Editorial

Use of antibiotics in the ambulance for sepsis patients: is earlier really better?

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In their study entitled *Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial*, Dr. Nadia Alam and colleagues from the Department of Internal Medicine, VU University Medical Center and the Institute for Cardiovascular Research, Vrije University Amsterdam investigated, whether patients with sepsis could benefit from prehospital antibiotics in the ambulance.

Sepsis is still associated with an unacceptable high risk for morbidity and mortality. Despite a decline in mortality the total number of deaths from sepsis is still augmenting due to increasing incidence (1). As a consequence, early recognition and commencement of sepsis therapy is essential in the management of sepsis. Several retrospective studies showed that early antimicrobial therapy is associated with improved survival, and that any delay in administration of antibiotics after development of septic shock is associated with an increase in mortality (2). Therefore, the timely administration of antibiotics as cornerstone of therapy beside fluid resuscitation and supplementary oxygen was endorsed by the Surviving Sepsis Campaign (SCC) guidelines (3). Yet, to date, to our knowledge prospective studies failed to validate that use of early antibiotics has beneficial effects on mortality (4-6). To close this gap, Dr. Alam and colleagues designed the first prospective randomized controlled trial investigating the effects of early antibiotic administration in patients with suspected sepsis.

Emergency medical services personnel are with any doubt key actors for patients with time-dependent illnesses, such as myocardial infarction and trauma (7). The investigators investigated whether patients with sepsis could also benefit from an early prehospital care from specially trained EMS personnel (8). The designed trial tested the hypothesis whether or not increasing the awareness of sepsis with consecutive early administration of antibiotics could lead to an increase in survival of patients compared with those patients receiving usual care. This was implemented through special training for EMS personnel in recognizing sepsis and as a result initiating treatment with early prehospital administration of antibiotics. To ascertain if patients with sepsis could benefit from prehospital care they designed a nationwide controlled open-label trial in ten large regional ambulance services, serving 34 secondary and tertiary care hospitals in the Netherlands.

EMS personnel were trained in advance, to recognize and treat sepsis promptly and effectively.

Patients eligible for the study were recruited by EMS personnel and randomly assigned (1:1) to the intervention group or usual care group. As criteria to include patients to the study, they used the following decisive factors: patients needed to be at least 18 years old with a diagnosed or suspected infection, temperature >38 or <36 ℃ and at least one of the following systemic inflammatory response syndromes (pulse >90 beats per minute, respiratory rate >20 per minute) (8).

Envelopes containing a note with the group assignment (from centrally generated lists) were distributed to each participating ambulance. In the usual care group, patients received fluids and supplementary oxygen. In the intervention group, patients received additionally to the usual care treatment an antibiotic (i.e., ceftriaxone 2,000 mg intravenously) in the ambulance.

The trial had a high recruitment rate with 3,228 patients being screened and 2,698 patients being included and randomized (1,150 patients received usual care while 1,548 patients received the intervention). After excluding 13 patients from each group for different reasons, 1,137 patients remained in the usual care group and 1,535 patients in the intervention group. The primary outcome was all-cause mortality at 28 days and secondary outcomes were among others mortality during hospital stay and within 90 days, length of hospital stay, ICU admissions, time to antibiotics (TTA) in the emergency department for usual care group and time to antibiotics before hospital arrival for the intervention group. The results showed that 120 patients (8%) died within 28 days in the intervention group and 93 patients (8%) in the usual care group. In both groups, mortality increased with sepsis severity but there was no statistically significant difference found between the usual care and intervention group. Subgroup analyses did not show a significant effect on the 28-day mortality by any of the interventions. Especially for patients in the usual care group, there was no association between longer time to antibiotics and increased 28-day mortality. No significant difference was found in ICU admissions, length of hospital stay, 90 days mortality or for in-hospital mortality (8).

