipyretic therapy was prescribed in one-third of patients who developed body temperature between 38.5–39.4 °C, and more than half of patients that body temperature equal or more than 39.5 °C (7). However, high body temperature could be an optimal host response against infectious disease. Fever may result in reduced bacterial growth, promotion of the synthesis of antibodies, and activation of T cells, neutrophils and macrophages (11-13). In this regards, the antipyretics could be either friends or foes in patients with infection. It is unfortunate that the impact of antipyretics in infective patients has been unclear and there are no recommendations for body temperature control for febrile patients with infection (1,14).

One randomized controlled study in 1997, ibuprofen administration (10 mg per kilogram of body weight) significantly decreases fever and oxygen consumption in septic patients. This study did not show any benefit of

ibuprofen on the patients' centered outcome including the incidence of the acute respiratory distress syndrome and mortality (15) (*Table 1*). In this study, 44% of the patients in the placebo arm were received acetaminophen administration and 22% of those in the ibuprofen arm. In this regards, the impact of ibuprofen as an antipyretics on the outcomes in septic patients might not be able to determine in this study (18). However, one may consider that this study might show that the reduction of body temperature to normothermic range (36.5–37.0 °C) may be safe in septic patients.

Another randomized controlled study was conducted to assess the effect of external cooling in 200 febrile adult patients with septic shock who were sedated, required mechanical ventilation and received vasopressor. External cooling for 48 hours was reduced body temperature in the normothermic range (36.5–37.0 °C). External cooling significantly reduced the vasopressor requirement and mortality at 14 days after randomization (16) (*Table 1*). This trial also showed that the acquired infections for 14 days was tended to be increase in cooling arm in compared with non-cooling arm (32.6/1,000 vs. 23.8/1,000 ICU days, $P=0.25$). Then, the mortality benefit observed at Day 14th did not remain at ICU or hospital discharge. The major concerns to apply external cooling in febrile patients were patient's discomfort and potential shivering. To prevent shivering, sedative drugs may be required. We should note that they choose the septic patients who were sedated and required mechanical ventilation.

Although above RCTs reported the lack of adverse effect or potential benefit of lowering body temperature using ibuprofen and external cooling in septic patients, those

Table 1 Large randomised controlled trials to assess the antipyretics in febrile critically ill adults (number of patients in one arm equal or more than 100)

First author, year	Patients	Summary of study
Bernard <i>et al.</i> 1997 (15)	455 patients with sepsis	<p>Antipyretics</p> <p>Intravenous ibuprofen administration (10 mg/kg) every 6 hourly for eight doses (48 hours)</p> <p>Body temperature</p> <p>Ibuprofen administration significantly reduced body temperature</p> <p>Body temperature at 48 hours after randomization was 36.9 °C in ibuprofen group</p> <p>Outcomes</p> <p>Ibuprofen did not change the 30 day mortality</p> <p>Ibuprofen did not alter the incidence shock and ARDS</p> <p>Ibuprofen significantly decreased heart rate, oxygen consumption, serum lactate levels</p> <p>Second infection</p> <p>Second episodes of sepsis occurred in 8.2% in ibuprofen group and 11.1% in placebo group</p> <p>Complications</p> <p>Ibuprofen did not alter the renal function, the incidence of hemodialysis requirement, transfusion requirement and gastrointestinal bleeding</p>
Schortgen <i>et al.</i> 2012 (16)	200 patients with septic shock	<p>Antipyretics</p> <p>External cooling for 48 hours to maintain body temperature between 36.5 and 37 °C</p> <p>Body temperature</p> <p>External cooling significantly reduced body temperature</p> <p>Body temperature at 48 hours after randomization was 36.8 °C in cooling group</p> <p>Outcomes</p> <p>The percentage of patients with a 50% vasopressor dose decrease versus baseline was significantly higher in the cooling group at 12 hours after randomization. This difference was not remains at 48 hours</p> <p>Day-14 mortality was significantly lower in the cooling group. This difference was not remained at ICU and hospital discharge</p> <p>Second infection</p> <p>The density of acquired infections at Day 14 was 32.6/1,000 ICU days in cooling group and 23.8/1,000 ICU days in non-cooling group (P=0.25)</p> <p>Complications</p> <p>No patient developed hypothermia. In the cooling group, two patients with cooling stopped because of shivering</p>
Young <i>et al.</i> 2015 (17)	700 patients with fever and known or suspected infection	<p>Antipyretics</p> <p>1 g of intravenous acetaminophen every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death</p> <p>Body temperature</p> <p>Administration of acetaminophen significantly reduced body temperature</p> <p>Mean body temperature at Day 2 was 36.9 °C in acetaminophen group</p> <p>Outcomes</p> <p>There was no significant between-group difference in number of ICU-free days, 28-day mortality, 90-day mortality, or survival time to Day 90</p> <p>Second infection</p> <p>Not reported</p> <p>Complications</p> <p>The incidence of liver dysfunction led to discontinuation of the study drug was not significantly differed between two groups</p> <p>There was a patient with markedly elevated body temperature associated with death in one patient in control group</p>

