

# Acetaminophen for fever: treating the patient or the number?

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Article: Acetaminophen for fever in critically ill patients with suspected infection. Published in NEJM December 2015.<sup>[1]</sup>

## Why was this research done?

Acetaminophen is regularly prescribed in patients with fever. It is thought that lowering the patient's temperature is favourable since fever results in extra metabolic demand and physiological stress. On the other hand, fever is also considered to be a protective adaptive response to infection. It has been associated with an improved function of immune cells, inhibition of growth of microorganisms and higher activity of antibiotics.

So far there is no clear evidence for a beneficial or a negative effect of treatment of fever with acetaminophen in critically ill patients with a confirmed or suspected infection. The authors of this paper hypothesised that not treating fever would have a favourable effect and would thus result in more ICU-free days.

## Research question

Is the outcome of critically ill patients with a suspected infection treated with intravenous acetaminophen worse than those treated with placebo?

## How was this investigated?

An investigator-initiated, prospective, blinded, randomised, placebo-controlled trial was performed in 23 adult medical-surgical ICUs in New-Zealand and Australia between February 2013 and August 2014. Patients were included when they were aged 16 years or older, had fever (temperature  $\geq 38$  °C) within 12 hours before inclusion in the study and were receiving antibiotics for a suspected or confirmed infection. Patients with acute brain disorder, liver dysfunction or other contraindications to acetaminophen were excluded.

The primary outcome of this study was the number of ICU-free days, a composite outcome combining mortality and ICU length of stay. Secondary outcomes were all-cause mortality at day 28 and day 90 after inclusion, survival until day 90 and ICU and

hospital length of stay. Furthermore, the number of hospital-free days, days free from mechanical ventilation, days free from inotropes/vasopressors and days free from renal replacement therapy were examined as secondary outcomes.

Seven hundred patients were randomised to receive intravenous acetaminophen 1 g (n=346) or placebo (n=344) every six hours. Study medication was terminated 28 days after enrolment or earlier when a prespecified cessation criterion was met (i.e. discharge from ICU, resolution of fever, cessation of antibiotic treatment, death, or development of a contraindication to the study drug).

## Main conclusions

Early administration of acetaminophen to treat fever in critically ill patients with a suspected infection was not associated with a higher number of ICU-free days to day 28 (median 23 days vs. 22 days in those treated with acetaminophen vs. those treated with placebo, respectively,  $p=0.07$ ). Acetaminophen treatment was associated with a shorter ICU stay among survivors and a longer ICU stay in nonsurvivors compared with placebo. But it did not result in a different (all-cause) mortality at day 28 or day 90 or survival time to day 90.

There was a statistically significantly lower temperature in those patients treated with acetaminophen compared with those treated with placebo. However, the absolute difference was 0.25 °C and 0.28 °C for mean daily peak body temperature and mean daily average body temperature, respectively.

## Consequences for daily practice

This is a well-conducted randomised trial in patients admitted to the ICU studying treatment of fever with acetaminophen on an intention to treat basis. The study was performed in 700 patients in multiple ICUs in two countries. This randomised study shows no difference in the number of ICU-free days when patients treated with acetaminophen were compared with those treated with placebo (primary outcome). Also, when evaluating

the secondary outcomes, no statistically significant differences were observed. Although the mean daily peak and average body temperature were statistically significantly lower, the absolute effect was only a few tenths of a degree Celsius. The median number of doses of acetaminophen or placebo was 8 (IQR 5-14) and 9 (IQR 6-15), respectively. When expressed in time this equals approximately 48 hours of treatment. So, these results are primarily applicable to early and short treatment of fever with acetaminophen.

The result that acetaminophen is associated with a shorter ICU stay in survivors and a longer ICU and hospital stay in nonsurvivors is consistent with earlier studies that acetaminophen delays death. No conclusions can be drawn from this study on the underlying mechanism for this finding. Hypotheses suggested by the authors are an influence on the doctors' perception of the patient's illness severity and prognosis (or both) due to lowering of the temperature by acetaminophen. Alternatively, acetaminophen might have a biological effect on sepsis, such as reducing oxidative injury and improving renal function.<sup>[2]</sup>

The findings of this study suggest that treatment with acetaminophen per se does not seem indicated in patients

with fever and a suspected or proven infection. Nor did it show a harmful effect. Therefore, acetaminophen should still be considered in these patients, especially when an analgesic effect is wanted. Furthermore, other investigators have shown that there might actually be a beneficial effect of lowering body temperature and research is ongoing (e.g., Cooling And Surviving Septic Shock Study, CASS) and needed to bring more clarity to this subject.<sup>[3,4]</sup>

### Disclosures

The author declares no conflict of interest. No funding or financial support was received.

### References

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