Why did this trial fail to validate previous observational studies regarding the benefits of early antibiotic treatment? In this trial, usual care group patients received antibiotics on average within one hour of presentation to the emergency department. In previous studies time to antibiotics on the emergency department varied between 115 and 360 min (3,9-11). Thus "usual care" was much better which may relate to trial effects and a Hawthorne effect and reduces the differences to the intervention group in regard to expected effects. In fact, the time difference in time to antibiotics between the two trial groups was 96 min, which is much smaller than in other studies (8,12). Also, there was likely an improvement in recognizing sepsis and time to antibiotics in usual care for patients with sepsis and in the opinion of the investigators this was due to the training for EMS personnel. This again may explain the lack of difference between groups.

Strengths of this trial are certainly the large sample size and the broad study population which is an appropriate reflection of the overall emergency department population. Additionally, this trial is the first interventional study in this setting. Nevertheless, there are several limitations. The study population was screened in the ambulance; consequently, patients with varying degrees of sepsis severity were included in the study. Previous studies have focused on intensive care populations with patients mainly with septic shock. Therefore, this study is less comparable with previous studies. Further there was no significant benefit in survival resulting from early recognition and commencement of therapy. This might be due to the small number of patients with septic shock in this pre-hospital population as well as the short time to antibiotics in the usual care group. It remains unclear whether including more patients with septic shock or operating the trial in a pre-hospital setting with longer arrival times would have led to different results. Also, the generalizability to other countries is questionable. In the Netherlands the ambulance staff is well educated and very experienced in treating critically ill patients and primary care services (general practice) are well organized. General practitioners referred almost 75% of the study patients and 20% of these patients were already on antibiotic therapy before presentation. For this reason, it is difficult to apply the results of this study to communities with different health-care settings with much longer response and arrival times as well as less well-organized practitioner services. Another limitation is that more patients were included into the intervention group. This is mainly due to violation of the study randomization.

This trial also questions the validity of SIRS *vs.* qSOFA. There is an ongoing debate, whether the qSOFA is preferred over the used systemic inflammatory response syndrome criteria. If the trial would have used qSOFA score, some patients would not have been suitable for the study and therefore fewer patients would have been given antibiotics (8).

In conclusion, this study showed that there is no benefit of early antibiotic administration based merely on the clinical appearance and initial status of patients in the ambulance over usual care, but patient selection may have been the biggest issue here. In the future, the use of biomarkers, such as procalcitonin, for guiding antibiotic choices may help to improve the intervention by better selection of patients. Newer point of care tests may help to have procalcitonin results ready within a short time frame in the ambulance. Procalcitonin-guided antibiotic use in

respiratory tract infections has shown promising effects on survival in a large study from the Netherlands, and in a recent meta-analysis (13,14).

Dr. Nadia Alam and colleagues should be complemented for doing such an important study. Importantly, although pre-hospital antibiotics administration did not improve survival in this trial, training the EMS personnel on a regular base for early recognition of sepsis is effective to reduce time to treatment in the emergency department (8).

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Footnote

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References

1. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546-54.
2. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96.
3. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med 2017;45:486-552.
4. Ryoo SM, Kim WY, Sohn CH, et al. Prognostic value of timing of antibiotic administration in patients with septic shock treated with early quantitative resuscitation. Am J Med Sci 2015;349:328-33.
5. Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Crit Care Med 2011;39:2066-71.
6. de Groot B, Ansems A, Gerling DH, et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. Crit Care 2015;19:194.
7. Moyer P, Ornato JP, Brady WJ Jr, et al. Development of systems of care for ST-elevation myocardial infarction patients: the emergency medical services and emergency department perspective. Circulation 2007;116:e43-8.
8. Alam N, Oskam E, Stassen PM, et al. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med 2018;6:40-50.
9. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749-55.
10. Band RA, Gaieski DF, Hylton JH, et al. Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock. Acad Emerg Med 2011;18:934-40.
11. van der Wekken AJ, Hiltermann TJ, Groen HJ. The value of proteomics in lung cancer. Ann Transl Med 2015;3:29.
12. Seymour CW, Kahn JM, Martin-Gill C, et al. Delays From First Medical Contact to Antibiotic Administration for Sepsis. Crit Care Med 2017;45:759-65.
13. Wirz Y, Branche A, Wolff M, et al. Management of Respiratory Infections with Use of Procalcitonin: Moving toward More Personalized Antibiotic Treatment Decisions. ACS Infect Dis 2017;3:875-9.
14. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819-27.

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