Journal Club Eastern Virginia Medical School
Therapy Article

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CITATION: Young P., Acetaminophen for Fever in Critically Ill Patients with Suspected Infection.N Engl JMed. 2015 Oct 5.

I. **WHAT IS BEING STUDIED?**	
1. Study Objective	To determine if compared to placebo, administration of acetaminophen in the adult ICU in patients with fever and suspected infection would result in fewer ICU-free days (alive).
2. Study Design	Investigator-initiated, prospective, parallel-group (non-crossover), double-blinded, randomized, controlled trial. Occurred in 23 ICU's in Australia and New Zealand. 700 enrolled 690 patients total analyzed.
3. Inclusion Criteria	Age >16 years, temperature > or = 38C within 12 hours before enrollment, receiving antimicrobial therapy for known or suspected infection
4. Exclusion Criteria	Acute brain disorders and liver dysfunction that contraindicated use of acetaminophen, *requirement for ongoing NSAID use, therapeutic hypothermia, hyperthermic syndromes (like heat stroke), death imminent (perceived to be within 24 hours), rhabdomyolysis that is clinically significant, transferred from another ICU after >12 hours, pregnancy*
5. Interventions Compared	1g IV acetaminophen vs. infusion of 5% dextrose in water every 6 hours for 28 days after enrollment or the occurrence of pre-specified cessation criteria: (discharge from ICU, resolution of fever, cessation of antimicrobial therapy, death, or the development of a contraindication to the study drug). Also Rescue cooling permitted of T> 39.5. Open label APAP allowed after study med period was completed.
6. Outcomes Evaluated	Primary: median ICU-free days to day 28, death = 0 ICU free days. Secondary (within 90 day follow up): all-cause mortality at day 28 and day 90, survival time from randomization until day

	90, ICU and hospital length of stay, hospital free days, days free from mechanical ventilation, days free from inotropes or vasopressors, days free from renal replacement therapy, days in the ICU free from all 3, axillary temperatures, proportion of pts. who stopped drug due to liver dysfunction, CRP levels, CK levels
II. **Are the results of the study valid**	
1. Was the assignment of patients randomized?	Yes. Eligible patients were randomized in a 1:1 ratio
2. Was randomization concealed (blinded)?	Yes. Randomization was performed with the use of an encrypted Web-based system involving block randomization with a block size of six. Investigators were unaware of the randomization block size.
3. Were patients analyzed in the groups to which they were randomized?	Yes. All analyses were conducted on an intention-to-treat analysis
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Table 1 p.6 Characteristics of patients at baseline were similar.
III. **Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1. Were patients aware of group allocation?	No. The study medications were packaged in indistinguishable 100-mlglass bottles. (In supplement material)
2. Were clinicians aware of group allocation?	No. Investigators were unaware of study drug (supplement)
3. Were outcome assessors aware of group allocation?	Yes. P3 All analysis was performed prior to unmasking study group assignments. .
4. Was follow-up complete?	Yes. Only 10 patients (1.4%) lost to follow-up. No reporting on followed up beyond day 90
IV. What were the results? Answer the questions posed below	
1. How large was the treatment effect? (Difference between treatment and control group).	Table 2 Primary Outcome: No significant effect on number of ICU free days to day 28 23 days (IQR 13-25) in the paracetamol

	group vs. 22 days in the placebo group (IQR 12-25) CI 0-1; P=0.07 Secondary Outcomes: All cause mortality at 28 days: no significant difference 13.9% vs. 13.7% All cause mortality at 90 days: no significant difference 15.9% vs. 16.9%
2. What was the estimated treatment effect at a 95% confidence interval? (Precision)	As above. No statistical significance. CI's includes 1.0
V. **Will the results help me in caring for my patients? (Applicable?)**	
1. Were the study patients similar to my patient?	Maybe. Definitions of sepsis and septic shock the same. Non U.S. population.
2. Were all clinically important outcomes considered?	Arguable whether primary outcome measure is truly patient centered. Long term morbidity not studied in terms of conditions like neurological devastation or patients with new dialysis requirement
3. Are the likely treatment benefits worth the potential harm and costs?	Hard to say. No evidence of significant harms reported. Withholding of study drug and placebo because of liver dysfunction was insignificant (8.1 vs. 9.9 placebo OR CI95% 0.69-1.14) Difference in temperature between these patients was a Tmax of 0.5C, which does not seem to test the theory of permissive hyperthermia. Seems to be no benefit or cost health wise, so it does not matter if IV acetaminophen is given or not. However the cost of the medication could be enough to sway one to not use it if it provides no benefit.

Limitations

Median duration of study drug administration was only 8 days, so a longer treatment time could have more effect on outcomes.

Approximately 1/3 patients in both groups were exposed to open label acetaminophen while in the ICU and during study period.

Supp 4.2:

"Use of open label acetaminophen was not common in the first few days in the ICU; however, in

both treatment groups its use increased over the course of the ICU stay. After seven days, open label acetaminophen use exceeded use of study medication. Open label acetaminophen was administered in the ICU to 104 of 347 acetaminophen patients (30.0%) and 101 of 344 placebo patients (29.4%) (OR, 1.01; 95%CI, 0.86 to 1.19; P=0.86).

No per protocol analysis. Would be interesting to have reported on those groups who got NO off-protocol APAP

. No data collected on use of acetaminophen before study began or after study ended, so results limited to early use of acetaminophen in ICU in patients with suspected or known infection.

Degree of fever not studied. Tmax difference between groups was 0.5C Does this test benefits of permissive hyperthermia? Theoretically fever may inhibit bacterial growth, improve antimicrobial activity, diminish shedding period of viruses, and enhance antibody response to vaccination.

Clinical Bottom Line:

Methodologically, randomization, blinding, ITT analyses, pre-specified subgroups, f/u laudable. Unfortunately very high percentage of subjects received APAP. Also time in ICU was relatively short and total # of doses of APAP may not have fully tested hypothesis. Seems that there are no harms associated with use of APAP. Some studies have proposed a benefit to permissive hyperthermia however this data does not seem to have advanced that theory.