Critical Review Form
Therapy

PGY-3

HYPERLINK "http://pmid.us/29196046"Alam N, Oskam E, Stassen PM, et al; PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med. 2018 Jan;6(1):40-50.

Objectives: **"to test the hypothesis that increasing the awareness of sepsis through training of EMS personnel in recognising and initiating treatment with early prehospital administration of antibiotics leads to increased survival of patients with sepsis, severe sepsis, or septic shock compared with those patients receiving usual care." (p. 41)**

Methods: **This nationwide, open-label, randomized controlled trial was conducted in ten large regional ambulance services serving 34 hospitals in the Netherlands between June 30, 2014 and June 26, 2016. Adult patients aged 18 years and older with suspected infection, a temperature > 38°C or < 36°C with at least one other criterion for SIRS were eligible for enrollment. Exclusion criteria were allergy to beta-lactams, known pregnancy, and suspected prosthetic joint infection.**

After inclusion, patients were classified into three groups (uncomplicated sepsis, severe sepsis, and septic shock) according to the 2001 SSCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference guidelines. Patients were randomized in a 1:1 fashion to the intervention group and the control group. Patients in the intervention group received 2 grams of IV ceftriaxone (plus usual care) after drawing one set of blood cultures, while patients in the control group received usual care only. Prior to the study, investigators modified EMS programs to include a separate comprehensive sepsis protocol.

The primary outcome was all-cause mortality at 28 days. Secondary outcomes were misdiagnosis of patients enrolled in the study, mortality during hospital stay and within 90 days, hospital length of stay, need for ICU admission, ICU length of stay, time to antibiotic administration (TTA), microbiological data, adverse events, and quality of life one month after discharge.

There were 2698 patients enrolled during the study period, of whom 1548 were assigned to the intervention and 1150 were assigned to usual care. After 18 patients were lost to follow-up and 8 withdrew consent, there were 1535 patients in the intervention group and 1137 in the usual care group in the final analysis.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. "Eligible patients were randomly assigned (1:1) to the intervention group or usual care group using block-randomisation with blocks of size 4. Randomisation was stratified per region." (p. 42)
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Lists with random sequences were centrally generated and consecutively numbered indistinguishable envelopes containing a note with the group assignment (intervention or usual care) were put in all participating ambulances by the local research team." (p. 42) This should be adequate to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. " We analysed all data according to the intention-to-treat principle." (p. 43)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, level of EMS urgency, severity of sepsis, proportion of patients with qSOFA score ≥ 2, and presence and location of organ dysfunction. Patients in the intervention group were more likely to receive prehospital IV fluids (64% vs. 37%), but those who received fluid in each group received a similar median volume.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes. This was an open label trial with no attempt at blinding. Given the interventions and outcomes it is unlikely that performance bias on the part of patients would have affected outcomes.
2.	Were clinicians aware of group allocation?	Yes. It is possible that performance bias on the part of EMS personnel and hospital clinicians may have impacted care and hence outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors. The outcomes were overall quite objective and hence at low risk of observer bias.
4.	Was follow-up complete?	Yes. Eighteen patients were lost to follow-up (9 in each group) representing just 0.7% of the enrolled population. While the authors do not mention how outcomes were assessed beyond the

		hospitalization, there was presumably no other loss to follow-up. Only about a third of patients in each group returned the quality-of-life questionnaire.
II.	**What are the results ?**	
1.	How large was the treatment effect?	● There was no significant difference in 28-day mortality in the intervention group (8%) or control group (8%): RR 0.95, 95% CI 0.74-1.24. o No difference in 28-day mortality was seen for any of the three subgroups based on sepsis severity. ● There was no significant difference in ICU admission (RR 1.17, 95% CI 0.92-1.49), medial hospital length of stay (6 days in each group), or median ICU length of stay (4 days in the intervention group vs. 3 days in the usual care group). ● There was no difference in 90-day mortality between groups (RR 0.98, 95% CI 0.80-1.21). ● For those patients who returned the quality-of-life questionnaire, there was no significant difference between scores.
2.	How precise was the estimate of the treatment effect?	See above. This was a fairly large study with relatively narrow confidence intervals.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Somewhat. This study was conducted solely in the Netherlands, where a more ethnically homogenous population is expected than that seen in the US. Additionally, differences in prehospital care (including use of ambulance nurses) and transport times may also have affected the results of this study.
2.	Were all clinically important outcomes considered?	Mostly yes. The authors considered mortality at multiple time points, need for ICU admission, ICU/hospital length of stay, and quality of life. They did not report need for renal replacement therapy or need for mechanical ventilation.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. Based on the results of this study, there was no difference in 28-day mortality for the entire cohort or for subgroups based on sepsis severity.

Limitations:

1. **This was an open label trial with no attempt at blinding. Performance bias on the part of EMS personnel and hospital clinicians may have impacted care and hence outcomes.**
    a. **Patients in the intervention group were more likely to receive prehospital IV fluids (64% vs. 37%).**
2. **The authors do not specify how outcomes beyond the hospitalization were assessed.**
3. **The study was conducted solely in the Netherlands, where a more homogenous population and differences in prehospital care may limit the applicability of results to the US population (external validity).**

Bottom Line:

This large, multi-center study from the Netherlands found that prehospital administration of antibiotics for sepsis did not have any impact on 28-day mortality (RR 0.95, 95% CI 0.74-1.24) either in the cohort as a whole or in subgroups of sepsis severity.