of two may not be a major antipyretic used in critically ill patients. The administration of acetaminophen would be common antipyretic in critically ill patients. One retrospective study including 15,818 ICU patients had shown that 64% of study patients received at least 1 g of acetaminophen. And the administration of acetaminophen was independently associated with decreased mortality both in surgical and medical patients (19). However, antipyretic therapy may vary among countries. In a prospective observational study conducted in Korea and Japan including 1,425 critically ill patients had shown that acetaminophen was used in 10.4% of patients (7) and the administration of acetaminophen was independently associated with increased mortality in septic patients. This controversy seen in these two observational studies suggests that there may be major confounders on the association between the acetaminophen administration and mortality. Thus, the randomised controlled trial to assess the impact of acetaminophen in patients with infection was definitely necessary.

Acetaminophen for fever in critically ill patients with suspected infection

Recently, “the Permissive Hyperthermia through Avoidance of Acetaminophen in Known or Suspected Infection in the Intensive Care Unit (HEAT) trial” was published in *New England Journal of Medicine* (17) (Table 1). They included 700 patients with ≥ 38 °C of body temperature and known or suspected infection. Patients were randomly assigned to receive either 1 g of intravenous acetaminophen or placebo every 6 hours. The study drugs were stopped when body temperature was less than 37.5 °C for last 24 hours, antimicrobial treatment was stopped or patients were discharged from ICU discharge. They allowed using the physical cooling at body temperature equal or more than 39.5 °C. They also permit to use the open-label acetaminophen after the administration of study medication. They defined as the primary outcome as ICU-free day at 28 days after randomization.

In HEAT study, study medication was used 8 times in acetaminophen group and 9 times in placebo group. Open-label acetaminophen was administered approximately 30% of patients in each groups. The difference of mean daily peak body temperature in the ICU was -0.25 °C ($P<0.001$). They found that there was trend to increase the ICU-free day at 28 days after randomization in acetaminophen group (median of 23 vs. 22 days, $P=0.07$). They also found that acetaminophen administration increased length of ICU stay

in non-survivors and decreased it in survivors. There was no significant difference of mortality and length of stay both in ICU and hospital. The incidence of liver dysfunction was comparable between two groups.

The HEAT trial asked clinically relevant question and is largest randomized trial in this issue. This trial had planned well (20,21) and performed with excellent concealment and follow up. HEAT trial also had several limitations including high incidence of protocol violation and the use of open-label acetaminophen. Additionally the difference of body temperature between two groups was relatively small, which was maximized at Day 1 (about 0.5 °C difference between two groups), then disappeared after Day 3. This might be due to their protocol for the stop of study drug (they stopped it when patients body temperature was less than 37.5 °C for last 24 hours).

HEAT trial should be a mile stone study on the body temperature control in febrile critically ill patients. However, it is not the end of the story. Future study is necessary to address how long we should use the acetaminophen, how lower we should control body temperature, and what type of patients we should use acetaminophen.

HEAT trial tells us that the use of acetaminophen in infective critically ill patients is safe, but not affect to patients centered outcome. It might not be necessary to treat fever in ALL patients with suspected infection. We afraid that it might be reasonable to use acetaminophen in patients with fever related distress, as such a tachycardia and tachypnea. However, it is also acceptable not to use acetaminophen in patients that fever does not cause any stress response.

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Footnote

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