

# **Antipyretic in critically ill septic patients**

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# Introduction

Sepsis is defined as the systematic inflammatory response syndrome (SIRS) caused by suspected or documented infections, and it is often accompanied with fever. Over 1 million patients are hospitalized with sepsis annually in the United States, and sepsis is the leading cause of death in critically ill patients.

Ref: Lagu T, Rothberg MB, Shieh MS, et al: Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med 2012; 40:754–761

Sepsis is a major threat to human health and is among the most important causes of morbidity and mortality in the intensive care unit (ICU). In 2010, sepsis accounted for approximately 5% of deaths in England.

**Ref:** D. McPherson, C. Griffiths, M. Williams et al., "Sepsis associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010," *BMJ Open*, vol. 3, no. 8, Article ID e002586, 2011

Fever, the cardinal symptom of sepsis, occurs in approximately 40% of critically ill septic patients at some point during their ICU stay. It is an extremely complex physiologic response with potentially beneficial and harmful effects in septic patients.

Ref: Kushimoto S, Gando S, Saitoh D, et al. JAAM Sepsis Registry Study Group: The impact of body temperature abnormalities on the disease severity and outcome in patients with severe sepsis: An analysis from a multicenter, prospective survey of severe sepsis. Crit Care 2013; 17:R271.

Fever boosts several aspects of innate and adaptive immunity, inhibits microorganism growth, slows viral replication, and augments antibiotic efficacy.

At febrile temperatures, direct inhibition of heat-sensitive microorganisms, such as influenza virus and *Streptococcus pneumoniae*.

- Ref: 1. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: The immune system feels the heat. *Nat Rev Immunol* 2015; 15:335–349
2. Oxford JS, Corcoran T, Schild GC. Naturally occurring temperature-sensitive influenza A viruses of the H1N1 and H3N2 subtypes. *J Gen Virol* 1980; 48: 383-9.
3. Enders JF, Shaffer MF. Studies on natural immunity to pneumococcus type III. *J Exp Med* 1936; 64: 7-18.

Circiumaru et al. conducted the first study on the relationship between fever and mortality in critically ill patients during their ICU stays and found that fever lasting more than 5 days was associated with increased mortality ( $p < 0.001$ ).

Ref: “Estudio Nacional de Vigilancia de Infección Nosocomial en UCI (ENVIN-UCI) 2001–2009,” 2012<http://hws.vhebron.net/envin-helics/>.

- The management of fever induced by sepsis varies across different institutions and hospitals.
- Some clinicians believe that fever is potentially harmful because it increases oxygen consumption.
- Some other investigators suggest that fever control with antipyretic drugs is potentially harmful.

Ref: Mohr NM, Doerschug KC (2013) Point: Should antipyretic therapy be given routinely to febrile patients in septic shock? Yes. *Chest* 144: 1096–1098; discussion 1101–1093. pmid:24081339

Dimopoulos G, Falagas ME (2009) Approach to the febrile patient in the ICU. *Infect Dis Clin North Am* 23: 471–484. pmid:19665078

# Antipyretic Therapy in Critically Ill Septic Patients: A Systematic Review and Meta-Analysis

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**Data Synthesis:** Eight randomized studies (1,507 patients) and eight observational studies (17,432 patients) were analyzed. Antipyretic therapy did not reduce 28-day/hospital mortality in the randomized studies (relative risk, 0.93; 95% CI, 0.77–1.13;  $I^2 = 0.0\%$ ) or observational studies (odds ratio, 0.90; 95% CI, 0.54–1.51;  $I^2 = 76.1\%$ ). Shock reversal (relative risk, 1.13; 95% CI, 0.68–1.90;  $I^2 = 51.6\%$ ) and acquisition of nosocomial infections (relative risk, 1.13; 95% CI, 0.61–2.09;  $I^2 = 61.0\%$ ) were also unchanged. Antipyretic therapy decreased body temperature (mean difference,  $-0.38^\circ\text{C}$ ; 95% CI,  $-0.63$  to  $-0.13$ ;  $I^2 = 84.0\%$ ), but not heart rate or minute ventilation.

**Conclusions:** Antipyretic treatment does not significantly improve 28-day/hospital mortality in adult patients with sepsis. (*Crit Care Med* 2017; 45:806–813)



ORIGINAL ARTICLE

# Acetaminophen for Fever in Critically Ill Patients with Suspected Infection

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N Engl J Med 2015; 373:2215-2224 | [December 3, 2015](#) | DOI: 10.1056/NEJMoa1508375

**In conclusion**, early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days. There was no significant between-group difference in 28-day mortality, 90-day mortality, or survival time to day 90.

*Research Article*

# **Effect of Antipyretic Therapy on Mortality in Critically Ill Patients with Sepsis Receiving Mechanical Ventilation Treatment**

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mechanical ventilation treatment. **Results.** A total of 8,711 patients with mechanical ventilator were included in our analysis, and 1523 patients died. We did not find any significant difference in the proportion of patients receiving antipyretic medication between

95% CI: 1.20–1.66,  $p < 0.001$ ). **Conclusions.** The use of antipyretic therapy is associated with increased risk of mortality in septic ICU patients requiring mechanical ventilation. External cooling may even be deleterious.

# The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis

Sarah Jefferies, Mark Weatherall, Paul Young,  
Sally Eyers, Kyle G Perrin and C Richard W Beasley

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**Conclusion:** The studies included in this review were insufficient to allow a robust estimate of the effect of pharmacological antipyresis on mortality in critically ill patients with suspected infection. Further RCTs are required to resolve this important area of clinical uncertainty.

# Antipyretic Therapy in Critically Ill Patients with Established Sepsis: A Trial Sequential Analysis

Zhongheng Zhang

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## Conclusion

our study fails to identify any beneficial effect of antipyretic therapy on ICU patients with established diagnosis of sepsis. Due to limited number of total participants, more studies are needed to make a conclusive and reliable analysis.

Sepsis

## Antipyretic therapy in febrile critically ill adults: A systematic review and meta-analysis ☆

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### Results

Five randomized clinical trials in 399 patients were included. The temperature threshold for treatment in the intervention group was commonly 38.3°C to 38.5°C, whereas it was typically 40.0°C for controls. Four studies used physical measures and 3 used pharmacologic measures for temperature control. There was no significant heterogeneity among the included studies ( $I^2 = 12.5\%$ ,  $P = .3$ ). Fever control did not significantly effect ICU mortality with a pooled risk ratio of 0.98 (95% confidence interval 0.58-1.63,  $P = .9$ ).

### Conclusions

This meta-analysis found no evidence that fever treatment influences mortality in critically ill adults without acute neurological injury. However, studies were underpowered to detect clinically important differences.

# Discussion

Hypothesis that hyperthermia is potentially beneficial to septic patients. Some meta-analysis result was shown that fever does not confer any mortality benefit to the septic patients and sometimes has deleterious effect to the patients. Some meta-analysis was shown antipyretic has neutral effect on septic patients

Despite the potential benefits of fever in patients with sepsis, treatment with antipyretic therapies is common in the ICU. In a recent international survey of ICU practitioners in 23 countries, greater than 80% of respondents reported controlling fever in critically ill patients most or all of the time.

Ref: Niven DJ, Laupland KB, Tabah A, et al. EUROBACT Investigators: Diagnosis and management of temperature abnormality in ICUs: A EUROBACT investigators' survey. Crit Care 2013; 17:R289.

# Conclusion

- There is no consensus on the management of fever in patients with sepsis
- Antipyretic treatment does not significantly improve hospital mortality in adult patients with sepsis.



Thank You